Dimaval®

Scientific Product Monograph

Dimaval

Scientific Product Monograph

7th Edition

January 2008

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PRELIMINARY REMARKS

In order to facilitate the reading of this monograph, the male form of the third person will be used even when referring to female patients, subjects or physicians.

The drug products Dimaval® and Dimaval® (DMPS) 100 mg Hartkapseln are not approved by the FDA.

Dr. Johann Ruprecht
Scientific Department

Dimaval®

Dimaval® (DMPS)

100 mg Hartkapseln

(RS)-2,3-Bis(sulfanyl)propane-1-sulfonic acid, 1 H_2O sodium salt

Not approved by the FDA!

Scientific Product Monograph

7th Edition Date: January 2008

Contents

1 Foreword

The DMPS scientific product monograph has a long history. The first edition was published in 1990. Meanwhile we have reached the seventh edition. The monograph takes into account the existing literature on the active substance, DMPS, from 1951 – the year when it was first synthesised – to the present day. It thus contains a wealth of information acquired over more than 50 years. Numerous questions put to the Scientific Department of the HEYL Company since the last editions are answered in the latest version.

Dimaval® and **Dimaval® 100 mg Hartkapseln** contain (RS)-2,3-bis(sulfanyl) propane-1-sulfonic acid, 1 H_2O sodium salt as the active substance. The active substance was formerly known as (R,S)-2,3-**Di**mercapto-**p**ropane-1-**s**ulfonic acid (DMPS) sodium salt. The pharmaceutical active substance is unchanged but its name has been adapted in line with the latest regulations governing the naming of chemical substances. The abbreviated form, DMPS, which is derived from the previous name given to the active substance, is still used although it no longer correlates to the new name.

There is hardly ever any reference in the published data to indicate whether DMPS is used as the monohydrate or in the anhydrous form. As the monohydrate is the stable form on exposure to air, the evaluations in this monograph will be based on the monohydrate.

The most important change in the seventh edition is the comparison of DMPS with other chelating agents such as BAL, DMSA, DTPA or DPA. On the one hand, this helps to quickly identify the advantages of DMPS compared to other chelating agents, e.g. on intoxication of the kidneys with mercury poisoning. On the other hand, however, it also highlights the limitations in the use of DMPS. The physician thus obtains the necessary information to make a benefit-risk assessment for his patients and can decide whether the use of DMPS is indicated. Specialising in antidotes to combat heavy metal poisoning, this is our contribution to the responsible use of DMPS for the benefit of patients.

The conclusions are also new. They are personal conclusions drawn from the listed data regarding the safer, more effective use of DMPS.

Numerous other resources were consulted in addition to peer-reviewed publications, e.g. the Internet and various brochures or dissertations. A critical evaluation of the both printed and electronic media was indispensable. Various claims, particularly in the domain of the heavy metal burden arising from the environment and amalgam, are not confirmed. Some are not even comprehensible. In his extensive work, Cutler, for instance, claims that there are more fatalities during DMPS administration[<293>]. No such fatalities have, as yet, been reported to us as manufacturer. The authorities obviously have no idea of this either, or they would otherwise have contacted us.

As regards topics, which, according to the literature, are still subject to controversy, both viewpoints should, where possible, be compared.

The product monograph is a service offered by the HEYL Company for its customers. It is aimed at the medical profession and should be a reference work for all interested parties in that it summarises the latest up-to-date information relating to this active substance. It should provide the basis for the responsible use of Dimaval® and Dimaval® (DMPS) 100 mg Hartkapseln. This applies both to patients presenting with acute, life-threatening heavy metal intoxication as well as those with the clinical sequelae of chronic poisoning. The information sought can be quickly retrieved using the detailed contents list.

The number of interested parties confirms the interest in a reference work of this kind. We received requests for over 10,000 copies of the 6th German edition and more than 1,000 copies of the English-language equivalent. The product monograph is increasingly quoted as a source by research scientists in their publications.

As DMPS treatment can be associated with side effects, a careful benefit-risk evaluation must be carried out prior to use, as is the case with all medicinal products. Scientific knowledge of medicinal products and pharmaceutical active substances is subject to constant change. For the latest information on authorised indications, side effects, interactions, dosage or contraindications, please consult the valid Patient Information Leaflet and Summary of Product Characteristics for the **Dimaval®** injection solution and the oral pharmaceutical form, **Dimaval® (DMPS) 100 mg Hartkapseln**.

2. Introduction

Metals are toxic because of their interaction with various biomolecules such as enzymes or membrane components[<286,383a>]. Their arrangement on cysteine and histadine groups of proteins is mainly responsible. The properties of the biomolecules are altered by complex formation with the heavy metals. The normal substrate arrangement is disrupted, resulting in toxic reactions[<667, 673,911>]. Furthermore, they can oust Mg^{2+}, Ca^{2+}, Zn^{2+} and other elements from their protein complexes[<270,383a>]. Almost all organ systems can be affected by this[<286>].

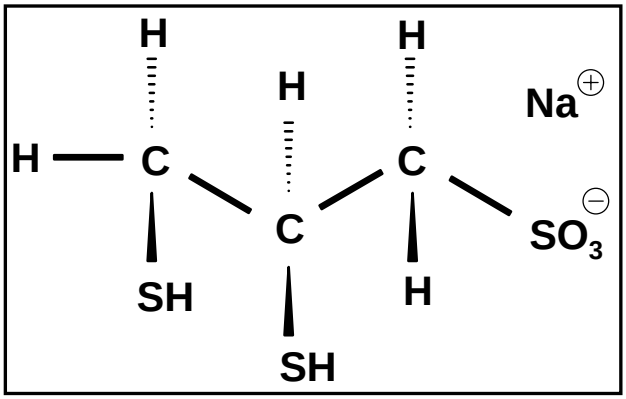
Heavy metals are elements and, unlike organic molecules, cannot be broken down in the body[<383a>]. Every treatment to combat intoxication must, therefore, target the excretion of heavy metals from the body[<278,286,744>] or reduce their toxicity by forming biologically inactive compounds[<278>].

If a metal is present in the body tissue in toxic quantities, then its elimination can be supported and accelerated by the administration of a suitable chelating agent[<63,911>]. The total body burden and the burden of individual tissue are thus reduced and the survival rate in acute poisoning increased.

Heavy metal intoxication can therefore be treated with causal therapy. “Timely consideration of mercury intoxication, for instance, can aid diagnosis through targeted investigation of symptoms and relatively straightforward assays in the urine and blood. Effective treatment with chelating agents can be administered, as required“[<697>].

If the increase in the excretion of heavy metals in the urine is measured before and after mobilisation with the antidotes, the values also provide diagnostic information on the heavy metal burden[<483,1270,1273,1292,1385>].

Most of the chelating agents currently used were developed in the 1960s[<911>]. Since then, they have formed the basis for the treatment of metallic poisoning[<341,343,675>]. DMPS was first synthesised in 1951 in the former USSR[<1269>] and has been used clinically (parenteral administration) since the late 1950s[<30,68,178, 418,770a,1269>]. DMPS (i.m.) has been used in China since 1963[<1532>]. DMPS is also a well-known active substance for which decades of experience have already been collected.



In the early 1970s, HEYL started to carry out its own research to make the chelating agent DMPS [(RS)-2,3-bis(sulfanyl)propane-1-sulfonic acid, formerly known as (R,S)-2,3-dimercaptopropane-1-sulfonic acid] available for the treatment of heavy metal poisoning. A patented synthesis process was initially developed for this purpose in order to produce sufficient quantities of an adequately pure active substance .

In addition, tests were carried out in conjunction with various institutes in Germany, the USA and Switzerland to determine the toxicology, metabolism and pharmacokinetic profile of the antidote. The efficacy of DMPS in acute and chronic heavy metal poisoning was investigated and compared with that of other chelating agents in laboratory animal experiments. The safety and therapeutic efficacy of DMPS therapy was also demonstrated in clinical trials in humans. Meanwhile, DMPS has become the drug of choice in various forms of heavy metal poisoning.

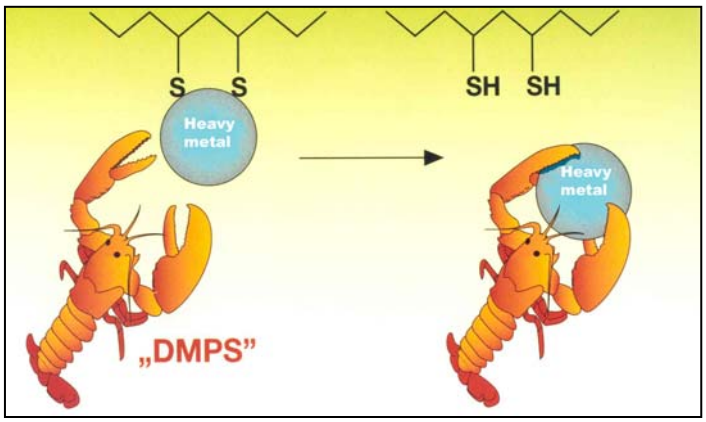
HEYL was the first company to introduce DMPS for oral administration. Nowadays, the active substance is marketed in capsules under the name of Dimaval® (DMPS) 100 mg Hartkapseln and as a solution for injection under the name of Dimaval®. The parenteral form can be administered via the intravenous and intramuscular routes.

In the western world, DMPS is marketed only as Dimaval®. No marketing authorisation application has ever been submitted to the FDA, Health Canada or the EMEA. Consequently, Dimaval® is not normally available in the USA or Canada[<52>]. It can be administered in emergency situations only under exceptional circumstances and with the consent of the authorities. This approach is increasingly being adopted.

Dimaval® und Dimaval® 100 mg Hartkapseln contain the sodium salt of (RS)-2,3-bis(sulfanyl) propane-1-sulfonic acid, monohydrate – formerly known as (R,S)-2,3-dimercaptopropane-1-sulfonic acid (DMPS) – as the active substance. DMPS is an antidote belonging to the group of vicinal dithiols[<87,675>]. It has a high affinity for many heavy metals due to the two adjacent SH groups[<663a,675>] and forms stable, mostly water-soluble complexes (chelates)[<87>] with these. As the chelating agents are excreted more effectively than the respective metal, the excretion of heavy metals mainly found in the extracellular space is promoted. Elimination is chiefly in the urine, via the kidneys[<87,667>]. Measurement of heavy metal levels in the urine confirms treatment efficacy. The biological half-life of the heavy metals in the body is reduced. The SH groups in proteins are protected from blockage by the poisons or existing blockade is abolished[<28,494,663a,1453>]. The enzymes retain or recover their ability to function[<166>].

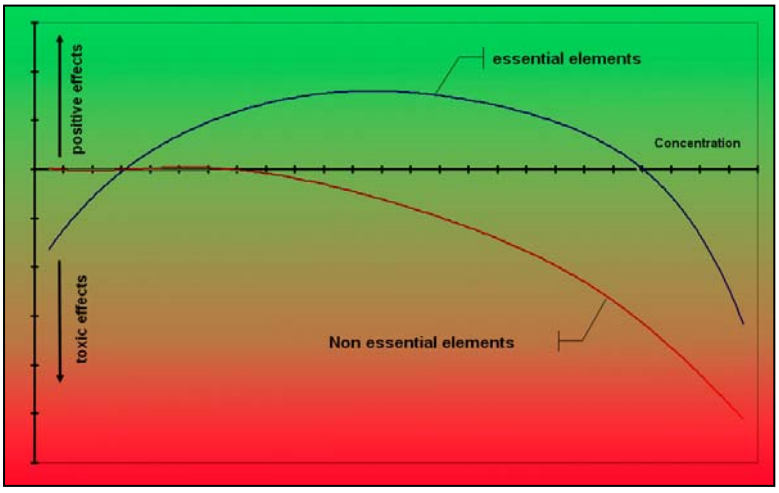
DMPS is thus an antidote according to the definition issued by the WHO and the international Poison Control Centres: "An antidote is a therapeutic substance, which is used in order to counteract the toxic effects of certain xenobiotics"[<647a,706>]. Antidotes reduce the bioavailability of toxins or increase the excretion of unchanged toxins or attack their metabolism[<141>].

Aims of "Antidote administration:
- Acceleration of excretion
- Acceleration of metabolism
- Binding of a poison (active charcoal, non-specific antidote)
- Transformation into less toxic substances
- Ousting of the poison from the site of action (antagonism, competitive inhibition)
- Abolishing of the effect (effect-antagonism)"[<270>]



The pincer-like action of DMPS is characteristic for chelating agents. Chelate is derived from the Greek word for lobster χηλη (chele = pincer, claw, clamps, scissors, etc.)[<706,911>]. Chelating agents grip the heavy metal ions like the claws of a lobster and form cyclical complexes[<58,706>]. Two functional groups are a pre-requisite for this – the vicinal SH groups in DMPS -, which allow a ring structure to be formed with the metal[<341>].

DMPS does not reach all depots in the body. The mobilisation and excretion of the heavy metals present in the extracellular space produces a shift in the steady state between the various compartments of the body in which the heavy metals are stored. Planas-Bohne *et al*. demonstrated this in erythrocytes, for instance[<1157>]. This exerts a "magnetic effect" on the metals that are in the depots, which are not directly accessible to DMPS. If the metals are not bound too firmly in these depots, then the body attempts to restore equilibrium between the depots. The heavy metals will then partly migrate into compartments where they can be accessed by DMPS[<63,87,88,243,304,666,1040,1163,1184,1205,1206>]. "Therefore, the Hg^{2+} urine and blood levels remain in constant equilibrium with the mercury body burden. A recent study showed that removal of mercury from the blood by chelation with DMPS resulted in about a 25% drop which lasted only 30 minutes before equilibrium brought the blood mercury level back to its prechelation state. This could only happen if the mercury body bur-



Antidotes	
Chelating agents	Adsorbents
• DMPS, DMSA, BAL • EDTA, DTPA • DPA • Desferioxamine • Trientine	• Active charcoal • Berlin Blue • Colestyramine
o Oral or parenteral administration o Absorption in the gastrointestinal tract	o Oral administration o No absorption
o Increased excretion in the urine and/or bile	o Prevention of absorption and increased excretion in the faeces

den was high enough to rapidly replace by equilibrium balance the mercury taken from the blood by chelation. This also strongly implies that mercury body burden is in great excess of the blood mercury levels measured"[<554a>]. This redistribution, however, requires a certain amount of time, which must be taken into account when establishing the intervals beween administration of the chelating agent[<1184>].

DMPS does not react selectively with the toxic heavy metals, but mobilises both toxic and essential metals[<436,672,675,706>]. Essential metals such as zinc and copper can also cause poisoning. They have a toxic effect when they exceed a value that the cell buffer system can still process[<1362>].

The extent of the mobilisation, however, varies considerably. It depends on the complex-forming constants, the concentration of the competitive metals and on the concentration of competing ligands[<436>].

The "hard-soft acid-base-theory" is useful when selecting the appropriate antidote. Soft metals (Hg, Au, Pt, Ag, Cd ...) are "sulfur seekers" and form stable complexes with sulfur-containing chelating agents. Hard metals (Fe, Al, Gd), however, are "oxygen seekers". The "borderline-metals" (Pb, Cu, Zn, Tc, Ni ...) can be complexed with chelating agents containing N, O or S. It therefore follows that chelating agents with vicinal SH groups such as DMPS can prove effective in the treatment of poisoning with soft and various "borderline metals"[<2,911>].

Various factors are crucial for the therapeutic efficacy of a chelating agent[<8,121,243,286,420,666,667,721,911,1173,1206>]. A good chelating agent must

1. be readily available in a form suitable for administration and should be as easy as possible to administer. It should, where possible, be available for both oral and parenteral administration;
2. be readily soluble in water and thus sufficiently soluble in a physiological medium;
3. reach the heavy metals in the body, e.g. intracellular spaces[<1624>]. Its distribution in the bodily compartments must correspond to that of the toxic metals (lipophilia/hydrophilia). Intracellular metal depots are mainly involved in "older" poisoning;
4. be as tolerable as possible. Neither the chelating agent nor the resulting complexes must be toxic and they should trigger as few side effects as possible;
5. should be only slightly toxic in order to facilitate administration of high dose levels. As complex formation is a balanced reaction, a dose as high as possible is required over a sufficient period of time in order to bind as much of the toxic metal as possible (possibly repeated dosing);
6. display no foetotoxic or teratogenic properties;
7. be suitable for the long-term treatment of chronic poisoning;
8. be able to loosen metals from their binding to biological molecules, i.e. must bind the metal ions more strongly than the biological compartments. To this end, a suitable number and type of functional groups are required in the chelating agent;
9. must form non toxic complexes with the toxic metals;
10. promote the excretion of metals from the body. The resulting complexes should be excreted as quickly as possible via the kidneys or the bile;
11. should prevent the redistribution of heavy metals in the body, e.g. it must not lead to any accumulation in the brain;
12. reduce the absorption of the heavy metal from the gastrointestinal tract;
13. display optimal selectivity and affinity for toxic metals. The binding of the chelating agent with the toxic heavy metals must be stronger than the binding with essential minerals, trace elements and H^+-ions. This applies in particular for calcium, which is present in larger

quantities in the plasma[<673>], as well as for zinc, iron and copper (high therapeutic index). This reduces the risk of side effects and boosts efficacy as the unnecessary use of DMPS, e.g. by Zn, is precluded;

14. be as stable as possible and display inert, metabolic properties. The chelating agent must not be inactivated by metabolic degradation or reactions;
15. form stable complexes at a physiological pH and in the acid pH of the urine.

Conclusion:
DMPS satisfies most of the requirements of an effective chelating agent:

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
√	√	± 1)	√	√	√	√	√	√	√	√	? 2)	√	- 3)	√

1) DMPS has a mainly extracellular effect, but also partially migrates into the cells.
2) Parenteral DMPS can be administered in order to prevent any increase in the absorption of poison from the gastrointestinal tract following intoxication with oral heavy metals.
3) DMPS is oxidized into disulfides relatively quickly. These can be partially reduced in the body and also have an antidote effect.

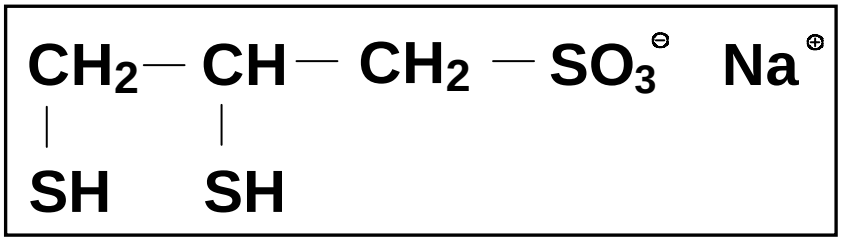
In addition to thermodynamic factors (complex-forming constants), kinetic factors also play a role in the selection of a suitable antidote:

- Rate at which the antidote concentration is lowered in the plasma.
- Clearance of the metal or complex from the plasma.
- Rate of reaction of the chelating agent to heavy metals bound to biological molecules.
- The ability of the chelating agent to track the heavy metal in its key depots within the body[<669>].

Due to the asymmetrical carbon [C2], DMPS can be present in two different optic isomers (R or S) and as a racemate (R,S)[<69,87>]. No significant differences in terms of absorption, toxicity or efficacy are observed between the various isomers in laboratory animal experiments[<617,706>]. Costly separation of the racemate can therefore be omitted in the production of the active substance. The following comments refer to the racemate.

3 Chemistry

(RS)-2,3-bis(sulfanyl)propane-1-sulfonic acid sodium salt – formerly known as (R,S)-2,3-dimercaptopropane-1-sulfonic acid (DMPS), is a chelating agent that belongs to the vicinal dithiol group[<675>]. It is available as a water-soluble chelating agent with two sulfhydryl groups and one sulfonate group for oral or parenteral administration with a mainly extracellular action[<1427>]. Redox and complex-forming reactions constitute its main potential for reaction[<1084>]. It has a high affinity for many heavy metals with an affinity for sulphur, due to the two adjacent SH groups, and forms stable complexes with these[<87,675,824,877)]. The hydrogens of the two sulfhydryl groups are replaced by the metal with an affinity for sulphur through the formation of a stable ring structure[<1473>]. The two sulfhydryl groups also trigger reductive properties[<824,1473>]. The polar sulfonic acid group primarily influences physico-chemical behaviour and is responsible for the water solubility of DMPS[<494,670,735,960,1062>] and thus for some of its pharmacokinetic properties (e.g. low lipid solubility[<69>]) .



EINECS No.: 223-796-3
Merck Index: 3197
ASK number: 165 42
SL number: 043 751
ABDATA No. : 959 102

Molecular formula: $C_3H_7NaO_3S_3$ [CAS No.: 4076-02-2]
Molecular weight: 210.27
DMPS usually contains 1 crystal water[<1138>]
$C_3H_7NaO_3S_3 \times H_2O$ [MW 228.28, CAS No.: 207233-91-8]

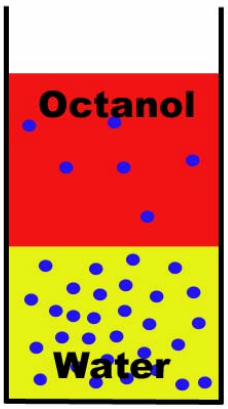
SI conversion:
mg/L x 0.053 = mmol/l[<663a>]

3.1 Physico-chemical parameters

Various physico-chemical parameters of DMPS or its complexes indicate whether and to what extent the antidote is effective in the treatment of heavy metal poisoning.

3.1.1 Octanol-water distribution coefficient

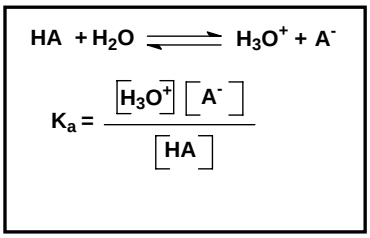
The octanol-water system is a model system for an initial, comparative assessment of the distribution of active substances between aqueous and lipophilic compartments in the body.



$$K_{OW} = \frac{C_{Octanol}}{C_{Water}}$$

Water and octanol are non-miscible and form a two-phase system. The octanol-water distribution coefficient, K_{OW}, describes the ratio of the concentration of a substance in octanol to its concentration in water after adjusting the steady-state. It is used to measure the water- or lipid-solubility of the compound. A $K_{OW} < 1$ means that the larger quantity is in the aqueous phase and is thus hydrophilic. A $K_{OW} > 1$ means that the highest concentration is in the octanol. The substance is, therefore, lipophilic. The higher the octanol/water distribution coefficient, the more lipophilic the substance, the lower the distribution coefficient, the more hydrophilic the substance. Another solvent that is non-miscible with water is occasionally used instead of octanol, namely chloroform.

3.1.2 Acid constants

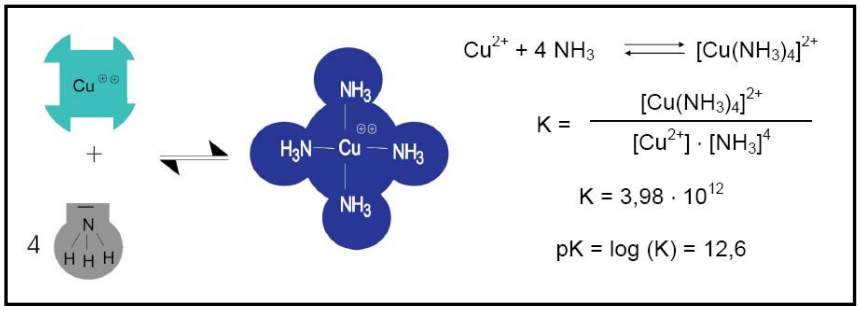


The acid constant (or pk_a value) indicates the strength of an acid. The lower the pk_a value, the stronger the acid, or the more acidic the compound. The pK_a value corresponds to the pH of a solution at which equal concentrations of HA and A^- are present. Sulfuric acid and acetic acid, for instance, have pK_a values of –3 and 4.75, respectively.

The pK_a value of DMPS or its complexes shows whether the substances are dissociated at a physiological pH, and are thus present in the form of ions. This is, amongst other things, significant for the passage from the blood into the brain via the blood-brain barrier, which protects the brain against harmful substances. The passage of ionic substances is not usually feasible.

3.1.3 Complex-forming constants (stability constants)

A complex is a compound in which a central atom (a Cu^{2+} ion in the example) is surrounded by one or more ligands (by 4 ammonia molecules in the example). The ligands (derived from the Latin term ligare = to bind) surround the central atom. The word complex is derived from the Latin term complexus = surrounds, to hold tightly.



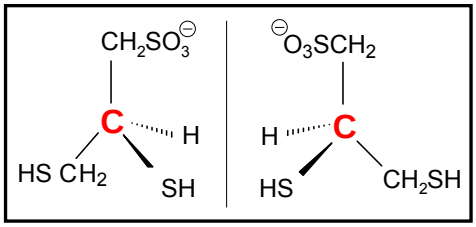
Complex formation is a balanced reaction. The more stable a complex is, the further the shift in equilibrium towards the complex and the less free, non-complexed metal remains. The complex formation constant, K, is calculated according to the law of mass action from the concentrations of substances involved in the balanced reaction. It is a yardstick for measuring the stability of the complex. The higher the K value, the more stable the complex. This is, therefore, also referred to as the stability constant. As the K values of stable complexes are very high, their decadic logarithms pk are used to give a clearer overview. Most figures are expressed to two decimal places.

A distinction is made between monodentate and polydentate ligands. Monodentate ligands such as ammonia form only one bond with the central atom. Polydentate ligands have several functional groups that bind to the central atom. DMPS is a bidentate ligand because of its two SH groups.

If a complex-forming agent has several ligands from which to choose, it will opt for those for which it has a greater complex-forming constant. Ligands with a high pK value oust ligands with a low pK value from their complexes. For the therapeutic efficacy of antidotes, this means: only when a chelating agent has a higher pK value with the metal than the biological molecule, is it capable of mobilising the heavy metal from its binding to this molecule.

3.2 Structure

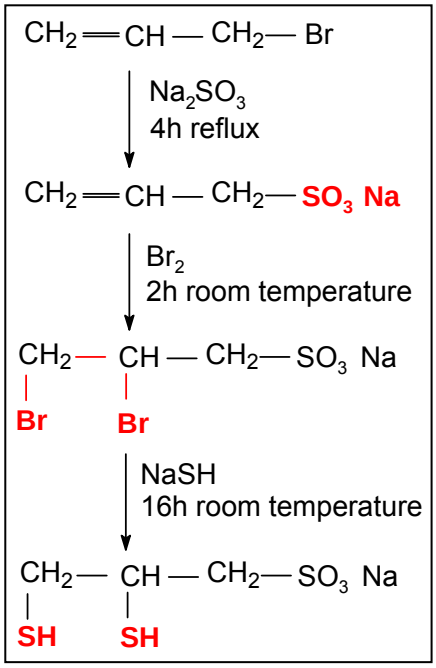
Due to the asymmetrical carbon, DMPS can be present in two different optic isomers (R or S) and as a racemate (R,S)[<69,87,295>]. No significant differences in terms of absorption, toxicity or efficacy are observed between the various isomers in laboratory animal experiments[<69,617>].



Various conformers separated by an energy barrier of 11 kJ/mol are formed by rotation around the C2-C3 binding. The binding can, therefore, be rotated freely at room temperature. The energetically most stable,

spatial structure of the neutral DMPS molecule is deduced by quantum mechanics. The distance between the two thiol groups was determined in the neutral molecule at 3.43 Å[<1480>].

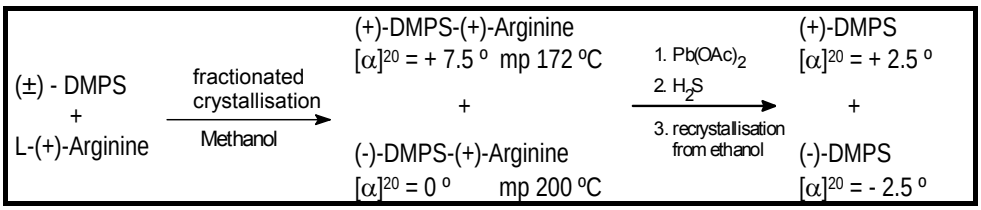
3.3 Synthesis



DMPS was first synthesised in 1951[<659,670,1138,1269>]. It is more difficult to synthesise than BAL[<673>] or DMSA[<1238>]. The HEYL Company developed its own manufacturing process. The advantages of this method are the increased yield, the purity of the product and the possibility of carrying out the synthesis as a "One-Pot Procedure"[<1118-1120>].

Bromine Br_2 required for the bromination of allyl sulfonic acid can also be produced electrochemically *in situ* from bromide. A high current density or higher temperatures will produce poorer yields. Whereas the 2,3-dibrompropane-1-sulfonic acid yield amounted to 93 % at a temperature of 28-30° C, it fell to 65% at a temperature of 50 °C[<1101>]. The bromine-SH exchange can also be carried out with KSH instead of NaSH in aqueous solution[<251,781>].

Purification of DMPS takes place by precipitation as lead salt[<251,1101,1118-1120>]. DMPS is released from the precipitate by H_2S. It is subsequently recrystallised from 90 % alcohol[<602, 1118-1120,1138>], acetone or ethyl acetate[<1528>]. Insoluble $PbCl_2$ is precipitated on decomposition of the dried lead salt in EtOH/HCl. The DMPS solution in ethanol can still be purified with active charcoal[<975>]. DMPS containing 98.7 to 100 % can be obtained by decomposing the lead salt in acidic alcohol solution with subsequent precipitation of DMPS[<756>].



Separation of the racemate from DMPS can be carried out with the aid of L-(+) arginine or brucine[<617>].

3.4 Properties

	DMPS	BAL	DMSA
Octanol/water	0.083	5.084	0.047
Octanol/phosphate buffer (pH 7.4)	0.0018	4.975	0.0017

Octanol-water/buffer coefficient of various dimercapto antidotes[<1210>]

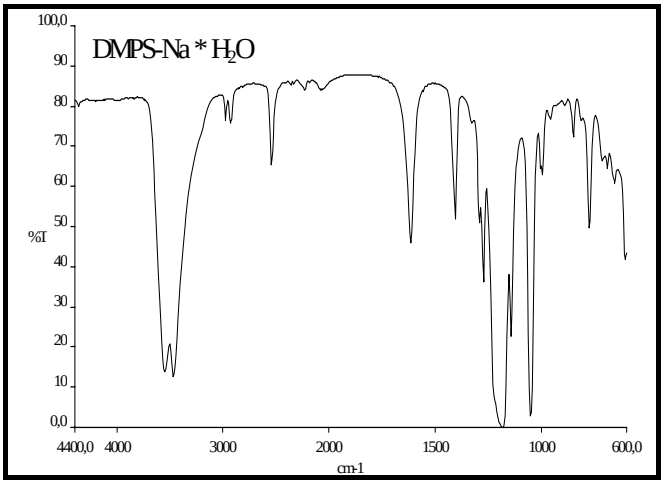
DMPS is a white to almost white crystalline powder[<69,260,285,295,735,1270>] with a weak, characteristic odour. The monohydrate is not hygroscopic[<141>], anhydrous Na-DMPS absorbs 1 mol of water on contact with the air. As the sodium salt of a sulfonic acid, DMPS is freely soluble in water[<141,260,295,602,734,735, 1270>], sparingly soluble in methanol[<611>], even less soluble in ethanol[<611,942>] and insoluble in non-polar solvents such as ether[<611>]. Solubility in water is 350 mg/mL and in DMSO 926 mg/mL[<1023>]. 100 g of a saturated DMSO solution contain 45.8 g DMPS[<1023>].

23 g of the free dimercaptopropane sulfonic acid dissolve at 25°C in 1 L of unbuffered water and lower the pH to 1.25[<997>]. With a rising pH the solubility of the acid In water at 25°C increases to: pH 1: 17 g/L, pH 2: 72 g/L, pH 3: 614 g/L[<997>].

The melting point is 235 ºC[<602,1138>]. The octanol/water distribution coefficient is 0.083[<552,1210>], and in phosphate buffer (pH 7.4), 0.0018[<1210>]. The polar compounds DMPS and DMSA are mainly present in the aqueous phase. Contrastingly, BAL is markedly less polar with a $K_{ow} > 1$. In contrast to DMPS, it can, therefore, penetrate the blood-brain barrier.

Two intensive peaks can be detected at 153 (-SH_2) and 155 m/z in the mass spectrum, in addition to the molecular peak at 187 m/z[<500>]. In the UV spectrum, DMPS absorbs at 240 nm[<1480>].

In the IR spectrum[<997,1084,1409>], the stretching vibration of the sulfonic acid group dominates at 3454 cm^{-1}. The SH groups can be seen at 1,636 cm^{-1} (stretching vibration) and 1190 cm^{-1-} (angle bending).



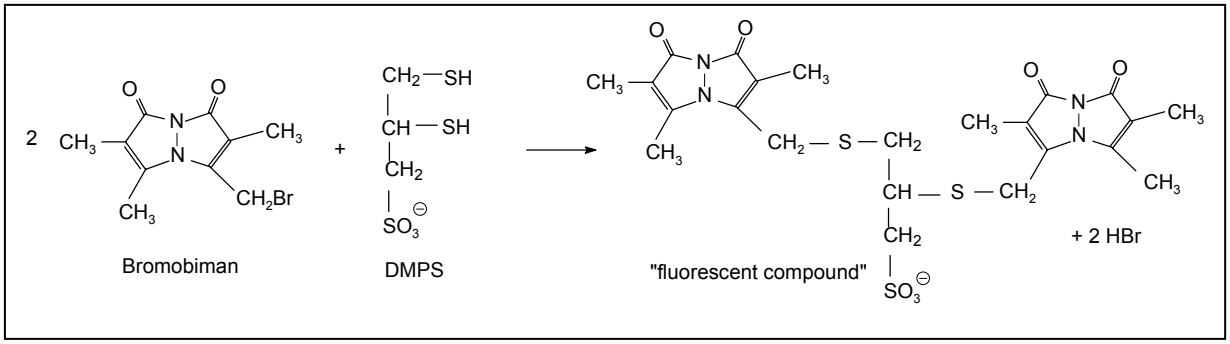
IR spectrum of DMPS-Na · 1 H_2O

DMPS can be detected by wet chemistry, thin-layer chromatography[<1395>] and HPLC. DMPS and DMPS disulfide can be separated by paper chromatography[<109>]. The purity of DMPS can be tested by HPLC. Concomitant spectrophotometric and electrochemical detection gives an indication of the nature of the impurities (oxidation products, "homodisulfides")[<229,230>].

Several methods for determining the DMPS content are described in the literature:

- Iodometric titration of the SH groups[<960,1249>]
- HPLC in comparison with a standard
- Photometrically at 412 nm after transformation with Ellmann's reagent[<145,247, 1516>]. The limit for this process is 0.3 µg/mL[<247>]
- Titration with N-bromsuccinimide[<526>]
- Reaction with 4,4'-dithiopyridine[<893>]
- Titrimetrically with $CuSO_4$. Titration with lead- or mercury nitrate is not reproducible due to problems with end point recognition[<1249>]
- Colometrically after the formation of coloured complexes, e.g. with iron[<1249>].

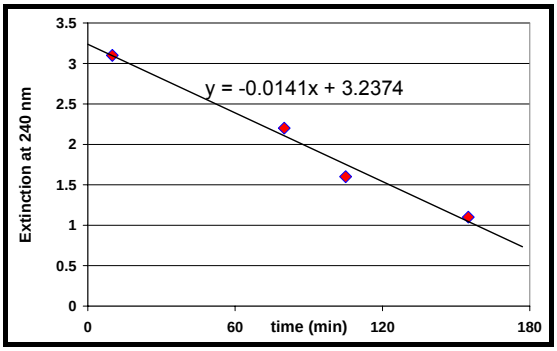
In HPLC investigations of biological samples, DMPS is often labelled with bromobiman because a fluorescent compound[<892,894>] is produced. In this way, a detection limit in the urine of 10 pmol per 20 µL (= 0.1 mg/L) can be achieved[<58>].



3.5 Oxidation

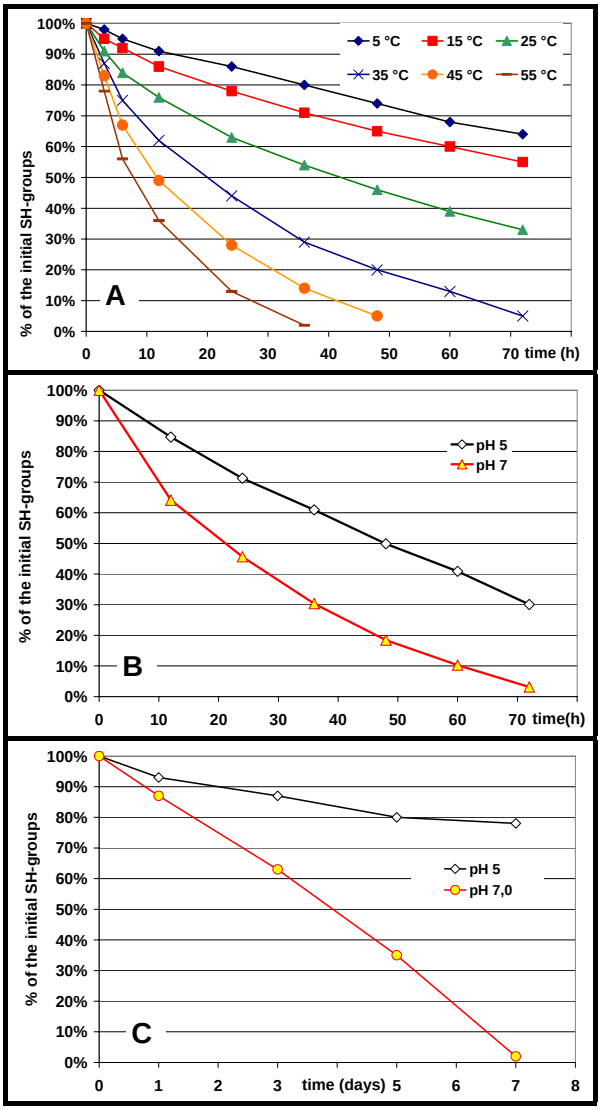
DMPS is stable in the crystalline form[<30,734>]. It retains its antidote action after heating for 2 hours at 140ºC[<69,870>]. Efficacy is maintained even after irradiation of a solution with X rays[<297>]. In the frozen state, a "solution" can be kept for 7 days[<71>]. DMPS is relatively stable in pure water. Only the presence of electrolytes accelerates oxidation[<642>].

In solution, DMPS is, like all dithiols, sensitive to oxidation[<1480>]. This applies especially in the alkaline range at pH > 7[<71,240,1480>]. Whereas at a pH of 7 at 20°C, the concentration of the SH groups halved within 3 days, the UV absorption of DMPS halved in 2 hours on contact with air at a pH of 12[<351,1480>]. The reaction takes place more rapidly in the presence of metallic catalysts[<960>] (e.g. iron[<69,1395>]) or at higher temperatures[<960>].

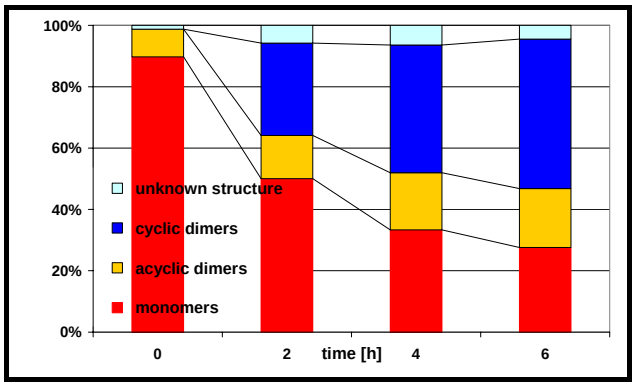


Time-based decrease in the extinction of a DMPS solution on contact with the air (0.35 mM DMPS in 0.01 m NaOH, pH=12)[<351,1480>]

Virtually all of the DMPS was oxidised after 30 minutes in a Krebs Ringer electrolyte solution (pH 7.4, 37°C) with continuous influx of 95% O_2/5% CO_2. The reaction half-life was 4.3 minutes[<744>]. In a physiological perfusion solution (pH 7.4, 25 °C), the number of free SH groups (detected with Ellman's reagent) fell by 20% in 5 hours and by 92.8% in 21 hours[<1597>]. No free SH groups could be detected after the passage of oxygen at 37°C for 24 hours. The mass spectra showed that > 90% of the substance presented as cyclic dimer and the rest as higher molecular cyclic oligomers[<643>].



A. Temperature dependence of the stability of an aqueous DMPS solution at pH 7.0
B. pH-dependence of the stability of an aqueous DMPS solution at 35°C (1 mmol/L, phosphate buffered saline solution, % of the initial SH groups)[<960>]
C. pH-dependence of the stability of an aqueous DMPS solution (0.1 mmol/L, 24ºC) (% of the initial SH groups)[<71>]

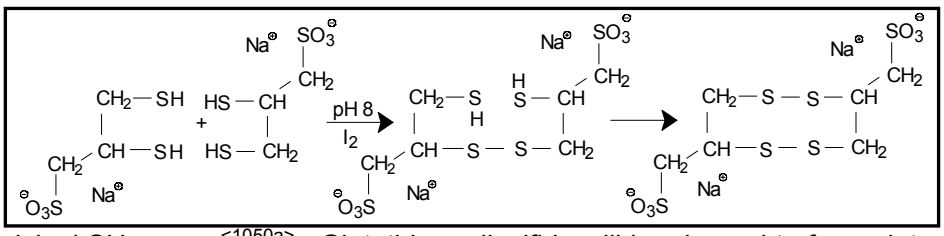


Spontaneous oxidation of an aqueous DMPS solution (monomers, acyclic dimers, cyclic dimers DMPS and DMPS of unknown structure) [pH 7.4, 37°C][<892>]

This gives rise on oxidation to disulfides either from two DMPS molecules or through reaction with other thiol compounds. As was demonstrated by HPLC and mass spectroscopy, the disulfides are predominantly present in the form of various cyclic compounds[<892>] (see 5.3 Metabolism). Addition of H_2O_2 to an aqueous solution of DMPS produces, under catalysis with $FeCl_3$, a mixture of various, charged DMPS oligomers, which can be reconverted to DMPS by reduction[<959>]. The same applies to oxidation with oxygen catalysed with $FeSO_4$ (pH = 9.0, 40°C). The end of oxidation can be recognised by the disappearance of the red colour of the iron-DMPS chromophore. No free SH groups can be detected with Ellmann's reagent[<873,1092,1395>]. Free DMPS is re-formed by reduction with dithiothreitol DTT[<1092,1395>]. Oxidation can also be carried out

electrochemically. Disulfides are thus initially formed, which subsequently react to form tetrasulfides. Sulfoxylates and sulfates were also detected[<1092>]. Mercaptane groups can also be oxidized electrochemically to sulfonic acid groups[<1373>].

DMPS can be converted quantitatively into DMPS tetrasulfide by oxidation with iodine. The SH groups are then no longer detectable. The reaction is reversible by subsequent reduction with DTT, sodium borohydride $NaBH_4$ or electrochemically. 99.3 % of the SH groups were again detectable experimentally[<893>].



Under physiological conditions (37°C, pH 7.4), DMPS reduces cystine or reacts with cysteine to form mixed disulfides[<1326>]. It can crosslink proteins *in vitro* due to its vicinal SH groups[<1050a>]. Glutathione disulfide will be cleaved to form glutathione in phosphate buffer[<58>]. DMPS reduces methylene blue particularly in an alkaline solution. The reaction is catalysed by selenite[<462>]. DMPS quickly and completely reduces dehydroascorbinic acid to vitamin C and is thus oxidised to disulfide[<785>].

The oxidation rate of DMPS with $NaNO_2$ varies with the earth's gravitational field[<1460>]. It should depend on the earth's gravitational pull, as demonstrated in numerous studies[<505>].

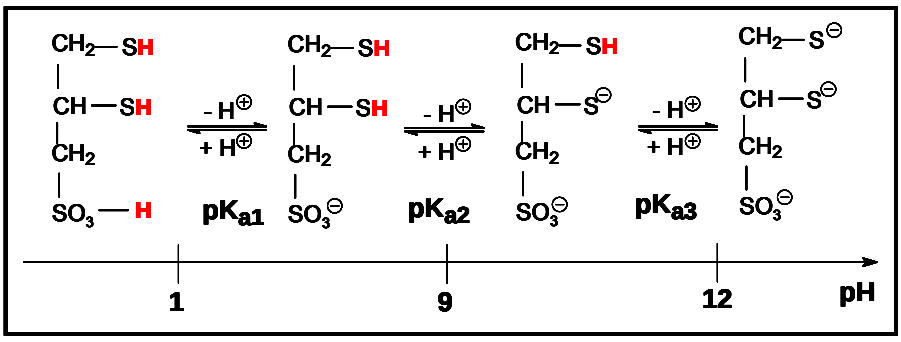
DMSA is less sensitive to oxidation than DMPS[<731>]. The following sequence of anti-oxidative effects was observed in the anti-oxidation test with DPPH (2,2-diphenyl)-1-picrylhydrazyl): Vitamin C > DMPS > DMSA > DPA[<238>]. At 20°C, the reaction of DPPH with vitamin E and with DMPS was completed after 2 and 34-35 minutes, respectively. At 37°C, the reaction with DMPS still lasted 8 minutes and at 50°C, 5.4 minutes. The reaction with the more reactive Fremy salt (potassium nitrosodisulfonate) was completed after 2 minutes[<1168>].

Depending on the concentration, DMPS extinguishes luminol chemiluminescence triggered by oxygen radicals[<158>].

Conclusion:
Once dissolved, DMPS is highly sensitive to oxidation. If possible, the solution must not, therefore, come into contact with the air. Dimaval solution for injection must be used immediately[<1238>]. Opened ampoules should not be stored and must be discarded. Thanks to a special manufacturing process, closed ampoules are stable for three years .

3.6 Acid base reaction

DMPS has three azide protons. DMPS is present in a non-dissociated form as a neutral molecule in a strongly acidic solution (pH < 1)[<1488>]. The protons are cleaved successively with increasing pH until a three-fold, negatively charged anion is finally produced[<351,1077, 1488>]. In an aqueous solution, the sulfonic acid group is complete and the sulfhydryl group partially dissociated[<1095>]. Both sulfhydryl groups are dissociated from a pH of 12 onwards[<1586>].



The charges of DMPS and DMSA are investigated by means of electrophoresis. Both antidotes present as an anion at pH 7. DMSA had a higher negative charge than DMPS because of the two carboxyl groups[<1576>].

	DMPS	DMSA
2 free SH groups	-1.23	- 1.71
1 SH group esterified with propionic acid	-1.10	-1.67
Both SH groups esterified with propionic acid	-1.04	-1.48

Electrical charging of DMPS and DMSA (pH 7, 20 °C)[<1576>]

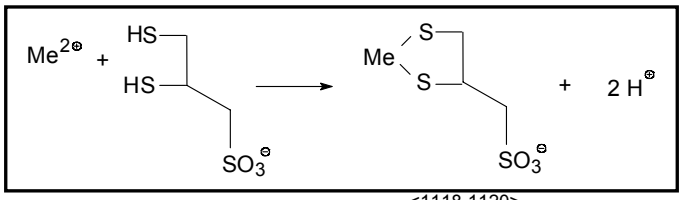
The proton release from the sulfonic acid group in water is exothermic (ΔH= - 0.56 kJ/mol), dissociation of the two sulfhydryl groups is endothermic[<1077,1487>]. A complex of methyl mercury and DMPS releases the third proton more rapidly (pK_{a3} = 7.6)[<84, 1360>]. The reason for this is the formation of the stable complex ring structure.

Reference	84	1305	47	103, 1488	1487	1056	1529	1077	664	1475	1147
pK_{a1}					1.1	1.3		1.1		1.1	
pK_{a2}	8.7	8.8	8.93	8.5	9.4	9.1	8.5	9.15		8.6	9.15
pK_{a3}	11.4	11.2	11.94	11.6	12.1	12.6		12.74	12.5	11.6	12.8

pK_a values of individual dissociation stages of DMPS

Conclusion:
DMPS is present as an anion in both plasma (pH 7.3-7.5) and urine (pH ≈ 4.8). On the one hand this means better solubility in both media and, on the other hand, less risk of side effects as DMPS is mainly found extracellularly in the plasma.

3.7 Complex formation

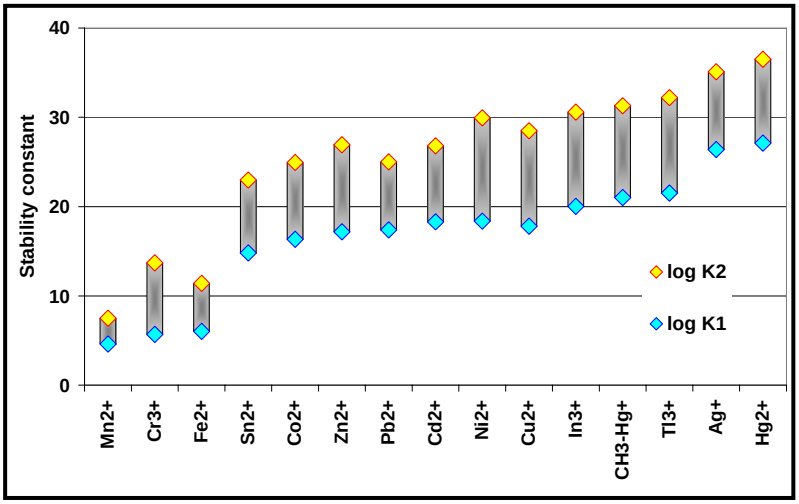


DMPS forms stable complexes[<58,260,673,690, 1586>] with many heavy metals in an exothermic reaction[<690>]. As a soft Lewis base, it prefers soft Lewis acids [<8,667>] or metals that form insoluble sulfides[<682,1480>]. Most complexes are water-soluble, only the lead complex is precipitated[<1118-1120>]. These are mostly chelates, i.e. complexes in which the heavy metals are bound in a ring structure[<58,494,993>] and which are characterised by relatively high binding constants[<666>]. The complexes are so stable that complexes of various metals can be separated chromatographically[<1076,1328>]. The stability of the ring structure is one reason why dithiols can loosen mercury more effectively from its binding to biomolecules than monothiols[<1198>]. Apart from Cd^{2+}, the DMPS metal complexes are more stable than those of BAL[<69>].

Various balanced reactions play a role in complex formation. These determine, amongst other things, the pH dependence of the chelate formation[<689>]. At an acid pH, 1:1 complexes are formed, at a pH > 6, 1:2 complexes[<1328>].

$DMPS\text{-}H_3]$	$\leftrightarrows [DMPS\text{-}H_2]^- + H^+$
$[DMPS\text{-}H_2]^-$	$\leftrightarrows [DMPS\text{-}H]^{2-} + H^+$
$[DMPS\text{-}H]^{2-}$	$\leftrightarrows [DMPS]^{3-} + H^+$
$[DMPS]^{3-} + Me^{2+}$	$\leftrightarrows [DMPS\text{-}Me]^-$
$2\ [DMPS]^{3-} + Me^{2+}$	$\leftrightarrows [(DMPS)_2\text{-}Me]^{4-}$
$MeOH^+ + OH^-$	$\leftrightarrows Me(OH)_2$
$Me^{2+} + OH^-$	$\leftrightarrows MeOH^+$
$H^+ + OH^-$	$\leftrightarrows H_2O$

The pK stability constants vary for the metals tested: the best binding is observed with mercury, while the binding to zinc is markedly weaker[<365,1055,1058,1360>]. A similar order is found for the solubility products of the binary sulfides of the metals[<437,960>]. The higher the pK_L value, the less soluble is the sulfide. This indicates that the formation of metal-sulfur binding is a decisive step for the stability of the complex.



Metal ion	pK_1 Me : 1 DMPS	pK_2 Me : 2 DMPS
Ag^{+}	26.38	35.12
Cd^{2+}	18.26	26.82
Co^{2+}	16.34	24.95
Cr^{3+}	5.7**)	13.7**)
Cu^{2+}	17.76	28.45
Fe^{2+}	6.02*)	11.4*)
Hg^{2+}	27.05	36.52
CH_3-Hg^{+}	21.0*)	31.3*)
In^{3+}	20.02	30.59
Mn^{2+}	4.62	7.51
Ni^{2+}	18.37	29.94
Pb^{2+}	17.42	25.05
Sn^{2+}	14.80	22.98
Tl^{3+}	21.51	32.21
Zn^{2+}	17.18	26.93

Stability constants of various metal-DMPS complexes (1:1 and 1:2)<1077>, *)690,1115, **)1096

Ag^{+}	As^{3+}	Cd^{2+}	Cu^{+}	Cu^{2+}	Fe^{2+}	Fe^{3+}	Hg^{2+}	Hg^{+}	Pb^{2+}	Zn^{2+}
50	25.3	27.9	50	40.2	21.6	27	51.2	53	28.6	21.7

pK_L values of solubility products for binary sulfides in aqueous solution<437,960>

Heavy metal	Reduction (%)
Hg^{2+}	95.3
Cu^{2+}	92.7
Co^{2+}	90.0
Ni^{2+}	88.5
Fe^{3+}	81.4
Fe^{2+}	73.5

Reduction in the heavy metal content of waste water by treating with polyethylene amine-DMPS compound<1095>

This order is also apparent in tests for free SH groups using Ellman's reagent in solutions of DMPS and metal salts. Whereas free SH groups were no longer detectable with Hg^{2+}, 20 - 30 % of SH groups were still present at Cd^{2+} and 70 - 80 % at Pb^{2+} <1049>.

DMPS can be attached to cationic polymers (e.g. polyethylene amine) via the sulfonic acid group. The resulting compound can be used to purify waste water. Hg^{2+}, Cu^{2+}, Co^{2+}, Ni^{2+}, Fe^{2+} and Fe^{3+} can thus be removed<1095>. The heavy metals with the highest stability constants bind best of all and are thus removed from the waste water.

3.7.1 Ag - Silver

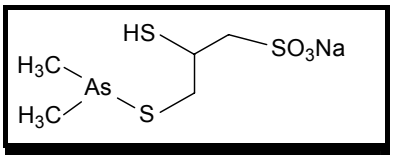
DMPS forms 1:1 and 2:1<1055,1077> complexes in an exothermic reaction with silver. The binding takes place via the SH groups and does not affect the sulfonic acid group<1515>. The absorption maximum for the 1:1 complex is at 335 nm, the instability constant is 1.6×10^{-26}<1371>.

$[Ag_1(DMPS)_1]^{2-}$	$\Delta_r H^o$ = -55.2 kJ/Mol	log K = 25.38
$[Ag_1(DMPS)_2]^{5-}$	$\Delta_r H^o$ = -92.1 kJ/Mol	log K = 35.12<1055,1077>

3.7.2 As - Arsenic

DMPS forms stable complexes with various organic and inorganic arsenic compounds<155,354,976, 977,1063>, predominantly with 1:1 stoichiometry<1063>, as shown mass spectroscopically, for instance, for monomethyl arsenite(III) [MMA(III)]<500>. According to investigations with ^{1}H- and ^{13}C-NMR, arsenic reacts with vicinal sulfhydryl groups to form a five-membered ring system<1062,1063> (2-arsa-1,3-dithiolane<956,960>), which is also confirmed by semi-empirical calculations of the chemical structure<155>. The As-S binding length is 2.15 Å<155>, which corresponds approximately to the sum of the covalent radii of sulfur (1.04 Å) and arsenic (1.21 Å)<1379>, and thus indicates single covalent binding between these elements<960>.

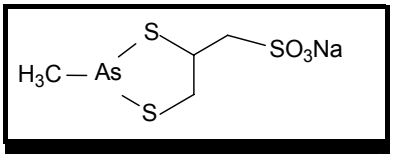
Contrastingly, only one SH group of DMPS binds with dimethylarsenic(III) [DMA(III)]. $Me_2AsDMPS$ therefore displays less stability and is more sensitive to oxidation. MeAsDMPS and $Me_2AsDMPS$



$Me_2AsDMPS$ [DMA(III)]

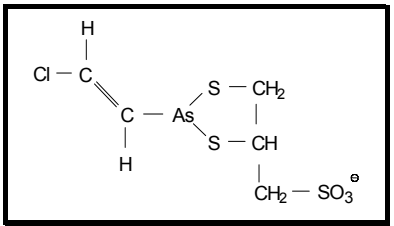
display various absorption peaks in the X-ray spectrum (XANES) both in solution and as a solid substance[<1358,1359>].

The complexes are soluble and form colourless solutions[<960>]. They are extremely stable and decompose only in strongly alkaline media (0.1 to 0.5 m NaOH)[<500>]. DMPS is capable of partly ousting monothiols bound to arsenic[<976,977>]. Glutathione-bound AS(III) is also mobilised by DMPS with the formation of a 5-atom ring structure[<458>]. Bound dyestuff derivatives containing As are also remobilised from their structures by the addition of DMPS[<15>].



MeAsDMPS [MMA(III)]

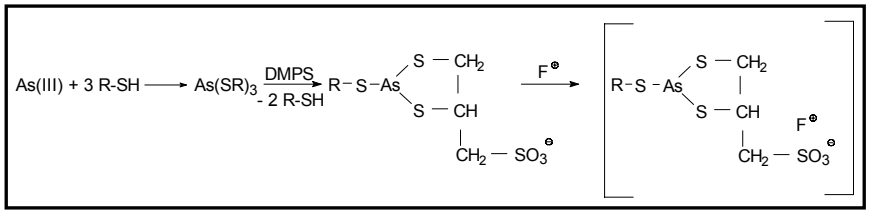
DMPS is suitable for masking arsenic on titration of alkaline earth metals or lanthane[<950>]. In chloroform/pyridine, nitrophenylarsenic acid chloride reacts with DMPS within 3 hours to form a corresponding dithioarsinanyl compound, which can be recrystallised from n-hexane[<213>].



DMPS-Lewisite complex[<1063>]

DMPS and BAL have similar binding constants to lewisite and phenyldichloroarsine, while that of DMSA is only about 10% of that[<667,1062>].

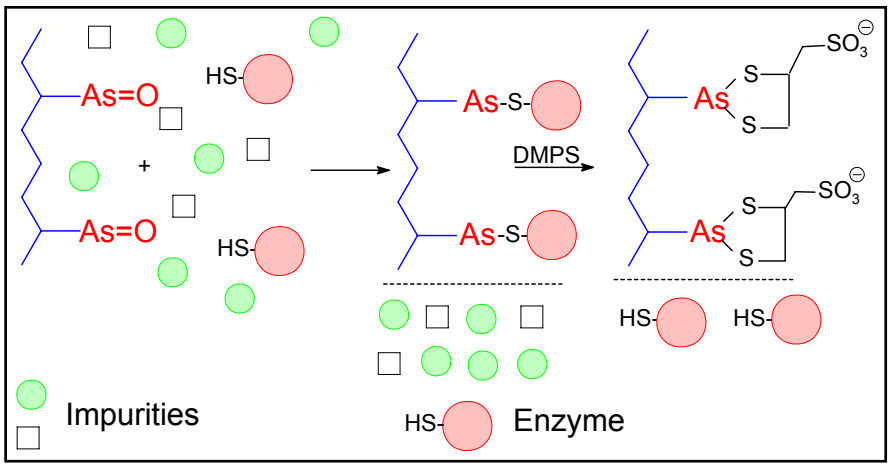
While arsenic(III) in aqueous solution is not bound to cholestyramine (a basic exchange resin for anions), it binds in the presence of DMPS to more than 50% to this substance. The reason for this is the formation of a stable, negatively charged arsenic-DMPS complex[<1209>].



The negatively charged DMPS-As complex reacts with basic dyestuffs F^+ (e.g. rhodamine G) with the formation of neutral ion associates, which are soluble in organic solvents[<976,977>]. This reaction permits the photometric determination of impurities by arsenic, e.g. in phosphoric acid.

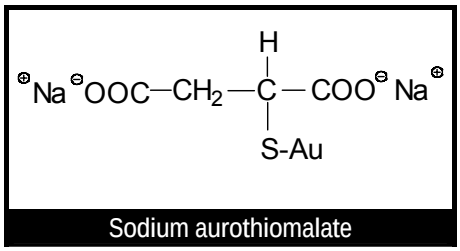
As(III) and As(V) can be determined in succession by chromatographic concentration of the As(III)-DMPS complex. As(V) is not retained. The limits of detection in drinking water are 0.11 µg/L for As(III) and 0.15 µg/L for As(V). In the air, As(III) can be detected up to a limit of 2.8 ng/m³[<616>].

The excellent binding between DMPS and arsenic can also be used to purify SH-containing enzymes. For this purpose, the protein solution is chromatographied on resins on which suitable arsenic compounds have been immobilised. The enzymes bound to the arsenic can again be released after washing out the impurities with DMPS[<658,1222,1439,1566,1626>]. Monothiols cannot do this[<658>]. Active proteins can be purified in this way[<1439>].



3.7.3 Au - Gold

DMPS forms highly stable, water-soluble complexes with Au^{3+} ions[<351,1308a,1586>] (pK = 35.12; $\Delta_r H^o$ = -62.5 kJ/mol[<1077>], pK = 45.4[<1371>]). The instability constant is 3.8×10^{-8}[<1371>].



Sodium aurothiomalate

NMR investigations show that, on addition of DMPS, gold is removed from sodium aurothiomalate (basic drug for chronic polyarthritis) and mercaptosuccinic acid is released[<700>]. A water-soluble gold-DMPS complex is thus formed[<765>]. Titration measurements show that, at a pH of 3.4, DMPS yields two protons per complexed Au^{3+} ion and forms an Au^{3+}:DMPS 1:1 complex. The stability constant is pH-dependent. At a pH of 3.6, it is 37.2[<351>] or 30.8[<1480,1586>]. Au^{+} forms a 1:1 complex with DMPS. The stability constant is 45.5[<520,1642>].

From a slightly acidic solution, DMPS adsorbs to gold surfaces and, within five minutes, forms intact DMPS monolayers[<1480,1586>], whereby every DMPS is bound to the surface by two S-Au bonds[<1586>]. At an alkaline pH, DMPS promotes the release of gold ions from the metallic surface[<1480>]. The soluble DMPS-Au complex (predominantly 1:1) can be used to apply gold decorations to ceramic[<1308a>].

3.7.4 B - Boron

DMPS forms 1:1 complexes with boric acid[<47>].

3.7.5 Bi - Bismuth

DMPS forms a yellow complex with $Bi(NO_3)_3$ and thus increases the water solubility of Bi. DMPS is, therefore, suitable for masking bismuth on titration of alkaline earth metals or lanthane[<950>]. As a hydrophilic compound, the complex is insoluble in butanol[<340>]. The halogenides of bismuth form innerspheric complexes with DMPS $[BiX_n \cdot (DMPS)_z]$ (X = Br, Cl or I)[<1169>].

The stability of the Bi-DMPS complex $[Bi \cdot (H_2O)_n \cdot (DMPS)_z]$ in perchloric acid is dependent on the acid concentration. In 0.5 mol $HC1O_4$, the binding constant is 2.41, and in 1 m $HClO_4$ 1.65[<1462>].

3.7.6 Ca - Calcium

DMPS does not react with calcium ions and therefore does not interrupt their titrimetric determination[<950, 1497,1498>]. The solution remains colourless[<960>]. The addition of DMPS prevents disruptions to the determination of calcium by other metals[<1122>], such as Cd, Hg, Pb, Sn or Zn[<1497>].

3.7.7 Cd - Cadmium

Complex formation between Cd^{2+} and DMPS was detected polarographically[<1049>]. Depending on the stoichiometry and pH of the solution, DMPS and cadmium form colourless[<960>], mostly polynuclear, charged complexes[<1624>] in an exothermic reaction[<1077>]. The distribution of polynuclear complexes depends on the concentration and pH[<103>]. The stability constants were determined by pH and conductance measurements[<103,365>].

$[Cd_1(DMPS)_1]^-$	**$\Delta_r H^o$ = -43.5 kJ/Mol**[<1077>]
$[Cd_1(DMPS)_2]^{4-}$	**$\Delta_r H^o$ = -80.0 kJ/Mol**[<1077>]

The stability of the Cd-DMPS complex is pH-dependent and increases with a rising pH in the alkaline range[<103>]. At a constant Cd-DMPS ratio (1:10), the fraction of the non-complexed heavy metal falls with increasing pH[<1204>]. Thus, no cadmium hydroxide is precipitated in alkaline solution

in the presence of DMPS[<103>]. 20-30 % of the free SH groups can still be detected in a Cd-DMPS solution using Ellman's reagent[<1049>].

Reference	1305	664	103	365	1077	1378	1117
$[Cd_1(DMPS)_1]^-$	16.7	17.3	18.0	18.0	18.26	18.6	18.0
$[Cd_1(DMPS)_2]^{4-}$	26.9	28.2	28.3	25.7	26.82		
$[Cd_2(DMPS)_1]^+$		28.2					
$[Cd_2(DMPS)_2]^2$		37.7					
$[Cd_3(DMPS)_3]^{3-}$			59.9				
$[Cd_3(DMPS)_4]^{6-}$			71.9				
$[Cd_5(DMPS)_6]^{8-}$			114.3				
$[Cd_7(DMPS)_8]^{10}$			156.7				

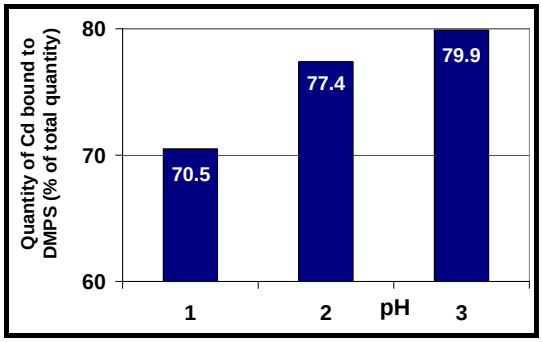
Stability constants of various DMPS-Cd complexes

DMPS is suitable for masking Cd on titration of alkaline earth metals[<950,1497>] or lanthane[<950>].

$$K = \frac{C_{Chloroform}}{C_{Water}} = 2 \times 10^{-3}$$

$$K_{OW} = \frac{C_{Octanol}}{C_{Water}} = 7{,}34 \times 10^{-5}$$

The Cd:DMPS complex is hydrophilic. The distribution coefficient between chloroform and water is very small, but in spite of this, the complex diffuses relatively well through artificial lipid membranes[<1378>]. The distribution coefficient for octanol/water for the 1:1 complex is 7.34×10^{-5} and for the 2:1 complex 4.8×10^{-5}[<1152>].



pH-dependence of DMPS-bound Cd (% of the total quantity of Cd; Cd:DMPS ratio = 1:10)[<1204>]

3.7.8 Co - Cobalt

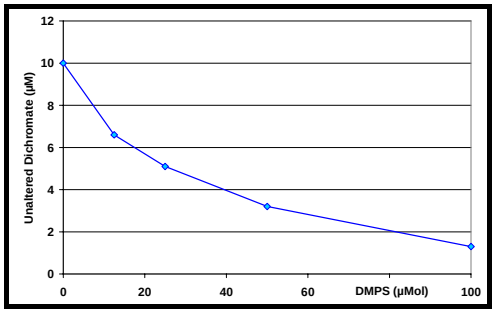
DMPS forms 1:1, 1:2 or 2:3 complexes with cobalt(II) in aqueous solution[<1079>]. The instability constant is 2.8×10^{-12} (-> pk = 11.6)[<1089>].

$[Co_1(DMPS)_1]^-$	Δ_rH^o = -95.0 kJ/Mol	log K = 16.34[<1077>]
$[Co_1(DMPS)_1]^-$		log K = 16.67[<1115>]
$[Co_1(DMPS)_2]^{4-}$	Δ_rH^o = -161.8 kJ/Mol	log K = 24.95[<1077>]
$[Co_1(DMPS)_2]^{4-}$		log K = 24.80[<1115>]
$[Co_2(DMPS)_3]^{5-}$		log K = 22.19[<1115>]

3.7.9 Cr - Chromium (dichromate)

Spectroscopic investigations showed that Cr(III) forms 1:1 and 1:2 complexes with DMPS[<1096>]. In the Cr(V) complex $CrO(H_2O) \cdot DMPS \cdot 2H_2O$, DMPS is bound by the thiolate sulfur and an oxygen from the sulfonic acid group to the heavy metal[<100>].

$[Cr_1(DMPS\text{-}H)_1]^+$	log K = 5.7[<1096>]
$[Cr_1(DMPS\text{-}H)_2]^-$	log K = 13.7[<1096>]



Dependency of the dichromate still present on the DMPS concentration (reaction time: 5 min., T = 35°°C, C_0(dichromate) = 10 µM[<1414,1415>]

In aqueous solution, DMPS swiftly reduces dichromate at physiological pH to Cr(III)[<284,1414,1415>]. With an increasing DMPS concentration, the quantity of dichromate that can still be detected in the solution after 5 minutes reaction time falls[<1414,1415>]. This is a first-order reaction in relation to DMPS as well as dichromate[<285>]. In this way, three DMPS molecules react with one dichromate, which indicates that only one sulfhydryl group per DMPS is involved in the reaction. Presumably, a chromium thioester is formed as an intermediate[<284>].

3.7.10 Cu - Copper

DMPS forms stable, water-soluble, blue[<960>] complexes with Cu(II)[<398>] and Cu(I)[<1057>]. The Cu:DMPS:H_20 ratio can be 1:1:1 or 1:2:2[<1082>]. Complex formation occurs exothermically. In the process, both SH groups bind to the heavy metal[<388>]. Cu^{2+} readily oxidises DMPS to disulfide in aqueous solution and is thus reduced to Cu^{+} itself[<675,833,1085>]. DMPS-Cu complexes are stable in an ammonia medium[<1350>]. On titration of the blue copper ammonia complex with DMPS, the colour changes at the equivalence point from dark blue to greenish yellow[Cu(II) → Cu(I)]. With oxygen, Cu(II) is reformed and the colour turns blue again. At the same time, the DMPS is oxidised to disulfide[<1085>].

Reference	1057	1085,1090	1077	1117
$[Cu_1(DMPS)_1]^{2}$	log K = 17.8	log K = 19.8	log K= 17.76	log K= 17.8
$[Cu_1(DMPS)_2]^{5-}$	log K = 28.5		log K = 28.45	
$[Cu_2(DMPS)_3]^{7}$		log K = 37.0		

Stability constants for copper(I)

$[Cu_1(DMPS)_1]^{2-}$	Δ_rH^o = -47.1 kJ/Mol
$[Cu_1(DMPS)_2]^{5-}$	Δ_rH^o = -87.8 kJ/Mol[<1057,1077>]

Complex formation can be used for the amperometric titration of the DMPS with a Cu(II) solution[<1131>]. When added to the solution, DMPS improves electroplating with copper[<833>]. The oxidation of butylmercaptane, which is catalysed by $CuSO_4$, occurs much faster in the presence of DMPS[<108>].

3.7.11 Fe - Iron

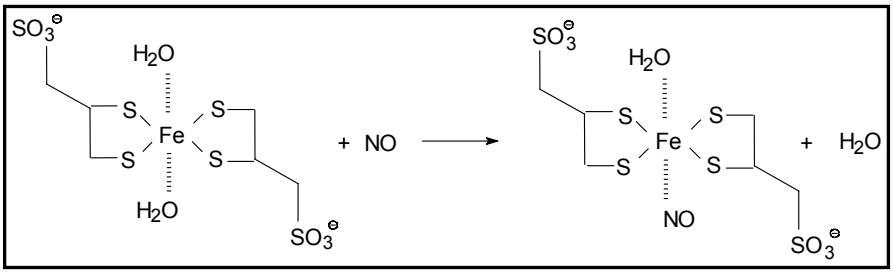
$[Fe^{2+}{}_1(DMPS)_1]$	pK = 6.02[<1115>]
	pK = 7.46[<1089>]
$[Fe^{2+}{}_1(DMPS)_2]$	pK = 11.42[<1115>]
$[Fe^{2+}{}_2(DMPS)_3]$	pK = 10.35[<1115>]

$[Fe_1(DMPS)_1]^{-}$	Δ_rH^o = -74.91 kJ/Mol[<1077>]
$[Fe_1(DMPS)_2]^{4-}$	Δ_rH^o = -143.4 kJ/Mol[<1077>]

$$K_{OW} = \frac{C_{Octanol}}{C_{Water}} = 7{,}3 \times 10^{-5}$$

Regardless of the pH of the solution[<12>], DMPS reacts with iron (II) in an exothermic reaction[<1077>] with formation of a reddish[<249,959,960,1092,1350>] 1:1 (Δ_rH_o = -74.9 kJ/mol r 2:1 complex (Δ_rH_o = -143.4 kJ/mol[<689,1077>]). The complex is water-soluble[<960>] and the solution is stable under anaerobic conditions[<224>]. The complex follows the Lambert-Beer law in a concentration range of 0.05 to 100 µg/L and a pH range of 8 - 13[<1091>]. The octanol/water distribution coefficient for the 1:2 complex is 7.3 x 10^{-5} and for the 1:4 complex 4.8 x 10^{-5}[<1152>]. Both are also hydrophilic. The absorption maxima are at 508 nm[<224, 249,1142>] and 358 nm[<224>]. The instability constant is 3.5 × 10^{-8}[<1089>]. Iron(III) is initially reduced by DMPS and subsequently complexed[<1093>].

In aqueous solution, $Fe(DMPS)_2$ readily stores nitric oxide NO in an exothermic reaction. The existing complex is characterised by an IR -band at 1702 cm^{-1}. At high NO concentrations, two nitric oxide molecules are stored per complex, as shown by additional IR bands at 1560 and 1830 cm^{-1}. The two molecules are not identically bound. Sulfur dioxide does not interfere with the reaction. In contrast, oxygen triggers the oxidation of Fe^{2+} to Fe^{3+} and thus reduces the binding capacity[<249,1142>]. The complex is thus suitable for removing NO from flue gases[<249,1142,1621>]. The complex can be re-released by subsequent electrochemical reduction. The nitric oxides are reduced in the process to ammonia[<249,1142>]. NO adsorption is pH-dependent. The optimal pH is 7[<1333>]. A NO group can also be converted to $[Fe(DMPS)_2]^{4-}$ by various S-nitrosothiol compounds. The equilibrium constant for this reaction is 2.1 x 10^{7} L/mol at 55°C [<1142,1333>].



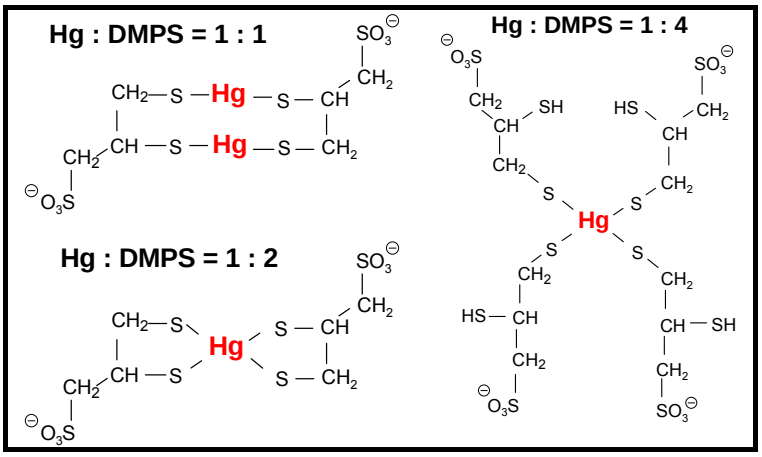
DMPS adsorbs to pyrrhotite ($Fe_{1-x}S$) and consequently makes its surface more hydrophilic, which can be used in the processing of the mineral[<1409,1410>].

3.7.12 Ge - Germanium

DMPS forms 1:1 or 2:1 chelates with germanium acids[<47>].

3.7.13 Hg - Mercury

In aqueous solution DMPS forms stable, thanks to the negatively charged sulfonate groups[<682>], water soluble[<682,960>], colourless[<960>] complexes of Hg^{2+} ions[<58,1248,1498>] and methyl mercury CH_3-Hg[<85,1360>]. This could be detected polarographically amongst other things[<1049>]. Optimal reaction is achieved at a pH of 6.0 – 6.5[<1529>].



Structures of potential DMPS-Hg complexes[<469>]

The Hg-S bond is visible at 298 cm^{-1} in the Raman spectrum[<58>]. For methyl mercury, the Hg-S bond is found in the IR spectrum at 330 cm^{-1}. Conversely, SH vibration can no longer be detected, which shows that both SH groups of DMPS have reacted[<85>]. Similarly, with Ellman's reagent, free SH groups can no longer be detected in the Hg-DMPS complex[<1049>].

The oxygen consumption of a DMPS solution in phosphate buffer falls drastically in the presence of $HgCl_2$[<731>] as oxidation to disulfides can obviously no longer take place. Investigations by means of X-ray absorption spectroscopy and model calculations show that various DMPS and Hg structures are energetically stable. The Hg-S bond length is approximately 2.3 Å[<469>], which corresponds to the sum of the covalent radii of S (1.04 Å) and Hg (1.21 Å)[<1046>].

The octanol/water distribution coefficient for the 1:1 complex is 1.5 x 10^{-4}[<1152>] and 1.04 x 10^{-3} (pH 5.2)[<1158>], and for the 1:2 complex 1.96 x 10^{-4}[<1152>]. For methyl mercury, the distribution coefficient is 5.6 x 10^{-3}[<85,236>]. With an excess of DMPS, 4.3 x 10^{-3}[<85>]. In the presence of cysteine, the complex formed is hydrophobic (distribution coefficient 1 x 10^{-2}) and in the presence of glutathione slightly hydrophilic (distribution coefficient 5 x 10^{-3})[<236>].

$$K_{OW} = \frac{C_{Octanol}}{C_{Water}} = 1.04 \times 10^{-3} \text{ (pH=5.2)}$$

$$K_{OW} = \frac{C_{Octanol}}{C_{Water}} = 2.4 \times 10^{-3} \text{ (pH=6.2-7.2)}^{<1158>}$$

	Solubility (mg/mL)	Octanol/water distribution
BAL	0.02	104
DPA	22.2	5.8 x 10^{-2}
DMSA	3.2	0.48 x 10^{-2}
DMPS	>1000	0.56 x 10^{-2}

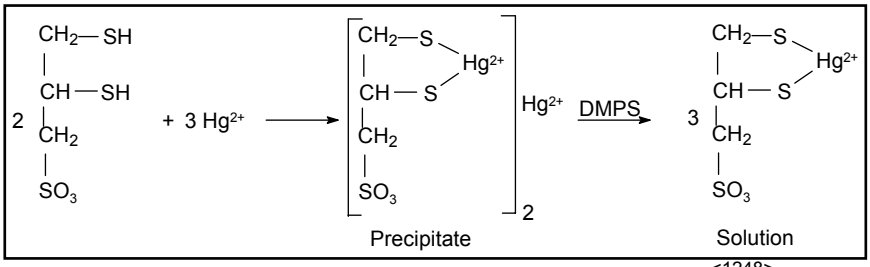
Solubility in water and octanol/water distribution coefficient of CH_3-Hg complexes of various chelates[<85,236>]

Calcium, magnesium, sodium and chloride do not interfere with complex formation unlike iron and manganese[<1529>]. DMPS is, therefore, suitable for masking mercury on titration of alkaline earth metals or lanthane[<950,1497,1498>]. Complex formation can also be used to remove mercury from industrial waste water[<141,1095>] or as an enriching agent on determining traces of heavy metals in drinking water or in the air[<1529>]. Chen *et al*. thus developed a technique with which they could determine approximately 60 ng of inorganic or 70 ng methyl mercury in one gram of hair[<252>]. DMPS allows monovalent and bivalent Hg to be determined in succession through amperometric titration[<1372>]. Excess DMPS (ratio 2:1) accelerates the cleavage of Hg from organic Hg compounds[<504>].

Complex formation occurs exothermically[<503,1056>]. Complex stability is shown amongst other things by the fact that the reduction ability of Hg^{2+} to $Hg^{\pm 0}$ is impeded

$[Hg_1(DMPS)_1]^-$	$\Delta_r H^o$ = -51.4 kJ/Mol
$[Hg_1(DMPS)_2]^{4-}$	$\Delta_r H^o$ = -100.0 kJ/Mol[<1056,<1077>]

by the complex formation. The Hg ions in the complex are still stable while free ions are already reduced to $Hg^{\pm 0}$<503>. The addition of DMPS to a Hg^{2+} solution triggers a change in the polarographic spectra; the redox potential of the heavy metal is shifted<1049>. EDTA does not affect the polarogram<1094> and binds more weakly to Hg than DMPS. In contrast to EDTA, the addition of DMPS also prevents the enzymatic reduction of Hg^{2+} to $Hg^{\pm 0}$<291>. On titration of a $HgCl_2$ solution with sodium hydroxide, there is no poorly soluble precipitate in the presence of DMPS<240>. The DMPS-Hg-H_2O complex can be isolated<58>. DMPS does not affect the AAS determination of Hg<355>.



If one slowly titrates a Hg solution with DMPS, then first of all turbidity or a precipitate $[Hg_3(DMPS)_2]$ forms, which then goes back into solution on further addition of DMPS<1473>. In contrast to the 1:1 and 1:2 complex, the $Hg_2(DMPS)_3]$ complex is also insoluble<1248>. In the case of polarographic reduction of DMPS, a poorly soluble bond to a Hg electrode is initially formed, which then goes back into solution with excess DMPS<1094>.

Data on the stability constants given in the literature vary considerably:

Reference	1473	1056	134	240	141	1077	84	1248	1267	1147	1117	291
$[Hg_1(DMPS)_1]^-$	26.3	27.1	41.8	42.2		27.05						
$[Hg_1(DMPS)_2]^{4-}$	36.0	36.5		53.1	40.0	36.52		53.1		39.7		
$[Hg_1(DMPS\text{-}H)_2]^{2-}$			11.3									
$[CH_3Hg(DMPS)_1]^{2-}$							21.0		9.1		21.0	
$[CH_3Hg(DMPS)_2]^{5-}$							31.3					
$[CH_3Hg(DMPS\text{-}H)_1]^-$							17.2					
$Hg\text{-}(cysteine)_2$												40.3

3.7.14 In - Indium

$[In_1(DMPS)_1]$	Δ_rH^o = -40.4 kJ/Mol	log K = 20.02
$[In_1(DMPS)_2]^{3-}$	Δ_rH^o = -76.5 kJ/Mol	log K = 30.59
$[In_1(DMPS)_2]^{5-}$	Δ_rH_o = -117.0 kJ/Mol	log K = 38.20<1077>

DMPS forms 1:1, 1:2 or 1:3 complexes with indium(III) in aqueous solution.

3.7.15 La - Lanthanum

DMPS does not react with lanthane<950>.

3.7.16 Mg - Magnesium

DMPS does not react with magnesium ions and therefore does not disrupt their titrimetric determination<950, 1498>. The solution remains colourless<960>.

3.7.17 Mn - Manganese

$$p = \frac{C_{Octanol}}{C_{Water}} = 7.3 \times 10^{-5}$$

At an alkaline pH, DMPS forms greenish-brown, readily soluble [Mn:DMPS] and [Mn:2 DMPS] complexes. At pH < 6, the reaction does not take place as Mn cannot oust any H+ ions from DMPS. The complex is destroyed within 30 minutes to 1 hour in the presence of oxygen in the air<1115>. The octanol/water distribution coefficient for the 1:1 complex is 7.3×10^{-5} and for the 2:1 complex 4.8×10^{-5}<1152>. The spectrophotometrically and potentiometrically

determined stability constants for the Mn:DMPS complex are 4.62, for the [2 DMPS:1 Mn] complex 7.51. The stability constants increase in the order Mn < Fe < Co < Ni[<1115>], which shows that DMPS is not an appropriate chelating agent for manganese. DMPS is not capable of ousting manganese from its binding to EDTA, such that Zn, Cd, Hg, Pb, Sn, As, Sb or Bi can be titrated with unithiol in the presence of Mn[<950>].

3.7.18 Mo - Molybdenum

In hydrochloric acid solution (optimum pH at 0.5), DMPS reacts with pentavalent and hexavalent molybdenum compounds to form yellow-coloured complexes (λ_{max} = 345 nm)[<1053>]. In this process, every Mo atom is bound with two DMPS molecules via the two sulfhydryl-sulfur groups[<1099>]. The reaction takes place more rapidly at higher temperatures[<1053>].

3.7.19 Ni - Nickel

$[Ni^{2+}{}_1(DMPS)_1]$	log K = 18.37[<1115>]
$[Ni^{2+}{}_1(DMPS)_2]$	log K = 29.94[<1115>]
$[Ni^{2+}{}_2(DMPS)_3]$	log K = 35.97[<1115>]

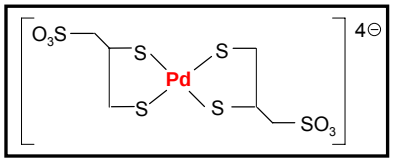
DMPS forms complexes with nickel salts. The composition and properties of complexes depend on the stoichiometric metal to ligand ratio and the pH of the solution[<1151>]. The formation of the $Ni_2(DMPS)_3$ complex takes place exothermically (Δ_rH^o = - 142.9 kJ/Mol)[<689>]. The instability constant is 2.7 × 10^{-10} (-> pk = 9.6)[<1089>]. DMPS is not capable of ousting nickel from its binding to EDTA, such that Zn, Cd, Hg, Pb, Sn, As, Sb or Bi can be titrated with DMPS in the presence of Ni[<950>].

In Ethanol, DMPS binds to nickel-diphosphine or Ni-phosphine arsinic complexes with the formation of “mixed ligand“ products[<653>].

3.7.20 Os - Osmium

The formation of complexes of Os(VI) and DMPS has been detected in aqueous solutions[<1476>].

3.7.21 Pd - Palladium



DMPS forms stable complexes with palladium. It reacts exothermically with Pd^{2+} to form a 1:1-$[Pd_1(DMPS)_1]^{1-}$ (Δ_rH_o = - 97.4 kJ/mol) or 2:1 complex $[Pd_1(DMPS)_2]^{4-}$ with two five-membered rings (Δ_rH_o = - 136,3 kJ/Mol)[<689,1077>] . Binding is carried out via both SH groups. The sulfonic acid group is unaffected[<1515>]. The absorption maximum for the 1:2 complex is at 324 nm, the instability constant is 7.9 × 10^{-22} (→ pK = 21.1)[<1371>].

In Ethanol, DMPS binds to palladium-diphosphine or Pd-phosphine arsinic complexes with the formation of “mixed ligand“ products[<653>].

3.7.22 Pb - Lead

Lead salts form stable, yellowish[<959,960>] complexes[<1058,1084>] with DMPS in aqueous solution in an exothermic reaction[<1058,1077, 1084>]. The complexes are insoluble in water[<960,1146>] (lemon yellow suspension)[<960>] with a decomposition point of 202 °C[<1138>]. Precipitation as lead salt can, therefore, be used for purification purposes during the preparation of

Reference	1077	1058
$[Pb_1(DMPS)_1]^-$	ΔrHo = -39.5 kJ/Mol	ΔrHo = -38.7 kJ/Mol
$[Pb_1(DMPS)_2]^{4-}$	ΔrHo = -77.3 kJ/Mol	ΔrHo = -76.1 kJ/Mol

Reaction enthalpies on the formation of Pb-DMPS complexes

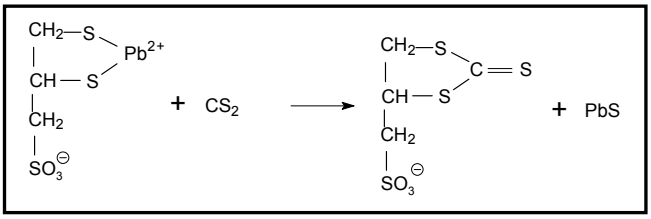
Reference	1058	1077	1146	1117
Pb^{2+} + $DMPS^{3-}$ ⇆ $Pb:DMPS]^{-}$	17.4	17.42	16.38	17.4
Pb^{2+} + 2 $DMPS^{3-}$ ⇆$Pb:(DMPS)_2]^{4-}$	25.0	25.05	22.21	

Stability constants (pK) for Pb-DMPS complexes

DMPS[<975>]. These give rise to 1:1 or 2:1 complexes[<1077>] (e.g. $Pb(NO_3)_2 \cdot 2$ DMPS$\cdot 2$ H_2O[<1084>]), with a five-membered ring structure[<1146>].

The addition of DMPS to a Pb^{2+} solution triggers a change in the polarographic spectra; the redox potential of the heavy metal is shifted[<1049>]. The absence of SH vibrations in the IR spectrum (ν' = 2.555 cm^{-1}) confirms the binding between the heavy metal and the sulfur of DMPS[<1084>]. Furthermore, tests carried out with Ellman's reagent show that only 20-30 % of the SH groups react[<1049>].

Even at a neutral pH, Pb-DMPS reacts with CS_2 with the formation of trithiocarbonates whereas, with other metals, this reaction is evident only at a pH > 11.5[<960>]. The DMPS-Pb complex is obviously more reactive than the complexes with other heavy metals.



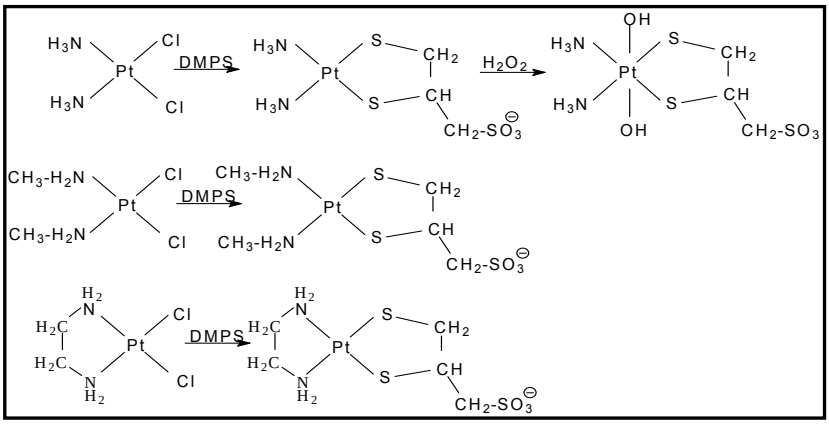
Complexing of lead with DMPS allows the titrimetric determination of alkaline earth metals in the presence of lead[<950,1497,1498>].

3.7.23 Po - Polonium

Polonium forms stable complexes with DMPS[<1137,1442>].

3.7.24 Pt - Platinum

DMPS is firmly adsorbed to platinum electrodes in acid solution[<898>], with greater adsorption in the alkaline than in the acid medium[<1593>]. From the ethanol solution, DMPS is deposited on the metallic platinum catalyst surface and changes the catalytic properties on hydration of ethylenes or acetylenes[<1367>].



In aqueous solutions, stable complexes with Pt(II) in the ratio 1:1, 1:2 or 2:1[<691, 715)] form in an exothermic reaction depending on the composition of the solution (DMPS to platinum ratio). The Pt(II) compounds react more rapidly than the Pt(IV) compounds as Pt(IV) is initially reduced to Pt(II)[<1087>]. The hydrogen ions released by the complex formation reduce the pH of the solution. The dissociation constant at 25°C is pK = 9.6[<715>], the instability constant for the 1:1 complex is approximately 10^{-4}[<1088>] and the equilibrium constant for the Pt:$(DMPS)_2$ complex 7.63 x 10^{7}[<1080>]. The pK value falls to 4.4 in 1 M KOH but increases to 10.1 in 1 M $HClO_4$ (25°C)[<715>]. Mixed complexes are formed with cis-platinum[<1623>]. IR investigations confirm formation of Pt-S binding[<1623>].

In Ethanol, DMPS binds to platinum(II)-diphosphine or Pd-phosphine arsinic complexes with the formation of "mixed ligand" products[<653>].

Amine ligands are not ousted from their platinum complexes by DMPS. Pt(II) complexes can be oxidised to Pt(IV) complexes with H_20_2) without the complexes being cleaved[<1623>].

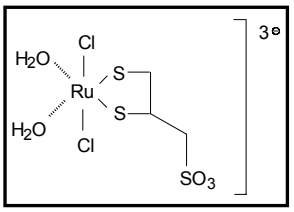
3.7.25 Re - Rhenium

If one adds DMPS to an aqueous solution of calcium perrhenate, then the chelating agent reduces the Re(VII) to Re(V) and forms a yellow complex with this. This is stable for a long time as a solid. It is soluble in water and insoluble in many organic solvents. The absence of SH oscillations at 2545 cm^{-1} and the recently observed Re-S oscillation at 250 - 270 cm^{-1} in the IR spectrum confirm that DMPS is bound to the heavy metal via its sulfur group. The sulfonic acid group is not involved in the reaction<1097>. The stability constant is pK = 4.3<1086>.

3.7.26 Rh - Rhodium

Rhodium forms 1:1, 1:2 or 1:3 complexes with DMPS<714>. In the rhodium-DMPS complexes, DMPS is bound to the heavy metal via the two mercapto groups<1081>.

3.7.27 Ru - Ruthenium



DMPS forms a negatively charged, water-soluble complex with a slightly yellowish colour with radioruthenium<39> and ruthenium(II)<824>. The complex cannot be separated chromatographically from non-complexed ruthenium<39>.

3.7.28 Sb - Antimony

Antimony forms complexes with DMPS. It can, therefore, be concealed with DMPS on titration of alkaline earth metals or lanthane<950>.

3.7.29 Sn - Tin

Zinc forms 1:1 $[Zn_1(DMPS)_1]$ and 1:2 $[Zn_1(DMPS)_2]^4$ complexes with DMPS<1077>. DMPS is, therefore, suitable for masking tin on titration of alkaline earth metals or lanthane<950, 1497>.

$[Sn_1(DMPS)_1]^-$	ΔrHo = -35.5 kJ/Mol	log K = 18.80
$[Sn_1(DMPS)_2]^{4-}$	ΔrHo = -67.5 kJ/Mol	log K = 22.98<1077>

3.7.30 Sr - Strontium

The addition of DMPS prevents disruptions to the complexometric titration via Cd, Hg, Pb, Sn or Zn<1497>.

3.7.31 Tc - Technetium (^{99m}Tc)

^{99m}Technetium forms stable complexes with DMPS<302>. If one adds DMPS to a solution of pertechnetate NH_4TcO_4, then the Tc(VII) is reduced to Tc(V), which forms a yellow complex with DMPS. The hydrophilic Tc-DMPS (1:2) complex has an absorption peak at 400 nm<1484,1485>. In the reaction of $[^{99m}TcO_4]^-$ with $SnCl_2$/Sn and DMPS, various complexes are formed<302> depending on the trial design (mol ratios, pH).

$$\log \frac{C_{Chloroform}}{C_{Water}} = 11.0 \text{ (pH 3 - 8)}$$

3.7.32 Tl - Thallium

In aqueous solution, DMPS forms 1:1, 1:2 and 1:3 Tl(III)-DMPS complexes[<1078>] with Tl^{3+} in an exothermic reaction. The stability constant for the Tl-DMPS complex was determined at 1.43 x 10^{17}[<961,962>] or 3.2 x 10^{21}[<1077>].

$[Tl_1(DMPS)_1]$	Δ_rH^o = -45.6 kJ/Mol
$[Tl_1(DMPS)_2]^{3-}$	Δ_rH^o = -89.8 kJ/Mol
$[Tl_1(DMPS)_3]^{6-}$	Δ_rH^o = -126.4 kJ/Mol[<1077>]

Complex	pK
Tl^{3+} - 1 DMPS	21.51
Tl^{3+} - 2 DMPS	32.21
Tl^{3+} - 3 DMPS	39.53

Stability constants of Tl^{3+} / DMPS complexes at 298 K[<1077,1078>]

3.7.33 W - Tungsten

The formation of DMPS-tungsten(VI) compounds was demonstrated by thermodynamic investtigations in aqueous sodium tungstate (Na_2WO_4)-DMPS solutions. Depending on the ratio of the mixture of substances, 1:1 ($NaWO_4 \cdot DMPS \cdot 2\ H_2O$) or 1:2 complexes ($Na_2WO_4 \cdot 2\ DMPS \cdot 3\ H_2O$) are formed. The absence of SH oscillations at 2545 cm^{-1} and newly developed W-S oscillations at 305-306 cm^{-1} in the IR spectrum of the complexes demonstrate that the DMPS is bound through its sulfur groups to the heavy metal. The sulfonic acid group is not involved in complex formation. In addition, water-soluble, yellowish brown tungstate(V) DMPS complexes are formed $[(Na_4W_2O_3 \cdot 4DMPS \cdot 2H_2O) \cdot 3H_2O]$[<1083,1098>].

3.7.34 Zn - Zinc

DMPS forms water soluble, colourless[<950>] complexes with Zn^{2+} ions in solution[<305,1506>]. Different and variously protonated polynuclear compounds[<664>] are formed depending on stoichiometry and pH. Zinc forms 1:1 $[Zn_1(DMPS)_1]$ and 1:2 $[Zn_1(DMPS)_2]^4$ complexes with DMPS[<1145)>].

$[Zn_1(DMPS)_1]^-$	Δ_rH_o = -39.7 kJ/Mol
$[Zn_1(DMPS)_2]^{4-}$	Δ_rH_o = -76.6 kJ/Mol[<1077>]

Complex formation between Zn^{2+} and DMPS could be detected polarographically[<1049>]. The stability constants were determined by pH and conductance measurements.

The octanol/water distribution coefficient for the 1:1 complex is $7.3x10^{-5}$ and for the 2:1 complex $4.8x10^{-5}$[<1152>].

Reference	365	1145	1077	1117	664
$[Zn_1(DMPS)_1]^-$	14.7	14.9	17.18	14.7	
$[Zn_1(DMPS)_2]^{4-}$	24.9	25.0		26.93	27.6
$[Zn_1(DMPS)_3]^{7-}$	27.0				
$[Zn_2(DMPS)_2]^{2-}$					33.6

pK stability constants of various zinc-DMPS complexes

Zinc can be determined titrimetrically using a DMPS solution. The reaction is, however, interrupted by a wide range of metals such as Co, Cd, Hg, Mn, Pb, Ni, Cu, Ca, Mg, Cr and Ag. Alkaline metals and small quantities of iron (< 5 mg/L) have no impact[1496]. On the other hand, complexing of zinc with DMPS allows the titrimetric determination of alkaline earth metals or lanthane in the presence of zinc[<950,1497,1498>].

Conclusion:
DMPS forms stable complex with various heavy metal ions. Its binding constant with mercury is very high. The affinity to the essential trace element, zinc, is significantly lower. DMPS does not react with the minerals calcium and magnesium. DMPS is thus a suitable chelating agent, especially for poisoning due to mercury and even other heavy metals. No impact on minerals is anticipated.

3.8 Condensation and other reactions

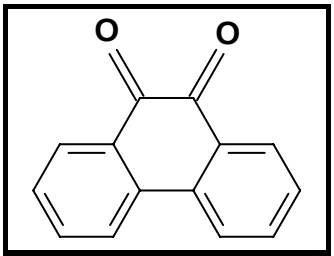
A high yield of 1,3-dithiolan-2-thioxo-4-methane sulfonate (DMPS-trithiocarbonate DMPS-TTC), is produced with CS_2. This appears to be poorly soluble in water and non-toxic in cell investigations[<654>]. Yellowish DMPS-TTC[<877,959,960>] is formed from a suspension of DMPS-lead salt in neutral solution through the addition of CS_2. Contrastingly, an alkaline pH is required for this reaction with As, Cd, Hg and Zn complexes[<960>].

Linear or cyclic copolymers from alternating polyethylene oxide and polyethylene sulfide units are formed from DMPS through multiple addition of appropriate polyalkaline ethers[<1459>].

With cystamine, a mixed disulfide is formed from DMPS and cysteamine in acid solution[<510>]. SH groups could no longer be detected after the reaction of DMPS with the pesticide ethylthioethyl sulfonate[<253>].

DMPS reacts with ketones[<1613>], e.g. under anaerobic conditions with phenanthraquinone, a component of diesel dust particles. The DMPS SH groups disappear in this process. Unfortunately, the authors do not comment on the potential clinical consequences of this reaction[<808>].

The SH groups are alkalised with iodoacetamide[<1512>]. Aziridines react with both the SH groups and the sulfonic acid groups[<1513>].



9,10-Phenanthraquinone[<808>]

Conclusion:
With its vicinal SH groups, DMPS belongs to the reactive compounds that can react with various substances. DMPS must not, therefore, be mixed with other solutions for injection, otherwise DMPS may react with the active substances in these solutions, thus rendering both medicinal products ineffective.

4. Toxicology

The potential toxic effects of chelating agents such as DMPS comprise three components:

- Direct toxic effect of the chelating agent and/or its metabolites;
- Effect of the chelating agent on essential trace elements;
- Effect of the metal complexes (e.g. enrichment in critical organs such as the brain or central nervous system)[<180>].

Hydrophilic complex-forming agents such as DMPS are generally less toxic than lipophilic substances[<1156>] since they are present in only very small quantities in the CNS[<1102>]. They can, therefore, usually be administered for longer periods at higher dose levels[<1156>].

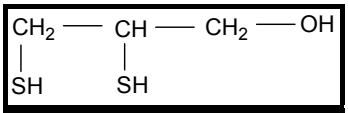
4.1 Investigations in bacteria or cell cultures

The potential toxic properties of DMPS were investigated in numerous experiments in cell cultures, on various cell components and in bacteria.

- In *in-vitro* experiments, DMPS did not trigger haemolysis of human erythrocytes in the concentration range tested (up to 100 µM)[<517>]. The addition of 12 µmol/mL (= 2.5 g/L) to a suspension of human or rat erythrocytes did not trigger haemolysis[<1157>].
- The δ-ALAD activity in human blood remained unchanged *in vitro* following the addition of DMPS[<1260>].
- *In vitro* investigations with isolated δ-aminolaevulinic acid-dehydratase (δ-ALAD) revealed DMPS- and DMSA-mediated, concentration-dependent inhibition of enzyme activity. The DMPS or DMSA and Hg^{2+} or Cd $^{2+}$ complexes possessed a greater inhibitory potential than the respective individual substances. The addition of Zn^{2+} did not alter the inhibitory potential of DMPS. Pb^{2+} was devoid of effect on inhibition. The presence of DTT on the other hand, prevented the inhibitory effect of DMPS, which indicates that the chelating agent SH groups play a role in the reaction[<1049>].
- DMPS did not act as the substrate of the methylcobamide enzyme: M methyltransferase coenzyme[<832>].
- The addition of DMPS to culture solutions of various lung cells (rat epithelial cells and human fibroblasts and small cell carcinomas) was devoid of effect on their protein synthesis[<1526>].
- DMPS did not show any effect on DNA synthesis of *in vitro* cultures of various cancer cells up to 8 µg/mL. At 30 µg/mL, the DNA synthesis of the cells (measured by means of incorporation of ^{3}H-thymidine) was only 10 - 40 %, depending on the cell line[<683>].
- 0.75 mM DMPS had no cytotoxic effect on HepG2 cells[<1065>].
- Pre-treatment of various cell cultures of human lung cells (epithelial cells, fibroblasts) with DMPS reduced the intracellular available zinc. This led to a reduction in the TNF-α-induced formation of eotaxin – a cytokine. The effect was not apparent on concomitant addition of zinc[<1230>].
- The inhibitory concentration (IC_{50}) of DMPS for the zinc-containing endothelial converting enzyme in experiments with endothelial cells was 44 µM[<93>], which reduced the incidence of endothelin ET-1-induced "sudden death" in mice[<94>].
- In various other cell lines the IC_{50} was over 10^{-4} mol/L (≅ 22.8 mg/L)[<414>]. Thus no cytotoxic effects were detected with HeLa-, CHO- or L-A-cells[<414,416,900,1203,1415>], renal cells (up to 60 µmol)[<1447>] or hepatocytes (up to 60 µmol)[<1447,1450>] up to this concentration. CHO cells displayed no signs of toxicity in a 20 mM DMPS solution[<1203>]. With human epithelial cells, no effect on cell growth was observed up to a concentration of 10^{-3} mol/L[<116>]. Inhibition of cell proliferation was detected only at higher concentrations (> 0.1 mM) in CHO-, HeLa- and fibroblast cells[<415>]. An IC_{50} > 1 mmol/L[<412>] was detected in Chinese hamster peritoneal cells.
- The IC_{50} for inhibition of ß-lactamase from *Pseudomonas aeruginosa* was 11 µM. The negatively charged sulfonic acid group was also involved in the reaction with the enzyme[<1346>].
- DMPS did not induce any breaks in the DNA strand of NB4 cells of a human leukemic cell line up to a concentration of 12 x 10^{-3} mol/L[<876>]. No DNA degradation, micronuclei, sub-G1 cells or

depleted colony formation were observed[<650>]. No elevated H_2O_2 concentration was detected intracellularly[<650>].

- DMPS was devoid of effect on glutamate binding in synaptic membranes isolated from rat brains[<1105,1362>].
- DMPS had no effect on glutamate binding in blood platelets[<195a,196>].
- DMPS had a three-fold less effect on the viability of MDCK cells than BAL [EC_{50} = 0.3 mmol (BAL), = 10 mmol (DMPS)][<844>].
- In contrast to BAL, DMPS had only a slight inhibitory effect on the peptide deformylase enzyme (EC3.5.1.31)[<1201>].



British-Anti-Lewisite (BAL)

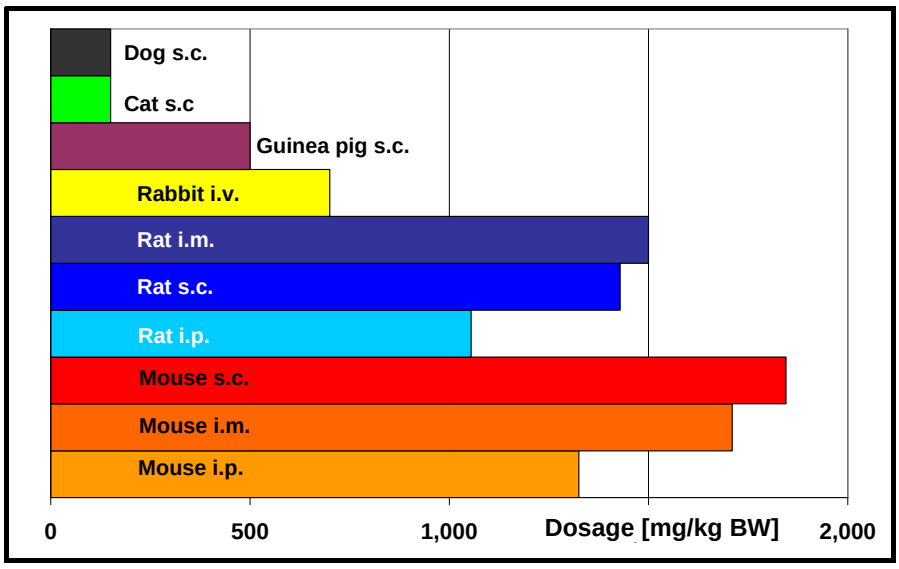
- A disulfide group is essential for the functionability of neuronal nicotine receptors in the chicken brain. DMPS does not affect the storage of nicotine[<1144>].
- Pre-treatment with DMPS increased the affinity of VLA-4, a protein belonging to the group of adhesion receptors in U937 cells[<264>].
- In cell cultures, DMPS reduced the proliferation of stimulated human T cells[<656>] and two leukemic cell lines[<655>].
- The addition of DMPS reduced the thermal inactivation of the caspase-3 enzyme[<1071>].

4.1.1 Binding of nitrogen monoxide NO

Various studies assume that the addition of DMPS to cell cultures binds the NO thus produced[<1297>]. The NO concentration in Nitrosomonas cell suspensions is reduced by adding DMPS[<15>]. There is no reference to the mechanism of this reaction. The formation of an iron-DMPS complex to which the NO thus produced can attach would be conceivable (see chapter 3.7.8). However, no study has described any red staining of the solution (colour of the DMPS-Fe complex).

4.2 Toxicity (LD_{50} and LD_{100})

4.2.1 Acute toxicity



LD_{50} values of DMPS in various animal species and various types of application

The investigations on acute toxicity (LD_{50} or LD_{100}) were carried out in various animals by single administration of DMPS. The sensitivity of the various species to DMPS decreased in the following order: Cat > dog > guinea pig > rabbit > rat > mouse[<69,734,735>]. The two optical isomers or racemate did not show any significant difference in the LD_{50}[<69,617>].

On i.m. administration of DMPS, no deaths occurred in rabbits up to 1,141.4 mg/kg BW[<409, 635>]. All animals survived i.v. administration of 380 mg/kg BW. At 543 mg/kg BW i.v., one of the three animals died, and at 760 mg, all three animals died[<499>]. 33.6 mg/kg BW was tolerated asymptomatically[<635>].

Following i.v. administration of 700 mg/kg BW DMPS, all three rabbits died within 3 hours[<409,635>]. Two out of 3 animals survived administration of 500 mg/kg BW and all three survived 250 mg/kg BW[<635>].

All mice survived the single i.p. injection of 400 µmol DMPS/kg[<206>] and 1,300 mg/kg [<1136>]. All mice survived oral administration of 1 mmol DMPS/kg[<70>]. In rabbits, repeated dosing with 75 µmol/kg did not trigger any symptoms[<68>].

Vomiting was observed in two dogs 3 minutes after i.v. administration of 150 mg/kg, and a bowel movement after 10 minutes. For 30 minutes, the animals were unable to stand upright. The effect was reversible and the symptoms completely disappeared within 2 hours[<1420>]. Other authors report similar reactions following administration of 50 mg/kg[<ref. in 1420>]. Higher doses were also tolerated with a slower rate of injection[<ref. in 1420>].

These LD values apply to healthy animals. Animals already weakened by heavy metal poisoning reacted more sensitively[<681,772>]. While all mice survived a DMPS dose of 1,352 mg/kg BW, 40 % of the control animals with cadmium poisoning died following administration of the same dose[<681>].

After administration of lethal doses, the animals were initially very irritable for a few minutes before they turned apathetic. They died relatively quickly within one day of administration. Apathy, seizures, diarrhoea, respiratory arrest and slowing of the heart rate were observed. Finally, cardiac arrest developed. Surviving animals recovered relatively quickly from the symptoms of intoxication[<69,635,706,735,1160>]. Death occurred within 3 hours[<1136>]; no further animals died after 12 hours[<1160>].

DMSA is toxic only at higher dose levels compared to DMPS[<52,663a>]. However, as the therapeutically administered doses are considerably lower than the LD_{50}, the higher DMSA LD_{50} had no therapeutic consequences[<52>].

	BAL	DMSA	DMPS
LD_{50} (mmol/kg) i.p.	1.48	13.73	6.53

LD_{50} of various CA in mice[<67>]

Species	Application	Dose (mg/kg BW)	Year	Ref.
Mouse	subcutaneous	2,400	1958	735
Rat	subcutaneous	2,000	1960	942
Rat	subcutaneous	1,500	1958	734,735
Guinea pig	subcutaneous	800	1958	734,735
Rabbit	subcutaneous	1,000	1980	492
Rabbit	subcutaneous	1,000	1958	734,735
Cat	subcutaneous	500	1958	734,735
Dog	subcutaneous	500	1959	734

Acute LD_{100} values of DMPS

Species	Application	Dose (mg/kg BW)	Year	Ref.
Mouse	i.p.	1,097	1981	72
Mouse	i.p.	1,187	1988	346
Mouse	i.p.	1,187	1996	1378
Mouse	i.p.	1,192	1982	70
Mouse	i.p.	1,335	1990	789
Mouse	i.p.	1,400	1985	131
Mouse	i.p.	1,450	1981	795,1421
Mouse	i.p.	1,491	1983 1985	67,617
Mouse	i.p.	1,495	1990 1985	1135,1136
Mouse	i.m.	1,689	1980	721
Mouse	i.m.	1,710	1978 1981	566,1422
Mouse	s.c.	1,491	1984	68
Mouse	s.c.	2,000	1958	735
Mouse		1,270	1958	777
Rat	i.p.	1,055	1980	1160
Rat	i.p.	1,141	1975	243
Rat	s.c.	900	1958	735
Rat	s.c.	1,000	1960	942
Rat	s.c.	1,857	1980	492
Rat	i.m.	1,500	1977	140
Rabbit	i.v.	700	1958	735
Guinea pig	s.c.	500	1958	735
Cat	s.c.	150	1958	735
Dog	s.c.	150	1958	735

Acute LD_{50} values of DMPS

4.2.2 Subacute and chronic toxicity

In addition to determining the LD_{50} after a single dose, the LD_{50} was also determined after repeated administration (cumulative LD_{50}). On 10-day i.p. administration to rats, this was 6.47 g/kg BW (30.8 ± 0.83 mmol/kg BW). The dose-response curve was very steep. The highest dose at which no animal died was 4.21 g/kg BW. The lowest dose at which all animals died was just about twice as high[<1160>].

Species	Application Type	No.	Interval	Dose (mg/kg BW) Single	Cumulative	Year	Ref.
Mouse	i.m	6	1 h	700	4,200	1978	566
Mouse	i.m.	6	1 h	703	4,218	1980	721
Rat	i.p.	10	24 h	646	6,460	1980	1160

Acute LD_{50} of DMPS after repeated administration

No reactions were observed in rabbits following repeated dosing with 8.4 mg/kg BW[<636>]. Histological examinations showed changes in the gall bladder in 2 out of 3 rabbits and, in addition, slight changes in the spleen in one animal following administration of 33.6 mg/kg[<635>]. Feeding with 5.6 g DMPS/kg feed (approximately 560 mg DMPS/kg BW/day) for two weeks led to a slight increase in body weight in rats. Water intake was also increased. Feed intake was identical to that observed in the control animals. Urine creatinine levels were slightly elevated and the weight of the bladder slightly reduced. Simple hyperplasia was detected on histological examination in 2 out of 10 animals[<283>].

Investigations on the chronic toxicity of DMPS were carried out in rats[<1160>] and beagles[<1420>]. In a 63-week study, rats were treated 5 times a week with 150 mg DMPS/kg BW orally. No differences in weight or in the biochemical and haematological parameters investigated were found in comparison with untreated animals throughout the treatment period. Similarly, autopsy did not reveal any macroscopic or histological changes of the organs and tissues. Only the copper level in the kidneys was reduced, but this reverted to normal within one week following withdrawal of DMPS[<1160>]. Zinc, iron, calcium, magnesium and manganese levels in the serum and the various organs did not reveal any notable differences[<1160>].

Beagles were given 2, 5 and 15 mg DMPS/kg BW i.v. or 45 mg DMPS/kg BW orally for 6 months. Again in this experiment, there were no changes in weight gain or in the biochemical and haematological parameters investigated (including creatinine, calcium, magnesium, iron, sodium, γ-GT, AST, ALT, CPK, AP, red and white blood cell count) in comparison with control animals (physiological saline solution). Autopsy did not reveal any macroscopic or histological changes of the organs and tissues. Only the copper level in the serum, liver, kidneys and spleen was reduced in a dose-dependent manner[<706,1420>].

The organs of dogs, which were given 40 or 60 mg/kg i.v. 3 times a day for 2 days and twice on the third day, were examined. Plethora (increased volume of a bodily fluid) of the internal organs, especially the kidneys, was observed, which, however disappeared after 15 days. “Fatty dystrophy of some epithelium was noted“ at the higher dose level. No change was detected in other tissues or organs[<ref. in 69>].

In a further study, 2 x 75 mg/kg BW daily was administered i.v. to dogs for 10 weeks. In these animals, the haemoglobin content and haematocrit of the blood were reduced by approximately 40 % and the iron content of the liver and spleen increased. A reduced alkaline phosphatase (AP) activity was found in the serum. In addition to a marked reduction of the copper concentration in the serum and organs, a reduction in zinc serum levels was also recorded. Apart from hepatic haemopoiesis in one animal, no findings were obtained in the histological examinations, which were attributable to toxic actions of DMPS[<706,1420>].

Dogs tolerated the slow i.v. injection of 40 –60 mg/kg very well when the rate of injection of 1 mL/min was not exceeded[<733>]. In two further studies in dogs, the slow injection of a 5% solution of DMPS (1 mL/min) up to doses of 60 mg/kg BW did not trigger any pathological changes[<1243,1259>].

Rabbits received 100 mg/kg s.c. , 50 mg/kg i.v. or 500 mg/kg p.o. twice daily for 6 to 10 days. No symptoms of poisoning were observed. Weight and the blood parameters investigated did not change over the 30-day observation period[<734>].

Rabbits received 50 mg DMPS/kg once a week for 10 weeks via slow, i.v. injection. The injections were well tolerated. Transient irregularities were observed only in breathing patterns. Weight gain

was similar to that of the control group (NaCl i.v.). The changes in various haematological parameters were similar in both groups. Similar changes were also evident in numerous biochemical parameters studied. Only the calcium content was somewhat lower at the end of the test series in the animals treated with DMPS. Magnesium plasma levels did not change in the DMPS group but increased by almost 900% in the NaCl group. The vitamin E level was lower in the DMPS group, albeit not to a statistically significant extent. The oxidation of DMPS may play a role here. The test for minerals in the myocardium revealed statistically lower magnesium values in the animals treated with DMPS. The authors did not discuss whether this was correlated with the changes observed in the serum levels. Calcium and potassium were also lowered, but not to a statistically significant degree. Iron- and selenium levels were unaffected. No morphological or physiological changes were observed in the heart. In the authors' opinion, their study confirms the low toxicity of repeated DMPS administration<482,607,608>.

Repeated oral or s.c. dosing with DMPS for 3 days did not trigger a negative outcome in rabbits<71>. I.p. administration of 150 mg/kg/day for three days to mice did not affect the feed and water intake. They were equivalent to the control animals in the behaviour tests<239>. The addition of DMPS to the feed (1 g DMPS/kg) did not affect weight gain or feed consumption in rats<1272>. No changes were observed in cats, dogs, guinea pigs, rabbits or mice in the 15-80 mg/kg BW dosing range<69>.

Administration of DMPS to rats for several days did not trigger any undesirable reactions<723>. Oral administration of 0.3 mmol/kg for 15 days did not trigger any significant change in body weight or in the weight of the spleen and thymus in rats<429>.

Conclusion:
DMPS is a relatively non-toxic compound. The therapeutic dose of DMPS is 3 to 5 mg/kg BW. It is is thus more than 30 times lower than the LD_{50} of the most sensitive animal species. DMPS was also well tolerated during prolonged administration of higher doses. No accumulation was observed. DMPS can, therefore, be administered for prolonged periods at high dose levels when required.

4.3 Influence on organs and systems

4.3.1 Body weight and food and liquid intake

A single dose of DMPS (100 mg/kg BW i.p.) did not trigger any change in the body weight of rats after 24 or 48 hours. The food and liquid intake corresponded to that of the untreated control animals and the placebo group treated with NaCl<1344>. Similarly, repeated dosing (100 mg DMPS/kg BW twice a day for 6 days) did not reduce the body weight in rats<1170>. Single i.p. administration of 400 µmol/kg did not affect body weight and had no significant effect on ALT, urea and AST in the plasma<205>. A single dose of DMPS (100 mg/kg BW i.p.) did not trigger any change in the body weight or water intake of rats<1343>.

The once weekly administration of i.v. DMPS for 10 weeks did not affect the body weight of rabbits<482,606>.

4.3.2 Kidneys

At therapeutic doses (5 mg/kg BW), DMPS did not have any effect on kidney function<260>. The treatment of 10 patients with 300 mg DMPS daily for 5 days did not trigger any renal damage<1449>. Determination of creatinine, N-acetyl-glucosaminidase and α1-microglobulin in human urine before and after administration of DMPS (3 mg/kg BW i.v.) did not give any indication of DMPS-induced kidney damage<304>.

Single parenteral administration of 132 mg/kg BW to mice<937> and up to 100 mg DMPS/kg BW to rats<937,1601> triggered no pathological findings in the kidneys. In rats, a single dose of DMPS (100 mg/kg BW i.p.) did not alter the weight of the kidneys <1343, 13443>. The excretion of hydroxyproline in the urine was unchanged<1343>.

A single dose of 400 µmol DMPS/kg had no effect on the "non-protein-SH concentration" in the kidneys[<206>]. A single s.c. dose of 1.6 mmol/kg DMPS lowered ALAD activity in the kidneys[<1261>]. Seven weeks' treatment with DMPS did not lead to any increase in ALA in the urine[<595>]. A high MDA concentration was recorded[<1261>]. Other investigations did not reveal any effect on lipid peroxidation[<158,457>]. The concentration of corresponding metabolites was similar to that observed in the untreated control animals. The concentration of superoxide dismutase SOD was reduced and catalase unchanged. DMPS reduced the peroxidation of liposomal membranes in a concentration-dependent manner. Oxidised DMPS was thus clearly less effective[<158,159>].

The activity of the AST, ALT and AP enzymes in mice was not changed by single injection of DMPS[<1457>]. DMPS did not significantly reduce porphyrin in the kidneys (100 mg/kg BW i.p.)[<1148>].

Chronic dosing with DMPS did not induce oxidative kidney damage in rats[<922>]. After six doses of 30 mg DMPS/kg i.p. for 3 days, no morphological changes were detected in the kidneys of the treated rats compared to the controls[<1417>]. The two injections of DMPS did not affect the weight of the rat kidneys[<1600>].

Oral administration of DMPS to rats had no effect on the metallothionein content of the kidneys. It lowered zinc levels (by approximately 16 %) and increased copper levels (by 65 %) compared to the control animals[<1427>]. Other studies described increased[<1261>] or unchanged[<921>] zinc levels.

Zn, Mg and Cu levels are unchanged following chronic dosing with DMPS. The enzyme activity of AST, ALT and AP were reduced whilst that of GSH and MT is increased. GSSG was only marginally affected[<921>].

A delay in diuresis followed by polyuria was observed in rats (100 mg DMPS/kg BW twice a day for 6 days) during the first 3 to 4 days[<1170>]. A diuretic effect of DMPS through reduced canicular reabsorption[<487,494>] was observed in rabbits[<487>] and dogs (15, 25 and 50 mg DMPS/kg BW i.v.) over 2 hours[<777>]. DMPS increased diuresis[<1606>].

In perfusion studies performed on rat kidneys, high concentrations of DMPS as well as DMSA or Ca-DTPA were nephrotoxic, which is also highlighted in a reduced GFR amongst other things[<1376>].

DMPS did not have any effect on the LDH activity of isolated renal tubular cells[<1599>]. At concentrations of less than 0.1 mmol, it did not affect the viability and gluconeogenesis of isolated renal tubular[<957>]. Only at high concentrations (> 300 mg/L ≅ 1.4 mmol) gluconeogenesis was inhibited *in vitro*[<1421>].

Conclusion:
The kidneys play an important role in the excretion of heavy metals. At therapeutic dose levels, DMPS is devoid of nephrotoxic effects following both oral and parenteral administration.

4.3.3 Liver

At therapeutic doses (5 mg/kg BW), DMPS did not have any effect on liver function[<260>]. The treatment of 10 patients with 300 mg DMPS daily for 5 days did not trigger any hepatic or renal damage[<1449>].

DMPS has no toxic effect on the liver in mice[<1457>]. Single i.p. administration of 132 mg/kg BW to mice[<937>] and up to 100 mg DMPS/kg BW to rats[<937,1601>] did not show any biochemically or morphologically detectable liver damage.

The oral administration of DMPS to rats did not alter the metallothionein content of the liver. However, it reduced copper levels in the liver (by approximately 50 %). The cytosol fraction of the liver, which contains mostly zinc or copper, was mostly affected[<1427>]. In other investigations, Zn[<921>] and Cu levels[<921,1261>] remained unchanged. Mg levels were lowered[<921>].

The single injection had no effect on the activity of the liver enzymes AST[<1457>], ALT[<1457>], γ-GT[<1457>] or ALAD[<1261>]. The activity of AP was reduced[<1467>]. Elevated GSH levels were recorded in rat liver[<429>]; these levels were lowered in mice following administration of DMPS[<233,712>].

The enzyme activity of AST and ALT was reduced after chronic dosing with DMPS. GSH and GSSG levels were only marginally affected[<921>]. Whereas some authors found transient increases in the activity of superoxide dismutase (110 %) in the liver after DMPS[<232>], others found a reduced activity[<158,159>]. The activity of catalase was not affected[<158>] or lowered[<712>]. No effect was seen on alcohol dehydrogenase and γ-aminolaevulinic acid dehydratase[<712>]. No change[<712>] or reduction in activity was described with alkaline phosphatase[<232>].

High concentrations of malondialdehyde were recorded in mice[<233,1261>], which indicates increased lipid peroxidation. The reactivity of a formed Fe:DMPS complex is assumed to be the cause[<233>]. In rats, the MDA concentration remained unchanged[<156,921,922>] and lipid peroxidation was unaffected[<158,467>]. The concentration of the SH groups was not increased. DMPS prevented the peroxidation of liposomal membranes in a concentration-dependent manner. Oxidised DMPS was thus clearly less effective[<158>].

Chronic dosing with DMPS did not trigger any oxidative damage[<921,922>]. DMPS reduced the oxidative stress of H_2O_2 on liver homogenates *in vitro*[<688>].

A single dose of 400 µmol DMPS/kg had no effect on the "non-protein-SH concentration" in the liver[<206>]. The prothrombin-forming function of the liver remained unchanged[<744>].

In the dog, therapeutic doses of DMPS increased the elimination of bile[<496,734>]. Increased quantities of bile components, bile acid, bilirubin and cholesterol were eliminated[<496>]. The elimination of bile was slightly reduced at toxic doses (150 mg/kg)[<496>].

DMPS increased sulfate uptake through SAT-1, a sulfate carrier in hepatocytes[<1194>].

4.3.4 Blood

No clinically relevant changes in various blood parameters were observed in humans following single administration of 300 mg DMPS[<582>] or after 5 days' treatment with 3 x 100 mg/d[<1449>].

The once weekly administration of i.v. DMPS for 10 weeks did not affect haematological parameters in rabbits[<482,606>]. Urea, creatinine, cholesterol, triglyceride and protein levels were equivalent to those recorded in the controls[<606>]. The "non-protein-SH concentration" in erythrocytes and plasma was not changed by DMPS[<208>]. Others observed an increase in the SH concentration in the blood[<263>].

The administration of 300 or 600 µg DMPS/mL in the drinking water to nude mice for 5 days did not show any acute haematotoxic effects (erythrocyte count, thrombocytes, leukocytes, lymphocytes, monocytes, eosinophils, neutrophils, concentration of sodium, glucose, BUN, creatinine, albumin, bilirubin, alkaline phosphatase, lactate dehydrogenase, aspartate aminotransferase and alanine aminotransferase). Similarly, the administration of 300 µg/dL for up to 93 days did not trigger any chronic haemotoxic reactions[<683>]. Contrastingly, reduced LDH activity was measured in the plasma[<1262>] following i.p. administration of DMPS (in conjunction with DMSO).

No changes in haematological parameters were observed following administration of DMPS to pregnant mice[<202>].

No changes in the glycogen parameters were recorded in the blood of dogs or rats[<734>]. Zn, Cu and Mg levels remained unchanged in rats[<921>]. In another study conducted in rats, oral administration of DMPS lowered copper (by 72 %) and zinc (by approximately 50 %) levels in the blood compared to the control animals[<1427>]. Oral administration of 20 mg/kg for three days lowered the erythrocyte count and Hb value in mink and foxes[<692>].

The activity of δ-ALAD was unchanged in mice following a single injection of DMPS[<1261,1457>]. δ-ALAD activity was equivalent to that of the controls even after repeated dosing[<921,1260>]. At higher concentrations, DMPS inhibited the activity of ALAD in the blood. Previous incubation with cysteine did not hamper the reaction. In contrast, DTT or $ZnCl_2$ reduced the inhibitory effect. The

subsequent addition of DTT also reinstated the activity. $ZnCl_2$ also increased activity, but did not reach the control values[<1048>].

Increased γ-globulins were recorded[<1330>] after 5 days' treatment to chronically Hg-exposed rats[<1330>]. SOD activity was reduced [<158,159>] whilst catalase activity was unchanged[<158>]. Chronic administration of DMPS increased ZPP and lowered haemoglobin and glutathione[<921>]. In rats, an increase in glutathione in the blood and a decrease in alkaline phosphatase and amino-oxidase levels were observed in rats[<734>].

The administration of DMPS to rats did not increase lipid peroxidation. The concentration of corresponding metabolites was equivalent to that recorded in the untreated control animals[<158>]. DMPS prevented the peroxidation of liposomal membranes in a concentration-dependent manner. Oxidised DMPS was thus clearly less effective[<158>].

In *in-vitro* experiments with human erythrocytes, DMPS removed zinc from carbonic anhydrase [EC 4.2.1.1] and thus triggered the binding of the enzyme to the erythrocyte membrane via the formation of SS bridges[<1225>].

4.3.5 Cardiovascular system

At therapeutic doses (5 mg/kg BW), DMPS did not show any adverse effects on the cardiovascular system[<260,494>]. The once weekly administration of i.v. DMPS for 10 weeks did not affect blood pressure or most of the haematological parameters studied in rabbits[<606>]. No functional, morphological or pathological changes were triggered in the rabbit heart[<608,1351>]. No cardiomyopathic changes were detected[<606>]. A hypotensive effect was observed only at high doses[<494>]. The administration of 200 mg/kg BW had no effect on blood pressure[<260>]. A fall in blood pressure was observed following administration of 500 mg/kg[<735>].

As investigations in dogs have shown, DMPS does not alter cardiac function (blood pressure in the aorta, pulse and pump performance)[<731>]. In contrast, DMPS has an acute, dose-dependent effect on the circulation. Dilatation of peripheral arteries is assumed to be the mechanism involved[<731>]. A rapid intravenous injection of mg/kg BW led to a slight, transient reduction in arterial blood pressure. Rapid injection of 75 mg/kg BW led to a marked, persistent lowering of blood pressure and 150 mg/kg BW caused transient respiratory arrest in the animals. They developed symptoms of respiratory shock with marked metabolic acidosis. In other investigations, the hypotensive effect at 200 mg/kg BW i.v. was, in contrast, rapidly reversible[<734,735>]. The reaction was irreversible from a dose level of 300 mg/kg)[<735>].

In rats, the i.v. administration of 10 or 30 mg DMPS/kg did not affect cardiovascular or respiratory function. 100 mg/kg BW led to a transient fall in blood pressure and pulse rate and to an increase in respiratory rate. The symptoms disappeared within 15 minutes. At the dose level of 300 mg/kg BW, the symptoms were reversible in only two out of three animals during the 40-minute observation period. The ECG was not altered at any of the dosages[<586>].

In the isolated frog heart, DMPS was devoid of any effect up to a concentration of 1×10^{-3} M. The heart was slower from a concentration of 1×10^{-2} M. From 5×10^{-2} M, DMPS triggered cardiac arrest. After washing with Ringer's solution, heart beat was restored after one minute. In the isolated rabbit heart, heart function was affected from a concentration of 1×10^{-3} M[<1073>]. Thus DMPS had no effect on heart beat induced by a pace maker[<1469>].

Conclusion:
As laboratory animal experiments show, DMPS can trigger a transient fall in blood pressure, especially if administered too rapidly via the i.v. route. The injection must, therefore, be administered slowly, i.e. over three to five minutes.

4.3.6 Thyroid gland

S.c. administration of DMPS to rats for 60 days increased the iodide deposit in the thyroid gland comparable to that observed in a control group (NaCl s.c.). The mean body weight of the animals was less than that of the control animals. The effect of DMPS on SH groups in the thyroid gland that (should) play a role in iodide deposits is discussed as a reason for this[<1592>].

4.3.7 Immune system

15 days' oral administration of 3 x 210 mg DMPS/kg/BW did not produce any immunotoxic effects in rats. Body weight as well as the weight of the spleen and thymus corresponded to those of the controls. The biochemical and immunological parameters were not altered. Cellular and humoral response was not influenced. The number of antibody-forming cells did not change[<429>].

In vitro, DMPS (300 or 600 µg/ml) did not prevent the attachment of monoclonal antibodies to specific cell antigens in mice serum[<683>]. The injection of DMPS did not increase antibody formation in the mouse spleen[<620>]. DMPS increased the proliferative response of spleen lymphocytes to mitogens *in vitro*[<620>].

Like other compounds containing thiol, at higher concentrations, DMPS activated the alternative complement system pathway *in vitro*. It reduced factor I activity and thus prevented the "deactivation" of activated C3 proteins. The effect was no longer detectable after alkylisation of the SH groups[<1512>].

In rabbits, s.c. administration of DMPS reduced the mortality rate due to immediate hypersensitivity on sensitisation with porcine serum[**<263>**].

4.3.8 Brain and nervous system

Unlike BAL, DMPS had no effect on the uptake of glutamate in synaptosomes or synaptic vesicles. Neither the basal nor the K^+-stimulated release from synapses was affected. DMPS does not, therefore, possess the neurotoxic effects associated with BAL[<1050>].

The addition of DMPS to cultures of cortical cells taken from mouse foetuses did not increase the cell mortality rate[<857>]. In studies carried out on corresponding homogenisates of rat brain, DMPS did not affect the D_2-dopamine receptors[<1274>].

Single administration of 1.6 mmol/kg DMPS s.c. did not affect ALAD activity in the brain. Zn concentrations and MDA levels were unchanged[<1261>].

I.p. administration of 150 mg/kg/day for three days to mice had no effect on biochemical and histological investigations of the cerebellum. The Purkinje cell count corresponded to that of the control animals[<239>].

DPA, DMPS and DMSA had no indirect stimulating effect on the sympathetic nervous system in isolated guinea pig papillary muscles[<554>].

4.3.9 Testes and sperm/spermatozoa

The administration of DMPS did not trigger any changes in the testes in mice. Lipid peroxidation, δ-ALA-D activity, haemoglobin concentration and vitamin C levels remained unchanged[<1262>].

Incubation with DMPS, DMSA or DL-penicillamine increased the motility of male sperm in a dose-dependent manner[<1574>]. The proportion of non-linear, motile sperm to mobile sperm was significantly reduced by the addition of DMPS. The straight line velocity of the spermatozoa was significantly increased by addition of DMPS. The zinc content of the sperm remained unchanged[<1575>].

4.3.10 Ear

A mild vasodilator effect was evident in the rabbit ear[<735>]. Perfusion with a DMPS concentration of 1 x 10^{-3} M triggered a vasodilator effect, which peaked after 15 to 25 minutes. No significant effect could be detected at a concentration of 1 x 10^{-5} M [<1073>].

4.3.11 Lungs

DMPS aerosols were well tolerated and had no effect on the ciliated epithelium[<1354>].

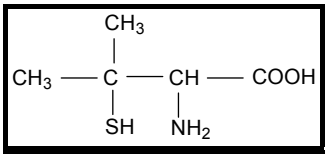
The incubation of rat lungs in DMPS solution up to a concentration of 10 µM triggered no change in δ-ALA-D activity. Enzyme activity was reduced at higher concentrations. Concomitant addition of DTT reduced the effect of DMPS; Zn^{2+} did not have a positive effect[<867>].

4.3.12 Gastrointestinal tract

DMPS is well tolerated on oral administration[<921,922>]. No irritation of the gastrointestinal tract mucosa[<868>] was observed even following administration of high doses for longer periods.

DMPS increased the contractility of the cat jejunum[<1413>] . The injection of DMPS into the jejunal loop of rabbits was devoid of effect on the enzymes adenylate cyclase (AC) and phosphodiesterase (PDE) as well as on the concentration of cyclic AMP[<1588>]. DMPS increased the permeability of the colon for PEG. The permeability of the duodenum was reduced[<1477>].

4.3.13 Collagen metabolism



D-Penicillamine (DPA)

In investigations on the influence of collagen and mesenchymal metabolism, DMPS did not show any effect in contrast to D-Penicillamine. This was attributed to the absence of an amino group in the DMPS molecule compared to the penicillamine molecule[<1631>]. The administration of DMPS to rats did not alter hydroxyproline (HYP) levels in the serum (marker for collagen metabolism). The proportion bound to free Hyp was reduced whereas that bound to protein was increased. The authors gave no explanation for this[<1344>].

4.3.14 General behaviour

Studies of the effect of DMPS on the general behaviour of mice (modified twin screening test) did not show any persistent changes. Only a slight, transient reduction in consciousness was observed on administration of 100 mg DMPS/kg BW[<586>]. The administration of 557 mg/kg (i.p.) did not lead to any abnormal behaviour in rats[<1331>].

4.3.15 Local reactions on parenteral administration

Multiple i.v. or i.m. administration to rabbits did not trigger any visible reactions at the injection site. Only a few changes were observed histopathologically in comparison with the positive controls (thiopental). After paravenous administration, a haematoma developed, which disappeared within half an hour[<1238>] to three days[<586>]. Local reactions were also observed even after intra-arterial injection[<586>]. 15 s.c. injections over 32 days did not trigger any reactions in rats[<64>].

At high i.m. doses (> 84 mg/kg BW), painful local reactions developed in rabbits [<635>]. Necroses and ulceration were described after i.m. and s.c. administration[<69>]. Severe tissue irritation was also observed at the injection site following administration of high-dose injections to rats[<1220>]. Similarly, repeated administration of high-dose s.c. injections (> 228 mg/kg BW) did not trigger any local irritations[<1499>]. Administration of s.c. or i.m. DMPS + dicaptol to calves induced local reactions that persisted for two to three weeks[<119>].

4.4 Mutagenicity

DMPS was tested for mutagenic effects using the Ames test. The mutagenicity test was negative. No increase in mutation rate was found at doses ranging from 0.004 µmol to 2.5 µmol[<69,586,841>]. In mice with inoculated tumours, DMPS did not influence either tumour growth or the formation of metastases[<1161>].

4.5 Reproduction toxicology

The teratogenicity of DMPS was tested in mice, rats and rabbits. 125 mg DMPS/kg BW was administered orally to female rats 5 times a week. They were mated with untreated males after 14, 26 and 60 weeks. Treatment with DMPS was continued during gestation and the lactation period. The pups were observed for 3 months. The number of offspring with the DMPS-treated rats, which were mated after 14 weeks, corresponded to that of the untreated controls. In the animals that were mated after 26 or 60 weeks, the litter sizes were only marginally smaller than those of the control animals. No abnormalities were found in the offspring themselves. The development of all the pups was normal. Only the weight gain of the eight-week old pups from rats that were mated after 26 or 60 weeks' treatment with DMPS was below that of the controls[<1160>].

Mice were treated orally with up to 300 mg/kg BW DMPS for 18 days after mating. None of the animals died and no premature births or miscarriages were observed. The pregnant animals displayed no change in weight development, feed intake, haematological or biochemical parameters or count, deformities, resorptions or gender ratio of the foetuses. A few differences were observed only in the trace element values, but these were, in any case, devoid of embryotoxic sequelae[<202>].

In mice that were treated with DMPS from the 14th day of pregnancy to the end of lactation, neither the dams (feed intake, body weight, lactation) nor the neonates showed any changes. The overall weight gain and the weight of various organs of the litter were identical at the end of the investigation to those of the control animals. The length of pregnancy and the birth were unaffected. The "no observable effect level" (NOEL) for the development of the newborn was 630 mg/kg BW/day, which is many times the usual therapeutic doses of 5 - 40 mg/kg BW/day[<341,345>]. The administration of up to 300 mg DMPS/kg BW between the 6th and 15th day of pregnancy did not lead to significant changes either in the dams or in the foetuses[<202,342,344,1123>].

Rabbits were treated from the 6th to the 18th day of pregnancy with up to 100 DMPS/kg BW i.v. daily. There were no indications of a teratogenic effect. The number and weight of the foetuses corresponded to those of the controls. No deformities were observed[<586>].

Investigations in mice poisoned with arsenic showed that the embryotoxic effects of arsenic were significantly reduced on administration of DMPS[<342,344>]. The number of "normal pregnancies" rose with increasing doses of DMPS and the number of resorbed foetuses subsequently fell. The toxic effects of arsenic were not, however, entirely preventable, even at high doses of DMPS. The danger of arsenic-medicated foetal deformities remained high despite DMPS therapy[<344>]. Similar observations were also made on poisoning with methyl mercury[<342>].

Conclusion:
The laboratory animal experiments carried out gave no indications of embryotoxic or teratogenic effects of DMPS. The harmful effects of heavy metals were reduced. The administration of DMPS can, therefore, also be envisaged during pregnancy in vital indications.

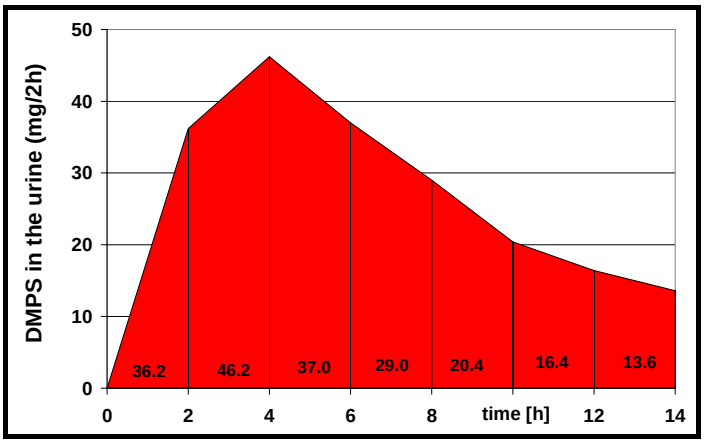
Although DMPS therapy did not adversely affect the development of the young animals during lactation in laboratory animal experiments, lactation should generally be avoided on safety grounds in the presence of heavy metal poisoning.

5 Pharmacokinetics and Metabolism

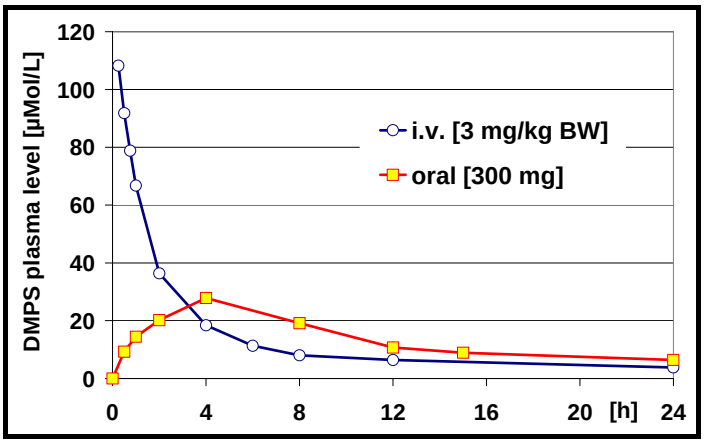
Pharmacological experiments with radioactively labelled DMPS(^{14}C, ^{35}S) and non-labelled DMS were carried out in various animal species (rabbit, rat, hamster, dog, chicken and monkey). In addition, investigations with unlabelled material were carried out in human volunteers.

5.1 Bioavailability

The absorption of DMPS after oral administration from the gastrointestinal tract is rapid<87, 919,1554>. As the absorbed fraction remained the same over a large dose range, uptake is presumably by means of passive diffusion through the intestinal mucosa<87,452>. In rats and rabbits, the peak concentration in the blood was achieved after 30 minutes<868>, and in dogs after 30 - 45 minutes<69,295,919, 1554>. In humans, it lasted 3.7 hours<87>. The absorption rate on oral administration to rats and monkeys was 30 - 40%<70,452,706,919> and in dogs, 50 - 60%<69,706,919,1554>. DMPS was also well absorbed in the hamster<919>. In humans, 45.6%<891> or 59.4%<1516> of the orally administered DMPS was detected in the urine. Bioavailability of 46% was determined by comparing the oral and i.v. administration of DMPS in 4 patients<626>.



Renal excretion of DMPS after oral administration of 400 mg of DMPS to 6 volunteers<1516>



DMPS plasma levels (total DMPS) in human subjects following oral or intravenous administration of DMPS<626,891>

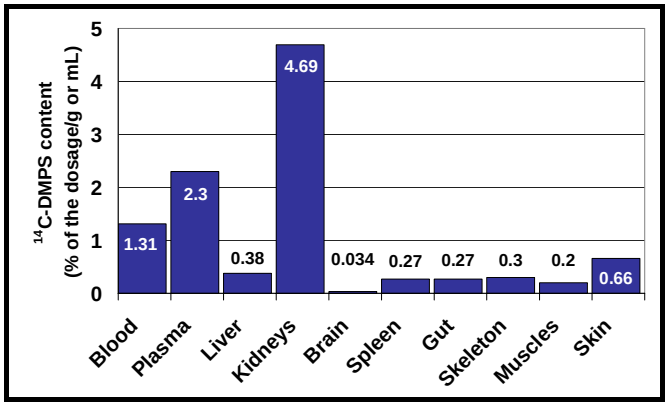
Following s.c. administration of ^{35}S-DMPS, the substance was rapidly absorbed from rabbit subcutaneous cell tissue. After 5 minutes, 32% of the activity was already evident in the blood. The peak blood concentration was reached after 30 minutes<734,735,870>, whereby DMPS was mainly found in the serum<870>. After 2 hours, 30% of the maximum value could still be measured compared to only small amounts after 5 hours and no activity after 24 hours. The half-life was 60 minutes<69,734,735>.

A 2.5-fold higher oral dose of DMPS was required in order to obtain the same effect as parenteral administration in mice poisoned with mercury<455>. With lead<1463> or copper<1159>, a three-fold oral dose had a similar effect to that observed following i.p. administration.

Conclusion:
The availability of DMPS following oral administration was approximately 50 %. This means that around half of the orally administered active substance is not absorbed but remains in the intestine and is excreted in the faeces. It could thus bind to heavy metals present in the intestine and increase their faecal elimination. This effect cannot, however, be significant as the elimination of heavy metals in the faeces is not significantly increased following oral administration compared to parenteral administration of DMPS.

5.2 Pharmacokinetics

After intravenous injection, DMPS achieved peak levels in the plasma and kidneys[<69,87,453>] independently of the dose administered. Similar levels were recorded in the renal cortex and outer medulla of kidney. No DMPS could be detected in the inner medulla[<744>]. Higher doses were also measured in the skin[<453>]. Only low quantities were found in the other organs, especially in the brain[<69,87,453>]. As a lipophilic substance, DMPS is obviously incapable of penetrating the lipid-enriched blood-brain barrier[<667>]. Under experimental conditions, DMPS did not reach a confluent single layer of kidney cells (MDCK-cells)[<956>].



Distribution of DMPS following i.v administration of 0.1 mmol ^{14}C-DMPS /kg to rats[<452>]

Conclusion:
DMPS did not reach the brain. It is, therefore, incapable of mobilising and triggering the excretion of heavy metals deposited in the brain.

The half life of DMPS in various organs is approximately 20 minutes[<452>]. Organ distribution does not depend on the dose[<452>].

From investigations in animals and humans[<1624>], it was initially assumed that DMPS is distributed only in the extracellular space[<30,70,178>]. The intracellular fraction is small[<178>]. Thus in monkeys, the radioactivity in the blood after administration of ^{14}C-labelled DMPS was limited to the plasma[<919>]. In studies carried out with ^{14}C-labelled DMPS in human and rat erythrocytes, 10 – 20% of the DMPS reach the cells; approximately 20% was adsorbed to the outer side of the erythrocytes, partly as a complex with heavy metals.

As demonstrated *in vitro* with human red blood cells, DMPS can penetrate the intact membrane of erythrocytes, presumably by means of a membrane-bound transport system[<667,1227,1558>] and accumulate in the cells[<1227>]. Transepithelial transport of DMPS was also observed in opossum kidney cells[<642>]. DMPS-concentration-dependent steady state was reached after approximately 3.5 hours[<1558>]. On the other hand, the system can also be used to transport DMPS from the cells into the surrounding medium until steady state is restored[<1227,1558>]. Uptake and elimination were inhibited by administration of corresponding anionic transport inhibitors[<1225,1226,1558>]. Low concentrations of sulfate stimulated the transport system and improved uptake[<1227>]. Binding to cytoplasmatic components of the membrane did not take place[<1225,1226,1558>].

	p.o.	i.v.
Urine	25.0	78.1
Faeces	69.3	0.8

DMPS elimination (% of the applied dose) in monkeys following p.o or i.v. administration (n=2)[<919>]

Parameter		Unit	Rat	Dog
Plasma half-life	$t_{½}$	min	19	43
Plasma clearance	Cl_p	mL/(min·kg)	8	2.6
Distribution volume	V_b	mL/kg	217	160
Plasma binding		%		70
Oral administration				
Absorption rate		%	30-40	60
Peak plasma concentration	t_{max}	min		30-45

Pharmacokinetic parameters of DMPS in rats[<452>] and dogs[<69,1554>]

DMPS is excreted relatively rapidly[<494,868>] via the kidneys[<69>]. The half-life in rat plasma was 19 minutes[<452,919>], in mice about 20 minutes[<35,566>], in rabbits about 30 minutes[<735>], in monkeys around 40 minutes[<919>], in beagles 43 minutes[<1269>] and in humans after i.v. administration 30-45 minutes[<87>] or 0.9 ($t_{½}\alpha$) and 19 ($t_{½}ß$) hours[<706>].

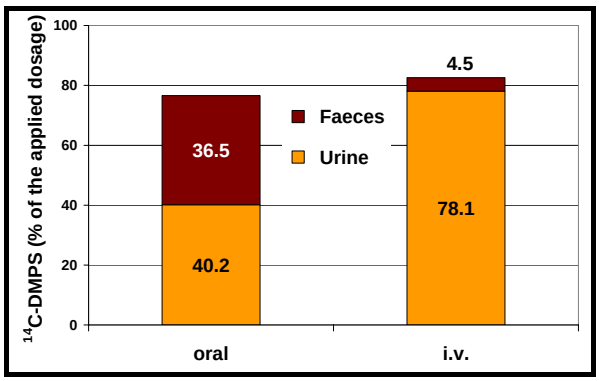
After 6 hours, more than half of the dose administered[452] and after 24 hours, about 90 %[452,919] was excreted in the urine or, after oral administration, also in the faeces.

		Unit	Plasma (oral)	Blood (oral)	Plasma (i.v.)	Blood
Half life	$t_{½}\alpha$ $t_{½}ß$	Hours	9.9	9.1	1.1 27.6	0.9 19.0
AUC		µmol/L	318	148	426	242
Plasma clearance		mL/min			37.8	67.4
Distribution volume		L			39	13
Steady-state concentration		µmol/L			17.7	10.1
Concentration peak	c_{max} t_{max}	µmol/L hours	25.3 3.4	11.9 3.7		

Pharmacokinetic parameters for DMPS in humans (300 mg DMPS oral n=10[52,891] or 3 mg DMPS/kg i.v., n=5[586])

Following s.c. administration to rabbits, the peak concentration in the urine was reached after 1 hour[734]. In rabbits, 91 % of the i.m. administered dose could be detected in the urine within 6 hours[65, 892]. In humans, the highest DMPS concentration in the urine was measured 2[893] or 3[891] hours after oral administration. 80% of the DMPS was excreted in the urine 5-6 hours post-dose[1069]. Overall, in humans, 84 % of the i.v. administered dose was detected in the urine[626]. As in the plasma, the concentration in the organs also fell rapidly[452]. No accumulation of the active substance was observed after repeated dosing[69,494,611,734,735,1269].

DMPS or its metabolites[870] were excreted chiefly via the kidneys[70,611,626, 735,868,870,919]. Renal clearance in isolated rat kidneys was 3.45 mL/(min x g)[744].



24-hour elimination of ^{14}C-DMPS/kg in rats following oral or i.v. administration of 1 mmol/kg[452]

As DMPS showed the same clearance as inulin in investigations in rats, it was originally assumed that DMPS is filtered through the glomeruli[453]. Experiments in chickens, however, indicated that up to about 90% of DMPS is excreted by tubular secretion[743,744,1395,1396]. The tubular secretion of DMPS could be completely inhibited[743,1395,1396] by probenicide or p-aminohippuric acid in chickens and in a dose-dependent manner in rats[743, 744].

Total excretion in the urine	11.3 µg min^{-1} g^{-1}
Tubular secretion	9.75 µg min^{-1} g^{-1}
Glomerular secretion	2.21 µg min^{-1} g^{-1}

Proportion of various mechanisms involved in the renal excretion of DMPS in rats[744]

As the excretion achieves a saturation limit, carrier-mediated transport plays a role[743,1395,1396]. OAT1 and OAT3 in the membranes of the proximal kidney tubules are responsible for the excretion of many anionic molecules[99]. More recent studies have shown that DMPS is actively transported in the proximal kidney tubules cells by means of these polyspecific, organic anion transporters[110,221,643,753,873]. Contrastingly, DMSA does not interact with OAT1[642]. DMPS reacts with both OAT1[99,643] and OAT3 orthologues in humans, mice and rabbits[99,1616]. This applies to monomers as well as to “oxidised“ DMPS[642]. DMPS bound to albumin or Hg^{2+} is not transported[643]. Transport no longer takes place after the cleavage of both SH groups[99]. Oxidised DMPS is mainly transported by OAT3[873], e.g. from rabbits[1616]. DMPS can be reduced[634] in the cell and bind mercury or other heavy metals. Active renal excretion and the possible cleavage of inactive disulfides in the kidneys produce excellent antidote action of DMPS in these organs[743,1395]. A pump mechanism (Mrp2) is also discussed[211a,642,643] on transporting the DMPS-Hg complex thus obtained through the luminal membrane, as indicated in investigations carried out on vesicles containing Mrp2 and Mrp2-deficient rats. Mrp2-deficient animals showed reduced excretion of Hg in the urine and faeces and higher Hg levels in the kidneys compared to the normal control animals following administration of DMPS[211a].

DMPS, but not the disulfides obtained through oxidation or the DMPS mercury complex, can also be actively transported through the basolateral plasma membrane of proximal kidney tubules via the sodium-dependent dicarboxylate transport system NaDC-3[219].

In rats with restricted renal function, a marked reduction in DMPS concentrations in the organs was also observed. Active secretion into the intestines with subsequent excretion via the faeces has been suggested for this[<453>]. The DMPS content also slowly decreased in rats without kidney function: 90% of the administered dose was detected in the body after 1 hour and 77% after 6 hours[<452>].

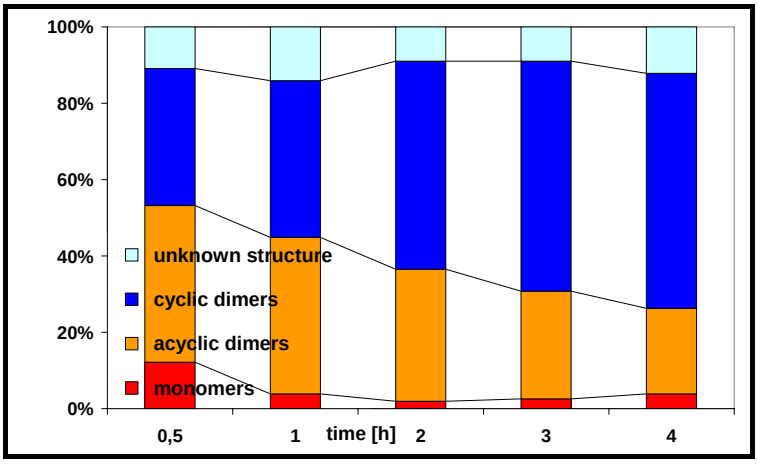
But even in the presence of normal renal function, DMPS is excreted via the bile[<73,1624>]. Contrastingly, no DMSA was detected in the bile[<52>]. Up to 40 % of i.v. administered DMPS could be detected in rat bile. Of this, 92 % was present as di- and higher sulfides. Peak concentrations were reached in the bile 30 minutes after injection[<52, 1624>]. In monkeys, only approximately 1% radioactivity was found in the faeces after i.v. administration compared to 69.3 % following oral administration[<919>].

Conclusion:
In the mobilisation test, DMPS triggers higher mercury excretion rates than DMSA. This may be due to its active transport through the membranes.

5.3 Metabolism

Orally administered DMPS is presumably absorbed unchanged from the gastrointestinal tract in humans. It is rapidly and extensively metabolised[<889,891>] in the blood, plasma and *in vitro*. It is predominantly oxidised to cyclic and acyclic polymeric sulfides[<5,52,611,626,706,743,770a,870,893,919,1395>]. The acyclic metabolites are presumably intermediate products in the formation of cyclic compounds[<870,892>]. Monomer DMPS [<743>] is derived from the metabolites following addition of DTT, a disulfide-reducing agent.

In addition, mixed disulfides with cysteine and glutathione are formed[<888,893,1516>]. Increased cysteine excretion (26.3 %) was thus measured in humans compared to the value prior to the administration of DMPS (from DMPS-cysteine-disulfide)[<626,889,1516>].



Changes in the fractions of various DMPS metabolites (monomers DMPS, acyclic dimers, cyclic dimers) and DMPS of unknown structure in rabbit urine following injection of DMPS[<892>]

In addition, cyclic and acyclic trimers and larger polymers are formed to less of an extent, becoming less prevalent over time, and thus indicating decomposition of these higher molecular forms to more stable dimers and trimers[<642>]. Methylated derivates may also develop[<59,889>]. There was no evidence of metabolic decomposition of DMPS[<450,743,611,706>].
No radioactive carbon dioxide was detected in the exhaled air of rats[<452>] or monkeys[<919>] following injection of ^{14}C-labelled DMPS.

Oxidation presumably takes place spontaneously, enzymatically (catalase, thio-oxidase) or catalytically (Cu^{2+}, Fe^{2+})[<58,893>]. A half-life of 9.9 hours was determined for the oxidation of DMPS in experiments with CHO cells. This was reduced to 2.2 hours in the presence of Cu^{+}[<576>].

Some of the metabolites must possess antidote properties as the concentration of DMPS monomers in the urine is greater than that of the excreted mercury[<891>].

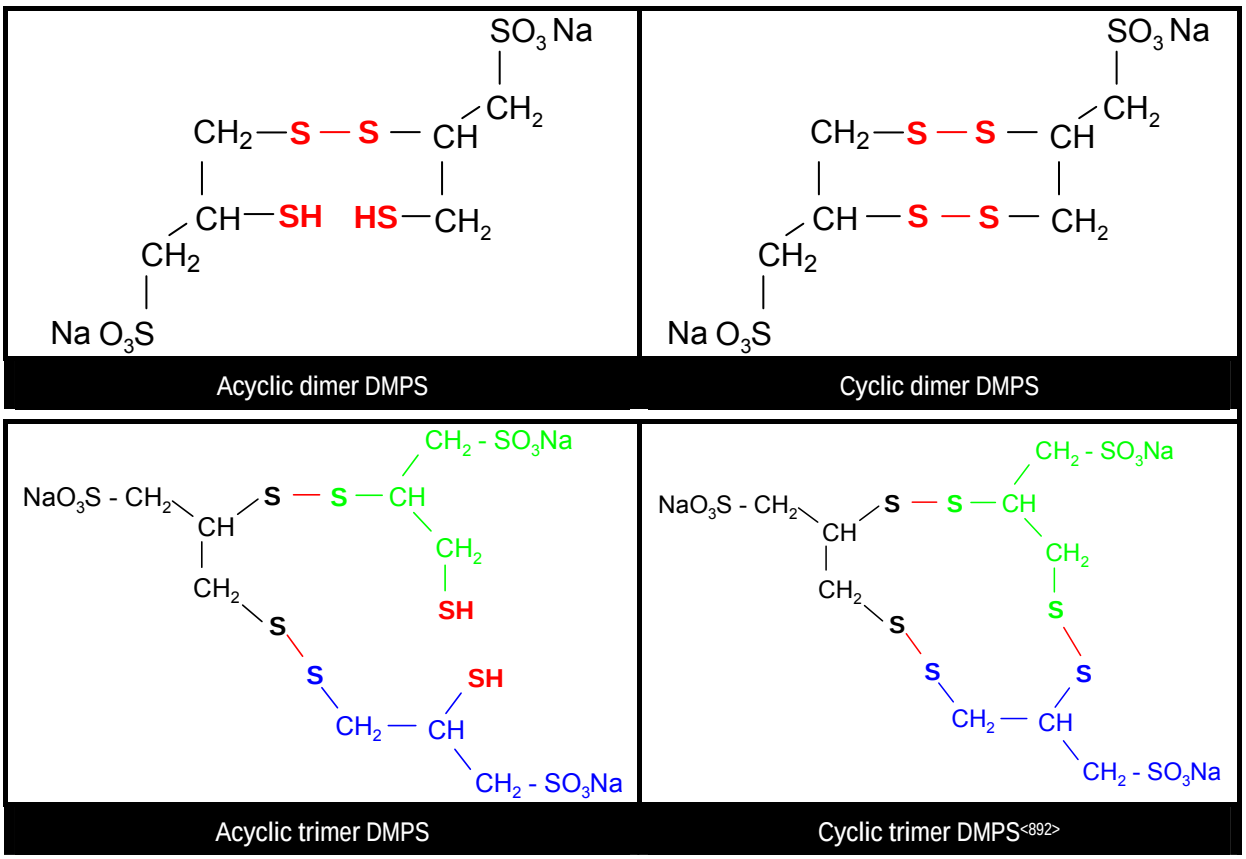
Whereas in humans about 20.6 % of the absorbed DMPS was still present in the blood in an unchanged form ½ hour after oral administration and < 1 %[<889>] after 5 hours, no unchanged DMPS could be detected after 12 hours[<891>]. 12 % unchanged DMPS was still present 15 minutes after i.v. administration[<626>].

The metabolites were also detected in the urine [891,892]. Over time, the fraction of unchanged DMPS in the urine fell[58] whereas that of changed DMPS rose[743,891,892]. Virtually only oxidised DMPS could be detected after 5 hours in rabbits[870,894]. Elevated SH concentrations were recorded in rat urine[460] 6 hours after i.v. administration of DMPS. 69 % of the excreted DMPS were detected as disulfides, 26 % as DMPS and 5 % as other oxidative products (could be transformed into DMPS through disulfide-reducing agents)[743]. The ratio corresponded to values in the blood[891].

In humans, distribution of the metabolites depended on the route of administration of the chelating agent. After i.v. administration, 12 to 20 % of the DMPS monomer[626,889] were excreted compared to only 0.5 % of the monomer after oral administration. Following i.v. administration of DMPS to 3 volunteers, 81.6 % was detected in the urine in the cyclic form, 17.1 % in the acyclic form and 1.95 % as a mixed disulfide with cysteine[888]. Only a small fraction (3.2%) was excreted unchanged in the urine following i.m. administration of DMPS to rabbits. The largest proportion was excreted in the oxidised form[65].

In chicken plasma, the half-life for the oxidation of DMPS was approximately 10 minutes[1395]. Oxidation does not occur as a steady-state reaction. No free DMPS is detected if DMPS-disulphide is administered in the plasma or blood[1395]. Contrastingly, in chickens[1395] and rats[743], it was found that oxidised DMPS was again reduced in the kidneys so that, in chickens, unchanged DMPS was excreted in considerably greater quantities (28 %)[1395]. Reduced glutathione and NADPH appeared to play an important role[1395].

DMPS was also detected in rat bile, which indicates that it reached the hepatic cells. It is chiefly found in the oxidised form in the bile. Unchanged DMPS is present only in small quantities[61].



Conclusion
As in solution, redox reactions play a crucial role in the metabolism of DMPS. No evidence of molecule decomposition could be detected.

5.4 Serum protein binding

In dogs and rats[<1154>] 65 – 70 %[<69,295,611>] and in humans 70 – 90 %[<69,87,295,611,888,889>] of DMPS were bound to plasma proteins. This was confirmed with gel filtration investigations with ^{14}C-labelled DMPS[<1154>]. The bound quantity was dependent on the administered dose[<1294>]. Greatest affinity was shown by α-globulin. However, albumin, transferrin and γ-globulin bound the chelating agent, whereby a steady-state was reached within one hour[<1294>]. In humans, 84 % was bound to albumin, presumably via S-S binding[<889>]. DMPS and oxidised DMPS are firmly bound to albumin[<642,643>]. Because of the rapid renal clearance[<919>] and as plasma clearance and the glomerular filtration rate were the same, the binding of DMPS to serum proteins overall does not appear to be very firm[<89,1294>].

6 Pharmacodynamics

6.1 Therapeutic effects in heavy metal intoxication

After uptake in the body, heavy metals form complexes with various biomolecules such as enzymes or nucleic acids. As these complexes possess different properties than the biomolecules, the enzyme is inactivated or activities change. Heavy metals can be detached from their binding to biomolecules through the administration of appropriate exogenic chelating agents, so that the biomolecules can continue to practise their normal function<667>.

DMPS is a complex-forming agent from the group of vicinal dithiols. It forms stable, mostly aqueous complexes with various heavy metals and metalloids through the two adjacent SH groups. As the chelating agents are excreted more effectively than the metal itself, DMPS promotes the excretion of metals mainly found in the extracellular space. Excretion is predominantly in the urine via the kidneys. A small quantity is also eliminated in the faeces<91>. Once the toxic heavy metals have been removed, the body can start to repair any damage caused if such damage is not already irreversible<666>. No laboratory animal experiments have been carried out to demonstrate the positive effect of chelating therapy in cases of only minor heavy metal contamination<706>.

As a thiol compound, DMPS can also trap oxygen radicals, thus helping to reduce oxidative stress triggered by the heavy metals<158,1116>. DMPS is also an aqueous anti-oxidant, which “intensifies” peroxide radicals, for instance<1613>. A DMPS-mediated reduction in disulfide compounds may also play a role<979>.

The good decorporation action of DMPS was observed in laboratory animal studies and in cell culture experiments<8,69,207,494,706>. DMPS has proved to be an effective antidote for poisoning with various heavy metals<70,207,218>. The binding of the metals in the DMPS complexes already reduces the toxicity of the metal<673,700,706,721>. The complexed heavy metal is no longer available for binding to sulfhydril groups containing essential biomolecules such as enzymes (and thus for the inhibition of these enzymes and the resulting functional disorders of the organs and tissues<260>)<57,91,207,564,734,942,1039,1293>.

Conclusion:
When extrapolating laboratory animal data to humans, it must be borne in mind, especially with acute poisoning, that in animals, treatment generally comprises only the administration of the chelating agent. This has often been administered only once. Further intensive medical care, such as that used in human medicine, is not carried out. The observation period was, in many cases, relatively short, such that slower recovery fromf heavy metal-induced changes could not be established.

6.1.1 Ac - Actinium

Concomitant administration of DMPS did not affect the biodistribution of α-irradiation ^{225}Ac in mice. Depots in the bones, kidneys and blood were unchanged. In Cynomolgus monkeys, the ^{225}Ac levels in the kidney and blood corresponded to those recorded in the control group<648>.

Conclusion:
Based on the few results obtained in laboratory animal experiments, DMPS is unsuitable for the treatment of actinium poisoning.

6.1.2 Ag - Silver

The administration of DMPS increased the LD_{50} of silver chloride in the mouse from 13.6 to 74 mg/kg<1135>. After i.v. injection of silver nitrate, it

AgCl	LD_{50} = 13.6	mg/kg BW
AgCl + DMPS	LD_{50} = 74	mg/kg BW<1136>

prevented the formation of toxic pulmonary oedema and a fatal clinical course in dogs[<1235>].

The inhibition of NaK-ATPase by silver, presumably caused by deposition of the metal on the numerous SH groups of the enzyme, was completely reversible on administration of DMPS. If the enzyme is deposited in liposomes, the administration of DMPS prevented deposition of silver. Already bound silver was mobilised and the functionability of the enzyme was restored[<629>].

Conclusion:
DMPS prevents the fatal clinical course of acute poisoning with silver. No investigations on chronic silver poisoning and the distribution of silver in the body have been carried out.

6.1.3 As - Arsenic

Water-soluble arsenic compounds (e.g. arsenic or sodium arsenite) are very well absorbed orally, by inhalation and through the skin. The distribution volume of arsenic compounds is relatively large. Part of the absorbed arsenic is bound to keratin in the case of only minor storage in the liver and kidneys"[<998>]. In the body, arsenic is, therefore, deposited in the nails (Mees strips) and hair in particular, followed by the skin and lungs[<672>]. Arsenic stored in the skin, keratoprotein and hair can still be detected several weeks after exposure. In the body, the pentavalent compounds are reduced to the more toxic trivalent forms. Other metabolic transformations occur through methylation. The elimination half life starts at 1-2 hours. The half-life is extended to between 30 and 200 hours in a second and third elimination phase. It takes several weeks for the entire amount to leave the body. Excretion is via the urine, faeces, sweat glands and milk. Arsenic can be detected in the urine 5-6 hours after ingestion[<998>].

DMPS is an effective antidote for arsenic poisoning[<73,706,911>]. In animal experiments, DMPS exhibited a good antidote action on poisoning with

- Arsenic (As_2O_3)[<24,67,71,566,721,796,869,871,883,884,886,887,941,942,960,1208,1215,1270,1421,1422>]
- Sodium arsenite ($NaAsO_2$)[<39,67,68,70,72,120,344,601,617,842,895,959,1421,1423>]
- Lewisite (dichloro-(2-chlorvinyl)-arsine)[<68,70,71,635,636,706>]
- Sodium arsenate (Na_2HAsO_4)[<119,120,426,842,886,887,959>]
- Monomethyl arsenate[<886>] and
- Phenyl arsenoxide (Ø-As=O)[<842,959,1208>].

In contrast, on poisoning with arsenic hydrogen, DMPS was inactive[<940,941>] and is contraindicated in this form of poisoning[<69,940>]. This opinion is, however, controversial[<69>]. Tests carried out with erythrocytes showed that haemolysis via AsH_3 is reduced in the presence of DMPS and DMSA[<1200>]. DMPS displayed no effect on dimethyl arsenite[<886>].

6.1.3.1 Investigations in cells and cell cultures

A disulfide group is essential for the functionability of neuronal nicotine receptors in the chicken brain. This can be readily reduced and blocked by the addition of arsenic compounds. On addition of DMS, arsenic-containing molecules were removed from the nicotine receptors[<943>]. The SH functions were again released as a result and the functional groups were reactivated[<49,354,858,1237>]. Reversibility depended on the DMPS concentration[<1237>]. DMPS did not affect the storage of nicotine[<1144>]. Storage was inhibited by reduction with DTT. Subsequent reoxidation reinstated functionability. It is surprising to note that DMPS can carry out this reoxidation. The authors do not discuss the potential mechanism, e.g. intermediate binding of $(DMPS)_{ox}$ by atmospheric oxygen. Reoxidation is blocked by p-aminodichloroarsine. DMPS mobilised the arsenic compound such that reoxidation was once again feasible[<1144>].

The addition of DMPS to cultures did not prevent the herbicidal action of sodium methane arsonate (MSMA). However, the authors do not state whether the access of oxygen to the Petri dishes and thus oxidation of the DMPS was prevented during the 28-day observation period[<385>]. In other studies, DMPS did not change the attachment of Ph-AsO to leukemic cells[<378>].

The pyruvate dehydrogenase enzyme complex is a primary target for arsenic (III) in mammals[<73,617>]. It is unclear as to whether arsenic inhibits enzyme efficacy directly by attachment to dithiol groups or indirectly via induction of reactive oxygen compounds[<50>]. Blockade of the enzyme activity reduced the formation of lactate and pyruvate and prevented gluconeogenesis, which can eventually lead to hypoglycaemia[<73>] (IC_{50} = 0.5 µM Ph-AsO, 7 µM arsenite, 70 µM arsenate[<73,958>]). The addition of DMPS abolished the blockade both *in vivo* and *in vitro*[<68,617,793,959,960,1213,1421,1422>]. The individual optic isomers of DMPS display the same efficacy[<617>]. When administered prophylactically, DMPS prevented this inhibition[<617>]. After greater intervals between arsenic and DMPS administration and thus a longer duration of action for arsenic, the changes were, however, irreversible[<1212>].

DMPS reduced arsenic-inhibited gluconeogenesis *in vitro* in isolated rat tubules. Oxidised DMPS was not capable of doing this[<960>]. Inhibition of the thioredoxin reductase enzyme containing selenium by PAO was abolished by DMPS[<658>].

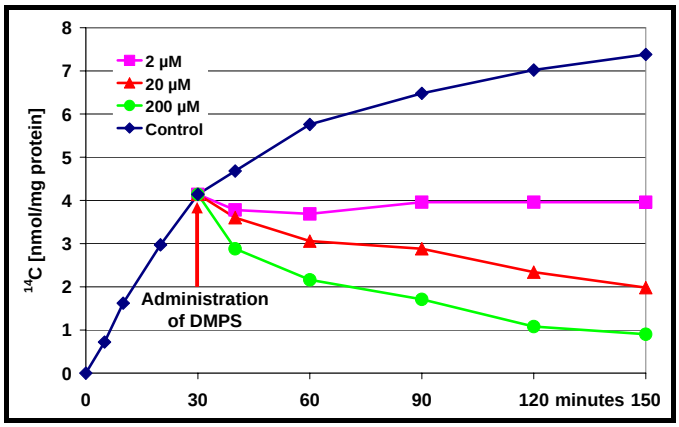
Phenylarsine oxide PAO inhibited platelet aggregation triggered by collagen or thrombin, for instance. If DMPS were given before or with the arsenic compound, it prevented this effect of PAO[<391,521>]. Administration of DMPS after PAO was, in contrast, ineffective. DMPS obviously reduced the uptake of PAO in the thrombocytes, but is apparently unable to mobilise arsenic compounds absorbed intracellularly[<521>].

The toxic effects of lewisite in cell cultures of human keratinocytes were completely reversible following the immediate addition of DMPS. DMSA displayed the same efficacy[<704>]. DMPS prevented the toxic damage of mono-substituted organic arsenic compounds at confluent single layers of kidney cells (MDCK cells)[<989>].

In-vitro, DMPS removed arsenic from its binding to enzymes or prevented enzyme blockade by PAO[<156,190>] or sodium arsenite[<693>], thus restoring activity.

In the green algae, *Acetabularia acetabulum*, the addition of DMPS prevented mono-methyl arsenic(III)-induced death[<332,1451>].

Increased attachment of arsenite to sediment proteins in guinea pig brain homogenisate or neuroblastoma cells (Neuro2a) occurred in the presence of BAL, DMPS or DMSA. The precise mechanism involved is not known. The formation of dithiol-protein complexes is considered a possibility. As regards the clinical relevance of the effects observed, the author states that, since DMPS and DMSA cannot cross the blood-brain barrier, they are not expected to increase the binding of arsenite to central nervous system proteins *in vivo*[<995,996>].



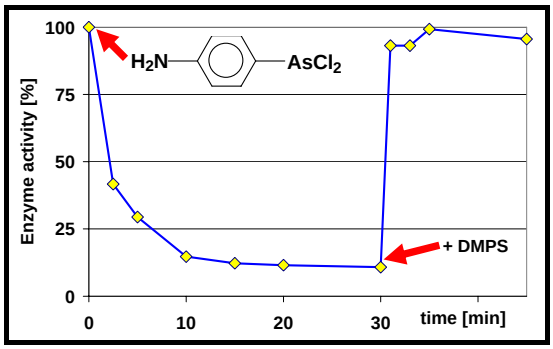
Effect of DMPS on ^{14}C-PhAsO [2 µM] content in MDCK cells[<845>]

DMPS prevented the intake of PAO in the confluent single layer of kidney cells (MDCK-cells) or mobilised the PAO absorbed[<844,945,956>]. The blockade of glucose uptake in the cells was consequently eliminated. The effect of DMPS, however, occurs more slowly than that of BAL. Whereas BAL took effect within 10 minutes, DMPS required 1 – 2 hours[<844>]. The toxic effects on cell viability were reduced. Concomitant administration of BAL and DMPS proved to be the most effective (synergistic effect). Combination of 2 µM BAL and 198 µM DMPS were as effective as 200 µM BAL. Traces of BAL obviously work as an As shuttle through the cell membrane[<844>].

DMPS did not affect the uptake of diphenyl arsenic acid (DPAA $Ø_2$-As(OH)) in HepG2 cancerous liver cells. Contrastingly, it completely blocked the uptake of the glutathione-DPAA-Adduct and thus prevented its cytotoxic effect[<1064>].

In vitro, the addition of DMPS abolished the blockade of the enzyme lecithin cholesterol acyltransferase by p-aminophenyl arsenic dichloride within one minute[<654>]. Pre-treatment with DMPS prevented the effect of PAO on the Ca^{2+}-metabolism of rat neutrophilic granulocytes[<1530>].

The DMPS and diphenyl arsenic acid ($Ø_2$-AsO_2H)) complex displayed cytotoxic effects on HepG2 cells. Almost all of the cells perished. Conversely, the two individual substances were tolerated. A highly reactive compound is obviously formed from arsenic binding with DMPS. This effect did not occur with arsenite. In this instance, DMPS prevented cytotoxic effects[<1065>].



Effect of p-aminophenyl arsenic dichloride and DMPS on the enzyme activity of human lecithin-cholesterol-acyltransferase *in vitro*[<654>]

In contrast to DPA or DMSA, in the presence of DMPS or BAL, As^V was reduced to As^{III} in cytosols taken from rat liver[<983>]. A similar effect was observed with solubilised erythrocytes[<982>].

The As compounds induced cell damage in *in-vitro* experiments involving various cell lines and different As(III) compounds. The concomitant administration of high concentrations of DMPS, DMSA or DTT reduced the damage. At low concentrations, however, increased toxicity of As compounds was observed[<650>]. The authors provide no explanation for the mechanism involved and do not discuss the clinical relevance.

6.1.3.2 Lethality

In cases of poisoning with arsenic compounds, more animals survived with oral[<68,71,868>] or parenteral[<68,71,72,795,887,942,960,1421,1423>] DMPS treatment. In mice and rabbits, the LD_{50} for arsenite and arsenic was increased more than 4-fold[<70,72,721,789,1422>]. The therapeutic dose of DMPS, with which 50 % of animals survived normally fatal poisoning (ED_{50}), fluctuated between 12.6 and 15.1 mg/kg BW on intoxication with sodium arsenite[<65,68,70,72,617>]. It was the same for both optic isomers of DMPS[<69,617>]. There was no difference in terms of effect compared to the racemate[<68>].

	LD_{50} As_2O_3 (mg/kg)
Control	16.8
DMPS	69.9
DMSA	74.4
DPA	15.4
NAPA	17.3

Influence of various CA (i.m. immediately and after 90 min) on the LD_{50} of $NaAsO_2$ (s.c.) in mice[<72>]

Due to the rapid toxic effect of arsenic, the effect depended on the time between ingestion of the arsenic and administration of DMPS[<789>].

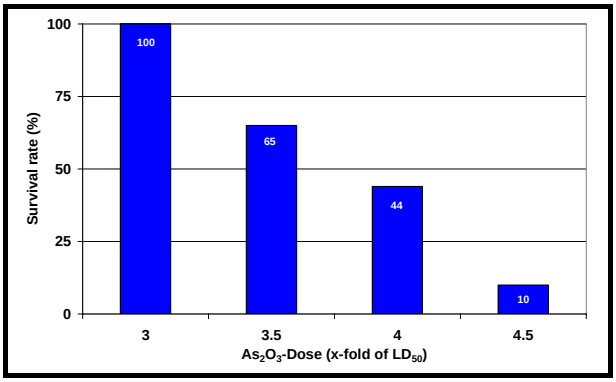
A pre-requisite for the efficacy of DMPS was the presence of two free SH groups. If these were blocked, e.g. by oxidation or reaction with carbon disulfide, the compounds were no longer effective[<959,960>].

6.1.3.2.1 Arsenic(III)

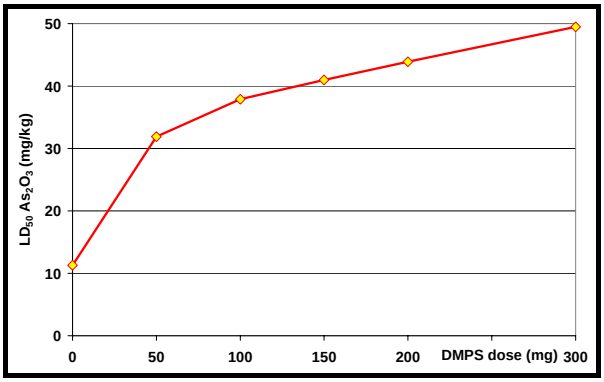
Treatment with DMPS within one hour of exposure prevented the lethal effects of arsenic (As_2O_3), sodium arsenite ($NaAsO_2$), calcium arsenite ($Ca[AsO_2]_2$), Schweinfurt or Paris Green ($Cu(CH_3COO)_2 \cdot 3Cu(AsO_2)_2$) or Neosalvarsan[<69>].

After 2 i.p. injections of DMPS (immediately and after 90 minutes), the LD_{50} of $NaAsO_2$ increased more than 4-fold from 0.129 mmol/kg to 0.538 mmol/kg in mice[<70>]. The effect of DMPS on the survival rate was dose-dependent[<70>]. At sufficient doses, all animals survived whereas all of the control animals died. When treatment was initiated rapidly with higher dose levels of DMPS, all 10 rabbits and 11 out of 20 rats survived arsenic poisoning with 2-fold LD_{100}[<942>]. Seven out of 10 mice survived a dose of 20 mg/kg BW whereas all of the control animals died within 3 hours (LD_{99} = 13 mg/kg BW)[<960>]. The survival times were also prolonged[<71,959>]. Loss of efficacy due to delayed onset of treatment of up to 2 hours after poisoning could basically be counteracted by increasing the dose of DMPS measured in the survival rates or increase in the LD_{50} of the arsenic

compound[566,1423]. When treatment was initiated 2 hours after administration of $NaAsO_2$, 85 % of the mice survived whereas all 20 animals in the control group died[70].



Dependence of the survival rate of mice on the As_2O_3 dose (x-fold LD_{50}) when treatment is started immediately with 200 mg DMPS/kg[721]



Dependence of the LD_{50} of As_2O_3 in mice on the dose level of DMPS when treatment is initiated immediately[721]

	Start of treatment	
	Immediate	After 30 min
Control	11.3	11.3
BAL	24	22.6
DMPS	48	29.4
DMSA	96	27.1

LD_{50} of As_2O_3 (s.c., mice) on immediate or administration of BAL, DMPS or DMSA (i.p.)[795,1421]

In cases of extremely severe poisoning, e.g. with six times the LD_{50} of arsenic, a therapeutic effect could still be achieved with DMPS when the latter was administered at a high starting dose and re-administered at half-hourly intervals thereafter[721]. Only 1 of 7 mice survived following oral administration of DMPS 30 minutes after s.c. injection of As_2O_3[792]. In contrast to DMPS or DMSA, DPA did not increase the survival rate of mice following acute As_2O_3 intoxication[70,793]. NAPA was also ineffective[70,1423].

DMPS (mg/kg)	Survival rate (%)
0	0
16	79
32	88
57	100
91	100
183	100

Survival rate of mice with arsenite poisoning when treatment with DMPS is initiated immediately[70,1423]

DMPS (mg/kg)	Survival rate (%)
0	0
27	0
57	85
114	80
160	80
228	89

Influence of prophylactic administration of DMPS on survival rate in acute poisoning with $NaAsO_2$[70,1423]

Time (min)	Increase in LD_{50}
0.5	4.4
5	3.5
15	2.5
30	2.6

Increase in LD_{50} of As_2O_3 compared with the untreated control group in relation to the time between poisoning and the start of therapy[566,789]

Following therapeutic administration of DMPS, the prophylactic use of DMPS (15 minutes before administration of the poison) also prevented the fatal outcome of sodium arsenite intoxication (LD_{100})[70,1423]. There was no significant difference between the D and L forms of DMPS in this respect[617].

Time to start of treatment (min)	Survival rate (%)
0	100
60	84
90	95
120	84

Dependence of survival rate on the time between poisoning and the start of treatment (all untreated animals died)[70,1423]

DMPS also displayed positive effects with monomethyl arsenite (MMA^{III}). DMPS had no effect on dimethyl arsenite (DMA^{III})[885]. The phenyl arsenoxide (Ø-As=O)-induced inhibition of gluconeogenesis was not eliminated and the survival rates did not increase[959].

DMPS slowed down the death of green algae by MMA^{III}[899]. In earthworms, DMPS increased the LD_{50} for arsenite from 191 to 250 µmol/kg BW, and for phenyldichloroarsine from 189.5 to 287.7 µmol/kg BW[842].

6.1.3.2.2 Arsenic(V)

DMPS had a positive effect on acute poisoning with arsenate in mice[<885,887>]. Treatment with DMPS within one hour of exposure prevented the lethal effects of sodium arsenate (Na_3AsO_2)[<69>]. In earthworms, DMPS increased the LD_{50} for arsenate from 519.4 to 841 µmol/kg BW[<842>].

Conclusion:
In animals, DMPS increased the survival rates following poisoning with both As(III) and As(V) compounds. It is, therefore, important to initiate treatment as soon as possible and to administer a sufficiently high dose.

6.1.3.2.3 Lewisite

DMPS (mg/kg BW)	Survival rate (%)
0	0
45.6	67
91.3	100

Survival rates of rabbits following administration of lewisite with prophylactic, oral DMPS therapy (initiated 45 minutes before administration of the warfare agent)[<68,71>]

DMPS has anti-lewisite properties[<68,70>]. It reduced the lethal effect of lewisite[<70,71,706>] and increased the survival rates[<68,70>]. Efficacy in terms of survival rates fell in the following order: DMSA > DMPS > BAL[<70>]. Following percutaneous administration of the warfare agent, the LD_{50} in rabbits as a result of DMPS administration more than doubled from 5.3 to 13.0 mg/kg BW[<635>], and increased from 1.8 to 2.2 mg/kg BW after i.v. administration[<636>]. The survival rate could be increased from 6 to 83 % if DMPS treatment were initiated immediately (repeated s.c. administration of 7.9 to 15.7 mg/kg)[<68,71>]. As lewisite had a rapid onset of efficacy following parenteral administration, swift introduction of treatment was required[<636>]. All of the rabbits survived when the first high dose of DMPS was given prophylactically prior to administration of lewisite[<68,71>]. Lewisite-induced lung and liver damage was reduced[<635>]. DMPS alleviated the immunotoxic effects of acute lewisite poisoning in rats. However, the effect was not entirely reversible[<1589>].

Lewisite mg/kg BW	DMPS mg/kg BW	Survival rates 1d	2d	7d
10	0	4/9	1/9	0/9
10	8.4	6/6	4/6	3/6
10	33.6	6/6	5/6	5/6
14	33.6	5/6	1/6	1/6
20	33.6	6/6	2/6	2/6
28	33.6	6/6	0/6	0/6

Survival rates of rabbits depending on the dose of lewisite (percutaneous) and DMPS (i.m.) administered[<635>]

Conclusion:
In laboratory animal experiments, DMPS reduced the lethal effect of lewisite. Treatment should, however, be initiated as early as possible due to the rapid onset of action of the warfare agent. The prophylactic use of DMPS is even more beneficial.

6.1.3.3 Excretion

6.1.3.3.1 Distribution and excretion

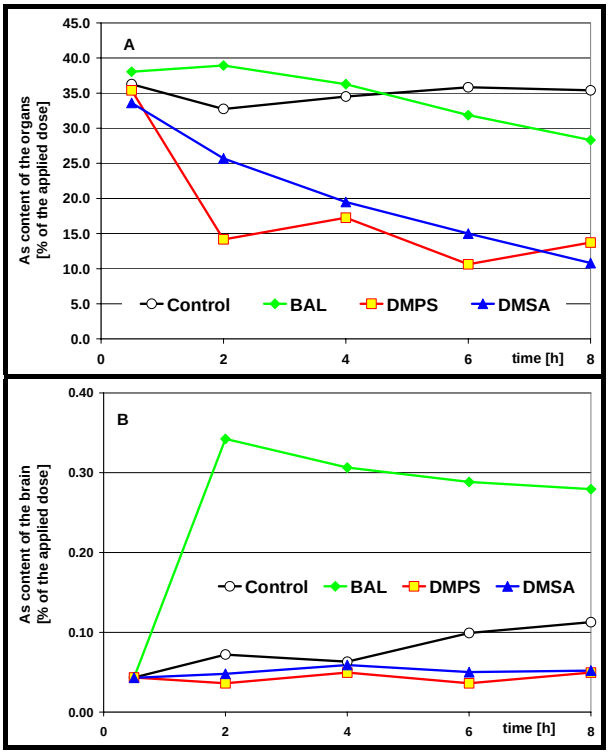
DMPS accelerated the excretion of arsenic[<8,791,868,871,883,884,886,895>], whereby elimination in the urine and faeces was increased[<791>]. Arsenic levels in the organs and tissues were reduced[<789-791,794,796, 871,1270>]. Four hours after DMPS administration, 8 %[<791>] or 9 %[<796>] of the arsenic dose administered could still be detected in the body. In the untreated controls, the burden was still 50 %[<791>] or 28 %[<796>]. After 12 hours, 40 % of the arsenic administered remained in the control group and <10 % in the DMPS group[<791,796>]. DMPS was more effective than DMSA[<791>]. The combination of DMPS and DMSA displayed no synergistic effects[<789,1270>].

	As level
Control	28 %
BAL	16 %
DMPS	9 %
DMSA	12 %
DPA	28 %

Total body As content in mice 4 hours after s.c. administration of As_2O_3 (% of the dose applied)[<796>]

6.1.3.3.1.1 Arsenic(III)

Chronic exposure through the addition of As(III) to the drinking water triggered elevated arsenic levels in the blood, kidneys, liver and brain of male rats. Subsequent treatment with DMPS and DMSA significantly lowered levels in the blood, liver and kidneys. DMSA was more effective than DMPS. The increased value in the brain was unchanged by both chelate-forming agents. Changes in the biochemical parameters tested, e.g. neurotransmitters in the brain, did not improve. Similarly, the biochemical liver, blood and plasma parameters were unchanged <1458>.



Influence of oral administration of BAL, DMPS or DMSA on arsenic concentrations throughout the body [A] and brain [B] of mice after s.c. administration of As_2O_3 <1270>

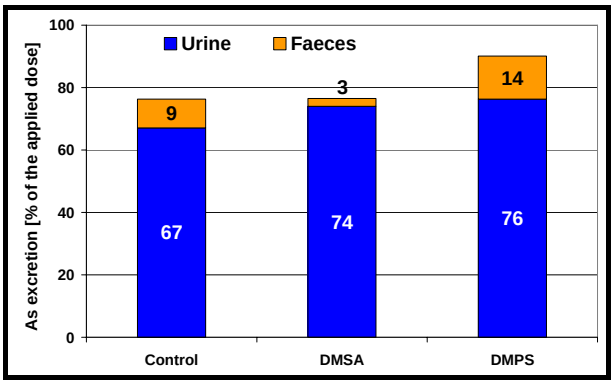
On concomitant single i.p. administration of DMPS or DMSA and As_2O_3, both significantly increased the elimination of As in the urine on day one whilst elimination on days 2 and 3 mirrored that observed in the control animals <886>. DMPS increased both renal and faecal elimination in mice and rats <1584>.

Rats received an oral suspension of oral gallium arsenide over 3 x 5 days. This led to increased gallium and arsenic values in the blood, liver, kidneys, brain and spleen. Subsequent i.p. administration of DMPS triggered a statistically significant decrease in concentrations, except in the brain. DMSA displayed less efficacy in all organs <423>.

In perfusion experiments conducted on the rat jejunum, the addition of DMPS mobilised lewisite, phenyl arsenic oxide and sodium arsenite such that the arsenic content in the intestine was reduced. In contrast to BAL and DMSA, the physiological parameters (water- and glucose uptake) were consequently reversible <956>. As_2O_3 exposure inhibited glucose- and water uptake in the rat jejunum. This inhibition was not observed on concomitant perfusion with DMPS. With subsequent administration of DMPS, the As content in the mucosa was reduced without, however, significantly increasing the absorption function <624>.

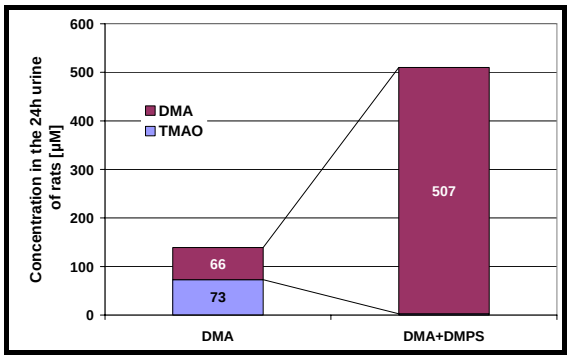
6.1.3.3.1.2 Arsenic(V)

The immediate administration of DMPS after consumption of sodium arsenate increased the elimination of arsenic both in the faeces and in the urine compared to untreated animals. DMSA increased the renal elimination of arsenic but reduced elimination in the faeces such that total elimination remained unchanged compared to the control group <938>. With monomethyl arsenic acid, neither antidote increased elimination <939>.



As elimination within 40 hours of s.c. administration of $NaAsO_4$ and DMPS or DMSA (immediate i.p.) as a % of the dose administered <917>

Rats that ingest feed containing DMA^V excrete more arsenic in the urine on concomitant oral administration of DMPS. DMA^V-induced hyperplasia of the bladder epithelium was prevented by DMPS <1081>. Histologically, findings resembled those recorded in the control group <90, 283>. DMPS inhibited the biomethylation of As^V. Rats that ingested DMA^V $[CH_3)_2As^VO(OH)]$ in feed, eliminated unchanged DMA^V and trimethylarsenic



Concentration of arsenic metabolites DMA^V and TMAO in 24-hour urine after oral administration of DMA^V or DMA^V combined with DMPS<861>

oxide $[CH_3)_3As^VO]$ (TMAO) in approximately the same concentration. If DMPS was also added to the feed, arsenic would be found chiefly in the form of unchanged DMA^V in the urine.

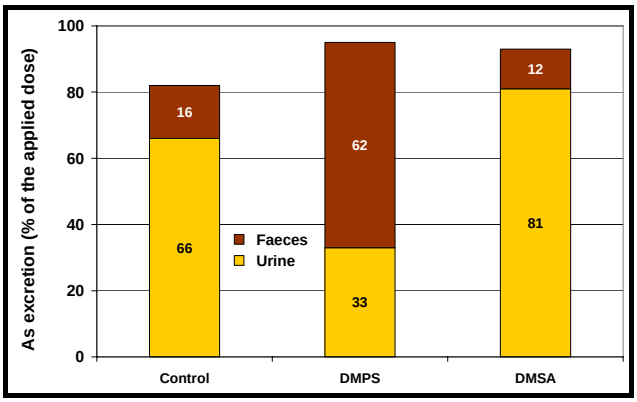
After chronic Na_2HAsO_4 exposure, oral administration of DMPS or DMSA increased As elimination in rat urine and reduced As levels in the blood, liver and kidneys. Various biochemical parameters improved. Histopathological changes in the liver and kidneys partly regressed. DMSA was more effective than DMPS<426>. This can probably be attributed to greater oral bioavailability.

		DPA	BAL	DMPS	DMSA	DMPS+ DMSA
Liver	Mouse	90	68	22	42	32
	Guinea pig	121	70	24	7	7
Kidneys	Mouse	127	56	30	40	26
	Guinea pig	159	57	33	43	41
Lungs	Mouse	120	65	19	35	30
	Guinea pig	126	72	29	57	37
Brain	Mouse		253	52	67	53
	Guinea pig		189	40	63	42
Testes	Mouse		159	23	50	13
	Guinea pig		69	47	66	93
Skin	Mouse	88	47	21	38	30
	Guinea pig	113	82	46	78	51
Muscles	Mouse	94	55	43	47	32
	Guinea pig	113	84	47	45	38
Blood	Mouse	111	77	50	56	35
	Guinea pig	150	94	56	131	74
Total body	Mouse	102	57	27	45	
	Guinea pig	129	73	36	46	

As content of murine or guinea pig organs following single administration of various CA [0.7 mmol/ kg i.p.] 30 min. after acute poisoning with As_2O_3 [0.043 mMol/kg s.c.] (% of untreated controls)<789,793>

6.1.3.3.1.3 Urinary excretion

DMPS increased As excretion in the urine<69, 426,886,1209>. Reduced excretion was observed in an investigation conducted in mice. The DMPS-mediated increase in arsenic elimination in the urine could only be measured within 24 hours with one DMPS treatment<67>. If DMPS were administered 24 hours after poisoning, renal elimination would remain unchanged<886,887>.



24-hour elimination of arsenic in mice following administration of $NaAsO_2$ (s.c.) and concomitant administration of DMPS or DMSA (i.p.)<884>

6.1.3.3.1.4 Faecal excretion

Faecal excretion was high in most investigations<73,884,1208,1209>. In one study, DMPS (i.p. or oral) did not increase arsenic elimination in the faeces in guinea pigs<1209>. After i.v. administration of $NaAsO_2$, i.p. administration of DMPS increased the As content of rat bile more than 6-fold. DMSA and DPA were devoid of effect<24>.

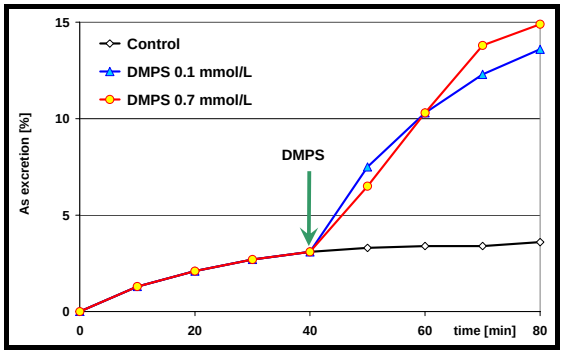
	0.1 mmol/kg antidote	0.7 mmol/kg antidote
Control	8.3	8.3
BAL	10.6	19.2
DMSA	13.6	28.7
DMPS	43.0	43.0

Elimination of arsenic in the bile (% of the dose) in guinea pigs poisoned with arsenic<1210>

Only small quantities of arsenic were directly secreted into the intestine<1207>. DMPS increased the excretion of the semi-metal in the bile<24,78,1207,1210-1213,1215>. (BAL < DMSA < DMPS)<1215>. The concentration ration of arsenic in the bile to arsenic in the blood was increased by DMPS from 40 to more than 200<1210>.

Perfusion experiments in isolated livers of guinea pigs poisoned with arsenic showed that arsenic excretion could not be increased with higher doses of DMPS. An active transport mechanism was thus assumed for the excretion[<1210-1215>].

The increase in arsenic excretion in the faeces (+ 240 %) was lower than the rise in arsenic concentration in the bile after administration of DMPS (+ 540 %)[<1208>]. Enterohepatic circulation must, therefore, be assumed for the complex[<1210-1215>].



Cumulative elimination of As in the bile (% of the quantity of As administered). The arrow marks the time at which DMPS (0.1 or 0.7 mmol/L) was added to the perfusion solution[<1211>]

The As excretion in the faeces was not increased by additional oral administration of active charcoal, salt, DMPS or cholestyramine. If the antidote and cholestyramine were administered orally in addition to the parenteral administration of DMPS, then the faecal elimination increased three-fold. This observation was explained by the formation of a negatively charged DMPS-arsenic complex in the intestine, which binds to the positively charged anionic exchange resin, cholestyramine. This interrupted the enterohepatic circulation and increased excretion in the faeces[<956,1208-1210>].

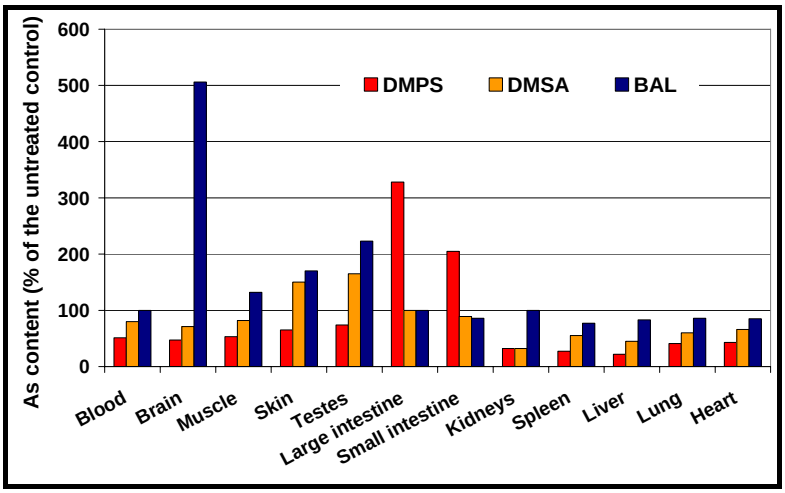
Treatment		Arsenic	
i.p.	Oral	Faeces	Urine
NaCl	NaCl	3.6	14.0
DMPS	NaCl	8.2	21.6
DMPS	Cholestyramine	6.6	19.5
DMPS	DMPS	6.0	33.8
DMPS	DMPS+Cholestyramine	18.5	33.4

Effect of different treatments on the faecal and renal excretion of arsenic in guinea pigs poisoned with arsenic[<1209>]

6.1.3.4 Distribution of arsenic in the body

6.1.3.4.1 Blood

DMPS lowered As levels in the blood compared to the untreated control animals[<421,789,790,793,794,1270>]. They nevertheless exceed normal values[<421>].



Effect of the oral administration of CA 30 minutes after s.c. administration of As_2O_3 on the As content in murine organs (2 hours after administration of As)[<1269>]

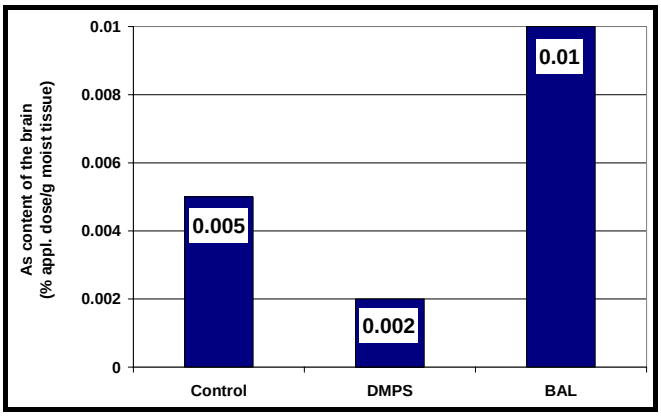
In rats, the biochemical parameters for oxidative stress in the blood following chronic arsenite poisoning were partially to completely reversible with DMPS. The arsenic-induced changes in the biochemical parameters in the blood and urine (δ-aminolaevulinic acid dehydratase, zinc protoporphyrin, ALA) improved during treatment with DMPS. Disorders affecting the glucose balance reverted to normal. Prophylactic administration of DMPS prevented these disorders[<120>]. DMPS could prevent the reduction in ALAD activity in mice[<1457>].

The SH groups of the serum proteins blocked by arsenic, were again freed by DMPS. If DMPS was administered concomitantly with arsenic, there was no reduction in free SH groups in the serum[<869>].

6.1.3.4.2 Brain

As levels were lowered by DMPS compared to the untreated control animals[<65,68, 601,789-791,794,796,1270>], but still exceeded normal values[<421>]. In another study, DMPS had virtually no effect on the As content of the brain[<1270>]. In contrast, BAL led to an accumulation, which was 2.5 times that of the controls[<65,601,791,1269,1270>].

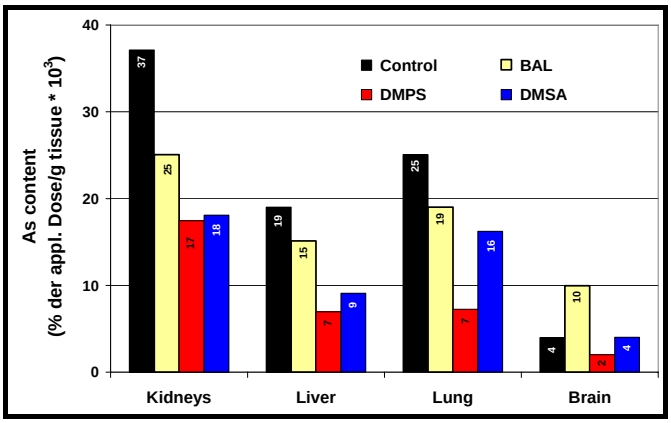
In rats, the biochemical parameters for oxidative stress in the brain following chronic arsenite poisoning were partially to completely reversible with DMPS[<120>].



As levels in the brain (% dose administered/g moist tissue) of rabbits which received DMPS or BAL 1 hour after $NaAsO_2$ <52,601>

6.1.3.4.3 Liver

As levels in the liver were reduced during administration of DMPS[<68,789,791,793,794,796,1270>]. In another study, As levels in the liver were unaffected[<887>]. In a murine liver homogenisate, As(III) reduced the activity of AST and increased that of ALT and AP. The addition of DMPS reduced this effect. *In vivo,* the injection of As(III) increased the activity of enzymes γ-GT, AST, ALT and AP. Single administration of DMPS [30 minutes after As(III) injection] reduced the effect of As(III) on γ-GT. The effect on the other enzymes was insignificant. The authors nevertheless conclude that DMPS prevents acute biochemical/clinical symptoms in the liver following administration of arsenic[<1457>]. Similarly, lewisite-induced pathological changes in the liver were reduced in rabbits[<635>].



Effect of dithiols on ^{74}As levels in rabbits. ($NaAsO_2$ s.c., 1 hour later CA i.m.)[<68>]

6.1.3.4.4 Kidneys

DMPS reduced the As load in the kidneys[<68,789,791,793,794,796, 1270>]. In another study, As levels in the kidneys were unaffected[<887>]. The administration of As(III) increased the activity of the AST, ALT and AP enzymes in the kidneys compared to the control animals. Single administration of DMPS [30 minutes after As(III) injection] reduced this effect. The authors thus conclude that DMPS prevents the onset of arsenic-induced, acute biochemical/clinical symptoms in the kidneys[<1457>].

6.1.3.4.5 Testes

DMPS reduced the As burden in the testes[<65,790,793,794,796,1270>]. No effect was observed in mice[<65>]. In contrast, BAL triggered higher As levels in the testes[<791>].

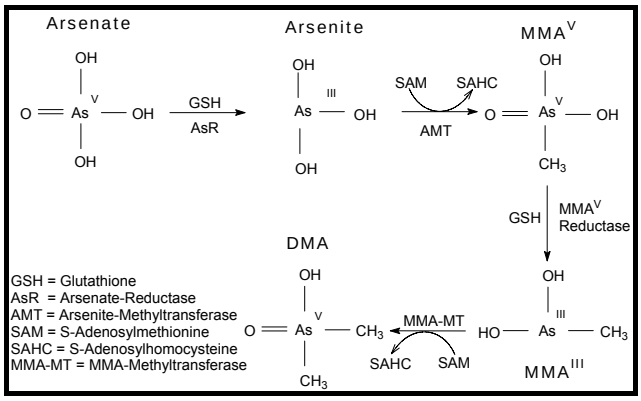
6.1.3.4.6 Other organs

In perfusion experiments, DMPS reduced the arsenic content in the rat jejunum[<956>]. DMPS reduced the As load in the spleen[<790,794,796>], lungs[<68,789,790,793,794,796,1270>], skin[<789,790,793,794,796,1270>] and muscles[<789,790,793,794,796>].

Conclusion:
DMPS increased the excretion of arsenic in both the urine and the faeces. The metalloid content was reduced in all organs, whereby DMPS was almost always superior to DMSA. In contrast to BAL, DMPS did not lead to an accumulation of arsenic in the brain. Laboratory animal experiments show that, of the known antidotes, DMPS is the most effective in the treatment of arsenic poisoning.

6.1.3.5 Metabolism of arsenic compounds

The various arsenic compounds vary in terms of toxicity. Thus, As(III) is more toxic than As(V), and methylated arsenic is less toxic than inorganic arsenic compounds [As(V) < As(III) < AsH_3][<344,419,895,960>]. Toxicity increases in the following order: arsenite > arsenate > mono methyl arsenate MMA > dimethyl arsenite DMA[<419>]. While As(III) reacts preferentially with sulfhydryl groups and thus inhibits the catalytic activity of enzymes, e.g. pyruvate dehydrogenase[<1419>], $[AsO_4]^{3-}$ can be incorporated in the metabolism in the place of phosphate $[PO_4]^{3-}$ [<63,385>]. Stepwise methylation in the liver is, therefore, an important process in the physiological detoxification of As(III) and As(V) compounds[<328,895>].



Biotransformation of inorganic arsenic[<50>]

	Control	DMPS	DMSA
Arsenite $[AsO_2]^-$	1	6	6
Arsenate $[AsO_4]^{3-}$	18	43	14
Methyl arsonate $[CH_3\text{-}AsO_3]^-$	17	28	36
Dimethylarsenite $[(CH_3)_2AsO_2]^-$	52	18	32
Unknown As	12	5	9

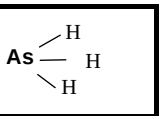
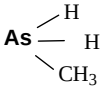
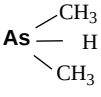
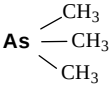
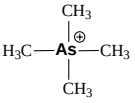
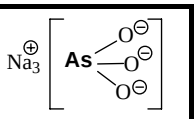
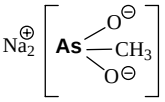
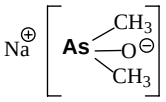
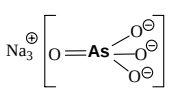
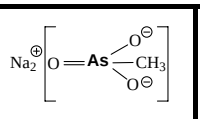
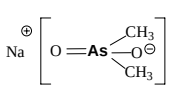
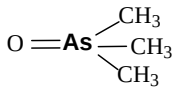
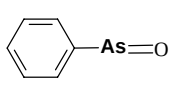
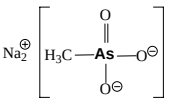
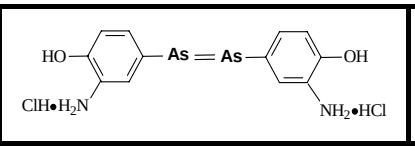
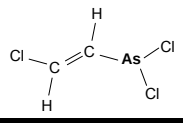
Fractions of the excreted arsenic compounds (%) in the 24-hour urine of rabbits given $NaAsO_2$ and, one hour later, DMPS or DMSA i.m.[<67,895>]

Determination of the metabolites of the administered arsenic compounds in the urine showed that DMPS influenced the biotransformation of arsenic. The precise mechanism of action has not yet been elucidated[<67,895>]. In tests with rat liver cytosols, DMPS increased the reduction of As(V) to As(III) via purine-nucleoside phosphorylase. BAL was clearly more effective whilst DMSA was devoid of effect[<522>]. Rats that ingested feed containing DMA(V) eliminated mainly DMA(v) in the urine following concomitant administration of DMPS whereas TMAO was mainly found in the control animals[<283>].

In *in-vitro* investigations with rabbit liver cytosols, the addition of DMPS reduced the formation of DMA(V) in a dose-dependent manner[<328>]. Tests carried out with human liver cytosols showed that this reaction is not enzymatically controlled. As(III) is already methylated by methylcyanocobalamine in the presence of GSH. Small quantities of DMA are also formed. DMPS stimulates this reaction like sodium selenite[<1594>]. However, the authors make no reference to the mechanism involved.

In experiments with rabbit[<328,329>] or rat liver [<217>] cytosols, the addition of DMPS inhibited the methylation of As(III) and As(V) compounds. With DMSA, this effect occurred only at higher concentrations[<217>]. In patients chronically poisoned with arsenic through drinking water, increased monomethyl arsenic compounds were also detected following administration of DMPS whereas, without DMPS, 60 to 80 % of the arsenic was present as dimethyl arsenic (V). DMPS presumably binds the monomethyl compound and thus prevents the second methylation stage. MMA(III) DMPS was detected in the urine. No complexes of DMPS with inorganic arsenic or dimethylated arsenic compounds were found[<500>]. Other authors challenge this interpretation as DMA(III) is instable in aqueous solution and is also oxidised to DMA(V) within 17 hours at -20°C[<438>].

DMPS increased the arsenate-reductase activity of human purine nucleoside phosphorylase (PNP) isolated from the human liver in a concentration-dependent manner. The greater the quantity of DMPS added, the more arsenite was formed from arsenate[<1199,1256>]. Monomethyl arsenate (MMAV) was not reduced[<1256>].

					As_2O_3
Arsine, Arsenic hydrogen	Methylarsine	Dimethylarsine	Trimethylarsine	Tetramethyl-arsonium [TETRA]	Arsenic [As(III)]
					
Arsenite [As(III)]	Monomethyl-arsenite [MMA(III)]	Dimethylarsenite [DMA(III)]	Arsenate [As(V)]	Monomethyl-arsenate [MMA(V)]	Dimethylarsenate [DMA(V)]
					
Trimethylarsin-oxide [TMAO]	Phenylarsenoxide [PAO]	Methylarsinate	Salvarsan		Lewisite

Conclusion:
DMPS affects As metabolism. Details of this action have not yet been elucidated.

6.1.3.6 Influence of arsenic on copper metabolism

The administration of arsenic also led to a change in copper metabolism. In rats, the copper content of the kidneys was increased after administration of arsenic. If the animals were treated with DMPS, then the copper content of the urine was increased as well as that of the arsenic[<886>].

	DMPS	Arsenic	As + DMPS
Kidneys	73	207	160
Urine	229	121	274

Cu content of the kidneys and Cu excretion in the urine of rats following administration of arsenic[<886>]

6.1.3.7 Embryotoxicity of arsenic

In pregnant mice DMPS exhibited protective effects against the teratogenic and embryotoxic effects of arsenic[<342,344>]. At sufficiently high doses of DMPS, the toxic effects of sodium arsenite on the dams (death, haemorrhage) were only slight. The number of absorbed foetuses fell and the fraction of normal pregnancies increased the higher the dose of DMPS administered. Visible foetal deformities were prevented and skeletal changes reduced. The toxic effects were not, however, completely abolished even with high doses of DMPS.

Experiment	I	II	III	IV	V
Sodium arsenite (mg/kg)	0	12	12	12	12
DMPS (mg/kg)	0	0	75	150	300
No. of dams at the start	24	22	17	19	20
No. of dams dying	0	3	0	2	0
Dams with haemorrhage	0	6	3	1	0
Total absorption of the litter	0	7	6	4	0
Dams with foetuses	24	6	8	12	20
Average weight of the foetuses (g)	1.37	0.99	1.25	1.15	1.22
Dead or absorbed foetuses (%)	1.4	76.0	69.8	47.8	34.3
Foetuses with external deformities (%)	0	26.4	9.4	4.7	0
Foetuses with skeletal abnormalities(%)	12.5	84.2	93.3	52.6	35.3

Influence of arsenic and DMPS on the embryotoxicity of sodium arsenite in mice[<344>]

The risk of arsenic-induced foetal deformities remained somewhat high despite DMPS therapy[<344>].

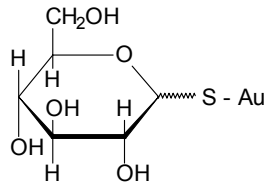
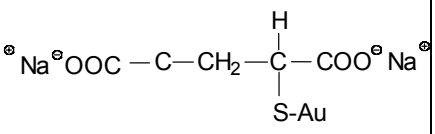
Conclusion:
DMPS can also be administered in the treatment of arsenic poisoning in a vital indication during pregnancy. In the laboratory animal experiment, all of the dams survived arsenite poisoning when sufficient doses of DMPS were administered. The number of foetuses with deformities or skeletal abnormalities decreased, but still did not correspond to that of the control animals without arsenic poisoning.

6.1.4 At - Astate

The effect of prophylactic administration of DMPS on the distribution of the heavy halogenide, ^{211}At, in organs was investigated in mice. The i.p. administration of DMPS 24 hours or 1 hour before administration of astate had only a minor effect on the distribution of the α-emitter[<818>].

Conclusion:
With a DMPS biological half-life of approximately 20 minutes in mice, this effect was anticipated. Whether or not DMPS is effective in the management of astate-induced poisoning cannot be deduced from these investigations.

6.1.5 Au - Gold

		$Na_3[Au(S_2O_3)_2]$	**Keratin-bound gold (aurothio-polypeptide)**
Aurothioglucose	Sodium aurothiomalate (AuTM)	Sodium auro-thiosulfate	Goldkeratinate

DMPS is an effective antidote for gold poisoning[<672,706>]. The effect of DMPS on the toxicity of various gold compounds used as basic therapy in the treatment of chronic polyarthritis was investigated in laboratory animal experiments.

Chelating agent	Survival rate (%)
Controls	0
DPA	20
DMPS	80
DMSA	90

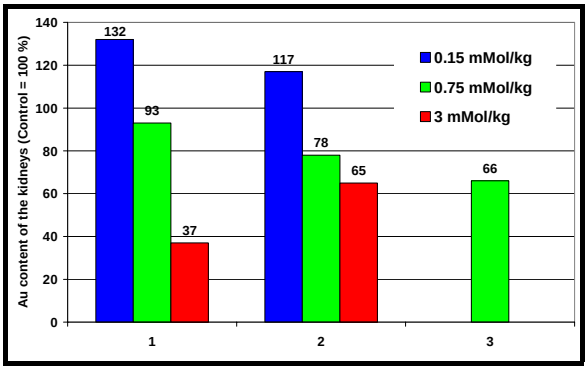
Survival rate of mice following administration of sodium aurothiosulfate (approximately 2-fold LD_{50}) and administration of various CAs[<131>]

^{1}H-NMR investigations on erythrocytes showed that the gold [Au(I)] from aurothiomalate is partially bound to the cysteine of glutathione. On addition of DMPS, the gold was first released from the monothiol thiomalate. At higher doses, the gold was also mobilised from the glutathione[<1106>].

After acute poisoning with sodium aurothiosulfate, 80% of the mice treated with DMPS survived whereas all animals in the control group died[<131>].

DMPS increased gold excretion especially in the urine[<449,602,765,1426>]. Faecal excretion also rose[<449,602>] or was not significantly affected[<765,766,1426>] by elimination of the complex via the bile. Investigations using gel chromatography showed that the gold in the urine was exclusively bound to DMPS. In addition to the DMPS-gold complex, binding of the gold to the amino acid, cysteine, and to high-molecular proteins could also be demonstrated in the bile[<765>].

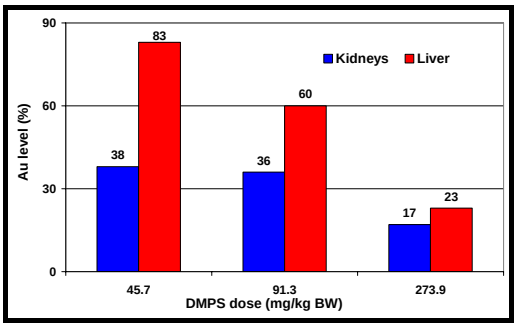
Au levels were lowered in 5 of the 8 organs examined[<69>]. The gold concentrations in the kidneys[<449,766,1424,1426>], liver[<449,766,1424,1426>], skin[<449>] and muscles[<449>] were reduced.



Effect of the DMPS concentration (mMol/kg) on the Au content of the kidneys<449>
1: Single dose of DMPS 30 min. after Au injection
2: Single dose of DMPS 24 hours after Au injection
3: 10- days' administration of DMPS after 10 days of Au injection

The immediate administration of DMPS lowered the gold content of the liver<449,766,1424>. Both the immediate and delayed onset of treatment lowered the Au content of the erythrocytes and plasma<449>. The effect was dose-dependent; higher doses of DMPS were more effective<449,1425>.

Both the immediate<449,766,1425,1426> and the delayed<449> administration of DMPS reduced the heavy metal content of the kidneys at an adequate dose level<449>. DMPS thus prevented the harmful effect of gold on the kidneys<766,1424-1426>. DMSA was more effective in this respect than DMSA or DPA<766,1426>. Gold-induced changes in biochemical parameters (increased excretion of glucose, proteins and aspartate amino transferase AST, increased blood urea nitrogen level BUN) were reduced<766,1424-1426>. Concomitant administration of sodium aurothiomalate (i.m.) and DMPS (i.p.) prevented the change in biochemical parameters<766,1424> without significantly influencing the effect of the gold compound on adjuvant arthritis<1424>.



Effect of a single dose of DMPS on the gold content of the kidneys and liver (as % of the untreated control animals)<1425>

	Kidneys				Liver			
	Cu	Zn	Fe	Ca	Cu	Zn	Fe	Ca
AuTM	308	128	114	90	209	115	121	107
AuTM + DMPS	304	132	119	85	126	109	107	117

Influence of sodium aurothiomalate (AuTM) and DMPS on the trace elements of the liver and kidneys(control animals = 100 %)<1424>

The administration of gold led to increased copper levels in the liver and kidneys of rats. Zinc, iron and calcium content was unaffected. DMPS lowered raised copper levels in the liver, but not in the kidneys<1424>.

Conclusion:
DMPS increases the survival rate in animals poisoned with gold. The gold content of the liver and kidneys is reduced and changes in biochemical parameters are avoided. DMPS therefore appears to be a suitable antidote for the treatment of gold poisoning.

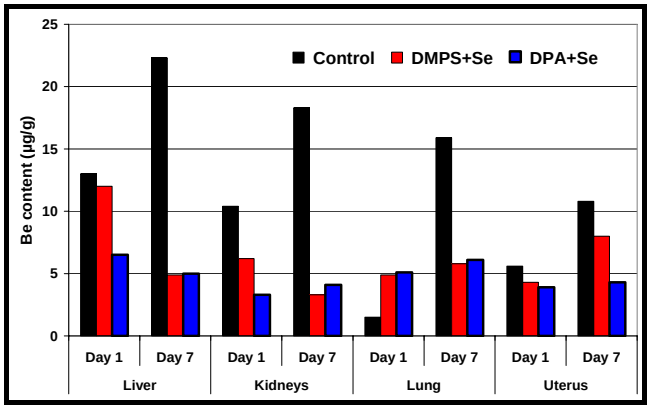
6.1.6 Be - Beryllium

DMPS increased the mortality of mice with acute beryllium poisoning. The effect was not, however, statistically significant<1135,1136>.

$BeCl_2$	LD_{50} = 214 mg/kg BW
$BeCl_2$ + DMPS	LD_{50} = 277 mg/kg BW<1136>

Female rats received one i.m. bolus dose of $Be(NO_3)_2$. DMPS (i.p.) was then administered three times with Na_2SeO_2 (s.c.). Berylllium-induced changes in the various biochemical parameters in the kidneys, liver, lungs, uterus and blood consequently improved. The combination of DPA with selenite was more effective whilst glutathione was less effective. Be levels in the examined organs were lowered to a similar extent through the three treatments but, even after three doses, still not reach the comparative value of the control animals not exposed to beryllium<660,661>.

Male rats were given parenteral beryllium nitrate for three weeks. The animals then received 25 or 50 mg DMPS/kg BW twice daily for five days. The treatment increased beryllium excretion, especially in the faeces. The higher dose was more effective. The metal content in the blood was



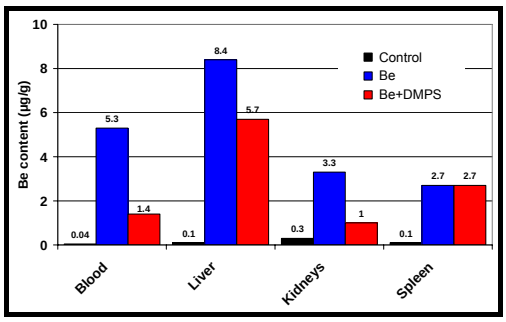
Effect of 3-day combination therapy of DMPS or DPA with selenium on the beryllium content of various rat organs compared to the untreated animals one or seven days after treatment<660,661>

increased whereas the metal content in the liver, kidneys and spleen fell. Beryllium-induced changes in the hepatological and haematological parameters (e.g. ALP, ALAD, GOT and GPT) partly improved. Histopathological changes in the kidneys and liver were reduced following administration of DMPS<425>.

Male rats were given 50 mg DMPS/KG BW each for three days immediately after a single i.p. administration of beryllium (as $Be(NO_3)_2$). The changes in various biochemical liver parameters were prevented by administration of the chelating agent. Histopathological examinations of the liver and kidneys confirmed the protective effect of DMPS. Beryllium levels in the blood, liver and kidneys were reduced, bud did not achieve the value of the normal group that had not received any berylllium, even after three doses of DMPS. DMPS was more effective than DMSA<908>.

	Controls	Beryllium exposure 0 mg DMPS/kg BW	25 mg DMPS/kg BW	50 mg DMPS/kg BW
Blood (µg/100 mL)	0.6	14.8	17.2	24.1
Liver (µg/g)	0.4	16.5	14.4	10.0
Kidneys (µg/g)	1.6	7.5	8.1	4.9
Spleen (µg/g)	0.2	4.1	2.7	1.6
Urine* (µg)	1.0	5.4	6.3	7.1
Faeces* (µg)	0.9	6.1	11.1	13.0

Influence of treatment with DMPS on the be content of organs (*total excretion of be during the 5-day treatment)<425>



Influence of the administration of DMPS on Be levels in the blood (µg/100 mL) and various organs (µg/g)<908>

Conclusion:
DMPS has a minor effect on mortality rates in mice following acute beryllium poisoning. Faecal excretion is essentially increased whereas levels in most organs fall. DMPS should thus be considered as an antidote if treatment of this type of poisoning is required.

6.1.7 Bi - Bismuth

All the mice poisoned acutely with bismuth (LD_{95}) that were treated with DMPS survived. All the animals that were in the untreated control group died<132>.

Rats that were chronically poisoned with bismuth for 14 days exhibited a 4-fold increase in the urinary excretion of the metalloid after administration of DMPS. Bismuth levels in the blood, kidneys, liver, spleen and brain were reduced. The content of the bones was unaltered<1356>.

DMPS (µg/mL)	2 hours	21 hours	28 hours	45 hours
100	105	27	29	19
300	108	12	13	9
600	79	8	5	5

Time-based reduction in the total body burden of Bi (% of the controls) following oral treatment with DMPS in drinking water (2 days before to 3 days after i.p. injection with bismuth acetate)<683>

Nude mice were given DMPS in their drinking water two days before to three days after i.p. injection of bismuth acetate. DMPS drastically increased the body clearance of bismuth and the total body burden with the metalloid fell rapidly as did the level in the kidneys,

which are the main target organs for bismuth. Deposition of the metalloid in the femur was more than halved, as a result of which the radiotoxic effects on the bone marrow were reduced[<683>].

Following i.v. injection of the ^{206}Bi-DMPS complex, the radionuclide did not accumulate in the kidneys of rats. After 24 hours, less than 1% of the injected dose could be detected in the kidneys of rats[<40>]. Thus the complex is not suitable for kidney scanning.

The α emitter ^{215}Bi is derived from ^{225}Ac, which is bound to monoclonal antibodies and used in radio-immunotherapy in cancer. In mice, the administration of DMPS prevented the deposition of ^{215}Bi in the kidneys. Oral administration with the drinking water was as effective as i.p. administration. DMPS was the most effective and surpassed both DMSA and Ca-DTPA. The additional administration of the diuretics, furosemide or chlorothiazide, further lowered Bi levels in the kidneys. DMPS also lowered ^{215}Bi deposits in the bones. Contrastingly, Bi levels in the blood were higher with DMPS than in the untreated controls. The total body burden was not, however, increased[<648>].

The administration of DMPS also prevented the renal accumulation of ^{215}Bi in experiments carried out with a Cynomolgus monkey. Blood levels were unchanged compared to experiments conducted in mice[<648>].

In-vitro dialysis experiments showed that DMPS at high doses mobilises bismuth from its protein bindings, thus increasing the dialyzability of bismuth from serum. The DMPS-Bi complex was only slightly bound to serum constituents. It was predominantly present in the free form and could, therefore, transfer to the dialysate[<1356>].

In contrast to BAL, DMPS and DMSA did not potentiate the antibacterial effect of bismuth compounds. The lack of lipophilia of the Bi-DMPS complex is discussed as a possible cause[<340>].

Conclusion:
DMPS increases the survival rates on acute poisoning with bismuth. Excretion is increased. The total body burden and organ levels decrease. DMPS is thus a suitable antidote for the treatment of acute and chronic bismuth poisoning.

6.1.8 Ca - Calcium

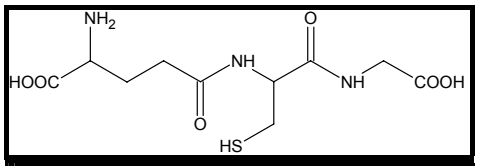
The administration of $CaCl_2$ triggered arrhythmia in rabbits. The number of SH groups fell. The administration of DMPS allowed SH concentrations to rise again and prevented the arrhythmias[<1387>].

Conclusion:
According to chemical legislation, DMPS is not expected to have a direct impact on calcium levels. DMPS is not, therefore, indicated in elevated Ca concentrations.

6.1.9 Cd - Cadmium

On chronic poisoning, cadmium is mainly deposited in the liver and kidneys. It is thus presumably bound to essential SH groups. It accumulates as it is only eliminated in small quantities. It can thus compete with zinc and calcium. It is quickly absorbed in the cells. Intracellularly, it induces the formation of metallothioneins[<1153>]. It is firmly bound to these SH-rich proteins. This is an endogenous protective mechanism. The symptoms of poisoning do not appear until the binding capacity of the metallothioneins is exceeded[<117,1206>]. On the other hand, this reaction of cadmium prevents cadmium from binding to chelating agents and thus the efficacy of the latter in the treatment of intoxication[<1153>].

6.1.9.1 Investigations in cell cultures or cell organelles



Glutathione (GSH)

In vitro, DMPS partially released cadmium from its binding to metallothioneins (consisting of up to 30% cysteine[<1305>]) relatively quickly and high-molecular plasma constituents[<664,912>]. As ^{1}H-NMR investigations showed, it mobilised the heavy metal from its binding to glutathione and haemoglobin in haemolysed erythrocytes. Efficacy increased in the following order: DPA < DMPS < DMSA[<1196>]. The cadmium bound to low-molecular structures in the plasma increased with higher concentrations of DMPS[<912>].

DMPS (mM)	Cadmium release (%)
0.35	9.4
3.5	12.5
20	14.2

Effect of DMPS on cadmium release from CHO cells (% of the added dose)[<1203>]

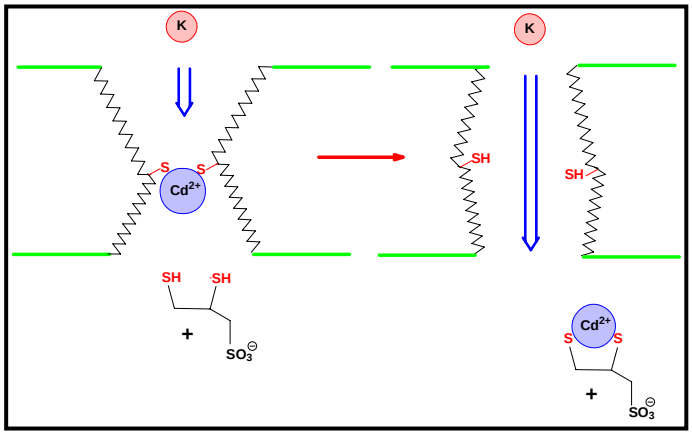
The tests carried out to determine the effect of DMPS on cadmium absorption in cell cultures yielded non-uniform results. They ranged from an increase in cadmium absorption in various cells[<1455>] via no effect[<414-416>] to inhibition of absorption in CHO cells (60 % compared to the controls)[<1203,1205,1206>]. In contrast to *in-vivo* experiments, only approximately 50% of the cadmium was bound to metallothioneins after 20 hours in cell cultures[<1203>]. Cadmium absorbed in CHO cells[<1203,1205,1206>] or human epithelial cells[<116>] was partially dissolved from metallothioneins once again and excreted in the medium following addition of DMPS to the nutrient medium. Absorbed cadmium was not mobilised in other cell experiments[<414,416>].

Chelating agents	Cd content (% of the control)
Ca-DTPA	0.6
DPA	94
DMPS	109
DMSA	344

Uptake of cadmium in CHO cells on addition of various chelating agents to the nutrient medium[<416>]

Even if DMPS did not increase Cd excretion from cells, the cytotoxicity of cadmium was slightly reduced[<415,416>]. The Cd-DMPS complex is obviously less toxic than the free heavy metal[<416>]. The cadmium-induced inhibition of protein synthesis in cancer cells[<162>] or lysed reticulocytes[<909>] was stopped on addition of DMPS. Inhibition of cell proliferation was partly reversible[<414>].

Cd^{2+} influences biochemical processes by adhering above all to the SH groups of various biomolecules.



- DMPS dissolved Cd^{2+}-ions, which were bound to cysteine-containing components in potassium ion channels, thus reinstating functionability[<852,979,1239,1240,1363>], e.g. control of the potassium flow through the neuron membranes[<384,1539>].
- Cd^{2+} reduced glutamate binding in synaptic membranes in rat brains. The addition of DMPS or DMSA, but not BAL, partially prevented this effect [<1362>]. DMPS also prevented the effect of cadmium on glutamate binding in
- blood platelets[<195a>].
- In erythrocytes, the administration of DMPS prevented the effect of Cd^{2+} on fat metabolism[<531,623>].
- The addition of DMPS reduced the inhibitory effect of $CdCl_2$ on microsomal Na^+-K^+-ATPase in rat brain microsomes in a concentration-dependent manner[<262>].
- $CdCl_2$ prevented veratrin-induced muscle stimulus by blocking the SH groups. DMPS stemmed this effect once again[<769>].
- From a CdO suspension (particle size < 5 µ) the metal bound to plasma proteins. In contrast to EDTA, the addition of DMPS did not have a significant effect on the bound quantity of metals[<439>].

6.1.9.2 Acute poisoning

6.1.9.2.1 Monotherapy

The results with respect to survival rates for acute cadmium poisoning after administration of DMPS fluctuated between 0 and 100 %. They depended on the DMPS dose, the cadmium load the time between poisoning and DMPS administration.

DMPS protected mice against the lethal effects of Cd poisoning[<63>]. The lethal doses were increased[<1135,1305>].

$CdSO_4$	LD_{50} = 57 µmol/kg BW[<992>]
$CdCl_2$	LD_{50} = 26.7 µmol/kg BW[<1378>] (Mouse, i.p.)
$CdCl_2$ + DMPS	LD_{50} = 41 µmol/kg BW[<1378>] (Mouse, i.p.)
$CdCl_2$	LD_{50} = 9.1 mg/kg BW
$CdCl_2$ + DMPS	LD_{50} = 15.2 mg/kgBW[<1136>]

	Survival rate (%)	Cadmium levels	
		Kidneys	Liver
Controls	50	12.5	34.0
Na_5DTPA	100	4.4	3.2
DMSA	100	1.4	0.9
DPA	100	15.4	12.5
DMPS	100	8.3	3.8

Effect of immediate oral administration of chelating agents on survival rate and Cd levels in the liver and kidneys after oral administration of $CdCl_2$ to mice[<130>]

The survival rate in mice was high when treatment was initiated immediately[<681,1305,1378>]. However, more animals still survived than in the control group when treatment was started after 1 hour[<70>]. 50% of rabbits survived an LD_{100}, 87 % a LD_{80} poisoning[<207>]. Oral administration of DMPS 15 minutes after oral administration of $CdCl_2$ to mice increased the survival rate from 70 to 90 %[<35>]. After 4 hours, neither DMPS nor DMSA, Ca-DTPA nor EDTA increased the survival rates in mice[<1579a>].

Higher doses of DMPS were more effective[<1305>]. All mice survived with higher doses of DMPS, even when treatment was initiated 60 minutes after i.p. administration of Cd, whereas all the animals receiving lower doses died[<680>]. This may be attributable to the firm binding of cadmium to metallothioneins (low-molecular, metal-binding proteins with a binding constant for cadmium of about 25.5[<135>]) and its storage in the cytosols of the cells[<1334>]. Cadmium induces the synthesis of these proteins in the body[<519>].

CA	Survival rate(%)
Zn-DTPA	80
Ca-DTPA	77
Triene	0
DPA	40
DMPS	0
DMSA	40

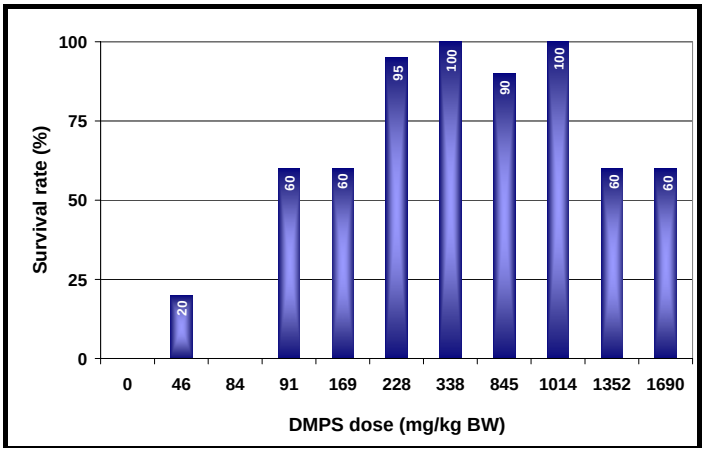
Survival rate (%) of mice following administration of $CdCl_2$ (i.p. LD_{97}) and dosing with various CA (i.p. after 20 min)[<133>]

	LD_{100}	LD_{80}
As	100	100
Hg	72	90
Cd	50	87
Ni	40	80
Cr	40	

Survival rates (%) of rabbits on administration of DMPS after poisoning with LD_{100} or LD_{80} of various heavy metals[<207>]

Following oral administration, DMPS was more effective than DMSA whereas i.p. administration of DMPS exceeded DMPS[<397,1378>]. The survival rate fell in the following order, DTPA > Zn-DTPA > DMPS following immediate administration of high-dose antidote therapy. Younger animals responded to the treatment better than older animals[<681>].

DMPS: Cd	DMPS (mg/kg)	Survival rate(%)
0:1	0	0
3:1	46	20
5:1	84,5	0
7:1	91	60
10:1	169	60
17:1	228	95
20:1	338	100
50:1	845	90
60:1	1.014	100
80:1	1.352	60
100:1	1.690	60



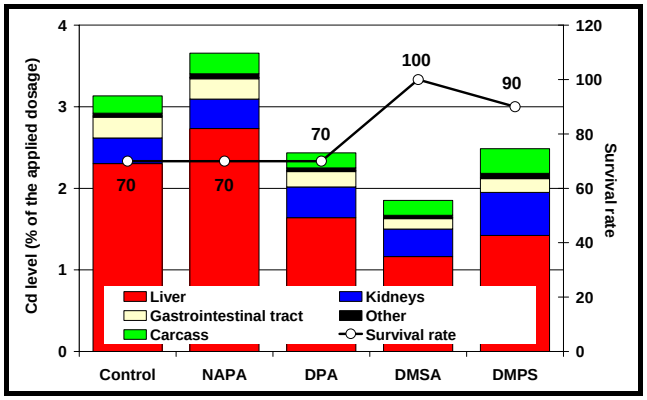
Survival rates of mice after cadmium poisoning depending on the DMPS dose[<681>]

When DMPS was administered immediately via the oral route following oral dosing with $CdCl_2$, all mice survived whereas 50% of the animals in the control group died. The cadmium content in the liver and kidneys was re-

duced compared to the controls[<130>]. Oral administration of DMPS 15 minutes after oral administration of cadmium increased the survival rate in mice from 7.5 to 80 % whereas i.p. administration proved ineffective[<34>]. However, the i.p. doses amounted to only 1/8 of the oral doses. At high doses, i.p. DMPS increased the survival rate in mice from 50 to 90%[<1378>]. All of the mouse died following i.p. administration of DMPS 20 minutes after injection of $CdCl_2$ (LD_{97})[<133>]. Irradiation of the DMPS solution with X rays did not reduce the efficacy of the solution[<297>].

Single oral administration of DMPS 15 minutes after oral dosing with $CdCl_2$ reduced the total body burden in mice. The survival rate rose from 70 to 90%[<35>].

DMPS showed its best effect when it was given immediately after the cadmium. Efficacy fell drastically over time[<668>]. The protective effect was mostly lost after 30 minutes[<1305>] or after 1 - 3 hours[<1154, 1161>]. After 24 hours, no further effect on cadmium distribution in the body was observed[<258,1504>].



Survival rate and cadmium content in various organs after oral administration of $CdCl_2$ and oral administration of CA (after 15 minutes) in mice[<35>]
Others = testes, heart, spleen, lungs and brain.

Conclusion:
After acute cadmium poisoning, only the immediate administration of DMPS increased the survival rate. Delayed onset of treatment is ineffective as the binding of cadmium to metallothioneins (pK = 25.5) is greater than that to DMPS (pK = 18.6).

6.1.9.2.2 Combination therapy

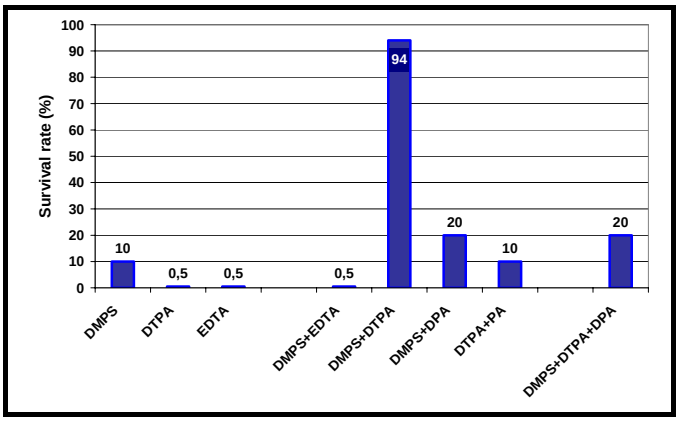
The results of combination therapy with DMPS and other chelating agents (mixed ligand chelate therapy MLC) have been assessed to varying degree in the literature. The immediate combination of EDTA and DMPS was less effective

	0.03 mmol Cd/kg Treatment after 1 h	0.06 mmol Cd/kg Treatment after 1 h	0.1 mmol Cd/kg Treatment after 5 min
Controls	59	77	86
DMPS	11	40	88
DMPS+EDTA	30	83	80

Effect of DMPS and EDTA combination therapy on cadmium mortality rates(%)[<1161>]

Treatment	Survival rate
Controls	0/10
DMPS (i.p.)	2/10
DMSA (i.p.)	2/10
$CaNa_3DTPA$ (i.p.)	4/10
Vitamin B_1 (i.p.)	1/10
Methionine (i.p.)	1/10
Zinc (i.p.)	2/10
DMPS (i.p.) + Vitamin B_1 (oral)	5/10
DMPS (i.p.) + Methionine (oral)	5/10
DMPS (i.p.) + Zinc (oral)	8/10

Effect of immediate mono- or combination therapy on the survival rate of mice after acute cadmium intoxication[<530>]



Effect of immediate mono- or combination therapy on the survival rate of mice after administration of $CdCl_2$ (approx. 2-fold LD_{99}) (DMPS: 0.2, Ca-DTPA: 0.04, EDTA: 0.1, DPA: 0.5 mmol/kg)[<1305>]

than DMPS alone in terms of survival rate in mice (2-fold LD_{99}). In contrast, the effects of DMPS and Ca-DTPA were cumulative[<1153,1305>]. All animals died during monotherapy with DMPS or Ca-DTPA. However, all the mice receiving combination therapy one hour after i.v. administration of CdCl2 survived[<1306>]. This effect was, however, surprisingly lost when DPA was also administered (triple therapy)[<1305>]. DPA alone was ineffective[<70>]. Combination with BAL[<1154>] or Zn-DTPA[<397>] did not show any synergistic effects. Concomitant administration of EDTA and DMPS was more effective[<1153>], equally effective[<680,1154,1161>] or less effective[<70,1305>] than treatment with DMPS alone.

Time (minutes)	Mortality (%)
5	10
15	60
30	100

Effect of time interval between the administration of $CdCl_2$ and the start of treatment with DMPS + Ca-DTPA[<1305>]

The efficacy of the combination therapy, however, fell rapidly. All animals died even when treatment was initiated 30 minutes after the injection of $CdCl_2$[<1305>].

Most mice survived after administration of $CdCl_2$ when combination therapy comprising DMPS (i.p.) and zinc (oral) was initiated immediately. The zinc presumably ousted cadmium from its binding to biomolecules, thus making it more accessible to DMPS[<530>].

6.1.9.3 Influence on the distribution of cadmium

The results of the various investigations focusing on the influence of DMPS on the distribution of cadmium in the body varied considerably. The efficacy of DMPS depended in particular on the dose and on the time that elapsed between cadmium administration and the onset of treatment.

The efficacy was time-dependent, whereby concomitant administration of cadmium and DMPS led to a marked reduction of the burden[<8,1204>]. This was due to the stable binding of cadmium to metallothioneins (log K = 25.5)[<8,258,1206>]. This complex accumulates intracellularly while DMPS has a primarily extracellular effect[<257,258,1206>]. The efficacy of DMPS is, therefore, limited to the short time span until sufficient metallothionein is formed[<257,258>]. After three hours, about 90% of the cadmium was bound to metallothioneins. 14-days' treatment could not reduce the total body burden more significantly[<1206>].

In mice, immediate injection of DMPS after i.v. administration of cadmium chloride did not reduce the total body burden. DMSA had a mild effect and Ca-DTPA reduced the burden by more than 50%f[<395>]. The organ contents did not change significantly. Levels in the kidneys, brain and testes were rather high with a tendential reduction in the liver and gastrointestinal tract.

Following intravenous administration of various DMPS-cadmium complexes[<397>] or on simultaneous administration of DMPS and cadmium[<1204>], cadmium levels in the kidneys exceeded the value recorded in animals that received only a corresponding quantity of cadmium chloride[<1206>].

	Total body	Liver	Kidneys
Cd:DMPS 1:1	99	91	121
Cd:DMPS 1:3	87	60	179

Cadmium levels in mice following i.v. administration of various Cd-DMPS complexes (as % in relation to the administration of $CdCl_2$)[<397>]

Time		Liver	Kidneys	Spleen	Testes	Blood
1 hour	Controls	60.2	1.1	0.54	0.24	0.47
	DMPS	10.4	2.3	0.10	0.24	2.69
24 hours	Controls	56.0	1.5	0.20	0.13	0.04
	DMPS	19.0	2.8	0.11	0.17	0.04

Cd levels (% of dose administered) 1 hour or 24 hours after i.v. injection of a Cd-DMPS complex (3:100) in various rat organs[<1206>]

Intravenous administration of DMPS enclosed in liposomes (unfortunately, the study provides no details about the time interval between the administration of Cd and DMPS) increased the renal excretion of Cd. Excretion via the faeces was also slightly increased. Compared to levels recorded in the control mice, Cd concentrations in the blood, liver, kidneys and spleen were lowered.

6.1.9.3.1. Excretion and total body burden

DMPS either increased the urinary excretion of cadmium[<117,145,259,1153,1154,1206>] or did not have any effect[<258>]. No correlation between excretion and renal burden could thus be detected[<256>]. Following a single dose of DMPS, the time required for the excretion of 70% of the cadmium dose administered was reduced from 38.5 to 29 hours[<35>]. Lipophilic Cd-DMPS complexes could be detected chromatographically in the urine[<396>]. The total body burden was reduced [<33,35,1153>] or unaffected[<396,1206>].

In mice, immediate administration (via both the oral and i.v. routes) increased Cd excretion via the urine on the first day. No increase in excretion compared to the control animals was observed on subsequent days. The effect was considerably less marked if treatment was only initiated after 30 minutes. The onset of treatment after 6 hours was ineffective[<117>].

The administration of i.v. DMPS one hour after i.v. injection of $CdCl_2$ increased Cd concentrations in rat urine approximately 15-fold[<257-259,1154>]. The administration of DMPS 24 or 72 hours after application no longer increased excretion[<257-259>] or only slightly. The increase was so minimal that it did not reduce the body load or lower Cd levels in the organs[<259,1205>].

Immediate administration of a single oral dose of DMPS after oral administration of $CdCl_2$ increased faecal excretion. Whereas 70% of the dose administered was eliminated in the faeces of the untreated control animals after 38.5 hours, this value was achieved after just 29 hours in mice treated with DMPS[<35>]. Faecal excretion was slightly reduced in other investigations[<1154,1206>]. The concentration in the bile remained unchanged[<63,117,145,257-259,1504,1624>] or was reduced[<1154>].

In rats[<1153,1154>] or mice[<395>], immediate administration of DMPS or other chelating agents reduced the total body burden with Ca-DTPA proving to be the most effective treatment. Renal excretion was increased with DTPA and renal and biliary excretion with BAL[<259,1154>]. Efficacy was, however, mostly lost after just 1 hour[<1153,1154>].

Immediate combination therapy with DMPS and Ca-DTPA reduced the total body burden[<397>]. Concomitant treatment with BAL and DMPS increased both urine and faecal excretion and reduced the total body burden[<1154>].

Chelating agents	Immediate administration	Administration after 1 hour
Controls	94.3	94.3
Ca-DTPA	7.6	89.3
BAL	75.1	89.5
DMPS	66.6	91.8
DMSA	67	

Cd-total body burden (% of the dose administered) in rats after immediate or delayed (1 hour) administration of chelating agents (0.1 mM/kg)[<1154>]

6.1.9.3.2 Kidneys

Chelating agents	Cd levels in the kidneys
Controls	2.63
Ca-DTPA	0.67
DMPS	6.52
BAL	21.1
DMSA	5.49

Cd levels in the kidneys (% of the dose administered) on immediate administration of chelating agents(0.1 mmol/kg[<1154>]

Most authors observed increased Cd depots in the kidneys in animals treated with DMPS[<33,35,395,992,1153,1154,1204,1334>] whilst others witnessed no effect[<145,258,836,1504>] or even reduced concentrations[<117,260,1378>]. Delayed dosing was ineffective[<117>]. I.v. administration of DMPS enclosed in liposomes reduced Cd concentrations via the retention effect and continuous release[<145>].

Immediate i.p. administration of DMPS after i.v. administration of ^{115m}Cd drastically increased Cd depots in the rat kidney[<992>]. Immediate i.p. administration of DMPS after i.p. administration of $CdCl_2$ reduced Cd levels in the kidneys with higher doses proving more effective[<1378>]. Immediate combination therapy with DMPS (i.p.) and Ca-DTPA (s.c.) also reduced Cd levels in the kidneys[<397>]. Renal Cd levels remained unchanged following administration of DMPS in animals not given additional Cd exposure[<1420>]. No linear correlation between the decrease in heavy metal in the kidneys and the increased excretion in 24-hour urine was observed in rats following oral administration of DMPS[<256>].

The administration of DMPS 24 hours after administration of $CdCl_2$ did not alter the Cd content of the kidneys in rats[<258,259,1205,1504>]. Similarly, treatment started one week after exposure had no effect on Cd levels in the kidneys of mice[<1334>] or rats[<835>].

In rats, i.v. administration of DMPS one hour after administration of $CdCl_2$ no longer altered the Cd content of the kidneys[<1161,1154>] or resulted in higher levels[<1154>]. Accumulation in the kidneys was lower following administration of a higher dose than a lower dose of DMPS[<1154>]. Similarly, a combination of DMPS and BAL had no effect[<1154>].

Immediate administration of a single oral dose of DMPS after oral administration of $CdCl_2$ doubled the cadmium load of the kidneys[<35>]. This also applies to the inhalation of a single dose of DMPS following nasal administration of $^{109}CdCl_2$. In contrast, no change in the Cd content of the kidneys was observed following 14 days' inhalation therapy[<836>].

Time	Liver	Kidneys	Blood
Simultaneous	26.2	4.8	0.7
20 seconds	40.1	4.5	0.5
60 minutes	58.5	2.8	0.5
Untreated controls	68.3	2.6	0.7

Effect of time interval between administration of Cd and the administration of DMPS on the Cd content of the organs (% of the injected dose 24 hours after administration)[<1204>]

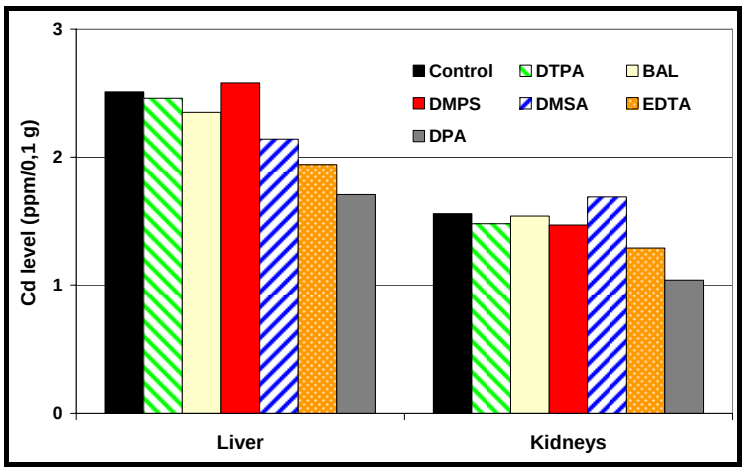
In another study, i.v. administration of DMPS led to an accumulation of Cd in rat kidneys. Efficacy depended on the time that elapsed between administration of the metal and administration of DMPS. Elevated cadmium levels recorded in the kidneys following single administration of DMPS was not only temporary but could still be detected after three days. The accumulation was even greater following administration of BAL. The accumulation of the heavy metal in the kidneys could be prevented by alkalising the urine with $NaHCO_3$[<1204>].

	Urine pH	
	7.5	10
DMPS	4.7	2.8
Controls	2.5	2.8

pH-dependence of the Cd content of the kidneys (% of the injected dose)[<1204>]

Comparison of various chelating agents showed that, when administered immediately, DTPA was the most effective substance and lowered cadmium levels in all organs. Contrastingly, DMPS and DPA, both of which are chelating agents with an SH group, increased cadmium depots in the kidneys. The lower pH (pH < 7) in the kidneys and urine compared to a pH ≥ 7 in the blood plasma is discussed as a possible cause[<992>].

The efficacy of DMPS, DMSA and Ca-DTPA on mobilising Cd^{2+} from the kidneys was compared using perfusion experiments. Male rats were injected several times with $Cd(Ac)_2$ i.p., which led to an accumulation of the heavy metal in the kidneys. 24 hours after the last injection, the right kidney was rinsed with a perfusion solution to which various concentrations of the chelating agent had been added. The left kidney served as a control. DMPS lowered the Cd content of the kidneys in a concentration-dependent manner and led to high Cd mainly in the perfusion solution and to less of an extent in the urine. Nevertheless, of the antibodies investigated, DMPS triggered the greatest excretion of Cd in the urine (DMPS >> DMSA > Ca-DTPA).



Effect of 10 injections of various CA on Cd levels in the kidneys and liver of rats following chronic Cd exposure[<835>]

Special active transport processes for DMPS and its chelates may play a role in the kidneys. If the perfusion experiments with DMPS were carried out after one or two weeks instead of after 24 hours, Cd concentrations in the perfusate were still high whilst urinary excretion remained unaffected[<1376>].

The addition of DMPS reduced the intracellular uptake of Cd^{2+} in the renal tubular and thus reduced its toxicity. Higher DMPS concentrations displayed greater effects whereas 30 µM reduced uptake by 39% and (95% at 200 µM). The complex obtained is obviously too big for the normal Cd transport mechanisms in the proximal renal tubular<1534,1534a>.

		1st day	2nd day	3rd day
Controls	Liver	68.3	62.3	61.2
	Kidneys	2.6	2.2	2.2
DMPS	Liver	26.2	40.2	41.7
	Kidneys	4.8	5	5

Time-related change in the Cd content in rats given a single dose of DMPS immediately after cadmium (% of the dose injected)<1204>

6.1.9.3.3 Liver

Data on the effect of DMPS on cadmium content in the liver vary compared to the control animals between reduced<17,35,117,397,836,992,1154,1161,1204,1378> via insignificantly affected<145,258,259,395,836,1153,1503> to high<836,1206>.

Immediate i.p.-<992> or i.v. administration<117,395,1154> of DMPS led to lower Cd levels in the liver whereas higher doses were more effective<1154,1378>. Over the next 72 hours, the value increased again but nevertheless remained below that of the untreated control group<1204>. In rats, the administration of DMPS one hour after $CdCl_2$ lowered the Cd content of the liver<1154,1161>. Later doses were ineffective<117>. The administration of DMPS 24 or 72 hours after administration of $CdCl_2$ did not alter the Cd content of the rat liver<258,259,1205,1504>. The cadmium content of the liver was raised<1334> or unaffected<835> in mice when treatment was initiated one week after exposure. In the case of animals not exposed to additional Cd, Cd levels in the liver remained unchanged after administration of DMPS<420>.

	Blood	Liver	Kidneys	Skeleton
EDTA	54.7	57.8	87.6	54.4
DTPA	13.8	28.3	36.1	24.9
DPA	56.5	48.0	905	68.5
DMPS	79.5	49.2	292	92.1

Effect of the immediate administration of a single dose of various CA on Cd content in rats poisoned with $CdSO_4$ (% of the untreated controls)<992>

Immediate administration of a single oral dose of DMPS after oral administration of $CdCl_2$ reduced the cadmium burden in the liver<35>. In contrast, inhalation of a single dose of DMPS after nasal administration of $^{109}CdCl_2$ led to higher Cd depots in the liver. After 14 days' inhalation therapy, no change was, however, observed in the Cd content of the liver compared to that of the untreated control animals<836>.

I.v. administration of DMPS enclosed in liposomes reduced Cd concentrations via the retention effect and continuous release<145>.

Immediate combination therapy with DMPS (i.p.) and Ca-DTPA (s.c.) reduced Cd levels in the liver<397>. A combination of BAL and DMPS one hour after administration of $CdCl_2$ had no effect in rats<1154>.

In another study, DMPS did not prevent the cadmium-induced reduction in δ-ALAD activity in the liver<1049>. The cadmium-induced reduction in CuZn-superoxide dismutase activity in the liver reverted to normal following administration of DMPS<232>.

6.1.9.3.4 Brain

Cd levels in the brain remained unchanged even when DMPS was administered immediately<35,117,395,1378>. A positive effect could be detected only at high dose levels<1378>.

6.1.9.3.5 Testes

Immediate administration of a single oral dose of DMPS after oral administration of $CdCl_2$ did not change the cadmium burden in the testes<35>. In contrast, other investigators observed a reduction in the Cd level<1262>. High values were recorded on immediate i.v. administration of DMPS after i.v. injection of $CdCl_2$ <395>. A reduction could be detected only at high dose levels<1154>. The administration of DMPS 24 hours after administration of $CdCl_2$ did not significantly alter the Cd content of the testes in rats<259>.

Cadmium-induced lipid peroxidation was reduced on excretion. The elevated haemoglobin concentration was lowered. The reduced δ-ALAD activity increased again. Reduced vitamin C levels in the testes, however, remained low during the 24-hour observation period[<1262>]. A combination of BAL and DMPS was devoid of effect[<1154>].

6.1.9.3.6 Placenta, uterus

Cadmium accumulated in the placenta following oral administration of $CdCl_2$ to gestating rats and triggered histopathological changes. High Cd levels were also recorded in the foetuses. Immediate administration of DMPS reduced accumulation and any changes, but the effect was not statistically significant[<837>].

$CdSO_4$ inhibited the contractile function of isolated rat urteri. The addition of DMPS partly or completely lifted this blockade[<1434>].

6.1.9.3.7 Heart

Immediate administration of a single oral dose of DMPS after oral administration of $CdCl_2$ did not change the cadmium burden in the heart[<35>]. Similarly, administration after 24 hours did not lead to any significant change in the cadmium content of the rat heart[<259>]. Cadmium levels in the heart remained unchanged following administration of DMPS to animals not exposed to any additional Cd load[<1420>]. In the isolated frog heart, DMPS induced recovery of amplitude and rhythm, which had been disrupted by $CdCl_2$[<207>].

6.1.9.3.8 Spleen

Neither immediate administration nor the administration of DMPS 24 hours after administration of $CdCl_2$ led to any significant change in cadmium concentrations in the spleen[<35,259>]. I.V. injection of DMPS enclosed in liposomes reduced cadmium levels through the retention effect and subsequent continuous release[<145>].

Immediate administration of lower doses of DMPS increased the Cd content of the spleen. The effect was no longer detectable at high dose levels[<1154>]. A combination of BAL and DMPS had no effect[<1154>].

6.1.9.3.9 Blood

Cd levels in the blood were not affected by either immediate[<117,1204>] or delayed (1 hour after i.v. administration of $CdCl_2$)[<1154,1204>] administration of DMPS[<117,259>]. Other authors report a decrease[<145,992>]. The administration of DMPS 24 hours after administration of $CdCl_2$ did not alter the Cd content of the blood in rats[<259>]. A combination of BAL and DMPS had no effect[<1154>].

I.V. administration of DMPS enclosed in liposomes reduced Cd concentrations via the retention effect and subsequent continuous release[<145>]. DMPS caused the effects of $CdCl_2$ on various blood parameters to revert to normal[<389>]. The marked oxidation of proteins and lipids in the serum was reduced[<390>]. The Cd-induced increase in the activities of the LDH, ALT and AST enzymes in the plasma was unaltered[<1262>].

6.1.9.3.10 Lungs

Immediate administration of a single oral dose of DMPS after oral administration of $CdCl_2$ more than doubled the cadmium burden in the lungs[<35>]. Administration 24 hours after injection of $CdCl_2$ did not alter the Cd content of the lungs[<259>].

Following nasal administration of $^{109}CdCl_2$, i.p. administration of DMPS had no effect on Cd levels in the lungs. In contrast, inhalation of DMPS led to a reduced, albeit insignificant reduction in cadmium levels. Contrastingly, a single dose of DMPS had no effect[<836>].

DMPS and DMSA could not prevent the effect of $CdCl_2$ on δ-ALAD activity in the lungs, and even potentiated it. The δ-ALAD activity of rat lungs was reduced with a 0.01 µM $CdCl_2$ solution. Concomitant addition of DMPS intensified this effect in a concentration-dependent manner[<867>].

6.1.9.3.11 Pancreas

The administration of DMPS 24 hours after administration of $CdCl_2$ did not significantly alter the Cd content of the pancreas in rats[<259>]. Cd levels in the pancreas remained unchanged following administration of DMPS to animals not given any additional Cd exposure[<1420>].

6.1.9.3.12 Gastrointestinal tract, intestine

Cadmium levels in the intestine were slightly reduced following administration of DMPS[<35>]. Immediate i.v. administration of DMPS following i.v. administration of $CdCl_2$ reduced the cadmium burden in the murine gastrointestinal tract. Ca-DTPA was more effective[<395>]. Immediate combination therapy with DMPS (i.p.) and Ca-DTPA (s.c.) also reduced Cd levels in the gastrointestinal tract[<397>].

6.1.9.3.13 Bones

Cadmium depots in the skeleton were either unaffected by the immediate administration of DMPS[<992>] or else were slightly reduced[<991>] compared to the untreated control animals.

6.1.9.4 Combination therapy

Following chronic Cd exposure ($CdCl_2$ i.p. daily for 5 days), rats were given oral DMPS, DMPS + cysteine or DMPS + NAC for 3 days. The Cd content of the liver was reduced by DMPS administration whereby the Cd content in the cytosol fraction in particular was reduced. No effect of DMPS could be detected in the mitochondrial fraction. The additional administration of cysteine or NAC did not display any greater efficacy. Cd levels in the blood remained unchanged. DMPS also reduced Cd concentrations in the kidneys. The greatest effect was once again observed in the cytosol fraction whereas only less of an effect was observed in the mitochondria. The additional administration of cysteine or NAC largely eliminated the positive effect of DMPS[<1427>].

	Blood	Liver	Kidneys	Brain	Heart
Control animals	0.15	1.67	0.55	0.05	0.06
$CdCl_2$ (i.p.) + NaCl (i.p.)	0.35	43.47	47.68	2.59	5.52
$CdCl_2$ (i.p.) + methionine (oral)	0.19	19.77	17.06	1.42	3.07
$CdCl_2$ (i.p.) + DMPS (i.p.)	0.24	24.60	22.36	1.75	1.70
$CdCl_2$ (i.p.) + methionine (oral) + DMPS (i.p.)	0.23	13.76	7.79	1.04	2.17
$CdCl_2$ (i.p.) + DTPA (i.p.)	0.23	31.81	29.94	1.54	2.92
$CdCl_2$ (i.p.) + methionine (oral) + DTPA (i.p.)	0.25	15.20	12.74	1.47	1.58

Effect of various treatments on the Cd content of the blood (µg/dL) and organs (µg/g fresh weight) in rats poisoned with $CdCl_2$[<1428>]

I.p. administration of DMPS 48 hours after the last i.p. dose of $CdCl_2$ did not alter the excretion of Cd^{+2} in the urine or faeces of rats. Cadmium levels in the blood, liver, kidneys, brain and heart were nevertheless lowered. Cd-induced changes in the biochemical parameters measured in the liver, kidneys, blood and serum were partly reversible. This also applies to changes in zinc, copper and iron levels in the organs. If methionine (an amino acid containing sulfhydryl) was administered orally in addition to DMPS, then the faecal elimination of Cd also increased significantly. This led to lower Cd levels in the liver, kidneys and brain than those observed with DMPS alone[<1428>].

6.1.9.5 Influence on zinc and copper levels

Cadmium triggered elevated zinc levels in the liver and kidneys, presumably due to the induction of metallothioneins. DMPS did not affect high zinc levels in the liver but nevertheless reduced kidney concentrations. The Cu content in the liver was not substantially changed following Cd administration. In the kidneys, it increased substantially, especially in the cytosol fraction. DMPS lowered the values but the values recorded in the control animals were not, however, reached. Whereas the additional administration of NAC did not have a significant effect on zinc, combined administration of DMPS and NAC caused a significantly more marked reduction in Cu levels in the kidneys and liver than DMPS therapy alone. The Cd-induced reduction in Cu levels in the blood increased once again during treatment with DMPS[<1427>].

		Kidneys (µg/g moist weight)	Liver (µg/g moist weight	Blood (µg/ml)
Copper	Controls	2.57	7.29	3.99
	Cd	18.65	8.20	0.91
	Cd+DMPS	10.87	7.48	1.55
Zinc	Controls	19.79	24.45	3.94
	Cd	43.53	44.43	2.38
	Cd+DMPS	26.38	53.92	3.8

Copper and zinc levels in rats following administration of $CdCl_2$ or $CdCl_2$ and subsequently DMPS[<1427>]

Conclusion:
Only the immediate administration of high doses of DMPS is effective in the treatment of cadmium poisoning, if at all. Delayed onset of treatment is ineffective. DMPS can thus lead to an accumulation of the heavy metal in the kidneys, which can be prevented by alkalisation. Ca-DTPA appears to be more effective than DMPS. The results of combination therapies with various chelating agents are difficult to assess.

6.1.10 Ce - Cerium

DMPS accelerated the excretion of ^{144}Ce in rats provided that this was not firmly bound to proteins[<1494>].

Conclusion:
The efficacy of DMPS in cerium poisoning cannot be assessed.

6.1.11 Co - Cobalt

DMPS significantly reduced the lethality of cobalt salts[<207>]. Seven out of 14 mice (50 %) survived a lethal dose of cobalt chloride whereas all the control animals died[<395>]. Out of 15 poisoned rabbits, 13 animals (87%) survived following 6 days' treatment with DMPS. Only 3 out of 28 animals (11%) survived in the untreated control group.

Chelating agents	Survival rate (%)
Controls	0
Ca-DTPA	100
DMPS	50
DMSA	68.8

Survival rate of mice following administration of $CoCl_2$ and immediate i.p. administration of CA[<395>]

On prophylactic administration of DMPS before the heavy metal, 12 out of 15 animals survived (80 %) and the usual intoxication symptoms were absent[<260>]. The hypertensive effect of cobalt was greatly reduced[<207,260>]. In rats, no increase in leukocytes and erythrocytes was observed on simultaneous administration of DMPS. Cobalt-induced dysfunction of the isolated frog heart was soon cured on addition of DMPS[<260>].

In rats, the oral administration of $CoCl_2$ for 60 days prevented the uptake of ^{131}iodide in the thyroid gland and potentiated the excretion of this

radionuclide. If oral DMPS was administered concomitantly with $CoCl_2$, a statistically significant difference compared to the control group (NaCl s.c.) was no longer apparent[<1592>].

The urinary excretion of cobalt increased with DMPS[<260>]. Lipophilic Cd-DMPS complexes could be detected chromatographically in the urine[<395>]. Nevertheless, no significant influence on total body content and the distribution of cobalt in the liver, kidneys, brain and gastrointestinal tract of mice was detectable. Ca-DTPA was more effective in terms of survival rates and total body burden[<395>].

Eight out of 15 rats survived the LD_{100} of NaCN through injection of the Co-DMPS complex. All of the animals survived with prophylactic therapy[<767>].

Conclusion:
DMPS reduces the lethality of cobalt poisoning. Cobalt-induced disorders are reduced and the urinary excretion of heavy metals is increased. DMPS therefore apears to be a suitable antidote for the treatment of cobalt intoxication.

6.1.12 Cr - Chromium (chromate/dichromate)

Administration of DMPS	Liver	Kidneys	OCT	Urine	Faeces
Concomitantly with dichromate	19	13	3	114	38
Immediately after dichromate	52	47	23	133	86
30 min after dichromate	94	97	81	68	126

Effect of the period between administration of dichromate and DMPS on the efficacy of the chelating agent (as % of the untreated controls)[<1466>]

Concomitant administration of DMPS reduced the toxic effects of sodium dichromate on homogenised liver, lungs and stomach[<154>]. The growth-inhibiting effect of the chromium compound on HeLa cells was reduced. Higher doses were thus more effective. The subsequent administration of DMPS was ineffective although the chromium content of the cells was somewhat reduced. Similarly, the prophylactic administration of DMPS proved to be ineffective, probably because the DMPS was already oxidised before addition of the dichromate[<1414,1415>]. In the presence of DMPS, the chromium uptake by erythrocytes from dichromate was 20 times less than in the controls. If DMPS was, however, added only latter, then already bound heavy metal was no longer excreted[<745>]. The metal bound to plasma proteins from a suspension of Cr_2O_3 (particle size < 5 µ) . In contrast to EDTA, the addition of DMPS did not have a significant effect on the bound quantity of metals[<439>].

The immediate administration of DMPS reduced the toxicity of dichromate in mice[<1414>]. 40 % of rabbits survived an LD_{100} poisoning[<207>]. DMPS was most effective on concomitant administration of potassium dichromate $K_2Cr_2O_7$ (application of a mixture). Administration after 30 minutes displayed only minor efficacy[<1466>].

Histochemical investigations showed that haemodynamic disorders and kidney and liver damage induced by acute dichromate poisoning were reduced by concomitant administration of DMPS and ephedrine. Regeneration was more rapid and more complete[<1325>].

The chromium content of the liver [<129,1414,1466>], kidneys[<129,1414,1466>], testes[<129>] and brain[<129>] was reduced. Chromium excretion was increased in the urine and reduced in the faeces[<1414,1466>]. The chromium-induced increase in ornithine carbamyl transferase OCT activity in the serum (indicative of the toxic effect of dichromate on the liver) was reduced[<1414,1466>].

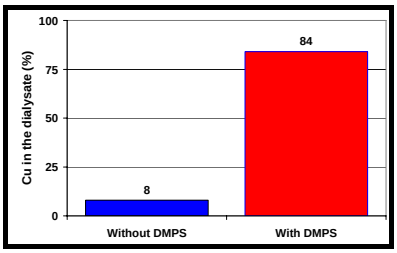
Conclusion:
Cr(VI) compounds are toxic due to their high oxidation potential. They are mutagenic and harmful to DNA. Cr(VI) can be reduced to less toxic Cr(III) by rapid administration of DMPS.

6.1.13 Cu - Copper

6.1.13.1 Cells and organelles

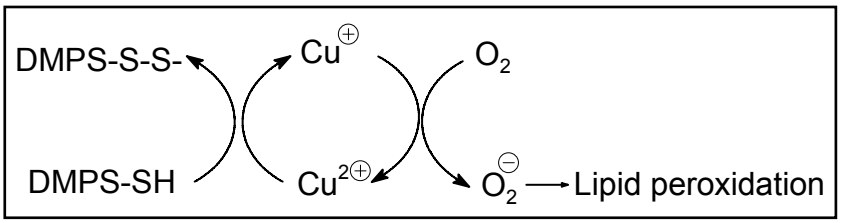
Cu^{2+} ions blocked the function of glutamate receptors through attachment to cysteine groups. The metal ions were mobilised by the effect of DMPS such that impulses were again triggered through glutamate[<1364>].

In vitro, DMPS loosened copper from its binding to proteins. The bluish red colour turned yellowish green – the colour of the DMPS-Cu complex[<1567>]. More copper diffused into the dialysate on addition of DMPS to haemolysed erythrocytes[<1227>].



Fraction of Cu in the dialysate after dialysis of haemolysed erythrocytes <1227>

In investigations in CHO cells, the addition of Cu^{2+} increased the toxic effects of DMPS on the cells[<575,576>]. The addition of the enzyme catalyse prevented this effect. The oxidation of DMPS with formation of H_2O_2 is believed to be responsible[<576>].



In vitro, copper sulfate and copper chloride exhibited haemolytic effects on human erythrocytes[<1,3,6>]. On addition of an equimolar quantity of DMPS, copper-induced haemolysis increased from 15 to 25 %[<5,6>]. Contrastingly, no corresponding activity was observed with the metal-free DMPS solution[<3>]. If excess copper remained, (Cu:DMPS = 3.1), no increase was observed[<7>]. With a Cu:DMPS ratio of 10:1, the lysis of erythrocytes was markedly reduced compared to the controls[<8>]. In contrast, DPA and DMSA reduced the rate to approximately 2 %[<1,6,7>]. Albumin[<1,6,7>], mercaptodextran[<3,6>] and triene[<7>] also lowered the rate of haemolysis. The reaction was also suppressed when DMPS was added to Cu(II)-treated erythrocyte membranes[<4>].

Inhibition of super oxide dismutase CuZn-SOD is assumed to be responsible for increased haemolysis[<7>]. Chemiluminescence measurements showed that, on interaction of copper(II) with DMPS, activated oxygen molecules were formed, which were responsible for the subsequent reactions. The reaction was suppressed by the addition of superoxide dismutase or catalase enzymes. The reduction of Cu^{2+} to Cu^{+} was suggested as a potential primary reaction. The Cu^{+} then transfers an electron to the oxygen. The superoxide radical obtained subsequently leads to haemolysis via lipid peroxidation[<4>]. The reaction products of lipid peroxidation (including malondialdehyde could be detected *in vivo* in the blood[<159>].

Conclusion:
DMPS increases the haemolysis of erythrocytes in vitro, in conjunction with copper. Possible clinical consequences must be investigated in vivo.

6.1.13.2 Acute poisoning

DMPS was shown in laboratory animal experiments (mice, rats, rabbits and sheep) to be an effective antidote to copper poisoning[<1,63,706,911>]. On acute intoxication, it increased the survival rates[<38,250,524, 676,678,937,1135,1136,1402,1405>]. Thus, 82% of the mice survived poisoning with the LD_{99} of copper sulfate[<676>]. The LD_{50} of $CuCl_2$ in mice was tripled[<58,1135>], the LD_{50} of $CuSO_4$ in rats was increased by more than a factor of 11 from 43 to 495 mmol/kg[<1402,1405>]. DMPS was the most effective of the chelating agents investigated[<678>].

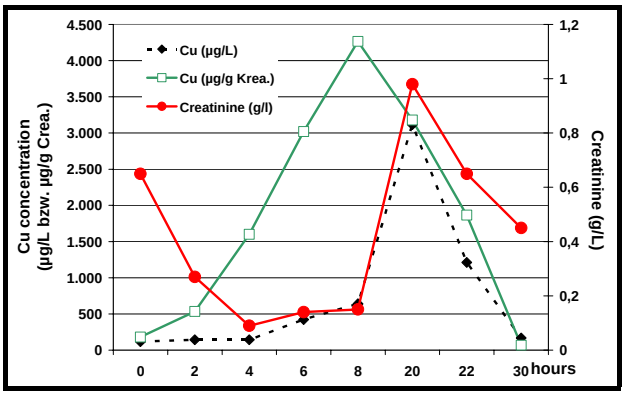
$CuCl_2$	LD_{50} = 59 mg/kg BW
$CuCl_2$ + DMPS	LD_{50} = 143 mg/kg BW[<1136>]
$CuCl_2$	LD_{50} = 0.67 mmol/kg BW
$CuCl_2$ + DMPS	LD_{50} = 2.01 mmol/kg BW[<58>]
$CuSO_4$	LD_{50} = 43 mg/kg BW
$CuSO_4$ + DMPS	LD_{50} = 495 mg/kg BW[<1402>]

Chelating agents	Survival rate $CuSO_4$ LD_{99} (%)	Survival rate $CuSO_4$ LD_{95} (%)	Survival rate $CuSO_4$ LD_{50} (%)
Ca-DTPA	13		53
Zn-DTPA	20	20	
BAL	20	20	
DMSA	20	20	80
Triene	33	33	40
DMPS	82	83	87
DPA	23	23	73

Influence of CA (i.p.) on the survival rate of mice 20 minutes after administration of $CuSO_4$ (LD_{50}, LD_{95} or LD_{99})<676,678>

The survival rates were higher than with DPA (3.3-fold)<678,1402>, which is recommended primarily for the treatment of Wilson's syndrome (copper storage disease)<578>. If copper and DMPS were administered as a complex, the mice survived the double LD_{50} of $CuSO_4$ without any symptoms of copper poisoning<937>. The mean survival time was prolonged from one day to 13.1 days<250>.

Alkalisation of the urine with $NaHCO_3$ did not have any significant effect on the survival rate, while acidification with NH_4Cl increased the mortality<38,1402>.



Dependence of survival rates of mice on DMPS dose on poisoning with 300 or 500 mg CuSO4/kg KG<38,1402>

	Survival rate (%)	Mean survival time (days)
$CuSO_4$	0	3
$CuSO_4$ + DMPS	90	12.0
$CuSO_4$ + $NaHCO_3$	40	4.6
$CuSO_4$ + NH_4Cl	0	2.0
$CuSO_4$ + DMPS + $NaHCO_3$	80	5.5
$CuSO_4$ + DMPS + NH_4Cl	20	3.1

Influence of alkalisation and acidification on the survival rates of mice (500 mg $CuSO_4$/kg KG s.c.)<38,1402>

Investigation of the dependence of the survival rates on the dose of DMPS administered ($CuSO_4$ 300 or 500 mg/kg BW s.c.), then a maximum can be found at a dose of ≈ 100 mg/kg BW. Above this, the survival rate again falls<38,250,1402>. As the LD_{50} of DMPS in the mouse is 1710 mg/kg<566>, it may be assumed that the DMPS-copper complex has toxic effects at higher doses<250>.

Conclusion:
DMPS increases the survival rate and survival time on copper poisoning. It has thus proved to be the most effective of the chelating agents investigated.

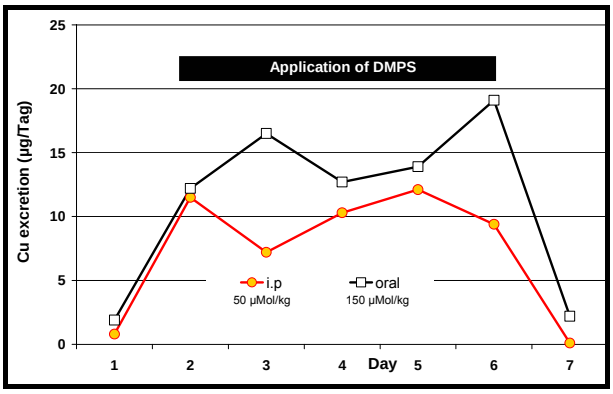
6.1.13.3 Excretion of copper

DMPS (mg/kg)	Cumulative Cu excretion
25	171 %
50	197 %
100	235 %

Dependence of the cumulative Cu excretion on the DMPS dose (as % of the untreated controls)<937>

CA	Cu in the urine (µg/24 h)
Controls	10.02
DTPA	10.76
BAL	12.84
DMSA	14.04
Triene	15.44
DMPS	24.64
DPA	26.26

Influence of i.p. administration of CA on Cu excretion in rat urine<1163>



Comparison of the oral and parenteral administration of DMPS on the renal excretion of Cu (µg/24 h)<1163>

The daily copper excretion was increased on administration of DMPS[<38,1163>]. Renal excretion in particular was raised [<1163,1369>] while faecal excretion was not affected[<1163>]. The cumulative total excretion rose with increasing doses of DMPS[<1163>]. DMPS thus displayed a similar effect to that of DPA, which is the drug of choice in the treatment of Wilson's syndrome. It was significantly superior to triene, which is also used in the treatment of Wilson's disease[<1163>]. A three-fold higher dose of oral DMPS must be administered in order to achieve the same effect as with i.p. administration[<1163>].

In two sheep previously given $CuSO_4$ for 5 weeks, oral administration of DMPS increased the urinary excretion of copper two- to three-fold[<1369>].

6.1.13.4 Distribution of copper

In chronic copper poisoning, the heavy metal accumulates particularly in the mitochondria of the liver[<699>], where it is bound to the SH groups of the proteins[<1402>]. The administration of DMPS led to a reduction, depending on the treatment regimen[<6,38,937,1163,1402>] or to no change[<699>] in the copper content of the liver. Higher doses were more effective[<1402>]. The reduction affected the various hepatular subfractions – the mitochondria, microsomes and cytoplasm[<1402>]. The copper level in the kidneys was reduced[<38,179,937,1163,1402>]. Higher doses were more effective[<1402>]. The heavy metal content of the blood, brain and intestines was not significantly affected[<38,1163,1402>]. Copper was removed from the erythrocytes by DMPS[<1226>].

DMPS (mg/kg)	Liver	Kidneys	Blood
50	72	50	76
100	41	46	99
200	31	42	99

Cu content in relation to the DMPS dose (as % of untreated controls)[<38,1402>]

Time (days)	Liver	Kidneys
1	66	14
2	48	27
5	120	88

Change in copper content in the liver and kidneys after a single dose of DMPS, 20 minutes after $CuSO_4$ (as % of the untreated controls)[<937>]

After withdrawal of the DMPS, there was a redistribution of the copper within the body. The liver and kidneys were again burdened with the heavy metal from other compartments[<937>]. The administration of DMPS disrupted the steady state between the various compartments in which copper is stored by reducing the liver and kidney reserves. It thus exerted a "drag effect" on depots that cannot be reached directly by DMPS[<1163>].

Animals developed renal tubular necrosis 24 hours after copper administration. The early administration of DMPS prevented the toxic effects of the metal on the liver and kidneys[<937>].

By alkalisation with $NaHCO_3$, the positive effect of DMPS on the liver and kidneys could be increased. Acidification with NH_4Cl, however, led to increased copper depots, especially in the liver[<38,1402>].

Concomitant administration of DMPS and triene or DPA did not show any synergistic effects[<1163>]. Concomitant administration of decholion (choleretic) suppressed the efficacy of DMPS[<250>]. Excretion increased in the presence of the tripeptide, glycyl-glycyl-histidine, GGH[<1163>]. The additional administration of phenobarbital did not affect Cu excretion[<1163>].

	Kidneys	Liver	Blood
$NaHCO_3$	88	81	95
NH_4Cl	167	100	98

Effect of alkalisation or acidification on the efficacy of DMPS therapy (as % of the animals treated with DMPS alone)[<38>]

The subconjunctival administration of DMPS prevented the toxic effects of copper foreign bodies in rabbit eyes[<534>].

Conclusion:
DMPS increases the renal excretion of copper. Heavy metal levels in the kidneys and liver were lowered. The efficacy of DMPS was equivalent to that of DPA, which is the drug of choice in Germany for the treatment of Wilson's syndrome.

6.1.14 Fe - Iron

In rats, the administration of DMPS 24 hours after administration of iron triggered a transient rise in the urinary excretion of iron but reduced faecal excretion at the same time. Overall iron excretion iron was reduced compared to that recorded in the control animals[<82>].

The subconjunctival administration of DMPS prevented the toxic effect of iron foreign bodies in rabbit eyes[<534>].

Conclusion:
The efficacy of DMPS in iron poisoning cannot be evaluated. Desferioxamin (infusion) or Deferasirox (oral) is the substance of choice in the treatment of iron poisoning.

6.1.15 Fr - Francium

Francium (^{221}Fr) is formed on the radioactive decomposition of the α-emitter, actinium (^{225}Ac). Concomitant administration of DMPS did not prevent ^{221}Fr depots from forming in the kidneys. In Cynomolgus monkeys, the ^{221}Fr levels in the kidneys and blood corresponded to those recorded in the control group[<648>].

Conclusion:
DMPS appears to be ineffective in the treatment of francium poisoning.

6.1.16 Ga - Gallium

Rats received an oral suspension of gallium arsenide for 3 x 5 days. This led to increased gallium values in the blood, liver, kidneys, brain and spleen. Subsequent i.p. administration of DMPS triggered a minor, albeit statistically insignificant, decrease in concentrations. DMSA was even less effective. The GaAs-induced changes in biochemical and immunological parameters partially improved[<423>].

Conclusion:
The efficacy of DMPS in gallium poisoning cannot be evaluated.

6.1.17 Hg - Mercury

Mercury has a high affinity for sulfhydryl groups[<564,727,991,1066,1294,1544>]. Almost every protein is, therefore, a potential reaction partner[<60,1544>]. Enzymes are generally inactivated through the deposition of heavy metals[<727,1066,1294,1453>], and physiological metabolism is disrupted[<727,1294,1453>]. The resulting clinical symptoms may possibly appear only after longer periods[<1066>]. The disorders could be prevented by prophylactic administration of DMPS[<1453>].

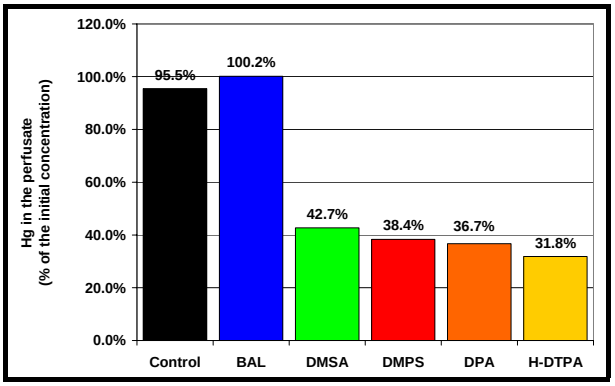
6.1.17.1 Investigations *in vitro* and in cells

The molecular biological effect of mercury essentially affects the reaction of mercury ions with sulfhydryl groups. Due to the varying distribution, organic and inorganic compounds have different effects. Inorganic compounds primarily affect kidney function. Contrastingly, organic compounds such as methyl mercury mainly affect the CNS due to their lipid solubility[<1102>]. In addition, organic compounds accumulate to approximately 90%[<1195>] in the erythrocytes[<1102>], where they are bound to the SH groups of glutathione and haemoglobin[<1195>]. The ratio of the mercury content in the erythrocytes to that in the plasma therefore allows conclusions to be drawn relating to the type of mercury compound[<1102>].

6.1.17.1.1 Inorganic mercury compounds

^{1}H-NMR investigations in erythrocytes showed that Hg^{2} initially reacts with glutathione and haemoglobin to form a complex. If everything was complexed with glutathione, the heavy metals would be deposited on ergothioneines. Following addition of DMPS, the mercury bound to the ergothioneine was first mobilised and, at higher concentrations, also that bound to glutathione, although the latter was not mobilised completely<1198>.

Investigations in human serum showed that DMPS releases Hg^{2+} from its binding to serum proteins in a concentration-dependent manner. The carboxyl bound heavy metal is initially mobilised followed by the heavy metal bound to the sulfhydryl groups whereas the globulin content remains unchanged<1294>. *In vitro*, DMPS mobilised over 90% of the mercury bound to albumin<9,10,1535>.



Hg remaining in the perfusate after *in-vitro* haemodialysis (90-minüte dialysis)<407>

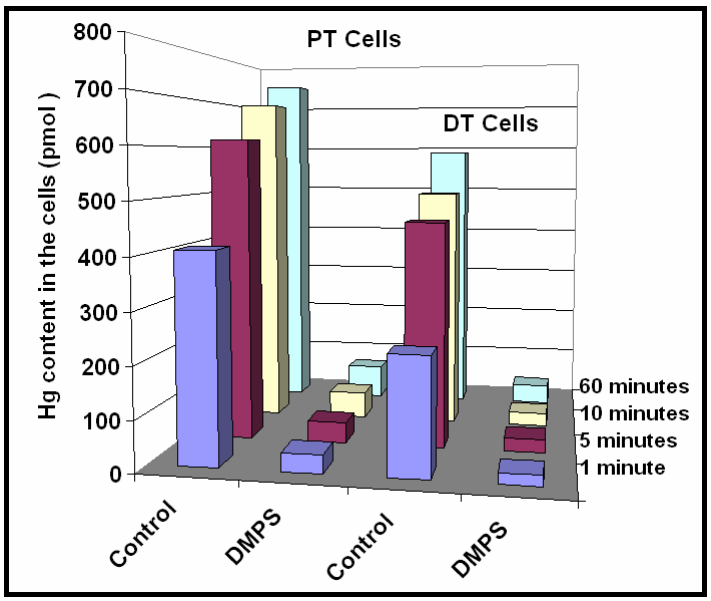
The Hg-DMPS complex is dialyzable. Haemodialysis experiments with plasma and $HgCl_2$ showed *in vitro* that the quantity of mercury passing into the dialysate is increased on addition of DMPS. Whereas 95.5% of the $HgCl_2$ remained in the plasma after 90-minute dialysis without addition of DMPS, only 38.4% were found in the plasma after adding 1 mmol DMPS<407>.

Phytochelatines, which are peptides containing sulfur, are part of the cellular detoxification system for plants in which they bind to heavy metals and thus reduce their toxicity. On addition of DMPS to isolated protein, mercury was released from its binding and unbound phytochelatin was again released. DMSA, on the other hand, cannot release Hg from its binding to phytochelatins<631>.

Histological sections of the renal cortex of rabbits treated with $HgCl_2$ were prepared. The sections of the poisoned animals were placed in fixing baths to which various chelating agents were added. The chelating agents lowered Hg levels in the following order: DMSA >> DMSA ≈ DPA >> EDTA. In a second series of tests, sections excised from untreated control animals were initially placed in a solution containing $HgCl_2$ and then in a chelating agent solution. These lowered Hg levels once again. DMSA >> DMSA ≈ DPA >> EDTA. All chelating agents also lowered the Zn levels in the sections in both experiments<705>.

In vitro, $HgCl_2$ inhibited the enzyme activity of lactase in the small intestine homogenisates of guinea pigs. The addition of DMPS reduced the inhibition. Enzyme activity was completely restored with a Hg:SH ratio of 1:1. Concomitant or delayed administration of DMPS reduced the $HgCl_2$-induced blockade of the Na-K-ATPase enzyme by up to 70%. Enzyme inhibition was, however, already irreversible on delayed addition<45,634>.

In the case of blood platelets, DMPS prevented the $HgCl_2$-induced uptake of glutamate binding<195a,196>. In experiments with opossum kidney cells, concomitant administration of DMPS prevented the cytotoxic effects of $HgCl_2$<238>. The addition of $HgCl_2$ to cortical cell cultures led to the destruction of



Reduction in Hg-uptake in proximal and distal tubular renal cells<820>

approximately 50% of the nerve cells. The addition of DMPS prevented this effect. EDTA was ineffective[<857>].

DMPS is a highly effective inhibitor of mercury accumulation in proximal and distal tubular renal cells. It prevented the uptake of Hg^{2+} in cells by up to 60%[<820>]. *In vitro*, Hg^{2+} is transported and bound in rat kidney luminal and basolateral membrane vesicles within 5 seconds. The addition of DMPS reduces the deposition of heavy metals[<1598>].

Perfusion experiments on proximal rabbit kidney tubules showed that Hg^{2+} is taken up relatively quickly and deposited in tubular epithelial cells. This leads to pathological changes and ultimately to cell necrosis. Concomitant administration of DMPS prevented Hg^{2+} uptake and thus the pathological changes. DMPS is thus obviously actively transported into cells via the OAT (Organic Anion Transport) system. The addition of the OAT inhibitor, glutamate, or PAH, prevented the effect of DMPS. If DMPS was added to the solutions after Hg^{2+}, already bound Hg^{2+} was again released and could be detected in the perfusion solutions[<1597>].

In vitro, DMPS blocked Hg-induced aggregation of spleen cells in a dose-dependent manner and thus reduced the proliferative response of spleen lymphocytes. *In vivo*, DMPS reduced $HgCl_2$-induced antibody formation in the spleen and deposition in immunocomplexes in the kidneys in sensitive mouse strains. It thus prevents Hg-induced immunological and immunopathological effects[<620>].

The addition of $HgCl_2$ triggered a reduction in glutamate binding to synaptic membranes isolated from rat brains. The addition of DMPS, DMSA or BAL did not prevent this effect (contrary to lead-induced inhibition)[<1362>].

Following incubation of CHO cells with inorganic mercury, the addition of DMPS lowered the Hg content of the cells and prevented any lethal damage[<900>]. In lysed reticulocytes, DMPS largely prevented the inhibition of protein synthesis by mercury[<900>].

Pre-incubation of renal cells and hepatocytes with DMPS reduced the cytotoxic effects of $HgCl_2$[<1447,1460>]. The ototoxic effects of mercury on the capillary cells of the "spiral organ" could be avoided in guinea pigs by concomitant administration of DMPS[<1332>].

Neither the prophylactic addition of DMPS nor the addition of DMPS after mercury prevented the destruction of D2 dopamine receptors in corresponding rat brain homogenisates[<1274>].

The excellent binding of DMPS to mercury was used for in cell experiments to remove any heavy metal bound to the cell exterior[<1127,1595>].

Conclusion:
In-vitro investigations and cell experiments confirm the excellent effect of DMPS on inorganic mercury poisoning.

6.1.17.1.2 Organic mercury compounds

Erythrocyte-bound methyl mercury was ousted from the cells on the addition of chelating agents[<1157,1195>]. To this end, it was mobilised from its binding to glutathione[<10,236>]. In the case of haemolysed erythrocytes loaded with methyl mercury, free glutathione could again be detected by ^{1}HMR spectroscopy following addition of DMPS[<1197>].

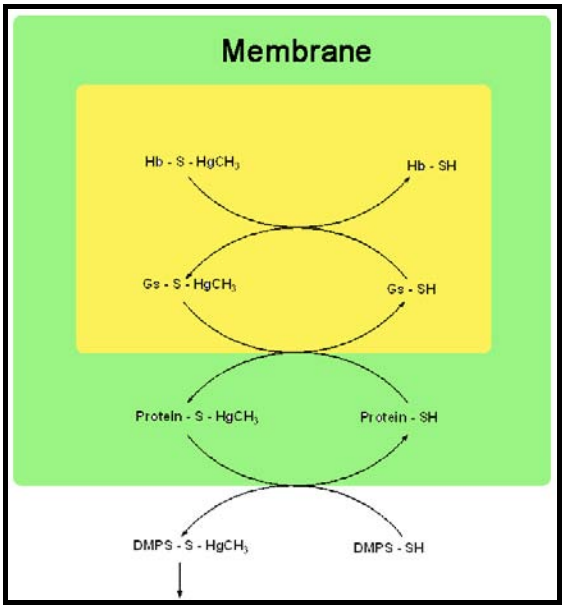
DMPS	21.0
Glutathione	11.5
Haemoglobin	10.7
Ergothioneine	7.9

Complex-forming constants for methyl mercury[<1195>]

Efficacy fell in the following order: DMSA > DMPS > DPA ~ N-Acetyl-Penicillamine. The efficacy of the chelating agents rose with increasing concentrations. DMPS mobilised up to 80% of the heavy metal deposited[<10>].

In contrast to DMSA, the DMPS methyl mercury complex was partly deposited in the erythrocyte membrane[<1157,1195>]. The effect was observed in both human and rat erythrocytes[<1158>].

^{1}H-NMR investigations showed that the addition of DMPS to a suspension of intact human erythrocytes released the cell-bound methyl mercury relatively quickly. Due to the rapid reaction, the authors presume that DMPS must not penetrate the cell membrane for this purpose but traps



Possible mode of action of DMPS on intracellularly bound methyl mercury (Hb = haemoglobin, Gs = glutathione)<1195>

the methyl mercury on the outside of the membrane, thus setting a chain reaction in motion via which the intracellularly bound heavy metal is transported from the cell<1195>.

In the case of hepatocytes, the deposition of methyl mercury in the cells was reduced by up to 90% on concomitant administration of DMPS<10>.

CH_3-Hg acted as a rat brain muscarinic receptor antagonist. *In vitro*, DMPS released the heavy metal compound from its binding and thus restored the functionability of the receptors<936,1552>.

CH_3-Hg passes through the blood-brain barrier where it is transported as a complex with S-containing amino acids by a special "L" carrier. This effect was investigated under experimental conditions on single layers of endothelial brain cells of calves. DMPS and the DMPS-MeHg complex did not affect the cell uptake of ^{3}H-leucine, i.e. they were not transported by the carrier through the blood-brain barrier<945>.

In contrast to the MeHg-L-cysteine complex, the DMPS mercury complex is not ousted by the "Large Neutral Amino Acid Transporter" LAT1 and LAT2 in frog oocytes<1349>.

CH_3-HgCl blocks the Ca^{2+} channels in rat phaeochromocytoma cells. The blockade is partially removed on adding DMPS. DPA was ineffective<857>.

The excellent binding of DMPS to mercury was used to remove CH_3–Hg from the vessel exterior<882>. In *in-vitro* experiments on rat capillary membrane vesicles, the addition of DMPS removed the mercury bound to the surface of the vesicles<374>.

Conclusion:
In-vitro investigations and experiments in cells confirm the excellent effect of DMPS on organic mercury poisoning.

6.1.17.2 Acute poisoning

6.1.17.2.1 Survival rates

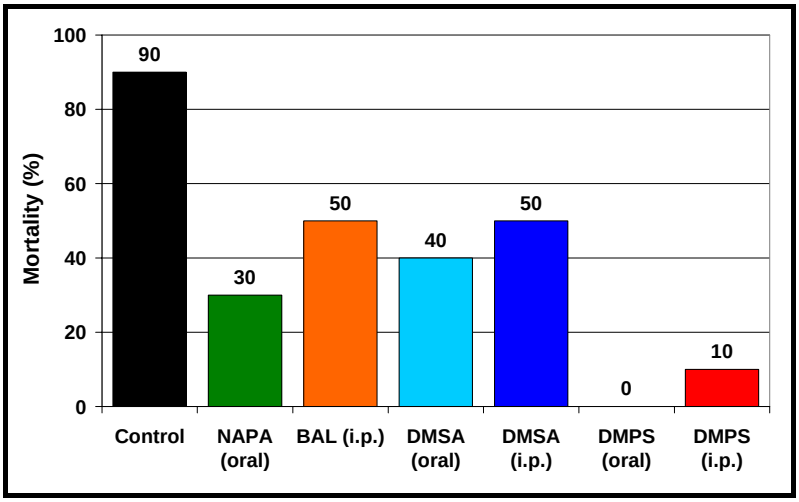
6.1.17.2.1.1 Inorganic mercury compounds

Both oral and parenteral administration of DMPS reduced the lethal effect of $HgCl_2$<990,991>. 60 - 80 % of mice survived poisoning with 10 mg $HgCl_2$/kg BW i.p. [LD_{50} ($HgCl_2$) = 6.72 mg/kg BW]<134,679>, while 93 % of the control animals died<679>. DMPS increased the survival rates<2,679,990,1164,1165,1417> and the survival times<1164,1165> on poisoning with inorganic mercury. The survival rates increased with the doses of DMPS. Histologically, only very slight, $HgCl_2$-induced pathological changes were detectable in the liver and kidneys<679>.

The mortality rate of mice following a single, oral dose of $HgCl_2$ was reduced from 90% to 10 or 0% following i.p. or oral administration (15 minutes after $HgCl_2$). DMPS was thus superior to NAPA, BAL and DMSA. The total body burden was reduced<990>. Six out of 10 rabbits survived a dose of 40 mg $HgCl_2$/kg BW<1072> following treatment with DMPS<1072>.

A prerequisite was an early start of therapy<1400>. If 5 days of oral treatment with DMPS was initiated 6 hours after i.v. administration of $HgCl_2$, the mortality rate fell in rats. If treatment did not

begin until 24 hours after administration of Hg, an effect could no longer be detected. The mean survival time was generally prolonged[<1164,1165>].



Mortality of mice following administration of $HgCl_2$ (400 µmol/kg oral). The CA (1.600 µmol/kg, BAL 400 µmol/kg) were administered 15 min. later[<990>]

$HgCl_2$ dose(mg/kg)	0.75	1.0	1.25
Controls	8.6	44.4	75
DMPS after 6 hours	0	5.6	42
DMPS after 24 hours	11/1	33.3	75

Influence of the onset of 5 days' treatment with DMPS (oral) on the mortality rate (%) of rats after i.v. administration of $HgCl_2$[<1164,1165>]

Concomitant administration of DMPS lowered the $HgCl_2$ mortality rate in rats. Whereas 4 out of 18 animals in the control group died, all of the treated animals survived. The activity of the carboanhydrase (CA) and ATPases enzymes from the mucosa of the duodenum or renal cortex decreased with increasing $HgCl_2$ concentrations. Concomitant administration of DMPS largely prevented this decrease. Morphological changes in the kidneys were prevented. Compared to the untreated animals, no evidence of necrosis was found on histological examination. The $HgCl_2$-induced rise in serum BUN values remained within the normal range in treated animals[<1417>].

CA	Survival rate (%)
BAL	38
DPA	52
DMPS	60
DMSA	48

Survival rate of mice following i.p. administration of $HgCl_2$ (LD_{98}) and various CA[<679>]

72% of rabbits survived LD_{100} poisoning with $HgCl_2$ and 90% LD_{80} following administration of DMPS. No protein and no increased nitrogen levels could be detected in the urine of the surviving animals. The necrotic changes in the liver were reduced. Diuresis occurred instead of anuria[<207>].

Conclusion:
DMPS increases survival rates following acute poisoning with inorganic mercury. It was thus the most effective of the antidotes investigated.

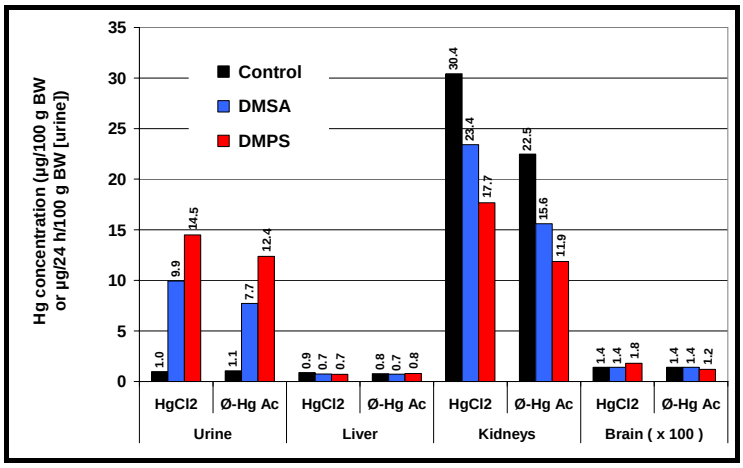
6.1.17.2.1.2 Organic mercury compounds

DMPS reduced the lethal effects of methyl mercury in pregnant dams and increased their survival rates[<498>]. Seven out of 10 rabbits survived poisoning with 30 mg/kg Granosan[<1072>], a pesticide containing mercury.

Conclusion:
DMPS increases survival rates following acute poisoning with organic mercury. However, only a few investigations have been carried out.

6.1.17.3 Subacute and chronic poisoning

6.1.17.3.1. Excretion and total body burden



Influence of DMPS or DMSA on Hg excretion in the urine and Hg levels in the liver, kidneys and brain of rats following chronic exposure to $HgCl_2$ or phenyl mercury acetate[<216>]

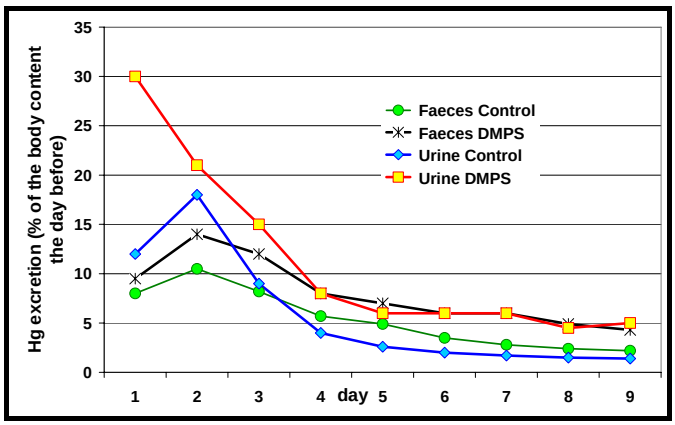
On poisoning with inorganic, organic, metallic or vapour mercury, DMPS accelerated the heavy metal excretion and thus led to a lower total body burden compared to the untreated control animals. Excretion was increased mainly at the start of treatment[<216,1294>].

In particular, the deposits in the kidney were reduced[<274,276,337,376>]. The increased excretion took place primarily via the urine. Factors other than chelate formation apparently play a role in the increase in renal excretion[<279>]. Because metabolisation was limited to approximately 40% of the kidney load per dose with increasing DMPS concentrations, an anionic transport mechanism may be involved[<744>]. Excretion via the faeces is usually only of minor significance.

Treatment efficacy depended on the time of DMPS administration. The highest heavy metal excretion and the most marked reduction in organ load were achieved by immediate onset of treatment[<455>]. Prophylactic administration of DMPS was also successful[<687,822>]. But even a delayed onset of therapy was worthwhile[<774>]. DMPS treatment was still effective even after more than one month post-administration[<179,216>]. However, when treatment is delayed, there is a risk that the heavy metal-induced pathological changes are already irreversible[<706,1535>].

In addition, efficacy also depended on the dose of DMPS administered. Higher doses were more effective. Both oral and parenteral administration of DMPS were effective[<991>]. On oral administration, a 2.5- to 3-fold higher dose was necessary in order to achieve the same effect as parenteral administration[<455>].

6.1.17.3.1.1 Inorganic mercury compounds



Effect of DMPS (i.p.) on the excretion of $HgCl_2$ (i.v.) in rats (% of the body content the day before[<1294>].

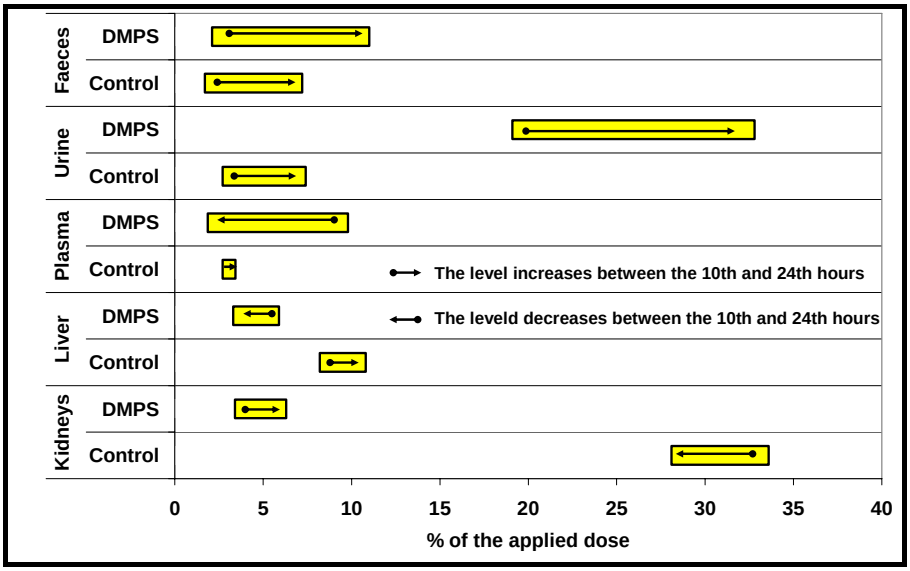
The administration of DMPS, whether administered immediately or delayed, increased mercury excretion in the urine[<10,211a, 627>]. Excretion was increased mainly at the start of treatment[<216,453,1294>]. Higher doses were more effective, early onset of treatment was more effective than a delayed start and parenteral administration was more effective than oral administration at the same dose (DMPS is not 100% bioavailable)[<696>]. Mercury-induced oliguria was markedly reduced[<1535>].

Excretion of the heavy metal in the bile was increased with DMPS[<276>] or equivalent to that of the controls[<278>]. While without DMPS, the heavy metal was bound only to high-molecular fractions of the bile, the heavy metal (Hg^{2+}) was found both *in vivo* and *in vitro* predominantly in the low-molecular fractions after administration of DMPS or BAL[<1441>]. The increased faecal excretion of DMPS was also detectable after parenteral administration of

DMPS[<211a,276,277,376,687,1600>], and not only affected the non-absorbed fraction of DMPS on oral administration. In other studies, the excretion in the faeces was unchanged[<10>] or somewhat reduced[<463>]

I.p. administration of DMPS for 9 days, beginning 6 hours after i.v. administration of $HgCl_2$, lowered the Hg content in rat organs from 32.3 to 3.2 % of the dose administered. Excretion via the urine increased from 37.5 % to 62 % and in the faeces from 29.6 to 32.5 %[<1294>].

The administration of i.m. DMPS 4 and 7 hours after i.v. administration of $HgCl_2$ increased Hg concentrations in rat urine approximately 4-fold. The Hg content of the bile, faeces and intestines was also raised. Both DMPS injections increased the total excretion of Hg 3-fold[<276,279>].



Change in the Hg levels in various rat organs. Administration of DMPS i.m. 4 and 7 hours after injection of $HgCl_2$. Mercury was assayed 10 and 24 hours after injection of $HgCl_2$-[<279>]

Six hours after the i.v. administration of $HgCl_2$, 5 days' treatment with various chelating agents (50 µmol/kg/day i.p.) was initiated in rats. DMPS was the only antidote investigated to increase the total excretion. Renal excretion was high, particularly on the first two days of treatment. Compared to the controls, faecal elimination was somewhat reduced[<453>].

Immediate i.v. injection of DMPS following i.v. administration of $HgCl_2$ reduced the total body burden in mice with higher doses proving to be more effective[<395>].

Prophylactic i.p. treatment with DMPS (last dose administered 2 hours before i.v. administration of $HgCl_2$ increased both the biliary and renal excretion of mercury in rats. Whereas in the control animals, 12.2 % of the dose administered was excreted within the first 24 hours, 1.4% of which was in the bile, the treated animals excreted 30.5% during the same period, including 2.6% in the faeces. The largest quantity was eliminated in the faeces within the first two hours[<278>].

Prophylactic i.m. administration 90 minutes before i.p. administration of $HgCl_2$ led to an increase in Hg excretion via the urine in rats within the first 24 hours. Faecal excretion did not change significantly[<687>]. Considering that the half-life of DMPS is approximately 19 minutes is rats, a more marked effect can be anticipated with a shorter waiting period between prophylactic administration of DMPS and the administration of the heavy metal compound.

Prophylactic administration of DMPS did not prevent $HgCl_2$-induced changes in the hydroxyproline content (parameter for collagen metabolism) in rat serum[<1344>]. The $HgCl_2$-induced excretion of hydroxyproline in the urine was again reduced to the control value in rats following single i.p. administration of DMPS.

I.m. administration of DMPS 4 and 7 hours after i.v. administration of $HgCl_2$ increased urinary excretion in particular but also faecal excretion in rats. Higher levels were determined in the bile[<1164>].

Both immediate and delayed (beginning 8 days after the administration of $HgCl_2$) therapy with 5 mg/kg DMPS i.v. lead to greater excretion of Hg in the urine as well as in the faeces[<376>] in rats.

I.m. injection of DMPS 4 and 7 hours after i.v. administration of $HgCl_2$ increased the urinary and faecal excretion of Hg in rats. Immediately after DMPS injection, Hg concentrations in the bile rose approximately 10-fold, decreasing rapidly thereafter. Hg levels in the organs and excretion were

measured 10 and 24 hours after Hg administration. Even without additional DMPS administration, urinary excretion in the DMPS group increased by 12.9 % of the Hg dose administered compared to just 4.7 % in the control group.

The addition of DMSA or DMPS increased the excretion of Hg in urine. Faecal elimination was unaffected[<10>] or increased[<211a>].

DMPS and DMSA (i.v., immediate administration) increased renal excretion and thus the cumulative total excretion in mice given i.v. $HgCl_2$. Faecal excretion remained unchanged. Hg levels were lowered to approximately 30% of those of the control animals[<9>] when oral treatment of 4 days' duration was initiated immediately[<9>].

Mice were given DMPS or DMSA one day after repeated dosing with $Hg(Ac)_2$. DMPS increased urinary excretion more than DMSA following both oral and i.p. administration. DMPS also increased faecal excretion, which, with DMSA, was less than that observed in the control animals. DMPS thus lowered the total body burden more effectively than DMSA[<459>].

	Liver	Kidneys	24-hour urine	24-hour faeces
Controls	11.3	31.9	15.6	5.3
DMPS	9.2	21.8	26.4	5.4
DMSA	11.1	25.1	22.9	6.2

$HgCl_2$ content in rats following single i.p. administration of DMPS or DMSA (50 mol/kg)[<1162>]

Rats were given 50 mol/kg DMPS or DMSA via the i.p. route 6 hours after i.v. administration of mercury. DMPS essentially increased excretion via the urine and was therefore the most effective antidote in lowering Hg levels in the kidneys[<1162>].

Rats were given oral DMPS or DMSA for 4 days 24 hours after i.v. administration of $HgCl_2$. Taking bioavailability into account, excretion was three times greater with DMPS than with DMSA. "Our experiments ... showing that at the moment DMPS is the most efficient chelant for removal of inorganic mercury from the mammalian body"[<1158>].

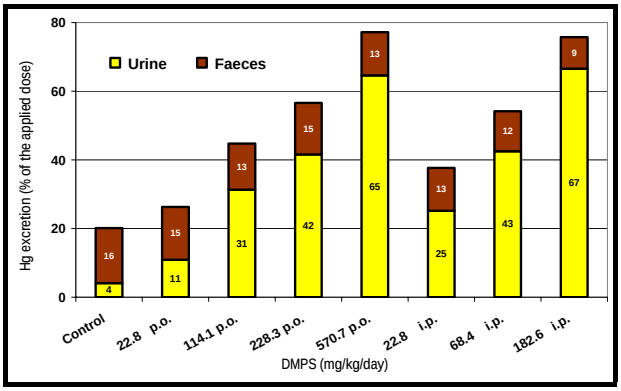
Conclusion:
DMPS increases the excretion of inorganic mercury and thus reduces the body burden. Early administration of high doses of DMPS is the most effective therapy. DMPS is more effective than DMSA.

6.1.17.3.1.2 Organic mercury compounds

On poisoning with organic mercury, DMPS accelerated the heavy metal excretion and thus led to a lower total body burden compared to the untreated control animals. The half-life of the heavy metal was shortened from 30.4 to 12.5 days[<1271,1400>]. Whereas faecal excretion predominated in the control group, in the DMPS group, excretion was chiefly via the kidneys[<1271,1400>]. Excretion was increased mainly at the start of treatment[<216>].

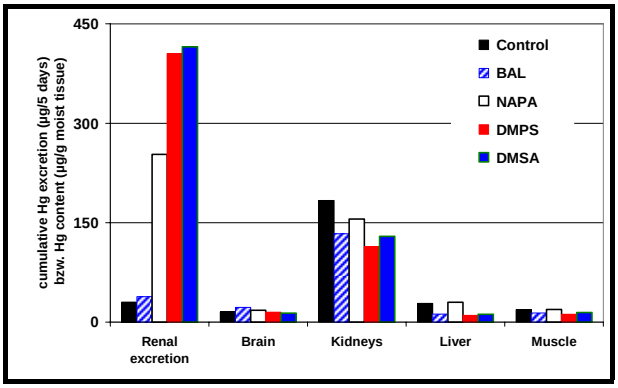
	Half-life
Controls	9.8 days
DPA	7.0 days
DMPS	4.3 days

Biological half-life of Hg om rats following administration of $CH_3{}^{203}HgCl$ (i.v.) and oral therapy for 5 days[<454>]

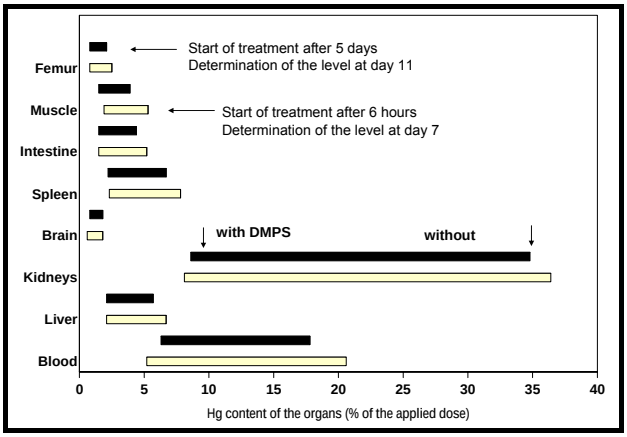


Comparison of oral and parenteral administration of DMPS at various dose levels on mercury excretion in rats[<455>]

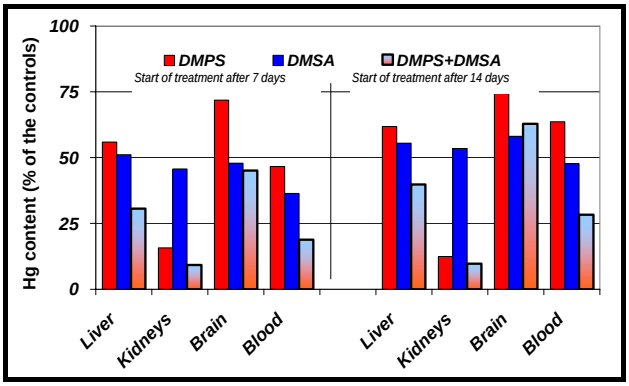
The addition of DMPS to the feed (228.3 mg DMPS/kg) increased the renal excretion of mercury in rats given i.v. CH_3HgCl 6 hours previously. Faecal excretion was only slightly changed. DMPS was more than twice as effective as DPA. This was accompanied by a reduction in the mercury content of all the organs examined, particularly in the kidneys. The biological half-life of ^{203}Hg was more than halved during treatment[<454>].



Influence of 5 days' treatment on Hg concentrations in various rat organs following chronic administration of CH_3HgCl<519,1159>



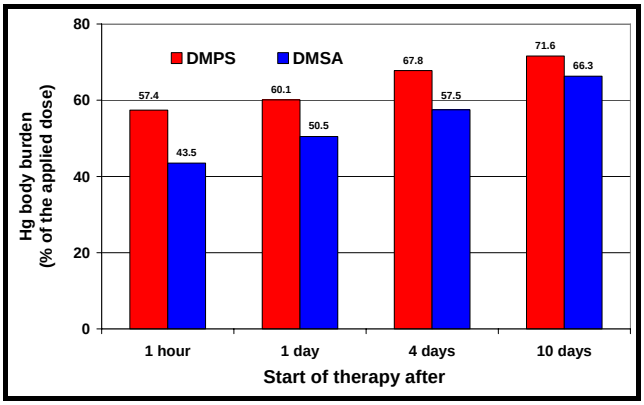
Influence of DMPS (228.3 µg/kg/day oral) for 5 days on Hg levels in the organs of rats poisoned with methyl mercury on immediate or delayed start of treatment<455>



Influence of the onset of treatment with DMPS, DMSA or DMSA + DMPS on the Hg content of the organs (% of the Hg content in the same organ of untreated rats)<1159>

Rats were injected with CH_3Hg i.v. Six hours and 5 days later, various quantities of DMPS were added to some of the animal feed. Various concentrations of DMPS were administered via the i.p. route to other animals. Cumulative Hg excretion increased following both p.o. and i.p. administration of increasing doses of DMPS. Urinary excretion was mainly raised. Parenteral administration was more effective than oral dosing. On oral administration, a 3-fold higher dose was necessary in order to achieve the same rate of excretion. The three-fold oral dose was approximately equi-effective to the parenteral dose in terms of Hg levels in the organs. Delayed onset of treatment also triggered a drastic rise in the urinary excretion of Hg whereas faecal excretion remained the same<455>.

Rats were given i.p. DMPS or DMSA following i.p. administration of CH_3HgCl. Both reduced the total body burden compared to the untreated control animals. Early administration of treatment was more effective than delayed therapy. Efficacy could still be measured even 10 days after administration. DMSA was more effective than DMPS<1159>.



Effect of the time interval between administration of CH_3HgCl and the antidote on the total body burden of Hg in rats<1159>

Oral treatment with DMPS for 8 days, beginning 4 hours after the i.v. injection of CH_3HgCl, increased renal excretion in mice. Faecal excretion was not affected<11>. The conclusions drawn by the authors, namely that DMSA is superior to DMPS in the treatment of poisoning and is therefore the drug of choice on methyl mercury poisoning<2,11>, can be qualified by the fact that chelating agents were added to the feed and the varying bioavailability was not taken into account.

One day after i.p. injection of $CH_3{}^{203}HgCl$, rats were given feed containing DMPS for 28 days. The biological half-life of Hg was shortened from 28.8 to 10.8 days. The mercury content was lowered in all the organs examined. The total body burden fell from 51.8% to 17.6% of the dose administered. Urinary excretion increased from 6.7 % to 35.3 % of the quantity

	Liver	Kidneys	Brain	Cumulative excretion
DMPS	99	33	68	556.9
DMSA	62	69	63	907.4

CH_3HgCl content in rats after three weeks' administration of DMPS or DMSA[<1162>]

administered. Faecal excretion was high, particularly on the first few days of treatment (41.6 -> 45.2%). Non-absorbed DMPS possibly binds CH_3HgCl, thus preventing its reabsorption and breaking the enterohepatic circulation[<1272>].

		NaCl	1st injection	2nd injection	3rd injection
Urine (µg/ml)	Hg^{2+}	1.1	6.0	7.9	2.6
	CH_3-Hg^+	1.1	19.0	17.9	11.5
Kidneys (µg/g)	Hg^{2+}	43.4	31.2	33.2	33.2
	CH_3-Hg^+	31.2	23.9	15.7	12.6
Brain (µg/g)	Hg^{2+}	0.30	0.30	0.25	0.20
	CH_3-Hg^+	2.59	3.54	2.51	1.99
Blood (µg/g)	Hg^{2+}	4.3	10.7	6.2	2.9
	CH_3-Hg^+	112.9	83.1	43.1	46.1

Influence of i.p. administration of DMPS on Hg levels (inorganic or organic) in the kidneys, brain, blood and urine of rats following chronic CH_3-Hg-OH exposure[<1149>]

Rats received drinking water containing CH_3HgCl had been added for 4 weeks. DMSA, DMPS, BAL or NAPA were then administered via the i.p. route for 5 days. DMPS and DMSA were the most effective in terms of renal mercury excretion (increased more than 10-fold). BAL was devoid of effect. Faecal excretion was not increased by any of the chelating agents. No significant difference was observed between DMSA and DMPS with regard to the effect on Hg deposits in the brain, kidneys, liver and muscles. BAL triggered higher Hg values in the brain[<519>].

	Kidneys (µg/g)		Brain (µg/g)		Urine (µg/ml)	
	Hg^{2+}	CH_3-Hg^+	Hg^{2+}	CH_3-Hg^+	Hg^{2+}	CH_3-Hg^+
Untreated	0.09	0.02	0.002	0.07	0.0	0.0
Controls (NaCl)	51.48	42.19	0.278	4.797	0.91	2.29
DMPS (100 mg/kg)	37.24	26.52	0.360	5.874	8.60	34.39
DMPS (200 mg/kg)	33.40	18.88	0.334	4.723	8.63	34.81

Influence of a single, i.p. dose of DMPS on Hg levels (inorganic or organic) in the kidneys, brain and urine of rats following chronic CH_3-Hg-OH exposure[<1149>]

Chelate therapy was administered to rats 8 days after i.v. injection of CH_3HgCl. The animals received DMPS or DMSA (100 mol/kg i.p.) 5 times a week for 3 weeks. The highest cumulative total excretion was recorded with DMSA. DMPS lowered the Hg content of the liver more effectively and DMSA that of the liver. Both antidotes displayed similar efficacy in the brain[<1162>].

DMPS increased the excretion of Hg in the urine. This changed the colour of the urine from normal yellow to steel grey. Prophylactic administration of DMPS prevented Hg-induced diuresis by mercusal – a diuretic containing mercury – in dogs. Dosing following administration of the Hg compound shortened the diuresis time[<777>].

Rats received drinking water containing CH_3HgCl for 9 weeks. Subsequent i.p. administration of DMPS increased the excretion of both inorganic and organic Hg. The Hg load in the kidneys was reduced. Partially elevated values were recorded in the brain[<1149>]. Organic mercury levels were particularly affected when DMPS was administered three times, at 72-hourly intervals[<1149>]. Concentrations of various porphyrins in the urine and kidneys as a result of mercury exposure were lowered in particular by the first injection[<1148>].

Conclusion:
DMPS increases the excretion of organic mercury particularly via the urine, thus reducing the body load. Early onset of treatment is the most effective approach. A delayed start after 10 days is, however, still effective.

6.1.17.3.1.3 Mercury vapour, metallic mercury

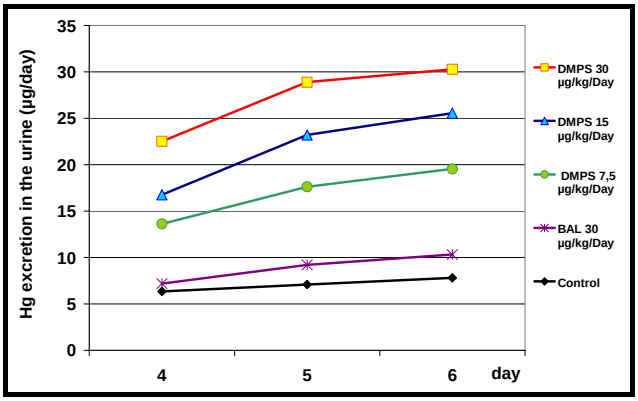
On poisoning with vapour[<140,216,254,256,822,1294>] or metallic[<627>] mercury, DMPS accelerated heavy metal excretion and thus led to a lower total body burden compared to the untreated control animals. Excretion was increased mainly at the start of treatment[<216,1294>].

In rats exposed to Hg vapour, single or repeated dosing with DMPS (oral or i.p.) increased excretion via the urine. DMSA was less effective than DMPS[<216>].

Rats were exposed to Hg vapour for 2 hours. After 4 days, various doses (7.5, 15 or 30 mg/kg/day) of DMPS were injected via the i.m. route. Hg excretion via the urine was significantly raised. Only a slight increase was observed in the faeces. Higher doses were more effective. BAL was less effective and Ca-EDTA ineffective[<140>].

If animals exposed to mercury vapour inhaled DMPS at the same time, renal Hg excretion was increased and the heavy metal deposits in the organs reduced[<822>].

In dogs given metallic mercury via the lungs, the oral administration of DMPS (4 mg/kg BW) increased mercury excretion in the urine over a period of 8 days[<627>].



Influence of the DMPS dose on renal Hg excretion of rats following Hg vapour exposure. Treatment initiated after 4 days[<140>]

Exposure of rats to mercury vapour led to elevated heavy metal levels in the kidneys, liver and brain. The administration of DMPS (oral or i.p.) led to a drastic increase in Hg excretion via the urine with the first dose mobilising more than the second. Parenteral administration was more effective than oral dosing at the same dose level. Mobilisation takes place mainly in the kidneys[<985>].

Single i.p. administration of DMPS increased renal Hg excretion in rats, there being no difference between poisoning with $HgCl_2$ and Hg vapour. Overall, 43% of the total body burden were removed. The quantity of Hg excreted from the kidneys thus corresponded to that mobilised from the kidneys. Excretion depended on the dose of DMPS administered but reached a plateau at high doses. The quantity excreted after DMPS correlated with the total body burden[<255>].

Conclusion:
DMPS increases mercury excretion following exposure to metallic or vapour mercury, thus reducing the body burden. The quantity excreted correlates with the total body burden.

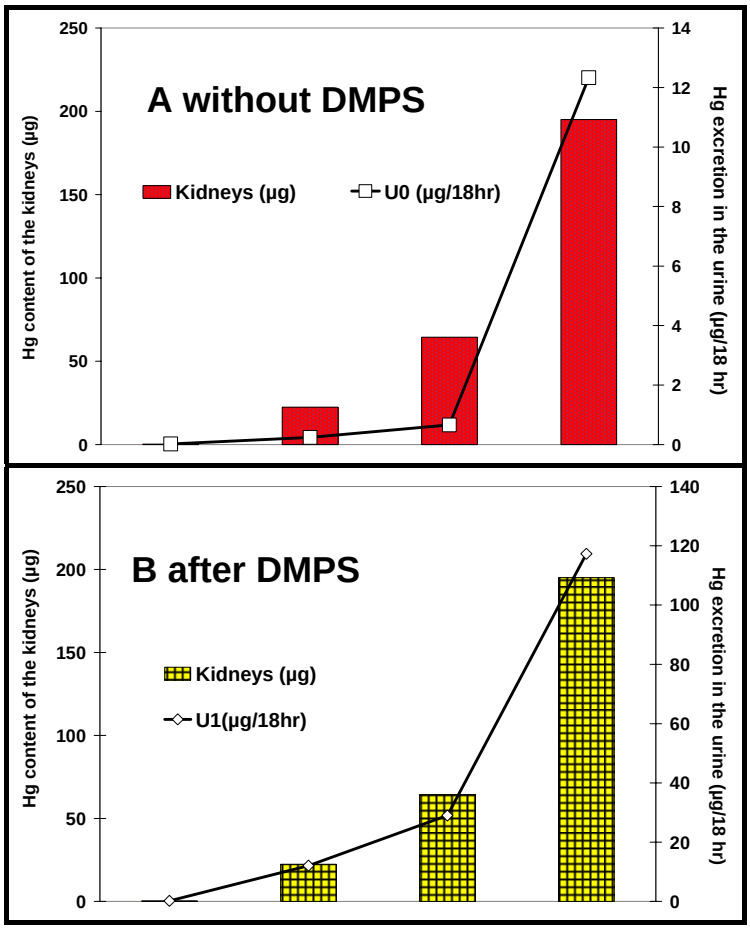
6.1.17.3.1.4 Influence on the bioavailability of Hg

The investigations published to date on the effect of the bioavailability of mercury following oral administration of DMPS are not consistent. In mice (given a single oral dose of $HgCl_2$), Hg levels in the liver, kidneys, spleen and brain were reduced following both oral and parenteral administration of DMPS. A comparison of the values recorded after oral and parenteral administration of DMPS provide no evidence to suggest that oral dosing of DMPS following oral administration of mercury promotes the absorption of Hg. The oral dose was, in fact, more effective. The non-absorbed portion of DMPS may bind Hg in the intestine and thus prevent its absorption[<990>].

In rats, the immediate oral administration of DMPS after oral dosing of $HgCl_2$ increased the mercury burden. If DMPS was not introduced until 24 hours later, then levels were lowered. This effect was not observed in “immature rats”. Similarly, no elevated values were recorded in adult rats even on parenteral administration. This means that oral DMPS promotes the absorption of Hg^{2}[<696>].

Conclusion:
Based on current knowledge, it is impossible to say whether the oral administration of DMPS after dosing with oral mercury increases the absorption of the heavy metal from the intestine. In such cases, the parenteral administration of DMPS should be considered.

6.1.17.3.1.5 DMPS test



Dependence of Hg excretion in the urine (µg in 18 hours) with and without DMPS (i.p.) on the Hg content of the kidneys in rats<274>

Rats were exposed either via the i.p. route with $HgCl_2$ or by inhalation with Hg vapour at various doses. After various waiting times, the quantity of Hg excreted in normal urine or in 24-hour urine after i.p. administration of DMPS was determined. While in normal urine there was no correlation between the quantity of mercury excreted and the total body burden, the quantity of Hg in the urine correlated linearly after DMPS administration with the total body burden of the animals at the time of DMPS injection. The type of Hg compound used did not make any difference. The mobilised Hg arose predominantly from the kidneys. With increasing doses of DMPS, the quantities of Hg initially increased but finally reached a limit value at the higher doses. 46% of the total body burden was then excreted<245,255>. Dependence was also demonstrated after oral DMPS administration<395>.

DMPS (62.5 mg/kg BW i.p.) was administered to rats after loading with various Hg vapour concentrations. The first injection mobilised 45-55 % of the heavy metal deposited in the kidneys. On the second injection, approximately 75 % of the quantity mobilised after the first injection was excreted. After 5 injections, 85-90% of the mercury deposited in the kidneys were excreted via the urine<274>. Parenteral administration was more effective than oral dosing at the same dose level. After the second dose, approximately 75 % of the quantity mobilised after the first injection was again detected in the urine<985>. Even with $HgCl_2$<216,256> and phenyl mercury acetate<216>, Hg concentrations in the urine correlated with the decrease in Hg levels in the kidneys.

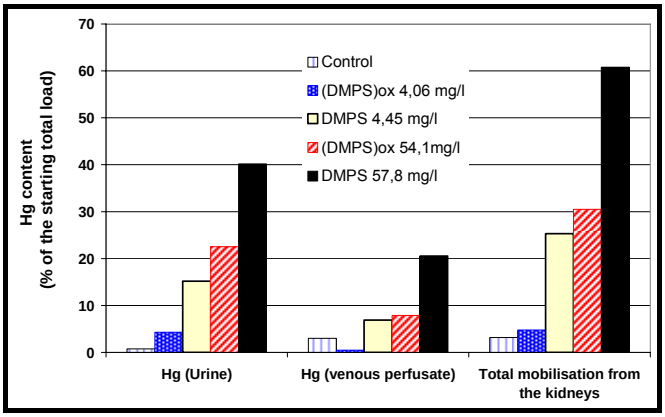
The linear correlation between the increase in mercury excretion in the urine and the mercury load<254-256,706> facilitated determination of the renal load by measuring the heavy metal content of the urine<254,256>.

Conclusion:
Mercury excretion following administration of DMPS correlates with the total body burden in rats. This correlation is not apparent in normal urine. Hg excretion in the urine after mobilisation with DMPS allows conclusions to be drawn regarding Hg total body burden, at least on recent poisoning.

It cannot be deduced whether this also applies after chronic exposure and far earlier exposure. In thse cases, it must be noted that there is a correlation between the total body burden and mercury deposits in the kidneys.

6.1.17.3.1.6 Efficacy of oxidised DMPS $(DMPS)_{ox}$

DMPS is oxidised relatively quickly into Di- and higher sulfides $(DMPS)_{ox}$ in the body. Although free sulfhydryl groups could no longer be detected[<337,244>], i.v. administration of $(DMPS)_{ox}$ to rats with $HgCl_2$ poisoning increased mercury excretion and reduced the heavy metal burden[<337,627>].



Comparison of the efficacy of monomer and oxidised DMPS on mercury mobilisation in perfusion experiments on rat kidneys[<744>]

	Controls	DMPS	$(DMPS)_{ox}$
Hg excretion in the urine	0.9	19.6	6.7
Hg levels in the kidneys	81.7	64.5	74.0
Hg levels in the liver	5.0	3.9	4.5
Hg levels in the total body	100.4	82.8	90.7

Comparison of the efficacy of DMPS and $(DMPS)_{ox}$ in rats (Infusion over 140 minutes, % of the starting total load)[<337>]

Oxidised DMPS lowered Hg levels in the renal cortex and outer medulla[<743,744>]. It was, however, less effective than monomeric DMPS. DMPS disulfide in the kidneys is obviously reduced[<337,743,744>]. Whereas DMPS was present in the perfusate virtually exclusively as the disulfide, approximately 25% of the DMPS could be detected in the reduced form in the urine[<743,744>].

Conclusion:
Oxidised DMPS also increases the renal excretion of mercury and lowers levels in the kidneys and liver as well as the total body burden. Efficacy is, however, less marked than that of monomeric DMPS.

6.1.17.3.1.7 Efficacy in nephrectomised rats

Following injection of $HgCl_2$, Hg was stored in particular in the renal cortex and renal medulla in nephrectomised and healthy rats. I.P. administration of DMPS lowered Hg levels in all regions of the kidney in both groups[<1600,1601>]. Hg levels in the blood and liver were also reduced. Hg excretion in the urine[<1600,1601>] and faeces[<1600>] was increased in both groups[<1600>].

The timely administration of sufficient doses of DMPS prevented $HgCl_2$–induced nephropathy[<1601>]. No signs of tubular or cellular necroses appeared in the rat kidneys following i.p. administration of 100 mg DMPS/kg 1 hour after i.v. administration of $HgCl_2$. This applies to normal rats as well as to animals with one kidney removed. No histopathological changes were observed in the renal tissue. The excretion of cellular enzymes LDH, γ-GT, AP, AST and NAG in the urine corresponded that of the controls. No elevated glucose, α-amino-nitrogen and albumin levels were recorded in the plasma and urine[<1601>]. A DMPS dose of 10 mg/kg tended to have an effect, but this was not always statistically significant[<1601>].

Pre-incubation of proximal renal tubular cells from both nephrectomised and controlled rats with DMPS protected the cells against the cytotoxic effects of $HgCl_2$[<821>]. Prior or concomitant administration of DMPS reduced the $HgCl_2$-induced decrease in LDH (lactate dehydrogenase) of proximal and distal renal tubular cells from both nephrectomised and control rats[<819>].

Conclusion:
As mercury has a nephrotoxic effect, renal excretion can be impaired on mercury poisoning. In nephrectomised animals, the administration of DMPS did not trigger any change in the remaining kidneys.

6.1.17.3.1.8 Influence of selenium

	Urine (µg/24h)	Kidneys(µg/g)	Liver (µg/g)
$HgCl_2$ (i.p.)	3.17	31.4	2.74
$HgCl_2$+Na_2SeO_3 (i.p.)	0,.7	0.03	15.8
$HgCl_2$ (i.p.) + DMPS (oral)	25.2	5.66	2.86
$HgCl_2$+Na_2SeO_3 (i.p.) + DMPS (oral)	1.81	1.29	15.3

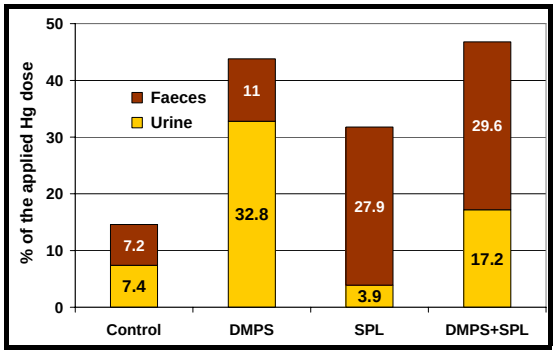
Influence of the concomitant administration of sodium selenite on the distribution and excretion of mercury in rats<686>

Rats received i.p. $HgCl_2$ alone or in conjunction with sodium selenite. Oral DMPS was administered 30 minutes later and the urinary excretion of Hg assessed. The Hg content of the liver and kidneys was examined 24 hours later. The addition of sodium selenite changed the distribution of the mercury and reduced the excretion of Hg in the urine<686>.

Conclusion:
Selenium redistributes mercury in the body. Levels in the kidneys and excretion via the urine are reduced, hence greater quantities of the heavy metal are deposited in the liver. Hg excretion due to DMPS is reduced by Se.

6.1.17.3.1.9 Combination with spironolactone

The additional administration of spironolactone, a synthetic steroid, reduced renal excretion compared to levels recorded with DMPS therapy alone<276,279>. Hg levels in the bile were increased 3-fold<276,279,1164>. Thiomestrone<398> had a similar effect. The kidney burden was consequently reduced<279>("Synergistic chelate therapy"<673>).



Influence of DMPS or spironolactone (SPL) on Hg excretion in rats following administration of $HgCl_2$<276>

The injection of DMPS (i.m. 4, 6, 24 and 30 hours after $HgCl_2$) increased the excretion of Hg in rat urine and faeces and reduced the total body burden. Administration of spironolactone (oral before and after administration of $HgCl_2$) and polythiol resin (oral after $HgCl_2$) in addition to DMPS did not subsequently reduce the total body burden. Most of the heavy metals was, however, excreted via the faeces<277>.

6.1.17.3.2 Blood, serum, plasma

Hg^{2+} binds very rapidly to plasma proteins in the plasma<1294>. In most investigations with inorganic or organic mercury, DMPS reduced the heavy metal level in the blood. Early onset of therapy was more effective than delayed<334,1159>.

6.1.17.3.2.1 Inorganic mercury compounds

Most investigations with inorganic mercury confirm that DMPS lowers mercury levels in the blood<211a>, whereas plasma levels either rise slightly<337,1600> or are also lowered<276,277,279,453,1294>. Some investigations also found unchanged<627,687,1535> or raised values in the blood<1578>. Early onset of therapy was more effective than delayed<455,1159>.

I.m. injection of DMPS 4 and 7 hours after i.v. administration of $HgCl_2$ lowered Hg levels in rat plasma<276>. The additional administration of spironolactone did not have any marked effect on Hg levels in the organs<1164>.

Immediate<9,993> and delayed administration of DMPS 24 hours after administration of $HgCl_2$<10> lowered Hg levels in the blood. Lower blood levels were still recorded in rats<376> even when

treatment was initiated 8 days after administration of $HgCl_2$. DMPS was more effective than DMSA[<1158>] following both oral and i.p. administration, but the differences were not statistically significant[<10>].

Acute poisoning with $HgCl_2$ reduced the number of free SH groups in the serum. The administration of DMPS led to an increase[<645>].

I.p. administration of $HgCl_2$ led to increased lipid peroxidation in the liver and kidneys of rats. No marked effect could be detected in the blood. The immediate oral administration of DMPS for 6 days increased the mercury-induced reduction in SOD concentrations in the blood[<158>].

Prophylactic i.p. treatment with DMPS (last dose administered 2 hours before i.v. administration of $HgCl_2$) increased the heavy metal content of the blood plasma in rats[<278>].

Following chronic Hg exposure ($HgCl_2$ in the drinking water for 5 days), subsequent DMPS therapy (0.3 mmol/day i.p.) lowered Hg levels in the blood. The number of SH groups increased[<1330>].

Prophylactic i.m. administration 90 minutes before i.p. administration of $HgCl_2$ did not alter the Hg content of the blood in rats.

Selenium and $HgCl_2$ were added to the feed and water of rats for 15 days. The subsequent administration of i.p. DMPS had no significant effect on Hg levels in the blood[<1578>].

Conclusion:
In most cases DMPS lowers Hg levels in the blood following poisoning with inorganic mercury. The SH groups in the biomolecules, which are blocked by the heavy metal, were again released.

6.1.17.3.2.2 Organic mercury compounds

In investigations with organic mercury, DMPS reduced the mercury level in the blood. The cellular mercury content fell[<453,454>] while the level in the plasma rose slightly[<1600>] or was reduced[<276,277,279,453,1294>]. Some investigations also found unchanged[<627,687>] or increased values in the blood[<1578>] or plasma[<337>]. Early onset of therapy was more effective than delayed[<455,1159>].

In rabbits, prophylactic administration of DMPS reduced the organic Hg-induced increase in γ-globulin and albumin. Tests with ^{35}S-labelled methionine showed that the Hg-induced increase in protein synthesis in the blood was prevented by the prophylactic administration of DMPS in rabbits and rats. Cholinesterase inhibition was reduced[<1453>].

Conclusion:
In most cases, DMPS lowers Hg levels in the blood following organic mercury poisoning. The biochemical changes in the blood are either prevented or at least reduced.

6.1.17.3.2.3 Mercury vapour and metallic mercury

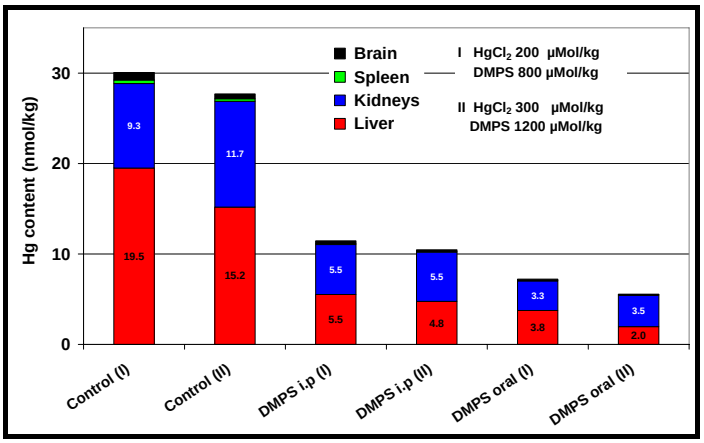
Rats were exposed to mercury vapour every day for two weeks. Mercury levels in the blood quickly reached steady state. Subsequent administration of DMPS increased renal excretion compared to that observed in the control group. High doses of i.p. DMPS (40 mg/kg BW/day) drastically exceeded the lower oral dose (10 mg/kg BW/day)[<984>].

In dogs given metallic mercury via the lungs, the oral administration of DMPS (4 mg/kg BW) for 8 days increased the urinary excretion of mercury without lowering blood values[<627>].

Conclusion:
Very little data is available regarding the effect of DMPS on Hg blood levels after poisoning with metallic or vapour mercury. An evaluation is, therefore, not feasible.

6.1.17.3.3 Kidneys

The kidneys are target organs for poisoning with inorganic mercury and accumulate this heavy metal whereby it is bound preferentially to metallothioneins[<254,1416>]. Thus, 48 hours after an injection of $HgCl_2$, about 50 % of the mercury was found in the kidneys[<337>]. It was deposited in both the proximal tubules and the epithelial cells[<1416>].



Influence of DMPS (i.p. or oral administration) on the Hg contents of various murine organs following oral administration of $HgCl_2$[<990>]

The kidneys were also the most severely burdened organs on poisoning with organic mercury. Initially, predominantly organic mercury was found in the kidneys. After 10 days, however, inorganic mercury predominated, even after poisoning with methyl mercury[<1159>].

The heavy metal is deposited particularly in the renal cortex and outer medulla[<743,1164,1600>]. On adding $HgCl_2$ to the drinking water of rats for a period of one to two months, the mercury content of the kidneys increased independently of the exposure time from 0.17 to 122 µg/g. Apparently a steady-state condition between uptake and excretion was achieved[<179>]. Furthermore, the weight of the kidneys increased from 1.3 to 1.6 g. In the kidneys, mercury led to necroses[<1164,1165,1365>] and to the release of alkaline phosphatase AP and leucine aminopeptidase LAP [<1164,1165>]. The serum levels of urea increased[<1365>].

DMPS mobilised the mercury and led to a reduction in the total burden of the kidneys whereby not all of the released heavy metal could be detected in the urine[<255,337,743>]. The number of free SH groups in the kidneys increased[<645>]. The addition of probenicide inhibited the excretion of mercury by DMPS[<743>].

6.1.17.3.3.1 inorganic mercury compounds

DMPS released inorganic Hg from its binding to endogenous renal ligands, thus preventing its toxic effects[<1596>]. Mercury levels in the kidneys were lowered[<74, 276,278,376,395,627,990,1164>]. The heavy metal was thus mobilised both in the renal cortex and in various regions of the renal medulla[<211a>]. DMPS was more effective than DMSA[<1596,1509>]. The active transport of DMPS by OAT1 in the renal cells explains the excellent effect of DMPS in the kidneys[<221>].

Both concomitant administration[<376,993>] and delayed administration of DMPS after 24 hours[<993>], 8 days[<376>] and more than one month[<179,216>] reduced mercury deposits in the kidneys. DMPS was particularly effective when treatment was initiated immediately[<74,179, 454,1159>]. The mercury content of the kidneys was, however, still significantly reduced even with a delayed start to therapy. Thus rats treated with DMPS 20 days after chronic $HgCl_2$ poisoning still showed a 46.4 % load reduction following an i.p. injection compared to the untreated controls[<74>]. Higher doses of DMPS were more effective[<337,395,454>].

Prophylactic administration of DMPS prior to injection of $HgCl_2$ also reduced Hg levels in the kidneys[<687>] and nephrotoxic repercussions[<1622>]. Concomitant administration of DMPS (i.p.) and $Hg(NO_3)_2$ reduced Hg levels in the skeleton, liver, kidneys and blood. The greatest effect was observed in the kidneys and spleen[<994>].

I.p. administration of DMPS for 9 days, beginning 6 hours after i.v. administration of $HgCl_2$, lowered the Hg content of the rat kidney by more than 90% compared to the control animals[<1294>]. Prophylactic i.m. administration 90 minutes before i.p. administration of $HgCl_2$ did not alter Hg levels in the kidneys[<687>]. The half-life of DMPS in rats can, however be assumed to be approximately 19 minutes.

48 hours after an injection of $HgCl_2$, about 47% of the applied dose was deposited in the kidneys.

	Serum urea (mg/100 mL)
Controls	24
$HgCl_2$ (s.c.)	180
$HgCl_2$ (s.c.) + DMPS (i.m.)	70
$HgCl_2$ (s.c.) + BAL (i.m.)	141
$HgCl_2$ (s.c.) + DPA (oral)	143

Influence of various chelating agents (administered 30 min and 8 h after $HgCl_2$) on urea concentrations in rat serum<1365>

The infusion of DMPS rapidly lowered (within 3 hours) both the Hg total body burden and the kidney content (equally in the renal cortex and outer medulla) in a concentration-dependent manner, and led to the excretion of the heavy metal in the urine. Peak excretion was achieved after 60 – 80 minutes<337>.

In rats with one kidney removed before the experiment, the mercury accumulated in the remaining kidney and could be mobilised by DMPS<1601>.

Additional administration of DMSO, which is used in pharmacology as a carrier substance, did not increase the renal excretion of Hg in rats<375>.

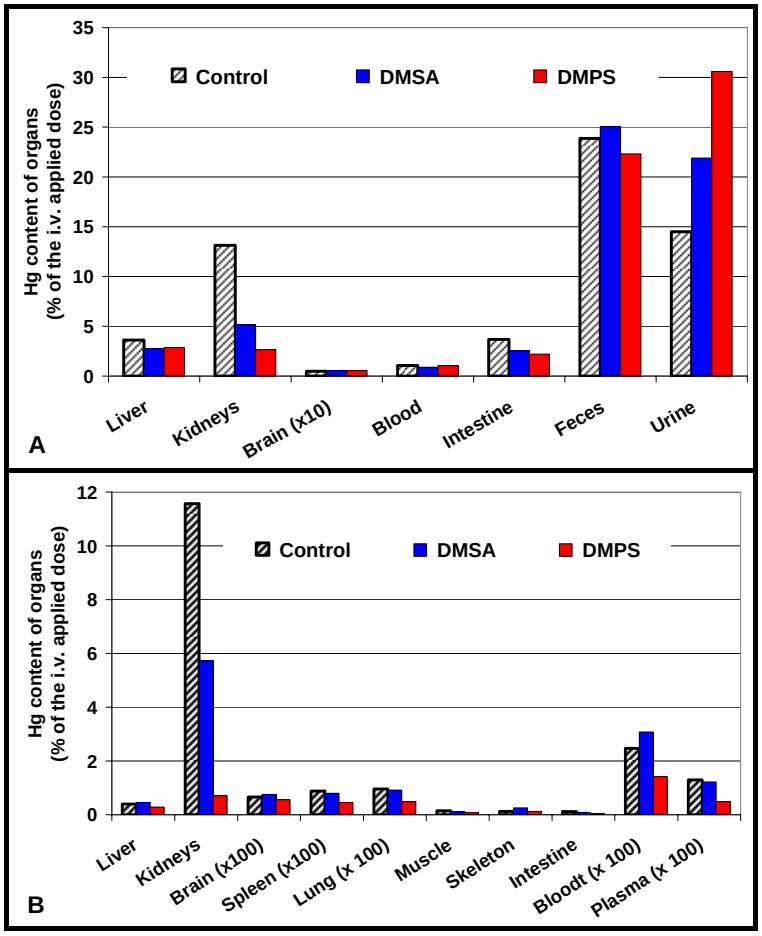
DMPS prevented pathological changes in the kidneys<207,1535>. The loads were reduced in both the renal cortex and the medulla<337,743,744,1578,1600>. The increased metallothionein content of the kidneys caused by the heavy metal was reduced, although no metallothionein-bound Hg was detected in the urine<255>.

$HgCl_2$ accumulated in the renal cortex. Here it caused necrotic changes relatively quickly and, depending on the dose of Hg, led to the transient release of alkaline phosphatase AP and leucine aminopeptidase LAP. Determination of the enzymes in the urine gave an early indication of poisoning with inorganic mercury. Treatment with DMPS caused AP excretion to return to normal. An effect on LAP excretion was observed only when treatment was initiated at an early stage<1164,1165>.

With sufficient dosing, DMPS prevented the onset of nephropathy<135> or necroses<1365,1417> due to inorganic mercury<1601>. BAL and DPA showed only slight signs (of efficacy) on regeneration of necrotic changes<1365>. Blockade of various renal enzymes by the heavy metal was abolished by DMPS<1417>. The increase in serum urea levels caused by Hg^{+2} were reduced by DMPS<1365>.

S.c. administration of $HgCl_2$ (Dose = LD_{50}) led to necrotic renal changes in rats. Serum urea levels increased. Two doses of DMPS via the i.m. route (30 minutes and 8 hours after $HgCl_2$) partly prevented these changes. The rise in urea levels was less marked. Evidence of a regression of morphological changes in the kidneys was observed on histological examination. BAL and DPA were less effective<1365>.

Free and glutathione-bound mercury catalysed oxidative damage in the kidneys (porphynuria by oxidation of uroporphyrinogens). This reaction did not, however, take place *in vitro* in the presence of DMPS<935>.



Mercury content of some organs and excretion by rats (% of the i.v. administered dose of Hg – controls: physiological saline solution)
A after 4 days' p.o. administration of DMSA (100 µmol/kg), DMPS (300 µmol/kg) or controls
B after 4 weeks' administration of i.v. administration of DMSA (100µmol/kg), DMPS (100 µmol/kg) or controls<1158>

DMPS prevented or reduced renal damage (histopathological and histochemical changes) due to inorganic mercury compounds[<2,935,1366>]. The heavy-metal induced increase in lipid peroxidation was not, however, reduced[<158>].

Pre-treatment with DMPS reduced $HgCl_2$-induced oxidative stress in the rat kidney[<1580>]. In rats, the immediate administration of DMPS (i.v.) prevented pathological changes in the kidneys caused by high doses of $HgCl_2$. Administration of DMPS 24 hours later no longer had a protective effect[<1535>].

No pathological kidney changes were observed in the control rats or rats treated with DMPS following administration of lower doses of Hg. Only delayed treatment lowered deposits in the kidney; immediate administration had no effect on the kidneys[<1535>].

Single administration of DMPS 24 hours after i.v. administration of $HgCl_2$ lowered Hg levels in the kidneys of mice. DMPS was more effective than DMSA, but the effect was not, however, statistically significant. The addition of DMSA or DMPS to the feed reduced the mercury load on the kidneys to approximately 30 % of that of the untreated control animals[<10>].

Rats were given $HgCl_2$ intravenously. Six hours later, they received 50 mol/kg DMPS or DMSA i.p. DMPS lowered Hg levels somewhat more effectively[<1162>].

Rats were given oral DMPS or DMSA for 4 days 24 hours after i.v. administration of $HgCl_2$. The DMPS dose was 3 times higher than that of DMSA in order to offset the difference in bioavailability. DMPS had a more marked effect on lowering the Hg content of the kidneys. On i.p. administration of equal doses of DMPS or DMSA, DMPS lowered levels in the kidneys, spleen, lungs, muscles, intestine, blood and plasma. DMSA, on the other hand, only reduced the Hg content of the kidneys[<1158>].

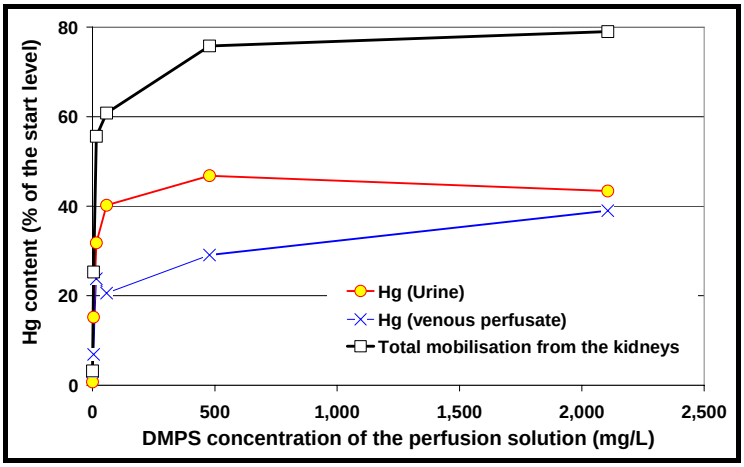
After chronic administration of $HgCl_2$ or phenyl mercury acetate, several weeks' treatment with DMPS lowered mercury levels in the rat kidney. Higher concentrations were more effective. The decrease in the kidney content was linear to the increase in urinary excretion. The same applied to DMSA while DMPS was more effective in the kidneys[<216>].

Rats were chronically exposed to Hg ($HgCl_2$ was administered in the drinking water for 5 days). Subsequent treatment with DMPS (0.3 mmol/day, i.p.) reduced Hg levels in the kidneys. The number of SH groups increased. The pathological effects were improved, whereby DMPS was more effective than BAL[<1330>].

I.v. administration of DMPS 24 hours after i.v. administration of $HgCl_2$ lowered Hg levels in the rat kidney to 60-70% of the control value. Contrastingly, BAL did not alter the kidney burden[<1535>].

Acute poisoning with $HgCl_2$ reduced the number of free SH groups in the kidneys. The administration of DMPS led once again to an increase in free SH groups in these organs[<645>].

Single i.p. administration of DMPS after acute $HgCl_2$ poisoning prevented a decrease in δ-ALA-D activity in the kidneys of mice. The increase in urea levels in the plasma was prevented. The increased metallothionein levels in the liver were unaffected. The concentration of "non-protein-SH" in the liver and kidneys remained high[<205,206>].



Concentration dependency of mercury mobilisation in perfusion experiments performed on rat kidneys[<744>]

Two i.p. doses of DMPS (0 and 24 hours) after i.v. administration of $HgCl_2$ lowered Hg levels in murine kidneys. The additional oral administration of metal-complexing polymers was devoid of effect[<396>].

I.p. administration of $HgCl_2$ led to increased lipid peroxidation in the kidneys of rats. Immediate oral administration of DMPS for 6 days did not have a marked, positive effect.

The Hg-induced reduction in SOD concentrations was potentiated by DMPS[<158>].

Rats were given a single i.p. dose of $HgCl_2$. The kidneys were then removed for perfusion experiments. The addition of DMPS to the arterial perfusion solution led to elimination of Hg from both the renal cortex and the outer medulla, the two most important storage centres in the kidney. The quantity of mobilised Hg increased with higher doses of DMPS. Part of it was excreted directly in the urine. The addition of probenecid inhibited the renal excretion of DMPS or the mercury-DMPS complex. The effect depended on the DMPS concentration and finally reached a plateau. Approximately 40% of the Hg content at most could be directly secreted in the urine. These observations indicate that an organic anion transporter is involved in the DMPS mechanism of action. DMPS was found in far greater quantities than Hg in the urine (300 – 11,000: 1). Hg was also detected in the venous perfusion solution[<744>].

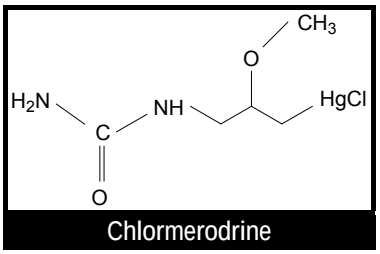
An eluate comprising radioactive Au with traces of Hg was given intravenously to rats. This was administered together with DMPS to some of the animals. After 22 hours, lower Hg levels were recorded in the kidneys of animals in the DMPS group (8.5 instead of 12.2% of the dose administered). Unfortunately, gold measurements were not recorded[<287>].

Conclusion:
After poisoning with inorganic mercury, both immediate and delayed administration of DMPS drastically lowered mercury levels in the kidneys. DMPS is thus signficantly superior to DMSA.

6.1.17.3.3.2 Organic mercury compounds

On poisoning with organic mercury compounds, DMPS also released Hg from its binding to endogenous renal ligands, thus preventing its toxic effects (histopathological and histochemical changes)[<1573,1596>]. The renal load was reduced[<11,454,455,1070,1159,1162>]. Mercury was excreted in particular from the metallothionein fraction of the kidneys[<254,880>].

The diuretic effect of mercusal (organic mercury compound) was reduced on delayed administration[<1535>] and prevented on prophylactic administration of DMPS[<777>].



Chlormerodrine

Renal damage due to radioactive mercury compounds used in scanning of the kidneys could be prevented[<1573>]. The administration of ^{203}Hg-labelled chlormerodrine triggered changes in the epithelium of the proximal sections of the renal tubular in rats. Treatment with DMPS (single dose of 15 mg/kg/day i.m.) for 6 days, beginning 2 hours after chlormerodrine, largely prevented radioactive Hg-induced renal damage[<1573>]. I.m. administration of DMPS (10 mg/kg/day in physiological saline solution) promoted the excretion of mercury from ^{203}Hg-chlormerodrine in rats, particularly in the urine. The kidney burden was reduced to 1.8 % of the administered dose after 9 days, whereas, in the control animals, 24.8 % of the dose of mercury administered was still emitted[<1070>].

DMPS was more effective[<1159>] than or just as effective[<519>] as DMSA. Combination therapy with DMSA and DMPS was more effective than the respective individual therapy. However, the quantity of antidote administered overall in the combination therapy was twice as high as that administered in the monotherapies[<1159>] such that a synergistic effect cannot be assumed.

DMPS and the methyl mercury-DMPS complex were actively ousted from the blood into the proximal renal tubular cells by the renal “Organic Anion Transporter-1“ OAT-1 . However, it is still not known how they reach the urine from the cells. In contrast, OAT-1 does not transport DMSA or the DPA complex of CH_3HgCl[<753>].

After chronic administration of $HgCl_2$ or phenyl mercury acetate to rats, several weeks’ treatment with DMPS significantly lowered the heavy metal content of the kidneys whereby higher concentrations proved to be more effective. The reduction in Hg levels in the kidneys was linear to the increased excretion via the urine[<216>].

Rats received drinking water containing methyl mercury for 9 weeks. Subsequent i.p. administration of DMPS increased the excretion of both inorganic and organic Hg. The Hg load in the kidneys was reduced[<1149>]. If DMPS was administered three times at intervals of 72 hours, levels of organic mercury were particularly affected[<1149>]. The high concentrations of various porphyrins in the urine and kidneys due to mercury exposure were lowered in particular by the first injection[<1148>].

Conclusion:
DMPS increases the excretion of organic mercury and thus reduces the body burden. DMPS had the greatest effect on Hg levels in the kidneys. Histopathological and histochemical changes were prevented.

	Controls	DPA	DMPS
	6,44	4.72	2.62
Plasma	0.12	0.07	0.04
Liver	4.44	3.56	2.07
Kidneys	25.56	16.72	8.07
Brain	1.16	0.92	0.60
Femur	1.56	1.28	0.81
Muscles	3.24	2.83	1.92
Spleen	4.87	3.70	2.25
Intestine	3.38	2.40	1.45

Hg content of the tissues (% of the administered dose (10g fresh weight) in rats given an antidote (1 mmol/kg/ day) in their feed 6 hours after i.v. administration of CH_3-HgCl[<454>]

6.1.17.3.3.3 Mercury vapour, metallic mercury

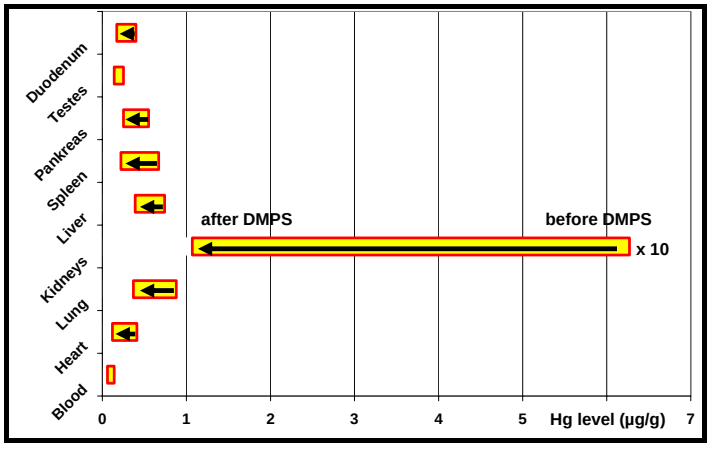
DMPS reduced the kidney load even on poisoning with metallic mercury[<627>] or mercury vapour[<140,216,256,984>].

After rats had been exposed to varying concentrations of Hg vapour, single administration of DMPS (oral, i.p.) led to a significant reduction in mercury levels in the kidneys accompanied by higher excretion in the urine. DMSA was less effective than DMPS. Lower kidney concentrations were still recorded even when treatment was initiated after 35 days[<216>].

DMPS (mg/kg/day)	Hg (µg/Kidney
0	34,3
7,5	25,5
15	20,3
30	10,1

Effect of the dose of DMPS on the Hg content of rat kidneys following Hg vapour[<140>]

Single i.p. administration of DMPS increased renal Hg excretion in rats, there being no difference between poisoning with $HgCl_2$ and Hg vapour. Overall, 43% of the total body burden and over 60% of the Hg were excreted via the kidneys. DMPS predominantly mobilised the heavy metal bound in the kidneys. The quantity of Hg excreted (µg/24 hours) after DMPS administration corresponded to the quantity mobilised from the kidneys, mobilisation occurring from all protein fractions of the kidneys. It correlated with the overall body burden. This did not apply to renal excretion without DMPS[<254,255>]. The MT content of the kidneys also regressed together with the Hg levels[<255>].



Reduction in Hg levels in various rats organs following single i.p. administration of DMPS. (The values for the kidneys must be multiplied by 10)[<255>].

After Hg vapour exposure, subsequent i.m. administration reduced the renal load of Hg, whereby higher doses of DMPS led to lower values. BAL was clearly less effective and Ca-EDTA ineffective[<140>].

Exposure to mercury vapour increased heavy metal levels in the rat kidney. The administration of DMPS (oral or i.p.) led to a drastic increase in Hg excretion via the urine with the first dose mobilising more than the second. Parenteral administration was more effective than oral dosing at the same dose level. Mobilisation took place essentially from the kidneys, i.e. the Hg content of the kidneys was successively lowered. I.P. administration was more effective than oral dosing[<985>].

In young rats following chronic Hg vapour exposure, DMPS lowered Hg levels in the kidneys to greater extent than DMSA at the same concentration. The other substances (vitamin C, glutathione or lipoic acid) and combinations of these substances were ineffective[<51>].

In dogs given metallic mercury via the lungs, the oral administration of DMPS lowered the Hg content of the kidneys[<627>].

Conclusion:
DMPS increases mercury excretion on poisoning with mercury vapour and thus reduces the body burden. DMPS has the greatest effect on Hg levels in the kidneys. The same obviously applies on administration of metallic mercury. However, no assessment can be carried out due to the lack of data.

6.1.17.3.3.4 Influence on copper levels in the kidneys

In rats, the administration of $HgCl_2$ in drinking water over a prolonged period led to copper deposits in the kidneys in addition to raised mercury levels. Copper levels increased from 10.7 to 80.0 µg/g. After a constant Hg load, the Cu load also reached a maximum value that did not increase any more even when prolonged exposure continued[<179>]. Mercury-induced formation of metal-othioneins is suggested as the cause[<1599>]. These bind the additional copper in the kidneys[<179>]. Cessation of Hg exposure spontaneously led to a marked decrease in the Hg burden of the kidneys (60 %) and to less of a decline in Cu values (91 %)[<179>]. In addition to mercury levels, elevated copper values were also reduced by DMPS[<179>]. Even when Hg exposure was further back in time, DMPS lowered the Hg and Cu content of the kidneys[<179>].

Conclusion:
Mercury induces the formation of metallothioneins in the kidneys. More copper from food is thus bound in the kidneys. The administration of DMPS also increases copper excretion in the urine. Increased copper excretion in the DMPS mobilisation test does not definitely indicate copper poisoning but can be the outcome of increased mercury load.

6.1.17.3.4 Liver

On poisoning with inorganic or elemental mercury, DMPS led to a reduction of the heavy metal level in the liver. Some investigations did not find any significant effects. The increased concentration of lipid peroxidation products caused by the mercury was partially reduced in rats[<158,159>].

6.1.17.3.4.1 Inorganic mercury compounds

DMPS either lowered Hg levels in the liver[<9,10,276,279,990,993,994,1535>] or did not change them[<211a,278, 376,395,396,627,1535>]. Slightly raised values were found in individual investigations[<395>]. DMPS proved to be slightly superior to DMSA[<1162>]. The values recorded in the animals treated with DMPS were somewhat lower than those in the DMSA group[<10>]. In other studies, both chelating agents were equi-effective[<211a,1158>].

Selenium and $HgCl_2$ were added to the feed and water of rats for 15 days. The subsequent administration of DMPS i.p. lowered Hg levels in the liver compared to the untreated control group[<1578>].

Prophylactic i.m. administration 90 minutes before i.p. administration of $HgCl_2$ reduced the Hg content of the liver in rats[<687>].

After chronic administration of $HgCl_2$ or phenyl mercury acetate, several weeks' treatment with DMPS lowered mercury levels in the rat liver. The same applies for DMSA[<216>].

I.m. administration of DMPS lowered Hg levels in the liver. The additional oral administration of spironolactone had no marked effect[<1164>]. The additional oral administration of metal-complexing polymers was devoid of effect[<396>].

Single i.p. administration of DMPS after acute $HgCl_2$ poisoning prevented a decrease in δ-ALA-D activity in the murine liver[<205,206>]. Another study found no effect[<1049>]. Increased metallothionein levels in the liver were unaffected. The concentration of "non-protein-SH" in the liver remained high[<9>].

I.P. administration of $HgCl_2$ led to increased lipid peroxidation in the liver of rats. The immediate oral administration of DMPS for 6 days partly prevented this effect but the concentration of the reaction products thus obtained did not correspond to those of the controls. The mercury-induced reduction in SOD concentrations was, however, potentiated by DMPs[<158>].

Rats were chronically exposed to Hg ($HgCl_2$ was administered in the drinking water for 5 days). Subsequent treatment with DMPS (0.3 mmol/day, i.p.) reduced Hg levels in the liver. The number of SH groups increased. The pathological effects of $HgCl_2$ were improved, whereby DMPS was more effective than BAL[<1330>].

Conclusion:
On poisoning with inorganic mercury, DMPS lowers Hg levels in the liver. However, the effect is substantially lower than in the kidneys.

6.1.17.3.4.2 Organic mercury compounds

On poisoning with organic mercury, DMPS triggered a reduction in the heavy metal levels in the liver[<11,454,455,1159>]. Other studies reported no significant effect[<9,216,395,627,10701535>]. Early onset of treatment was more effective[<1159>]. DMSA was either more effective than[<1159,1162>] or equi-effective[<216,519>] with DMPS. A combination of DMPS and DMSA was more effective as twice the quantity of antidote was administered[<1159>].

Conclusion:
After poisoning with organic mercury, DMPS lowers Hg levels in the liver. However, the effect is markedly less than in the kidneys.

6.1.17.3.4.3 Mercury vapour, metallic mercury

On poisoning with mercury vapour, DMPS triggered a reduction in the heavy metal levels in the liver[<216,985>]. Other studies reported no significant effect[<216>].

In dogs given metallic mercury via the lungs, DMPS did not affect Hg levels in the liver[<627>].

Conclusion
Very little data is available regarding the effect of DMPS on Hg levels in the liver on poisoning with mercury vapour or metallic mercury. An assessment is not, therefore, feasible.

6.1.17.3.5 Brain

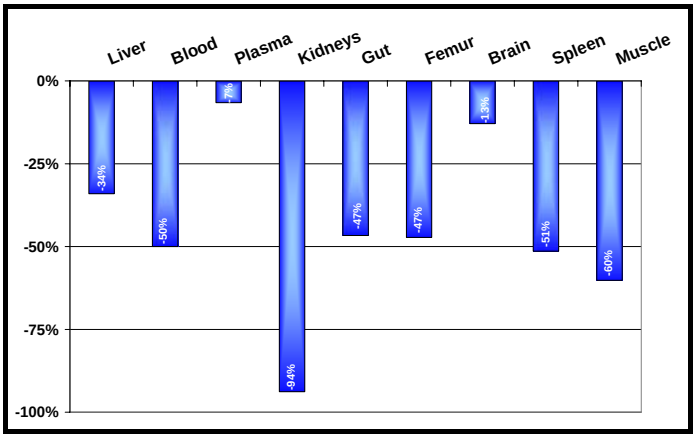
In rats, the administration of inorganic mercury ($HgCl_2$) over longer periods led to an approximately 100-fold increase in heavy metal in the brain[<74>]. Intermediate reduction to elemental mercury in

the body may play a role[<839>]. After three weeks' administration of inorganic or organic mercury (i.p.), heavy metal concentrations in the brain was approximately equally high in both groups. Higher values were found on mercury vapour exposure[<216>]. The mercury content of the brain was mostly unaffected by DMPS. Redistribution of the heavy metal in the brain did not take place[<74,880>].

DMSA displayed similar activity to that of DMPS[<1162>]. There was no evidence to suggest that, compared to DMPS, DMSA is capable of improved Hg mobilisation from the brain. In contrast to BAL, DMPS and DMSA did not lead to an accumulation of Hg in the brain. In contrast to the Hg-BAL complex, the Hg-DMPS complex is negatively loaded and cannot, therefore, penetrate the blood-brain barrier[<682>].

6.1.17.3.5.1 Inorganic mercury compounds

In most experiments, DMPS did not affect mercury deposits in the brain.



Reduction in the Hg content of the organs after 10 i.p. injections of DMPS in rats following i.v.administration of $HgCl_2$[<1294>].

- In rats, i.p. administration of DMPS after chronic mercury exposure ($HgCl_2$ i.p. for at least 32 days) did not affect mercury levels[<74>].
- The oral administration of DMPS or DMSA for 4 days did not significantly affect Hg levels in rats[<1158>].
- I.p. treatment with DMPS for 9 days, beginning 6 days after i.v. administration of $HgCl_2$ did not alter the Hg content[<1282>].
- Neither delayed nor immediate treatment with DMPS lowered Hg levels[<10>].
- Immediate i.v. injection of DMPS following i.v. administration of $HgCl_2$ had no significant effect on Hg levels in mice[<395>].
- I.p. administration of DMPS did not affect the Hg content in rats given $HgCl_2$ i.v.[<627>].
- I.v. administration of DMPS 24 hours after i.v. administration of $HgCl_2$ did not alter Hg levels in rats. Contrastingly, BAL doubled Hg deposits[<1535>].
- Prophylactic i.p. treatment with DMPS (last dose administered 2 hours before i.v. administration of $HgCl_2$) did not change the heavy metal content in rats[<278>].

In other experiments, Hg levels in the brain were lowered:

- Following chronic Hg exposure (HgCl2 in the drinking water for 5 days), subsequent DMPS therapy (0.3 mmol/day i.p.) lowered Hg levels. The number of SH groups increased[<1330>].
- I.m administration of DMPS 4 and 7 hours after i.v. administration of HgCl2 lowered Hg levels in rats[<1164>].
- Single administration of DMPS 24 hours after i.v. administration of $HgCl_2$ lowered Hg levels in mice. The effect was not, however, statistically significant. BAL led to an accumulation of Hg[<10>].
- The addition of DMSA or DMPS to the feed following i.v. administration of $HgCl_2$ reduced the Hg load in mice. The values recorded in the animals treated with DMPS were somewhat lower than those in the DMSA group[<10>].
- DMPS and DMSA (immediate i.v. administration) lowered Hg levels in mice given i.v. $HgCl_2$. Contrastingly, BAL doubled Hg deposits[<9>].
- In mice (given a single oral dose of $HgCl_2$), heavy metal levels were reduced following both oral and parenteral administration.
- I.m. administration of DMPS 4 and 7 hours after i.v. administration of HgCl2 lowered mercury levels in rats[<276,279>].

Following single i.p. administration of 1 mg $HgCl_2$ for 5 days a week, for 4 weeks, mice were injected with 220 mg/kg/day DMPS, 180 mg/kg/day DMSA or 5% $NaHCO_3$ (controls). Higher Hg levels were detected in the perikaryon of the spinal α cells in both groups. No heavy metal was found in the cell nucleus. The authors do not comment whether this observation is relevant for

DMPS or DMSA treatment in humans. No measurement was carried out to determine whether the heavy metal content of the brain was affected or whether brain structures altered[<392>].

Conclusion:
DMPS reduces the embryotoxic and teratogenic effects of mercury. The heavy metal levels in most of the dam and foetal organs examined are lowered. The survival rate of the dams is increased. There is no evidence of embryotoxic or teratogenic effects of DMPS.

6.1.17.3.5.2 Organic mercury compounds

On poisoning with organic mercury compounds, administration of DMPS did not trigger any significant differences in Hg levels in the brain[<11,1070>]. Transiently high values were recorded for both organic and resulting inorganic mercury only in one experiment[<1149>]. No significant differences were observed between DMSA and DMPS[<519>]. The mercury in the brain was not redistributed. BAL triggered higher values[<519>].

The addition of CH_3HgCl to the drinking water for 17 days led to Hg deposits in various structures of the cerebellum in mice. The number of purkinje cells decreased. The additional administration of DMPS (150 mg/kg/day, i.p.) on the last three days, reduced damage to the cerebellum. Hg deposits were reduced in all areas. The number of purkinje cells was similar to that of the control animals. The effects of CH_3HgCl in the behaviour tests were reduced. DMPS prevented an increase in malondialdehyde concentrations. The mercury-induced reduction in glutathione peroxidise activity was not affected. "This data render DMPS a promising molecule for pharmacological studies with respect to intoxication with not only inorganic, but also organic mercurials"[<239>].

Conclusion:
On poisoning with organic mercury, DMPS hardly affects Hg levels in the brain. Its effect is comparable to that of DMSA. There is no proof to support Daunderer's assumption, namely that DMSA removes poisons more effectively in the brain. The heavy metal in the brain is not redistributed with DMPS therapy.

6.1.17.3.5.3 Mercury vapour

Treatment with DMPS over the observation periods had virtually no effect on the Hg content of the brain. The levels generally corresponded to those recorded in the control animals. There was no indication that DMPS leads to an accumulation of mercury in the brain. Similarly, there was no evidence to suggest improved Hg mobilisation from the brain by DMSA compared to DMPS.

After exposure to varying concentrations of Hg vapour, single or repeated dosing with DMPS (oral or i.p.) had no effect on Hg levels in the brain[<216>]. A decrease was observed in one investigation[<274>]. Similarly, DMSA was devoid of effect[<216>].

Rats were exposed to mercury vapour every day for two weeks. Whereas mercury levels in the blood quickly reached steady state, the mercury content of the brain constantly rose. The subsequent administration of DMPS had no effect on the mercury content of the brain. Both the untreated animals and the animals given oral or i.p. DMPS showed the same decrease[<984>].

Exposure of rats to mercury vapour led to elevated heavy metal levels in the brain. The administration of DMPS (oral or i.p.) did not alter Hg levels in the treated animals compared to the controls[<985>].

In young rats following chronic Hg vapour exposure, neither DMPS nor DMSA, vitamin C, glutathione or lipoic acid (for 7 days) lowered Hg levels in the brain. Various combinations of these substances were also ineffective[<51>].

In dogs given metallic mercury via the lungs, the oral administration of DMPS (4 mg/kg BW) for 8 days lowered mercury deposits in the brain[<627>].

Conclusion:
After poisoning with mercury vapour, DMPS does not affect the mercury content of the brain. DMSA was also ineffective. There is no proof that DMSA is capable of improved Hg mobilisation from the brain as is occasionally claimed in the literature.

6.1.17.3.6 Heart

On poisoning with inorganic or metallic mercury, DMPS reduced heavy metal levels in the heart[<255>]. In dogs given metallic mercury via the lungs, the oral administration of DMPS (4 mg/kg BW) for 8 days lowered mercury levels in the heart[<627>].

DMPS reduced the positive inotropic effect of organic mercury compounds on isolated heart muscle. The contractile strength of the muscles did not regress[<551,552>]. The pathological effects of $HgCl_2$ were reduced, whereby DMPS was more effective than BAL[<1330>].

Conclusion:
After poisoning with mercury, DMPS lowers mercury levels in the heart. The pathological effects of the heavy metal are reduced or even prevented.

6.1.17.3.7 Bones, skeleton

The heavy metal content of bones was either reduced on administration of DMPS[<453, 776,993,994,1294>] or unaffected[<376,1070,1158>].

6.1.17.3.8 Muscles

In muscles, the heavy metal content on poisoning with inorganic[<376,453,1294>] and organic[<454,455>] mercury was reduced by administration of DMPS. Compared to DMSA, DMPS was more effective[<1158>] or no significant difference was observed[<519>].

6.1.17.3.9 Testes

DMPS reduced the heavy metal content of the testes on poisoning with inorganic and organic mercury[<255>].

6.1.17.3.10 Spleen

The heavy metal content of the spleen was either reduced on poisoning with inorganic[<9,255, 453,687,990,993,994,1158,1294>] or organic[<454,455>] mercury by administration of DMPS or was unaffected[<376,1070>]. DMSA war less effective[<10,1157>], but the effect was not always statistically significant[<10>].

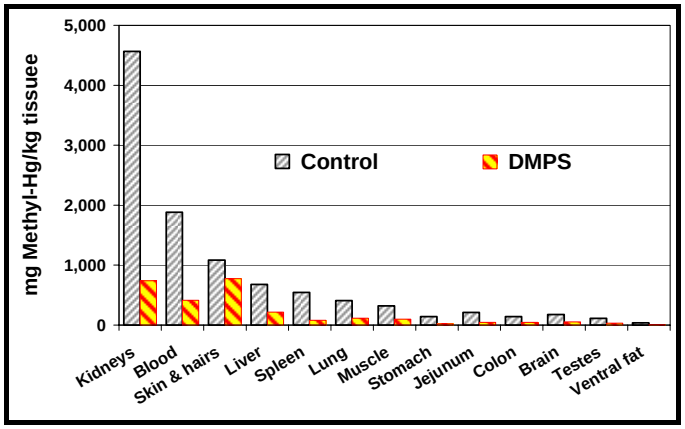
6.1.17.3.11 Thyroid gland

Prophylactic administration of DMPS prevented the increase in ^{131}J deposits in the thyroid gland of rats caused by organic Hg[<1463>].

6.1.17.3.12 Intestine, gastrointestinal tract

The heavy metal content of the intestine was reduced on poisoning with inorganic[<396,453,774,1158,1294,1417>] or organic[<454,455>] mercury by administration of DMPS. Prophylactic administration of DMPS was also effective[<278>].

Other studies found no effect[<376,395>]. The distribution of the heavy metal in various regions of the gastrointestinal tract was unaffected[<774>]. Mercury-induced inhibition of various enzymes in the intestinal mucosa was eliminated by DMPS[<1417>]. The additional oral administration of metal-complexing polymers was ineffective[<396>].



Effect of oral DMPS on the concentration of CH_3HgCl in various rat tissues compared to the untreated control animals[<1272>]

6.1.17.3.13 Lungs

Results relating to the effect of DMPS on the mercury content of the lungs vary. Four days/ treatment with i.p. DMPS, beginning 24 hours after administration of $HgCl_2$, lowered Hg levels in lungs of rats. Neither immediate nor delayed (beginning after 8 days) therapy with 5 mg/kg DMPS altered mercury deposits in the lungs[<376>] of rats. I.M. administration to rats did not have a significant effect on ^{203}Hg levels in the lungs[<1070>] following ^{203}Hg-chlormerodrine exposure.

6.1.17.3.14 Aorta

The administration of DMPS lowered the reduction in the number of SH groups in the aorta on acute poisoning with $HgCl_2$[<645>].

6.1.17.3.15 Skin

DMPS had no effect on Hg deposits in the skin. Neither immediate nor delayed therapy altered the mercury levels[<376,1070>].

Conclusion:
Results relating to the effect of DMPS on the mercury content of the bones, skeleton, muscles, testes, spleen, thyroid gland, intestine, gastrointestinal tract, lungs, aorta and skin depend on the nature of the experiment. They fluctuate between reduced and unchanged. No accumulation of the heavy metal is described.

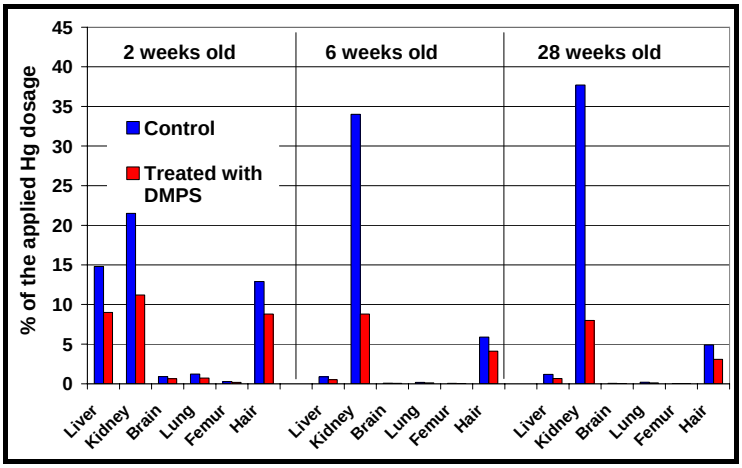
6.1.17.4 Age-dependency

The retention of mercury in the body and the efficacy of the chelating agents is age-dependent[<696>]. Immature rats store more mercury than the adult animals. The total body load is far higher than in adult animals. Oral administration of DMPS lowered these values whereas i.p. administration did not[<774,775>].

Higher mercury levels were recorded in young rats than in adult animals following oral, i.v. and i.p. administration of $HgCl_2$. This effect was particularly marked after oral administration when more than half of the inorganic mercury was still detected in the intestine of young animals 6 days later. Most of the mercury was absorbed by the adult animals[<696>]. If $HgCl_2$ and DMPS were administered orally, immediate DMPS administration reduced the mercury more effectively than delayed administration in young rats. In adult animals, only delayed onset of treatment triggered a

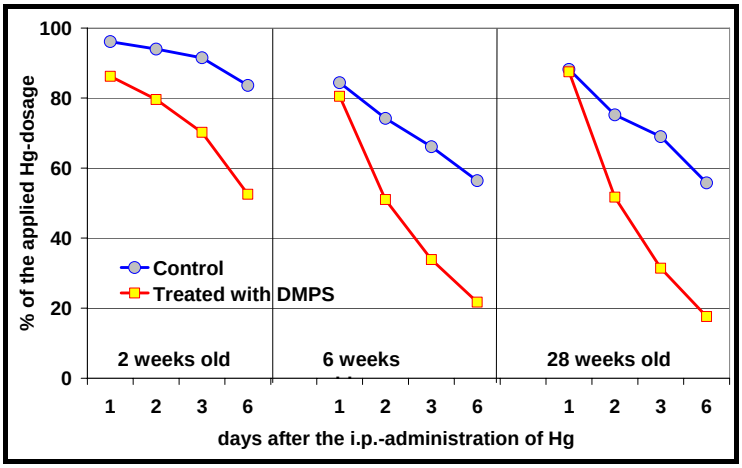
decrease in heavy metal concentrations. In contrast, immediate administration increased the mercury load. The DMPS-Hg complex was obviously absorbed more effectively from the intestine by these animals. No age-dependency was apparent with parenteral administration<773,776>.

Oral $HgCl_2$ was given to six day-old rats. Two-day oral therapy with DMPS (4 doses/day) was initiated immediately after or on the next day. The total body burden was reduced in both groups. The Hg load in the intestine was reduced by 50 to 70%<774>. Most of the mercury found in the intestine was located in the lower intestine and in the lower large intestine<774,776>. The distribution of the heavy metal in various regions of the gastrointestinal tract was unaffected<774>. DMPS prevented the inhibition of various enzymes in the intestinal mucosa<1417>. As the same total body burden was recorded with both immediate and delayed onset of therapy, DMPS obviously did not increase the absorption of the heavy metal in this age bracket.



Effect of DMPS on organ loads with ^{203}Hg in rats depending on the age of the animals<776>

Contrastingly, immediate oral administration of DMPS after oral dosing of $HgCl_2$ increased the absorption of Hg more than two-fold<78,773,775>. The effect was not apparent with Zn-DTPA and DMSA, but the total body burden was reduced<78,773>.



Effect of DMPS on the total body burden of $^{203}HgCl_2$ in rats depending on the age of the animals<776>

The total body burden was lowered in both young and adult mice following i.p. administration of $HgCl_2$ and oral administration of DMPS. Early onset of therapy was more effective in adult animals. No time-dependency was, however, apparent in young mice. Chelate therapy was more effective in adult animals than in immature young animals<773>. Hg levels in the various organs (liver, kidneys, brain, lungs, femur and hair) were lowered in all age groups. The effect in the kidneys – the target organ of mercury, was particularly marked<776>.

Conclusion:
DMPS is effective in both young and adult animals and can, therefore, be administered to all age groups. The differences in physiology between the age groups generate some differences in terms of the effects of DMPS.

6.1.17.5 Treatment of gestating animals

Methyl mercury is embryotoxic. In pregnant mice, DMPS reduced the embryotoxic and teratogenic effects (number of absorptions, number of dead foetuses and morphological defects) in a dose-dependent manner<393,395,498>. In addition, DMPS reduced the lethal effects of the toxin on the pregnant dams and increased their survival rates<498>.

Pregnant mice received 30 mg CH_3HgCl/kg via the oral route immediately followed by various doses of oral DMPS. The mortality rate of the dams was reduced from 55.3% in the control group to 11.1%. Higher doses proved to be more effective. There were fewer dams with completely absorbed foetuses and the number of surviving foetuses increased. The CH_3HgCl-induced reduction in the body weight of the foetuses was significantly smaller. Morphological foetal defects occurred less frequently<498>.

On administration of high doses of $HgCl_2$ to pregnant rats, the immediate administration of DMPS to the dams led to lower levels in the blood, liver and brain as well as in the placenta and foetal membrane. In contrast, the kidney value was twice as high as that recorded in the control animals. The renal excretion of Hg was increased. On delayed administration, the values in the blood, kidneys and brain were significantly lowered but liver levels were unchanged. The Hg content of the placenta was lowered when treatment was administered immediately or delayed. On immediate administration, the values in the blood, liver, kidneys and brains of the foetuses were unchanged. Higher deposits were detected in the liver and kidneys when treatment was delayed<1535>.

		Non-pregnant	Pregnant	
			Dam	Foetus
Blood	Controls	3.6	2.91	0.17
	Immediate	0.33	0.82	0.12
	24 h	0.38	0.42	0.10
Liver	Controls	20.9	15.5	0.44
	Immediate	1.74	5.43	0.56
	24 h	8.7	11.98	1.17
Kidneys	Controls	92.1	62.9	0.30
	Immediate	116	136.64	0.34
	24 h	27.6	24.65	0.48
Brain	Controls	0.21	0.2	0.08
	Immediate	0.11	0.12	0.08
	24 h	0.11	0.10	0.08
Placenta	Controls		9.52	
	Immediate		6.63	
	24 h		3.41	
Foetal membrane	Controls		80.00	
	Immediate		56.59	
	24 h		36.78	

Effect of immediate and delayed treatment (24 h later) with DMPS (250 µmol/kg i.v.) on Hg levels (nmol/g) in pregnant and non-pregnant rats or their foetuses ($HgCl_2$ 5,0 µmol i.v. <1535>

Conclusion:
DMPS reduces the embryotoxic and teratogenic effects of mercury. Heavy metal concentrations in most of the organs tested are lowered in both the dams and foetuses. The survival rates of the dams is increased. There is no evidence to suggest that embryotoxic or teratogenic effects occur with DMPS.

6.1.18 In - Indium

Immediately after i.p. injection of $InCl_3$, DMPS lowered the mortality rate in mice following acute poisoning with indium chloride. Comparison of the survival rates when various chelating agents are used yielded the following: Ca-DTPA ≈ DMSA > DMPS ≈ Zn-DTPA.

The indium total body burden was reduced following the immediate administration of DMPS. In levels in the kidneys, carcass and femur were lowered compared to those recorded in the control animals whereas liver values were raised<394>.

Conclusion:
DMPS appears to be a suitable antidote for the treatment of indium poisoning. Efficacy cannot, however, be evaluated due to the shortage of available data.

6.1.19 Li - Lthium

DMPS did not have any effect on the toxic actions of lithium salts in mice<1255>.

Conclusion:
Accprding to chemical legislation, DMPS is not expected to have a direct effect on lithium levels. DMPS is thus not contra-indicated even during lithium therapy.

6.1.20 Mn - Manganese

From a suspension of MnO_2 (particle size < 5 µ), the metal bound to plasma proteins. Unlike EDTA, the addition of DMPS did not have a significant effect on the bound quantity of metals[<439>]. In dogs, the urinary excretion of manganese rose during DMPS therapy[<1374>]. DMPS showed virtually no effect on rats with manganese poisoning[<805,1553>]. The urinary and faecal excretion of manganese corresponded both on immediate and delayed start of treatment (one week after the administration of $^{54}MnCl_2$) to that of the controls[<1553>]. The manganese levels in the skeleton, liver, lungs, kidneys, brain, muscles and pancreas were not affected[<805,1553>]. In contrast the administration of DTPA lowered manganese levels[<805,1553>].

	Ca-DTPA	DMPS	DPA
Skeleton	5.4	81.8	94.5
Liver	9.8	119	89.1
Muscles	2.6	86.0	98.2
Kidneys	4.4	101	106
Pancreas	3.9	92.3	82.4

Influence of immediate administration of CA on Mn levels in rats (% of controls)[<805>]

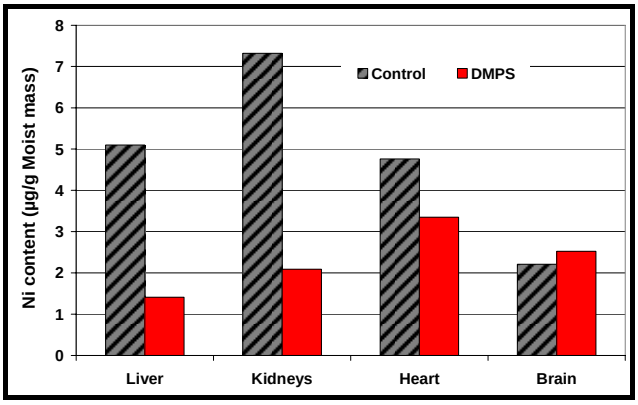
Conclusion:
DMPS obviously has no effect on manganese poisoning. DMPS is, therefore, not indicated in the treatment of this form of poisoning.

6.1.21 Mo - Molybdenum

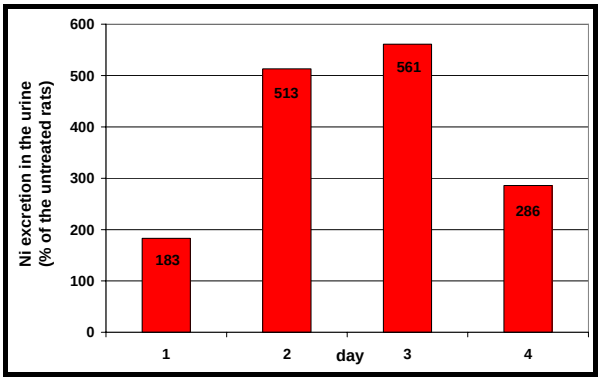
DMPS had a protective[<80,978>] and therapeutic[<978>] effect in mice on poisoning with sodium molybdate (Na_2MoO_4)[<80>] or molybdenum sulfide(MoS_3)[<978>].

The efficacy of DMPS on poisoning with molybdenum cannot be assessed due to the lack of available data.

6.1.22 Ni - Nickel



Influence of DMPS (1 Injection per day) on Ni levels in rats following chronic Ni exposure[<1331>]



Influence of the administration of DMPS (1 injection per day) on the urinary excretion of Ni (% of the untreated controls)[<1331>]

In experiments with NB4 (human leukaemia) cells and plasmids, the addition of dithiols increased the number of nickel-induced ruptures in the DNA strand (DMSA > DMPS > BAL). Intermediate oxygen radicals may be responsible for this, as with copper, since the addition of anti-oxidising agents prevents the reaction[<876>].

DMPS proved to be an effective antidote for nickel poisoning[<706>]. The administration of DMPS 20 minutes after administration of nickel acetate (LD_{50}) reduced the mortality rate in mice[<117,779>]. 50%[<779>] or 80%[<677>] of the animals survived while all the animals in the control group died. 40 % of rabbits survived poisoning with LD_{100} and 80% LD_{80}[<207>]. The presence of calcium ions did not affect the efficacy[<677>].

Chelating agents	Survival rate(%) Ni-Acetate<137>	$NiCl_2$<779>
Controls		0
Ca-DTPA	90	75
Zn-DTPA	0	0
BAL	10	
DMSA	60	93
Triene	70	
DMPS	80	50
DPA	100	67

Effect of the i.p. administration of CA on survival rates in mice<137,779>

After chronic poisoning with $NiSO_4$, the administration of DMPS did not increase nickel excretion in the urine whereas the faecal excretion of nickel was raised. Excretion was still high on the 4th day of treatment<1429>.

The biochemical parameters in the blood (glucose), plasma (ceruloplasmin, α-amino acids) and urine (α-amino acids), altered by the administration of nickel, improved. The heavy metal content of the liver, kidneys and heart was lowered. The nickel content of the brain was not statistically significantly affected<1331,1429>.

Conclusion:
DMPS increases the renal excretion of nickel. Heavy metal levels in the kidney, liver and heart are lowered. The survival rates are increased. DMPS therefore appears to be a suitable antidote for the treatment of nickel poisoning.

6.1.23 Pb - Lead

6.1.23.1 Investigations in cell cultures or cell organelles

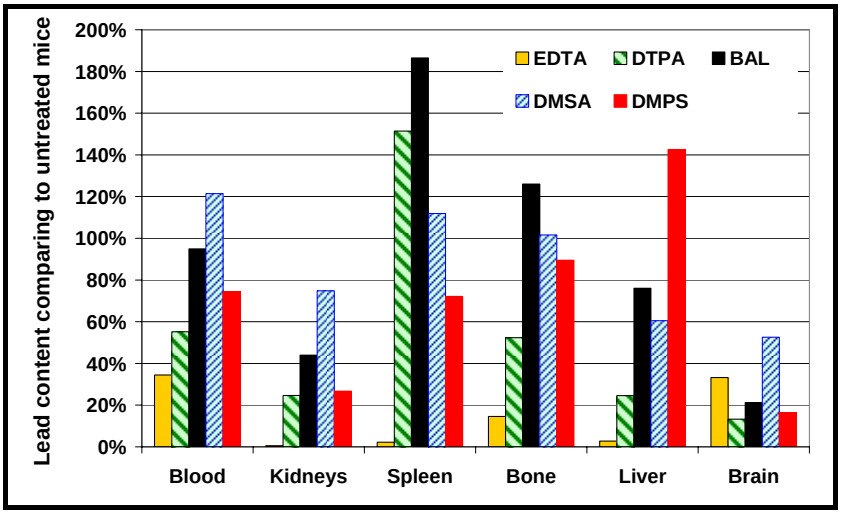
In investigations in peritoneal Chinese hamster cells, the concomitant administration of DMPS reduced the uptake of lead in the cells in a concentration-dependent manner, thus reducing its cytotoxic effects. Higher DMPS concentrations were more effective. In the case of cells previously incubated with lead, the addition of DMPS to the medium increased the excretion of the heavy metal from the cells<412,413>.

The addition of DMPS prevented lead-induced cytotoxicity in cell culture investigations<415>. In frog oocytes, the addition of DMPS completely abolished the lead-induced blockade of Ca^{2+} channels<181>.

The addition of lead triggered a reduction in glutamate binding to synaptic membranes isolated from rat brain. The addition of DMPS or DMSA, but not BAL, completely prevented this effect of lead<1362>. In the case of blood platelets, DMPS prevented an increase in glutamate binding<195a,196>. From a lead oxide suspension (PbO, PbO_2 or Pb_3O_4, particle size < 5 µ), the metal bound to plasma proteins. The addition of DMPS reduced the bound quantity of metal by 19-26 %<439>.

6.1.23.2 Acute poisoning

In acute lead poisoning, DMPS increased the lead excretion in the urine<853>. Oral administration of DMPS reduced lead levels in the blood, kidneys and liver in mice<424>. Faecal excretion was unchanged following i.p. administration. No statistically significant changes were observed in lead levels in the blood, spleen, bones, brain and liver. Kidney levels fell<853>. A combination of DMPS (oral) and EDTA (i.p.)



Effect of immediate, single, i.p. administration of chelating agents on lead distribution in mice following acute poisoning with lead acetate (LD_{50})<853>

was more effective than single DMPS therapy[<424>]. The treatment had no significant effect on lead levels in the brain[<424>]. The lead content was reduced in most organs, especially the kidneys[<424,853,1582>]. The lead-induced changes in various biochemical laboratory parameters improved[<424>]. Nevertheless, as with other chelating agents (EDTA, DPA, DMSA[<424>]), neither the survival rates[<424,595,771,853,1582>] nor the survival times[<771>] increased. Similarly, a combination of EDTA and DMPS did not increase the survival rates[<424>]. On local irradiation therapy of spleen tumours with monoclonal antibodies loaded with radioactive lead, concomitant administration of DMPS did not prevent a fatal outcome despite an increase in lead excretion[<1242>].

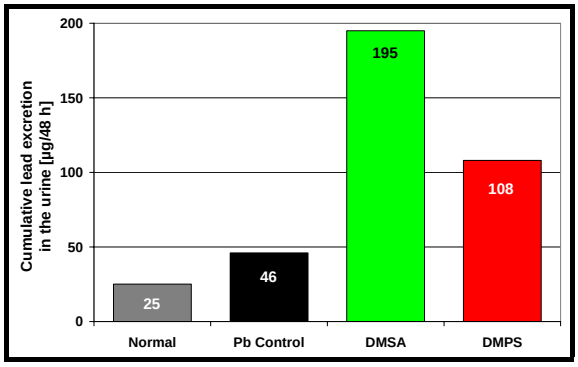
DMPS and other chelating agents did not affect mortality even when treating chronically-acutely poisoned rats (5 days' administration of high dose levels of lead)[<595>].

Conclusion:
DMPS increases lead excretion in the urine following acute poisoning. Lead levels in the organs are lowered. Nevertheless, DMPS, like other chelating agents, had no effect on mortality.

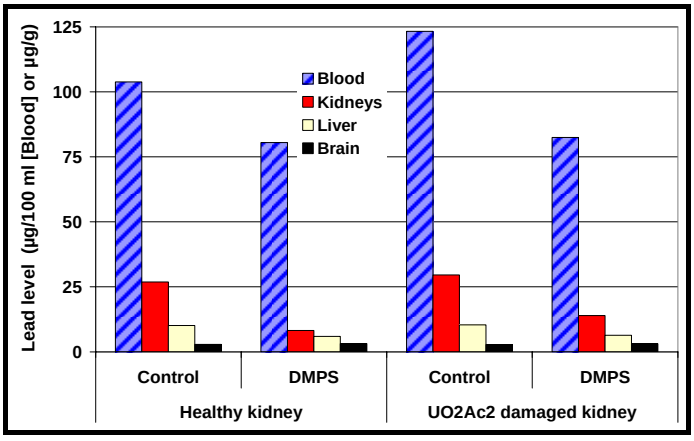
6.1.23.3 Chronic poisoning

6.1.23.3.1 Excretion

In chronic lead poisoning, DMPS increased the lead excretion in the urine[<58,256,417,427,428,430,538,595,1331,1374,1431,1464,1465>] and faeces[<427,428,1331>]. Excretion in the urine rose with increasing dose levels of DMPS[<1463>]. At the lower DMPS doses there was a linear correlation between the lead excretion in 24-hour urine and the decrease in heavy metals in the kidneys[<256,1463,1464>] (possibility of a mobilisation test[<256>]). At higher DMPS doses, additional lead from the liver and bones was mobilised[<271,595>]. The urine excretion with intact kidneys was higher than with damaged kidneys, but even then, it was always greater than in untreated controls[<431>]. Single administration of DMPS (i.p.) following chronic lead exposure increased renal excretion in rats. Lead levels in the urine were still high even on the days following administration of DMPS. DMSA was more effective than DMPS[<1431>].



Cumulative excretion of lead in the urine at the start of treatment three days after chronic $Pb(Ac)_2$ exposure[<58>]



Lead levels in rats with intact kidneys or kidneys previously damaged through single s.c. injection of uranyl acetate (UO_2Ac_2)[<431>]

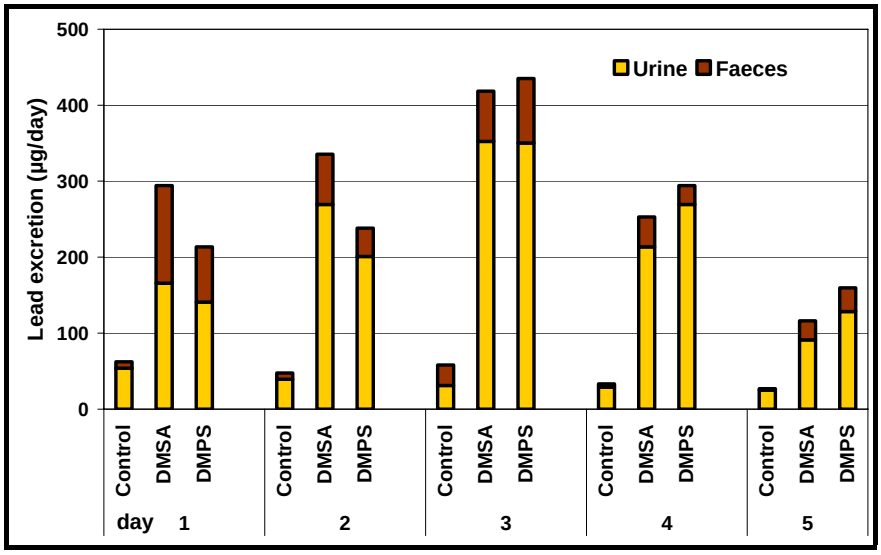
With the increased excretion of heavy metals, the clinical symptoms of poisoning (anaemia, limited mobility, loss of appetite, weight loss) also improved more rapidly[<538,595,771>].

On comparison of the route of administration of DMPS, the oral administration of 150 µmol/kg BW (= 34 mg/kg BW) has a similar effect on the heavy metal content of the kidneys and blood with injection (i.p.) of 50 µmol/kg BW (= 11 mg/kg BW). In the liver and bones, the parenteral administration was somewhat superior[<1463>].

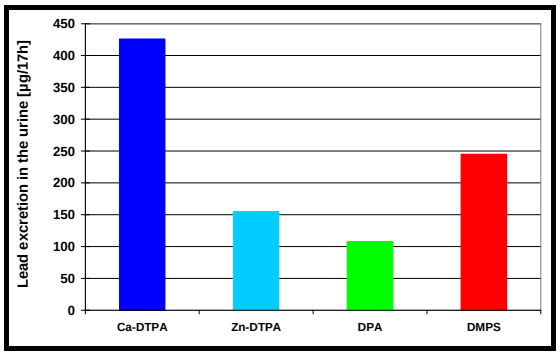
Following oral administration, both DMPS and DMSA increased the renal and faecal excretion of lead in rats with chronic lead poisoning. DMSA was somewhat more effective but only when

bioavailability was not taken into account. Lead-induced changes in the biochemical parameters in the blood (ALAD, ZPP) and urine (ALA) were partly improved. Lead concentrations in the blood, kidneys and liver fell significantly. However, the decrease in lead levels in the brain was not significant[<428>].

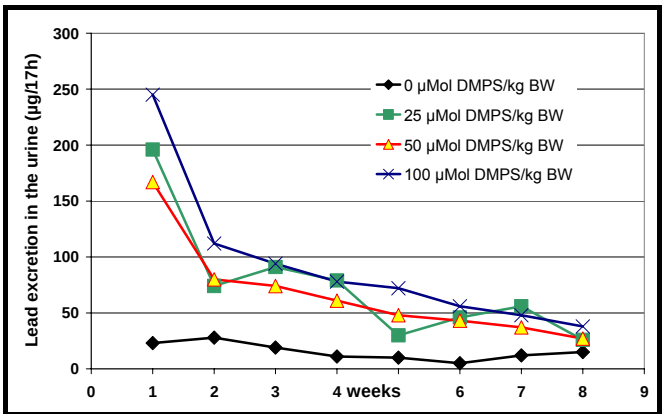
Following chronic lead poisoning, the i.p. administration of DMPS increased the excretion of lead in both the urine and the faeces. The following order was observed on renal excretion: DMSA > EDTA > DMPS. Only DMPS was effective in terms of faecal excretion. DMPS also increased renal excretion with a second treatment cycle after 5 days' antidote administration and a 5-day treatment-free interval[<1430>].



Daily excretion of lead in the faeces and urine of rats after chronic lead intoxication with equimolar oral administration of DMPS or DMSA[<428>].

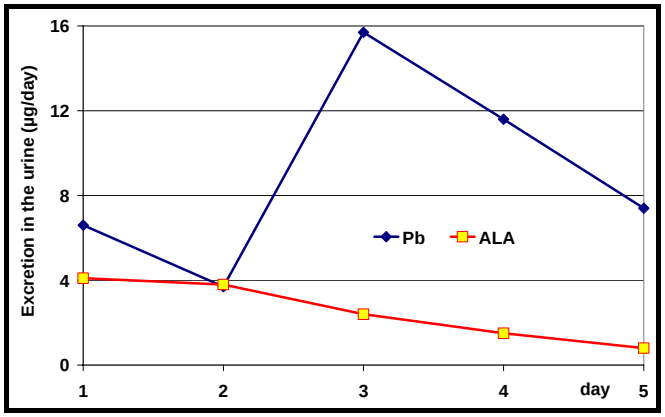


Pb excretion in the urine after chronic Pb burden (chelating agent: single administration of 100 µmol/kg i.p.)[<595>]



Dependence of Pb excretion in the urine on the DMPS dose (µmol/kg) (i.p.-administered for 5 days per week) after chronic loading/burden[<595>]

Lead excretion in the faeces[<1331>] and urine[<417,538,595,1331>] still clearly exceeded the levels recorded in the control animals even after longer treatment with DMPS. The differences in excretion following administration of the various dose levels of DMPS were thus surprisingly small[<595>].



Excretion of lead and ALA in the urine during DMPS treatment[<256,1465>]

15 rabbits were given drinking water containing lead for 3 months. Lead concentrations in the blood increased from 20 – 40 ng/mL to 200 ng/mL. Eight animals were treated with DMPS i.v. for 2 periods, each of 5 days' duration (starting on day 5 and day 30). The half-life in the blood was somewhat lower during the first treatment cycle with DMPS than in the untreated control animals. The effect was not, however, statistically significant. During the second treatment cycle, the half-life was reduced from 240-280 hours to 140-200 hours. Lead excretion in the faeces was between 50 and >90 %, which highlights

the slight absorption of lead following oral administration. Only smaller quantities of Pb were eliminated in the urine, whereby the concentration on the first day of DMPS treatment increased 3-fold[<571>].

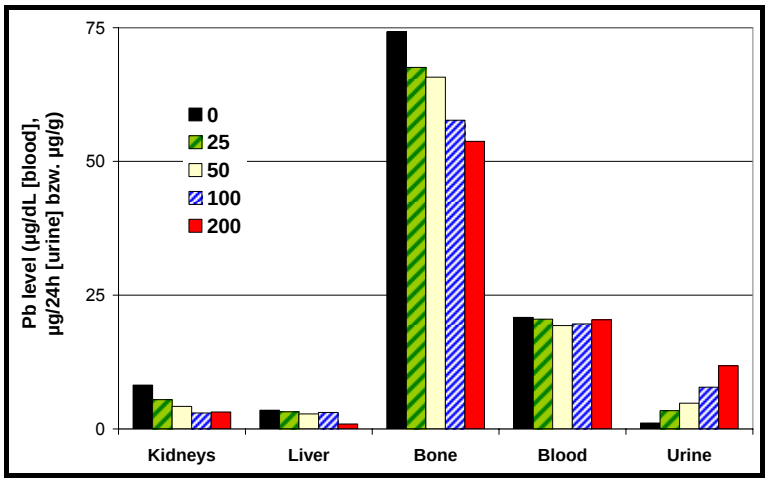
6.1.23.3.2 Distribution of lead in the body

The efficacy of DMPS on the heavy metal content of other organs depended on the design of the experiment. In this respect, immediate start of therapy proved to be more effective than a delayed start[<245,1463>].

	Liver	Kidneys	Skeleton
Control	2.94	4.45	31.5
Treatment started immediately	0.37	0.61	11.7
Treatment starting after 24 hours	3.33	1.28	32.7

Pb content in rats following immediate or delayed onset of treatment with DMPS (% of the i.v. administered dose of Pb)[<245>]

Mice were given 1.75 mmol DMPS/kg s.c. for 5 days following chronic lead exposure. The lead-induced decrease in δ-ALAD activity in the blood and liver was enhanced by DMPS just like BAL or DMSA. No statistically significant change was observed in the brain with all chelating agents. BAL and DMSA decreased the activity whereas DMPS triggered no change[<1260>].



Pb excretion in the urine and Pb levels in rat organs depending on the dose of DMPS applied (µmol/kg BW)[<1463>]

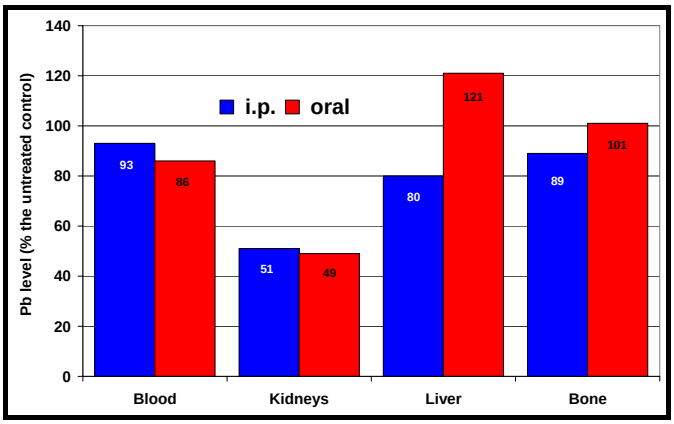
Immediate i.p. administration of DMPS after i.v. administration of $Pb(NO_3)_2$ reduced the Pb content in the rat liver, kidneys and skeleton. The start of treatment after 24 hours affected only Pb levels in the kidneys[<245>].

Lower lead concentrations were observed in the liver, kidneys and muscles [<1613>] of chickens whose feed was mixed with DMPS.

Histopathological changes in the kidneys, liver and gastrointestinal tract improved. Prophylactic administration of DMPS prevented the changes[<535>].

6.1.23.3.2.1 Blood

Lead acetate inhibits δ-ALAD activity in human blood *in vitro*. Prophylactic administration of DMPS did not change this but rather potentiated the effect . The subsequent addition of DMPS did not restore lead-inhibited activity but reduced it even further. The DMPS-Pb complex obviously has an inhibitory effect on enzyme activity[<1260>]. In *in-vitro* dialysis experiments, the administration of DMPS increased the clearance of lead from human blood but not as effectively as EDTA or DMSA[<1587>].



Effect of the route of DMPS administration on Pb content[<1463>]

Lead concentrations in the blood fell during DMPS therapy[<428,431,723,1266,1331>] or remai-

ned the same[1463,1465]. The reduction in lead blood concentrations took longer[723]. Biochemical parameters in the blood were partially improved[1266].

	Kidneys	Liver	Bones	Blood
Single dose of DMPS, 2 days after the last Pb injection and determination 1 day later	32	86	88	89
Single dose of DMPS, 2 days after the last Pb injection and determination 6 days later	90	92	87	95
Two doses of DMPS, 2 and 6 days after the last Pb injection and determination 1 day later	57	99	86	100
Single dose of DMPS, 6 days after the last Pb injection and determination 1 day later	51	80	89	93

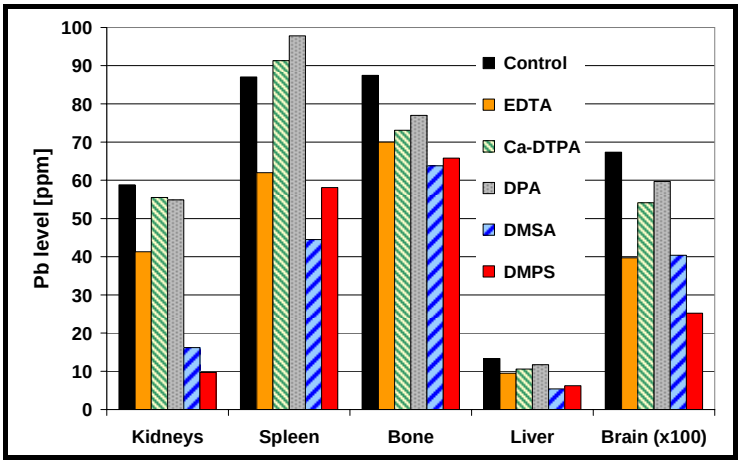
Dependence of the lead burden of various organs on the treatment schedule (% of untreated control animals)[1463]

6.1.23.3.2.2 Kidneys

The DMPS-induced increase in lead excretion led to a reduction in the heavy metal content in the kidneys[74,245,256,424,427,428,430,431,595,1331,1431,1463,1465,1474]. Other studies reported no significant effect[457]. The lead concentration fell rapidly[74]. A higher dose of DMPS triggered a greater effect[595,1463]. If the antidote therapy was interrupted, blood concentrations in the kidneys rose again[1463].

"Natural" Pb levels in the kidneys fell during DMPS therapy in animals that were not previously given any extra lead[1420].

Lead-induced changes in biochemical clinical parameters improved in most studies as a result of DMPS administration[537,538,723,1266]. Heavy metal-induced lipid peroxidation in the kidneys was reduced[457]. In dogs, coporphyrin continuously increased after lead poisoning whereas they fell in animals treated with DMPS[537]. The activity of δ-aminolaevulinic acid-dehydratase (ALA-D) increased again[426-428,430,723,1331,1431] whereas the urine level of aminolaevulinic acid (ALA) fell[428,430,431,595,771,1331,1431]. The increased blood levels of zinc protoporphyrin (ZPP) were reduced[428,430,431,1331,1431].

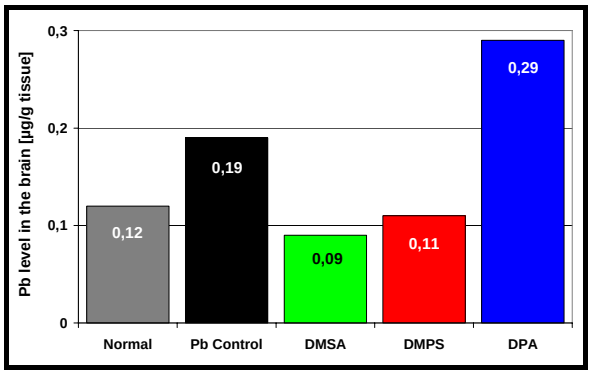


Effect of several days' treatment with CA on lead distribution in mice after chronic poisoning with Pb acetate[1582]

6.1.23.3.2.3 Brain

Following chronic lead exposure ($Pb(Ac)_2$ in the drinking water, i.p.[74] or oral[1266] administration of DMPS triggered no change in lead concentrations in the brain and did not, therefore, lead to any accumulation. Biochemical parameters in the brain were partially improved[1266].

Most studies showed an unchanged[74,256,424,428,430,431,1266,1331,1465] or reduced[58,1431,1582] heavy metal content in the brain. With DPA[58] or $CaNa_2EDTA$[1266], it exceeded that recorded in the control animals.



Lead concentration in the brain following chronic $Pb(Ac)_2$ exposure and two days of antidote therapy[58]

6.1.23.3.2.4 Bones

The lead content in the bones was lowered[<245,256,595,1464,1582>] or unaffected[<909>].

6.1.23.3.2.5 Spleen

Lead concentrations in the spleen were lowered[<1582>] or unchanged[<1463,1464>].

6.1.23.3.2.6 Liver

Lower[<245,424,428,430,431,1266,1331,1582>] or unchanged values[<1463,1464,1465>] were also measured in the liver. Immediate i.p. administration of DMPS after chronic Pb exposure (one i.p injection of $Pb(Ac)_2$ per day for 6 days) even increased lead values in the liver[<457>].

"Natural" Pb levels in the liver fell during DMPS therapy in animals that were not previously given any extra lead[<1420>].

Biochemical liver parameters were partially improved[<1266>]. Heavy metal-induced lipid peroxidation was reduced[<457>]. In another study, DMPS did not prevent the lead-induced reduction in δ-ALAD activity in the liver[<1049>].

6.1.23.4 Combination therapy

Concomitant administration of DMPS and EDTA reduced lead concentrations in the blood, femur, kidneys and liver more than the administration of individual chelating agents[<424,1430>]. No statistically significant effect was observed in the brain[<1430>]. Biochemical parameters in the blood (ALAD, ZPP) and urine (ALA, protein) improved[<1430>]. The effect was not, however, cumulative[<1430>]. The combination of EDTA and DMSA was more effective[<1430>]. A positive effect on the bones and blood was observed following combination therapy with DMPS and BAL[<271,1465>]. In another study, a combination of DMPS (oral) and EDTA (i.p.) had no synergistic effect following chronic lead exposure[<1266>].

Concomitant administration of vitamin B_1 and DMPS did not increase the overall excretion of lead in faeces and urine, but nevertheless led to lower lead concentrations in the kidneys compared to those observed with DMPS monotherapy. This effect could not be detected in the blood, liver or brain[<427,428>]. Lead-induced high levels of ZPP in the blood were lowered more effectively with a combination of vitamin B_1 and DMPS than with DMPS alone. As regards other biochemical parameters, vitamin B_1 did not increase the efficacy of DMPS[<428>].

The additional administration of zinc or zinc + methionine increased DMPS-induced lead excretion[<427,1431>]. The heavy metal content of the liver, kidneys and blood was lowered. The laboratory parameters in the blood (ALAD and ZPP) and urine (ALA) improved during concomitant administration of zinc, methionine and DMPS[<1431>].

6.1.23.5 Influence on trace elements

The concomitant administration of copper and zinc (oral) and DMPS (i.p.) reduced the excretion of lead whilst

	Liver			Kidneys			Brain			Blood		
	Pb	Zn	Cu	Pb	Zn	Cu	Pb	Zn	Cu	Pb	Zn	Cu
Controls	1.1	39.9	7.9	1.2	23.2	8.0	0.07	17.5	2.8	5.0	6.8	4.2
Pb	12.5	35.4	6.1	17.2	20.1	6.2	0.42	15.3	2.6	74.9	4.3	2.9
Pb + DMPS	6.4	42.3	5.7	10.2	21.0	7.2	0.55	15.5	2.6	36.5	4.8	2.0
PB+DMPS+Zn+Cu	5.5	63.3	10.9	10.8	25.3	8.2	0.62	15.7	3.0	28.9	9.2	4.7

Effect of concomitant administration of DMPS and zinc + copper on lead, zinc and copper levels in various organs[<430>]

the daily excretion of zinc rose continuously. Lead concentrations in the blood were reduced. Several biochemical parameters were also positively affected. The addition of zinc and DMPS did not have any effect on the heavy metal content of the liver, kidneys and brain[<430>].

The administration of lead resulted in lower zinc and copper levels in the blood. The zinc content of the liver, kidneys and brain was not significantly affected. The copper content of the kidneys and liver was reduced, but the copper content of the brain remained unchanged. The administration of DMPS did not alter these levels. If DMPS, copper and zinc were administered concomitantly, the zinc and copper levels of various organs were increased despite antidote therapy. Some biochemical parameters were also positively influenced by the concomitant administration of trace elements[<430>].

The chronic administration of lead resulted in lower zinc levels in the brain and reduced copper levels in the kidneys in rats. The administration of DMPS did not change these levels. Only the fall in zinc levels in the brain disappeared whereas the lowered copper levels in the kidneys persisted[<1266>].

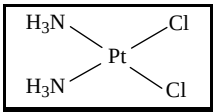
Conclusion:
DMPS increases lead excretion in the urine and faeces after chronic poisoning. Lead concentrations are lowered especially in the kidneys. Lead depots in the bones are prevented only by immediate administration of DMPS. Heavy metals already deposited are not mobilised. The efficacy of DMPS appears to be comparable to that of DMSA and better than that of EDTA and DPA.

6.1.24 Pd - Palladium

In mice, the immediate administration of DMPS had no effect on the acute toxicity of palladium chloride $PdCl_2$. Lethality was not reduced. Similarly, DMSA, DPA and Ca-DTPA did not lower the mortality rate[<953>].

Conclusion:
The efficacy of DMPS on palladium poisoning cannot be assessed. It is obviously devoid of effect on acute poisoning.

6.1.25 Pt - Platinum



Cisplatin

Immediate administration of DMPS increased the survival rate in mice following acute poisoning with cisplatin but was less effective than DMSA[<701>].

DMPS increased the urinary excretion of Pt in rats injected with i.v. cisplatin. The effect was, however, too slight to reduce the kidney burden. Ca-DTPA had no effect. In contrast, four days' treatment with DMSA led to lower Pt levels in the kidneys[<1155>].

The prophylactic administration of DMPS had positive effects on the ototoxic effects of cisplatin in guinea pigs[<189>].

Chelating agents	Pt content of the kidneys	Pt excretion in the urine
Controls	2.21	10.1
DMPS	2.21	13.6
DMSA	1.76	13.5
Ca-DTPA	1.90	10.0

Influence of 4 days' treatment with various chelating agents in rats following administration of cisplatin and the Pt content of the kidneys and Pt excretion in the urine (% of the injected dose)[<1155>]

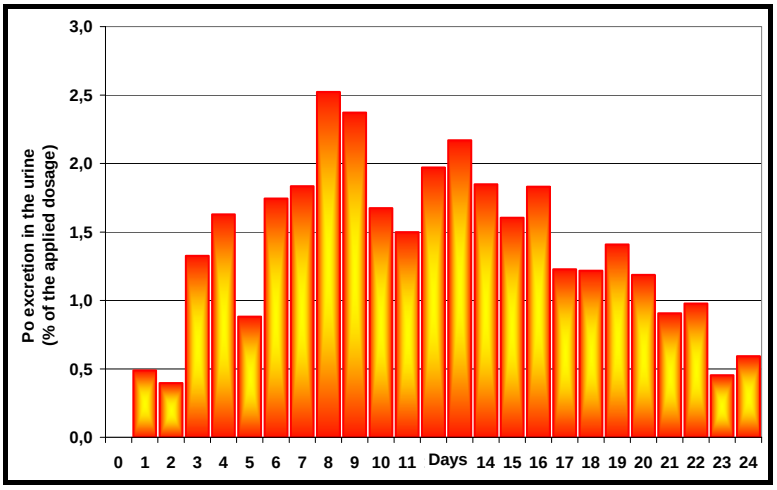
Conclusion:
The efficacy of DMPS on platinum poisoning cannot be assessed.

6.1.26 Po - Polonium

Polonium reacts with SH groups of proteins and has a high affinity for erythrocytes. The most important storage organs for polonium are the blood, liver, spleen, kidneys, lymph nodes and bone marrow. Excretion is chiefly in the faeces[<1320>].

If blood from rats given ^{210}Po intravenously 2 days earlier was incubated with DMPS, 63% of the α-emitter bound to the erythrocytes were removed compared to just 1 to 2% without DMPS. An incubation period of 1 or 9 hours made no difference. If the blood was not collected from the animals until 7 days later, the longer incubation periods proved to be more effective (53% after 9 hours compared to 45% after 1 hour). This means that, meanwhile, ^{210}Po was redistributed in compartments that were difficult to mobilise[<1495>].

DMPS increased the excretion of Po in rats[<387,1170>] and thus led to a reduced total body burden [<1499>] as well as to increased survival rates (1.5 to 3-fold) in rats and dogs[<1170>]. DMPA or DMPS, but not DMSA will mobilize ^{210}Po in rats and increase its excretion[<49a>].



Daily excretion of ^{210}Po in rat urine during treatment with DMPS (% of the injected ^{210}Po dose)[<1228,1320>]

S.c. administration of DMPS to rats for 5 days led to increased excretion of the α-particle emitting radionuclide in the urine and faeces and thus to a reduced total body burden. ^{210}Po levels were reduced in all of the organs investigated[<1219,1499>] apart from the kidneys. The effect was dose-dependent. High doses of DMPS reduced the accumulation of ^{210}Po in the kidneys[<1499>]. DMPS was more effective than DMSA at the same dose[<1499>]. Compared to DMPS therapy alone, concomitant administration of DMPS and dithiocarbamates reduced the total body burden. Po accumulation was lower especially in the muscles, but also in the kidneys but the radionuclide content of the liver and brain was raised[<1499,1501>].

	Blood	Plasma	Liver	Bones	Brain	Spleen	Kidneys
DMPS oral	28	48	94	21	27	14	971
DMPS i.p.	16	57	124	15		8	850
Ca-DTPA i.p.	77	106	131	108		92	120
DPA i.p.	37	94	111	64		42	326
DPA oral	66	91	83	85	73	74	171

Influence of DMPS, DTPA and DPA on the ^{210}Po content of various rat organs (% of the ^{210}Po content in untreated control animals)[<1320,1502>]

The immediate injection of DMPS increased the uptake of s.c. administered Po. 30-40% of the dose administered remained at the injection site without DMPS compared to just 12-14 %[<1640>] after administration of DMPS. A delayed injection had no effect[<1640>]. Surgical excision of the wound is, therefore, an essential first-aid measure[<1639>].

In laboratory animal experiments, immediate dosing with DMPS increased the survival rates after administration of polonium by increased excretion[<1137>] and rapid removal of the α-emitter from radiosensitive areas (bone marrow, spleen)[<1170,1474,1502>]. Higher doses and more frequent dosing were more effective[<1137>]. While 78 % of the treated rats survived following immediate treatment with DMPS, only 23 % of the control group survived[<64>]. The onset of treatment after 12 hours led to increased elimination but the survival rate did not increase[<1137>]. In rats, the survival rates increased by a factor of 3 to 4 following early injection of high doses of DMPS (100 mg/kg BW). The excretion of ^{210}Po in the urine was increased 30 to 40-fold whereas faecal elimination doubled compared to the controls[<1638>]. The mean survival time more than doubled[<64,387,1474>]. DMPS also

increased the survival rate in dogs[<1171>]. DMPS probably acted not only as a chelating agent but also had an additional protective effect against radiation damage[<1476>].

DMPS increased the excretion of ^{210}Po in the urine[<1501>] and faeces. Total excretion rose significantly[<1219,1228,1320>].

Administration of DMPS	Blood	Plasma	Liver	Spleen	Skeleton	Kidneys	Brain
1.5 minutes	15	58	124	8	15	773	
1 hour	27	56	112	58	44	389	
1 day	19	59	134	68	56	249	
2 days	104	78	83	75	82	243	87
4 days	100	83	96	97	97	196	94
8 days	88	90	98	81	103	182	89

Dependence of the efficacy of DMPS on the time between the administration of polonium and the chelating agent (% of the untreated controls)[<1501>]

DMPS was most effective when it was administered immediately after polonium. Efficacy decreased with increasing time intervals between administration of the radionuclide and the chelating agent[<1501>]. With continuous administration of DMPS, rats excreted significantly more ^{210}Po in the urine than the untreated control animals [<1228,1320>] even after 24 days.

Single administration of DMPS 1 hour after administration of $^{210}Po(NO_3)_2$ increased the total body burden. The radionuclide content was

- reduced[<64,1320,1499,1501,1502>] or raised[<1221>] in the blood
- reduced[<1320,1500-1502>] or unchanged[<1221>] in the plasma
- reduced[<64,14993>] or not significantly affected[<1221,1320,1500,1501>] in the liver
- reduced in the bones[<64,1221,1320,1499,1501,1502>]
- reduced in the muscles[<1221>]
- reduced in the heart[<64>]
- reduced in the lungs[<64>]
- reduced in the testes[<64>]
- reduced[<64,1320,1499,1501,1502>] or unchanged[<1221>] in the spleen
- unchanged[<1221,1499,1500>] or lowered[<64,1320,1501,1502>] in the brain

In the kidneys, treatment led to a marked accumulation of the radionuclide[<64,1170,1221, 1228,1320,1499,1501, 1502>]. The risk of a kidney tumour was thus increased[<1170>]. Other authors did not observe any change compared to the controls[<64>]. Alkalisation of the urine did not prevent this accumulation[<1501>]. Higher doses were more effective[<1501>]. Continuous administration of DMPS led to another decrease[<1228,1320>].

Treatment with DMPS (s.c.), which was initiated 1 hour after s.c. administration of ^{210}Po and continued for over 20 days. reduced ^{210}Po levels in the liver, lungs, blood, spleen, heart, testes, bones and brain. The ^{210}Po load in the kidneys was equivalent to that of the control animals[<75>].

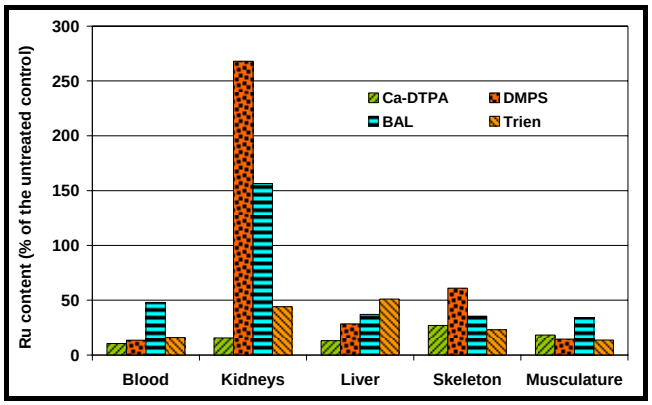
DMPS was effective both orally and via the i.p. route[<1320, 1502>]. The same dose administered parenterally was three times more effective[<1502>]. Three times the i.m. dose had to be administered in order to obtain the same effect orally[<1499>].

The increased radiation load of the kidneys led to pathological changes, which were partially reversible, but which also led partly to nephrosclerosis[<387,1170,1171,1502>]. In contrast, damage to the haematopoietic system was reduced[<387.1474,1502>]. The increased renal deoxycytidine excretion resulting from the effect of polonium on DNA metabolism was lowered[<1474>].

Conclusion:
DMPS increases the survival rates on poisoning with polonium. The excretion of the radionuclide is increased whereas Po levels and thus the radiation load in most organs is reduced. In particular, early administration of high doses over a prolonged period was effective. DMPS, however, leads to an accumulation of polonium in the kidneys, thus increasing the risk of pathological changes including kidney tumour.

6.1.27 Ru - Ruthenium

On concomitant administration of ruthenium and DMPS, the radionuclide accumulated predominantly in the kidneys (268 %[<1321>] or 1,352 %[<39>] compared to the control animals without DMPS). It is presumably bound to metallothioneins[<39>]. The maximum concentration in the kidneys was achieved after 7 – 10 hours with 40 – 50 % of the injected dose. Thereafter, the Ru content fell slowly[<39>]. After 24 hours, up to 36 % of the dose injected could still be detected in the kidneys[<40>]. The DMPS-complex of the ß emitter is thus suitable for kidney scanning. In contrast, DTPA and triene lowered the retention of the radionuclide in all organs[<1321>].



^{106}Ru content of the organs on the 2nd day after concomitant i.v. injection of $^{106}RuCl_3$ and chelating agents (% of the untreated control animals)[<1321>]

Later mobilisation also led to accumulation in the kidneys. The metal content was lowered in the other organs and in the blood[<39,1321>]. The effect was pH-dependent and more ruthenium was stored in the acid range[<39>].

pH	Blood	Liver	Spleen	Pancreas	Intestine	Kidneys	Lungs	Muscles	Skeleton
4.5	17	42	26	27	31	1,855	22	46	39
7.2	10	31	16	20	19	1,352	9	31	37

pH-dependency of the ruthium content of various organs after mobilisation with DMPS (% of the untreated control animals)[<39>]

Conclusion:
DMPS leads to an accumulation of ruthenium in the kidneys. The effect is less marked at a neutral pH than at an acid pH. The kidneys can be scanned using the ß emitter ^{106}Ru . Levels in the other organs are lowered.

6.1.28 Sb - Antimony

DMPS reduced the acute toxicity of antimony(III) compounds[<168>]. No information has been collated with regard to Sb(V) compounds[<137>]. Out of 30 mice poisoned with the lethal dose (twice the LD_{50}) of antimony, 19 survived (63 %), while all the animals in the control group died. The survival rate fell at higher antimony doses in spite of increased DMPS doses[<137>]. The LD_{50} for the s.c. administration of potassium tartrate was increased by a factor of 8 compared with untreated control animals[<265>].

Potassium tartrate (mg/kg BW)	Survival rate (%)
80	100
100	100
120	63
140	40
170	20

Dependence of the survival rate on a dose of potassium tartrate with administration of DMPS (Sb:DMPS = 1:10)[<137>]

Chelate-forming agent	Survival rate (%)	
	Potassium tartrate 2 x LD_{50}	Antimony citrate(LD_{95})
Control	0	0
BAL	0	
DPA	40	90
DMPS	63	100
DMSA	93	100

Survival rate of mice following administration of potassium tartrate (2-fold LD_{50}) or antimony citrate (LD_{95}) and various CA[<132,135>]

The pathological effects of antimony on the brain were prevented[<499>]. The morphological and histological changes in the liver of rats and rabbits were positively affected[<784>]. The metal content of the blood and liver were unchanged while levels in the heart were lowered[<168,716>].

Concomitant administration of DMPS reduced the systemic toxicity of potassium tartrate by half without adversely affecting the antischistosomial efficacy of the antimony compound[<168,716>].

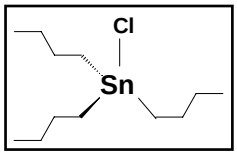
Conclusion:
In animals, DMPS increased the survival rates after acute poisoning with antimony compounds. The symptoms partly improved. DMPS therefore appears to be a suitable antidote for the treatment of antimony poisoning.

6.1.29 Se - Selenium

The administration of DMPS did not have any positive effect on the clinical symptoms of poisoning with sodium selenate. The reduced body weight gain was not improved. Selenium excretion in the faeces and urine was unchanged[<1124>]. In rats that were given selenium and mercury concomitantly, high mercury levels (presumably due to the deposits of mercury selenide) were detected particularly in the liver. The administration of DMPS reduced both mercury and selenium levels in the blood, kidneys and liver[<1578>]. DMPS is obviously capable of cleaving mercury selenide. Released selenium is then presumably excreted in larger quantities without binding to DMPS.

Conclusion:
Only a few investigations have been carried out to determine the efficacy of DMPS on selenium poisoning. DMPS is consequently not effective with selenium.

6.1.30 Sn - Tin



Hydrophilic tri-n-butyl tin $(C_4H_9)_3SnCl$ displayed haemolytic effects on human erythrocytes at concentrations ≥ 5 µM. DMPS was unable to inhibit this haemolysis[<516,517>].

In vivo, the administration of DMPS increased the LD_{50} of dimethyl-, dibutyl-, dipentyl- and dihexyl tin chloride. The toxic effects on the organs (thymus atrophy, liver damage, pancreatitis and bile duct lesions) were reduced. With dialkyl compounds with alkyl chains of more than 6 carbon atoms, a positive effect with DMPS could no longer be detected[<930>].

A single dose of DMPS (oral or i.p.) lowered zinc concentrations in the bile fluid by up to 70% in rats. This led to lower Sn levels in the pancreas and liver. The toxic effects on the organs (thymus atrophy, liver damage, pancreatitis and bile duct lesions) were consequently reduced. Changes in various serum parameters fell to less of an extent. Sn excretion in the urine was raised[<929>].

Conclusion:
DMPS appears to have positive effects in acute and chronic poisoning with tin. However, efficacy cannot be assessed due to an insufficient number of investigations.

6.1.31 Sr - Strontium

DMPS had no effect on the survival rate of mice with acute strontium poisoning[<346,1135,1136>].

$SrCl_2$	LD_{50} = 3,000 mg/kg BW
$SrCl_2$ + DMPS	LD_{50} = 2,930 mg/kg BW[<1136>]

Conclusion:
DMPS has no effect on acute strontium poisoning. No investigations have been carried out on chronic poisoning.

6.1.32 Tc - Technetium

Protein binding of the ^{99m}Tc-DMPS complex was 95 %[<1484,1485>]. After i.v. administration, it was excreted relatively rapidly (60% within 2 hours)[<1068,1484,1485>]. Higher radioactivity was found in particular in the renal cortex[<1067,1485>].

Time	Kidneys	Liver	Intestine	Blood	Lungs	Urine+Faeces
1 h	35	13	6	5	1	13
2 h	45	6	5	1	0.1	20
3 h	68	3	1	1	0.01	29

Distribution of the ^{99m}Tc-DMPS complex in rat organs (% of the dose administered)[<1068>]

After i.v. injection of the ^{99m}Tc-DMPS complex to rats, the radionuclide accumulated in the kidneys[<40,1068>]. 32.7% of the dose injected could still be detected after 24 hours[<40>]. Production of renal scans in rats, rabbits and dogs was feasible in this manner[<1067,1068,1484,1485>]. In contrast, the content in the blood, liver, lungs and corpse fell constantly[<1068>].

Conclusion:
The Tc-DMPS complex accumulates in the renal cortex, thus facilitating production of renal scans using the γ emitter ^{99m}Tc.

6.1.33 Tl - Thallium

DMPS had no effect on the survival rate of mice with acute thallium poisoning[<1135,1136>]. In contrast to Berlin blue, repeated i.p. administration of DMPS (5 mg/kg BW) did not have any effect on the thallium-induced reduction in weight gain in rats. The thallium content in the brain, liver, heart and kidneys as well as thallium excretion in the faeces were unchanged. Only thallium levels in the blood were lowered with DMPS. Thallium excretion in the urine was not specified. Combination therapy with Berlin blue (oral) and DMPS (i.p.) was not more effective than monotherapy with Berlin blue[<961,962>].

Tl_2SO_4	LD_{50} = 49.0 mg/kg BW
Tl_2SO_4 + DMPS	LD_{50} = 54.5 mg/kg BW[<1136>]

Conclusion:
DMPS has no effect on acute poisoning with thallium. It does not support the efficacy of Prussian blue.

6.1.34 U - Uranium

Immediate administration of DMPS reduced the lethality of uranyl nitrate [$(UO_2)(NO_3)_2$ x 6 H_2O] on acute poisoning of the rats by 30 %. If treatment was started after one day, a protective effect could no longer be detected. Excretion in the urine and faeces was unchanged. The heavy metal level in the kidneys was not reduced and was even raised in the bones[<644>].

Conclusion:
DMPS reduces the lethality of uranium binding only when treatment is initiated immediately. Overall, not enough investigations have been carried out in order to assess the efficacy of DMPS on poisoning with uranium.

6.1.35 V - Vanadium

Chelating agent	Survival rate(%) Na_3VO_4	$VOSO_4$
Ca-DTPA	60	70
DPA	80	90
DMPS	60	20
DMSA	90	20
Vitamin C	100	70

Survival rate in mice following i.p. administration of sodium vanadate or vanadyl sulfate (LD_{50}) and administration of various chelating agents<674>

DMPS had no effect on the mortality of mice or rats that were poisoned with sodium metavanadate ($NaVO_3$)<778>, sodium vanadate Na_3VO_4<674>, vanadium chloride (VCl_3)<81> or vanadyl sulfate ($VOSO_4$)<674>. In contrast, 8 out of 10 rats treated with Ca-DTPA survived the administration of an LD_{100} of VCl_3<81>. DMPS had a moderate effect on with sodium vanadate.

Vanadyl sulfate or sodium metavanadate were introduced into fertilised hens' eggs and these were further incubated. The vanadium-induced increase in the death rates of the embryos, reduced body weight and reduced weight of feet and claws was not affected by additional administration of DMPS. Only the vanadium concentrations I the feet and claws were somewhat reduced<1463>.

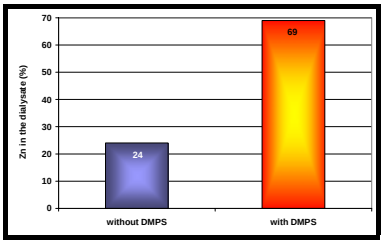
Conclusion:
DMPS has no effect on the lethality of vanadium conmpounds. It is, therefore, not suitable for the treatment of vanadium poisoning.

6.1.36 Zn - Zinc

6.1.36.1 Investigations in cells and cell components

The efflux of zinc from erythrocytes was increased through incubation with DMPS<1227>. *In vitro*, DMPS released zinc from the enzyme carboanhydratase<1227>.

The addition of $ZnCl_2$ to cultures of various lung cells decreases protein synthesis in the cells by 10 - 40%. If DMPS was added to the culture solution after removal of the $ZnCL_2$, this reduced the toxic effect of the zinc and further increased protein formation. DMPS was the most effective of the chelating agents investigated. (DMPS ≥ DPA > BAL ≥ EDTA ≥ NCA)<1525,1526>.



Proportion of mobilised zinc in the dialysate on dialysis of haemolysed erythrocytes<1227>

In vitro, DMPS released zinc from its bindings to high-molecular plasma constituents<664>. With increasing DMPS concentrations, the concentration of the metal bound to low-molecular structures increased<912>. The metal was deposited in plasma proteins from a suspension of ZnO (particle size < 5 µ) . The addition of DMPS reduced the bound quantity of metal by 15%<439>.

6.1.36.2 Acute poisoning

On acute poisoning, DMPS reduced the lethality of zinc<136,347,854,855>. On immediate administration of a sufficient dose, 100 % of the mice survived an LD_{50} dose of zinc acetate. 50 % survived an LD_{99} dose. With Ca-DTPA, all the animals survived an LD_{99} dose<854>. The efficacy of the various chelating agents on the survival rate decreased in the following order: Ca-DTPA ~ DPA > DMPS >> DMSA<347>.

Chelating agents	Ca-DTPA	Triene	DPA	DMPS	DMSA
Survival rate (%)	87	20	80	73	87

Survival rates in mice following i.p. administration of $ZnSO_4$ (1.4-fold LD_{50}) and i.p. administration of CA after 20 minutes<136>

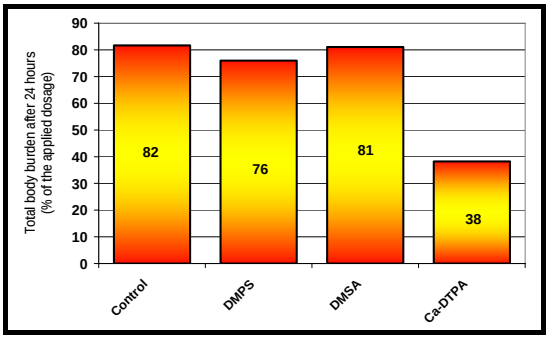
6.1.36.3 Excretion and organ distribution

	Ca-DTPA	DMPS	DPA
Skeleton	16.2	51.4	55.0
Liver	22.4	53.7	55.2
Muscles	14.5	55.0	57.6
Kidneys	36.6	51.3	64.6
Pancreas	29.6	44.6	63.1
Prostate		74.2	95.5
Testes	14.8	61.6	63.3
Blood	17.8	53.6	59.0

Effect of immediate administration of CA on Zn levels in rats (% of the controls)<1538>

Following administration of DMPS, zinc excretion in the urine was increased but reduced in the faeces. The total excretion exceeded that of the controls<347>. In mice, immediate injection of DMPS after i.v. administration of zinc chloride slightly reduced the total body burden<395>.

The Zn load in most of the organs investigated was reduced following administration of DMPS <347,1538>. Compared to the controls, the decrease was statistically significant in the blood and the heart<347>. DMPS displayed no efficacy whilst Ca-DTPA halved the total body burden. Zinc levels in the liver, gastrointestinal tract, kidneys, brain, testes and corpse corresponded to those recorded in the control animals treated with DMPS and DMSA. They were significantly reduced with Ca-DTPA<395>. In contrast to DTPA, DMPS had no effect on Zn metabolism in adult rats <633>.



Total body burden in mice following i.v. administration of ZnCl2 and immediate injection of the chelating agents after 24 hours<395>

Conclusion:
DMPS increases the survival rate on acute poisoning with zinc. Excretion is increased. DMPS is thus a possible antidote for the treatment of acute and chronic poisoning with zinc. However, Ca-DTPA appears to be the most suitable.

6.2 Influence on essential metals

As a chelating agent, DMPS not only accelerates the excretion of toxic heavy metals but also reacts with essential trace elements<706>.

It should, however, be noted that poisoning with heavy metals can also lead to changes in trace elements. The induction of metallothioneins is presumably the cause<1427>. High copper levels were thus detected in the kidneys of animals poisoned with gold<1424> or mercury<179>. Heavy metals induced the formation of metallothioneins, which retained more copper. This effect was not observed with nickel<1433>.

High copper values can also have an effect in various diseases. Higher copper levels were observed in rats with *Mycobacterium butyricum*–induced adjuvant arthritis whereas zinc, iron and calcium levels were unaffected<1424>.

6.2.1 Ca - Calcium

Published information relating to the effect of DMPS on calcium levels varies. According to chemical legislation, DMPS is not expected to have a direct effect. However, an indirect effect due to the effect on hormones can be envisaged<202>. Chronic dosing with DMPS did not trigger any reduction<69,1424>. In dogs, Ca levels in the brain, heart, kidneys, testes, spleen, lungs, liver, pancreas and serum were not significantly affected<1420>. In other studies, DMPS (50 mg/kg i.v.) triggered a reduction in calcium levels in rabbits<736>. The once weekly administration of i.v. DMPS for 10 weeks lowered Ca levels in the plasma and heart of rabbits<606,608>.

In pregnant mice, calcium levels in the kidneys, liver and plasma were reduced whilst those in the foetuses and intestine were unchanged following oral administration of up to 300 mg/kg BW <202>.

6.2.2 Co - Cobalt

DMPS increased urinary excretion in rats[<1137>].

6.2.3 Cr - Chromium

Chromium levels in the blood, liver, heart and kidneys remained unchanged with DMPS[<492>].

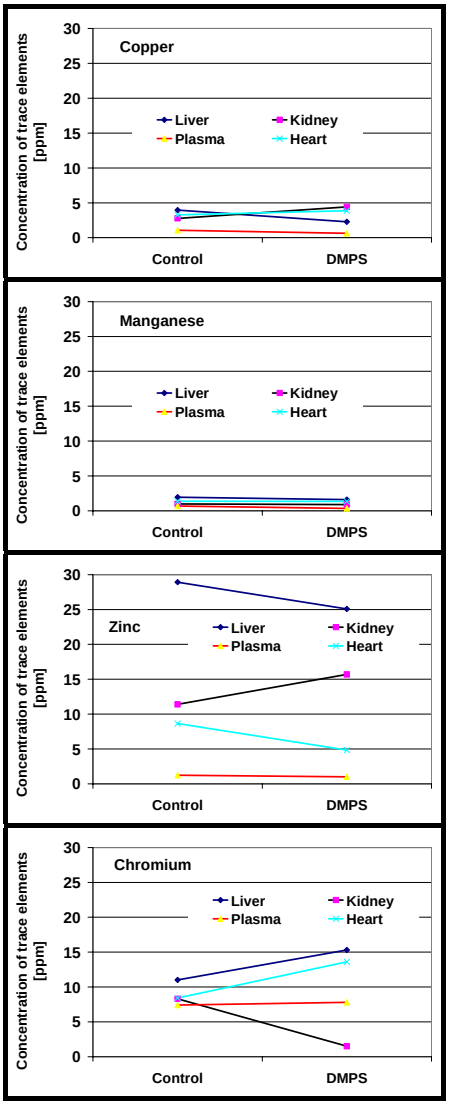
6.2.4 Cu - Copper

DMPS also mobilised any copper intracellularly present in the erythrocytes [<1225,1227>]. Nevertheless, the activity of the metal-containing enzyme, superoxide dismutase (SOD) was not affected by DMPS. Protection against oxygen toxicity remained intact[<1223>]. In experiments with rats, the intensified, prolonged effect of bradykinin was observed, for which inhibition of the metal-containing kininases was discussed[<904,1338,1340>].

Chelating agents	Copper excretion (µg/24 hours)
Saline	3.74
DPA	45.36
DMPS	32.82
DMSA	17.92

Cu excretion in the urine of rats during treatment with various CAs[<62,58>]

The excretion of copper in the urine was increased in all investigations, particularly at the start of DMPS administration[<62,70,132, 712,886,892,1137,1426>]. This effect regressed during treatment and the excretion eventually corresponded to that observed in the control animals[<712>]. Copper excretion in the urine was also increased in dogs during DMPS therapy[<1374>].



Trace element levels [ppm] in the organs of rats following s.c. administration of DMPS (100 mg/kg BW daily for 30 days)[<492>]

Cu levels in the liver and blood were reduced[<1427>] and increased [<1427>] or unchanged[<886,921>] in the kidneys. In other long-term investigations, copper levels in the liver[<921,1165>], skin[<1160>], intestine[<1160>], blood[<921>] and spleen[<1160>] were unchanged in rats. Copper levels in the kidneys fell but returned to normal within one week once DMPS was discontinued[<1160>]. Following s.c. administration of DMPS to rats, Cu levels in the kidneys were raised, those in the liver and heart unchanged and concentrations in the plasma reduced[<1160>]. In dogs, Cu levels in the brain, heart, kidneys, testes, spleen and lungs were not significantly affected while liver, pancreas and serum concentrations were reduced[<1420>]. In pregnant mice, copper levels were reduced in the intestine, increased in the placenta and unchanged in the kidneys, liver and foetuses following oral administration of up to 300 mg/kg BW [<202>].

Poisoning with $CdCl_2$ lowered copper levels in the blood, liver and kidneys of rats. In contrast, Cu levels in the brain and heart were increased. Subsequent treatment with DMPS did not trigger any further decrease but resulted in an increase. It partly eliminated the effects of Cd^{2+} without reaching the values recorded in animals not given any $CdCl_2$[<1428>].

Chronic poisoning with $NiSO_4$ did not change copper levels in the blood, liver, kidneys, brain and heart in rats. Subsequent administration of DMPS lowered copper levels[<1429>], except in the brain.

In mice poisoned with potassium tartrate, the administration of DMPS did not change Cu levels in the blood[<168>].

Chronic administration of AuTM led to increased copper levels in the liver and kidneys of rats. The additional administration of DMPS lowered deposits in the liver but not in the kidneys[<1424>].

Perfusion experiments with DMPS on isolated rat kidneys given $HgCl_2$ 48 hours earlier, did not show any loss of copper from the kidneys[<744>].

The administration of AsO_3 led to increased copper levels in the kidneys of rats. These concentrations were slightly reduced following administration of DMPS[<886>].

6.2.5 Fe - Iron

I.P. administration of DMPS did not increase Fe excretion in 24-hour rat urine[<451>]. Other studies have shown increased Fe excretion in the urine of rats[<1137>] and dogs[<1374>] during DMPS treatment. In rabbits, DMPS (administered via the i.v. route once a week for 10 weeks) did not change Fe levels in the heart[<606,608>]. In dogs, Fe levels in the brain, liver, heart, kidneys, testes, spleen, serum and lungs were not significantly affected whereas levels in the pancreas were reduced[<1420>].

In pregnant mice, iron levels in the liver and foetuses were reduced and those in the kidneys, intestine and placenta unchanged[<202>] following oral administration of up to 300 mg/kg BW.

Poisoning with $CdCl_2$ lowered iron levels in the blood, liver, kidneys, brain and heart in rats. Subsequent administration of DMPS caused this decrease to partially regress. A further decrease in Fe levels occurred only in the heart[<1428>].

Chronic poisoning with $NiSO_4$ lowered iron levels in the liver and heart of rats. The administration of DMPS caused this effect to partially regress. However, Fe levels fell in the heart. Iron levels in the blood and brain were unchanged following administration of both $NiSO_4$ and DMPS. Iron levels in the kidneys following administration of $NiSO_4$ were high, and were increased even further by DMPS[<1429>].

Chronic administration of the gold compound, AuTM, did not alter iron levels in the liver and kidneys of rats. Similarly, the administration of DMPS did not trigger any decrease in these animals[<1424>].

6.2.6 K - Potassium

The once weekly administration of i.v. DMPS for 10 weeks did not change K levels in the heart[<606,608>] and blood[<482>] of rabbits.

6.2.7 Mg - Magnesium

According to chemical legislation, DMPS is not expected to affect magnesium levels. In dogs, Mg levels in the brain, heart, kidneys, testes, spleen, lungs, liver, pancreas and serum were not significantly affected[<1420>]. Chronic administration of DMPS did not change magnesium levels in the blood and kidneys of rats. A slight decrease was observed in the liver[<921>]. In another study conducted in rabbits, DMPS (administered via the i.v. route once a week for 10 weeks) lowered Mg levels in both the heart[<608>] and the blood[<482>].

In pregnant mice, magnesium levels in the liver, kidneys, placenta and foetuses were reduced and those in the intestine unchanged[<202>] following oral administration of up to 300 mg/kg BW.

In mice poisoned with potassium tartrate, the administration of DMPS did not change Mg levels in the blood[<168>],

6.2.8 Mn - Manganese

Manganese excretion in the urine was increased[<402>] or unchanged[<451>] with DMPS. Changes in the concentrations in the organs or serum were, however, evident only several weeks after

administration of high doses of DMPS[<492>]. Following s.c. administration of DMPS to rats, Mn levels in the kidneys, liver and heart were unchanged and those in the plasma reduced[<1160>]. In dogs, Mn levels in the brain, heart, kidneys, testes, spleen, lungs, liver, pancreas and serum were not significantly affected[<1420>].

6.2.9 Na - Sodium

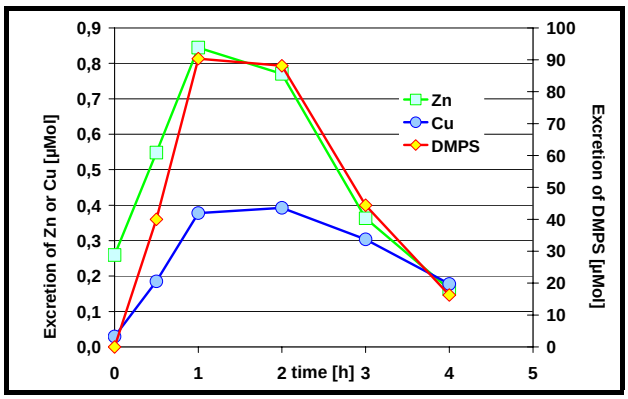
The once weekly administration of i.v. DMPS for 10 weeks did not affect Na levels in the blood of rabbits[<482>].

6.2.10 Se - Selenium

The once weekly administration of i.v. DMPS for 10 weeks did not affect Se levels in the heart of rabbits[<608,606>].

6.2.11 Zn - Zinc

DMPS also mobilised any zinc intracellularly present in the erythrocytes[<1225,1227>]. Nevertheless, the activity of the metal-containing enzyme, superoxide dismutase (SOD) was not affected by DMPS. Protection against oxygen toxicity remained intact[<1223>]. In other experiments with rats, the intensified, prolonged effect of bradykinin was observed, for which inhibition of the metal-containing kininases was discussed[<904,1338,1340>]. The high lipid peroxidation and lowered glutathione concentration observed in the liver of mice was attributed to the formation of complexes between DMPS and minerals[<712>]. The incubation of human spermatozoa with DMPS did not reduced the zinc content[<1575>]. The fixing of sections of rabbit renal cortex in DMPS solution lowered the Zn content of the tissue[<705>].



Excretion of Zn, Cu and DMPS in rabbit urine following injection of DMPS[<892>]

Comments on the effect of DMPS on zinc metabolism vary. Observations on zinc excretion during DMPS therapy range from high[<70,451,892,1137,1430>] to unaffected[<62,712,1426>]. Zinc levels were

- unchanged[<921,1430>] or lowered[<1427>] in the blood
- unchanged in the serum[<1420>]
- lowered in the plasma[<1160>]
- unchanged in the skin[<11601>]
- lowered in the bones[<1430>]
- unchanged in the heart[<1160>]
- unchanged in the testes[<420>]
- unchanged in the spleen[<11601,1420>]
- unchanged in the intestine[<1160>]
- unchanged in the lungs[<1420>]
- unchanged in the liver[<921,1160,1427,1430>]
- unchanged[<921,1420,1427,1430>] or lowered[<1160>]. in the kidneys However, the levels returned to normal within one week after DMPS was discontinued[<1160>].
- unchanged in the brain[<921,1420>]
- unchanged in the pancreas[<1420>].

No change in zinc levels were observed in the liver, kidneys and muscles[<1613>] of chickens whose feed was mixed with DMPS. In pregnant mice, zinc levels were reduced only in the intestine and unchanged in the kidneys, liver, foetuses and placenta [<202>] following oral administration of up to 300 mg/kg BW.

Like EDTA and DMSA, DMPS (i.p.) led to an increase in renal excretion of zinc on lead poisoning. The least effect was, however, observed with DMPS. Faecal Zn excretion remained unchanged with DMPS[<1430>]. In contrast to DTPA, DMPS had no effect on Zn metabolism in adult rats[<633>].

Poisoning with $CdCl_2$ lowered zinc levels in the liver, kidneys, blood, heart and brain of rats. Subsequent administration of DMPS caused this decrease to partially regress. Higher Zn levels were recorded in animals treated with DMPS than in untreated control animals, but even so, these values did not equate to those recorded in animals that did not receive Cd^{2+} [<1428>].

Chronic poisoning with $NiSO_4$ did not change zinc levels in the blood, liver, kidneys, brain and heart of rats. Subsequent administration of DMPS lowered Zn levels[<1429>], except in the brain.

In mice poisoned with potassium tartrate, the administration of DMPS did not change Zn levels in the blood[<168>],

Chronic administration of AuTM did not alter zinc levels in the liver and kidneys of rats. Subsequent administration of DMPS did not alter the values[<1424>].

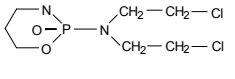
Perfusion experiments with DMPS on the isolated kidneys of rats given $HgCl_2$ 48 hours earlier, did not show any loss of Zinc from the kidneys[<744>]. Five days' treatment with DMPS increased Zn levels in rats given chronic exposure to Hg.

Conclusion:
Considering the effect of DMPS on minerals and essential trace elements, it should be noted that heavy metal poisoning itself can lead to changes. No clinically relevant changes in minerals and trace elements are anticipated following administration of therapeutic doses of DMPS, even if the excretion of these substances may be temporarily increased.

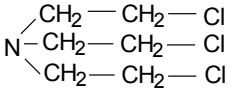
6.3 Other effects

In addition to its action as a chelating agent on intoxications with metals and metalloids, other pharmacological reactions have been reported, especially in Russian and Chinese literature[<69>].

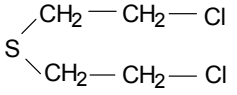
6.3.1 Alkylating compounds (mustard gases, cytostatics)



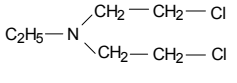
Cyclophosphamide



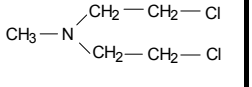
Nitrogen mustard (HN-3)



Mustard gas()



HN-1



HN-2

	LD_{50} HN-3 (mg/kg)
Controls	3.6
DMPS	9.1
DMSA	6.0
DPA	7.4

LD_{50} of HN-3 (s.c.) on immediate administration of CA (mouse, i.p.)[<1422>]

Alkylating compounds such as cyclophosphamide or HN-3 (tris-(2-chlorethyl)-amine) react in an electrophilic reaction with amino or thio groups of biological macromolecules and lead to cross-linking of the proteins[<1226>]. The alkylating of DNA warrants particular significance[<732>].

DMPS acted as an alkyl trap and was able to prevent the effects of alkylating reagents[<1457>]. "Radical scavengers such as DMPS … display major prophylactic and considerable therapeutic effects"[<577a>].

Pre-incubation with DMPS reduced the alkylating action of HN-3 on erythrocyte membranes in that it protected especially cytoplasmatic proteins (haemoglobin, spectrin) of the erythrocytes from reaction with HN-3[<1226,1227>]. Incorporation of HN-3 in proteins of the hepatocytes was reduced by over 80% on prophylactic administration of DMPS[<764>]. Subsequent administration of DMPS was ineffective[<764,1226>]. The toxicity of nitrogen mustard in mice could also be reduced *in vivo* by DMPS

by a factor of 2.5[<1422>]. In the case of mustard gas, pre-treatment with a high dose of DMPS had a moderate effect on induced oxidative stress[<1116>].

DMPS itself does not have an anti-tumour effect[<1181>] in mice but can inhibit the tumour-inducing action of chemicals. DMPS prevented the toxicity of the anti-tumour agent, dactinomycin in mice[<348>]. The toxicity of adriamycin was also reduced (decreased mortality, longer survival time in mice)[<191,609>]. In contrast, the toxicity of 5-fluoruracil, bleomycin and vincristin was potentiated[<348>].

DMPS reduced the efficacy of N-methylformamide (MF). The tumours were 1.2-fold greater on administration of MF and DMPS than with MF alone. There were less metastases but those present were 2.5-fold greater[<1181>].

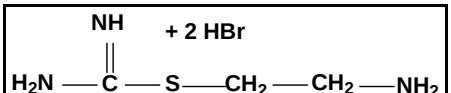
Cyclophosphamide or ifosphamide are cleaved in the body to the reactive aldehyde, acrolein, CH_2=CH-CHO, which is responsible, amongst other things, for the urotoxicity of cytostatics[<764,1226>]. Concomitant addition of DMPS reduced the incorporation of acrolein in proteins, microsomes, erythrocytes and erythrocyte membranes[<1226>] and thus reduced the cytotoxic effects[<1226,1559>]. The urotoxicity of ifosfamide was reduced in rats, whereby higher doses were more effective[<212>]. DMPS also had positive effects on poisoning with acrylonitrile[<646>].

The addition of DMPS reduced the alkylation of free SH groups of the nicotine acetylcholine receptor by bromacetylcholine bromide. It did not influence the activity of the functional groups (disulfide bridges). DMPS was not, however, in a position to displace the substance again from its site of attachment and thus restore the functioning of the receptor[<858>].

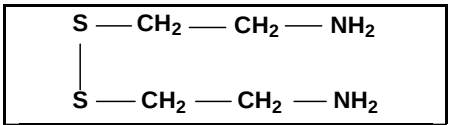
Conclusion:
Prophylactic or immediate administration of DMPS prevents or reduces the toxic effects of various alkylating compounds. The substances for which DMPS administration is useful cannot, however, be assessed given the lack of investigations carried out.

6.3.2 Protection against radiation

DMPS has a protective effect against radiation damage[<77,584,585>]. In mice, administration before irradiation significantly increased the survival rates. Whereas 75% of the animals in the control group died, the mortality rate for mice given 12 mg DMPS/20 g mouse i.p. 20 minutes earlier, fell to 44%[<211>]. The protective effect was observed on administration of DMPS 20 minutes to 2 hours before irradiation[<77>]. Even when treatment began 15 minutes after radiation, 30% of the mice still survived whereas all of the control animals died[<514>]. However, subsequent administration did not have any positive effect on the DNA content of the bone marrow cells of irradiated guinea pigs[<1406>]. The repairing effects of vitamins after radiation exposure were increased in rats by the additional administration of DMPS[<698>].



2-(β-Aminoethyl)isothiuronium bromide hydrobromide (AET)



Cystamine (oxidised cysteamine)

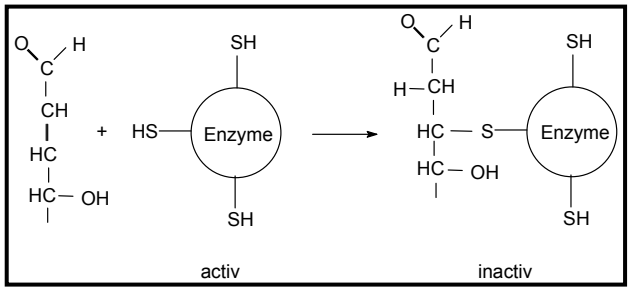
Previous administration of DMPS reduced the toxic effects of cysteamine in CHO cells[<510,511>], dogs[<508>] and mice[<510,511>]. The LD_{50} was increased[<510,511>]. The survival rates of mice[<520,511>] increased through the potentially higher doses of the radiation protective agent. Protection against neutron emitters was increased by 10 to 20%[<509>]. DMPS also reduced the toxic effects of AET and ER-1065[<510,511>].

In rats, pre-treatment with DMPS prevented hyperlipoproteinaemia (elevated VLD and LD lipoprotein) triggered by the presence in a permanent magnetic field[<713>].

Conclusion:
Prophylactic and immediate administration of DMPS cam protect against radiation. DMPS can also reduce the toxicity of other radiation-protection agents so that the latter may be administered in higher doses.

6.3.3 Lipid peroxidation, carbon tetrachloride

As a dithiol compound, DMPS can also act as an oxygen radical scavenger and prevent lipid peroxidation and "oxidative stress"[<482>]. Lipid peroxidation (caused by ionising irradiation or oxygen radicals) is always associated with the formation of aldehyde products. The most important representative is 4-hydroxynonenal (HNE) that already has cytotoxic, genotoxic and mutagenic effects at low doses[<330,1347>]. In aqueous solutions, DMPS reacts rapidly and virtually completely with HNE[<330>]. In addition, DMPS acts as an oxygen radical scavenger[<3,157,158>] and prevents lipid peroxidation[<157>].



DMPS did not have any effect on the toxicity of CCl_4[<1401>] and aliphatic halogen hydrocarbons[<113>]. In rats, it was not capable of preventing CCl_4 -induced peroxidation in the liver. The increased concentration of malondialdehyde was not statistically and significantly lowered and the reduced content of glutathione was not increased. Instead, the administration of DMPS produced, at least briefly, an increase in lipid peroxidation in the liver. Interaction with iron-containing enzymes, which are natural antagonists for lipid peroxidation, has been suggested as a reason[<233>].

In contrast, in rats, DMPS reduced liver damage caused by the administration of CCl_4 and ethanol. Peroxidation and the fall in glutathione were reduced[<1353>]. DMPS could not halt galactosamine-induced liver necrosis[<879>]. Ethyl chloride-induced pancreatic ischaemia in rats was less severe following concomitant administration of DMPS, vitamin C and vitamin E[<1244>].

6.3.4 Antimutagenic effect

The addition of DMPS (0.25 – 0.5%) reduced the mutagenic properties of nitrosoguanidine on bacteria[<806>].

6.3.5 Bacterial toxins

In animal experiments, DMPS exhibited positive effects on the treatment of endotoxin shock[<527,725>] and on the toxicity of endotoxins[<527>]. With enterotoxins of *Escherichia coli,* it is presumed that the cleaving of SS bridges leads to a loss of activity[<383>].

The injection of DMPS and $MgSO_4$ reduced lipid peroxidation due to endotoxins of Gram-negative bacteria in the liver of mice. The fall in cAMP in the liver and lungs was less marked while the LD_{50} was raised[<529>].

BAL	92,7
DMPS	86,3
DMSA	28,2
DPA	39.8

In-vitro inactivation (%) of the enterotoxin STa from *E. Coli*[<383>]

Lysates of *Salmonella typhimurium* activate processes resulting in the formation of free radicals. The combination of DMPS and $MgSO_4$ revert this reaction to normal[<528>].

DMPS and vitamin E protect against the lethal effects of *Shiella sonnei* lysates[<528>].

On poisoning with botulinum toxin, DMPS had a positive effect in rats by reverting the activity of Na, K, Mg-ATPase to normal[<261>]. *In vitro,* DMPS inhibited Botulinus Neurotoxin A[<554a,567>]. With an IC_{50} of 0.58 mM, DMPS is one the most potent inhibitors[<554a>] Interaction with protease[<567>] zinc or the effect of the sulfonic acid group[<554a>] is assumed to be the mechanism involved.

DMPS did not have any effect on the haemolytic properties of the α toxin of *Clostridium perfringens*[<149>].

The influence of the cholera endotoxin on adenylate cyclase and thus on the concentration of cyclic AMP in the intestinal mucosa of rabbits was reduced by DMPS. Cleaving of an SS bridge in the endotoxin is assumed to be the mechanism involved[<1588>].

6.3.6 Alcohols

On poisoning with ethanol, DMPS increased the survival time but did not lead to higher survival rates[<1491>]. Combination therapy with various vitamins and DMPS had a positive effect on alcohol-induced polyneuritis in rabbits[<632>]. In rats, the administration of DMPS reduced the withdrawal symptoms following chronic alcohol intake[<485>]. DMPS had no effect on the microsomal transformation of ethanol into acetaldehyde[<1193>]. The toxic effects of allyl alcohol on the liver were reduced in rats[<1352>].

6.3.7 Binding of nitrogen monoxide NO

The bacterium, *Nitrosomonas eutropha*, can oxidise ammonia producing, amongst other things, nitrogen monoxide, NO, which can react further depending on the culture conditions. The DMPS added to the cell cultures reacted with existing or added nitrogen monoxide and thus prevented the effect of NO on these oxidation reactions[<1299,1607>]. The authors do not give any further details about the type of reaction (formation of a complex with the iron from the nutrient solution according to Section 3.7.8 or the direct reaction of DMPS with NO?). Similarly, the effect of potential redox reactions of DMPS is not discussed. In neutrophils, DMPS has an antagonistic effect on GEA3162, an agent released by NO[<618>].

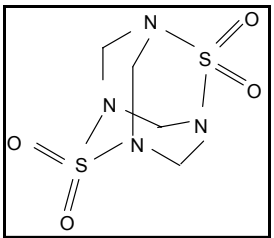
6.3.8 Cardiac glycosides

In frogs, high doses of DMPS (700 mg/kg) prevented cardiac arrest due to digitalis or strophanthin K. At lower concentrations, it prevented their toxic effects. In cats, the prophylactic administration of DMPS delayed the time to onset of cardiac arrest following administration of strophanthin K from 33-44 minutes to 82-99 minutes. In chronic experiments in dogs, DMPS prevented the typical ECG changes associated with strophanthin K[<403>]. Blockade of physiological SH groups by cardiac glycosides is discussed as the mechanism involved[<403,749>].

In dogs, the administration of DMPS reduced the cardiotoxic effects (extrasystoles and bradycardia). When administered prophylactically, DMPS prevented toxic reactions[<749>]. A reduction in the toxic effects of cardiac glycosides was also observed in rats[<495>].

6.3.9. Insecticides, pesticides, rodenticides, bactericides and herbicides

6.3.9.1 Tetramethylene Disulfotetramine (TETS)



TETS

Prophylactic and immediate administration of vitamin B_6 and high doses of DMPS reduced the mortality rate induced by the rodenticide, TETS[<253,1188,1617,1618>] in mice. The effects of TETS on the GABA metabolism of rats was prevented[<1618>], the onset of seizures was delayed and the symptoms reduced[<1408>]. Earlier onset of treatment was more effective[<1408>]. If treatment was initiated 10 minutes after poisoning, all animals survived. When onset of treatment was delayed, the survival rate was only 40%[<1550>]. The LD_{50} almost doubled from 0.262 mg/kg to 0.502 mg/kg[<253>]. DMPS also displayed an anticonvulsive effect on acute poisoning with TETS[<1617>]. DMPS thus had no effect on the pharmacokinetics of TETS. It neither lowered plasma concentrations nor increased excretion in the urine[<1619>].

6.3.9.2 Sodium-Ammonium-Dimethyl-2-Propano-1,3-Dithiosulfate (SCD)

	LD_{50}
Controls	97
DMPS 250 mg/kg i.p.	374
DMSA 1.000 mg/kg i.p.	251

Effect of the prophylactic administration of DMPS or DMSA on the LD_{50} (mg/kg) of SCD in mice[<253>]

Combination therapy with diazepam and DMPS reduced the toxicity of the insecticide SCD[<864,865>]. Both the prophylactic and therapeutic administration of DMPS lowered the mortality rate in rabbits and prolonged the survival time[<253>]. Prophylactic i.p. administration of 250 mg DMPS/kg BW 20 minutes before poisoning increased the LD_{50} from 97 to 374 mg/kg[<237,253>] in mice. DMPS was thus superior to

DMSA or cysteine[<237,253>]. BAL had only a minor effect on SCD-induced paralysis[<237>]. In rabbits, DMPS prevented SCD-induced neuromuscular blockades and respiratory depression [<237>].

6.3.9.3 Other insecticides, pesticides, rodenticides, bactericides and herbicides

In mice, DMPS increased the LD_{50} for bactericide 402 from 118 to 214 mg/kg[<253>].

Cholinesterase activity, which was blocked by the insecticide, dimehypo, could be partially restored in rats through treatment with pralidoxim and DMPS[<1527>].

Prophylactic administration of DMPS prior to application of the herbicide, bromoxynil, reduced the toxic effects of the latter. The survival time was prolonged and the survival rates increased. A combination of DMPS and NAC was even more effective[<862>].

DMPS and vitamin E protected male rats from the side effects of the insecticides deltamethrin and dichlorvos (activity of the anti-oxidative enzyme, memory capacity). The combination increased the anti-amnesic effect[<525>].

DMPS had a protective effect against the lethal effect of CDM in mice, rats and pigeons. Combination with methylthionium chloride boosted the effect[<253>]. Prophylactic administration of DMPS increased the lethal dose from 258.9 mg/kg to 518.2 mg/kg in mice[<253>].

DMPS proved to be an effective antidote for poisoning with the insecticide Nereistoxin (4-N,N-Dimethylamino-1,2-dithiolan)[<237>].

Prophylactic administration of DMPS increased the LD_{50} of the insecticide Cartap (di-hydronereistoxin dicarbamate) from 130 to 375 mg/kg[<237>] in mice[<237>].

Conclusion:
The prophylactic administration of DMPS in particular reduced the mortality rate due to various insecticides, pesticides, rodenticides, bactericides and herbicides.

6.3.10 Other investigations with DMPS

DMPS inhibited D,D-Dipeptidase VanX, which is responsible for the resistance of anti-vancomycin bacteria[<461,1579>]. Chelate formation with the zinc of the enzyme is assumed to be the cause[<1579>].

DMPS reduced the activity of the dopamine, ß-Hydroxylase, *in vitro* in a concentration-dependent manner. A reaction with the copper of the enzyme is a potential reason[<1404>]. In the case of *Daphnia Magna* (Straus), it protected against the toxic effect of the dopaminergic neurotoxin, MPTP[<1168a>].

Rats with experimentally induced pancreatitis showed increased activity of the anti-oxidative protective enzymes (superoxide dismutase, catalase, glutathione peroxidase) in pancreatic and liver tissue. In contrast, the activity in the blood was reduced. Pre-treatment with DMPS promoted the increase in enzyme activities[<1252>].

DMPS had an antihypertensive effect in hypertensive rats. It reduced the pressor effect of angiotensin-1 and increased and prolonged the depressor effect of bradykinin[<904,1338,1340>]. The effect was reversible on administration of atropine[<1340>]. *In vitro*, the activity of kininase II was reduced (83 %[<1270>] or 30-50 %[<1412>]) and the degradation of kinin blocked[<1413>].

Prophylactic administration of DMPS prevented the onset of dithizone-induced diabetes in approximately 70 % of rats[<825>] and in rabbits[<826>],

Treatment with L-dopa and DMPS had positive effects in rabbits aged 2 to 4 weeks and presenting with chronic intrauterine hypoxia whereby DMPS increased the number of free SH groups in sub-cortical brain structures[<1433>].

DMPS dilated the blood vessels in the isolated rabbit ear[<1606>].

DMPS did not have any effect on the sleeping time of rats following administration of hexobarbital[1403,1404] and phenobarbital[1585].

In mice, the prophylactic administration of DMPS reduced amphetamine-induced motor activities[1403,1404].

Dogs with acute blood loss reacted positively to the addition of DMPS to isotonic physiological saline solution[210].

DMPS reduced the renal effects of strophanthin in dogs[1113].

A protective effect on embitol poisoning was evident only in newborn mice[148].

In 8 out of 18 guinea pigs, concomitant administration of DMPS reduced the ototoxic effects of streptomycin[17].

Prophylactic administration of DMPS prevented the toxic effects of novembichin[151] in mice. The effect was, however, apparent only in newborn and adult animals, but not in very old animals [150].

All rats survived an LD_{00} dose of embichin[901] through combination therapy with DMPS and serotonin, sodium thiosulfate or mercaptoethylamine.

In rabbits poisoned with padan, the SH concentrations reverted to normal within 5 days during DMPS therapy. They were only 70% in the untreated control animals after 10 days[856].

Prophylactic administration of high doses of DMPS reduced the toxicity of cyanides in mice by accelerating the enzymatic transformation of cyanide into rodanide[816]. Whereas 90% of the untreated mice died, the mortality rate in the DMPS group was 37 %[816]. In the presence of $Na_2S_2O_3$, DMPS increased the enzymatic transformation into thiocyanates[816,817].

Concomitant administration of DMPS and xylidene prevented the formation of methaemoglobinaemia in rats. The administration of DMPS after one hour reduced methaemoglobin levels in the blood by 50% [1446].

DMPS inhibited aniline hydroxylase activity in rats. The complex cannot be separated chromatographically from non-complexed ruthenium[39].

DMPS is an effective inhibitor of botox-A[949].

In rabbits, pre-treatment with DMPS had no effect on the cardiotoxicity of daunorubicin[606,607]. Nevertheless, daunorubicin reduced body weight gain. Nephritic syndrome was not prevented[606].

In rats, DMPS increased the LD_{50} of the acetylcholinesterase inhibitor, proserine, by a factor of 1.5 and in combination with atropine, by 4.5[1456].

Following exposure to ammonia inhalation, the inhalation of DMPS aerosol halved the mortality rate and reduced the increase in the weight of the lung[1612].

DMPS had a regulating effect on amyloid formation[222].

DMPS prevented the formation of “heat shock proteins” in HeLa cells[622].

DMPS was devoid of any inhibitory effect on HIV-1 in U937 cells but displayed an inhibitory effect of 50 % in Jurkat cells at a concentration of 30 µg/mL[333].

DMPS proved to be an effective, non-toxic stabiliser for the antiviral activity of sensitive interferons[468].

DMPS had an antioxidant and reparative effect in chronic hepatitis in “immature“ rabbits. Efficacy was delayed on administration of microcapsules of DMPS[1174]. The adenylate-cyclase system reverted to normal[79].

In rats with streptozotocin-induced diabetes, DMPS restored the activities of the antioxidant enzymes to normal, reduced lipid peroxidation and reverted polyol metabolism and glutathione levels to normal[803,1332].

Dimethylformamide (DMF) disrupts the steady state between the oxidant and anti-oxidant systems of the liver. DMPS can reduce the activity of the XOD and SOD enzymes in the liver and thus

restore the steady state. It protects liver function and can be used in the treatment of acute DMF poisoning[<863,933,1189>]. NAC or DMSA also protect liver function [<863>].

The administration of acetyl cysteine or DMPS to guinea pigs sensitive to *Candida maltosa* prevented any change in the lipid peroxidation and enzyme activity of various enzymes after sensitisation[<1336>].

DMPS increased the sensitivity of the Papain enzyme test for the detection of erythrocyte antibodies[<780>].

DMPS improves the detection of IgG antibodies in the AB0 system of human blood groups by inactivating anti-A- and anti-B-IgM antibodies. Efficacy was equivalent to that of 2-mercapto-ethanol[<931>].

DMPS increased the haemolysis of sheep erythrocytes via the toxin O-streptolysin, even in the presence of $Na_2S_2O_3$. The authors assumed that the reduction of SS bridges was the mechanism involved. DMPS and Na_2SO_3 thus react with various S-S bridges[<152>].

In mice, low doses of DMPS (≤ 50 mg/kg), triggered an increase whereas higher doses (≥ 100 mg/kg) caused a reduction in pain reaction (number of spasms)[<1339>].

Conclusion:
DMPS is used in the treatment of various other diseases in addition to poisoning with heavy metals. These are mostly individual observations. However, not enough data are available to facilitate assessment.

7 Clinical use

The individual treatment of heavy metal poisoning can be divided into various stages[<436,733>]. With poisoning, as with all emergency situations, symptomatic treatment is of prime importance in order to maintain vital organ function[<923>]:

Treatment principles for acute poisoning:
I. Maintenance of vital functions
II. Prevention of subsequent absorption
III. Acceleration of toxin elimination
IV. Administration (of specific) antidotes"[<270>]

- Maintenance of vital functions and the water and electrolyte balance[<702>]
- Determination of the poison source[<422,493>] and subsequent termination of exposure[<91,214,493, 932,1232,1278>]. There is little point in administering chelating agents if exposure is not terminated but this is then useful for lowering the total body burden[<50>].
- Prevention of the absorption of orally ingested metals by removing the poison still present in the gastrointestinal tract through gastric and intestinal lavage[<290,702,932,1102,1318>]
- Prevention of the local caustic effect of metals on the mucosa
- Binding of the metals in the body fluids (particularly blood) and transfer into less toxic complexes
- Increase in the excretion of the metals via the urine, bile and/or intestinal wall
- Remission or prevention (with prophylactic therapy) of the clinical symptoms of poisoning
- Cautious removal of heavy metal deposits in the body in order to prevent acute relapses or the chronic effects of metals

International anti-poison centres have approved the following procedures for gastric and intestinal lavage:

- "No gastrointestinal decontamination should be performed later than 60 min after ingestion.
- Activated charcoal (1 mg/kg) should be given in ingestions of toxic doses of agents that bind to therapeutic dose of charcoal in a sufficient way.
- Emesis should be induced in poisonings with toxic doses of agents that do not influence consciousness and adverse-effects reflexes.
- Gastric lavage should be performed in selected poisonings with lethal dose of agent.
- Use of laxatives is restricted to very few poisonings.
- All procedures are not recommended if there is substantial doubt about time of ingestion or ingested dose"[<331>].

In the case of poisoning with heavy metals, treatment with an appropriate chelating agent should be initiated as early as possible [<657>] before irreversible damage occurs[<702>]. DMPS therapy can, however, still be envisaged some time after Hg exposure[<290>].

This use of chelating agents is one of the most successful therapeutic measures for the treatment of poisoning due to heavy metals[<1154,1378>]. "Chelation is indicated in the treatment of metal poisoning, in the treatment metal-storage diseases … and to aid the elimination of metallic radionuclides"[<702>]. Two mechanisms are involved.

- The toxicity of the heavy metals is reduced through complex formation("forming an inert complex with the poison"[<203c>])
- The antidote promotes the excretion of the metal[<1102>].

On ethical grounds, clinical trials with poisons are difficult if not impossible to implement. Individual case histories therefore almost always have to be examined when evaluating clinical efficacy[<647a>]. Reference is thus mostly made to elevated excretion in the faeces or urine[<667,1018>] and to the lowering of blood or plasma levels[<647a>]. These parameters are easy to assess. It would, however, be more important to take into account the reduced burden of critical target organs and recovery from pathological changes[<406,647a>]. Thus heavy metal concentrations in the organs can be lowered without altering the blood level. The decrease in the levels without therapy after exposure has been terminated must also be taken into account when evaluating efficacy[<706>]. These parameters are, however, more difficult to determine[<209>].

As with all therapeutic measures, care should also be taken with poisoning to ensure that the patient is not exposed to the risk of additional iatrogenic damage through unwarranted procedures[<923>]. Due to the lack of well documented, controlled, clinical studies, it is often difficult

with poisons to pinpoint the right approach between therapeutic nihilism and over-reaction fostered by uncertainty[<923>]. "Their use should be restricted to patients with clinical signs of toxicity"[<1389>]. An individual benefit-risk assessment is essential in every case[<506,986>]. The danger of redistribution of the heavy metal in critical organs (e.g. the brain, which has been demonstrated for other chelating agents but not for DMPS[<74,601>]), must also be taken into account[<41,406,506,706>]. It is unclear whether the oral administration of DMPS promotes gastrointestinal metal absorption. Conflicting results have been obtained in laboratory animal experiments with mercury[<406>]. Further studies are therefore required[<506>].

As with any other treatment, a benefit-risk assessment is essential in chronic poisoning with lower values. From what load is the use of chelating agents justified? In this instance, it should be considered whether the chelating agent can reach the heavy metal, e.g. lead in the bones. Moreover, it has not yet been clarified to what extent chelate therapy has a beneficial effect on the clinical course of chronic metal poisoning. No reliable clinical studies have been carried out to conform that increased metal excretion is also accompanied by a more favourable clinical course[<406,647a>].

7.1. General recommendations regarding the use of DMPS

DMPS is an antidote for poisoning with heavy metals[<405,1505>]. "Today, therapy with DMPS (2,3-Dimercapto-1-propanesulfonic acid, Dimaval®) is state of the art and the method of choice in many cases of heavy metal intoxication"[<355>]. "Available in oral and injectable forms, DMPS has become the drug of choice for most-heavy metal poisoning in Asia and Europe"[<1176a>]. For Horn *et al.*, DMPS is the best heavy metal antidote that can also be used if heavy metal intoxication is suspected[<604>]. According to the recommendations of the Commission, "Recognition and treatment of poisoning" of the BgVV, DMPS is indispensable for the treatment of acute metal poisoning[<1032>]. "It appears that western clinicians have not yet fully realised the value of DMSA and DMPS"[<29>].

Experience shows that DMPS obviously has a broad spectrum of action[<928>]. The Northern Poison Information Centre recommends DMPS as an antidote in "numerous cases of heavy metal poisoning, e.g. lead, organic and inorganic mercury and arsenic"[<336>].

In the antidote section of the Rote List, DMPS is listed under the "life-saving antidotes"[<1629>]. The efficacy of DMPS in the treatment of poisoning with various heavy metals can nowadays be considered as confirmed. DMPS displays good clinical efficacy coupled with low local and systemic toxicity[<932>]. China (since 1963)[<1532>] and the former Eastern block states have many years of experience with DMPS. In Europe[<513,603>] and Asia[<513>], DMPS is the product of choice for the treatment of poisoning with metals and metalloids. It is preferable to treatment with BAL[<31,573,610,657,847,1103>] due to its lower toxicity, greater ease of use[<1202>] and varied method of administration (oral, i.v., i.m.)[<52,1102>]. "For several years now 2,3-dimercaptopropanesulfonic acid (DMPS) and 2,3-dimercaptosuccinic acid (DMSA) have been the alternatives to BAL. In contrast to BAL, both of these chelating agents are less toxic, much more soluble in water, and hence have limited solubility in lipids, and are effective when taken orally. The use of both DMSA and DMPS in combating heavy metal poisoning has been examined, specifically for mobilizing inorganic mercury, cadmium, arsenic, copper, lead, gold and antimony"[<1520>]. "DMPS, an analogue of dimercaprol, is effective in accelerating metal excretion without severe adverse effects in acute and chronic intoxication by inorganic and organic mercury, bismuth, arsenic, and chronic lead poisoning"[<702>]. The Scientific Committee for Human Medicines (CPMP – Committee for Proprietary Medicinal Products) of the European Agency, EMEA, considers BAL as a second-line product due to its toxicity and painful application[<1011>].

The Centre for Drug Research and Pharmaceutical Practice (ZAPP in Germany) belonging to the ABDA (National Union of German Pharmacists' Associations) gives preference to the use of DMPS over DMSA[<169>]. Other associations see no particular advantages for DMSA over DMPS[<573>].

7.1.1 Indications

Dimaval® (DMPS) 100 mg hard capsules and Dimaval® are currently **approved** by the BfArM (Federal Institute for Drugs and Medical Devices) in the following indications:

Dimaval® (Solution for Injection)	**Dimaval® (DMPS) 100 mg Hard Capsules**
Acute poisoning with mercury (metallic, vapour, inorganic and organic compounds) when oral treatment or treatment via a gastric catheter is not feasible.	• Clinically manifest, chronic and acute poisoning with mercury (inorganic and organic compounds, vapour, metallic mercury), • Chronic lead poisoning

Reference	Ag	As	Au	Bi	Cd	Co	Cr	Cu	Hg	Ni	Os	Pb	Pu	Sb	U	V	Zn	Pt
1032	(X)	X				(X)	X	(X)	X	(X)		X		X				
169		X		X					X			X						
1018,1039		X				X	X	X	X			X		X				
1506	(X)	X	(X)	(X)		(X)	(X)	(X)	X			X		X			X	
1629	(X)	X				(X)	X	(X)	X	(X)		X		X				
610	(X)	X	(X)	(X)		X	X	X	X	(X)		X		X			(X)	
1019,1546	X	X	X			X	X	X	X			X	X	X	X			
418		X	(X)	X				X	X			(X)						
306		X	X	X	X	X		X	X		X			X		X	X	
43		X		X				X	X			X						
58		X					X		X			(X)		X				
1035,1180			X		X	X			X	X		X						
295	X	X			X	X	X	X	X			X		X			X	
604		X	X				X		X			X		X				
180		X		X				X	X			X						
401	X	X				X	X	X	X			X		X				
160		X							X			X						
1556		X							X									
1061		X	X	(X)			X		X					(X)				
1236		X			X		X	X	X			X					X	
839a		X		X		X	X		X			X		X			X	
702		X		X					X			X						
1186		X	X	X			X		X			(X)						X

Overview of the indications for DMPS recommended in the literature. (X) The indications given in brackets are possible as far as the authors are concerned, but not necessarily proven.

Metal	1st choice	2nd choice
Mercury - metallic - organic - inorganic	 DMPS DMPS DMSA, DMPS	 DMSA DMSA
Lead	DMSA	DMPS
Arsenic	DMPS, DMSA	BAL
Chromium	DMPS	
Antimony	DMPS	

Recommended CAs for various forms of heavy metal poisoning<58>

The source of the heavy metals is therefore insignificant. Furthermore, DMPS is also recommended in the literature for the treatment of poisoning with other heavy metals.

When recommending certain chelating agents, the local availability of the various antidotes and their pharmaceutical forms in the various countries must be taken into account<179a>. For instance, DMPS is not approved in the USA<105,286,513,565,663a,1176a,1236> and is, therefore, difficult to obtain<203>. In emergency situations, it must be imported or produced in Compounding Pharmacies<105,204a,286,565,663a,770a>. As poisoning is, therefore, mainly treated with BAL in the USA<814>. In other countries, the cost of medicinal products

plays a crucial role[<1254>]. In prolonged treatments, BAL, which is more reasonably priced, may have to be used due to the fact that DMPS is not available in sufficient quantities due to cost[<484>]. "There is another important implication that it is important to point out. Even though DMPS and DMSA have proved superior to other chelators as mercury mobilizing agents, clinicians are often forced to choose less effective therapy for their patients [e.g.; BAL, D-penicillamine] because of the unavailability of the DMPS and DMSA in many countries worldwide"

Conclusion:
In the case of poisoning with heavy metals or radionuclides, an authorised antidote is available only in very few cases. In Germany, for instance, no chelating agent is currently authorised for the treatment of arsenic or bismuth poisoning. If treatment is required, it can only be used off label. DMPS is recommended by experts for various other forms of poisoning in addition to the authorised indications.

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7.1.2 Availability and stockpiling

Treatment with DMPS should be started as early as possible[<657>] and monitored in the laboratory by determining the metals in the urine[<657,706,1018>]. "In all cases of acute poisoning, it is important to ensure as favourable a clinical course as possible and survival without delayed sequelae through rapid and effective treatment methods"[<923>]. Therefore, treatment with the appropriate chelating agent should be initiated as early as possible in the case of metal poisoning[<1318>]. Supplies of the required antidotes is, therefore, essential[<1247,1317>] in order to ensure that these products are readily available[<1317>]. Thus, supplies should be stored as specified by the WHO: "In some countries stockpiles include other specific agents (e.g. DMPS)"[<1129>]. However, this is not always the case in reality[<590>]. "Adequate supplies of antidotes and decontamination agents such as chloramine T, BAL, and DMPS, etc. can be a problem"[<456>]. "In the event of mass poisoning, the success of treatment depends essentially on the rapid availability of the antidotes required"[<1518>]. In such cases "the time factor for the availability of larger quantities of antidotes may have a deleterious effect on patient treatment and chances of survival"[<1517>]. Furthermore, delayed onset of treatment is mostly associated with a prolonged duration of treatment and higher costs.

The IPCS of the WHO demands that DMPS be available in 2 to 6 hours[<1035,1180>]. According to the European Union, DMPS should be available within two hours at most[<1044>]. In the UK, DMPS should be available within 6 hours, but this is not the case in reality[<1317>]. Others demand that DMPS be available for use within 30 minutes[<1506>]. The Berufsgenossenschaft (Occupational Health Service) recommends that antidotes such as DMPS should also be available from certain companies[<160,847>].

DMPS has been registered in Russia since 1958[<770a,1236>]. It is an essential item in the emergency team kit and is the antidote most frequently used to treat poisoning with various heavy metals[<1100>]. DMPS supplies are also kept in countries where this product has not been granted a marketing authorisation. Supplies of DMPS have been kept in emergency hospitals in Hong Kong since mid 2005[<248>]. In Sweden, hospitals are advised to keep supplies of DMPS (solution for injection)[<1556>]. The Bundesamt für Gesundheit der Schweiz (Swiss Health Service) recommends that supplies of DMPS be kept in various regional centres[<999>]. The same applies for the British Association of Emergency Medicine[<298>]. Supplies of DMPS are thus kept in the Poisons Unit at Guy's and St. Thomas' Hospitals in London [<662>].

Conclusion:
Treatment should be started as early as possible, especially in the case of acute poisoning with heavy metals or radionuclides. The essential antidote should, therefore, be immediately available. This is ensured only when adequate supplies are available.

7.1.3 Method of administration

An important advantage of DMPS compared to BAL is the fact that, because of its water solubility, it can be administered orally, intravenously and intramuscularly[<63,69,95,657,1069,1102,1236,1532>], which is

less painful for patients than BAL[<1130>]. Intravenous administration must be carried out slowly, over 5 minutes (1 mL/min)[<663a,706,770a,1200a>]. Basically, DMPS should only be administered via the parenteral route when oral intake is not feasible[<1018>].

Parenteral administration of DMPS is recommended[<406,573,657,706,932,1032>]

- in most acute cases;
- in oral poisoning as otherwise a chelating agent will be present in the gastrointestinal tract and heavy metal absorption may be increased;
- in chemical burns to the gastrointestinal tract or mucosal ulcers in the upper gastrointestinal tract, as oral administration may prove difficult[<1318>].

S.c.[<69,625,1069,1385,1393>], intraperitoneal[<70>] or inhalation administration as an aerosol[<1069>] is also described. There is also reference in the literature to topical use in the tooth root canal in arsenic-induced periodontitis[<1139>].

Approved methods of administration for Dimaval®:
- oral
- intravenous
- intramuscular

The literature also refers to the "sniffing " of DMPS[<303,352,823>] to clear intoxication from the CNS in particular[<352>]. However, the authors do not publish any values relating to heavy metal excretion using this method. Information relating to the quantity of "inhaled" DMPS is missing along with explanations how the resulting DMPS-metal complex can be ousted through the blood-brain barrier.

Buttar has developed a solution of DMPS for transdermal use, which is supposedly effective primarily in the treatment of autistic children[<225,226,467,1231>]. Once again, there is no reference to scientific investigations to determine the transdermal absorption rate of DMPS[<339>] and the renal excretion of heavy metals. "There are many anecdotal reports of behaviour improvements with transdermal preparations, but no laboratory evidence of increased excretion of heavy metals in the urine after a single challenge dose"[<657a>]. In one study, Buttar also describes the onset of skin reactions[<226>]. Whether DMPS or another of the many other substances in TD-DMPS, mercury or a possible lack of tin is responsible for this, has not been investigated.

Similarly, there is no reference to heavy metal concentrations in the urine for the homeopathic use of DMPS. "We see good effects"[<204a>] with the rectal administration of DMPS as a suppository[<14,1231>] and the renal excretion of mercury and lead is supposedly high[<1190>]. No values are, however, given. For $CaNa_2EDTA$, the bioavailability for this type of administration to mice is 36.3 %[<385a>].

Klinghardt recommends treating heat rash with a procaine-DMPS mixture(9:1)[<738>]. Once again, no laboratory values are published. In addition, no investigations have been carried out to determine the stability of the mixture. Given the ability to react and the oxidation sensitivity of the SH groups, DMPS ampoules must not be mixed with other infusion solutions[<706,1200a>].

Meanwhile, Daunderer rejects the earlier recommendation written on his homepage, namely to inject DMPS directly onto the jaw[<823>].

Conclusion:
I cannot imagine that adequate blood levels of DMPS are achieved by sniffing, transdermal or homeopathic administration in order to mobilise and excrete deposits of heavy metals in the body. Furthermore, the sensitivity of the active substance to oxidation must be taken into account with these methods of administration. DMPS should, therefore, be administered only via the oral or parenteral (i.m. or i.v.) route.

7.1.4 Dosage and duration of treatment

If need be, DMPS can also be administered to children [<164,738>] if urgently indicated[<573,610>]. A 2½ year old boy was treated with 100 mg DMPS every day for a year without any complications[<1141>]. Children under one year have also been given DMPS[<215,290,1506,1564>]. Bonnet treated approximately 200 babies and young children with 4 mg DMPS/kg BW i.m.[<195>].

Administration of chelating agents is, however, justified only when poisoning has been confirmed[<1232>]. The dosage and duration of administration of DMPS basically depend on the nature

and severity of the poisoning. The dose of DMPS administered mostly depends on the quantity of heavy metal excreted in the urine[<401>]. Thanks to its relatively low toxicity, DMPS can be used for prolonged periods[<2>].

"Acute poisoning → often through single intake of poison, immediate measures are possible, symptoms mostly appear directly or relatively shortly after ingestion, also regressing quickly on survival.
Chronic poisoning→ Poisonous substance accumulates to form toxic concentrations over a prolonged period, difficult to detect, often caused by environmental burden (exhaust fumes, contaminated water, etc.), no immediate measures possible"[<270>]

7.1.4.1 Acute poisoning

7.1.4.1.1 Adults

Day	Single dose [mg]	Number of doses	Interval [h]	Daily dose [mg]
1	250	6 – 8	3 – 4	1.500 – 2.000
2	250	4 – 6	4 – 6	1.000 – 1.500
3	250	3 – 4	6 – 8	750 – 1.000
4	250	2 – 3	8 – 12	500 – 750
5, 6	250	1 – 3	8 – 24	250 – 750

Doses of DMPS administered parenterally to adults with acute heavy metal poisoning[<573,610,1018,1019,1200a>]

DMPS is mostly administered via the i.v. route in cases of acute intoxication. The starting dose is 10 - 30 mg/kg BW per day, administered as 6 to 8 individual doses of 3-5 mg/kg, every 3-4 hours[<178,246,406,418,932,1021,1032,1506>]. If possible, treatment should be switched to oral dosing with 2 – 4 x 100 mg[<932,1021,1506>] after 4-6 days (e.g. if no gastrointestinal lesions are present[<932>]). Treatment is continued until the heavy metal concentrations in the blood and urine are below the limit values. Thereafter the patient must be monitored in case levels rise again once DMPS is discontinued[<932>], e.g. by the release of lead from the bones.

To begin with, adults with acute poisoning are given an oral dose of 1,200 – 2,400 mg/d, administered at equal intervals throughout the day (100 – 200 mg, 12 times a day)[<999,1506>] with a starting dose of 300 mg[<999>]. The maintenance dose is 1 to 3 x 100 – 300mg/d[<573,610,1019,1506>].

7.1.4.1.2 Children

Paediatric doses have not generally been stipulated to date[<1021>]. In acute intoxication, 20 up to a maximum of 30 mg/kg i.v. is initially administered in several divided doses throughout the day[<573,610,1032>]. The maintenance dose is 1.5 to 15 mg/kg[<573,610>]. The single dose is 5 mg/kg BW[<1506>]. The dosage can be reduced to 1 x 5 mg/kg BW i.v. or switched to oral administration from the 4th to 5th day, depending on the clinical condition[<573,610>].

Day	Single dose [mg/kg]	Number of doses	Interval between doses [h]	Daily dose [mg/kg]
1	5	6 – 8	3-4	30-40
2	5	4 – 6	4-6	20-30
3	5	3 - 4	6-8	15-20
4-5	5	1 – 3	8 – 24	5–15

Dose levels of DMPS administered parenterally to children with acute heavy metal poisoning[<573,610,706,1200a>]

7.1.4.2 Chronic poisoning

An advantage of DMPS compared to other chelating agents is that it may be administered orally in cases of chronic intoxication[<657>]. In the event of chronic poisoning or serious symptoms, the highest dose of antidote should be avoided in order to prevent marked mobilisation of the heavy metal[<706>].

7.1.4.2.1 Adults

In chronic poisoning, 200 - 400 mg DMPS/day are generally administered orally[<43,178,246,418,573,610,1019,1021,1032>]. (if possible before meals[<610>]) – in three divided doses[<406,418>]. In serious cases, the daily dose can also be increased[<573,1018>]. The maximum overall dose should not exceed 200 mg/kg BW in subjects with sufficient renal function[<610>].

Alternatively, outpatient therapy with 2 x 250 mg DMPS i.v. for two days followed by three treatment-free days may be administered to employees exposed to mercury[<1452>].

7.1.4.2.2 Children

For children with chronic poisoning, a daily dose of 5 mg/kg BW oral DMPS[<419,706, 1032>] is administered in three divided doses[<406>]. From the 3rd day, the dosage can be reduced to 2 x 2.5 mg/kg[<573,610>]; others recommend 50 to 100 mg/m² 4 times a day and 2 x 200 mg/day[<43>] in Wilson's disease.

Conclusion:
DMPS is indicated for all age groups, ranging from infants to the elderly. The method of administration, dosage and duration of treatment will depend on the nature and severity of the poisoning. Subsequent treatment requirements can be controlled by regular monitoring of the excretion of the toxic heavy metal in the urine.

7.1.5 Administration in cases of renal insufficiency

As the kidneys are the most important excretion organ for DMPS and its complexes, a particularly cautious benefit-risk assessment must be carried out for patients with limited kidney function (serum creatinine values > 2.5 mg/dL)[<770a,831,839a,1021,1133,1134,1454,1633>]. The dose may have to be adjusted[<1021>]. Extracorporeal elimination methods may prove necessary. "Use of DMPS as an adjunct to haemodialysis or haemofiltration in patients with anuric renal failure due to mercury salts and bismuth has been reported"[<770a>].

Conclusion:
DMPS and its complexes are dialysable. Administration of the antidote only with concomitant dialysis may prove useful in patients with renal insufficiency (kidney failure).

7.1.6 Use during pregnancy and lactation

The safety of DMPS administration during pregnancy has not been confirmed in humans[<539>] given the lack of experience with the use of DMPS during pregnancy and lactation[<513>]. "Its safety in pregnancy and lactation has not been studied"[<663a>].

No evidence of embryotoxic or teratogenic effects have been observed in laboratory animal experiments[<178,341,770a>]. "Pregnancy issues: Not embryotoxic"[<839a>]. In fact, DMPS reduced the teratogenic effects of various heavy metals[<342,343>]. The safety and efficacy of DMPS in the final trimester of pregnancy cannot be assumed on the basis of laboratory animal experiments[<43>]. DMPS-induced teratogenic effects in pregnant women have not been reported to date.

Pregnancy is not a contraindication in a vital indication[<573,1238>]. However, on safety grounds, DMPS therapy should, if possible, be avoided during pregnancy and lactation[<43,1133,1134>]. This applies to the DMPS test in particular[<1133>]. A stringent benefit-risk evaluation must be carried out in every case prior to the use of DMPS during pregnancy. It must also be taken into account that embryotoxic damage with As, Cd, Pb and Hg has been reported in the literature[<341>].

If the administration of DMPS is essential during pregnancy on the grounds of a vital indication, then minerals and trace elements (especially copper and zinc) should be monitored in order to ensure paediatric treatment[<202,341,663a,1123>]. Other chelating agents are known to possess teratogenic effects due to zinc depletion caused by such substances[<682>]. Zinc plays an important role in enzymes, amongst other things, for collagen formation and maturation. Zinc deficiency causes damage in the developing embryo[<341>].

Lactation should generally be avoided following heavy metal exposure[<543>].

Conclusion:
There is a lack of adequate data regarding the use of DMPS during human pregnancy. No damage to the embryos following adminstration of DMPS during pregnancy have, however, been reported to date. This also applies to women who receive DMPS treatment without knowing that they are pregnant. The laboratory animal experiments conducted do not give any indication of the embryotoxic or teratogenic effects of DMPS. Therefore, in the case of a vital indication, the administration of DMPS can be justified during pregnancy.

7.1.7 Contraindications and checkup

DMPS must not be administered to patients who are hypersensitive to DMPS or its salts<770a,839a>. Trace elements must be regularly monitored during prolonged administration<1506>.

Particular caution must be exercised when DMPS injections are administered to patients presenting with allergic, asthmatic symptoms. The risk of side effects appears to be high in this patient group. This applies because of the effect of DMPS on zinc metabolism, even in patients with acute infections, because zinc plays a key role in the body's defence mechanisms<1633>.

7.1.8 Additional measures

Other therapeutic measures may be required (intensive care, primary elimination of poison, e.g. by gastric lavage) in addition to antidote treatment<610,1018>. Special symptom-specific treatments may be required, e.g. treatment of any chemical burns in the gastrointestinal tract or lungs<610,1102>.

A combination of antidote therapy and extracorporeal elimination techniques such as:

- Haemodialysis
- Peritoneal dialysis
- Haemoperfusion
- Haemofiltration
- Blood or plasma exchange

are always available in the presence of acute renal failure<1102,1543>. DMPS can thus boost the efficiency of dialysis as it releases the heavy metal from its firm bindings to erythrocytes and tissue<1102> and, in so doing, make it dialyzable.

Sufficient quantities of fluid should be consumed during DMPS therapy in order to support the renal elimination of the poison<326>.

There is very little clinical data on combination therapies with various chelating agents<706>. New studies are required<506>. Recently, certain groups have been advocating the combination of DMPS and Zn-DTPA<180>. A combination of lipophilic and hydrophilic antidotes<32>, e.g. combination therapy with DMPS and BAL<911>, would be feasible. Treatment with DMPS would be initiated first of all until all of the accessible deposits are emptied. Additional administration of BAL could then mobilise intracellular heavy metals and possibly those deposited in the brain. This would rule out the risk of heavy metal accumulation in the brain. "The rationale in using two different complexing agents to produce a synergistic effect is that first agent should be sufficiently lipophilic to mobilize the metal from intracellular binding sites and promote its release into the blood, whereas a second agent will promote ligand exchange to form an ionized chelate that can be excreted in the urine"<702>.

7.2 Therapeutic use in metal and metalloid poisoning

"Heavy metal intoxication mostly manifests as a 'colourful' and non-specific picture of numerous symptoms. This certainly makes diagnosis difficult. ... The danger lies in the fact that, given the rarity of diagnosis, heavy metal intoxication may not be taken into consideration"<201>. "The presenting features may be entirely non-specific, the clinical examination giving no lead on the cause of the illness"<702>. Since doctors rarely incorporate toxic substances in their differential

diagnosis[20], the length of time until appropriate treatment is introduced may be unnecessarily long. Lack of treatment, expensive hospital stays and unnecessary suffering are the consequences of this[432]. "A diagnosis of metal poisoning can be confirmed in the acute stage and often in the chronic stage by finding an increased concentration of the suspected metal in the appropriate medium"[702].

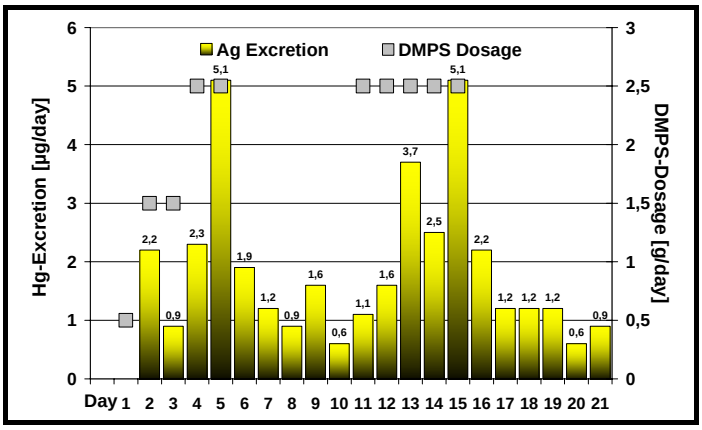
Acute poisoning with heavy metals such as lead, mercury, arsenic or cadmium seldom occurs nowadays[29,42,89,121,727,1544]. Only around 400 occupation-induced cases of heavy metal intoxication including arsenic poisoning are reported annually in Germany[1543]. Since the 1970s, however, there have been increasing warnings of heavy metal poisoning with mercury, lead or ayurvedic products contaminated with arsenic[20,875,1001,1002].

Consequently, clinical experience with DMPS concerns only a limited number of patients. Comparative clinical trials on the therapeutic use of DMPS and other chelating agents are seldom published[42,272, 281,917,918]. Most of the literature focuses on individual case histories of poisoning.

7.2.1 Ag - Silver

Silver is mainly deposited in the skin following absorption (Argyria)[121,166]. DMPS increases renal silver excretion[1061] and offers a possible means of treatment for silver poisoning[306].

A 60 year-old worker treated erosion of the gums topically with a 3% silver nitrate solution. Three years later, his hair turned silver grey, and 5 years later, his skin began to darken. In particular, areas exposed to the sun were bluish grey. Biopsies showed a 100-fold increase in the silver level and a 10-fold increase in selenium. Fifteen years after exposure (!), treatment with various chelating agents was attempted and, of these, only DMPS displayed an effect by increasing the silver excretion in the urine. In the course of two treatment cycles with up to 2,500 mg DMPS daily, however, only 1% of the total quantity of silver was removed from the body. Because the investigations showed that the silver was present predominantly as silver selenide and only a little as silver sulfide, the authors suggested that, while DMPS was able to remove the small portion of the sulfur-bound silver, the chelating agent was unable to mobilise the silver selenide[5].



Daily silver excretion in the urine during treatment with DMPS[5]

In a patient with silver poisoning (argyrosis), the silver excretion in the urine during treatment with DMPS (300 mg orally per day) was increased up to 100-fold. Treatment with D-penicillamine proved ineffective[657].

Conclusion:
The efficacy of DMPS on chronic and acute silver poisoning cannot be assessed due to the lack of clinical and experimental laboratory animal data available.

7.2.2 Al - Aluminium

Mean Al levels in the urine were higher in the group treated with DMPS than in the group not given chelating agents[180]. The mean 24-hour excretion increased from 1.8 to 2.5 g/day in 65 subjects receiving 500 mg DMPS via the parenteral route[479]. Neither investigations, however, provide any data relating to the excretion of Al by individual patients before and after administration of DMPS. No conclusion can, therefore, be drawn as to the

	n	Al in the urine (µg/g Crea)
Without chelating agents	550	124
DMPS	184	253
DMPS+ Zn-DTPA	505	264
DMPS+ Zn-DTPA+ DMSA	206	263

Urinary excretion of Al during administration of various chelating agents (µg/g Crea.)[180]

possible efficacy of DMPS in the treatment of Al poisoning. Deferoxamine is recommended for the treatment of Al intoxication[<1505, 1629>].

Conclusion:
Al is a metal with an affinity for oxygen. According to chemical legislation, DMPS is not expected to be effective in the treatment of Al intoxication. No investigations have been carried out on Al-DMPS complex formation. Likewise, no laboratory animal experiments have been carried out. Therefore, DMPS is not indicated in the mangement of Al poisoning.

7.2.3 As - Arsenic

Al	200
As	10
Cd	5
Cr	50
Cu	2,000
Fe	200
Mn	50
Ni	20
Pb	10
Sb	5

Maximum allowed quantities in drinking water (µg/L)[<1022>]

Arsenic is one of the non-essential half metals or metalloids[<383a,955, 1543>]. Meanwhile its use has been banned in numerous industrial products due to its high toxicity. Nevertheless, 1,000 cases of arsenic poisoning are reported annually in the USA[<522>]. Arsenic compounds are odourless and tasteless[<1029>]. The main source of the oral arsenic load is the consumption of fish and seafood, especially young herrings. Fish and muscles can contain up to 150 µg As/g[<166>]. Substantially high arsenic levels are detected in the urine for up to 5 days after the consumption of young herrings[<1543>] or seafood[<1010>]. According to the 2001 EU drinking water directive, 10 µg of inorganic arsenic/L is permitted[<1022>]. The US Environmental Protection Agency (EPA) wants to reduce the arsenic content from 50 to 5 µg/L in drinking and mineral water[<1029>]. The tolerable daily dose was set at 2 µg inorganic arsenic per kg BW by the WHO[<960>]. The lethal dose for humans is 1 to 3 mg/kg[<1029,1483>]. No chronic effects are anticipated if the US-EPA reference dose of 0.3 µg/g BW/day is maintained[<1010>].

The natural presence in the soil burdened the ground water and gave chronic arsenic poisoning to millions of people in Argentina, Bangladesh, India, Taiwan, Chile, Inner Mongolia and Pakistan[<55,422, 464,555,1419>]. Since early June 2002, arsenic trioxide has been commercially available for the treatment of acute promyelocytic leukaemia (APL). Patients receive an average daily dose of 0.15 to 0.16 mg/kg BW i.v.[<1020>].

Arsenic levels in persons not particularly subjected to exposure are 2.5 µg As/L in the blood and 10 – 50 µg/L in the urine[<55>]. The following are given as reference values (without fish consumption 48 hours before sampling, people who eat fish have a higher arsenic excretion in the urine[<575b>]):

- urine: 15 µg/L[<1010>], 20 µg/L[<1543>] and 100 µg/24h[<20>]
- hair: < 0.06 µg/g[<20>]
- occupational medicine limit value (EKA, exposure equivalent for carcinogenic materials) 130 µg/L“[<1543>].

Various mechanisms may be involved in the toxic effects of arsenic:

- Inhibition of cellular ATP formation following competition with phosphate[<1010>]
- Inhibition of sulfhydryl groups in enzymes[<1010>], e.g. pyruvate dehydrogenase and thus disruption of carbohydrate metabolism[<1029,1419>]
- Chromosomal damage[<1010>].
- Triggering of oxidative stress[<420>].

Intra-individual sensitivities due to genetic polymorphism is also discussed[<50>]. Arsenic compounds are carcinogenic[<420,422,464,1543>] as well as teratogenic and embryotoxic[<343>]. It is not known exactly whether these effects are concentration-dependent or whether a “threshold“ limit exists[<464>].

Arsinic
> inorganic As(III)
> organic As(III)
> inorganic As(V)
> organic As(V)
> Arsonium compounds
> elementary arsenic

Order of toxicity of the various arsenic compounds[<166>]

Arsenic can appear as an inorganic or organic compound[<422,1029>], which differ in terms of toxicity. Inorganic, water-soluble, trivalent As compounds react with sulfhydryl groups of various enzymes[<422,995>] and are approximately 2 to 10 times more toxic than pentavalent arsenic

compounds[<995,1010,1419>], which are found in seafood amongst other things[<603>]. Organic compounds are less toxic than inorganic compounds[<422,1029>].

Up to 80 % of soluble arsenic compounds are generally absorbed in the upper gastrointestinal tract[<603,1029>]. Arsenic compounds are also well absorbed after inhalation[<1543,1029>]. Methyl arsenic compounds are not demethylated into inorganic As[<1029>]. Absorbed arsenic is bound to erythrocytes in the blood[<1543>]. From there it is redistributed relatively quickly in all organs[<1029>] ($t_{½}$ < 1 hour, after 24 hours less than 0.1 % of the quantity of arsenic originally present can be detected in the blood[<1543>]). Arsenic reached the placenta and the foetus. It was also detected in small quantities in breast milk[<1029>].

The total body half-life is 10 – 30 hours[<165>]. Up to more then 75 % of both organic and inorganic arsenic is excreted in the urine. A mixture of As(III), As(V), MMA and DMA is mostly found. Only small quantities are excreted in the faeces[<1029>].

The clinical picture of arsenic poisoning depends on the nature and type of ingestion, the chemical composition and the dose[<603>]. On acute poisoning, reactions of the gastrointestinal tract predominate. Vomiting, sometimes blood-stained diarrhoea and development of a shock state as a result of massive loss of fluid with collapse are typical symptoms. This state can be aggravated by cardiovascular disorders, leading to death within 24 hours[<422,603,1543>].

Doses below 50 µg As/kg/day for weeks or months led to gastrointestinal, haematological, hepatic, dermal and neurological effects. Years of exposure with 1 µg As/kg/day in drinking water leads to skin reactions as well as to skin, bladder, kidney and liver cancer[<1029>].

In chronic exposure, late and long-term sequelae through accumulation of arsenic predominate[<63,422,917,960,1543>]:

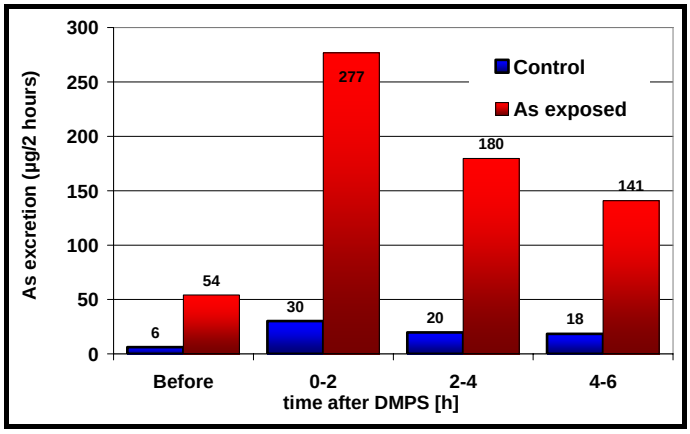
- Skin (hyperpigmentation, keratoses, leg oedema, gangrene of the toes, malignoma, alopecia)
- Nails (Mees' lines)[<121,422>]
- Liver (arsenic compounds are partly reduced or reduced and methylated and thus transformed into less toxic arsenic compounds[<166,1029>], fibrosis of the liver)
- Lungs (malignoma)
- Cardiovascular system (myocardial damage, disorders of peripheral circulation, anaemia)
- Kidneys (kidney failure)
- Nervous system (peripheral neuropathy, impairment of hearing and sight, burning sensation in the eyes)
- Muscles
- Spleen
- Bones
- Fatigue, exhaustion. Weakness, loss of appetite, salivation, apathy.

The risk of skin, lung or gastrointestinal cancer is increased[<121,1543>]. In animal experiments it has been shown that arsenite and arsenate have embryotoxic actions[<178,341,770a>].

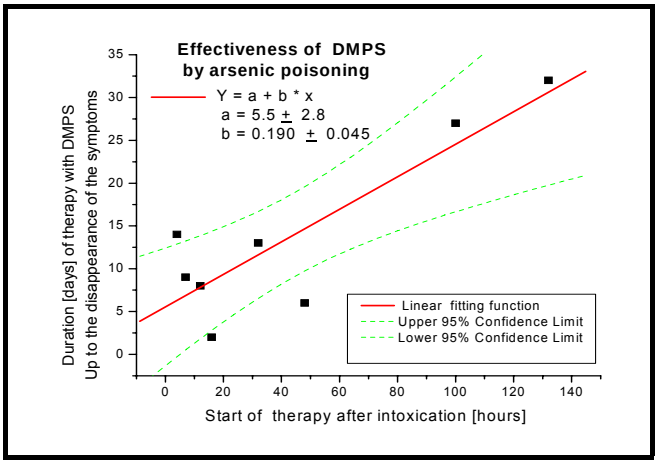
"Arsenic (As) is one of the oldest poisons known to men. Its applications throughout history are wide and varied: murder, make-up, paint and even as a pesticide. Chronic As toxicity is a global environmental health problem, affecting millions of people in the USA and Germany to Bangladesh and Taiwan. Worldwide, As is released into the environment by smelting of various metals, combustion of fossil fuels, as herbicides and fungicides in agricultural products. The drinking water in many countries, which is tapped from natural geological resources, is also contaminated as a result of the high level of As in groundwater. The environmental fate of As is contamination of surface and groundwater with a contaminant level higher than 10 particle per billion (ppb) as set by World Health Organization (WHO). Arsenic exists in both organic and inorganic species and either form can also exist in a trivalent or pentavalent oxidation state. Long-term health effects of exposure to these As metabolites are severe and highly variable: skin and lung cancer, neurological effects, hypertension and cardiovascular diseases. Neurological effects of As may develop within a few hours after ingestion, but usually are seen in 2–8 weeks after exposure. It is usually a symmetrical sensorimotor neuropathy, often resembling the Guillain–Barré syndrome. The predominant clinical features of neuropathy are paresthesias, numbness and pain, particularly in the soles of the feet. Electrophysiological studies performed on patients with As neuropathy have revealed a reduced nerve conduction velocity, typical of those seen in axonal degeneration. Most of the ad-

verse effects of As, are caused by inactivated enzymes in the cellular energy pathway, whereby As reacts with the thiol groups of proteins and enzymes and inhibits their catalytic activity. Furthermore, As-induced neurotoxicity, like many other neurodegenerative diseases, causes changes in cytoskeletal protein composition and hyperphosphorylation. These changes may lead to disorganization of the cytoskeletal framework, which is a potential mechanism of As-induced neurotoxicity“[<1477a>].

”By far the most important step in Arsenic related interventions for protection of human health is interruption of the primary route of exposure. If this can be accomplished, there are chelating agents that show promise as reagents for rapid arsenic dispersal and excretion. These include DMPS and DMSA”[<92a>]. DMPS has been found to be effective in arsenic poisoning in humans“[<663a>]. BAL and DPA can also be used for treatment[<1277a>], whereby DPA is no longer generally recommended[<555>], as its efficacy is not confirmed[<29>]. The same applies for DMSA: ”The role of DMSA as an effective antidote in chronic arsenic poisoning should therefore be questioned”[<934a>]. “The estimate that BAL is the drug of choice is obsolete[<13,1483>] . DMPS is less toxic[<663a>] and approximately 10 times more effective than BAL[<30>]. ”Given low rates of adverse reactions to DMPS and DMSA, it is possible these drugs may replace dimercaprol as the drug of choice for the treatment of acute arsenic poisoning”[<234>]. Three patients in Munich suffering from As poisoning were thus treated with DMPS. They survived and did not develop polyneuropathy, which is associated with BAL[<1419>].



Arsenic excretion (µg/2h) following oral administration of 300 mg DMPS in subjects exposed to As and in volunteers[<1419>]



Effect of the start of treatment on the duration of treatment with DMPS until symptoms disappear[<1566a>]

DMPS has proved effective in the treatment of poisoning with arsenic compounds[<770a,955,1021,1061,1117>]. ”DMPS although known for its antidotal efficacy against mercury, it has been reported to be an effective drug for treating arsenic poisoning“[<419>]. ”Although the clinical studies are limited, it would appear that DMPS is the best drug available for increasing the excretion of arsenic and improving the conditions of humans exposed to various forms of this metalloid“[<50>]. DMPS is also recommended for paediatric use[<522>].

Treatment should be initiated as early as possible[<1004,1029,1560>]. Administration of DMPS within the first few hours after poisoning could prevent the development of toxic symptoms[<153>] and shorten the length of time until symptoms disappear[<1566a>]. DMPS is effective in the treatment in the management of inorganic and organic arsenic compounds[<1276>]. In China, DMPS is recommended for the treatment of As poisoning[<178>]. It is also recommended for the treatment of poisoning with warfare gas, lewisite[<798,1541>] and arsenic-containing nasal and pharyngeal irritants[<732>]. The United States Environmental Protection Agency recommends 100 mg DMPS every 8 hours for 3 weeks to 9 months in the treatment of poisoning due to arsenic-containing pesticides[<1216>]. The administration of a chelating agent is mandatory in the treatment of symptomatic patients with As poisoning[<178>]. “Chelate therapy is indicated in the treatment of symptomatic and asymptomatic patients with urine concentrations exceeding 200 µg/“[<518,603>], possibly in conjunction with haemodialysis[<1542>]. The end point of chelate therapy would be reached with urine levels below 50 µg/L“[<603>].

The urinary excretion of arsenic is increased by the administration of DMPS<56,96,153,324,471,476,478,480,740,1139,1191>. However, DMPS also raises the biliary excretion of As<1419>. The clinical symptoms improved<153,1139>. The arsenic-DMPS complex is dialyzable (Haemodialysis)<306>. Additional haemodialysis is therefore recommended in oliguria or anuria<518,610> (high-flux haemodiafiltration<1506>).

7.2.3.1 Mobilisation of arsenic

Volunteers		As excretion				Type of mobilisation test			
n	Patients	before DMPS	after DMPS	Unit	In-crease	DMPS dose	Route of admi-nistra-tion of DMPS	Collec-tion period	Litera-ture
501	Men and women	3.4	14	µg/g crea	4.1	10 mg/kg BW	oral	2 h	479,480
30	Women	2.9	17	µg/g crea	5.9	10mg/kg BW	oral	2 h	474
71	Women	2.6	11	µg/g crea	4.2	10mg/kg BW	oral	2 h	474
84	Women with abortions	4.8	15.9	µg/g crea	3.3	10 mg/kg BW	oral	2 h	470
19	Controls	0.8	10.1	µg/L	12.6		i.v.		722
26	Patients with atopic eczema	1.2	29.5	µg/L	24.6		i.v.		722

Increase in arsenic excretion via the urine following a single dose of DMPS to various patients or control groups

Oral or parenteral administration of DMPS leads to increased urinary excretion of arsenic in humans. In volunteers with normal environmental exposure without acute arsenic poisoning, excretion of the metalloid is increased by 24.6-fold on injection and around 6-fold on oral administration, which confirms the efficacy of DMPS in arsenic poisoning.

7.2.3.2. Acute poisoning

1st day	250 mg DMPS/hour parenteral
2nd day	125 mg DMPS/hour parenteral
Up to the 5th day	62.5 mg DMPS/hour parenteral
Up to the 12th day	600 to 700 mg DMPS/day oral

"Ultra high doses of antidote therapy" with DMPS<603>

In acute poisoning, the earliest possible support of vital functions and the introduction of chelate therapy are important<1483>. "Acute arsenic intoxication, often with suicidal intent, can be treated with 2,3-dimercaptopropane sulfonic acid (DMPS). Haemodialysis will mostly be essential. Subjects survived arsenic intoxication with excretion of arsenic in the urea of 360 mg/L"<1543>. "Dimercaptopropane sulfonate (DMPS) has become the treatment of choice for acute arsenic poisoning and has been used safely in high doses<91a>.

Nevertheless, many cases have a fatal outcome<814>. A 4 month-old boy was inadvertently given an arsenic-containing herbicide. BAL administered at 4-hourly intervals, was initiated 7 hours later. As the child's condition deteriorated dramatically, treatment was switched to i.v. DMPS. The child nevertheless died 36 hours after ingestion of As<1536>. Unfortunately, the report does not contain any information relating to As levels in the blood and/or urine.

In another patient, arsenic concentrations of 63 µg and 20 µg/L (normal < 1 µg/g) were recorded in the urine and hair, respectively. Mees' lines were visible in the nails and hyperkeratosis also developed. Various reflexes could no longer be induced. After 6 weeks, weakness of the limbs and difficulties in walking appeared. Treatment with 100 mg DMPS t.i.d. for three weeks and 400 mg DMSA t.i.d. for two weeks produced no improvement. The symptoms still persisted after two years<711>. Meanwhile, the symptoms were obviously irreversible.

A 21 year-old man swallowed more than 600 mg arsenic trioxide, approximately three to five times the lethal dose, with suicidal intent. Intensive medical procedures were initiated (gastric lavage, sufficient volume of approximately 27.5 L in 5 days and forced diuresis) approximately 7 hours after ingestion. Parenteral "ultra high doses of anti-dote therapy" with DMPS was introduced using a perfusor. The DMPS dose was gradually reduced. From the 6th day, treatment was switched to the oral administration of 600 to 700 mg DMPS per day. Overall, a total of 15,225 mg DMPS was administered over 12 days and was well tolerated by the patient. No relevant side effects developed. Only a transient, slight rise in GOT and GPT levels was observed. This reaction has, however, also been described for the therapeutic use of arsenic trioxide. The severe, systemic effects of arsenic could be prevented by rapid emergency treatment and subsequent hospital admission. An examination carried out approximately 9 months later revealed "no delayed, organic damage and, in particular, no evidence of neuropathy or CNS damage"[<574,603>].

Day	Arsenic concentration in the serum (ng/ml)	Arsenic concentration in the urine (µg/L)	Urine volumes (ml)	Renal arsenic clearance (mg)	Urine clearance (g/L)	DMPS dose (mg)
1	143	210.000	4.700	987,0	3.26	3.850
2	29	3.800	2.400	9.1	0.25	2.250
3	10	1.675	3.300	5.5	0.37	1.500
4	10	1.310	3.900	5.1	0.33	1.500
5	1	821	3.000	2.5	0.31	1.500
6	<1	138	2.750	0.4	0.36	1.325
7	<1	124	2.650	0.3	0.55	1.015
8	<1	115		0.2	0.66	700

Changes in laboratory parameters on acute arsenic intoxication during DMPS therapy[<603>]

Comparison of BAL and DMPS in the treatment of acute As intoxication confirmed the substantially greater efficacy of DMPS. Two out of three patients with As blood levels of 540 and 620 µg/L died despite treatment with BAL. The third is still suffering from poisoning-induced paraplegia. In contrast, two of the three patients treated with DMPS (peak As blood levels of 2,240 µg/L and 4,469 µg/L), one of whom was anuric, were discharged as cured. Because of the early onset of DMPS therapy, the third patient presented with only mild symptoms of poisoning despite having an As blood level of 245 µg/L. DMPS therapy was initially introduced at the dose level of 250 mg. Between 100 and 500 mg/h were subsequently infused. The biological half-life could thus be reduced to 4 and, with anuria, to 5 hours. As far as the authors are concerned, meanwhile DMPS is the drug of choice for the treatment of arsenic poisoning. Additional extracorporeal elimination techniques including haemodiafiltration are required only in the presence of existing kidney failure[<13>].

A 24 year-old male student was admitted to hospital 16 hours after ingesting arsenic. On the first two days he received 1.2 g DMPS per day via the i.v. route. During the first 17 hours, he excreted 6,475 mg arsenic in the urine and 74.18 mg on the second day. Dialysis and CAVHDF were only slightly effective and hardly removed any arsenic. Apart from nausea, the clinical course was free from any complications. The authors therefore conclude as follows: "In arsenic poisoning without kidney failure, DMPS is a hundred times more effective than all secondary elimination measures put together"[<1630>]. "Extracorporeal elimination enhancement procedures are useful only in patients with impaired renal function"[<1419>].

A 27 year-old female swallowed 9 g of arsenic with suicidal intent. After admitting herself to the emergency unit, she was treated with gastric lavage, active charcoal, $NaHCO_3$ and BAL and DMSA. Although the urinary excretion of As increased up to 14,000 µg/L, abnormalities appeared on the ECG and she became increasingly confused. Treatment was, therefore, switched to 250 mg DMPS i.v. every 4 hours on the 5th day. Hydroxocobalamine, folinic acid, methionine, $NaHCO_3$ and glutathione were administered concomitantly in order to support the development of less toxic MMA. The patient's clinical condition improved within 48 hours and the ECG returned to normal[<1483,1488>].

A 33 year-old female was admitted to hospital 2-3 hours after ingesting 20 g As_2O_3. Arsenic levels in the urine were 355 µg/L. Gastrointestinal lavage was immediately carried out with the addition of active charcoal, 500 mg DMPS i.m. and sodium thiosulfate i.v. were administered and haemodialysis was carried out. As DMPS was no longer available, BAL (800 mg i.m./day) was

administered for the next 4 days followed by DPA (4 g oral/day) for 7 days. On the 3rd day As levels in the urine amounted to 84.7 and on the 7th day to 115.4 µg/L. The patient was discharged symptom-free after 15 days[<484>].

Following the ingestion of sodium arsenate with suicidal intent, an As concentration of 25,542 µg/L was measured in the normal urine of one patient in the USA. The patient was effectively treated with BAL and DMPS i.v. As levels of 7,866.5 µg/L were recorded in the first 24-hour urine. The delay in obtaining a DMPS solution for injection posed a problem[<203>].

July 1994	Peripheral neuropathy of unknown origin was diagnosed in a 33 year-old female.
Autumn 1994 - Spring 1995	The neuropathy improved but there were repeated skin reactions.
September 1995	The patient was admitted to hospital with severe pancytopenia. In addition, she developed cardiovascular reactions and progressive neuropathy.
29.10.95	Arsenic poisoning was diagnosed. The arsenic level in the urine was 1,030 µg/L. Oral treatment with DMSA was initiated. The arsenic excretion did not increase. The clinical symptoms of progressive neuropathy deteriorated further. The patient finally had to be ventilated and could no longer move her limbs.
16.11.95	Start of parenteral administration of DMPS (250 mg i.v. slowly over five minutes, in 9 divided daily doses). The arsenic level in the urine rose from 101 to 300 µg/L. Within 72 hours of starting DMPS therapy, a dramatic improvement in neuropathy was observed.
17.-18.11.95	Injection of 250 mg DMPS every 6 hours.
19.-29.11.95	Injection of 250 mg DMPS every 8 hours. On the 5th day of treatment, the arsenic level in the urine was 130 µg/L, falling thereafter during the course of the treatment to 56 µg/L. The injections were tolerated without adverse reactions. There was no evidence of hypertension or skin reactions. At the end of the 14-day DMPS therapy, the patient could be extubated. She was able to sit up in bed and again developed strength in her limbs.
March 96	The patient could walk again without any aid[<1537>].

A similar long-term history was suffered by a 41 year-old wine-grower who swallowed 8 – 9 g of arsenic with suicidal intent[<491>].

February 1984	Poisoning by ingestion of 8-9 g of arsenic. Nausea and diarrhoea developed within a few hours. The arsenic level in the urine was 7.5 mg/L (normal < 8.5 µg/L). Start of treatment with dialysis and BAL.
10th day	Numbness in the hands and feet, weakness, permanent burning sensation in the feet.
14th day	The arsenic level in the urine had fallen to 0.2 mg/L.
7th week	Mees' lines in the nails, hyperkeratosis of the soles of the feet, loss of reflexes in the arms and legs. Nerve conduction tests indicated axonal neuropathy. Arsenic excretion in the urine 52 µg/day (normal < 12.5 µg/day). Start of treatment with DMPS and increase of arsenic excretion in the urine. Arsenic was detected in the biopsies of the nerves. Slow improvement of neurological symptoms.
9th month	Completion of DMPS therapy
3rd year	Repeat nerve biopsy. Arsenic was no longer detectable. Regeneration of the nerves was observed morphologically.
February 1988	The neurological findings were still not within the normal range. Nevertheless, there was no longer any weakness of the leg muscles so that walking without crutches was no longer necessary.

Two case histories from the Poisons Unit, Guy's Hospital, London, show that timely treatment with high doses of DMPS can prevent arsenic-induced polyneuropathy. A 21 year-old male took 4 g of arsenic (As_2O_3) (toxic dose 120 - 200 mg)

3rd hour	Abdominal pain, nausea, vomiting

6th hour	Creatinine level of 160 µmol/L (normal <100 µmol/L), which further increased to 280 µmol/L. Urine excretion fell simultaneously. Fall in blood pressure.
26th hour	Arsenic level in the blood 400 µg/L (toxic > 50 µg/L).
32nd hour	Intubation due to onset of dyspnoea. Successful resuscitation of cardiac arrest. Onset of DMPS therapy with 5 mg/kg BW i.v. every 4 hours. Increase in blood pressure and quantity of urine.
2½ days	Extubation
7th day	Investigations with EMG and nerve velocity studies did no show any evidence of arsenic-induced neuropathy. Treatment switched to 400 mg oral DMPS every 4 hours for the next 7 days.
13th day	Patient was discharged.
6th week	Normal kidney function and no evidence of neurological dysfunction.

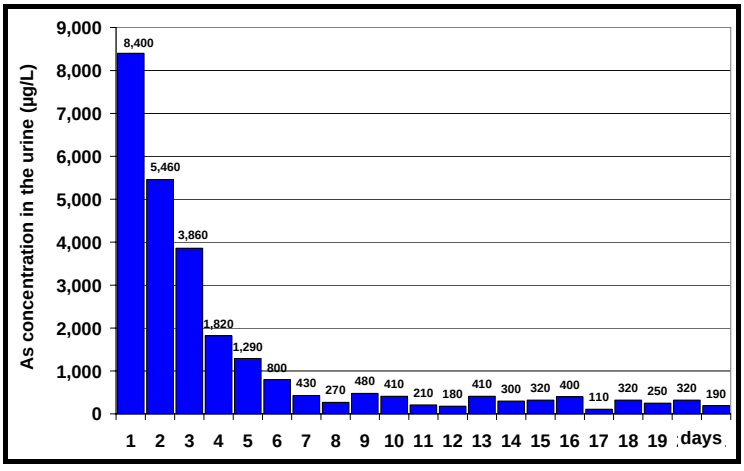
In the 19 year-old brother who had taken 1 g of arsenic, an arsenic concentration of 98 µg/L was measured in the blood after 36 hours. He was initially treated with i.v. DMPS (5 mg/kg BW every 4 hours) for 24 hours followed by 400 mg oral DMPS every 4 hours for the next 5 days. Similarly, no signs of neurological dysfunction were observed in this patient<95,666,948>.

Arsenic poisoning was also effectively treated with parenteral administration of DMPS in the USA. Sixteen members of an evangelical church in Maine drank coffee poisoned with arsenic. One of them died but 15 were saved. They were treated with BAL and/or DMSA. "The trauma and pain associated with the injections, as well as the allergic reactions by some to the peanut oil used in its composition, prompted the physicians to consider the water-soluble form of the antidote which could be given i.v."<1130>. The particularly serious cases were given i.v. DMPS although the preparation has not been granted a marketing authorisation by the FDA. Special authorisation was, therefore, required<1130>. The symptoms improved and the patients were saved<177,1117,1444>.

In Canada, an unknown number of people drank coffee assumed to be poisoned with sodium arsenite. Treatment with 100 mg oral DMPS t.i.d. was initiated more than two weeks after the criminal attempt in 33 patients whose As concentrations in the urine exceeded 50 µg/L (the highest value measured was 1,121.8 µg/L). Eight of them developed skin reactions one week after the start of treatment. Four of these had to be admitted to hospital and Stevens Johnson syndrome was suspected in two of these patients. Treatment was, therefore, withdrawn. All patients recovered and the arsenic concentrations were within the normal range<975a>.

Unpublished case reports also confirm the positive effects of DMPS on arsenic poisoning<598>. Two patients who had taken lethal doses of arsenic with suicidal intent were treated shortly after ingesting the poison. As DMPS was not immediately available in the clinic and because of the acute situation, preference was given to a chelating agent for parenteral administration. Hence dimercaprol was initially used but was then replaced by DMPS. In addition to drug therapy, the patients were simultaneously treated with haemodialysis and haemoperfusion to remove the poison. Both cases recovered without complications<586>.

One male patient with acute arsenic poisoning was given DMPS from the outset. Due to the uncertainty about the quantity of arsenic ingested (initial As concentration in the urine of 200 µg/L was known only sometime later), the patient was given 14 g (!) of oral DMPS on each of the first two days in divided daily doses. This case also recovered without complications<586>.



As excretion in the urine during DMPS therapy + haemodialysis<800>

A male patient exhibited typical symptoms of arsenic poisoning 5½ weeks after ingesting the arsenic after recovering from the acute phase. A gradual improvement in the patient's clinical condition was observed during approximately 4 weeks' treatment with DMPS with

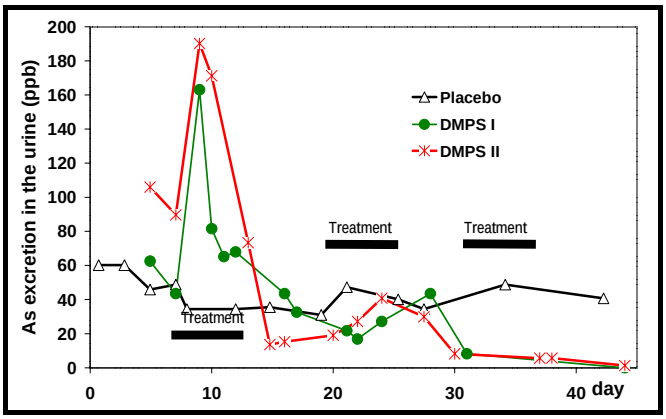
slowly falling arsenic concentrations in the urine[<586>].

A 33 year-old female accidentally took an ointment containing 1,850 mg arsenic trioxide, which was several times the lethal dose. Within 3 hours, she developed burning sensations in the mouth, nausea, dizziness, diarrhoea and abdominal pain. She was admitted to hospital 100 hours after swallowing the poison. She was given DMPS (250 mg i.v., 4 times a day for 2 days, 250 mg i.v. t.i.d. for 2 days and 250 mg i.v. b.i.d. for 23 days) in addition to active charcoal. 12-hour haemodialysis was also carried out at the same time. The patient recovered completely and the development of serious, neurological symptoms could be avoided[<800>].

Conclusion:
In laboratory animal experiments, DMPS increased the survival rates on acute poisoning with various arsenic compounds. DMPS therapy was also effective in the case reports published. The onset of serious neurological symptoms can be avoided when treatment is initiated early at a sufficiently high dose. DMPS is thus suitable for the treatment of acute arsenic poisoning even if it is not the drug of choice.

7.2.3.3. Chronic poisoning

The most important stage in chronic poisoning is to stop exposure. Otherwise the effect of DMPS therapy is only transient and devoid of long-term efficacy[<850>]. With delayed onset of treatment, melanosis can be prevented but keratosis remains unchanged[<1253>].



Arsenic excretion in the urine during DMPS therapy (2 patients) and placebo[<917>]

The efficacy of DMPS on chronic arsenic poisoning was confirmed in a prospective, placebo-controlled study involving patients whose drinking water was contaminated with arsenic (As > 50 µg/L). Eleven patients were treated with oral DMPS in three courses of treatment. Treatment with 400 mg DMPS per day for one week followed a treatment-free week. Ten control patients received placebo instead of DMPS. All volunteers received clean drinking water during the study so as to avoid any new exposure. No adverse reactions were reported with DMPS. The haematological parameters tested were unchanged after treatment. DMPS increased the excretion of arsenic in the urine, particularly during the first course of treatment. It also led to an improvement in the clinical symptoms (significant improvement in the scores compared to the placebo group)[<916,917>]. Weakness, neuropathy and lung disease-related symptoms particularly improved. Urea, creatinine, cholesterol, triglyceride and protein levels were equivalent to those recorded in the controls[<606>]. Histological changes in the skin biopsies were unaffected in the DMPS, DMSA and placebo groups[<917,1125>]. DMSA had no effect on clinical symptoms in a study conducted in parallel[<916,918>]. The change in the scores corresponded to that observed in the control group[<916>]. The symptoms may already have been irreversible or the 7-week observation period too short in order to eliminate the effects of an average of 22 years' exposure to arsenic. As early as possible onset of treatment therefore appears to be essential.

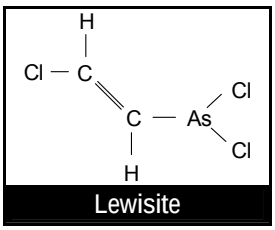
Two patients suffered from chronic arsenic poisoning through the use of an 'alternative' medicine. The arsenic could be eliminated by DMPS and the neuropathy improved[<95>]. The neuropathy was already irreversible in one other case[<711>].

Ninety patients with arsenic-induced periodontitis were treated locally with DMPS. The symptoms disappeared more rapidly than in the controls who were treated with water, camphor or clove oil[<1139>].

Conclusion:
DMPS increases the urinary excretion of arsenic. If treatment is initiated before the symptoms are irreversible, the clinical symptoms of poisoning improve. DMPS is, therefore, also an antidote for the treatment of chronic arsenic poisoning. Very few reports are, however, available.

7.2.3.4 Poisoning with chemical warfare agents containing arsenic

In the year 2000, the storage of 6,745 tonnes of lewisite was reported to the Organisation for Prohibition of Chemical Weapons[<175>]. "Arsenic-containing irritants cause severe damage to the skin and mucosa and lead to general organ failure following systemic ingestion"[<1010>]. British-Anti-Lewisite (BAL) is[<1233>] or was the standard treatment for poisoning with arsenic-containing warfare agents. Many countries still keep supplies for this purpose, even today[<52>].



Lewisite

DMPS has proved to be an effective antidote[<334,347a>] on absorbed intoxication with arsenic-containing warfare agents such as lewisite[<334,708>], phenylarsinic dichloride, ethyl arsinic dichloride or methyl arsinic dichloride, and can alleviate the systemic effects of lewisite[<628>]. As it is less toxic[<703,1233>], DMPS is better tolerated than BAL[<1000>] and can be administered orally [<798,1233>] or via the i.v. route[<1233>]. DMPS is also superior in terms of efficacy[<106,1026>] ,"DMPS proved the most potent and BAL the least potent drug"[<1026>]. Although clinical uses of DMPS on poisoning with arsenic-containing warfare materials have not yet been published, various authorities and organisations discuss their use, e.g.

- WHO[<1233>]
- the Scientific Committee for Human Medicines (CPMP – Committee for Proprietary Medicinal Products) of the European Agency, EMEA[<1011>]
- the German Bundeswehr (Federal Armed Forces)[<703,1012>], which hold supplies of DMPS for this purpose[<334,347a>]
- German Katastrophenschutz (Disaster Control)[<334>]
- the Swedish Socialstyrelsen(National Board of Health and Welfare)[<1556>]
- the Australian Emergency Management[<1026>]
- the Austrian Feuerwehr (Fire Brigade) and medizinische Erstversorgung (Emergency Medical System)[<1541,1627>]

In investigations of "Suspected Armament Contaminated Soils" where arsenic-containing warfare materials may be found, DMPS should be readily available [<1176>], which, in reality, is not always the case. "Adequate supplies of antidote, including DMPS amongst others, is, however, a problem"[<456>].

The recommended treatment regimen depends on the nature and severity of the poisoning. The following treatment is recommended for intoxication with arsenic-containing warfare gases[<732,798,1541,1627>]:

Mild absorptive poisoning: ⇒ 200 mg oral DMPS t.i.d.
Severe absorptive poisoning: ⇒ 200 mg i.v. DMPS or 400 mg oral DMPS
100 - 200 mg i.v. DMPS every 2 hours
or 200 - 400 mg oral DMPS
gradual reduction in the daily dose

The Scientific Committee for Human Medicines (CPMP – Committee for Proprietary Medicinal Products) of the European Agency, EMEA, recommends the following dosage schedule:

- First 48 hours: 250 mg every 3-4 hours
- Next 48 hours: 250 mg every 6 hours
- Next 14 days: 250 mg every 8 hours.

The antidote should be administered orally or intravenously in physiological saline solution[<1011>].

Other treatment recommendations for systemic intoxication are provided in the literature:

- 200 mg i.v. DMPS t.i.d.<703>
- initially 2 to 4 Dimaval capsules (depending on the severity of the poisoning<456>) and 1-2 capsules every 2 hours thereafter<456,1000>
- 250 mg i.v. every 3-4 hours<1000>

Conclusion:
Case reports on the clinical use of DMPS on poisoning with arsenic-containing warfare gases have not been published to date. In laboratory experiments, the antidote prevented the fatal effect of lewisite. DMPS is, therefore, recommended by various organisations for the treatment of lewisite poisoning, whereby treatment should be initiated as early as possible given the rapid onset of efficacy of the warfare gas.

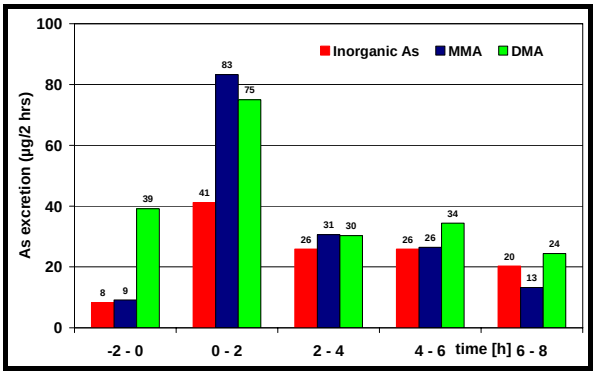
7.2.3.5. Poisoning with arsenic hydride (Arsinic AsH_3)

"Accidental inhalation of the highly toxic gas, arsenic, leads to massive haemolysis within a few hours, the first sign of which is red-stained urine"<1010>. It can also quickly lead to kidney failure<55>. There is no special therapy for the treatment of arsenic poisoning<732,1419,1506>. DMPS can be administered on arsinic poisoning but is only of limited effect and does not replace the essential exchange transfusion and haemodialysis<1103>. According to other authors, DMPS is not indicated or is even contraindicated<573,663a,702,839a,1018,1039,1506> on arsinic poisoning.

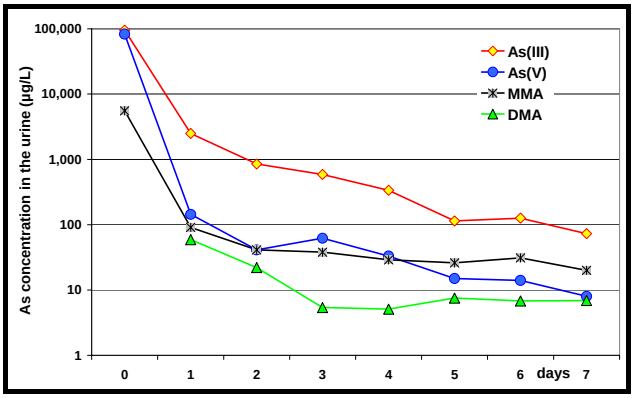
A 32 year-old employee attended hospital with red-stained urine half a hour after accidental AsH_3 exposure. Following an exchange transfusion with 1 L of blood, arsenic levels on the following evening were 1,122 in the whole blood and 358 µg/L in urine collected over 6 hours. 110 µg/L lead and 15 µg/L antimony were also measured in the urine. After several days' "stimulation" with DMPS, the arsenic concentration in the urine increased to 3,000 – 5,600 µg/L. The patient recovered after subsequent exchange transfusion, haemodialysis and intubation, and was discharged after 4 weeks for outpatient follow-up<542>.

Conclusion:
Arsinic poisoning is primarily treated by exchange transfusion and haemodialysis. DMPS can also be administered to promote the excretion of arsenic.

7.2.3.6 Influence on arsenic metabolism



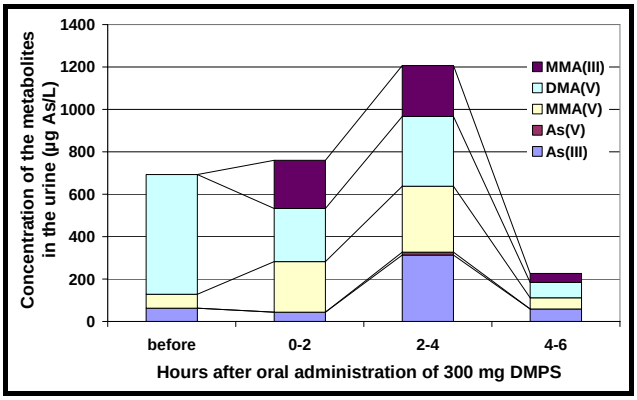
Excretion of As and its metabolites following single, oral administration of 300 mg DMPS to exposed volunteers in South America<54,55>



Arsenic excretion in the urine following acute poisoning with arsenic following high doses of DMPS therapy<574>

After ingestion of a normally lethal dose of arsenic (As(III)) and immediate administration of DMPS, the quantity of arsenic excreted via the kidneys was predominantly unchanged as trivalent As. As(V) and MMA were also detected. Like in laboratory animal experiments, DMPS also prevents

the formation of DMA in humans. Arsenic bound to DMPS is obviously no longer methylated[<500,574>]. A reduction in DMA^{V} to MMA^{III} via DMPS was ruled out under experimental conditions[<828>].



Concentration of As metabolites in the urine of subjects from Mongolia following administration of DMPS[<827>]

On chronic exposure, As is chiefly excreted as DMA[<828>]. The arsenic excreted in the urine comprises 10-15% inorganic arsenic, 10-15 % MMA and 60-80 % DMA[<121>]. In contrast, MMA predominated with DMPS[<828>].

A mono-methyl arsenic-DMPS complex was also detected in the urine during DMPS therapy following exposure to inorganic arsenic[<500>].

Volunteers from South America[<54,55>] or inner Mongolia[<53>] exposed to chronic arsenic through contaminated drinking water (593 µg/L and 568 µg/L) excreted most of the arsenic as DMA. Following administration of DMPS, MMA (total of MMA^{III} and MMA^{V}) increased in particular but levels of inorganic arsenic and DMA also rose. After 2–4 hours, the three metabolites were present in similar quantities. Thereafter, DMA again predominated[<54>]. DMPS obviously prevents the binding of DMA or promotes the excretion of MMA. As shown in *in-vitro* investigations with isolated enzymes, the DMPS--MMA^{III} complex is not a suitable substrate for MMA-methyltransferase and is excreted in the urine. Any reduction from MMA^{V} to MMA^{III} via DMPS could be ruled out[<53>].

7.2.4 Au - Gold

Gold intoxication damages in particular the kidneys (nephritic syndrome), skin (allergic reactions and dermatitides) and the bone marrow[<166>]. DMPS is recommended as an antidote for gold poisoning[<29,1061>] - especially in the event of persistent symptoms and severe poisoning[<1560>]. In the sodium aurothiomalate summary of product characteristics, it is listed as an antidote for the treatment of overdose[<1003>].

Presumably toxic effects following gold treatment for polyarthritis were treated with several days' administration of DMPS in a 61 year-old female patient. Unfortunately, the authors do not comment on the dose administered or if treatment was successful[<26>].

In one patient with iatrogenic gold poisoning, DMPS therapy produced an increase in gold excretion. Nevertheless, the patient died of heart failure[<95>].

Conclusion:
According to laboratory animal experiments, DMPS appears to be a suitable antidote for the treatment of gold intoxication. Unfortunately, no relevant clinical case histories have been published.

7.2.5 Be - Beryllium

No specific treatment is known for chronic berylliosis. There are no clinical data regarding the use of DMPS on beryllium poisoning. Laboratory animal experiments, however, show that: "2,3-Dimercapto-1-propane sulfonic acid (DMPS) appears to be suitable for the treatment of acute exposure"[<1542>].

7.2.6 Bi - Bismuth

Bismuth is a non-essential metalloid[<733>]. Its compounds are an active substance of various gastritis- and ulcer agents and are used in the treatment of *Helicobacter pylori*. Chronic administration of high doses and ingestion with suicidal intent can lead to bismuth intoxication. The metalloid thus accumulates essentially in the kidneys, lungs, liver, brain and muscles. Arrhythmias, liver damage and impaired kidney function culminating in reversible liver failure and encephalopathies may develop at high doses. The biological half-life is 20-30 days[<121,1436>]. DMPS therapy is recommended for overdose in the Angass®, De-Nol™ and Telen® summaries of product characteristics[<1013,1014,1038>]. In addition, radioactive bismuth ^{213}Bi develops as a daughter element on α-degradation of ^{225}Ac, which is used bound to monoclonal antibodies for radioimmunotherapy[<648>].

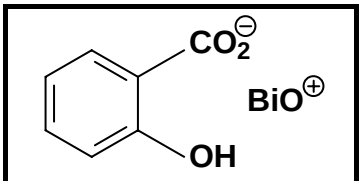
	Blood	Urine
Therapeutic	< 0.1 µg/L	0.8-1.6 µg/L
"Warning range"	To 50 µg/L	
Toxic	> 50-100 µg/L	

Reference values for bismuth[<121>]

Bismuth levels of >100 µg/L in the blood are considered as the lower toxic limit[<1103>].

DMPS is recommended in the treatment of bismuth intoxications[<29,1061>] and is even described as the drug of choice[<30>]. Treatment with the chelating agent, DMPS, has proved effective in chronic poisoning with bismuth compounds[<1013>]. "We conclude that DMPS is effective in eliminating bismuth, and should be considered as a chelating agent for bismuth poisoning"[<592>]. "DMPS is effective for increasing urinary excretion of bismuth - DMPS in combination with haemodialysis is effective in reducing serum bismuth levels in patients with renal failure"[<1021>]. The administration of 250 mg i.v. DMPS increased bismuth excretion in the urine from 0.1 to 4.1 µg/L in one patient[<612>]. Haemodialysis is also indicated in the management of kidney failure[<1038>].

A 49 year-old woman with 5 years' chronic bismuth abuse developed typical bismuth encephalopathy with advancing dementia, dysarthria and myoclonia one week after increasing the dose. The Bi level in the serum was 550 µg/L (normal value < 5 µg/L). The bismuth preparation was discontinued and treatment with valproate and clonazepam introduced. DMPS was also administered orally, albeit only at a daily dose of 100 mg, in order to increase Bi excretion. Despite a fall in the Bi level in the plasma and a marked increase in Bi excretion in the urine, the clinical symptoms deteriorated so that DMPS was stopped once again after 3 days. Over the next 3 weeks, the Bi level fell to 30.4 µg/L. This was associated with a continuous clinical improvement[<1436>].



Bismuth subcitrate

A 22 year-old female Turk swallowed 5.4 g of colloidal bismuth subcitrate with suicidal intent. She was admitted to hospital as an emergency two hours later. She initially developed oliguria (< 500 mg/dL), which deteriorated into anuria with elevated creatinine (7.8 mg/dL) and urea values (38.4 mg/dL) within three days. Ulcerated tonsillitis developed eight days after poisoning. Treatment with i.v. DMPS and concomitant haemodialysis were introduced 60 hours after ingestion. The time between the injections was thus successively prolonged. The patient received 28 injections with a total of 7 g DMPS over eight days. During therapy, the Bi level in the serum fell from 640 µg/L to 15 µg/L within 6 days. In the dialysate, the Bi concentration fell from 66 µg/L to < 2 µg/L. Kidney function was reinstated after 10 days with the elimination of Bi. The intervals between the dialyses were extended. Haemodialysis was stopped 14 days after it was started. At the follow-up examinations performed after 6 and 12 weeks, kidney function had returned to normal and the tonsils had healed. According to the Swiss authors: "Treatment with the chelating agent DMPS in combination with haemodialysis is highly effective in reducing the serum bismuth level in patients with acute renal failure"[<614,615>].

Day 1 - 2	250 mg DMPS i.v. every 4 hours
Day 3 - 4	250 mg DMPS i.v. every 6 hours
Day 5 - 8	250 mg DMPS i.v. every 12 hours

Dosage regimen for DMPS[<615>]

Twenty-four subjects, who had been treated with a colloidal bismuth-containing antacid for 28 days, received a single dose of 30 mg/kg DMPS or DMSA. The high doses were tolerated without any problem. Both chelating agents increased renal Bi excretion about 50-fold, whereby the greatest proportion was excreted within the first four hours. During DMPS therapy, bismuth levels in the blood remained virtually unchanged, increasingly continuously with DMSA during the period

of investigation (4 hours). DMSA obviously led to a redistribution of bismuth from the tissue into the blood[<1355>]. DMPS appears to be the more effective chelating agent for bismuth poisoning considering the lower bioavailability of DMPS compared to DMSA. In contrast, DPA did not increase the urinary excretion of bismuth[<1060>].

5 mg DMPS/kg BW i.v. every 6 hours	5 days
5 mg DMPS/kg BW i.v. every 8 hours	5 days
5 mg DMPS/kg BW i.v. every 12 hours	17 days
200 mg DMPS oral every 8 hours	10 days
200 mg DMPS oral every 12 hours	14 days

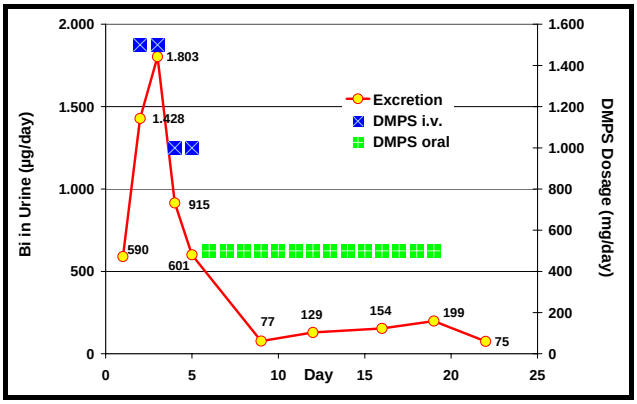
Dosage regimen for DMPS[<300>]

Confusion and tremor developed within 2 weeks in a 66 year-old man following treatment of an extensive wound with a bismuth-iodoform-paraffin paste. Bismuth concentrations increased to 340 µg/L and 2,800 µg/L in the blood and urine, respectively. The paste was discontinued and DMPS introduced for a total of 61 days. The antidote was initially administered via the i.v. route and thereafter, orally. Confusion and tremor improved continuously. Bismuth levels reverted to normal within 55 days. Kidney function was never affected[<300>].

Treatment with 4 x 200 mg DMPS/day was administered to a 30 year-old man one day after ingesting 4.8 TBD. After 10 days, the dose was reduced to 2 x 200 mg DMPS daily and treatment continued for a further 10 days. The original bismuth level of 424 µg/L in the blood fell to 17 µg/L on administration of the antidote. Similarly, urine levels decreased from 10,000 µg/L to 37 µg/L. Treatment was well tolerated and bismuth-induced kidney failure was prevented[<301>].

A 68 year-old man with restricted kidney function inadvertently took twice the quantity of a bismuth-containing antacid, TBD (tripotassium-bismuth(III) dicitrate, 864 mg Bi/d). The bismuth content of the blood rose to 880 µg/L. Clinical symptoms of encephalopathy (cerebral dysfunction, hallucinations and ataxia) developed. After withdrawing the bismuth therapy, the bismuth blood level fell slowly. With oral administration of 100 mg DMPS daily, the renal clearance could be increased 10-fold from 0.24 to 2.4 ml/min despite limited kidney function. The bismuth level within 50 days from 800 to 46 µg/L, whereby the fall at the time of the DMPS therapy was steeper. Cerebral dysfunction improved completely and the EEG no longer showed any discrepancies. No adverse reactions were observed[<95,592,1166>].

A 44 year-old patient quickly developed kidney failure after a single dose of 12 g TBD. The bismuth level in the blood was reduced within 11 days from 960 µg/L to 36 µg/L by administration of DMPS and haemodialysis. Symptoms of encephalopathy did not occur[<592>].



Bismuth excretion in the urine during DMPS therapy (µg Bi/day)[<1394>]

beginning:	**250 mg DMPS i.v. every 4 hours for 2 days**
then:	**250 mg DMPS i.v. every 6 hours for 2 days**
subsequently:	**250 mg DMPS oral every 12 hours for 14 days.**

A 21 year-old man developed anuria with serum creatinine level of 837 µmol/L 48 hours after an overdose of TBD. Further symptoms were nausea, diarrhoea, vomiting and exhaustion. The bismuth level in the blood was 590 µg/L (normal range 1 – 15 µg/L). After initial treatment with active charcoal and oral polyethylene glycol as well as i.m. BAL and dialysis, therapy was switched to DMPS. In contrast to BAL treatment, this resulted in significant bismuth excretion. Daily haemodialysis (1 hour after i.v. administration of DMPS) was continued. From the 8th day, urine excretion returned and, on the 13th day of treatment, dialysis could be stopped. Within the first six days, the Bi level in the blood was reduced to less than 50 µg/L[<1394>].

In a 13 year-old girl, treatment with DMPS (30 mg/kg/day, oral) was introduced for 10 days 24 hours after ingestion of 24 tablets containing a total of 2.88 g bismuth subcitrate. This was followed by 10 m/kg DMPS per day for 9 days. The Bi serum level fell rapidly from 300 µg/L (4 hours after ingestion) via 14 µg/L (48 hours after ingestion) to 8 µg/L (72 hours after ingestion). No adverse

reactions were observed. Thanks to early onset of treatment, the girl remained asymptomatic and dreaded kidney failure could be prevented. ”This treatment appears to be safe and should be considered in all cases of significant bismuth overdose. In this case it is likely that renal failure has been avoided by the early use of chelation therapy”[<188>].

From the experience gained with this patient, Stevens *et al.* recommend the following treatment for overdose with colloidal bismuth[<1394>]:

1. Gastrointestinal lavage with addition of active charcoal and polyethylene glycol
2. Determination of the bismuth level
3. Early administration of DMPS (250 mg i.v. every 4 hours), haemodialysis (membrane with large pores), dialysis for at least 6 hours. Continue dialysis until kidney function is again normal.
4. Continuation of DMPS therapy with 500 mg daily orally for 14 days (subdivided into two doses)

Conclusion:
DMPS is an effective antidote in the treatment of acute and chronic bismuth poisoning. Blood levels are reduced and clinical symptoms either regress or do not appear in the first place. Efficacy is recognised by the various marketing authorisation authorities, which, according to the summary of product characteristics for bismuth preparations, have approved the treatment of DMPS for overdose.

7.2.7 Cd - Cadmium

HBM I (Men)	1 (children) or 3 µg/g crea (urine)
HBM II	3 (children) or 5 µg/g crea (men)
Reference values:	adults < 1 g/g crea (urine)
(Background exposure)	children < 0.5 µg/g crea (urine)[<1288>]
Reference values:	adults < 1.0 g/L (blood)
(Background exposure)	children < 0.5 µg/L[<1288>]

	Whole blood	Urine
Non-smokers without occupational exposure	Up to 1.0 µg/L Ø 0.5 µg/L	Up to 1.0 µg/L Ø 0.3 µg/L
Smokers without occupational exposure	Up to 3.0 µg/L Ø 1.0 µg/L	Up to 2.0 µg/L Ø 0.5 µg/L
Recommended limit value following occupational exposure	15 µg/L	15 µg/L

Reference and limit values for cadmium[<1398>]

Cadmium is a non-essential heavy metal[<63,383a1504>]. It is used in colour pigments, batteries, for galvanising and in corrosion protection products[<63,1543>]. It is also used in large quantities in the tobacco industry[<63,181>]. Hence smokers have high cadmium concentrations in their blood and urine levels[<121,575b,1543>]. Pregnant smokers also have higher concentrations of cadmium in their amniotic fluid than non-smokers[<481>].

No. of cigarettes/day	Cd in the blood(µg/L)
<5	0.40
5-10	0.74
10-20	0.88
>20	1.07

Effect of daily cigarettes on Cd blood levels[<1549>]

In the general population, the dietary intake of cadmium (potatoes, wheat, certain types of mushrooms, liver and kidneys) accounts for approximately 90 % of the overall intake[<1398>].

Between 5 and 15 % of orally ingested cadmium is absorbed (on iron deficiency). Between 30 and 60 % are inhaled[<1543>]. Cadmium has a half-life of approximately 100 days in the blood and 10 – 30 years in the tissues. It therefore continuously accumulates in the body with age[<1543>]. “Cadmium concentrations in the urine depend considerably on age“ and increase with advancing age[<471,1398>].

Cadmium is preferentially stored in the liver and kidneys[<181,1376>]. It has a biological half-life of 10 – 20 years in the kidneys[<1376>].

The critical organs for cadmium exposure are the kidneys (tubules), lungs and bones[<121,343>]. In addition, embryotoxic effects[<343>] and an increased risk of lung cancer following years of high-level exposure[<1398>] have been demonstrated. The half-life in humans is between 16 and 33 years[<63,121>]

The symptoms of chronic poisoning following oral cadmium ingestion are: exanthema, kidney damage (tubular dysfunction, proteinuria), gastroenteritis, mineral metabolism disorders, osteoporosis (Itai-Itai disease), gingivitis and central nervous disorders[<121,166,1398>].

According to the DGAUM[<1398,1542,1543>] guidelines and the opinion of certain scientists[<178,286,1560>], there is no causal therapy for chronic cadmium intoxication. The administration of complex-forming agents such as EDTA, DMPS, BAL or DPA is contraindicated due to cadmium retention in the kidneys. DMPS is "not used for cadmium removal"[<839a>].

A single oral dose of 300 mg DMPS did not alter cadmium levels in the blood and urine in non-exposed subjects[<583>].

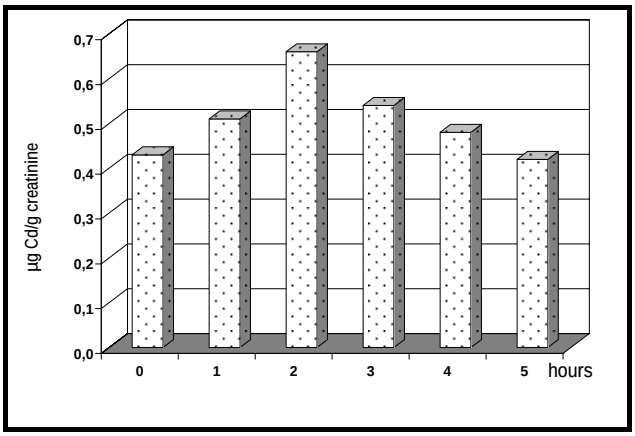
Age	Cd levels in the urine before DMPS	Cd levels in the urine after DMPS
≤ 24 years	0.20	0.34
25 - 29 years	0.25	0.42
30 - 34 years	0.28	0.49
≥ 35 years	0.33	0.59

Age-dependency of renal Cd excretion (in µg/g crea) before and 2 hours after oral administration of DMPS (10 mg/kg BW)[<471,478>]

Volunteers		Cd excretion				Type of mobilisation test			Literature
n	Patients	Before DMPS	After DMPS	Unit	Increase	Dose of DMPS	Administration of DMPS	Collection period	
85	Women with a history of abortion	0.32	0.54	µg/g crea	1.7	10mg/kg BW	oral	2 h	228
398	Women without a history of abortion	0.26	0.44	µg/g crea	1.7	10mg/kg BW	oral	2 h	228
32	Women	0.31	0.59	µg/g crea	1.9	10mg/kg BW	oral	2 h	474
32	Women	0.24	0.53	µg/g crea	2.2	10mg/kg BW	oral	2 h	474
501	Women	0.40	0.70	µg/g crea	1.8	10 mg/kg BW	oral	2 or 3 h	471, 479, 480
111	Women with a history of abortion	0.52	0.86	µg/g crea	1.7	10 mg/kg BW	oral	2 h	470

Increase in cadmium excretion via the urine following a single dose of DMPS in various patient or control groups

Other investigations revealed an increase in Cd excretion[<1191>]. With a 2-fold increase, this was, however, substantially less than that observed with other heavy metals and is an indication of the inadequate efficacy of DMPS in the management of cadmium poisoning. A woman who had worked for many years in a cadmium processing plant exhibited various symptoms of cadmium poisoning. Cd excretion in the urine rose from 1.8 to 4.2 µg/L after administration of DMPS[<305,306>].



Urinary excretion of cadmium (µg/g creatinine) following oral administration of 10 mg DMPS/kg BW[<481,478>]

Cadmium can be mobilised only to a slight degree by DMPS[<87,1532>] because of its intracellular[<87,478,481>] and especially firm binding to metallothioneins[<519>] . Treatment is, therefore, effective only when introduced at an early stage. "Chelation therapy can be very effective in cadmium (Cd) intoxication if started immediately after incorporation of the metal but loses its efficacy if started only one hour afterwards"[<1205>]. Markedly higher quantities of cadmium are excreted following combination therapy with DMPS and Zn-DTPA (both i.v.) compared to DMPS alone[<180>].

Conclusion:
No reports on the treatment of cadmium poisoning with DMPS are available. According to results obtained in laboratory animal experiments, DMPS is unsuitable in such cases. This is also confirmed by cadmium mobilisation studies. The DMPS-induced increase in cadmium excretion in the urine is relatively small and substantially lower than the values recorded for arsenic, lead, copper or mercury.

7.2.8 Co - Cobalt

Cobalt is mainly used in the steel industry. Its compounds are also used as catalysers and coloured pigments, amongst other things.

Cobalt is an essential heavy metal (vitamin B_{12}), but is toxic at higher quantities. In addition to reduced activity of the thyroid gland and goitre formation, cardiomyopathy has also been discussed as a symptom[<124>]. Furthermore, foetotoxic[<343>] and carcinogenic[<124,1543>] effects are not ruled out. Absorption in the gastrointestinal tract depends on the solubility of the cobalt compound and is normally between 5 and 20 %. Cobalt is chiefly stored in the liver and kidneys. 80 to 90% are excreted with a half-life of a few days[<124>]. The reference values for cobalt in the urine and blood are < 1.0 and < 0.9 µg/L, respectively[<1288>].

For normal subjects, food is the main source of cobalt intake[<124>]. DMPS is recommended as an antidote to cobalt poisoning[<306,1388>]. After cobalt poisoning, it increased the cobalt excretion[<707>]. The cobalt content in the urine of patients receiving DMPS was higher than that recorded in patients not treated with a chelating agent[<180>].

Two children aged 2 years 9 months and 5 years who suffered acute cobalt poisoning through swallowing a cobalt compound from a chemical experiment kit were initially treated with 25 mg D-penicillamine/kg BW. From the 5th day, treatment was switched to 50 mg DMPS p.o. t.i.d. The cobalt level in the serum initially rose slightly, presumably due to the increased mobilisation of the heavy metal from its deposits. Treatment was continued until the cobalt excretion in the urine was again within the normal range. The children survived the acute intoxication without complications and without myocardial damage[<586,963>].

DMPS was administered to a 14 year-old boy about 16-20 hours after swallowing the poison. After initially high serum (up to 1,360 µg/L) and urine concentrations (up to 26,400 µg/L), there was a marked fall in the cobalt level within a few days. The course of the poisoning was without complications apart from vomiting, and there were no symptoms of intoxication[<586>].

Conclusion:
In laboratory animal experiments, DMPS proved to be a suitable antidote for the treatment of cobalt intoxication. This is corroborated by the three known case histories. The information provided is not, however, sufficient for a final evaluation to be made.

7.2.9 Cr - Chromium/chromate

Chromium is an essential heavy metal. The daily requirement is approximately 50 µg[<166>]. It is important for the release of insulin from the islets of Langerhans[<1041>]. Chromium is used as an alloy constituent in steel, in electroplating and as a component in dyestuffs and pigments[<1543>].

Cr(VI), which is reduced to Cr(III) in the body, is toxicologically significant such that Cr(III) is mainly nd in the urine[<1543>]. Cr(VI) mainly irritates the skin and mucosa (eczema, tumours). “Chromate asthma” is known to develop in chronic poisoning. Chromate (especially zinc chromate $ZnCrO_4$) is carcinogenic (bronchial cancer). Cr(III) and Cr(VI) are also two of the most common contact allergens[<166,1543>].

The biological half-life of chromium is in the region of several weeks. The normal value in the urea for the general population is 0.5 µg/L. The EKA value for chromium is 20 µg/L[<1543>].

The administration of DMPS is a possibility for treating poisoning with chromium[<350,610,611,1542>]. Immediate treatment with DMPS, high doses of vitamin C and N-acetyl-cysteine are recommended on chromate poisoning[<1276>] (reduction of Cr(VI) to Cr^{3+}). The chromium content of the urine in patients receiving DMPS was higher than in patients not receiving a chelating agent[<180>].

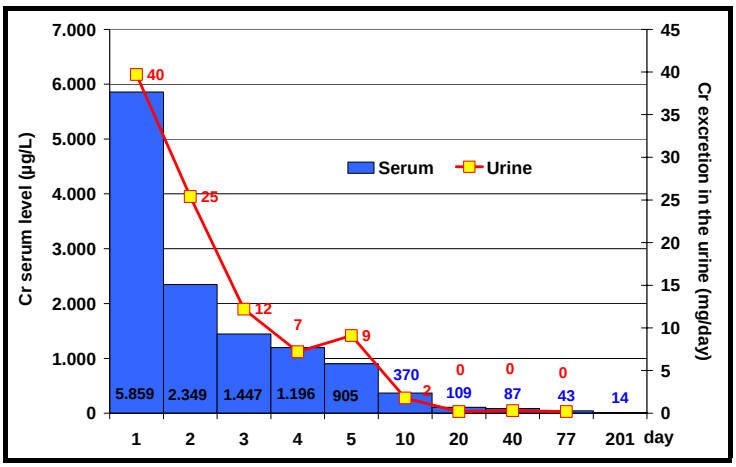
Sixty-seven patients with early symptoms of chromium poisoning were treated with DMPS and "endonasal electrophoresis". The chromium excretion in the urine rose and the clinical symptoms improved[<1583>].

A 20-year old swallowed 10 to 30 g of potassium dichromate, which is several times the lethal dose, with suicidal intent. Chromium concentrations of 3.8 mg/L in the plasma and 159 mg/L in the urine were measured at the start of treatment. Despite rapid hospital admission with immediate gastric lavage, the fatal outcome of the intoxication could not be prevented by various dialysis procedures and initiation of DMPS therapy (250 mg DMPS i.v. every four hours, starting, however, only 13 hours after admission to hospital!). The cell damage caused by the high oxidation potential of dichromate was already irreversible. The chromium levels found in various organs on autopsy were more than 1000 times higher than normal[<292,1186>].

Cr Haemofiltration clearance	
Without DMPS:	31.2 – 56.6 mL/min
With DMPS:	21.3 – 46.0 mL/min

A 49 year-old female patient developed metabolic acidosis and kidney and liver failure as well as corrosive damage in the digestive tract following ingestion of 17 g potassium dichromate ($K_2Cr_2O_7$) with suicidal intent. The following Cr values were measured on admission to hospital: Whole blood 13,000 µg/L, serum 7,000 µg/L, urine 60,000 µg/L. With intensive therapy (exchange transfusion, administration of DMPS, haemofiltration, continuous venous haemofiltration CVVHD, albumin dialysis), the next few days could be bridged and, after 7 days a transplant carried out due to liver failure. Before the operation, Cr levels in the whole blood had fallen to 1,900 µg/L and in the serum to 600 µg/l. Overall, 225 mg Cr were eliminated. 183 mg extracorporeal procedures, 21 mg faeces, 15 mg exchange transplantation, 6 mg urine so that the transplant was not damaged again[<400,404>].

A 42 year-old man sustained skin abrasions in an accident with his tanker. He was also covered with tanning solution (CrO_3, As_2O_3, CuO). He suffered from headaches, hypertension, excitation and conjunctivitis. Four hours after exposure, the urine level of As was 1,650 and of Cr 870 µg/L. The serum, Cu concentration was within the normal range. 320 mg BAL i.m. and 200 mg DMPS were initially administered followed by 6 x100 mg DMPS daily (the method of administration is not stated) for 14 days. During this therapy, which was well tolerated, As excretion via the urine fell exponentially with a half-life of 17.1 hours. The half-life for chromium was 48.2 hours. In the interim, a transient rise in aspartate-transaminase (AST) levels was observed. The blood picture and kidney and liver function were unchanged[<1241>].



Effect of DMPS therapy on serum levels and chromium excretion in the urine[<649>]

A worker fell into the chromic acid bath of an electroplating form and swallowwed some of the liquid. High dosed oral treatment with DMPS was initiated within an hour in addition to forced diuresis. The dose was gradually reduced (12 x 2 capsules/ day for 5 days, 4 x 2 capsules/day for 5 days and 2 x 2 capsules/day for 14 days). The excretion of chromium in the urine rose drastically and reached a peak with 13,614 µg/mL, 14 hours after the start of therapy. The patient survived despite a serum level of 5,850 µg Cr/L and short-term anuria (dialysis). Approximately half is normally considered to be the fatal

limit[<350,611,649,925>].

In Taiwan, a 22 year-old worker developed multiple organ failure despite adequate treatment with fluid, after falling into a dichromate tank. Through intensive medical care (ventilation, plasmapheresis and haemofiltration) and the administration of DMPS and N-acetyl cysteine, the patient's condition initially stabilised and he was discharged without any long-term damage after 33 days[<846>].

One hour after accidental ingestion of a dyestuff containing $SrCrO_4$, a 15 month old boy vomited profusely. The Cr level in the whole blood was 390 µg/kg (reference value < 1 µg/kg). The child remained asymptomatic during treatment with vitamin C (1 g/day) and DMPS. Kidney function parameters remained normal with only a slight rise in GOT levels. Chromium levels fell to 6 µg/kg[<647,652>] during DMPS therapy of 4 months' duration.

Pudill *et al*. recommend the following treatment on acute poisoning with bichromate[<1186>]:

1. Elimination of poison through gastric lavage
2. Administration of charcoal and magnesium oxide
3. Introduction of DMPS antidote therapy as soon as possible
   - ✶ Initial dose with 250 mg i.v.
   - ✶ Followed by 250 mg i.v. every 4 hours for 24 hours
   - ✶ Then 250 mg i.v. every 6 hours
4. Continuous arteriovenous haemofiltration

Conclusion:
On poisoning with Cr(VI), rapid administration of a reducing agent, e.g. high doses of vitamin C, is essential in order to reduce the highly toxic Cr(VI) to Cr(III) The addition of DMPS also has a reducing effect. Furthermore, it increases chromium excretion in the urine. Poisoning with a lethal clinical course can normally be controlled, even in children, with this treatment supported by extracorporeal elimination procedures, as required.

7.2.10 Cs - Caesium

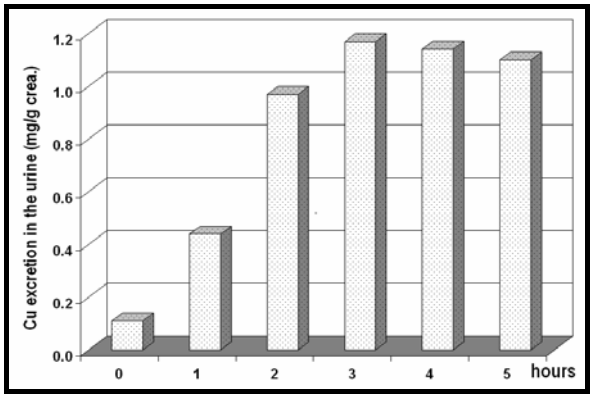
The caesium content in the urine of patients receiving DMPS corresponded to that recorded in patients not treated with a chelating agent. No higher values were recorded during combination therapy comprising DMPS + Zn-DTPA or DMPS+DMSA+Zn-DTPA[<180>].

Conclusion:
DMPS is not effective on poisoning with stable or radioactive isotopes of caesium. Berlin blue (Radiogardase®-Cs) is the drug of choice for this type of poisoning.

7.2.11 Cu - Copper

After iron and zinc, copper is the third most common essential trace element. The recommended daily allowance for adults is 2 - 4 mg Cu[<166>]. Between 50 and 120 mg are present in the body of an adult. Copper is important for the haem synthesis and absorption of iron, amongst other things[<125>].

Absorption following oral ingestion of copper differs from one individual to the next, varying between 15 and 97 %. Between 65 and 70 % of the copper contained in food are usually absorbed. Approximately 2 mg are thus ingested daily. The



Copper excretion in the urine (mg/g creatinine) after oral administration of 10 mg DMPS/kg BW[<481>]

greatest concentrations are found in the liver (18 – 45 mg Cu/g dry weight), bile, brain, heart and kidneys. Copper is excreted via the faeces (1 – 2 mg/day) and the urine (40 – 50 µg/day)[<125>].

Toxic effects may appear if more than 1 g of copper salts is ingested. 10 to 20 g copper is generally fatal in an untreated adult. Massive haemolysis, kidney and liver dysfunction as well as rhabdomolysis have been observed as symptoms of acute poisoning[<125>]. Symptoms of chronic copper intoxication are: Impaired concentration, ataxia, severe tremor, headaches, depression and liver damage[<318>].

In addition to DMPS[<43,179a,306,318,610,1263,1532,1629>], copper poisoning can also be treated with BAL, DPA or EDTA[<351a>]. "Based on experimental studies, DMPS is probably the best chelator"[<203a>]. Treatment is generally recommended in symptomatic patients. In asymptomatic patients, however, the need for treatment is confirmed only by laboratory tests[<351a>]. DMPS can be administered as the 2nd treatment of choice when DPA is not possible[<1506>]. It increases copper excretion in the urine[<76,306,324,480,481,1040>]. The copper content in the urine of patients receiving DMPS was higher than that recorded in patients not treated with a chelating agent[<180>]. It has also displayed positive effects in heptolenticular degeneration[<69>] and has been used successfully[<494>]. It is thus an alternative to DPA[<1021>].

7.2.11.1 Mobilisation of copper

Volunteers		Cu excretion				Type of mobilisation test			Lite-rature
n	Patients	Before DMPS	After DMPS	Unit	In-crease	Dose of DMPS	Administra-tion of DMPS	Collection period	
7	With previous occupational Hg exposure	16	173	µg/24h	10.8	300 mg	oral	24h	1251
31	Normal subjects	17.7	438	µg/g crea	24.7	300 mg	oral	3-4 h	981
31	After amalgam removal and clearance	11.1	293	µg/g crea	26.4	300 mg	oral	3-4 h	981
82	Patients	0.08	1,22	µmol/mol crea	15.3	300 mg	oral	4 h	76
36	Normal subjects	37	350	µg/g crea	9.5	300 mg	oral	?	89
36	Normal subjects	37	350	µg/g crea	9.5	300 mg	oral	?	89
29	Normal females	44	1.265	µg/g crea	28.8	10mg/kg BW	Oral	2 h	474
501	Normal females	39	1.378	µg/g crea	35.3	10 mg/kg BW	Oral	2 or 3 h	471,474, 480,
6	Female patients with HELLP	59.7	1.969,8	µg/L	33.0	3 mg/kg	i.v.	30-45 min	563
?	Patients	38.4	451,9	µg/L	11.8	3 mg/kg	i.v.	30-45 min	563
57	Children	68	2.072	µg/L	30.5	3 or 10 mg/kg BW	i.v. or oral	45 min or 2 h	1572
34	Mothers	58	1.688	µg/L	29.1	3 or 10 mg/kg BW	i.v. or oral	45 min or 2 h	1572
83	Normal subjects	37	1.545	µg/g crea	41.8	250 mg	i.v.	?	89
65	Normal subjects	96.6	806	µg/L	8.3	250 mg	i.v.	45 min	143
38	Neurodermatitis	29.1	550	µg/g crea	18.9	250 mg	i.v.	45 min	637- 639
7	Controls	1.18	232	mg/L	196.6		i.v.		722
26	Patients with atopic eczema	1.35	550	mg/L	407.4		i.v.		722

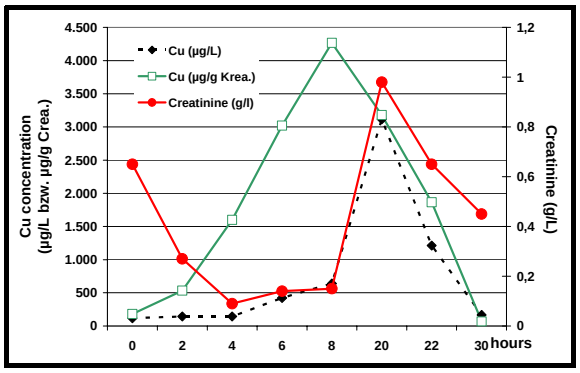
Increase in copper excretion in the urine following a single dose of DMPS in various patient or control groups

DMPS increases the renal excretion of copper in humans. Both oral and i.v. administration trigger sometimes drastically increased copper values in the urine of humans with normal environmental exposure to copper, thus highlighting the efficacy of DMPS on copper poisoning.

7.2.11.2 Acute poisoning

A 3 year-old boy swallowed more than 3 g of copper sulfate. The initial copper concentration in the blood was 118 µg/L. Within one hour, gastric lavage was carried out and treatment with DMPS initiated. The copper level in the urine rose to more than 20-fold (maximum value 3,116 µg/L). The value fell to below the toxic limits within 24 hours. The serum level was always below toxicologically alarming values. The child could be discharged from hospital after two days<350,925>.

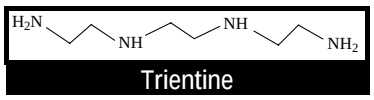
Conclusion:
In laboratory animal experiments, DMPS proved to be the most effective chelating agent in terms of the increase in survival rates following acute copper poisoning. The only case history available confirms the efficacy of DMPS in acute poisoning with copper salts.



Creatinine and copper excretion in the urine during DMPS therapy<925>

7.2.11.3 Wilson's disease

Wilson's disease (hepatolenticular degeneration), an autosomal, recessive inherited disease, leads to copper deposits in the liver, brain and other organs due to impaired copper transportation (excessively low ceruloplasmin concentrations). Clinical manifestations of the disease include mental and motor changes (dysarthria, dysphagia, ataxia and writing difficulties), haemolytic anaemia, renal disorders and fulminating liver failure<125>. DMPS "may be effective for Wilson's disease"<839a>.



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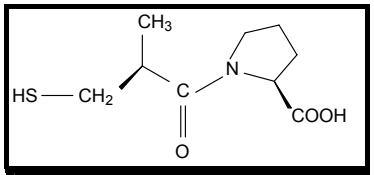


Captropril

A 13 year-old boy with Wilson's disease did not tolerate either DPA (drug of choice) or trientine (1st alternative for DPA intolerance). He was, therefore, given DMPS (200 mg b.i.d.). Copper excretion was increased as a result from 2,000 to 3,000 µg a day and the plasma level fell. The cupuresis was comparable to that observed with DPA or trientine treatment. The copper concentrations in the plasma and urine during long-term treatment with DMPS were, therefore, markedly lower than in the treatment-free intervals and only marginally higher than with DPA or trientine treatment. Clinically, the child was well during the 2-year observation period<1522,1523>. In other patients, good copper excretion could be achieved <1523> by administration of test doses of DMPS. In 2 further patients, good cupuresis was also achieved. In these cases, however, treatment had to be stopped due to adverse reactions<1523>.

The efficacy of captopril and DMPS were compared in a clinical trial with 28 previously untreated youths presenting with Wilson's disease (14 – 20 years old). Seven of the patients received i.v. DMPS for 8 weeks (20 mg/kg/day in 500 mL of a 5% glucose solution) and 7 were treated with DMPS and captopril combination therapy. DMPS significantly increased the urinary excretion of copper in all of the patients. The number of free SH groups in the serum rose simultaneously. A linear correlation therefore exists between copper excretion and the number of free SH groups. DMPS was more effective than captopril. The combination therapy did not show any advantages over DMPS therapy alone<1533>.

After one week's treatment with DMPS, liver function and fibrosis parameters had still not improved in 61 patients presenting with Wilson's disease<1582a>. The subsequent clinical course is, unfortunately, not described.

Up to 155 patients with Wilson's disease received 20 mg/kg DMPS i.v./day and an oral Chinese herbal remedy for the treatment of Wilson's disease. The condition of most of the patients had

improved after one month. No effect or even a deterioration was seen in only very few patients. Despite the relatively high dose of DMPS, there is no reference in the study to possible adverse reactions[<621,1218>].

Conclusion:
DMPS proved to be an effective alternative for the treatment of Wilson's disease in various studies conducted in China. No corresponding clinical trials in Europe or America have been published.

7.2.12 Hg - Mercury

Mercury is a non-essential heavy metal[<63,383a,733>]. Positive effects on the human body are unknown[<807>].

Mercury is the heaviest and densest known liquid. With a density of 13.6g/cm³, it is also 13.6 times more dense than water[<1143>]. It is the only liquid metal under standard environmental conditions, has a high vapour pressure and already evaporates on room temperature[<280,1033>]. High concentrations can thus be reached in closed rooms[<1278>] leading to poisoning through vapour inhalation[<280>]. The Agency for Toxic Substances and Disease Registry (ATSDR) recommends a limit value of 0.05 µg/m³ [<493>]. In the environment, mercury vapour is mainly formed from the burning of fossil fuels containing Hg. Industrial processes, gold abrasions, crematoria and volcanoes thus contribute to environmental exposure[<493>]. 112 tonnes of mercury are released annually into the atmosphere through volcanic activity[<1054>].

Mercury is used in alkali-metal chloride plants, batteries, pharmaceutical and dental products, fungicides, catalysers, protective paints, electronic products and measuring devices such as thermometers and barometers[<142,564>].

Mercury is available in various forms[<1030>] that vary in terms of toxicological and kinetic profiles:

- Inorganic mercury
- Organic mercury
- Mercury vapour
- Metallic mercury

Toxicity increases as follows $(Hg)_2^{2+}$ < Hg^{2+} < organic Hg[<142,1110>], organic mercury poisoning is the most toxic.

	Elementary Hg	Inorganic Hg	Organic Hg
Inhalation	80 - 100 %	50 (Aerosol)	>80 %
Oral	< 0.01 %	5-25 (-40) %	80 - 100 %
Dermal	< 3 %	2 – 3 %	3-5 %
t½ Blood	45 days	20 – 66 days	50 days
t½ Excretion	58 days	1 – 2 months	70 – 80 days

Pharmacokinetic profile of Hg[<91,121,290,393,1030.1033,1110.1267>]

The symptoms of mercury poisoning depend on the following:

- the type of ingestion (oral, inhalation, transdermal or parenteral)
- the type of mercury compound (elementary, vapour, inorganic or organic)
- the quantity of mercury compound absorbed
- the duration of intake (acute, chronic)
- individual disposition such as age, nutritional status and genetic factors[<91,1059>].

The main mechanism for the toxic effect of mercury concerns its deposition on sulfhydryl groups, as a result of which physiological function of the corresponding enzymes, for instance, is disrupted or changed[<142,727,1509,1543>]. No carcinogenic effects have been confirmed with Hg[<1543>].

In contrast to acute poisoning, symptoms of chronic mercury poisoning have an insidious character[<1411>]. Tremor, erethism and gingivitis are the cardinal symptoms of chronic intoxication[<142>]. Damage to the CNS generally predominates[<1045,1411>]. On exposure to low levels of mercury, in particular, the symptoms are extremely non-specific[<435>]. In addition to general complaints of fatigue, poor concentration, headaches and dizziness, loss of appetite, pressure in the stomach, nausea, salivation, alopecia, sweating, hyperhidrosis and unsteady gait have been mentioned[<435,1045,1411>]. The first objective symptom is a fine tremor, especially of the hands, followed by tremor in the region of the eyelids and tongue. In addition, there is increased salivation, which, in some cases, is accompanied by gingivitis. Later on, the subjects are easily

irritable and suffer from insomnia with a constant feeling of fatigue and loss of energy as well as depressive moods. Psychological changes in the form of personality changes and emotional lability[<481>] in the form of anxious shyness and indecisiveness are characteristic[<944>].

Mercury remains in the blood for only a relatively short period. It is further transported to other compartments of the body[<1232>] with a half-life of approximately 3 days[<121,570, 1232>] or 45 days[<570>] (two compartments). In the brain, the half-life fluctuates between 20 days[<121>] and several years[<1543>].

Excretion is via urea (inorganic Hg) or faeces (organic Hg)[<1543>] with a total body half-life of 58[<121>] to 60 days[<1543>].

The upper normal limit for persons without occupational exposure is 6.5 µg As/L in the blood and 3.0 µg/L in the urine. 100 – 600 mg/g are found in the hair[<1102>]. The BAT values (8 hours' daily exposure) are 25 µg/L in the blood and 100 µg/L in the urea[<1543>]. The most sensitive individuals begin to react from a level of 35 µg/L in the blood and 150 µg/L in urea with non-specific early symptoms. Impaired pre-clinical, neurological and renal function are evident from levels of 20 µg/L and 50 µg/L in the blood and urine, respectively. Concentrations not exceeding 10 µg/L in the blood or urine are non-toxic.

Organic Hg accumulates in the erythrocytes[<570>]. The ratio of the Hg content in the erythrocytes to that in the plasma therefore allow conclusions to be drawn relating to the type of mercury compound. An erythrocyte to plasma concentration quotient > 10 is indicative of organic Hg compounds[<1103>].

DMPS, "the currently most effective chelator of mercury in case of mercury poisoning"[<538a>], is used or recommended as an antidote in both chronic and acute mercury poisoning[<1276>], even in children[<1104>] , or as prophylactic treatment in workers exposed to mercury[<1453>]. "The very early administration of DMPS can influence the prognosis in severe, acute cases of poisoning[<1506>]. It is the drug of choice, except in the USA[<42,1236>]. "Dimaval (DMPS) is nowadays the most effective drug for the treatment of acute or chronic mercury poisoning"[<623a>]. Other complex-forming agents such as EDTA[<27>], DPA[<27,142,1278>] or BAL[<142,702,1278>] trigger more adverse reactions and are less effective. DMPS may also be more effective than DMSA in the treatment of Hg intoxication[<27>]. "DMPS has been considered to be the optimal antidote for inorganic mercury poisoning and DMSA is more effective in organic mercury, but this requires verification"[<702>].

"Early treatment with DMPS is indicated in all cases of mercury poisoning. Treatment should be continued until symptoms disappear or until the mercury concentration in the urine falls to below 20 µg/L"[<1560>]. The treatment of Hg poisoning with DMPS is recommended in the case of severe symptoms or in asymptomatic patients excreting > 200 µg/L in the urine[<227>].

Up to 2,000 mg/day of DMPS (p.o. or i.v.) has proved effective in the acute treatment of mercury poisoning. Normal kidney function is, however, crucial in this respect, controlling the 10- to 100-fold excretion of mercury with the urine[<1278>]. Haemodialysis may also be required in subjects with limited kidney function[<227,1542,1543>]. "Where extracorporeal renal support is required for the management of renal failure, there is some evidence that continuous veno-venous haemofiltration is more effective than haemodialysis at removing DMPS-mercury complexes"[<203b>].

DMPS accelerated mercury excretion via the urine, regardless of the nature and severity of the mercury poisoning[<57,324,478,480,506,740,902,1021,1040,1075,1385>]. The Hg concentration rose markedly after DMPS administration, even when the basal values before treatment were in the normal range despite the presence of clinical symptoms[<1510>]. It generally reached a peak within a few days during the course of treatment. In particular, DMPS mobilises Hg from the kidneys[<744>].

In individual investigations, mercury concentrations were measured in the blood[<92,97,281,809,1318>], serum or plasma[<184,185,1102,627>]. A generally slow reduction in mercury concentrations in the blood was found. In various cases, a unique, transient increase in Hg concentration was found at the start of treatment[<92,974>] or several peaks were observed during the course of treatment[<185,809,872, 1104,1318>]. This "rebound" phenomenon has been attributed to mobilisation (dissolution of mercury from its bindings in the organs) and redistribution of the mercury from the tissues to the blood[<1102>].

The excretion of mercury during DMPS therapy was not continuous but occurred in several phases, which can possibly be attributed to mobilisation of the heavy metal from various

compartments of the body. Increased excretion persisting for approximately 5 days occurs immediately after the start of treatment. This is presumably due to the elimination of Hg from the blood/plasma. A massive increase again occurs after 8 days due to elimination of the heavy metal from the kidneys, as indicated by mercury clearance investigations. A third excretion peak occurs on the 25th to the 27th day[<1102>].

The i.v. administration of DMPS causes a significant decrease in Hg levels in the blood (25 – 30%) in persons with amalgam. This further increases after 2 hours due to redeposition and mostly reverts to the baseline value after 24 hours[<1481>]. Single administration of DMPS did not lower Hg levels in the blood of 4 patients[<1150>].

In the treatment of acute mercury poisoning, other measures (gastric lavage, haemodialysis, peritoneal dialysis, haemodialysis, peritoneal dialysis, haemofiltration, haemoperfusion, plasma exchange and forced diuresis)[<974,1506>] were often used in addition to administration of DMPS. With DMPS therapy, twice the clearance could be achieved with peritoneal dialysis compared to that of BAL therapy. With haemodialysis, the mercury clearance was even 5 to 10 times higher than that observed with BAL[<974>].

In acute, life-threatening poisoning, parenteral administration was generally preferred, where available. Administration of i.v. DMPS was characterised by a more rapid onset of efficacy compared to oral administration. After a single dose, approximately 50% of the total daily dose were already excreted within the first hour, while with oral administration, this lasted several hours[<1281,1283>]. In the course of therapy, however, treatment was generally switched to oral administration because of easier handling. The DMPS dose was slowly reduced during the course of treatment in accordance with excretion and the clinical symptoms.

For chronic mercury poisoning, oral dosage forms are preferred because of the simpler procedure for long-term therapy. The antidote was generally given at a dose of 100 mg t.i.d.[1018], and in small children at 50 mg t.i.d.[<706>]. The longest period of treatment reported with DMPS was 4½ years[<96>]. Occasionally, DMPS treatment was carried out as an interval therapy[<184,1104>]. Some papers describe the parenteral administration of DMPS for chronic Hg poisoning[<92,114>]. DMPS was given over 3 – 7 days at doses of 125 – 400 mg/day. This treatment was then generally repeated several times (interval therapy) with a few DMPS-free days between.

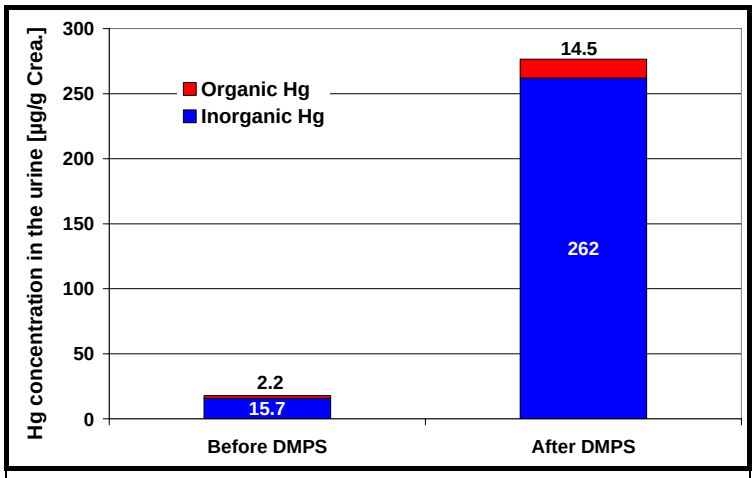
In chronic mercury poisoning in which damage to the nervous system predominated, improvement of the neurasthenic symptoms such as sleep disorders, nervousness, headaches, paresthesia, arthralgia, increased salivation and sweating were reported during DMPS therapy[<92,153,184,185,235,568>]. In children, the clinical symptoms of mercury-induced Feer's disease (acrodynia) was improved with DMPS[<185,1509,1510>]. "Chelation therapy with DMPS can enhance mercury elimination and there are case reports demonstrating that chelation therapy can reverse mercury-induced neurological damage"[<203b>]. Other authors, on the other hand, maintain: "There is a clear evidence that these chelating agents [DMPS and DMSA] are unable to remove mercury within nervous system as well as they did not improve outcome in neurological patients who had been exposed to mercury"[<538a>].

Even without treatment with a chelating agent, slow improvement of clinical symptoms in patients with mild to moderate chronic mercury intoxication was observed once the source of the poisoning had been removed[<114>]. However, without additional therapy[<235>], deterioration of the patient's clinical condition has been describe despite removal of the source of poisoning. The neurological symptoms of poisoning that persisted in patients who received DMPS treatment were less marked than those in patients not given this therapy[<276,279>]. During a two-month observation period, the symptoms in the patients treated with DMPS improved more rapidly than in patients without DMPS treatment[<1620>].

In order to prevent irreversible damage, it is generally important to initiate treatment with adjusted doses of an appropriate chelating agent as early as possible and to carry out laboratory monitoring procedures[<568,1104,1506>]. Delayed onset of treatment cannot prevent a fatal clinical course despite increasing the excretion of mercury as the mercury-induced changes become irreversible[<142>]. Severe neurological disorders can scarcely ever be corrected with treatment[<114,153,568>]. DMPS treatment should, therefore, be started as early as possible after recognition of mercury poisoning and before the onset of serious central nervous damage[<1301>].

7.2.12.1 Mobilisation of mercury

DMPS increases the renal excretion of inorganic and organic mercury as well as mercury vapour. ”Penetration of DMPS into the kidney cells allows mobilization of mercury accumulated in renal tissues. Once chelated with DMPS, mercury is filtered into urine, which represents the most important route of elimination after mobilization. Considerable clinical and experimental evidence suggests that DMPS is capable of removing a substantial amount of mercuric mercury deposited in human tissues”[<538a>]. The excretion of inorganic Hg increased 16-fold and that of organic mercury more than 5-fold following administration of 200 mg oral DMPS to gold miners exposed to mercury vapour in the Philippines[<355,356>].



Renal mercury excretion of 75 gold miners in the Philippines before and 2-3 hours after oral administration of 200 mg DMPS[<355,356>]

The following composition of the single dose of DMPS to various patient groups shows the partly drastic increase in mercury excretion following administration of the chelating agent and thus the efficacy of DMPS in the management of mercury poisoning.

Subjects		Hg excretion				Type of mobilisation test			Literature
n	Patients	Before DMPS	After DMPS	Unit	In-crease	DMPS dose	Admin-istration of DMPS	Collec-tion period	
46	Controls	0.8	3.6	µg/24 h	4.5	4 mg/kg BW	Oral	24 h	1472
20	Controls	0.63	1.84	µg/24 h	2.9	4 mg/kg BW	Oral	24 h	985
36	Dentists and assistants	13.2	97.1	µg/24 h	7.4	4 mg/kg BW	Oral	24 h	1472
12	Dentists and assistants	9.57	73.5	µg/24 h	7.7	4 mg/kg BW	Oral	24 h	985
6	Occupational exposure	144.5	1736	µg/24 h	12.0	4 mg/kg BW	Oral	24 h	274
9	Occupational exposure	58.5	730	µg/24 h	12.5	4 mg/kg BW	Oral	24 h	274
36	Workers in alkali metal chloride plants	129	1319	µg/24 h	10.2	4 mg/kg BW	Oral	24 h	1472
43	Workers in alkali metal chloride plants	94.6	841	µg/24 h	8.9	4 mg/kg BW	Oral	24 h	985
24	Workers in alkali metal chloride plants	20.5	751.9	µg/g crea	36.7	4 mg/kg BW	Oral	24 h	1470
24	Workers in alkali metal chloride plants	43.2	557	µg/g crea	12.9	4 mg/kg BW	Oral	24 h	1471
8	Users of Hg cream	737	4074	µg/g crea	5.5	200 mg	Oral	24 h	463
75	Gold miners	37.5	909	µg/g crea	24.2	200 mg	Oral	2-3 h	355
60	Gold miners	51.4	1049	µg/g crea	20.4	200 mg	Oral	4 h	199
35	People living near a Hg-contaminated river	8	74.9	µg/g crea	9.4	200 mg	Oral	4 h	199
2.223	Patients	1.7	47	µg/g crea	27.6	200 mg with BW<60, 300 mg with BW 60-80, 400 mg with BW > 80 kg	oral	4 h	559
36	Normal subjects	2.8	4.9	µmol/mol crea	1.8	300 mg	oral	3 h	951
18	Occupational exposure	25.7	463.4	µmol/mol crea	18.0	300 mg	oral	3 h	951
31	Normal subjects	1.52	66.1	µg/g crea	43.5	300 mg	oral	3-4 h	981
31	After amalgam removal and clearance	1.35	26.3	µg/g crea	19.5	300 mg	oral	3-4 h	981
11	Occupational exposure (Skin Lotion maker)	333	4,282	µg/L	12.9	300 mg	oral	6 h	501,890

Subjects		Hg excretion				Type of mobilisation test			Literature
n	Patients	Before DMPS	After DMPS	Unit	In-crease	Dose of DMPS	Admin-istration of DMPS	Collec-tion period	
8	Skin Lotion User	63.5	2,051	µg/L	32.3	300 mg	oral	6 h	890
9	Without amalgam	1.32	22.2	µg/L	16.8	300 mg	oral	6 h	890
13	Normal subjects	3	37.2	µg/L	12.4	300 mg	oral	6 h	502
10	Dental assistants	29.7	481	µg/L	16.2	300 mg	oral	6 h	502
15	Dental assistants	1.07	8.1	µg/L	7.6	300 mg	oral	6 h	377
5	Dentists	19.8	275	µg/L	13.9	300 mg	oral	6 h	57,502
34	Dentists	0.89	10.08	µg/L	11.3	300 mg	oral	6 h	377
10	Dental technicians	29.7	481	µg/L	16.2	300 mg	oral	6 h	57
11	Manufacturer of cream containing Hg	113	5037	µg/6 h	44.6	300 mg	oral	6 h	54,57
8	User of Hg cream	16.2	1410	µg/6 h	87.0	300 mg	oral	6 h	54,57
8	Normal subjects	0.49	18.4	µg/6 h	37.6	300 mg	oral	6 h	54,57
10	With amalgam	0.7	17.16	µg/9 h	24.5	300 mg	oral	9 h	54,57,60
10	Without amalgam	0.27	5,1	µg/9 h	18.9	300 mg	oral	9 h	54,57,60
7	Previous occupational exposure to Hg	4.3	34	µg/24 h	7.9	300 mg	oral	24 h	1251
36	Without amalgam	1.1	3.9	µg/24 h	3.5	300 mg	oral	24 h	729
7	Without amalgam	0.3	2.6	µg/24 h	8.7	300 mg	oral	24 h	580,581
8	Without amalgam	0.2	1.3	µg/24 h	6.5	300 mg	oral	24 h	1603,1604
191	With amalgam	2.6	19.5	µg/24 h	7.5	300 mg	oral	24 h	729
21	With amalgam	0.7	4.9	µg/24 h	7.0	300 mg	oral	24 h	1604
9	2-5 amalgam fillings	0.6	3.75	µg/24 h	6.3	300 mg	oral	24 h	1603
12	6-14 amalgam fillings	1.16	9.64	µg/24 h	8.3	300 mg	oral	24 h	1603
30	Normal subjects	1.47	10.55	µg/24 h	7.2	300 mg	oral	24 h	1273
22	Dentists	1.5	13.2	µg/24 h	8.8	300 mg	oral	24 h	1604
42	Dental assistants	2.8	28.1	µg/24 h	10.0	300 mg	oral	24 h	1604
4	Other employees	0.9	19.1	µg/24 h	21.2	300 mg	oral	24 h	1604
2	Occupational exposure	138	1725	µg/L	12.5	300 mg	oral	24 h	104
172	Normal subjects	0.94	3.65	µg/L	3.9	300 mg	oral	24 h	1390
19/14	With amalgam	1.52	9.95	µg/L	6.5	300 mg	oral	24 h	914
27	Patients with “amalgam sickness“	0.65	4.26	µg/L	6.6	300 mg	oral	24 h	754
27	“Amalgam healthy“ subjects	0.77	5.71	µg/L	7.4	300 mg	oral	24 h	754
10	4 weeks conventional amalgam	0.95	4.94	µg/L	5.2	300 mg	oral	24 h	1632
10	4 weeks non-γ2 amalgam	0.6	3.69	µg/L	6.2	300 mg	oral	24 h	1632
10	Without amalgam for a long period	0.44	1.31	µg/L	3.0	300 mg	oral	24 h	914
20	Without amalgam	0.36	1.67	µg/L	4.6	300 mg	oral	24 h	1632
10	Without amalgam	0.46	1.53	µg/L	3.3	300 mg	oral	24 h	914
27	Without amalgam	0.19	0.89	µg/L	4.7	300 mg	oral	24 h	754
19	Without amalgam	0.5	2.2	µg/g crea-µg/d	4.4	300 mg	oral	24 h	1273
50	With amalgam	1.4	10	µg/g crea-µg/d	7.1	300 mg	oral	24 h	589,1273
25	Occupational exposure	6.4	134.2	µg/g crea-µg/d	21.0	300 mg	oral	24 h	1273,1281
59	Subjects with subjective amalgam symptoms	1.7	6.1	µg/g crea	3.6	300 mg	oral	24 h	1311
59	Subjects without subjective amalgam symptoms	1.5	5.9	µg/g crea	3.9	300 mg	oral	24 h	1311
51	Dentistry students before phantom course	0.76	9.95	µg/g crea	13.1	300 mg	oral	24 h	1557
51	Dentistry students after phantom course	1.02	10.77	µg/g crea	10.6	300 mg	oral	24 h	1557
28	Persons with amalgam fillings	1.5	12.5	µg/g crea	8.3	300 mg	oral	24 h	241
38	Persons with amalgam fillings	2.7	20.9	µg/g crea	7.7	300 mg	oral	24 h	241
6	Persons with amalgam fillings in the past	0.6	2.6	µg/g crea	4.3	300 mg	oral	24 h	241

Subjects		Hg excretion				Type of mobilisation test			Literature
n	Patients	Before DMPS	After DMPS	Unit	In-crease	Dose of DMPS	Admin-istration of DMPS	Collec-tion period	
4	Persons with amalgam fillings in the past	0.9	7.9	µg/g crea	8.8	300 mg	oral	24 h	241
5	Occupational exposure	1.2	6.8	µg/24 h	5.7	300 mg	oral	24 h	1274
2	Dental assistants	1.6	22.6	µg/24 h	14.1	300 mg	oral	24 h	192
1	Dentist with amalgam	0.9	12.2	µg/24 h	13.6	300 mg	oral	24 h	192
21	6-17 amalgam fillings	2.1	19.87	µg/24 h	9.5	300 mg	oral	24 h	588
18	With amalgam	1.5	10.3	µg/24 h	6.9	300mg	oral	24 h	1283
3	With amalgam	1.3	8.2	µg/24 h	6.3	300 mg	oral	24 h	192
51	With amalgam	1.11	12.13	µg/24 h	10.9	300 mg	oral	24 h	588
15	Without amalgam	0.68	7.29	µg/24 h	10.7	300 mg	oral	24 h	588
12	Without amalgam	0.7	1.2	µg/24 h	1.7	300 mg	oral	24 h	839
71	Normal subjects	1.25	21.8	µg/g crea	17.4	300 mg	oral	?	89
20	Normal subjects	5.05	11.88	µg/L	2.4	10 mg/kg BW	oral	2h	587
102	Women with several miscarriages	5.4	94.25	µg/g crea	17.5	10 mg/kg BW	oral	2 h	470
31	Normal subjects (F)	1.5	77	µg/g crea	51.3	10 mg/kg BW	oral	2 h	474
75	Normal subjects (F)	1.4	68	µg/g crea	48.6	10 mg/kg BW	oral	2 h	474
501	Normal subjects (F)	2.4	109	µg/g crea	45.4	10 mg/kg BW	oral	2h	471,480
490	Normal subjects	2.4	109	µg/g crea	45.4	10 mg/kg BW	oral	2 h	479,480
7	Occupational exposure to phenyl-HgCl	66	1868	µg/24 h	28.3	250 mg	i.m.	24h	497
5	Normal subjects	11	18	µg/24 h	1.6	250 mg	i.m.	24h	497
21	Without amalgam	1.4	2.8	µg/g crea	2.0	2 mg/kg BW	i.v.	30 min	1482
21	Healthy with amalgam	4.8	10.8	µg/g crea	2.3	2 mg/kg BW	i.v.	30 min	1481,1482
20	Ill with amalgam	3.8	9.8	µg/g crea	2.6	2 mg/kg BW	i.v.	30 min	1481,1482
20	Amalgam removed 1-8 years ago	1.9	3.3	µg/g crea	1.7	2 mg/kg BW	i.v.	30 min	1481,1482
6	Patients with HELLP	1.83	383.7	µg/L	209.7	3 mg/kg BW	i.v.	30-45 min	563
?	Patients	0.5	25.4	µg/L	50.8	3 mg/kg BW	i.v.	30-45 min	563
80	“Amalgam sickness“	5.14	314.3	µg/L	61.1	3 mg/kg BW	i.v.	3 h	489
10	Amalgam patients who have undergone cleaning and clearance	1.4	10.7	µg/L	7.6	3 mg/kg BW	i.v.	3 h	489
10	Without amalgam	1.8	39.1	µg/L	21.7	3 mg/kg BW	i.v.	3 h	489
10	Dental staff	10.2	330	µg/L	32.4	3 mg/kg BW	i.v.	3 h	489
9	Dental assistants	13	516	Nmol/L	39.7	250 mg	i.v.	30 min	1392
23	Amalgam patients	12	888	Nmol/L	74.0	250 mg	i.v.	30 min	1392
11	Amalgam removed	7	206	Nmol/L	29.4	250 mg	i.v.	30 min	1392
5	Amalgam patients	19.6	420.5	µg/L	21.5	250 mg	i.v.	45 min	143
82	Normal subjects (F)	1.4	96.4	µg/L	68.9	250 mg	i.v.	45 min	460
38	Neurodermatitis	4.4	41.5	µg/g crea	9.4	250 mg	i.v.	45 min	637-639
15	Psoriasis	2.5	46	µg/g crea	18.4	250 mg	i.v.	45 min	637-639
11	Normal subjects	1.6	10.1	µg/g crea	6.3	250 mg	i.v.	45 min	639
261	Normal subjects (F)	2.9	183	µg/g crea	63.1	250 mg	i.v.	45 min	472
148	Female patients	1.7	130.8	µg/g crea	76.9	250 mg	i.v.	45 min	223
150	Patients	<5	347	µg/g crea	69.0	250 mg	i.v.	90-120 miin	488
15	Amalgam patient	13	114	Nmol/L	8.8	250 mg	i.v.	24 h	1392
83	Normal subjects	1.25	267	µg/g crea	213.6	250 mg	i.v.	?	89
47	Persons with amalgam fillings	1.08	29	nmol/µmol crea	26.9	300 mg	i.v.	30 min	1391
162	Without amalgam	1.28	111	nmol/µmol crea	86.7	300 mg	i.v.	30 min	1391
57	Children	1.75	109	µg/L	62.3	3 or 10 mg/kg BW	i.v. or oral	45 min or 2 h	1572

Subjects		Hg excretion				Type of mobilisation test			Literature
n	Patients	Before DMPS	After DMPS	Unit	In-crease	Dose of DMPS	Admin-istration of DMPS	Collec-tion period	
34	Mothers	2.5	112	µg/L	44.8	3 or 10 mg/kg BW	i.v. or oral	45 min or 2 h	1572

Increase in mercury excretion in the urine following single administration of DMPS in various patients or control groups

Conclusion:
The list shows that DMPS increases the excretion of mercury in the urine. It also shows that there is no generally fixed DMPS test for mercury. Instead, many different techniques are used, which differ depending on the dose, method of administration of DMPS, the urine collection period and the measuring units used.

7.2.12.2 Inorganic mercury compounds

Acute poisoning with inorganic mercury primarily affects the kidneys (nephrotoxicity)<2,142,1104,1599>. An accumulation of Hg in the kidneys leads to impaired kidney function with sublimate nephrosis and anuria<435,990,1294,1354>. Furthermore, oral ingestion of inorganic mercury compounds can cause corrosive damage (ulcerations, perforations and haemorrhaging) in the gastrointestinal tract<142,280, 493>. Mercury-induced inhibition of peristalsis can further potentiate the local toxic effects<990>.

DMPS is the drug of choice for inorganic mercury<29,30>. "The water-soluble sodium salt of 2,3-dimercapto-1-propane sulfonic acid (acronym DMPS) has been considered by the World Health Organization Expert committee as the first-line drug for ascertained inorganic mercury acute and chronic poisoning"<538a>. "DMPS is the drug of choice for the clinical treatment of inorganic mercury poisoning because not only is it well tolerated and can be administered orally, but it is also highly potent"<642>. "Severe sublimate poisoning with renal tubular damage is a fatal condition, but this prognosis can be considerably improved by therapeutic measures. In acute poisoning, DMPS will efficiently mobilize mercury from the kidney and reduce biological half-life for mercury. … The experimental evidence is that the damaged tubules can regenerate to a considerable extent. In cases of acrodynia or pink disease, DMPS or DMSA should be used for mobilization of mercury from the body"<163>.

7.2.12.2.1 Acute poisoning

Normally fatal mercury intoxication could often be managed by rapid, high-dose DMPS therapy (initially i.v., then oral) and intensive medical care. The clinical symptoms followed a relatively mild course. In some cases of acute mercury poisoning, no symptoms of intoxication appeared<760,809> following DMPS therapy despite the initially extremely high mercury concentrations in the blood (up to 2.4 mg/L). An intermediate rise in mercury levels in the serum may occur as a result of mobilisation from deposits<167>. Treatment is continued until Hg (blood) is < 100 µg/L and Hg (urine) < 300 µg/L<932>

A 38 year-old teacher drank 100 ml of a mercury chloride solution of unknown concentration. Nausea, blood-stained faeces and blood-stained vomiting occurred. After admission to hospital and gastric lavage, active charcoal was given and a single dose of BAL was injected. Tubular necroses and oliguria developed.

8 hours Transfer of the patient to a specialised hospital. The urine output was less than 10 ml/h. The mercury concentration in the blood was 14,300 µg/L (!). A concentration of more than 220 µg/L is normally considered to be fatal. Hypovolaemic shock developed, which was controlled by administration of plasma expanders.

10 hours Administration of 250 mg DMPS in 0.9% physiological saline solution i.v. every 4 hours for 48 hours.

12 hours	Haemodialysis was initiated because of total kidney failure with anuria while continuing high-dose DMPS therapy. The biological half-life of the mercury was 2.5 days (normally 40 – 60 days). No Hg(II) could be detected in the dialysate (Cl_{HD} < 1 mL/min). The heavy metal was excreted via the bile and intestines.
2nd day	Gastrointestinal endoscopy showed massive ulcerative changes. The pH of the stomach was adjusted to ≥ with drugs.
3rd day	Blood transfusion because of the anaemia induced by the loss of blood. Administration of i.v. DMPS every 6 hours for 48 hours.
5th day	Administration of i.v. DMPS every 8 hours.
6th day	The mercury level in the blood was still above 2,000 µg/L. The kidneys were, nevertheless, functioning again and the mercury was excreted renally. Haemodialysis was stopped. The biological half-life of mercury was 8.1 days.
21st day	The mercury concentration in the blood was 700 µgL.
4th week	Switch to oral administration of DMPS (300 mg t.i.d.) without deterioration of mercury excretion.
6th week	Healing of the ulceration in the upper gastrointestinal tract.
7th week	Completion of the DMPS therapy. Mercury concentration in the blood < 100 µg/L, and in the urine < 300 µg/L. Copper and zinc levels in the serum were not affected by the DMPS therapy.
6 months	Complete recovery of the patient; no recurrent rise in mercury values in the blood or urine[<1443>].

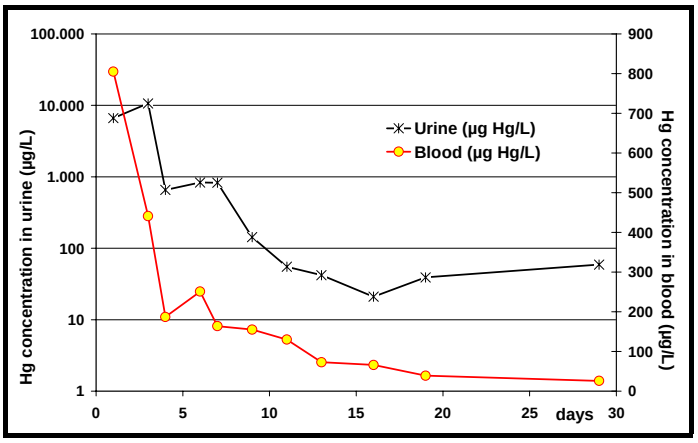
A 40 year-old man ingested approximately 1 g $HgSO_4$ with suicidal intent. Thanks to immediate intensive therapy, the man survived a normally fatal dose:

2 hours	Admission to the emergency department with haematemesis and increasing confusion.
2.5 hours	Intubation and ventilation, Hg (blood): 15,580 µg/L
4.5 hours	Onset of DMPS therapy with 250 mg i.v. every 4 hours, moved to intensive care unit.
7 hours	Start of continuous haemodiafiltration. Overall, 127 mg Hg was excreted in the dialysate.
12 hours	Anuria
27.5 hours	Hg (blood): 3,370 µg/L
4th day	Development of an erythematous maculopapular rash on the lower legs. DMPS therapy could be continued after reducing the dose (250 mg i.v. DMPS every 8 hours).
8th day	Extubation
9th day	Treatment of gastritis and two gastric ulcers
10th day	Treatment switched to 200 mg oral DMPS every 12 hours.
11th day	Urine excretion reinstated, however oliguria persisted until day 43
14th day	Haemodiafiltration adjustment, switch to normal ward
19th day	Completion of the DMPS therapy.
50th day	Discharged as asymptomatic patient, Hg (blood): 32 µg/L
5 months	Hg (blood): 5 µg/L, Hg (urine): 7 µg/L, normal creatinine clearance[<299>].

Nausea and abdominal pain developed one hour after ingestion of inorganic mercury salt in a 48 year-old man. Kidney failure occurred within 24 hours. Initial haemodialysis after previous administration of BAL lowered Hg levels in the whole blood from 5,200 to 3,800 µg/L within 5 hours. Treatment was switched to i.v. DMPS due to BAL intolerance (4x250 mg/d for 7 days, 250 mg t.i.d. for 1 day, 2x250 mg/d for 12 days and 1x250 mg/d for 7 days). As haemodialysis no longer had any effect under these conditions, treatment was switched to haemofiltration(CVVH). Several plasma exchange treatments were also carried out. A mercury concentration of 15,300 µg/L was recorded in the bile fluid on the 4th day. Urine excretion was reinstated on the 10th day. The patient survived the normally fatal intoxication[<1112>]. The authors attribute the poor efficacy of haemodialysis to the large molecular volume of the DMPS-Hg complex, its load and form[<1112>]. A relatively solid hydrate sheath can also play a role. According to the information supplied by the device manufacturer, this problem is also known to occur with phosphates. The membrane used in haemodialysis had 6 times smaller pores than that used for haemofiltration, hence it was complex-permeable.

A 42 year-old Chemistry teacher with severe acute mercury poisoning (1 g $HgCl_2$) was given a total of 2 g i.v. DMPS on the first day, in 8 divided doses. The daily dose was reduced to 1.5 g DMPS i.v. administered in 6 divided doses over the next two days. Given the short-term unavailability of parenteral DMPS, treatment with 0.8 g DMPS/day was administered for two days. This was followed by 9 days' treatment with 0.75 g/day i.v. and 19 days' treatment with 0.1 g oral DMPS/day. In addition, haemodialysis, haemoperfusion and plasma exchange were carried out. The patient was saved. Despite a mercury concentration of 600 µg/L in the blood, kidney function was not adversely affected<98>.

A 19 year-old Chemistry student drank 29 g of mercury nitrate with suicidal intent. After 1½ hours, BAL was administered whereupon acute tubular necroses developed and the patient became hypotensive. High doses of DMPS (i.v.) were then given along with haemodialysis, haemofiltration and plasma exchange. The patient survived acute poisoning (mercury concentration in the blood was initially 12,000 µg/L), which normally would have been fatal within a few hours because of multiple organ failure. "We suggest DMPS should be available worldwide for such cases"<98>.



Hg concentrations in the blood and urine following DMPS therapy administered after ingestion of $HgCl_2$ <290>

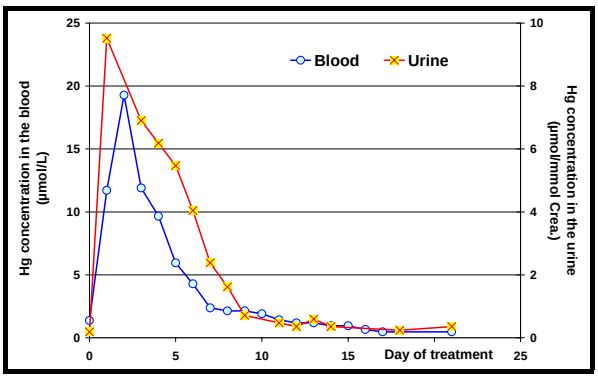
One hour after ingestion of 1 g mercuric chloride (suicide attempt, fatal dose in adults: 200 – 400 mg), a 19 year-old female patient exhibited nausea, retching and difficulties in swallowing (Hg in the blood 805 µg/L, Hg in the urine 6,625 µg/L). Haemodialysis, forced diuresis and DMPS therapy (300 mg initially, 300 mg/day orally for approximately 1 month) were started immediately. The mercury levels in the blood and urine fell continuously. No Hg-typical symptoms were observed during the patient's hospital stay. Strict kidney function diagnosis remained normal. Despite several weeks' treatment with DMPS, serum concentrations of copper, zinc and iron remained within the reference range such that there was no need for substitution<166,290>.

Mercury clearance with DMPS:
Peritoneal dialysis: 0.39 - 0.45 mL/min
Haemodialysis: 3.5 - 5 mL/min

Mercury clearance with BAL:
Peritoneal dialysis: 0.172 mL/min
Haemodialysis: 0.6 mL/min

A 19 year-old female was admitted to hospital about ½ hour after an attempted suicide (3 g mercuric chloride, lethal dose: 200 - 400 mg) with vomiting. Gastric lavage was carried out immediately. Complete anuria developed 1 hour later, so that peritoneal dialysis had to be started. In addition, haemodialysis was carried out. DMPS was also administered (up to 1,800 mg orally or 400 mg i.v.). Treatment with BAL was also attempted in-between. After 10 days, urine excretion restarted and after 20 days, there was a polyric phase. 100 days after intoxication, creatinine clearance had reverted to normal<974>.

In a 53 year-old man who had taken 50 g mercuric iodide (HgJ_2) with suicidal intent, DMPS treatment was started eight hours after taking the poison (blood 1,197 nmol Hg/L, urine 159 nmol/mmol creatinine). Initially, 250 mg i.v. DMPS were administered every four hours for 60 hours. NaCl and dextrose solution were also administered. Thereafter, treatment was continued orally for 18 days. A largely complication-free clinical course was achieved with this "aggressive" DMPS therapy. In particular, no signs of renal damage were observed<36,418>.



Hg levels in the blood and urine during DMPS therapy after poisoning with HgJ_2<36>

A 36 year-old patient presented with a serum

concentration of 11,153 µg Hg/L following ingestion of $HgCl_2$ with suicidal intent. Acute kidney failure developed 30 minutes after his admission to hospital. The serum level constantly fell with dialysis treatment and the administration of DMPS (oral and i.v.) and D-penicillamine. Urine production had reverted to normal one month later[<308>].

A 17 year-old patient was saved with DMPS after ingesting 10 g of inorganic mercury despite 10 days' acute renal failure[<95>].

A patient with acute sublimate poisoning was initially treated with 1.2 g DMPS/day for six days, administered in twelve divided doses. Treatment was then switched to oral DMPS at the dose level of 2.4 g/day, administered in twelve divided doses, for 38 days. Treatment was without complications[<586>].

Day	1:	6 x 5 mg DMPS/kg BW i.v.
Days	2 - 3:	4 x 5 mg DMPS/kg BW i.v.
Days	4 - 9:	2 x 2.5 mg DMPS/kg BW i.v.
Days	10 -15:	2 x 2.5 mg DMPS/kg oral

Similarly, in small children, rapid DMPS therapy was able to prevent damage induced by acute mercury poisoning. A one year-old boy vomited twice after ingestion of an inorganic mercury(II) compound. Gastric lavage was carried out and active charcoal and sodium sulfate were administered one hour after ingestion of the poison. The mercury level in the blood was 400 µg/L and in the urine, 2,500 µg/L. DMPS was administered as a short-term infusion. On the 4th day of treatment, the child developed motor restlessness and on the 15th day, transient exanthema. Otherwise, the child did not show any notable changes and even the laboratory parameters remained within the normal range. The mercury levels in the blood and urine fell continuously and measured 13 µg/L and 55 µg/L, respectively, after 11 days[<697>].

In another one year-old child, vomiting and cyanosis developed 30 minutes after swallowing an ointment containing 0.5 g inorganic mercury. He was admitted to hospital one hour later. Mercury levels of 368 and 8,260 µg/L were recorded in the blood and urine, respectively. Oral treatment with DMPS was introduced (initially 15 mg/kg BW, followed by 2 x 2.5 mg/kg BW/day). After four days, the levels had fallen to 107 in the blood and 195 µg/L in the urine. After seven days, 38 µg/L was still recorded in the blood and 27 µg/L in the urine. No typical symptoms of acute mercury poisoning appeared. No shifts in the electrolyte balance and no treatment-related adverse reactions were observed[<1564>].

In some cases of acute mercury poisoning, a fatal outcome could not be prevented despite all of the therapeutic efforts[<95,338,586>]. In one case, there was massive intraperitoneal poisoning through abdominal irrigation with mercury oxycyanide. About twelve hours after the irrigation, the female patient already presented with marked symptoms of shock and considerable heavy-metal induced peritonitis. Extensive measures to remove the poison were initiated. While the mercury blood level could be reduced within twenty days from 2.4 mg/L to 0.2 mg/L, the development of intestinal necroses, progressive intestinal disintegration and putrefaction of the abdominal cavity could no longer be prevented[<586>]. Another patient died 48 hours after instillation of $HgCl_2$ on surgical treatment of colonic carcinoma with acute kidney failure (blood mercury level: 560 µg/L)[<95>]. In a further case, symptoms of shock, anuria, blood coagulation disorders and cardiac arrest were already present after intravenously sublimate and initial dimercaprol treatment and dialysis before starting DMPS therapy, initially via the oral route and then i.v., one day after ingestion of the poison. Although Hg levels in the blood consequently fell rapidly, the patient died on the 3rd day after sublimate injection[<338>].

The treatment of acute mercury poisoning by oral administration of DMPS has been described many times[<272,760,809,872,1564,1610>]. In most cases, other measures to accelerate the elimination of the poison were carried out simultaneously with the antidote therapy. The DMPS dosing schedules and duration of treatment varied considerably.

Because the parenteral form of DMPS was temporarily not available, another case of severe sublimate poisoning was treated orally with DMPS (1.2 g/d for 2 days, in twelve divided doses, followed by 0.4 g/d for 2 days). After three days' attempted therapy with BAL, 4 x 0.1 g DMPS was administered parenterally for 16 days. Subsequently, the patient was treated for a further 77 days with oral DMPS[<974>].

In a 20 year-old female patient already presenting with anuria following ingestion of $HgCl_2$ with suicidal intent, the mercury level in the blood was 950 µg/L. This did, however, revert to normal following administration of 100 mg DMPS t.i.d. in conjunction with haemoperfusion, haemofiltration and haemodialysis. Diuresis was reinstated after 43 days and after 77 days, the patient was discharged from hospital. DMPS therapy was continued on an outpatient basis<1318>.

A swab saturated with Stievers solution (containing 5% $HgCl_2$) was used to stem the flow of blood in a 2 year-old boy during surgery. The error was noticed after 5 minutes and the swab removed. Nevertheless, Hg levels in the blood had risen to 156 µg/L after 30 – 60 minutes. Hg levels reverted to normal with oral DMPS therapy and clinical symptoms regressed within 24 hours<1407>.

Conclusion:
DMPS is the antidote of choice on acute poisoning. In numerous case histories, its efficacy is also documented in children. It is, however important, to initiate therapy as early as possible.

7.2.12.2.2 Subacute and chronic poisoning

In the presence of symptoms and measurably high levels (even below 50 µg/L), several weeks' DMPS therapy is indicated until symptoms disappear and urine levels fall to below 20 µg/L. DMPS is administered at the daily dose level of 2 x 2 mg/kg. The mercury deposit in the brain is only slightly emptied by DMPS, if at all<1110>. The mercury-induced reduction in the hormone function of the adrenal cortex increased again during DMPS therapy<1427>.

Over 3 months, chronic mercury poisoning can lead to massive peripheral neuropathies, which even persist for up to two years after exposure had ended. Mercury levels in the blood and urine, however, are within the normal range.

May 1995 A schizophrenic man took a herbal remedy containing mercury sulfate amongst other things (Hg 10.000 ppm, Pb 116 ppm, As 18.9 ppm, Cd 0.97 ppm) for over 3 months because of hallucinations. After three months,

in August 1995, he presented with weight loss, numbness in the arms and legs, general weakness and muscle weakness. Lead poisoning was ruled out. The mercury values were not determined. The symptoms deteriorated over the next 3 months despite the fact that plasma pheresis was carried out on two occasions. In

January 1996, 6 months after exposure was stopped, the following mercury values were recorded: blood 9.9 µg/L, urine 5.4 µg/L, hair on the head 14.2 µg/g (reference < 5.5 µg/g), pubic hair 9.1 µg/g (reference 1.6 µg/g). A nerve biopsy confirmed nerve damage.

Two years later, only a marginal improvement was observed. The patient could not lift his arm or extremities, or move his body<271>. Stopping the source of the exposure without adding DMS therapy was obviously inadequate.

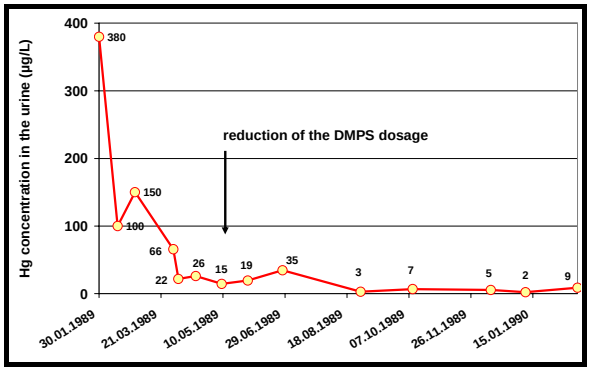
	Whole blood (µg/L)	Urine (µg/L)
At the start of treatment	76	84
After 10 days	25	65
After 26 days		5,3

Mercury levels in the whole blood and urine during DMPS therapy<1544>

Through treatment with an inadvertently excessively high dosed homeopathic mercury preparation (3 x 206 mg HgJ_2 daily), the 4-year history of psoriasis in a 68 year-old female patient deteriorated. The heavy metal probably acted as a trigger. The mercury level in the blood was 76 µg/L and in the urine, 84 µg/L. 100 mg DMPS t.i.d. was prescribed for detoxification. The chelating agent increased renal excretion by a factor of ten. This produced rapid excretion of the heavy metal associated with a continual improvement of the skin findings<1544>.

A one year-old girl developed diarrhoea and transient proteinuria after swallowing a button-shaped mercury battery (HgO). The mercury level in the serum after 7 days was 120 µg/L. With DMPS therapy (over 5 days), the urine level rose to 590 µg/L on the second day of treatment. After treatment, the serum level fell to 16 µg/L<586>. Two further children were also treated with DMPS after swallowing batteries<95>.

Psoriasis, which had been known to exist since childhood, was treated externally by a 59 year-old man for 40 years with a mercury-containing mixture (8 g Hg/100 g ointment) (≈ 100 g ointment/ year). A raised mercury level was found in the blood. Daily treatment with oral DMPS was started and after 4 months, the dose was reduced to 100 mg DMPS weekly and continued for a further 8 months. Tachyarrhythmia, which had developed before DMPS treatment, remained[<306>].

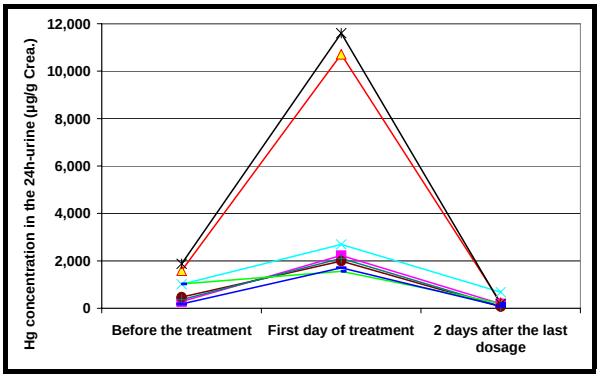


Urinary excretion of Hg during DMPS therapy[<306>]

After 4 years' use of a cosmetic bleaching cream containing mercury, the finger nails of a 56 year-old female patient turned greenish black. The toe nails were unaffected. In addition, she had difficulties in sleeping through the night, nervousness and marked nocturnal sweating. Normal findings were obtained on neurological investigations such as handwriting tests. With DMPs, the mercury level in the serum fell within 2 weeks from 64 to 15 µg/L. The mercury excretion in the urine rose and reached a peak of 1,660 µg/L on the 10th day of treatment. On completing the treatment, the mercury level in the serum rose again, probably due to the release of mercury from the facial skin so that a second series of treatment lasting three weeks was necessary. On this occasion, the peak mercury excretion in the urine was 3,724 µg/day, thereafter falling to 88 µg/day. Dimaval was well tolerated by the patient. The dyschromia of the nails disappeared as the nails grew[<184>].

A 21 year-old man treated extensive eczema for three weeks with an ointment containing 10% mercury(II) amide chloride. He developed massive neurological (including polyneuropathy, depression, tremor and sleep disorders) and renal (including nephritic syndrome, proteinuria, reduced glomerular filtration rate GFR) symptoms. Hypertension was also diagnosed. This was treated by atenolol and ramipril. Type I diabetes, which had existed prior to poisoning, was difficult to control. The dose of insulin had to be more than doubled. 252 µg Hg/L were recorded in the urine. Dimaval treatment was administered for 12 days. No adverse reactions were observed. The mercury level in the urine thus rose to a peak of 2.10 mg/L. Clinical improvement was observed 3 months later. Polyneuropathy could no longer be detected. Proteinuria, which was originally 53 g/L (11.1 g/24 h) fell to 2.3 g/day after 4 months and to 0.62 g/24 h after one year. The GFR continued to rise. The dose of insulin could be further reduced, atenolol discontinued and ramipril reduced. The 20 kg lost at the beginning of the poisoning was regained[<1126,1250>].

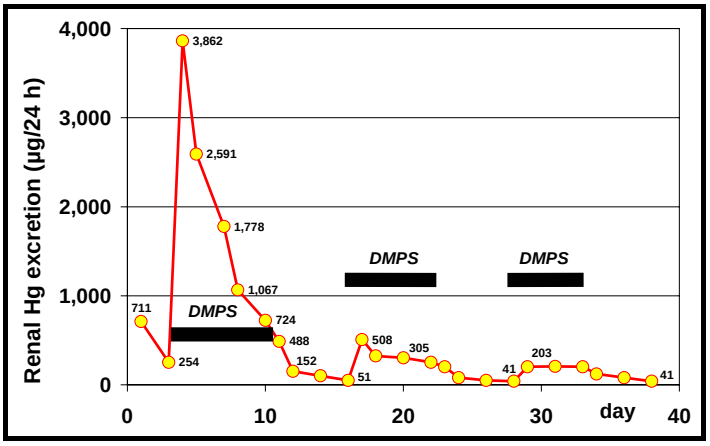
High values were recorded in the 24-hour urine of 8 women who had used a face cream containing calomel for up to 10 years. Six of the women were asymptomatic while two suffered from exanthema and tremor. The women were treated with oral DMPS (200 mg/day) for 5 days. Hg excretion in the urine sometimes increased dramatically and, on completion of treatment, was below the baseline values in all subjects. The exanthema disappeared in both women and tremor in one. Tremor persisted in the other patient[<463>].



Hg concentrations in 24-hour urine in users of calomel-containing face cream[<463>]

A 13 month-old girl developed diarrhoea three days after inadvertently swallowing a button-shaped battery containing HgO. When half the battery and the mercury were found in the faeces on the 7th day, the child was admitted to hospital where the other half of the battery was found in the colon. Transient proteinuria developed. The Hg level in the serum was 120 µg/L. Oral DMPS therapy of 5 days' duration was started on the 9th day. The mercury level in the urine peaked at 590 µg/L (day 11). The level in the serum had fallen to 16 µg/L on the 17th day[<1438>].

After 3 months' treatment with a cream containing mercury (27% Hg), a 4 year-old child from Iraq was admitted to hospital with hypertension, tachycardia, weakness, insomnia, irritability and seizures with evidence of toxic encephalopathy. The symptoms improved during treatment with antihypertensives and Dimaval[<834>].



Average Hg excretion in workers exposed to Hg_2Cl_2 during interval therapy with Dimaval[<501>]

Eight workers (5 men and 3 women) in a cosmetic plant with occupational exposure to Hg_2Cl_2 showed a 44-fold increase in mercury excretion in the urine in an oral DMPS test. This shows that DMPS therapy can reduce the body load. Interval therapy with Dimaval (400 mg/day) was, therefore, carried out. At the start of each of the three treatment cycles, mercury excretion in the urine increased, falling slowly once again over the next few days[<501>]. This shows that, on the treatment-free days, mercury was redistributed from deposits that could not be mobilised and was thus accessible to DMPS in the next treatment cycle.

Fifty-six patients suffered mercury poisoning after dermal use of an ointment containing mercury (Hg in blood up to 800 µg/L; gastrointestinal disorders, nephropathies, hepatopathies, fever and dermatitis) and were treated with DMPS. Haemoperfusion was also carried out in extreme cases of poisoning. Early onset of treatment prevented more serious complications[<768>].

Conclusion:
DMPS increases the renal excretion of heavy metal on chronic poisoning with inorganic mercury, even in children. The symptoms improve when treatment is introduced punctually. If treatment is initiated too late, then the symptoms may already be partially irrreversible.

7.2.12.3 Organic mercury compounds

Short-chain organic mercury compounds ($R\text{-}Hg^+$, R-Hg-R) can be extensively distributed in the body due to their lipophilic nature. They primarily affect the haematopoietic and nervous systems (Minamata disease and central nervous disorders)[<22,1294,1599>]. Foetotoxic effects are confirmed[<22,281,966,1104>].

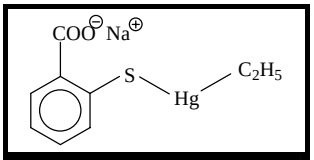
Long-chain and aromatic organic mercury compounds tend to be dealkylised after absorption[<142,280,493,1030>] and subsequently accumulate as inorganic mercury in the kidneys[<1599>]. In the normal population, the mean blood mercury level is 1.7 µg/L, and daily intake 2 µg/L[<602a>].

The CNS is the "target organ" for methyl mercury[<2>]. Acute poisoning with organic mercury compounds therefore mainly damages the nervous system. The dose-dependency latency period from absorption up to the appearance of the symptoms of poisoning ranges from weeks to months. Symptoms include malaise, paresthesia, impaired field of vision, impaired speech and hearing and ataxia. Severe poisoning leads to coma and death[<1033>]. Dimethyl mercury – a colourless fluid[<1030>] - appears to be particularly hazardous. It even penetrates latex gloves and is absorbed through the skin. Even exposure to a few drops can lead to degeneration of the central nervous system and, ultimately, to death[<619>].

The symptoms of chronic poisoning with organic mercury compounds are the same as after acute poisoning, with a rapid transition to severe damage[<1033>].

In the environment, methyl-Hg is formed through micro-organisms from elementary Hg and accumulates in the food chain. Shark, mackerel, swordfish and large tuna are mostly affected[<1033>]. Fish is, therefore, the main source of methyl Hg exposure for humans.

In addition to agrochemicals, drugs such as thiomersal (preservatives), phenyl mercury salts (antiseptics, disinfectants) and mercurochrome (wound disinfectants) often play a role in poisoning with organic mercury compounds[<807,1027>]. Lowell *et al.*, for instance, report on patients who developed thiomersal-induced symptoms of poisoning following high doses of hepatitis B immunoglobulins[<859>]. The European registration authorities demand that thiomersal, as a preservative, should be replaced as soon as possible on safety grounds[<1028>]. The sensitising effect of organic mercury compounds is confirmed through investigations carried out in humans and laboratory animal experiments[<1027>].



Thiomersal = 2-(Ethylmercurithio)benzoic acid, sodium salt

Organic Hg compounds are virtually completely absorbed in the gastrointestinal tract[<1033, 1313>] and are quickly distributed over the entire body[<1313>]. Moreover, they are capable of crossing the blood-brain barrier[<1104>] and diffuse into breast milk[<493>]. They also cross the placenta and accumulate in the foetus. The levels in the foetal blood are higher than those recorded in the mother. Up to 90% of the substance is excreted via the faeces[<493>]. The biological half-life of methyl mercury is 48 – 65 days[<493,1030>].

DMPS was an effective antidote for organic mercury poisoning[<947>]. ”In experimental models, DMPS has been suggested as a useful drug to prevent fatal damage in foetus associated with methyl mercury exposure during pregnancy. This chelating agent was also able to protect the pregnant mice against methyl mercury exposure”[<538a>]. Treatment with DMPS can still be useful even weeks and months after the poisoning[<63>]. However, DMPS cannot always improve neurological and psychological symptoms on chronic poisoning[<1532>]. Others recommend DMSA[<29>] or DMPS and DMSA[<1103>] combination therapy on methyl mercury poisoning. ”Good experimental and clinical evidence shows that haemodialysis with N-acetylcysteine or cysteine infusion combined with oral administration of DMPS can drastically reduce the concentration of alkyl mercury in the brain and the body. This therapy should be the first choice in any progressive state of intoxication. The treatment can be followed by continuous therapy with DMPS to reduce the body from alkyl mercury further”[<163>].

The following recommendation is given for phenyl- and methoxy ethyl mercury: ”Severe renal damage from these compounds should be treated with oral administration of DMPS…. BAL is contraindicated because it forms lipid-soluble complexes with the organic mercury compounds and redistributes mercury to the brain, whereby it may cause severe disturbance in the CNS”[<163>].

7.2.12.3.1 Acute poisoning

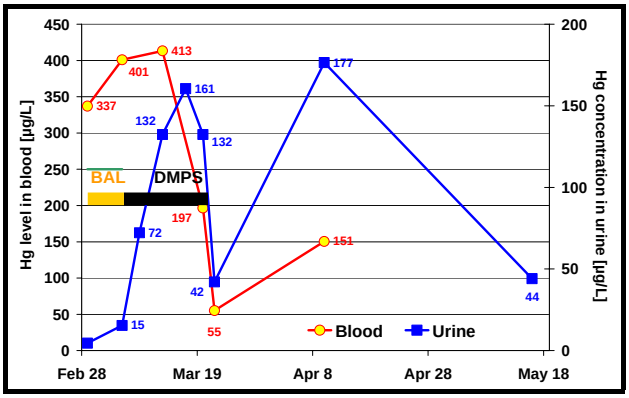
A 20 year-old patient was treated with haemodialysis (with concomitant administration of N-acetylcysteine) and D-penicillamine after swallowing, amongst other things, a methyl mercury-containing fungicide with suicidal intent. After three days, treatment was switched to 200 mg oral DMPS every 6 hours, for 14 days. DMPS was more effective than DPA in terms of mercury excretion. The patient survived the poisoning without any major symptoms of intoxication. Serum levels of zinc and copper remained within the normal range during therapy[<872>].

A 40 year-old man drank an aqueous solution of 5 g thiomersal with suicidal intent. Five minutes later, he vomited spontaneously and was admitted to the local hospital with nausea and vomiting. After gastric lavage and administration of 300 mg DMPS via a gastric tube, he was transferred to a university hospital. There, blood-stained gastritis was also diagnosed. In addition to oral DMPS, DMPS was also administered parenterally and DMSA orally.

1st day	Start of acute polyuric kidney failure, which improved within 40 days on conservative therapy.
4th day	Fever of up to 40ºC without infection.
6th day	Gingivitis and exanthema, development of polyneuropathy.
11th day	Delirium culminating in coma, changes in the EEG.

16th day Start of mechanical respiration.
19th day Improvement in the neurological symptoms. The blood level fell to less than 100 µg/L.
148th day The patient had largely recovered. Impaired sensitivity remained only in two toes.

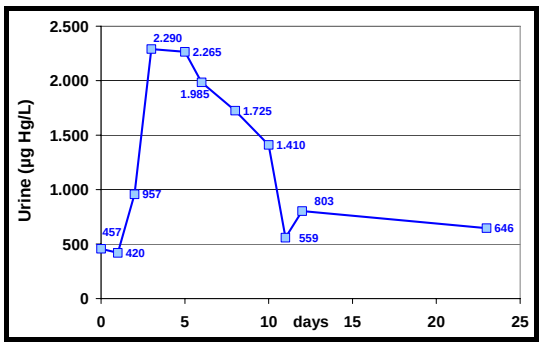
The peak levels were 14 mg/L in the blood, 1.7 mg/L in the serum, 25 µg/L in the cerebrospinal fluid and 10.7 mg/L in the urine. There was no correlation between concentrations in the blood and the CSF. During the first three days of treatment, more heavy metal was excreted than in the remaining 140 days. The half-life of the mercury was $t_{½}\alpha$ = 2.2 days and $t_{½}ß$ = 40.5 days. Although the patient survived this massive thiomersal poisoning, no clear effect of DMPS and DMSA could be detected from the laboratory parameters in this case on the renal mercury excretion. No investigation was carried out to establish whether faecal excretion was high<1059,1140>.



Excretion of mercury during BAL therapy (Feb 29 – Mar 6) and 6 x 50 mg DMPS/day (Mar 6 – Mar 20)<586>

A 15 year-old boy was admitted to hospital because of swallowing an unknown quantity of Fusariol (cyanoethyl mercury). After gastric lavage, active charcoal and sodium thiosulfate were administered and forced diuresis was started. The patient was initially treated with BAL before switching to DMPS, with which a marked increase in mercury excretion was achieved. During the administration of DMPS, nausea, retching and headaches developed, but these were controllable. No changes in the blood picture, transaminase levels or serum electrolytes were observed<596>.

A 49 year-old woman was admitted to hospital two hours after ingestion of the methoxy ethyl mercury chloride fungicide [CH_3-O-CH_2-CH_2-Hg-Cl] (= 4.375 mg Hg) with suicidal intent. The compound is known to decompose relatively quickly with formation of inorganic Hg^{2+}. Despite vomiting and gastric lavage, 700 – 1,000 mg Hg were absorbed, 11 mg of which were removed by haemoperfusion. The blood level was thereby halved. In addition, forced diuresis was introduced. Alternating therapy with 300 mg DPA t.i.d. and 100 mg oral DMPS t.i.d. for 12 weeks led to the renal excretion of 500 mg Hg. The chelating agent reduced the protein binding of the fungicide and thus increased its renal excretion. The patient was discharged after 4 weeks without toxic symptoms in the kidneys or central nervous system despite blood levels of up to 2,400 µg/L<760>.



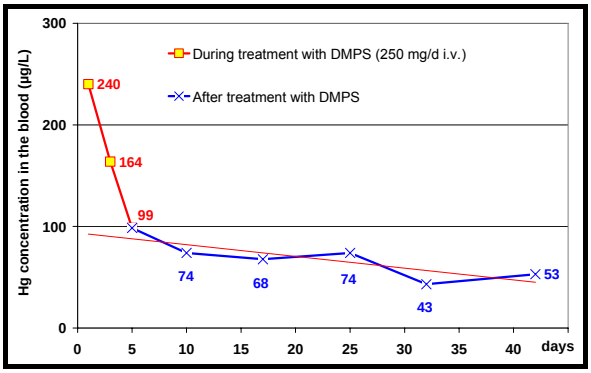
Excretion of mercury in the urine during DMPS therapy after poisoning with merbromine<290>

A 2½ year-old boy was admitted to hospital without any clinical symptoms 10 hours after drinking 10 mL of 2 % merbromine solution. Hg levels of 62.1 µg/L and 457 µg/L were recorded in the blood and urine, respectively. Oral treatment with 40 mg DMPS/day was initiated. This was continued on an outpatient basis 10 days after the patient was discharged<290>.

Merbromine solution was administered intrathecally to a 69 year-old woman. Neurological symptoms developed within 24 hours. High Hg levels were recorded in the cerebrospinal fluid, blood and urine. In addition to surgery (debridement, drainage), DMPS was administered parenterally (no details of dosage were given). The patient was extubated after 3 days and transferred from the intensive care unit to the normal ward. Treatment was switched to DMSA due to potential intolerance<1386>.

An 84 year-old female dialysis patient inadvertently took approximately 100 mL of a 2% solution of merbromine. A blood level of 240 µg/L was recorded shortly afterwards. Conventional treatment with gastric lavage and active charcoal was initially administered. DMPS therapy was initiated 10 hours after ingestion. 250 mg i.v. DMPS were administered every day for 5 days. Haemodialysis was also carried out. A marked, continuous decrease in Hg levels in the blood was observed during therapy<591>. The Hg level in the blood fell only slowly once treatment was withdrawn.

Compounds with radioactive mercury (chlormerodrine ^{203}Hg) are used for renal scans as the heavy metal accumulates in this organ. Nuclide elimination was promoted by subsequent i.m. administration of DMPS. Whereas 39.7% of the ^{203}Hg dose administered was excreted in the urine of the untreated control group over the next 7 days, the 9 patients investigated (6 ampoules of i.m. DMPS over 3 days) excreted 74.5% of the dose over the same period. As the scans showed, the ^{203}Hg level and thus the radiation burden of the kidneys were thus rapidly decreased. No adverse reactions were observed with DMPS therapy[<742,1069>].



Hg concentration during and after treatment with DMPS in a female patient requiring dialysis[<591>]

Conclusion:
On acute poisoning with organic mercury, DMPS increases the excretion of the heavy metal via the kidneys, even in children. However, few details have been published regarding the extent to which this is known to affect the clinical course.

7.2.12.3.2 Chronic poisoning

6,530 people in Iraq ate bread produced from corn contaminated with methyl mercury in 1972. 459 of these people died. Mainly organic but also small quantities of inorganic Hg were detected in the blood. Some were treated with various antidotes and the effect on the biological half-life of mercury was compared. Ten patients between 3 and 35 years of age received i.m. DMPS with an interval of up to 150 days between ingestion of the poison and the start of treatment. Mercury levels in the blood at the start of treatment fluctuated between 931 and 5,700 ppb. The female patient with the highest exposure died despite treatment. The administration of DMPS reduced the half-life in the blood from 62 days (placebo and no treatment) to 10 days. Elimination was chiefly via the urine. No adverse reactions were observed. Haematocrit values remained within the normal range. Organic mercury was mostly detected in the urine and blood. Only traces of inorganic heavy metal compounds were found (<10%). DMPS was the most effective compared to the other antidotes. DMPS was also superior to DPA in terms of the urinary excretion of mercury. Hg levels in the blood were approximately 10 times higher. As regards the clinical symptoms, the authors nevertheless state, "It is our belief, that when there was severe structural damage after a long period of heavy exposure, little could be achieved by the drugs tested"[<22,114,281>].

Chelating agent	Patients	Half-life
Controls	16	62 days
Thiol-polystyrol resin (oral)	8	20 days
DPA (oral)	12	26 days
NAPA (oral)	17	24 days
DMPS (i.m.)	10	10 days

Half-life of Hg in the blood on poisoning with methyl mercury and administration of various antidotes[<281>]

Course	Quantity of Hg absorbed mg C_2H_5HgCl/kg BW	Mercury in the urine		
		Before treatment µg/L	Before treatment µg/Tag	During treatment µg/L
Mild	0,5 - 1	28	54	95
Moderate	1 - 2	69	140	165
Severe	2 - 3	39	75	310
Lethal	>4			

Clinical course of the condition and mercury values in 40 patients poisoned with ethyl mercury[<1620>]

For five months, a previously healthy girl (9¾ years old) complained of abdominal pains. Within three months, a shaky script developed as a result of tremor and restless movements of the left arm and the lips. After diagnosis of mercury intoxication, long-term therapy with DMPS (a total of 2.2 g DMPS) was initiated. The mercury levels fell and the clinical symptoms improved slowly but continuously. The source of poison was identified as mercury-

treated seeds on which the child had frequently chewed[<201>].

Forty-one patients still suffered from symptoms of poisoning 5 months after eating rice that had been treated with ethyl mercury. Interval therapy with DMPS (250 mg i.m.) was started in 27 patients and DMSA (2 x 500 mg i.v.) in 13 patients for three days. After a 4-day treatment pause, therapy was administered for another 3 days. The patients received up to 8 treatment cycles. DMPS was found to be slightly superior to DMSA. The symptoms were, however, partially irreversible such that not all of the patients were symptom-free any longer. In contrast, symptoms improved only slightly in the 13 untreated patients. There was a correlation between the severity of the symptoms and the mercury levels during DMPS therapy but not, however, with the mercury values prior to treatment[<1620>].

Out of 22 workers suffering from occupational exposure to mercury compounds (diethyl mercury, ethyl mercury) and mercury vapour, 7 presented with mild, 10 with moderate and 5 with severe mercury poisoning. All of the workers received 50 mL of a 5% DMPS solution via the i.m. route for 7 days. The injections were mostly well tolerated but some pain developed at the injection site, which persisted for up to one hour. A transient deterioration in existing symptoms (headaches, pain in the extremities, disrupted sleep or general weakness) occurred in 6 patients on the 2nd to 3rd day. Skin changes of allergic origin were observed in 2 patients during DMPS therapy. The mercury excretion in urine and faeces, however, rose in general as a result of DMPS administration ad subjective symptoms also improved[<92>].

DMPS was administered to 9 workers as an aerosol. The patients inhaled 5 mL of a 5% solution twice a day for 10 days. Treatment was well tolerated and no dysesthesia was observed. Mercury excretion in the urine and faeces increased considerably and the symptoms of poisoning disappeared. DMPS was also administered prophylactically as an aerosol[<92>].

In workers exposed to organic mercury compounds, the oral administration of 2 x 500 mg DMPS every day for 3 days triggered a marked rise in Hg excretion in the urine. Protein formation in the blood reverted to normal. The patient felt better. No adverse reactions were reported with the oral dose of DMPS[<1453>].

Conclusion:
In chronic poisoning with organic Hg, DMPS lowers the half-life of the heavy metal in humans. Renal excretion is increased even when the start of treatment is delayed. In most cases, this leads to an improvement in symptoms, even if the changes are already irreversible.

7.2.12.4 Mercury vapour

Mercury already evaporates at room temperature. The evaporation increases as the temperature rises. Mercury vapour is colourless and odourless[<1030>]. Poisoning with mercury vapour may, for instance, occur at workplaces where it is processed[<204,1075,1282,1385>] or after breaking a mercury thermometer[<1506,1510>].

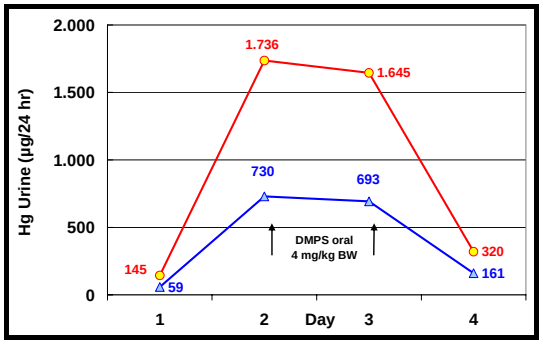
Mercury in the vapour form is readily absorbed because of its lipophilic nature and high diffusion capacity[<18>] (absorption rate in the lungs: 80 %[<121,280,1033,1313>]) and is quickly distributed in the body. It crosses both the blood-brain barrier and the placenta[<839,1313>], and accumulates in the foetus[<493>]. Inhaled mercury can, therefore, reach the brain and the CNS[<272,1236>] and slowly lead to neurological symptoms[<2>]. The absorbed mercury is oxidised to mercury ions in the body by catalases[<235,1018,1030,1236>]. This makes Hg elimination difficult in the brain ("mercury cases"[<290>])[<204,282,493,1143,1236>]. Hence deposits can remain for years[<1236>]. Therefore, up to ten times more Hg is detected after Hg intoxication following inhalation compared to the same mercury burden with mercury salts[<1104>].

Symptoms depend on time and dose[<204>]. At high concentrations, Hg vapour can lead to lung damage and death due to respiratory failure[<493>]. On acute poisoning, damage to the respiratory tract (dyspnoea, irritant cough, lung oedema and lung necroses) dominate the clinical picture[<121>]. Patients exposed to Hg vapour also complain of a metal taste in the mouth[<1030,1033>], nausea,

inflammatory processes in the oral cavity and respiratory tracts, dyspnoea, haemoptysis, salivation, impaired speech and movement, anuria and kidney failure<1033>.

The half-life in adults is 60 days. Excretion is chiefly in the faeces but partly via exhalation<493>.

DMPS is the drug of choice in the treatment of Hg vapour intoxication<204>. It increased the renal excretion of mercury<274> in subjects suffering from occupational exposure and was superior to BAL<782>. DMPS increased Hg excretion<910> and reduced the half-life from 33.1 to 11.2 days<1030> in workers with prolonged mercury contact. The oral administration of DMPS increased Hg excretion in 24-hour urine in two workers who used to work in a mercury mine. Hg levels in the blood remained unchanged<402>. "The prognosis in pronounced intoxication by mercury vapour involving severe tremor and mental changes is, according to what is found in the literature, remarkably good with complete regression if exposure ceases. Cases of successful treatment with DMPS have been reported in the literature"<163>. „Although there are no controlled clinical data to show that chelation therapy improves outcome in patients with neurological features of mercury poisoning, DMPS, 30 mg/kg/day p.o., increases urinary mercury elimination and reduces blood mercury concentrations. Case reports suggest benefit", as shown in a handwriting test, for instance<203d>. "If the diagnosis of inhaled poisoning is confirmed, antidote therapy must be initiated without delay. With normal kidney function, the urinary excretion of Hg with the complex-forming agent, dimercaptopropane sulfonic acid-sodium, is increased 10 to 100-fold. … Haemodialysis or haemoperfusion is occasionally required." Treatment with D-penicillamine or BAL (2,3-dimercaptopropaneol is less effective and triggers more adverse reactions"<386a>.



Hg excretion of 2 workers suffering from Hg exposure, before, during and after DMPS<274>

Conclusion:
DMPS had no effect on acute poisoning with mercury vapour. The heavy metal concentration in the blood was lowered in both known case histories but the patients nevertheless died 24 and 39 days after intoxication, respectively.

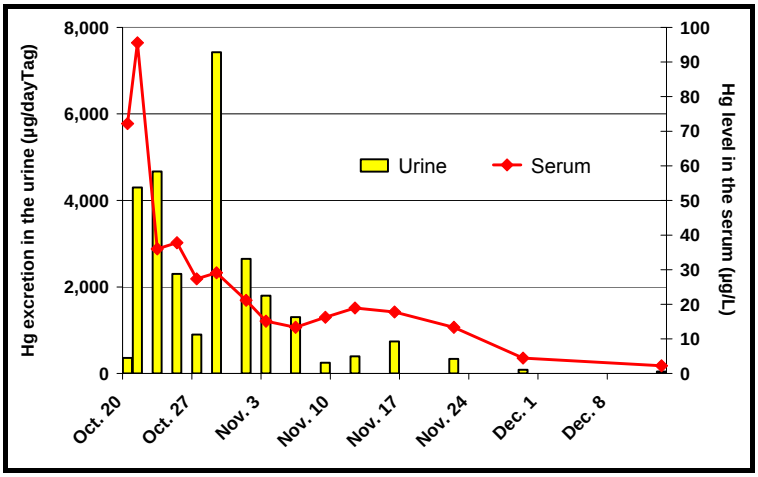
7.2.12.4.1 Acute poisoning

In an 87 year-old man, inhalation of mercury vapours produced on heating mercury sulfide, led to acute lung failure. The patient had to be mechanically ventilated. Mercury intoxication was not identified until 6 days later and treatment with DMPS, DPA and methyl prednisolone was initiated. Although the mercury levels in the serum fell from 330 µg/L to 27 µg/L, the damage to the lungs was already irreversible and the patient died 39 days after intoxication<593>.

A 19-year old heated mercury with suicidal intent and breathed in the vapours for 6 hours. He was admitted to hospital 12 hours later and was already anuric. The Hg level in the blood was 1,800 µg/L, increasing to 5,300 µg/L. 6,000 µg/L were measured in the bronchial secretion. BAL was initially administered followed by DMPS (no information given regarding dosage and method of administration). Dialysis, haemoperfusion and plasma separation were also carried out. The Hg levels in the blood fell. Diuresis restarted after nine days. Hg concentrations of 600 – 800 µg/L were recorded in the urine. The patient nevertheless died from uncontrollable respiratory insufficiency 24 days after intoxication<569>.

7.2.12.4.2 Chronic poisoning

In a 14 year-old girl, the initially predominant psychological and neurological symptoms were interpreted for a long time as a neurotic anxiety syndrome. Some time later she suffered from



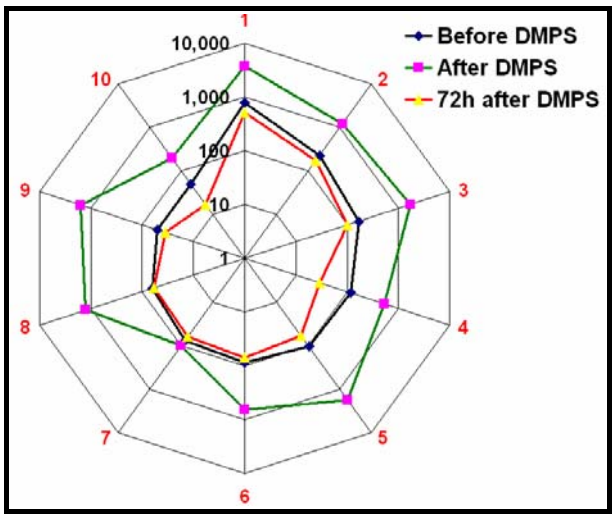
Mercury excretion in the urine and Hg levels in the serum during DMPS therapy in a 14 year-old girl[<1104>]

marked sweating and insomnia at night. As the investigations carried out did not show any pathological findings, the symptoms were interpreted as an expression of a psychological disorder.

Tremor at rest, loosening of the teeth and exanthema with generalised pruritus developed before chronic Hg intoxication was diagnosed three months later. The cause was split Hg, which could not be removed from the carpeting with a vacuum cleaner. Treatment with 3 x 100 mg every two days was initiated. The urine excretion was increased more than 14-fold. The treatment was well tolerated by the patient. The symptoms of the illness slowly regressed as the serum level fell[<185,1104>].

Six patients who had inhaled mercury vapour on smelting amalgam were treated with oral DMPS (2 x 100 mg/day) for up to 15 days. Hg excretion in the urine was increased. Two of the patients developed transient exanthema. There was, however, no confirmation that DMPS was the direct cause of this[<902>].

A 13 year-old boy played with metallic Hg and distributed it in his bedroom. Over the next 3 weeks, slight proteinuria, hypertension, seizures, changes in the EEG and skin reactions occurred before Hg intoxication was diagnosed. DPA treatment was switched to BAL after 10 days and then to DMPS after a further 10 days (10 mg/kg/day). The authors do not, however, give any indication as to the method of administration. During this period, Hg levels in the blood fell from 5.9 to < 2 µg/L. Blood pressure reverted to normal. One month later, the boy unexpectedly died. As no autopsy was carried out, there is no indication of the cause of death[<783>].



Hg excretion in the urine (µg/g creatinine) in 10 workers before and 24 h and 3 days after the last dose of 3 x 100 mg oral DMPS[<1449>]

Ten workers in a mercury processing plant who had urine levels of over 50 µg Hg/g creatinine were treated with 100 mg oral DMPS t.i.d. for 5 days. The urine excretion of the heavy metal was significantly increased. It is striking that, with similar mercury excretion before DMPS (workers 6-10), excretion in the first 24 hours after starting DMPS therapy differed by up to a factor of 15[<1449>].

A 40 year-old worker at a chemical plant suffered from nausea, lower abdominal pain, headaches, high temperature and symptoms of gingivitis. The neurological examination revealed nystagmus, and the Romberg test was positive. Extremely high mercury levels were recorded in the urine (830 µg Hg/L). This was caused by a defective face mask filter. The symptoms disappeared and mercury levels in the urine reverted to normal during parenteral administration of DMPS. No damage to the internal organs was established. The neurological symptoms disappeared within a few months. No sequelae of acute Hg vapour intoxication could be detected during a follow-up examination carried out 1 ½ years later[<1637>].

A total of 225 people in Great Britain were contaminated by playing with 5 to 10 litres of metallic Hg. Thirteen of them developed clinical symptoms. Five of these were treated with DMPS. This treatment led to a decrease in Hg levels in the blood[<1059>].

Workers whose job consisted of the recycling of fluorescence lamps, displayed symptoms of mercury poisoning 6 months after taking up their post. Hg levels in 24-hour urine increased from 118 to 2,208 µg/L and from 158 to 1,242 µg/L after a single oral dose of 300 mg DMPS[<104>]. The excretion immediately decreased once treatment was discontinued[<274>]. "Saturation therapy with DMPS" was initiated for a patient presenting with nephritic syndrome[<651>]. Two i.m. doses, each comprising 250 mg DMPS, increased mercury concentrations in the urine up to 200 times or partly over 10,000 µg/L in workers exposed to mercury (thermometer production, chlorine-alkali electrolysis). The increase was only 20-fold in the control group. In addition, urine concentrations were below 100 µg/L in all cases after mobilisation. Furthermore, the administration of DMPS also doubled mercury concentrations in the bile. A combination of DMPS and spirolactone even led to mercury concentrations 7 times higher in the bile[<276>].

Sixty inhabitants in the vicinity of a gold mine in the Philippines (Mt. Diwata), where gold was obtained using Hg, were diagnosed with Hg poisoning. A further 35 subjects living downstream on the banks of the river in which the Hg waste was disposed of (Monkayo), also suffered from this form of poisoning. Tests carried out on the hair confirmed that these subjects had primarily been exposed to methyl mercury. Neurological symptoms such as tremor were identified in the majority of the 95 patients. All received 2 x 200 mg DMPS/day (children 5 mg/kg BW) for 14 days. (The duration of treatment was fixed in advance as the Hg could not be assayed on site!) In one girl, treatment was discontinued after the first dose due to the onset of an allergic skin reaction. Despite the relatively short treatment period, over 2/3 of the patients reported a perceptible improvement although they still lived in the exposed region. Various neurological investigations and neuro-psychological tests confirmed the subjective patient reports. 3% of those treated announced a deterioration in their condition. However, the Hg values in the blood and urine were still high on completion of therapy, which suggests that the treatment period fixed at 14 days was no longer sufficient[<199>].

		Mt. Diwata	Monkayo
No. of cases		60	35
Hg hair before treatment	ng/g	6.93	6.03
Proportion of CH3-Hg in the hair	%	82	31
Hg-blood before treatment	µg/L	22.1	19.2
Hg urine before treatment	µg/g crea	5.4	8
Hg urine 4 hours after the first dose of 200 mg DMPS	µg/g crea	1049	74.9
Hg urine on completion of treatment	µg/g crea	97.4	10.2
Hg blood on completion of treatment	µg/L	21.8	15.2

Effect of 14 days' treatment with DMPS on Hg parameters in subjects in the Philippines presenting with chronic Hg intoxication[<199>]

Twenty-two workers with occupationally induced Hg intoxication (organic Hg, Hg vapour) exhibited increased fatigue, sexual impotency, neuralgia, polyneuritis and pathological changes of internal organs. They were treated with i.m. DMPS. The injections were well tolerated. Occasionally there was transient pain at the site of the injection. In two cases, allergic skin reactions were observed during therapy. Hg excretion in the urine and faeces rose markedly as a result of DMPS administration and the subjective well-being of the workers improved. Six of the workers experienced short-term deterioration of the symptoms because of marked Hg mobilisation from the deposits[<92>].

	n	Improved	Unchanged
Loss of appetite	27	23	4
Finger tremor	42	5	37
Memory disorders	78	9	69
Headaches	50	41	9
Fatigue	78	58	20
Irritability	42	10	32
Insomnia	60	52	8
Pain	45	33	12
Dizziness	71	60	11
Sweaty hands	53	31	22
Gingival atrophy	46	0	46
Gingival haemorrhage	56	42	14
Toothache	55	45	10
Loss of teeth	43	0	43

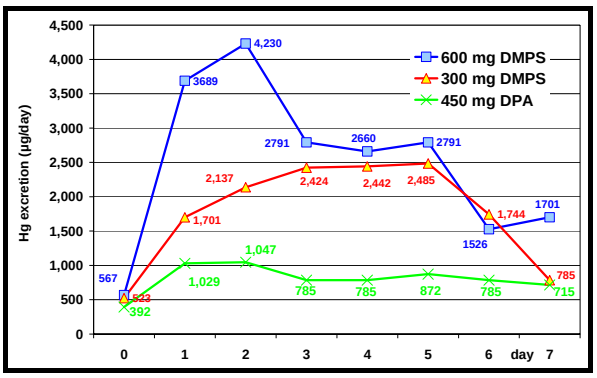
Effect of stopping exposure and treatment with DMPS on the symptoms of workers at an Hg refinery[<568>]

Two workers intoxicated with mercury vapour were treated with DMPS (300 to 400 mg oral/day) for 60 days. The biological half-life was reduced from an average of 33 days to 11 days. The symptoms disappeared in one of the workers whilst no symptoms appeared in his colleagues despite excretion of 832 µg mercury in 24-hour urine. No treatment-related adverse

reactions were observed[<235>].

Eighty-four employees who had worked for 2 to 10 years in a Hg refinery were treated with DMPS (4 x 125 mg i.m. DMPS/week) for 4 weeks. The mean mercury level in the urine fell from 224 to 41.3 µg/L. The clinical symptoms partially improved. However, the neurological symptoms in particular were already irreversible[<568>].

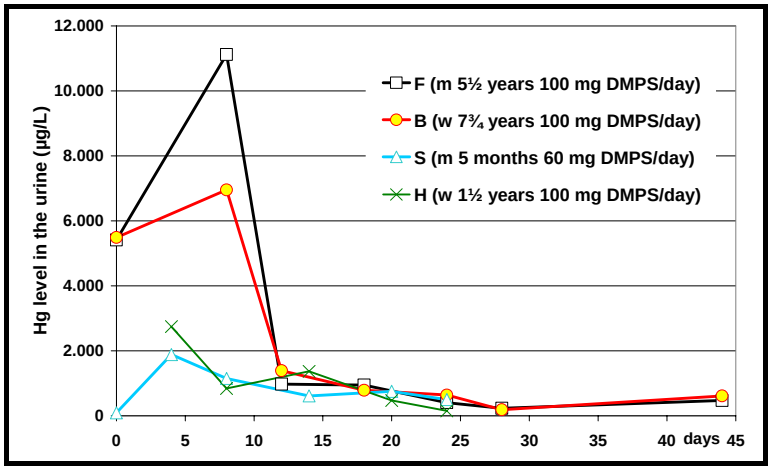
As the heavy metal was predominantly inhaled via the lungs, DMPS was administered to nine workers as an aerosol. The treatment was well tolerated. The symptoms of intoxication improved. Mercury excretion in the faeces and urine increased. The heavy metal was excreted even in workers in whom no mercury could be detected prior to treatment[<92>]. DMPS was also administered by inhalation as prophylaxis for mercury vapour poisoning[<92>]. Long-term investigations in 219 employees exposed to mercury vapour showed an improvement in the condition of the upper airways through prophylactic inhalation of the antidote[<433>].



Comparison of the renal excretion of mercury (µg/d) during various treatments[<272>]

19 underground railway construction workers were unwittingly exposed to mercury vapour for 20 – 40 hours when liquid mercury of unknown origin flowed out of the soil on tunnelling. Clinical symptoms such as lesions of the oral mucosa, fatigue, headaches and haw pain, insomnia, tremor, hypersalivation, dyspnoea and speech disorders developed. The patients were treated either with 3 x 200 mg DMPS/day (n=6), 3 x 100 mg DMPS/day (n=6) or 3 x 150 mg D-penicillamine/day (n=7) in a randomised, single-blind study. Hg excretion initially increased in all groups. Hg levels in the blood fell during the 7-day treatment period. The highest excretion in the urine was achieved in the high-dose DMPS group. DPA displayed only inadequate efficacy at the dose administered. No adverse reactions were observed[<272,1610>]. Therefore, "mild and abortive intoxications should also be treated as the symptoms arising due to mercury residues in the body may develop, indicating residual effects"[<272>].

An 8 year-old girl was admitted to hospital with loss of appetite, lethargy, pain in the legs and fingers, sweating and exanthema 4 months after a temperature thermometer had broken in the children's bedroom. Tachycardia was also diagnosed. The mercury concentration in the urine was 18.6 µg/L and 31.5 µg/L creatinine. After the introduction of Dimaval therapy, mercury concentrations in the urine increased to almost 200 µg/g creatinine and gradually fell during the course of treatment. As the symptoms deteriorated during treatment, the parents discontinued therapy[<1507>].

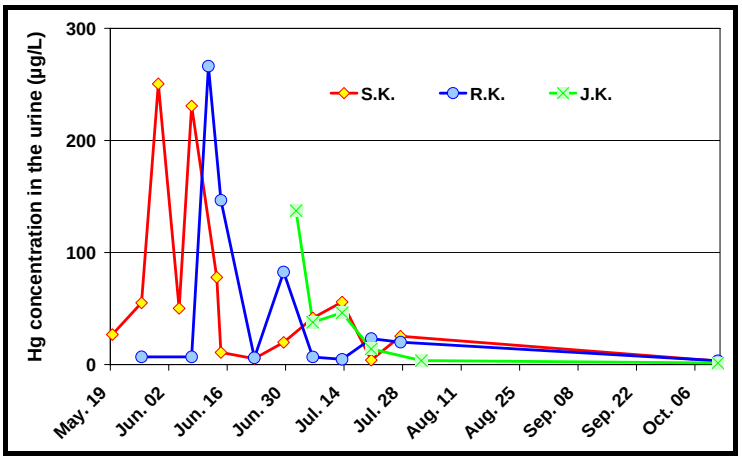


Hg excretion in the urine of 4 children receiving DMPS after exposure to Hg vapour[<290>]

A father wanted to destroy wasps with liquid mercury. During the process, the container broke and the majority of the heavy metal spread over the carpet. The parents tried to remove the mercury with a vacuum cleaner. The mother experienced symptoms of poisoning such as headaches and nausea as early as the next day. The four children (7 months to 7¼ years old) developed severe bronchitis after eight days. Six to ten days after exposure, treatment with 60 to 100 mg DMPS/day was introduced and was administered in two divided doses. No treatment-related adverse

reactions were observed. After four weeks, the children were discharged in a good state of health, without any symptoms of mercury poisoning. The excretion of copper (maximal 218 µg/L) and zinc (maximal 2,500 g/L) was markedly raised whilst that of iron (maximal 130 µg/L) was in the upper normal range. Since no deficiency was detected in the blood plasma, no additional replacement therapy was required<166,290,657,706>.

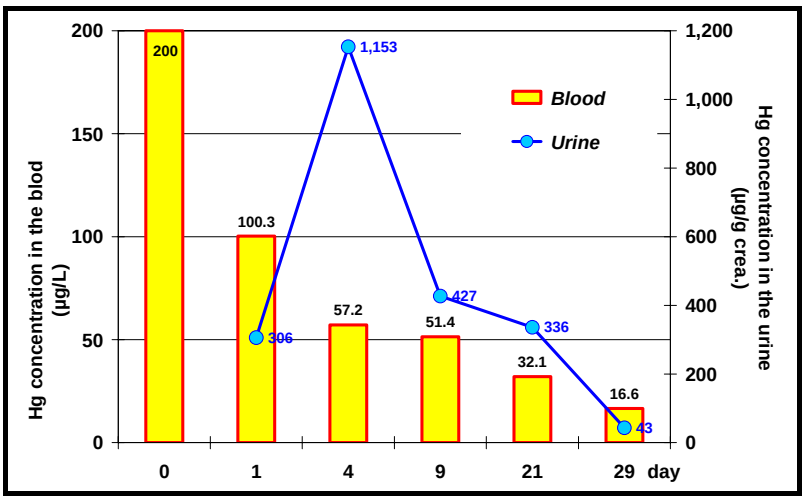
A 2¾ year-old girl (S.K.) suffered from weeping eczema for four months until chronic mercury poisoning was diagnosed. She later developed loss of appetite, diarrhoea and photosensitivity. Eight months previously, a mercury thermometer had been broken in the children's bedroom (wall-to-wall carpeting, underfloor heating) . Two siblings (R.K. 1¾ years old and J.K. 7 years old) were also found to have symptoms of Hg intoxication (Feer's disease). Treatment with 50 mg DMPS t.i.d. for two days was introduced. Therapy was then continued at a dose level of 30 mg b.i.d. for four months. The clinical status reverted to normal. It was noted in particular in patient R.K that the mercury concentrations in the urine before the administration of DMPS were still within the normal range despite the clinical symptoms. Only after administration of the chelating agent was the mercury intoxication visible in the urine<1506,1510>.



Mercury excretion in the urine (µg/L) during DMPS therapy. Starting dose 3 x 50 mg/day for 2 days and 2 x 30 mg thereafter<1506,1510>

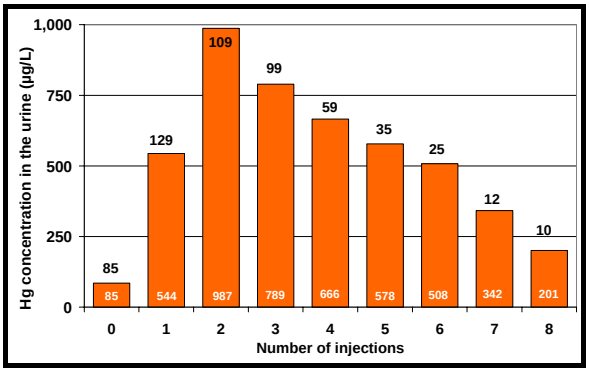
Children found a bottle containing metallic mercury and distributed the metal in two children's rooms. Three of the children developed fine muscular tremor, atactic movement disorders and weakness 4 to 6 weeks later. Hg poisoning was finally diagnosed on the basis of blood tests, which were even carried out in the asymptomatic children. Blood plasma concentrations reached 1,500 µg/L and urine concentrations up to 2,700 µg/L, there being no correlation between the levels and the severity of the symptoms. The children were treated with oral DMPS in four treatment cycles and after spending approximately six weeks in hospital, were discharged for subsequent outpatient treatment with a substantial reduction in blood levels (about 60 µg/L) and urine concentrations that were still high (up to approximately 2.000 µg/L).<545>.

A 9 year-old boy was admitted to hospital with abdominal and joint pain as well as renal and neurological symptoms (including ataxia, peripheral neuropathies, defective reflexes and writing difficulties). The Hg level in the serum was 200 µg/L (normal value < 6 µg/L). The source of the heavy metal was mercury, which was traced in the bed and carpet after having been spilled and "removed" with a vacuum cleaner. DMPS therapy (administered parenterally for 4 days and orally for 14) was carried out, during which time Hg concentrations in the serum fell continuously). Hg excretion in the urine initially increased, thereafter also falling. Meanwhile, the boy developed presumably Hg-induced hypertension, which temporarily required 3 antihypertensive agents, which could again be discontinued over time. The neurological damage slowly improved. It took 6 months for the boy to recover<1224>.



Hg concentration in the whole blood and urine during DMPS therapy of a boy with Hg poisoning<1224>

Stantschew examined 1,156 workers, previously exposed to mercury, with a spontaneous urinary excretion of mercury of at least 20 µg/L. The values were determined in the overall nocturnal quantity of urine. A Hg deposit was assumed if the mercury elimination after the first injection of DMPS (10 mL of a 10% solution = 1,000 mg of DMPS i.m.) exceeded a value of 250 – 300 µg/L and if even higher concentrations of mercury were detected in the urine after a second injection. A peak urine value of 11,200 µg/L was reached. The largest mercury deposits were also decorporated after a further 3 to 8 or, in exceptional circumstances, up to 15 DMPS injections. Copper excretion was slightly high with DMPS but did not, however, lead to a clinical deficiency. The loss was satisfactorily compensated for by the copper intake with food[1385].



Average Hg excretion in workers exposed to Hg after several i.m. injections of DMPS. The black numbers above the bars indicate the number of patients[1385]

Mercury vapour led to severe neurological damage in one patient. This improved both subjectively and objectively with three DMPS treatment cycles (30 mg/kg/day p.o.).

Conclusion:
Numerous case histories describe the efficacy of DMPS in chronic mercury vapour poisoning. The renal excretion of the heavy metal is increased whilst blood levels fall. The symptoms improve provided that the damage is not already irreversible.

7.2.12.5 Metallic, liquid mercury

The effect of the injection of metallic mercury varies considerable from one patient to the next. Some tolerate the heavy metal for years, obviously without any symptoms, whilst others exhibit pulmonary embolism through mechanical obstruction of the vessels due to Hg spheres[142,564] or react with symptoms of acute or chronic Hg intoxication. Lethal clinical courses are also described[564]. In poisoning with metallic mercury, the toxic effects develop mainly through the mercury ions produced[306,532,1565] (e.g. kidney damage[142]), as these may react with free SH groups of biomolecules[1565]. Metallic mercury can, therefore, form a deposit, which leads to chronic resorptive mercury intoxication[532]. There is some dispute whether poisoning with metallic mercury must be treated in every case. "There were no controlled studies examining the efficacy of any treatment measures for elemental mercury toxicity"[237a]. When taken orally, some people consider it to be non-toxic[18,1492] (absorption from the gastrointestinal tract < 0.1 %[166,493]), while others consider that treatment is necessary[532,809,1104]. "Metallic mercury in fatty tissue is, however, highly toxic because of its lipid solubility and needs treatment with chelating agents"[1104]. Thus, treatment was carried out for six months in one case with s.c. mercury incorporation[167].

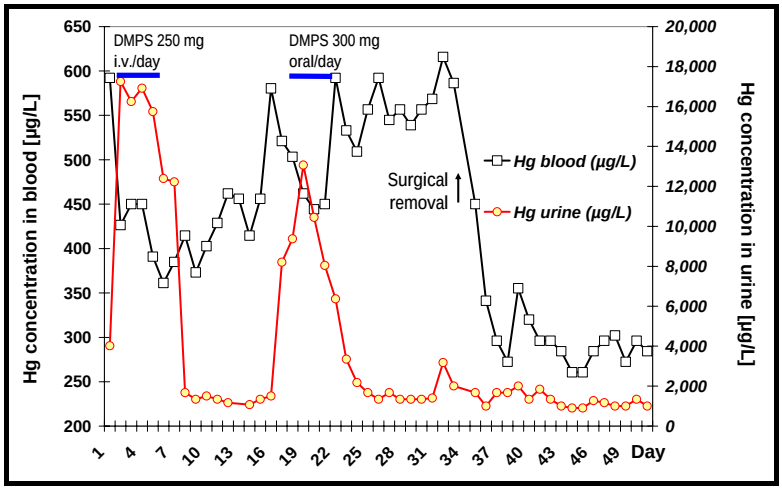
The administration of DMPS is absolutely essential in cases of increased mercury excretion in the urine or high mercury concentrations in the blood following incorporation of metallic mercury[809]. A mercury concentration of 20 mg/dL in the urine or 2 mg/dL in the blood suggests poisoning [1329], which should be treated.

Serious symptoms of poisoning can also be anticipated when metallic mercury is deposited in other tissues, warranting a combination of surgical and internal procedures as soon as possible[913].

Metallic mercury itself is not mobilised by DMPS. It can, however, bind to erythrocytes, for instance, and be oxidised to inorganic mercury[1565], which can then react with DMPS.

7.2.12.5 i.v. administration of mercury

"Parenteral applications can remain symptom-free for years but can also trigger serious absorption intoxication "[<166>].



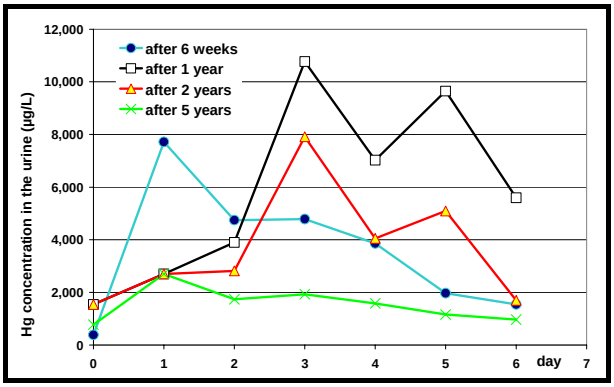
Mercury concentrations in the blood an urine[<1565>]

A 22 year-old male drug addict injected 8 g of mercury (= 0.6 ml) via the i.v. route with suicidal intent and also drank 100 mL. Within a few days, the symptoms of acute Hg poisoning appeared characterised by gastroenteritis, Colitis stomatitis, a metallic taste and intensive urge to micturate. Severe tremor of the hands, exhaustion and insomnia developed one to two weeks later. On admission to hospital after 6 months without treatment, the patient reported an increasing inability to concentrate, speech disorders and tremor. An X-ray revealed various mercury deposits in the body but not, however, in the heart. The Hg level in the blood was 680 µg/L. During 7 days' treatment with DMPS (50 mg i.v. per day), the Hg concentration in the urine increased up to 12,050 µg/L. During the second treatment cycle, the urine level was still 4,250 µg/L. A third treatment cycle increased the Hg concentration in the urine from 786 µg/L to 4,880 µg/L. The Hg level in the blood fell only to 478.8 µg/L. Depression, tremor and weakness in the left hand persisted. The patient refused to undergo surgical removal of the Hg deposit. Tremor still persisted two years later. The blood level was between 500 and 600 µg/L. Two further treatment cycles with 250 mg i.v. DMPS and 300 mg oral DMPS for 5 days caused blood levels to fall to 400 µg/L. After treatment, however, these slowly rose once again, finally reaching the baseline value. This was followed by the surgical removal of the mercury from the left *Fossa cubitalis*, whereupon approximately 75% of the Hg deposit could be removed. The Hg level in the blood fell to 250 - 300 µg/L but did not decrease any further over the next few days. The authors do not, however, explain why they discontinued chelate therapy after 5 days although mercury concentrations in the urine exceeded 10,000 µg/L. Subsequent treatment cycles with DMPS will, however, be considered[<1565>].

A 26 year-old employee attended hospital ½ an hour after intravenous injection of mercury. 11 days' treatment with i.m. BAL was introduced. DMPS was then administered for 2 years (no dosing details given). DPA was also administered during the second week. In addition, mercury deposits were surgically removed. During DMPS therapy, the mercury level in the blood fell from 200 µg/L to 60 – 80 µg/L. Mercury excretion in the urine increased from 60 µg/day to 2,600 µg/day and subsequently levelled off at around 600 µg/day (normal value < 20 µg/day) within a few weeks. The lady remained asymptomatic during the period in question[<37>].

In three of the four people, mercury was visible on X-ray after intravenous injection (0.5 to 20 mL). Hg levels increased to 20 to 2,000 µg/L in 24-hour urine and to 5 - 25 µg/L in the blood. The administration of DMPS triggered only a transient decrease. However, none of the patients developed the typical symptoms of mercury poisoning[<758>].

A 16 year-old male heroin addict injected the mercury from a thermometer intravenously with suicidal intent. On admission to hospital Hg levels of 21.4 µg/L and 183.3 µg/L were recorded in the blood and urine, respectively. Two treatment cycles with DMPS administered for a total of 17 days lowered the blood level to 8.1 µg/L whereas the urine level increased to 397.6 µg/L six weeks after treatment. X-rays confirmed Hg deposits in the lungs, which gradually disappeared completely. Due to early diagnosis and an immediate start to chelate therapy, no signs of Hg intoxication were evident apart from a transient rise in NAG enzyme levels and N-acetyl-ß-glucosaminidase indicative of mild kidney damage[<139>].



Hg concentration in the urine during 6-day treatment cycles with 3x200 mg DMPS/day in one patient, beginning at various times after i.v. injection of metallic Hg<1448>

A 35 year-old man suffered from gingivitis, muscle weakness, hyperpyrexia, abdominal pain, diarrhoea and loss of appetite 6 weeks after i.v. injection. X-rays revealed heavy metal deposits. Over the next 5 years, the patient received 4 treatment cycles (3 x 200 mg oral DMPS/day for 6 days). Slight hypersensitivity in the form of a skin reaction was observed at the start of treatment, but this disappeared spontaneously after 2 days. Metallic Hg was still apparent on X-rays taken 5 years later. Tremor and weakness of the lower extremities persisted<1448>.

A 27 year-old man injected approximately 1.5 mL (20 mg) of mercury intravenously with suicidal intent. Thirteen hours later he was admitted to hospital with chest pain, severe sweating and tingling sensations in the extremities. Hg particles were highlighted in the lung region on X-ray. Hg deposits were found in the vessels of various organs on CT scanning. Five days' treatment with DMPS (200 mg every 8 hours) was started 37 hours post-injection. A total of 8 mg Hg was excreted renally over this period. After a 3-day treatment pause, the patient was treated with DMSA (500 mg/day, administered in 3 divided doses) for 5 days. Hg excretion was 3 mg. The serum concentration was not significantly affected by treatment. No further treatment was administered as a result and since no severe symptoms were present (Hg level in the serum: 190 µg/L, in 24-hour urine: 589 µg/L). "Although treatment with DMPS or DMSA was associated with marginally increased renal excretion of Hg in our patient, clinically relevant elimination did not occur and evidence of benefit is doubtful"<399>.

Following i.v. injection of mercury, the mercury content of the body gradually decreased over the years without any further treatment. However, mercury deposits could still be detected in the lungs and the right cardiac ventricle on X-ray, even after 19 years. During this prolonged contact time, chronic mercury poisoning can develop through absorption, mainly manifesting in the kidneys. Such was the case described by Stier in relation to a patient who developed kidney failure 19 years after injection.

A 39 year-old patient was given short-term treatment with 300 mg oral DMPS after i.v. injection of Hg with suicidal intent<1540>. In a 21 year-old nurse, the renal excretion of mercury increased from 484 to 1,304 µg/g<532> following administration of DMPS, 14 months after injection of the heavy metal.

Transient dyspnoea and pain on breathing developed in a 39 year-old man following intravenous injection of 40 mL of mercury. He was admitted to hospital 3 years later with still intense tingling sensations in both legs, profuse sweating, pain in the region of the heart and headaches. The mercury level in the blood was 96.3 µg/L and in the urine, 602 µg/L. Mercury deposits could be detected on X-ray. No findings were observed on urinalysis and there was no evidence of kidney damage. 300 mg Dimaval was administered per day for 6 months. The mercury concentration increased to 2,240 µg/L. Although high levels of zinc and copper were excreted in the urine, no deficiency of these trace elements was detected in the blood<596>.

In a 23 year-old man, the Hg level in the blood increased to 294 µg/L following i.v. injection of mercury. Treatment with DMPS (300 – 800 mg daily orally) was started and continued for 4½ years. The blood level rose in the interim to 1,608 and the urine level to 73,500 µg/L. The patient nevertheless remained asymptomatic and fit for work. Side effects did not occur and the plasma levels of copper, zinc and selenium were not lowered<96>.

A 32 year-old female patient who had intravenously injected approximately 2 g of metallic mercury from a thermometer, was initially treated with N-acetyl penicillamine for 4 months. Treatment was changed to the more effective DMPS due to intolerable side effects. The heavy metal excretion in the urine was increased by DMPS (1 x 250 mg) from 560 to 3,700 µg/L daily. The similarly

increased quantities of trace elements excreted, namely zinc and copper, were consequently replaced during DMPS therapy[<166,167>].

"Multiple foreign bodies, the thickness of metal, were detected under both lungs" on X-ray in a 34 year-old man presenting with occasional, right-sided chest pain. The mercury level in the blood was 170.4 µg/L and in the urine, 105 µg/g creatinine. No further symptoms were present. "Intravasal mercury poisoning" was established as the cause and DMPS therapy was initiated[<540>].

A female patient who intravenously injected the contents of two thermometers with suicidal intent was only observed for almost four months as the mercury level in the urine did not exceed the BAT value of 200 µg/L. Oral treatment with 3 x 100 mg was then introduced when Hg levels reached 220 µg/L. Acute kidney failure with anuria developed just one day later warranting 14 days of haemodialysis. DMPS treatment was stopped. DMPS had obviously mobilised the deposits of mercury and, in such quantities, saturated the kidneys, thus resulting in kidney failure[<564,1389>]. Gülden *et al*. therefore recommended the following: "Treatment with chelating agents (e.g. Dimaval) thus appears to be essential, even in patients with a low injection dose and no symptoms, in order to prevent renal damage"[<532>].

Conclusion:
Surgical dissection appears to be the most important step following injection with metallic mercury. The additional administration of DMPS increases renal excretion. The need for a long-term therapy remains a controversial topic for discussion.

7.2.12.5.2 Oral administration

The solubility of elemental Hg is extremely low (6 µg/100 g of water, 0.3 µg/100 g n-hexane[<1059>]. Its gastrointestinal absorption is, therefore, very slight[<1033,1059>]. Clinical symptoms rarely occur[<142>], but individual cases of poisoning cannot be ruled out[<1543>]. "Massive treatment is essential, especially active charcoal and isotonic sodium thiosulfate as a laxative following oral ingestion of metallic Hg (not finely distributed). Excretion can be monitored on X rays"[<386a>].

A 35 year-old man with subileus of the small intestine ingested metallic mercury into the gastrointestinal tract through rupture of the balloon of a Miller Abbot probe. It was presumably partly absorbed by ileus-induced epithelial lesions. A raised mercury level of 940 µg/L was detected in the blood after approximately 24 hours. Dimaval therapy with 58 capsules over 7 days was, therefore, started immediately. The blood level fell rapidly and had decreased to 230 µg/L in the whole blood after just 24 hours. Urine levels rose briefly to 700 µg/L. The clinical course was without complications despite elevated mercury levels in the blood. There was no evidence of renal damage at any point in time such that the patient was discharged after 12 days without any symptoms[<809>].

A 33 year-old female patient became ill 10 minutes after drinking 1,000 mL of liquid Hg (approximately 13 kg!). She had to vomit on three occasions. 16 hours later, she was seeking hospital admission due to abdominal pains. Hg levels of 180 µg/L and 653.4 µg/L were recorded in the blood and urine, respectively. X-rays confirmed that the Hg had been completely excreted after 3 weeks. DMPS therapy was also administered for 5 weeks (250 mg i.m. DMPS/day for 3 days followed by a 4-day pause). Hg excretion in the urine increased to 2,585.34 mg/d (the author confirmed the value when asked!), thereafter regressing to 241.24 mg/d up to the end of treatment[<1370>].

DMPS therapy was given to a 32 year-old man who had swallowed elemental mercury although mercury was still visible on the X-ray after no clinical symptoms developed[<1375>].

Conclusion:
As orally ingested mercury is only absorbed in very small quantities, no antidote is generally required.

7.2.12.5.3 Other method of administration

In a 2½ year-old boy, a deposit of metallic mercury developed in the left eye socket after an accident with a thermometer. As complete surgical removal of the heavy metal was impossible, additional treatment with DMPS therapy (100 mg/day) was initiated. At the start of treatment, there was a rise in the mercury concentration in the 24-hour urine from 24 µg/L to 443 µg/L. The treatment, which was carried out for more than one year, was well tolerated without any side effects and will be continued as mercury deposits can still be detected on X-ray and the mercury level in the urine is still slightly raised<1141>.

A 25 year-old female schizophrenic developed headaches and photosensitivity following intraocular Hg injections. Foreign bodies visible on X-ray lead to the diagnosis. The eyes were irreversibly damaged. DMPS treatment was initiated for 18 days after bilateral nucleation. On the first two days, the patient received 200 mg of oral DMPS every 2 hours, whereupon the Hg excretion in the urine (240 µg/g creatinine) rose drastically. The patient subsequently received 4 x 100 mg/day<101,684>.

Metallic mercury became embedded in both arms of a 33 year-old archer during a sporting accident. This was initially unnoticed. X-ray deposits were not detected on X-ray until metallic mercury began to seep from an abscess. A large section was surgically removed. However, finely distributed particles remained. Treatment with Dimaval was introduced simultaneously. Despite high mercury values (serum 393 µg/L, urine before Dimaval 982 µg/L, urine during Dimaval 3,380 µg/L), the patient was neurologically normal at the time in question. Pathological blood and urine values were still recorded during a follow-up appointment six months later. Neurological symptoms, speech and memory disorders, impaired taste and minor tremor were also exhibited. Despite the continuously high excretion rates, Dimaval therapy was discontinued as it did not lower mercury levels in the blood<913>. Presumably, mercury from the metallic deposits continuously replaced the heavy metal excreted in the urine.

A 61 year-old women inadvertently aspirated metallic mercury into her lungs. After eight months, isotope investigations confirmed that the organic mercury had formed and accumulated in the kidneys. The patient had develop mild proteinuria after 6 months. Six days' treatment with DMPS (300 mg/day) increased the mercury excretion in the urine and lowered the level in the kidneys from 104 µg/g to 71 µg/g. Mercury levels in the plasma and erythrocytes remained unchanged<627>.

Vomiting and fainting developed in a 21 year-old patient two days after aspirating a large quantity of mercury. Metallic deposits were visible on the X-ray. Slight EEG changes and a reduction in nerve conduction velocity were observed after 6 weeks. Emotional lability and a slight short-term memory loss were seen after 14 months. Kidney function was normal apart from intermittent proteinuria. No abnormalities were found on spirometry. The density of the metal shadows on the X-rays decreased. Despite intermittent treatment with DMPS and DPA, Hg levels in the plasma and urine were markedly high<138>.

Conclusion:
Surgical dissection is the most important stage with other forms of metallic mercury ingestion. Each case must be assessed individually in order to ascertain whether additional administration of DMPS is required.

7.2.12.6 Unknown type of mercury

Mercury poisoning was assumed to be the cause of erythromelalgia in a 4 year-old girl. No improvement was elicited with over 2 months' administration of 100 mg DMPS/day. However, Hg levels in the blood and urine were within the normal range at the start of treatment. Hg excretion immediately after the start of DMPS therapy was not determined<903>.

Patients with chronic Hg poisoning had high mercury levels in the cerebrospinal fluid in addition to raised blood concentrations. Levels in both the blood and the cerebrospinal fluid were lowered following DMPS therapy<851>.

7.2.13 Ni - Nickel

Nickel is used in the production of specialist steel, in electrotechnology and electroplating as well as a material for fashion jewellery.

Nickel is an essential trace element as a constituent of some metalloenzymes[<166>]. It also acts as an enzyme activator[<93,94>]. On the other hand, it is a potent carcinogen[<343>] (carcinoma of the nose, sinus cavities and the bronchial tract[<1543>]), which plays a crucial role in the recognition of occupational nickel intoxication[<1543>]. Foetotoxic effects are also known[<343>]. Nickel possesses a high sensitising potential on contact with the skin. The biological half-life depends on the solubility of the nickel compound and is 30 – 40 days for nickel oxide. It is mainly excreted via the urine. The EKA value for nickel is 45 µg/L. The normal limit for the general population is 4.0 µg/L in the urea[<1543>]. The reference values for nickel in the urine and blood are < 1.7 and < 3.3 µg/L, respectively[<1288>].

DPA[<1543>] and DMPS are both potential antidotes for nickel poisoning[<306>]. The urine measurements published are not, however, consistent. The nickel content of the urine in patients receiving DMPS was the same as[<1191>] or somewhat higher than that observed in patients receiving no chelating agent[<180,707>].

Conclusion:
According to laboratory animal experiments, DMPS appears to be a suitable antidote for the treatment of nickel intoxication. However, there are no clinical observations to confirm this.

7.2.14 Pb - Lead

Lead is one of the non-essential heavy metals[<63,383a,733>]. No physiological requirement as a trace element has been detected in humans to date[<965>]. The daily lead intake in food is, according to estimates by the WHO, 100 to 300 µg[<166>]. Lead is used in dyestuffs, various industrial products (e.g. accumulators and batteries) and was also used as an additive to motor fuels for many years[<63,1454>]. Lead glassware or defectively manufactured ceramic crockery are key sources of poisoning. Acid foodstuffs or drinks can release lead[<476,481,543,544,572,1543>]. Contaminated foodstuffs and drinking water containing lead are also possible sources of exposure[<1454>]. Medicinal products and cosmetics from exotic “healers“, e.g. “Indian tablets“[<572>] sometimes contain larger quantities of lead[<121,1002,1545>]. The heavy metal can be inhaled on smoking illegal lead-containing drugs such as marijuana and opium[<1002a,1377>]. ”The World Health Organization estimates that 120 million people are overexposed to lead and 99 percent of the most serious cases are in the developing world”[<1489a>].

The absorption of lead in the gastrointestinal tract is less than 10% in adults, but is approximately 5 times greater in young children[<121,539,1543>], who are, therefore, particularly at risk[<539>].

Following ingestion, lead is also redistributed in the deeper compartments (bones, brain), which affects clearance. Up to 95 % of the total lead burden is deposited in the bones where it forms a pool with a long half-life (10 - 28 years). This can post a problem on severe bone changes or decomposition (e.g. post-menopause, pregnancy, kidney failure or treatment with cis-platinum)[<121,539>]. Up to 95% of the inorganic lead present in the blood is bound to erythrocytes[<570>]. Critical organs on lead poisoning are the central and peripheral nervous systems[<2>].

It is known to cross the placenta[<1508>]. Embryotoxic and teratogenic effects may occur[<1454>]. No carcinogenic effects have been reported with lead[<1543>].

Organic lead poisoning, on the other hand, mainly affects the central nervous system due to the lipophilic nature of the toxin. As organic blood is not bound to erythrocytes, lead concentrations in the blood are not that high[<121>].

Up to 65-75 % are excreted in the urine and 25-30 % via the bile. Smaller quantities can be found in the sweat and milk[<539>]. After brief exposure, the biological half-life of lead in children is 8 – 11 months compared to 20 – 38 months following long-term exposure due to its release from the

"Symptoms of lead poisoning:

Non-specific symptoms:
Headaches, fatigue, sleep disorders, lack of drive, muscular weakness, unsteady gait and weight loss

Specific symptoms:

- *Skin*: "anaemia due to lead poisoning' (pale grey-yellow pallor)
- *Gastrointestinal tract:* anorexia, salivation, "blue line" (greyish black discolouration on the edges of the gingiva and at the dental root), "lead colic' (painful abdominal spasms), constipation (paralytic ileus)
- *Blood:* Hypochromic anaemia (basophilic spotting of the erythrocytes, Polychromasia, anisocytosis, reticulocytosis)
- *Nervous system*: ‚Bleilähmung' (Schlaffe Lähmung of the extensor muscles through paresia of the *N. radialis* ‚*N. peronaeus*); lead encephalopathy (confusion, excitability, hallucinations, seizures, somnolence possibly culminating in coma)
- *Cardiovascular*: bradycardia, hypertension, peripheral vasoconstriction
- *Eyes*: Atrophy of the optic nerve (induced by spasms of the retinal arteries)
- *Liver*: Hepatomegaly
- *Kidneys*: ‚"Saturnine atrophic kidney" (toxic glomerular-capillary damage)"[<1002b>]

bones[<41>]. The half-life in the erythrocytes is approximately 20 days, in the soft tissue 40 days and in cortical bone up to 28 years[<166,539,1543>].

Lead reacts with sulfhydryl groups of various enzyme systems and thus reaches various metabolic regions[<539,1543,1545>]. It also interacts with essential elements such as calcium, iron or zinc[<539>].

Neurological and gastrointestinal disorders are typical symptoms of lead poisoning[<118>]. Cardinal symptoms after a certain latency period[<1173>] are: Gastrointestinal colic, anaemia, paresis, impaired kidney function (lead nephropathy[<121>]) and general lethargy[<1454,1543>]. A reduced sperm count, infertility, impaired menstruation and spontaneous abortions have also been reported[<539>]. Lead can also impair the growth of children. A negative correlation has been found between the blood lead level and the height of children[<44>].

Behavioural disorders have been reported in children suffering from lead exposure[<481>]. Adverse repercussions on cognitive and behavioural development can may be expected in children with blood lead levels of 100-150 µg lead/L[<506>]. "Recently neurobehavioural research has produced considerable evidence for harmful effects of lead in children at blood lead levels as low as 10 µg/dL and the US Center of Disease Control has reduced the lead allowable threshold from 25 µg/dL of blood to 10 µg/dL"[<1348>]. "New evidence suggests that even very low blood lead levels, less than 10 µg/dL, can be associated with neurological injury"[<1569>]. "Lead is associated with negative outcomes in children, including impaired cognitive, motor, behavioural, and physical abilities. In 1991, CDC defined the blood lead level (BLL) that should prompt public health actions as 10 µg/dL. Concurrently, CDC also recognized that a BLL of 10 µg/dL did not define a threshold for the harmful effects of lead. Research conducted since 1991 has strengthened the evidence that children's physical and mental development can be affected at BLLs <10 µg/dL"[<996a>].

"The problems with lead poisoning are based on the fact that, given the non-specific symptoms in the early stages, lead poisoning is not suspected. In addition, the sources of the contamination are often difficult to pinpoint and the lead will often have been ingested several

Lead concentration in the blood(µg/L)	Symptoms
< 100	Crosses the placenta with adverse
↓	effects on the foetus
100	Growth disorders, impaired hearing,
↓	lower IQ
↓	Increase in EP
	Elevated protoporphyrin
200	Reduced ALAD activity, Increase in
↓	ALAU,
	Impaired nerve conduction velocity
300	Disruption of vitamin D metabolism
↓	
400	Hypertension,
↓	Impaired haemoglobin synthesis
500	Fatigue, sleep disorders, headaches,
↓	loss of appetite, metallic taste, gastrointestinal pain, constipation, myalgia, paresthesia
800	Anaemia, abdominal colic,
↓	Azothaemia, encephalopathy,
1.000	nephropathy, paralysis
↓	Acute encephalopathy, delirium,
> 1.200	coma, death

Clinical symptoms of lead poisoning according to lead levels in the blood[<1173,1508,1548>]

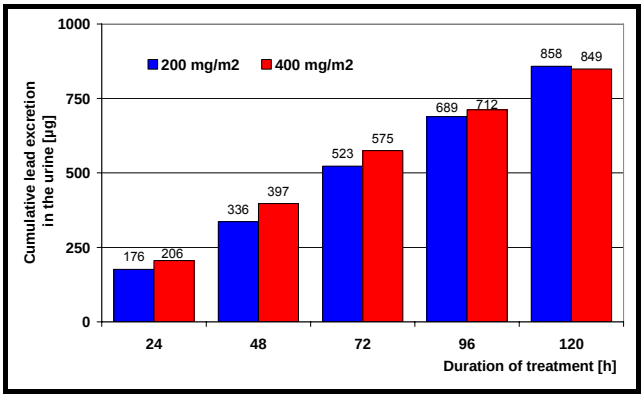
BAT (2003)	400 µg/L blood (men and women ≥ 45 years) 100 µg/L blood (women up to 45 years)
HBM I	150 µg/L (children and women up to 45 years old) and 150 µg/L (men)
HBMII	150 µg/L (children, women up to 45 years old) and 250 µg/L (men)
Reference values	Men < 120 g/L (blood)
Background load	Women < 90 µg/L (blood) Kinder < 60 µg/L <1454, 1288>
PTWI	25 µg/kg BW<1200a>

months earlier. Lead poisoning can, however, be confirmed on the basis of laboratory chemical tests and, together with a detailed medical history, can be subsequently diagnosed“ <730>. In the event of unclear symptoms, lead poisoning should not, therefore, be overlooked in a differential diagnosis<1545>. ”Our report highlights the importance of taking a detailed occupational history and considering lead poisoning in the differential diagnosis of acute abdominal colic of unclear cause”<1334a>. Nowadays, lead intoxication can generally be cured without any sequelae<1543>.

Lead concentrations of 100 to 200 µg/L are considered acceptable in adults<685>. Blood lead concentrations ranging from 200 to 450 µg/L can be assumed to be indicative of a certain degree of lead exposure. The source of the exposure must be determined and eradicated. Medication may have to be introduced in order to reduce the lead levels. Concentrations ranging from 450 to 700 µg/L warrant medicinal therapy (chelate therapy). Concentrations exceeding 700 µg/L are classed as a medical emergency requiring immediate treatment“<539,572,770,1103,1200a>. According to other experts, treatment is indicated with lead levels in the whole blood of >250 µg/L for men and >150 µg/L for women of child-bearing age<1002b>. Administration of an antidote to children with lead levels < 450 µg/L is subject to controversy. An antidote is generally considered essential for levels > 450 g/L<641,1200a>. Lead poisoning with acute encephalopathy in babies and young children requires immediate treatment<1200a,1506>.

DMPS, DMSA, EDTA and DPA are possible antidotes for the treatment of high lead values and marked symptoms of intoxication<512,513,1002a,1200a,1327,1454,1543>. BAL is contraindicated<1454>. DMPS is the drug of choice in Germany<1061>. It triggers fewer adverse reactions than treatment with DPA<1002a,1002b,1542> or EDTA<1542>. DMPS and DMSA are the drugs of choice for lead poisoning in Austria<724>.

DMPS was effectively used in the treatment of lead poisoning in sea eagles and a horse<709>. The sea eagles absorb the lead in the form of shot when they consume shot birds that have managed to flee their hunters<964>.



Cumulative Pb excretion in children receiving DMPS therapy<269>

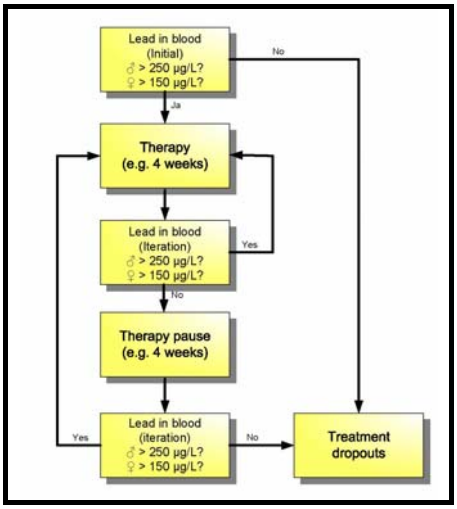
Following administration of the antidote, the excretion of heavy metal via the urine increases<95,306,476,478,480,740,1040,1191> and blood levels fall<1021>. Long-term treatment is mostly required<306> due to the often large quantities of lead deposited in the bones (half-life ≈ 20 years<63>) .

Complex-forming agents are hardly effective in organic lead poisoning<1560>. Excretion remains unaffected<543>.

The recommended dose of DMPS is 5 mg/kg BW every 6-8 hours p.o, .i.m. or i.v. The DGAUM (German Society for Occupational and Environmental Medicine) recommends treatment with 10-30 mg/kg BW i.v. or 100 mg oral DMPS t.i.d.<1454>. The Bundesinstitut für Risikobewertung (Federal Institute for Risk Assessment) recommends the following for the treatment of chronic lead poisoning in adults and children:

- 250 mg i.v. every 4 hours for 7 days.
- 100 mg p.o. every 6 hours until blood levels fall, followed by a dose reduction.
- 100 mg p.o. every 12 hours<542>.

On completion of treatment, there may be a delayed rise in blood lead concentrations through release from the bone deposits. "The blood lead concentration should be checked 14 to 21 days after cessation of antidote treatment to monitor the rebound in blood lead due to redistribution from bone stores"<1200a>. A new course of treatment is required in the event of a recurrent rise in the lead concentrations in the whole blood <250 (men) and <150 µg/L (women)<1002b>.



Recommended in the treatment of chronic lead poisoning<1002b>

7.2.5.1 Mobilisation of lead

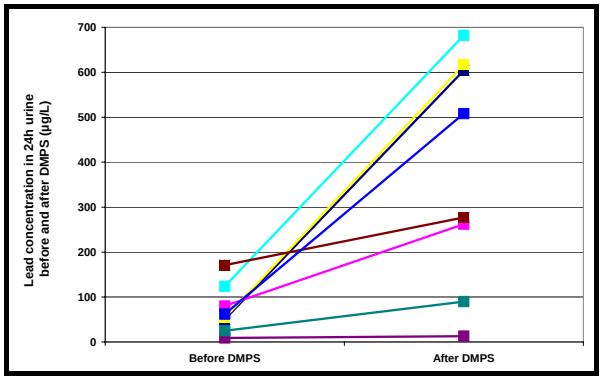
DMPS increases the urinary excretion of lead in humans<489>. Lead blood levels ranging from 51 to 871 µg/ were recorded in 8 employees exposed to lead oxide-containing dust in their work for 2 to 13 weeks. In 7 of these subjects, values exceeded the valid BAT level. Lead excretion in 24-hour urine ranged from 9 to 171 µg/L and increased to between 13 and 682 µg/L on single oral administration of DMPS. Thus no correlation was found between lead concentrations in the urine before and after administration of DMPS. Similarly, there was no correlation between the length of exposure or the blood lead level and the increase in the excretion of lead via the kidneys following administration of DMPS. Nevertheless,

Volunteers		Pb excretion				Type of mobilisation test			Literature
n	Patients	before DMPS	after DMPS	Unit	Increase	DMPS dose	Method of administration of DMPS	Collection period	
11	Manufacturer of cream containing Hg	5	22.8	µg/6 h	4.6	300 mg	oral	6 h	57,890
8	Users of cream containing Hg	4.4	22.7	µg/6 h	5.2	300 mg	oral	6 h	57,890
9	Subjects without amalgam	4.8	36	µg/6 h	7.5	300 mg	oral	6 h	57,890
13	Subjects without amalgam	1.8	3.3	µg/24h	1.8	300 mg	oral	24 h	1524
129	Subjects with amalgam	1.7	22.6	µg/24h	13.3	300 mg	oral	24 h	1524
85	Women with history of abortion	2.25	31	µg/g crea	13.8	10 mg/kg BW	oral	2 h	228
398	Women without history of abortion	2.06	27	µg/g crea	13.1	10mg/kg BW	oral	2 h	228
100	Women with history of abortion	3.9	37.32	µg/g crea	9.6	10 mg/kg BW	oral	2 h	470
501	Control patients	2.9	32	µg/g crea	11.0	10 mg/kg BW	oral	2 h	471, 479,480
30	Women	2.6	30	µg/g crea	11.5	10 mg/kg BW	oral	2 h	474
73	Women	2.2	34	µg/g crea	15.5	10 mg/kg BW	oral	2 h	474
38	Neurodermatitis	6	30	µg/g crea	5.0	250 mg	i.v.	45 min	637-639
15	Psoriasis	5	27	µg/g crea	5.4	250 mg	i.v.	45 min	637-639
6	Female patients with HELLP (haemolysis, elevated liver enzymes and low platelets syndrome)	5.3	37.4	µg/L	7.1	3 mg/kg	i.v.	30-45 min	563
?	Control patients	2.8	8.3	µg/L	3.0	3 mg/kg	i.v.	30-45 min	563

Increase in the urinary excretion of lead following a single dose of DMPS in various patient or control groups

the authors deemed that no additional information was to be gained from determining the quantity of lead that could be mobilised. The lead concentrations in the blood were lowered in 7 out of the 8 employees by administration of a single dose of DMPS<1309,1310>. A single oral dose of 300 mg DMPS did not alter lead levels in the whole blood and urine in non-exposed subjects<583>.

Oral or parenteral administration of DMPS leads to increased urinary excretion of lead in humans. In volunteers with normal environmental exposure without acute lead poisoning, excretion of the metal increased 7.1-fold on injection and approximately 15-fold on oral administration.



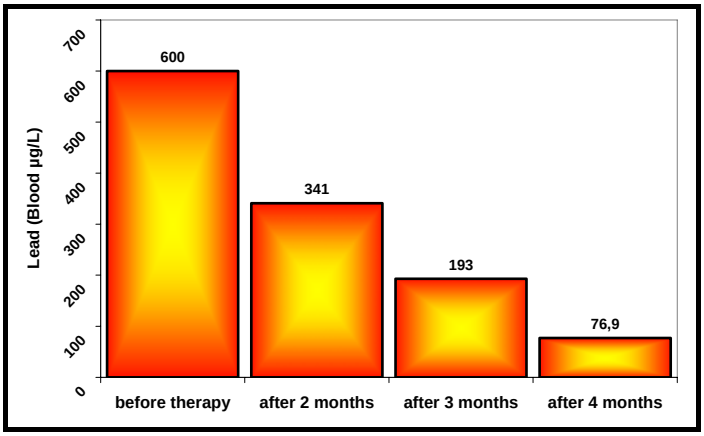
Lead concentration in 24-hour urine in 8 employees before and after oral dosing with 300 mg DMPS<1309>

7.2.5.2 Chronic and acute poisoning

250 mg i.m. DMPS were administered daily for 20 days to 60 men with chronic lead poisoning in comparison to a patient group given only symptomatic treatment. The lead excretion in the urine was increased and the lead concentrations in the blood fell. The clinical symptoms improved subjectively and objectively. Thus, for example, the symptoms of anaemia disappeared. Haematological parameters, porphyria and liver function improved after treatment in more patients in the DMPS group than in patients receiving symptomatic treatment. The clinical picture of lead poisoning improved more rapidly during DMPS therapy than in the controls so that DMPS patients could be discharged from hospital up to 6 weeks earlier<28,69,418>. The prophylactic administration of DMPS is, therefore, recommended on lead exposure<69>.

Children aged 31 to 53 months old who were still asymptomatic with chronic lead poisoning (initial lead concentrations in the blood ranging from 400 to 600 µg/L) were treated for 5 days with oral DMPS at a daily dose of 200 mg/m^2 body surface (≈ 4 x 30 mg/d)<266,269>. To make it easier for the children to take the preparation, the active substance was dissolved in cold orange or apple juice and immediately administered<266,269>. After 5 days, the lead level had fallen to 72% of the baseline value. Doubling of the DMPS daily dose reduced blood lead levels to 68% of the baseline value. The effect of DMPS on lead concentrations in the blood was thus comparable with that of calcium disodium edetate $CaNa_2EDTA$ (reduction to 60 %)<1437>. DMPS had the advantage over EDTA that the blood levels of zinc and copper were unaffected. The cumulative excretion of lead in the urine after 5 days' DMPS therapy was 2 to 6 times the excretion before therapy<268,269>.

A 24 year-old administration employee suffered from diffuse, partially colic-like abdominal pains, constipation and weight loss for two weeks. Various misdiagnoses were postulated and corresponding ineffective treatments introduced. Lead poisoning was finally diagnosed. The lead concentration in the serum was 600 µg/L (norm: < 90 µg/L), in 24-hour urine 1,700 µg/L (norm < 800 µg/L). A Greek ceramic cup from which the female patient had drunk two lemon teas every day for 2½ months was identified as the source of the heavy metal. Oral treatment with 400 mg DMPS t.i.d. was introduced. After two days, the dose was reduced to 100 mg t.i.d. and treatment was continued for 4 months in order to gradually eliminate the heavy metal released from the bones. Treatment was well tolerated. Zinc, copper and magne-



Reduction in the lead levels in whole blood during oral DMPS therapy<102>

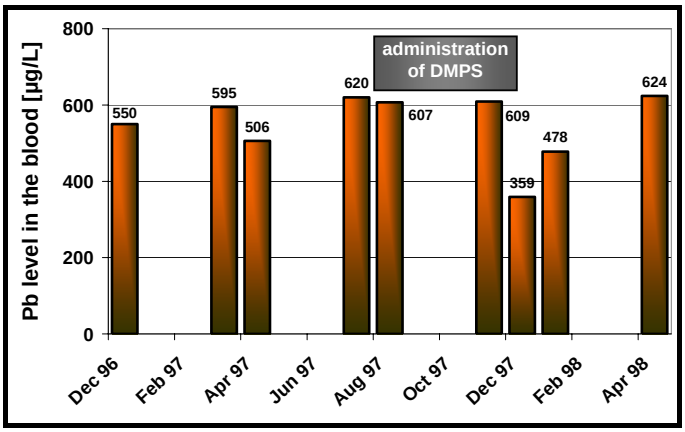
sium levels remained within the normal range. Iron was replaced. Symptoms rapidly disappeared[<102>].

A 59 year-old Slovenian woman suffered from non-specific, gastrointestinal symptoms. PB levels in the blood were 864 µg/L. The enamel on a jar was identified as the source of the lead intoxication. Symptoms disappeared after a few days following treatment with DMPS (short i.v. infusion of 250 mg every 4 hours on the 1st day, every 6 hours on the 2nd day followed by 100 mg oral DMPS t.i.d. for 10 days). As the blood level at 534 µg/L was still high, a second course of treatment was administered (4 days i.v., 8 days oral). The blood levels fell to 111 µg/L. Most of the laboratory parameters (with the exception of erythrocytes and porphyrin) reverted to normal. Treatment with DMPS was effective and was tolerated without any complications or adverse reactions. The trace elements – zinc, magnesium, copper and iron – remained within the normal range[<1264>].

A female adult poisoned herself with lead over a period of 6 – 8 months by drinking lemon tee from a ceramic Crete carafe. She was finally admitted to hospital after suffering from abdominal pain similar to colic. The initial lead concentration in the blood was 760 µg/L. Dimaval treatment was initiated. In the second week, treatment had to be switched to DPA due to allergic reactions. The blood level slowly fell. No further symptoms were observed[<544>].

A 68 year-old woman suffering from fatigue, nausea and abdominal pain was admitted to hospital for the first time after one month. Hypertension and anaemia were diagnosed in the hospital. She was readmitted to hospital one month later with seizures. The neurological symptoms deteriorated and the patient was again readmitted to hospital 3 months later with speech disorders and weakness of the extremities. Lead poisoning was finally diagnosed. Lead concentrations of 10.2 µmol/L (normal < 1.0) and 637 nmol/L (normal < 310) were recorded in the blood and urine, respectively. The tetraparesis improved over 5 days' treatment with DMPS and Ca-EDTA i.v. Lead concentrations in the blood fell to 3.9 µmol whilst urine levels increased to 4,247 nmol/L. The source of the lead poisoning could not be established. Blood levels had increased once again 6 months later. Treatment with EDTA and DMPS was, therefore, repeated. On this occasion, a lead-containing lip cream was identified as the source of the poisoning[<432>].

Four children between 4 months and 3 years of age were suffering from acute encephalopathy due to acute lead poisoning (lead concentrations in the blood ranged from 740 to 2,690 µg/L). Two of the patients were already comatose. I.V. DMPS therapy was introduced following initial symptomatic treatment (artificial ventilation and neurosurgical decompression). One child was also given EDTA. Lead blood levels consequently fell to approximately 30 – 40% of the baseline value. The clinical symptoms improved and the children were discharged. Treatment with oral DMPS was continued. In one of the children, DMPS therapy was switched to EDTA due to an increase in transaminase levels, which occurred in the meantime. DMPS treatment was, however, subsequently administered without any complications[<215,544,755,1506>]. Control tests carried out in one girl revealed markedly high lead blood levels of 300 to 400 µg/L, which continued for many years[<755>].



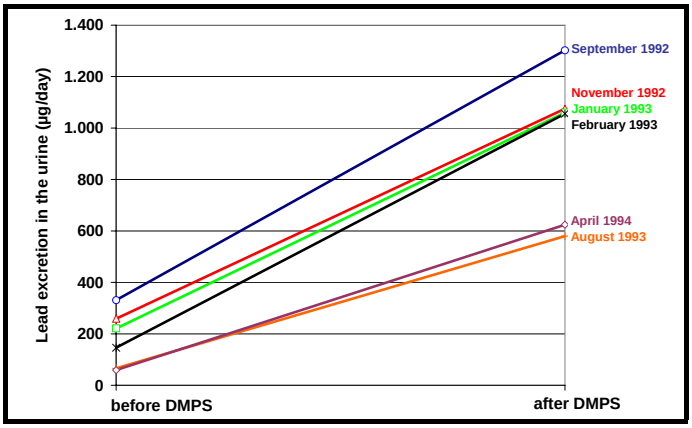
Long-term lead levels in the blood before, during and after DMPS administration[<1555>]

Chronic lead intoxication confirmed by additional porphyrin diagnosis and anaemia was diagnosed in a 68 year-old female patient after a medical history of almost two years' duration characterised by recurring, partly life-threatening abdominal colic (resulting in 4 hospital admissions!). The patient also presented with hypertension, which is a recognised symptom of chronic lead poisoning. Lead blood in the blood were 600 µg/L. Despite a thorough investigation (home inspection, tests with work colleagues and other occupants of the house), the source of the poisoning could not be determined. This was possibly a case of lead mobilisation from the bones

due to osteoporosis as the patient had been exposed to high levels of lead in her former job (worked in lead ovens). However, the lead may also have been consumed with food. I.v. DMPS therapy was initiated. This was changed to oral treatment after four days. The treatment was continued until the blood lead level fell to 359 µg/L. Treatment was well tolerated by the patient and no adverse reactions occurred. The copper and zinc concentrations in the blood remained within the normal range. The patient became symptom-free. Follow-up examinations revealed that the concentration of lead in the blood had again risen to 624 µg/L but the symptoms did not reappear<1555>.

Day	Dosage
1	6 x 250 mg DMPS i.v.
2	4 x 250 mg DMPS i.v.
3	3 x 250 mg DMPS i.v.
4	2 x 250 mg DMPS i.v.
From day 5	3 x 100 mg DMPS oral

Dose of DMPS in the treatment of chronic lead poisoning<1555>



Lead excretion in the urine (µg/day) before and after administration of Dimaval<1418>

Lead poisoning was diagnosed in a mechanical engineer who suffered upper abdominal pain for 6 years. The lead concentration in the whole blood was 778 µg/L. 331 µg/L were excreted in the urine over 24 hours. Without treatment, no reduction in the high lead concentration was detected within 4 weeks. Interval therapy with Dimaval (800 mg/day for 2 weeks, followed by a 2 weeks' pause) was, therefore, initiated. Despite increased lead excretion, the lead concentration in the blood fell only slowly, possibly due to the continued release of lead from the skeletal deposits. The laboratory parameters improved in parallel to the treatment. No treatment-related adverse reactions were observed<1418>. It is striking to note that DMPS increased the lead secretion by almost 10-fold, even after treatment for 1½ years.

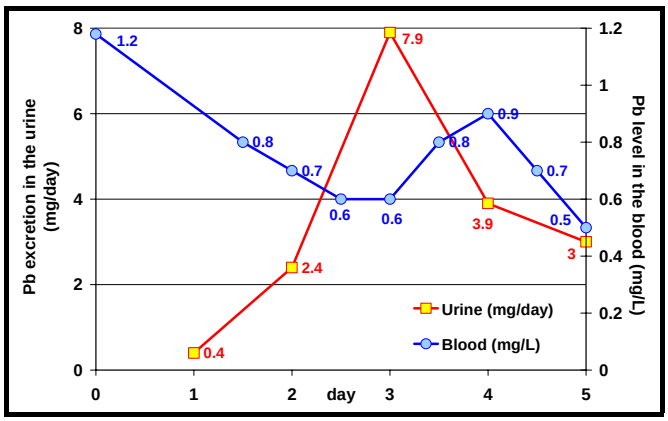
A 45 year-old welder fell ill with recurrent vomiting, abdominal pain and paralytic ileus. Conservative ileus therapy was administered in hospital. The general practitioner subsequently treating the patient detected high lead values and referred the patient once again to the hospital where he was treated with Dimaval for 2 weeks. The continuous release of lead from the bones probably prevented a decrease in lead concentrations in the blood such that the elevated values and the basophilic spotting evident on the differential blood count continued even after treatment. Continuation of lead intoxication can, therefore, be assumed such that after a 2-week break in treatment, a repeat course of Dimaval would have been initiated<730>.

A seasonal worker who removed minimum (red lead)-containing protective grating from high-voltage masts attended hospital with abdominal cramps after just one month. Lead poisoning with anaemia, increased δ-aminolaevulinic acid and coproporphyrins was diagnosed. Lead concentrations of 1,440 µg/L and 432 µg/L were recorded in the blood and urine, respectively. Treatment with 1,500 mg i.v. DMPS/day was initiated. Lead excretion via the urine increased from 144 µg/24 hours to 5,600 µg/24 hours. DMPS was then administered orally at doses ranging from 400 to 600 mg. Treatment was discontinued due to medication-induced exanthema. The patient was discharged symptom-free after 4 weeks to be followed up by the outpatients' department<542>.

A 51-year old Spanish male patient, who had worked in lead smelting for 30 years suffered from abdominal pain for 8 months before lead poisoning was diagnosed (blue colouration of the gingiva, basophilic spotting, increased haemoglobin value of 11.5 mg/dL). A lead concentration of 1,300 µg/L was recorded in the blood. The patient was treated with $CaNa_2EDTA$ for 10 days and thereafter with DMPS for 4 weeks. The abdominal pain disappeared and lead levels fell to 500 µg/L. A concentration of 380 µg/L was still recorded during a follow-up examination performed two years later. The patient remained symptom-free<1047>.

Over a 9-month period, a 39 year-old female patient regularly took various Ayurvedic herbal remedies, which she had brought with her from a treatment centre in India. Chemical analyses later showed that one of the mixtures contained 37 mg of lead per pill. Hyperchromic, microcytic

anaemia, a continuing decrease in physical and mental performance, loss of appetite with flatulence and constipation, sleep disorders and bilateral radial paresis finally culminated in the diagnosis of "chronic lead poisoning due to the ingestion of Ayurvedic medicine pills". A lead concentration of 880 µg/L was measured in the whole blood. The neurological symptoms including radial paralysis slowly regressed during treatment comprising EDTA injections for 16 days and subsequent administration of DMPS (200 mg daily p.o.) for 4 weeks. Hb reverted to normal. The serum lead concentration was still 320 µg/L 19 months after diagnosis[<1545>].



Changes in lead blood levels (mg/ml) and the excretion of lead in the urine (mg/d) during DMPS therapy (DMPS treatment was withdrawn on days 3 and 4)[<611>]

A 64 year-old woman exhibited symptoms of lead poisoning with weakness, fatigue, weight loss, anaemia, hypotension and neuropathy after using a lead-containing ointment for one year. Oral treatment with Dimaval capsules was introduced. Initially, 16 capsules were given in 12 hours. The patient was subsequently given 15 capsules per day for 5 weeks. Thereafter, the dose was reduced to 8 capsules per day for 4 weeks. Within 36 hours of starting treatment, lead levels in the blood fell from 1,150 µg/L to 570 µg/L. Peak lead excretion in the urine of approximately 7,300 µg/L was achieved on the 3rd day. Treatment led within 9 weeks to almost complete emptying of the lead deposits in the body, to disappearance of the symptoms of intoxication and to normal haematopoiesis[<171,349,611>].

The ingestion of lead-contaminated Ayurvedic incense pills, again from India, resulted in lead intoxication with symptoms such as recurring nausea, vomiting, constipation, loss of appetite and generalised myalgia over 7.5 months in a 60 year-old female patient. Clinical-chemical tests revealed normochromic anaemia, basophilic spotting of the erythrocytes and an increased lead concentration in the whole blood (852 µg/L, norm < 100 µg/L). Lead excretion via the urine was also high and further increased following an oral mobilisation test with DMPS. Treatment at the dose level of 4 x 100 mg DMPS/day was introduced. This led to the complete disappearance of abdominal pain and to stabilisation of the haemoglobin value. Treatment had to be switched to DPA after 14 days due to allergic skin reactions[<1286>].

A 44 year-old Persian sales assistant was admitted to hospital with progressive symptoms (cramp-like upper abdominal pain and low back pain and intermittent opiate-induced colic). A lead concentration of > 1,400 µg/L (norm < 150 µg/L) was measured in the serum. Lead levels in the serum continuously fell during administration of 4 x 100 mg oral DMPS/day, amounting to approximately 600 µg/L after 5 days. The heavy metal requirement fell parallel to the decrease in the lead concentration. Lead-contaminated opium, which the patient regularly smoked on returning to his homeland, was discovered to be the source of the intoxication[<1377>]. In the Leipzig region, 130 people were poisoned by smoking marijuana containing lead[<1002a,1002b>].

A particularly rare form of lead poisoning is described in the following case history: A special process applied to bathtubs led to increased concentrations of lead in the bath water (40 µg/L). Prolonged contact times in the bath tub gradually led to poisoning with continuous abdominal pain, impaired intestinal function and high lead concentrations in the blood (1,490 µg/L). The lead concentrations fell during treatment with Dimaval and penicillamine, only to increase once again after the antidotes were withdrawn. A new course of treatment triggered another rapid fall[<1295>].

Chronic lead intoxication with generalised pruritus, a burning sensation of the skin and muscles and intermittent bouts of fever (4 –5 / year) were observed in a 68 year-old male. The source of the lead was presumed to be lead shot, which had remained in the body for over 40 years following a gunshot wound. A high lead concentration of 55,000 µg/L (norm < 150 µg/L) was found, particularly in the skin. A concentration of 225 µg/L wad detected in the blood. The urinary excretion of lead increased from 15 to 260 µg/g creatinine following administration of 3 mg DMPS/kg BW. The clinical course was improved and the number of bouts of fever was reduced to

one per year through the administration of complex-forming agents. DMPS was superior to DTPA in terms of both therapeutic effect and increased excretion[<965>].

In a case of optic nerve atrophy caused by lead deposition in the eye, DMPS treatment (parenteral + local, two 5-day treatment cycles) improved visual acuity, field of vision and adaptation to darkness[<296>].

A fall in the lead concentration in the blood from 310 to 220 µg/L within 9 days with an increase in urine concentration from 60 to 500 µg/L was achieved on administration of DMPS to a 10 year-old boy with chronic lead poisoning[<586>].

In a female patient with acute lead poisoning, the lead level in the blood slowly rose again after 5 days' treatment with $CaNa_2EDTA$. Five days' administration of DMPS lowered the blood level from 800 auf 500 µg/L[<1111>].

The symptoms of lead encephalopathy improved within a few days in two children (aged 2½ years and 4 months)[<1506>].

A boy barely 3 years of age living close to a lead crystal glass factory presented with severe, treatment-refractory combined epilepsy, stunted growth and considerable retardation. Blood levels in the urine increased from 76 µg/L to 1,310 µg/L within one hour of administration of 50 mg i.v. DMPS. The administration of EDTA one month later increased the renal excretion of lead 10-fold. As the patient displayed limited creatinine clearance, the incidence of attacks markedly increased after administration of the antidote, which corresponds to a redistribution of lead in the body. Subsequent antidote therapy was, therefore, dispensed with[<201>].

Conclusion:
Lead poisoning is also described as Plumbismus or Saturnismus in German. The failure to recognise lead poisoning results in unnecessary patient suffering and unnecessary costs for the health services. DMPS increases the urinary excretion of lead, which, on chronic poisoning, does not always have to be accompanied by a decrease in lead concentrations in the blood because of the release of the heavy metal from the bones. Nevertheless, symptoms improve as the case reports show. As DMPS cannot mobilise lead deposited in the bones, patients must be further monitored once treatment has been discontinued. If need be, several courses of treatment should be administered in order to obtain a persistent reduction in lead concentrations in the blood.

7.2.15 Pd - Palladium

On an industrial scale, palladium is used as a catalyser[<166>]. It is also a component of various gold alloys.

DMPS increases the renal elimination of palladium[<306,637,638,1245>]. The palladium excretion in the urine before and after administration of DMPS (oral or i.v.) was determined in 50 volunteers. The elimination rose from 0.3 to 38 µg/g creatinine. No significant difference was observed between the oral and parenteral administration[<88,1245>].

Subjects		Pd excretion				Type of mobilisation test			Literature
n	Patients	Before DMPS	After DMPS	Unit	Increase	Dose of DMPS	Administration of DMPS	Collection period	
38	Neurodermatitis	12	49	µg/g crea	4.1	250 mg	i.v.	45 min	637-639
15	Psoriasis	10	55	µg/g crea	5.5	250 mg	i.v.	45 min	637-639

Increase in the urinary excretion of palladium following a single dose of DMPS in various patient or control groups

Conclusion:
DMPS increases the palladium excretion in the urine. However, there are no reports to confirm whether this improves the clinical picture. Similarly, there are no investigations to determine the efficacy of DMPS on acute palladium poisoning.

7.2.16 Po - Polonium

”Each month about 8 g of Po-210 are shipped to the United States from Russia. Should such quantities of Po-210 be used by terrorist in a radiological incident (e.g., dirty bomb), havoc could ensue. … An ingestion intake as small as 1 µg of Po-210 may be lethal for the most radiosensitive members of the population; ingesting (or inhaling) a few tents of a milligram would be expected to be lethal for all. … Children would be expected to be at higher risk of harm than for adults for the same level of intake of Po-210 because of their smaller body masses and relatively higher radiation doses”[<1318a>].

“^{210}Po is one of the most hazardous radioactive materials. It displays an affinity for soft tissue and also binds to thiol groups and metallothioneins, especially in the liver“. “Polonium 210 absorbed orally or by inhalation, or injected, thus has a varying pattern of distribution. … The relatively heavy and rapid alpha particles destroy cell structures and cell nuclei, damage DNA and may culminate in cell death“[<943a>].

”The difficulty with an isolated and unsuspected case of radiation poisoning is identification. The initial symptoms of vomiting are fairly non-specific, and delay in diagnosis and, therefore, early treatment are almost inevitable”[<708a>]. In addition to BAL, DPA[<538b,708a>], DMPS[<1004a,1234>] and DMSA[<1234>] are recommended in the treatment of polonium ingestion. ”Use of DMSA or DMPS may also be justifiable options“[<1437a>]. They are equi-effective but trigger fewer adverse reactions. There is no experience with any of the antidotes in the treatment of ^{210}Po intoxication in humans[<1234>]. A 5% DMPS solution has proved to be the most effective in removing ^{210}Po from human skin[<380>].

”New, medical countermeasures-related as well as supporting and other modelling research is needed in order to be best prepare for dealing with mass casualties in the event of Po-210 use by terrorist for the purpose of causing harm to U.S. citizens and others”[<1318a>]. ”WHO will continue to monitor promising/potential treatments such as … DMPS/ DIMAVAL_ pero os and i.m. (polonium)”[<1129>].

Conclusion:
As the case of the former Russian spy, Litwinenko, shows, there is a need for antidotes to treat polonium poisoning. As far as I am aware, there have been no publications to date on the use of DMPS or other antidotes in humans following ingestion of polonium. Various laboratory animal experiments have, however, been carried out to highlight the efficacy of DMPS on polonium poisoning.

In laboratory animal experiments, DMPS increased the survival rates following administration of polonium through rapid removal of the α emitter from radiosensitive areas (bone marrow and spleen). DMPS presumably acts not only as a chelating agent in this respect, but also offers protection against radiation damage.

DMPS is most effective when administered immediately after polonium. The longer the interval between administration of the radionuclide and the chelating agent, the less effective DMPS is. ^{210}Po levels were lowered in all of the organs investigated, apart from the kidneys. Elevated radiation exposure to the kidneys leads to pathological changes, which are partly reversible, but which can sometimes lead to nephrosclerosis. The risk of a kidney tumour is also increased. An individual benefit-risk assessment is, therefore, essential prior to administration.

7.2.17 Pt - Platinum

On an industrial scale, platinum is mainly used as a catalyser. A car catalyser thus contains approximately 2 g Pt. Therapeutically, it is used as cisplatin in tumour therapy[<166>]. DMPS is recommended as an antidote for platinum poisoning[<1186>].

Conclusion:
No clinical investigations have been carried out to determine the clinical efficacy of DMPS in acute or chronic poisoning with platinum.

7.2.18 Sb - Antimony

Sb is one of the non-essential metalloids[<733>]. Daily ingestion with food is estimated at approximately 5 - 20 µg[<166>]. Following absorption, Sb(V) compounds remain predominantly in the extracellular regions and up to 80% are excreted via the kidneys over 24 hours. In contrast, Sb(III) is bound with high affinity to the thiol groups of erythrocytes and only around 25% is consequently excreted in 24 hours. Trivalent Sb compounds are approximately 10 times more toxic that pentavalent compounds[<166>]. Sb is deposited essentially in the skin, hair, lungs and adrenal glands. Symptoms of intoxication are: vomiting, diarrhoea, abdominal pain, cough, hypoxia, liver failure, oliguria, weakness, ECG changes, dermatitis, thrombophlebitis, electrolyte imbalance and alopecia[<121,166>]. The reference values for Sb in the urine and blood are < 1.1 and < 3.5 µg/L, respectively[<1288>].

DMPS is a suitable antidote for Sb poisoning[<29,95,610,1506>], even in children. The antimony content in the urine of patients receiving DMPS was higher than that recorded in patients not treated with a chelating agent[<180>]. In 3 children (aged 1 year 4 months to 4½ years) who were suffering from poisoning with potassium tartrate, the renal antimony excretion was increased by oral administration of 50 mg DMPS every 8 or 12 hours. Urine levels fell from 7.615 µg/L (6 hours after ingestion) to 75.3 µg/L (after 10 days' treatment). No treatment-related side effects were observed[<166,657>].

A 3 year-old girl swallowed about 2.3 g antimony potassium tartrate, which is several times the lethal dose for children. After 1 hour, she vomited profusely. This was followed by massive diarrhoea, exsiccosis and a rapid, flat pulse. The child developed increasing apathy. First of all, forced diuresis was initiated. After "severe antimony potassium tartrate poisoning" had been diagnosed, 65 mg DMPS was administered initially via the i.v. route and subsequently 100 mg DMPS t.i.d. was administered orally for 10 days. The dose was then reduced to 50 mg t.i.d. and continued up to the 20th day. Given the fact that antimony is known to bind to erythrocytes, a exchange transfusion/exchange was undertaken 39 hours after ingestion of the poison. When DMPS therapy was withdrawn, there was punctate, papulous, generalised exanthema with severe itching, especially on the arms and hands. The effects on the heart and liver described for antimony poisoning, such as ECG disorders and changes in immunoglobulin values, did not occur[<586,630>].

DMPS has been tested for reducing the toxicity of antimony compounds during schistosomiasis treatment with good results[<716>].

Conclusion:
Laboratory animal experiments confirm the efficacy of DMPS on antimony poisoning. The use of DMPS was also effective in the 4 case histories published. DMPS is, therefore, suitable, for the treatment of antimony poisoning.

7.2.19 Se - Selenium

Selenium is an essential trace element[<63,166,343>]. In excess, however, it is toxic[<343>]. Foetotoxic effects are known to occur at high doses[<343>]. Subjects exposed to amalgam or occupational mer-

cury, excrete less selenium in the urine than non-exposed subjects. It is presumably retained in the body as mercury selenide[<598>].

The caesium content in the urine of patients receiving DMPS corresponded to that recorded in patients not treated with a chelating agent[<180>]. The administration of 200 mg oral DMPS did not change selenium levels in the plasma of two former employees of a mercury mine[<402>]. In contrast, higher values were recorded during combination therapy comprising DMPS + Zn-DTPA or DMPS+DMSA+Zn-DTPA[<180>].

DMPS is listed as an antidote for selenium poisoning[<306>]. Accelerated selenium excretion in the urine was observed[<598>] in 80 subjects immediately following single i.v. administration of 2 mg DMPS/kg BW, with peak excretion being reached after approximately 30 minutes[<597>]. The overall excretion of selenium in the urine was, however, only slightly increased[<598>].

Conclusion:
No investigations have been carried out to establish whether elevated selenium excretion in the urine concerns a direct Se-DMPS effect. A more probable explanation is that DMPS cleaves available HgSe by binding with Hg. The selenium released can then be excreted. According to laboratory animal experiment, DMPS is not effective in the treatment of selenium poisoning.

7.2.20 Sn - Tin

Tin is a component of the gastric enzyme, gastrin, and is, therefore, an essential trace element[<166>]. With tin, the organic tin compounds in particular are toxic. These are used as biocides in the country and as anti-rotting products in boat construction[<121>]. The reference value for tin in the urine is < 2 µg/L[<1288>].

	n	Sn Urine (µg/g crea)
Without chelating agents	550	4.2
DMPS	184	20.5
DMPS+Zn-DTPA	505	24.7
DMPS+Zn-DTPA+DMSA	206	21.1

Tin excretion in the urine during administration of various CAs (µg/g crea)[<180>]

Oral or parenteral administration of DMPS leads to elevated tin excretion in the urine in humans with normal environmental exposure without acute tin poisoning. The tin content in the urine of patients receiving DMPS was higher than that recorded in patients not treated with a chelating agent[<180,1191>]. DMPS increased the renal excretion of tin[<1291>] 8- to 10-fold[<1191>]. An increase of up to factor 12 suggests that DMPS is effective in the treatment of tin poisoning.

Subjects		Sn excretion				Type of mobilisation test			Literature
n	Patients	Before DMPS	After DMPS	Unit	Increase	Dose of DMPS	Administration of DMPS	Collection period	
30	Women	2.6	20	µg/g crea	7.7	10mg/kg BW	oral	2 h	474
68	Women	1.9	19	µg/g crea	10.0	10mg/kg BW	Oral	2 h	474
38	Patients with neurodermatitis	1.3	1.5	µg/g crea	1.2	250 mg	i.v.	45 min	639
64	Women	1.4	10.4	µg/L	7.4	250 mg	i.v.	45 min	460
57	Children	5.1	38.2	µg/L	7.5	3 or 10 mg/kg BW	i.v. or oral	45 min or 2 h	1572
34	Mothers	2.8	24.4	µg/L	8.7	3 or 10 mg/kg BW	i.v. or oral	45 min or 2 h	1572

Increase in the urinary excretion of tin following single administration of DMPS in various patient or control groups

A dental assistant suffered from marked tin exposure through kneading amalgam in the unprotected palm of the hand. Following administration of DMPS, tin excretion in the urine

increased to 1,094.4 µg/L (549.9 µg/g creatinine). The clinical symptoms of fatigue, lack of drive, migraines, dizziness and tremor improved[<306,613>].

In other female patient, the excretion of tin in the urine increased three-fold from 6.2 to 20.3 µg/L after DMPS injection[<613>]. An increase from 4.9 to 5.3 µg/g creatinine was observed in 50 volunteers[<1246>].

Conclusion:
DMPS increases the excretion of tin in the urine. The efficacy of DMPS in chronic or acute poisoning with tin compounds cannot, however be assessed due to a lack of detailed, clinical case reports.

7.2.21 Tc - Technetium

The ^{99m}Tc-DMPS complex accumulated especially in the kidneys after i.v. administration. In contrast, the content in the liver and blood fell rapidly. Kidney scans could thus be recorded with a γ camera in 4 patients up to 180 minutes after administration of the complex[<840>].

Conclusion:
As shown in laboratory animal experiments, the Tc-DMPS complex also accumulates in the human kidneys and thus allows the kidneys to be scanned.

7.2.22 Tl - Thallium

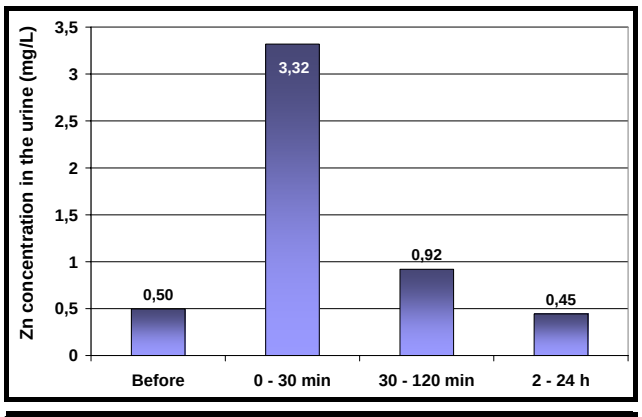
In China, combined therapy with Berlin blue and DMPS is the standard treatment in thallium poisoning[<1440>]. One of 3 patients survived acute thallium poisoning through immediate haemodialysis with concomitant administration of DMPS and potassium iodide. The other two patients died[<523>].

Conclusion:
As shown in laboratory animal experiments, DMPS is also devoid of effect on acute thallium poisoning in man. The drug of choice in this respect is Berliin blue (Thallii-Heyl® antidote).

7.2.23 Zn - Zinc

Zinc is mainly used in the electroplating industry. As zinc is an essential trace element (component of over 200 enzymes[<126>])[<63,343,733>], various zinc compounds are also used as active substances in the pharmaceutical industry[<126>].

High doses of oral zinc can lead to nausea, vomiting, abdominal pain, anaemia, pancreatitis and gastroenteritis. Corrosive damage may occur in the gastrointestinal tract with zinc chloride. If inhaled, zinc oxide can trigger "metal fume fever"[<126>]. Between 20 and 40% of the orally administered dose is absorbed[<126>]. Zinc is contained in virtually all tissues and body fluids. The human body contains between 1.3 and 2.4 g zinc[<126>]. Excretion is chiefly in the faeces (70 – 80%). Between 15 and 25% are excreted renally and the rest in sweat. The biological half-life of zinc is 100 – 500 days[<125>].



Zinc excretion in the urine after a single i.v. dose of DMPS (2 mg/kg BW)[597>]

Oral or parenteral administration of DMPS

Subjects		Zn excretion				Type of the mobilisation test			Literature
n	Patients	Before DMPS	After DMPS	Unit	Increase	DMPS dose level	Administration of DMPS	Collection period	
7	Previous occupational Hg exposure	657	1132	µg/24h	1.7	300 mg	oral	24h	1251
36	Normal subjects	202	944	µg/g crea	4.7	300 mg	oral	?	89
31	Normal subjects	360	1215	µg/g crea	3.4	300 mg	oral	3-4 h	981
31	Following amalgam removal and clearance	340	1050	µg/g crea	3.1	300 mg	oral	3-4 h	981
83	Normal subjects	202	8595	µg/g crea	42.5	250 mg	i.v.	?	89
38	Neurodermatitis	343	2250	µg/g crea	6.6	250 mg	i.v.	45 min	637, 639
40	Normal subjects	441	2653	µg/L	6.0	250 mg	i.v.	45 min	143
7	Controls	88	660	µg/dL	7.5		i.v.		722
26	Patients with atopic eczema	101	2250	µg/dL	22.3		i.v.		722

Increase in the urinary excretion of zinc following single administration of DMPS to various patient or control groups

leads to elevated zinc excretion in the urine in humans with normal environmental exposure without acute zinc poisoning. Excretion in the urine could be increased by up to 13-fold following administration of DMPS[<304,>].

A zinc level of 2,590 µgL was recorded in the serum of a 2 year-old boy after dinking soldering fluid (solution of ammonium tetrachlorozincate $(NH_4)_2[ZnCl_4]$). During treatment with 6 x 50 mg DMPS/day, i.v., the value fell to 120 µg/L within 24 hours thus dispensing with the need for treatment[<586>].

Conclusion:
DMPS increases zinc excretion in the urine. However, no clinical case reports are available regarding the efficacy of DMPS on chronic or acute poisoning with zinc compounds. Based on my estimate, in these cases, preference should be given to Ca-DTPA (Ditripentat-Heyl®), which triggers more effective mobilisation of zinc. Zinc deficiency has been described in the literature during DTPA therapy in contrast to DMPS.

7.3 Heavy metals from the environment and amalgam

Environmental burden is increasingly discussed as part of a multifactorial occurrence in the development of chronic diseases[<1308>]. Pollutants can accumulate in the body until the metabolic functions and the immune system are overloaded, possibly leading, over time, to clinical symptoms[<740,804>].

Autopsy reports in a subject who worked with mercury have confirmed that mercury burden remains in the body for prolonged periods. An employee developed acute poisoning with Hg vapour as the result of an accident after 10 years of occupational Hg exposure, and was subsequently treated with DPA. He resigned three years later. He died from lung cancer 17 years after exposure and 14 years after leaving his job. Investigations in tissue specimens still highlighted drastically high mercury values in the brain, lungs and kidneys[<1074>]. Similarly, another employee with occupational exposure to mercury presented with high deposits of Hg in the brain and kidneys 16 years later[<561>]. A patient was admitted to hospital with global heart failure and kidney failure 19 years after injecting 5 ml of mercury

	Workers exposed to Hg vapour	Normal population
Brain (cerebellum)	2,190	11
Kidneys	1,650	290
Lungs	600	40
Liver	70	110

Mercury concentration (µg/kg BW) in the organs 17 years after Hg vapour exposure[<1074>]

- "Suicide – an intentional act resulting in death.
- Accidental poisoning – an exposure to a poison resulting in symptoms which arises by an accidental action. Accidental poisoning is common in young children, but may occur in adults in the home, workplace, or as a result of fire or transport accident.
- Deliberate poisoning – this forms part of the spectrum of disorders now classified as deliberate self-harm. It has also in the past been referred to as parasuicide, though this term is now out-dated.
- Occupational poisoning – occurs in the context of employment.
- Environmental poisoning – refers to exposure resulting from presence of a chemical either in the air, in food or water"[<237a>].

intravenously with suicidal intent. X-rays confirmed the persistence of mercury deposits in the lungs, heart, liver and kidneys[<1397>].

In persons exposed to Hg and whose blood and urine mercury levels were still largely within the normal range, a marked increase in the urinary excretion of mercury was recorded following administration of DMPS[<1273>]. Mercury levels in the urine fluctuated between 28 and 64 µg/L in the urine in a thermometer factory employee. A single oral dose of 300 mg 1½ years after exposure had ended, caused Hg levels to rise from 28 to 850 µg/L. In a colleague, the Hg concentration in the urine rose from 27 to 732 µg/L[<1273>].

7.3.1 Mechanisms of action of metals

The following dose-effect relationship applies in toxicology: "From this perspective, many clinical signs and symptoms of possible intolerance to metals contained in amalgam (especially mercury) could not be plausibly explained in scientific terms"[<1503>]. Various mechanisms are discussed, the clinical effects of which cannot always be separated and which, overall, may appear as "allergotoxic Amalgam-Syndrome ATAS"[<483>]. In toxic reactions, the heavy metals[<128,143,182,208,448,466,483,866,1268>], i.e. the extent of the load, are the crucial factors. Essential metals have a toxic effect when concentrations exceed the cell tolerance thresholds[<1362>].

A burden must be present in allergic reactions, but there is no direct dose-effect relationship. Subtoxic loads are also disease-relevant for "sensitised" patients[<128>]. "In the case of genetic disposition, even very low Hg concentrations may lead to immunological reactions. It is basically difficult to give a threshold dose for such effects""[1033]. A positive patch test is one indicator[<182,208,466,483,866,1268>]. A lymphocyte transformation test (LTT) can be used if findings are unclear[<1503>].

Antagonistic effects on trace elements (e.g. zinc and selenium) are also feasible[<442>]. Hol *et al*. detected the same mercury levels in patients who attributed their symptoms to amalgam as in control groups. The selenium levels in the blood were, however, significantly lower[<599>]. "Selenium status should be determined, if need be, as selenium deficiency can increase the toxicity of mercury (the serum selenium concentration should exceed 50 µg/L)"[<380a>].

Metal-induced autoimmune phenomena is also possible, as confirmed in laboratory animal experiments and in clinical observations in individual patients[<560,972>]. "Mercury-containing amalgam may be an important risk factor for patients with autoimmune diseases. MELISA is a valuable tool for selection of patients for amalgam replacement and also for monitoring of metal allergies"[<1178>]. Undefined, homeopathic effects[<442>], the impact of tension fields in the mouth, reaction blockades for healing stimuli[<182>] and effects in subtoxic doses[<182,483,866,1268>] (amalgam disease) in conjunction with amalgam are speculative[<866>].

7.3.2 Amalgam

Amalgam has been used in dentistry for two hundred years[<282>]. Amalgam is the name for the liquid or oral alloying of mercury with metals. It is derived from the Arabic term "al-malgam" meaning emollient ointment. "German people still have approximately 200 to 300 million amalgam fillings in their teeth. Every year in the EU around 70 tonnes of mercury (Hg) is used for new amalgam fillings – 20 tonnes in Germany alone"[1300a].

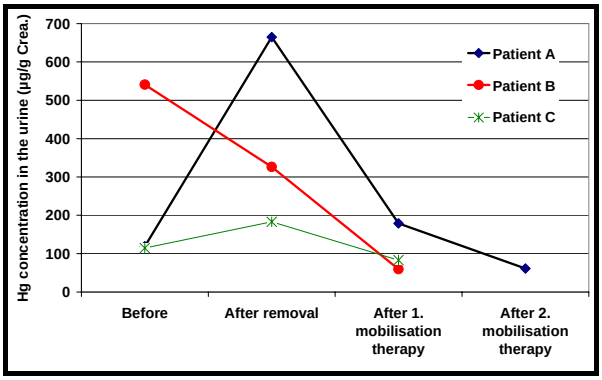
All of the amalgams used in dentistry, even the non-γ2-containing forms, are a mixture of approximately 50% liquid mercury and about 50% "alloy powder" or "filings". The alloy powder

varies in composition according to supplier and contains at least 40% silver and not more than 32% tin, 30% copper, 3% mercury and 2% zinc<1018,1030>.

7.3.2.1 Release of mercury from amalgam

Whereas it was previously assumed that the mercury was firmly bound on hardening of the amalgam<282,361>, it is nowadays generally recognised that the mercury is released from the hardened surfaces<545a,1006,1030,1634>. According to the "Methoden und Qualitätssicherung in der Umweltmedizin" (Methods and Quality Assurance in Environmental Medicine) Commission of the Robert Koch Institute in October 2007: "Mercury is released in small quantities from amalgam fillings. Dental amalgam in addition to fish consumption is the main source of mercury ingestion in man"<380a>. The mercury is released 24 hours a day, mainly in the form of mercury vapour<83,165,193,443, 1018,1289,1380,1482>. "In this respect, it should be especially remembered that when an amalgam filling is inserted, a source of mercury is implanted, which releases mercury continuously throughout the entire period of retention, i.e. generally for many years"<361>. The quality of the fillings should thus be taken into account<353>. Polished fillings thus release less Hg due to their smaller surface area. However, only 5% of fillings are polished<83>.

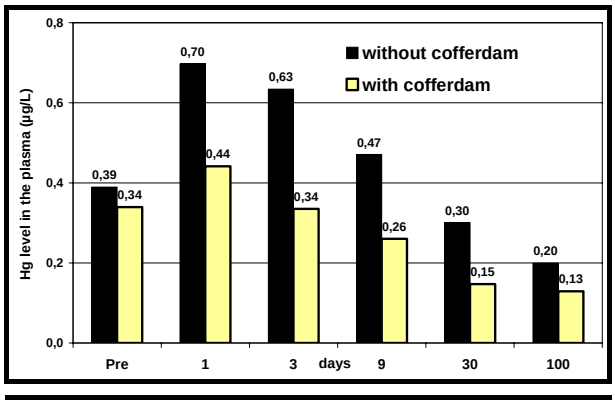
Especially large quantities of mercury are released on the insertion and polishing of new fillings and on boring out old fillings<323,577,839, 1036,1167>. After insertion of 4 – 5 amalgam fillings, the mercury excretion in the urine rose from 0.5 to 2.5 µg/L and, after removal was as high as 4 µg/L. the mobilisation test also showed higher values<831>. The daily release rate of fresh amalgam fillings was 1 – 5 µg Hg/cm^2. After 5 days, it fell to 0.1 – 0.3 µg Hg/cm^2<466> (passivation<605>).



Result of the DMPS mobilisation test according to Daunderer, before and after removal of amalgam fillings in 3 patients<831>

Hg concentrations in the urine increased continuously over time after inserting the amalgam. After 4 weeks, subjects given conventional amalgam had higher Hg levels in the urine than subjects receiving non-γ-2-containing amalgam, both before and after administration of DMPS<1632>.

Increased mercury and silver levels were detected in the faeces after insertion and removal of amalgam fillings<1167>. The cofferdam provided only partial protection against mercury uptake<547,788>. The load can also be kept lower by processing well, extracting vapour, underfilling, polishing and avoiding various metals in the mouth<182>. After the removal of amalgam fillings, the mercury level in the blood fell once again<547,549,550>.



Hg concentration in blood plasma before and after removal of amalgam fillings<547>

Various release mechanisms are discussed<174>:

- mechanically by chewing, bruxism and cleaning the teeth<121,174,282,321,986,1167,1184, 1268>. Whereas the expired air of amalgam-free subjects contained only 0.06 µg/m³ Hg, 1.9 µg – 4.9 Hg/m^3 were measured with intact amalgam fillings: The value increased to 8.2 – 29.1<320,546,549>after cleaning the teeth and to 13.7 µg Hg/m^3<1509> after chewing gum. Without mechanical load, 9 ng were released per minute and on chewing gum (removal of the oxidation layer<546,550>) 76 - 98 ng of mercury were released<549,550>. The mercury content in the saliva after 10 minutes of chewing gum increased from 4.9 to 12.5 µg/L. In patients without amalgam

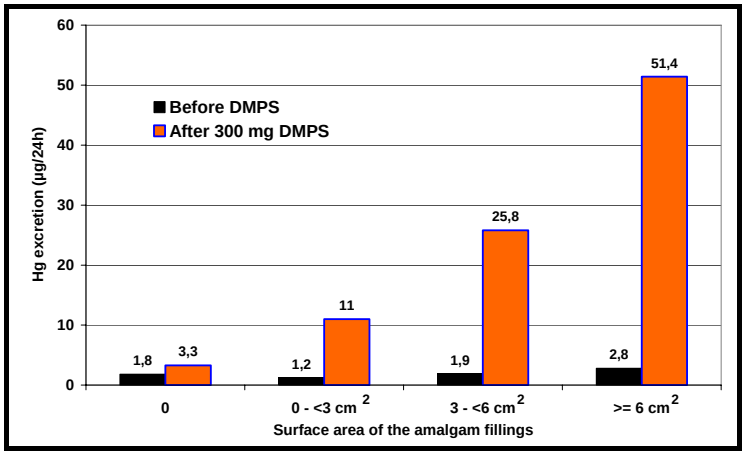
fillings, 0.4 µg Hg/L was measured in the saliva. Mercury excretion in the urine was 1.36 µg/24 hours on chewing gum in subjects with amalgam and approximately half that (0.7 µg/24 hours) in subjects with amalgam who did not chew gum.

- chemically by acids or hot meals and drinks[<174,321,986,1167,1268>] or fluorine-containing toothpaste[<1167,1268>]. In 14 students, the Hg level in the blood increased from 0.19 to 0.53 µg/L after drinking hot lemon juice for 20 minutes. Selenium levels fell simultaneously[<762,763>].
- electrochemically through contact of local elements with other metallic materials in the oral cavity[<174,627,1167,1268>]. Lechner in particular could not detect any correlation between intraoral current measurements and mercury load[<831>]. Patients given gold or other dental alloys in addition to amalgam fillings displayed similar excretion rates in the DMPS test. The other metals present had no significant effect on Hg content. On average, combinations had lower Hg levels in fasting secretion[<223>] and chewing secretion[<223,460>]. The same applied in the mobilisation test[<223,1300>].

7.3.2.2 Absorption of mercury

It is scientifically undisputed that the mercury released from amalgam is partially absorbed by the body and reaches the various organs via the circulation[<547,971a,1006>]. "Mercury released from amalgam fillings is undisputedly absorbed and contributes to the overall mercury burden in the body"[<562>]. Nowadays, it is also generally acknowledged that higher mercury values are recorded in the urine of subjects with amalgam fillings than in amalgam-free subjects[<1381,1383>].

Hg levels in the organs (kidneys, brain[<1280>]), blood (1.3 - 4.3 µg/L) and in the urine (1.4 - 4.8 µg/L) correlate with the number of amalgam fillings[<878,1311>] or the number of amalgam surfaces[<460>]. The Hg content of the renal cortex increased with the number of amalgam fillings in 55 corpses[<878>].

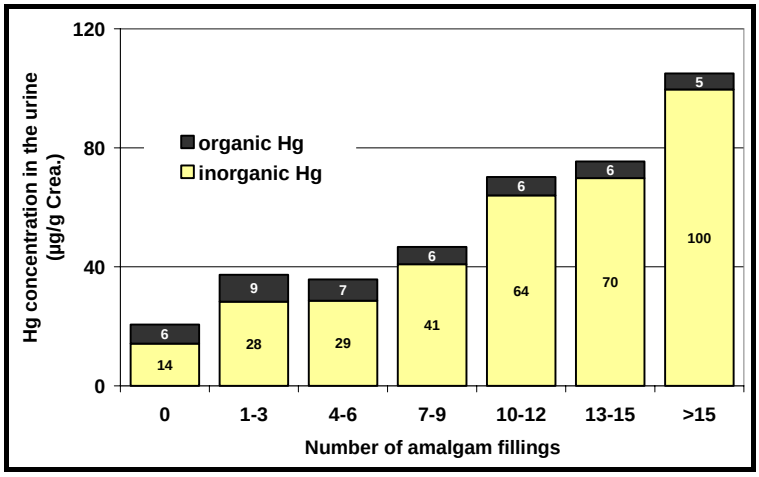


Hg excretion before and after oral administration of DMPS depending on the surface area of the amalgam fillings[<1524>]

However, the mercury load fluctuated by more than a factor of 10 with the same number of amalgam fillings[<1314>]. Others therefore maintain: "Since low quantities of mercury were also excreted in numerous patients with many amalgam fillings, it can be assumed that elevated quantities of excreted mercury can be explained more so by the processing of the amalgam fillings (underfilling, polishing), the type of amalgam used or the age of the fillings than by the number of fillings alone"[<729>]. Patients whose amalgam fillings were removed again presented with lower Hg excretion in the urine 3 years later. Levels remained the same without removal of the amalgam[<1391>]. The mobilisation values gradually fall on removal of the amalgam fillings. Two years after removal, the values were equivalent to those recorded in amalgam-free subjects[<545a,1291>]. According to Daunderer, lower values were recorded in the DMPS test 6 months after removal of amalgam compared to levels in patients who retained amalgam[<489>]. After removal of the amalgam fillings, the biological half-life of Hg is 2.3 months measured in terms of Hg excretion in the urine and 1.7 months measured in the DMPS mobilisation test[<559>]. Tests carried out in dentistry students, who initially worked with amalgam, revealed continuously rising mercury levels in the urine and plasma during this period, subsequently falling on completion of work, but still not decreasing to the baseline value after 3 months[<1561>].

Higher concentrations of inorganic Hg were recorded in the saliva of subjects with amalgam fillings compared to those without fillings. The values recorded in subjects whose amalgam fillings were removed, were equivalent to those obtained in subjects who had never had such fillings. It is assumed that patients with a "normal" number of amalgam fillings are exposed to between 1 and 3

µg Hg vapour daily[<665>]. However, the content of organic mercury in the saliva was greater in persons with amalgam fillings than controls. This means that oral DMPS promotes the absorption of Hg[<840>].



Inorganic and organic Hg in the urine 30-45 minutes after i.v. administration of 250 mg DMPS depending on the number of amalgam fillings[<1291>]

"The absorption of mercury from amalgam fillings is continuous exposure through small quantities of mercury"[<577>]. Average Hg concentrations of 0.3 µg/L and 1.5 µg/L were recorded in the blood and urine, respectively, in subjects without amalgam. These levels can be largely attributed to the intake of methyl mercury with food. In comparison, levels of 0.7 µg/L in the blood and 9 µg/L in the urine were observed in subjects with amalgam[<838>].

2.5 to 17.5 µg Hg are absorbed from amalgam fillings on a daily basis[<193,1030,1257>]. Other estimates range from 0.3 – 5.8 µg Hg/day. In 1991, the WHO calculated an up to 6.5-fold rise in total Hg intake from amalgam fillings compared to other sources[<1279>]. More recent investigations are based on the following Hg intake by man per day: 0.2 µg via respiratory air, 0.05 µg via drinking water, 3 µg via foodstuffs and 2 – 6 µg from amalgam fillings[<1033>]. Hg uptake from the amalgam is thus far below that recorded during occupational exposure (171 µg/day)[<757>].

Source	Hg vapour		Inorganic Hg		Organic Hg	
	Intake	Absorption	Intake	Resorption	Intake	Absorption
Air	0.03	0.024	0.002	0.001	0.008	0.0064
Fish	0	0	0.6	0.042	2.4	2.3
Other foodstuff	0	0	3.6	0.25	0	0
Drinking water	0	0	0.05	0.0035	0	0
Amalgam	3.8 - 21	3.1 - 17	0	0	0	0
Total	3.9 – 21	3.1 - 17	4.3	0.3	2.41	2.31

Daily intake of mercury (µg/day) by subjects with no occupational exposure[<393,849,1033>], based on WHO estimates

Age (years)	Small children 3 – 4	Children 5 – 11	Adolescents 12 -19	Adults 20 – 59	The elderly ≥ 60
Total Hg intake (µg/day)	3.28	5.56	6.72	9.44	6.79
Including from amalgam (µg/day)	0.79	1.10	1.91	3.38	2.08
Proportion of amalgam (%)	34	32	40	50	42

Daily mercury intake in Canada (1995)[<1229>]

The heavy metal is not continuously cumulated as a result. A steady state between uptake and excretion is achieved after approximately 1 year, depending on the number of amalgam fillings[<549,550>]. Thus, Hg is not a storage toxin that constantly accumulates[<545a,546>].

"Also, mercury from maternal amalgam fillings leads to a significant increase of mercury concentration in the tissues and the hair of foetuses and newborn children. Placental, foetal, and infant mercury body burden correlates with the numbers of amalgam fillings of the mothers"[<971a>]. Mercury concentrations of < 0.25 to 20.3 µg/L were detected in the breast milk immediately after birth. The values correlate with the number of amalgam fillings. In a 2nd investigation carried out after two months of lactation, values had substantially regressed (< 0.25 to 11.7 µg/L). There is now no longer any correlation with the amalgam fillings, but with fish consumption[<364>].

The inhalation of mercury vapour and uptake via the lungs is the most important absorption path for mercury[<472,545a,546,577>]. Approximately 10% of the Hg vapour formed reaches the lungs[<878>] where up to 80% are absorbed[<143,545a,1509>]. "Elemental mercury vapour released from dental

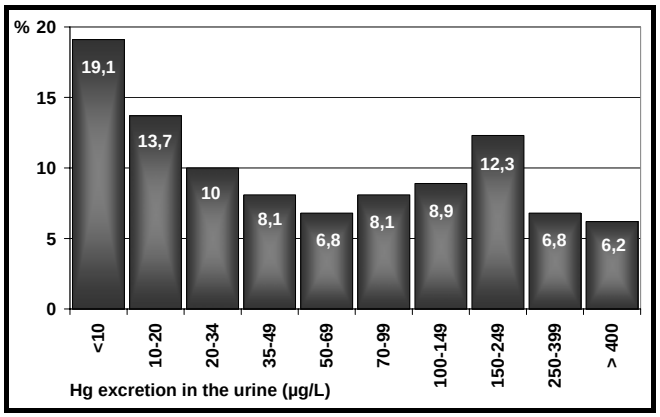
amalgam surfaces into the mouth is the predominant source of human exposure to mercury in the general population with low frequency of fish consumption. Depending on the number of fillings, daily intake of mercury vapour amounts to 4 - 21 µg. In contrast, dietary intake of inorganic mercury compounds is about 4 µg/day and, recently, for German children a dietary mercury intake of only 0,4 µg was found on days without fish consumption"[<1561>]. In addition, mercury-containing dust can also be inhaled[<182>].

Absorption in the gastrointestinal tract after swallowing mercury released through friction, corrosion or chemicals is below 5%[<878>] and is therefore of less significance[<143,182,545a,1134,1167,1184>]. Inorganic mercury is only poorly absorbed in the intestine. The greatest proportion is excreted with the faeces[<472>].

Direct transport of the mercury from the amalgam via the tooth root and the jawbones is discussed[<143,182,1134,1167,1184>], especially in the absence of underfilling[<143>]. Some people suggest retrograde axonal transport of the mercury along the olfactory nerve directly into the brain as particularly high concentrations have been measured in this region[<143,473,475,759,1167,1184>].

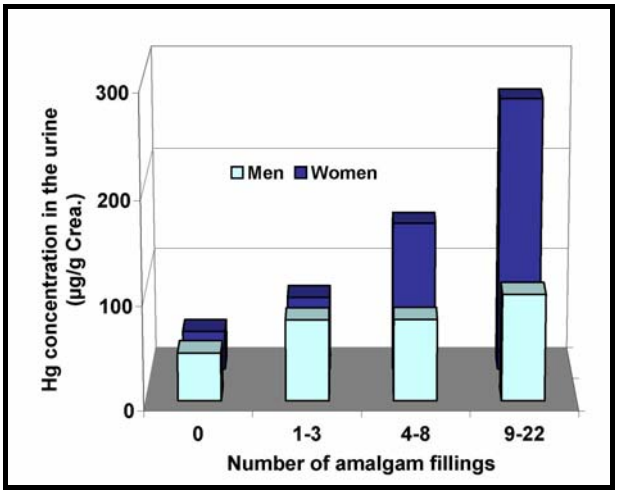
Absorption via the oral mucosa is also discussed. However, there is insufficient evidence to corroborate this hypothesis[<759,910,1033,1036>].

The quantity of mercury released increases on average with the number of amalgam fillings[<88,729>] or the amalgam surface area [<1524>]. Marked differences can, however, exist in individual cases. A few patients with numerous fillings exhibited lower mercury values than those with few fillings[<480,729,966, 1291,1314>]. In a cohort of 643 patients, values below 50 µg Hg/g creatinine[<1291>] were recorded in 51% of patients with amalgam in the DMPS mobilisation test.

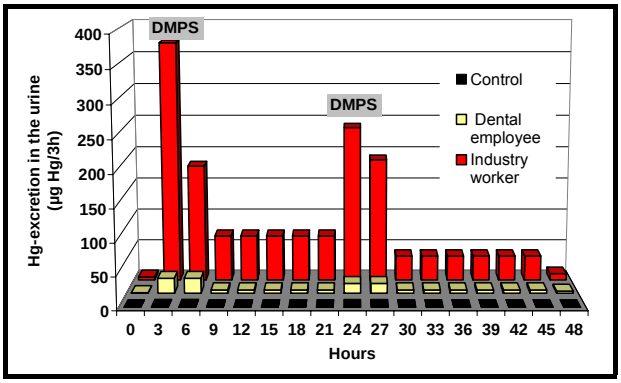


Percentage distribution of Hg excretion in the urine (µg/L) after mobilisation with 250 mg DMPS i.v. (n=643)[<1291>]

Every one has mercury in his body[<288>]. The individual mercury loads fluctuate very markedly. Women exhibited higher levels than men in the mobilisation test despite having the same number of amalgam fillings[<241,444,446, 1291>]. Higher values were recorded in women in both the native urine and mobilisation urine[<241>]. In contrast, no gender-specific dependency was found on autopsy[<362>]. This discrepancy cannot be explained at the present time[<359>].



Mean values of the Hg concentration in the urine 30 – 45 min after administration of DMPS (250 mg i.v.) in men and women depending on the number of amalgam fillings[<1291>]



Hg excretion in the urine (µg Hg/3 hr) in exposed industrial employees, dentists, dental assistants and the control groups (two doses of 300 mg DMPS oral)[<985>]

Generally, the mercury load from amalgam is less than that measured in workers from mercury-processing facilities[<549,550,947,1108,1280, 1283,1285,1314>]. No pathological changes could be detected in many workers with occupational mercury exposure[<1314>].

Workers occupationally exposed to mercury vapour exhibited the highest excretion values both before and after administration of DMPS (300 mg oral). High Hg concentrations were also recorded in the urine of dentists and dental assistants. The lowest values were recorded in workers without occupational exposure (no details on amalgam status). The cumulative overall Hg excretion rates Hg within 24 hours following two doses of 300 mg DMPS were 1513 µg Hg in industrial employees, 132.6 µg in dental personnel and 3.78 µg in the controls. The greatest increase (U(II)/U(I)) was recorded in industrial employees and the lowest in the controls[<985>].

7.3.2.3 Effects of absorbed mercury

It is generally recognised that subjects with amalgam fillings exhibit higher mercury values in the urine compared to amalgam-free subjects[<1381,1383>]. The question must, therefore, be: Is the overall quantity of mercury absorbed by humans enough to trigger toxic reactions[<165,288>]? According to the "Methoden und Qualitätssicherung in der Umweltmedizin" (Methods and Quality Assurance in Environmental Medicine) Commission of the Robert Koch Institute in October 2007: "The use of amalgam in dentistry is associated with health risks, which, as with any medicinal product, must be weighed against the potential benefits. Whereas amalgam-related health risks are considered slight by most experts and are estimated to be negligible based on the benefit:risk assessment, controversy remains. Even very low amalgam-induced mercury exposure is not exempt from intolerable health risks"[<380a>]. Others do not share this view, "Amalgam cannot be called a safe dental filling material"[<971a>].

It is nowadays undisputed that amalgam can cause impairment of taste as well as allergic and lichenoid reactions with various clinical symptoms[<493,577,741,839,966,1006,1018,1381,1383, 1481>], essentially type 4 allergy[<1381>]. Köppel obtained a positive patch test to Hg[<759>] in 28 out of 60 (46.7 %) and Walt observed a definite positive reaction in 17 out of 193 (8.8 %) patients[<1524>]. Between 1993 and 2001, the Zahn-, Mund- und Kieferklinik Freiburg (Dental, oral and Maxillary Clinic in Freiburg) highlighted allergic reactions to the substances contained in the "amalgam block"[<1399>] in 114 out of 616 subjects with amalgam fillings (18.5%). Electrochemical reactions have also been known to occur when amalgam comes into contact with other metals in the oral cavity[<1383>].

The question whether the mercury absorbed leads to additional symptoms of intoxication or intolerance is still subject to controversy[<89,143,446,727,1134>]. "Whether the levels of exposure to mercury vapour from dental amalgam are sufficiently high to cause adverse health effects, and exactly what those effects are, continues to be researched and debated by scientists and health officials. U.S. government summaries on the effects of dental amalgam conclude that there is no apparent health hazard to the general population, but that further study is needed to determine the possibility of more subtle behavioural or immune system effects, and to determine the levels of exposure that may lead to adverse effects in sensitive populations. Sensitive populations may include pregnant women, children under the age of 6 (especially up to the age of 3), people with impaired kidney function, and people with hypersensitive immune responses to metals"[<1030>]. "To the limited extent that the ADA acknowledges the harmful effects of mercury amalgams, it is only in respect to the relatively small number of patients who suffer allergic reactions to mercury" …The American Dental Association claims that there is not enough scientific evidence to prove the case against mercury amalgams and maintains the position that "dental amalgam has been studied and reviewed extensively, and has established a record of safety and effectiveness"[<107>].

The toxicity of dental alloys depends on the quantity of metal ions released[<460>]. Investigations carried out in 2,223 patients that the PTWI (provisioned tolerance weekly intake) value is exceeded only in isolated cases. In most cases, it is not reached[<559>]. Mercury loads are measurable but are below the toxicological limit values[<18,589,1061,1283,1632>]. The measurements recorded in the blood and urine generally average 1 µg/L. The upper normal limit of 5 µg/L is exceeded only in exceptional cases[<1278,1381>] and values of up to approximately 10 µg/L are seldom found in the urine[<1278>].

It remains controversial as to whether these levels can lead to symptoms such as joint pain, headaches, dizziness, impaired memory function, fatigue and sleep disorders[<1481>]. Cases of mercury-induced glomerulopathies have also been described secondary to amalgam exposure[<924>]. According to the BfArM (Federal Institute for Drugs and Medical Devices), suspected toxic reactions are not justified[<577,1006>]. There is a 10-fold safety margin before reaching a toxic threshold[<549>], i.e. these are sub-clinical loads[<89>]. The German Gesellschaft für Pharmakologie (Pharmacology Society) concludes that, "The quantity of mercury released from fillings is not sufficient to trigger mercury poisoning"[<1380>]. Based on current scientific knowledge, there are no grounds to suggest that properly inserted amalgam fillings have a deleterious effect on health[<757,1018,1562a>]. Mercury is not usually anticipated to have a harmful effect on health[<493,1278>]. There is no corroborated evidence to suggest "amalgam poisoning"[<562,1390,1381,1383>]. Similarly, interciplinary investigations conducted at the University of Gießen did not provide any evidence[<579>]. Amalgam fillings are, therefore, not contraindicated[<1121>] on toxicological grounds and removal procedures are considered superfluous[<545a,757>]. The symptoms described by the patients have been diagnosed as psychiatric findings or psychological symptoms[<48,445,589,605,759,786,915>]. The positive effects of amalgam treatment are considered psychosomatic or as a placebo effect[<1493>]. "If it is true what amalgam opponents believe, amalgam would be implicated in virtually every disease, especially those of hitherto unknown aetiology"[<1279>]. An exchange of intact amalgam fillings is unethical[<107>] and is not necessary from a toxicological standpoint[<665,914,1381>]. More intensive procedures such as complete dental extraction are viewed as professional errors on the part of the dentist[<665>].

Others see amalgam as an "unnecessary disease focus" and the mercury released from amalgam as responsible for numerous diseases. They talk of chronic poisoning[<316>] and refer to amalgam as "poisonous waste" that should be removed in every case[<1184>]. Depending on the author, 50 to 85% of patients with environmental disorders are exposed to a persistent blend of potential (sub-) toxic or sensitising foreign bodies[<128>]. It is often amazing how symptoms disappear when amalgam fillings are removed"[<441,446>]. Even deaths have been attributed to amalgam[<313,316>].

- *Otitis externa* (inflammation of the auditory channel in one female patient deteriorated during amalgam removal by a dentist (increase in mercury exposure through amalgam removal[<763>]). The woman became symptom-free on subsequent DMPS treatment[<448>]. The loss of hair (alopecia) in another female patient also deteriorated initially during amalgam removal. On completion of the DMPS treatment, there was no longer any hair loss[<448>].
- Gerhard *et al*. showed in investigations involving 490 women that, with heavy metal loads (in the mobilisation test > 500 µg Hg/g creatinine), spontaneous pregnancies no longer occurred. After clearance of the heavy metals, various women were spontaneously pregnant, even after 12 to 14 years of ineffective therapy[<475,478,481>].
- In two female patients without any psychological problems, as the authors explicitly emphasised, headaches regressed after amalgam removal and clearance with DMPS[<147>].
- An incorrectly performed dental treatment with amalgam (absence of underfilling in 5 fillings) caused diffuse symptoms such as headaches, joint pain, dizziness, forgetfulness and fatigue in a previously healthy 15 year-old girl. The mercury level in the urine was 47 µg/L. After correcting the dental problems and treatment with DMPS, the heavy metal level in the urine fell to 0.7 µg/L. The appetite, body weight and activity of this teenager improved[<353>.]
- A 30-year old female patient with migraine-like headaches and dizziness had been unsuccessfully treated for 10 years by several different doctors. After removal of amalgam and several DMPS treatments, dizziness disappeared completely and only mild migraines persist[<444>.]
- In patients suffering from alopecia, the amalgam fillings were removed after ineffective attempts at treatment. Alopecia regressed in 13 patients, partly with the subsequent growth of new hair[<739>]. This investigation was, however, criticised because the various forms of alopecia were not differentiated and the "patients" were insufficiently defined, so that the causality of the alopecia by the amalgam was not demonstrated[<1608>].
- In a 37 year-old patient with chronic cough and nasal catarrh, removal of amalgam and clearance therapy were undertaken. The patient became free of infection[<444>].
- A mercury load of 401.5 µg/g creatinine was detected in a 33 year-old female patient with recurrent *Otitis externa* / inflammation of the auditory canal in the DMPS test according to

Daunderer. The value fell to 25.4 µg/g creatinine after amalgam removal and two clearance cycles with DMPS. “The female patient is subjectively symptom-free”[<448>].

- A mercury, copper, lead and palladium load was detected in patients presenting with atopic dermatitis or psoriasis using the DMPS test. A significant improvement was observed in most cases after amalgam removal followed by clearance (administration of DMPS every 5 – 6 weeks)[<639>].

Only very few subjects with amalgam poisoning suffered from single poisoning[<83,313,866>]. In most cases, critics also witness up to 3 additional exposures to poison[<313>]. In addition to the mercury from the amalgam, the background load from food and the environment must also be taken into account[<549,550>]. The other constituents of the amalgam or environmental exposure may also cause symptoms. The synergistic effect of various toxins must also be considered[<577>]. ”Human exposures to metals and metalloids such as arsenic frequently occur as mixtures, and hence it is important to consider interactions among these elements in terms of both mechanisms of action and for risk assessment purposes. Interactions among these elements may produce additive, synergistic/potentiative, or antagonistic effects that may be manifested as direct cellular toxicity (necrosis or apoptosis) or carcinogeniciity[052>]. Psychosomatic involvement is discussed[<307,466,866>]. The heavy metal load may also be combined with a deficiency in trace elements (zinc and selenium), which, in turn, can also trigger symptoms[<307,441,444 >].

The cause-effect relationship between amalgam and a disease can only rarely be established[<89>]. Not only dentists, but also general practitioners witness a clear improvement in the state of health of many of their patients once amalgam fillings have been removed[<1361>]. The cause-effect relationship is corroborated by the timely onset of symptoms following the insertion of amalgam fillings or an improvement in the clinical picture on removal of the amalgam[<327>]. Possible changes in lifestyle, e.g. change of diet or exercise, are not discussed[<915>]. Many observations correlate with the number of amalgam fillings. However, this does not confirm a cause-effect relationship[<165>]. For instance, amalgam is said to be responsible for increased smoking[<1342>]. The correlation can easily be explained, however, assuming that non-smokers with no amalgam fillings are more health-conscious.

The WHO has ascertained that there is no value that can be given up to which a mercury load is harmless[<1043>]. According to “orthodox medicine”, the lowest threshold values that can be detected for impaired functions are 20 µg/L in the blood and 50 µg/L in the urine[<193>]. No accurate data have come to light regarding the Hg threshold value in various organs[<546>].

“Nevertheless, a residual toxicological risk with a chronic effect cannot be ruled out even with small quantities of mercury in correspondingly disposed subjects[<166>]. “As a result of the wide scatter in the sensitivity of people with amalgam fillings, the World Health Organisation does not rule out at the individual level (i.e. on considering the individual case) that there may be a correlation to disorders of well being and health“[<966>]. In this situation, only careful follow-up of the patients by the general practitioner can help[<866>].

To date, there are no markers to identify these patients. The DMPS test is unsuitable for this purpose[<170>], as the Hg burden established in patients with fillings is no higher than that observed in healthy subjects[<1279,1482>]. Individual factors presumably play a role:

- Women tolerate poisons less effectively than men[<443>].
- Patients with a glutathione-S-transferase GST deficiency should have poorer amalgam tolerance[<307,750a>].
- Wojcik *et al*. found a correlation between chronic Hg intoxication and the apo-lipoprotein E4 genotype[<1568>].

The claim that uncertain symptoms are caused by amalgam can, in the last resort, neither be clearly proven nor rejected[<361,966,1383,1384>]. Similarly, in children, there is no confirmed evidence that increased mercury load can lead to disorders of development and damage[<361>]. The reason for this is the long latency period[<313>]. “Two recent prospective studies attempt to prove that amalgam fillings trigger no damage over a five- to seven-year period. However, the number of cases in both studies is far too small to prove a risk of less than 1%. Given the limited observation period, no definitive statements regarding potential long-term damage can be made, especially since increased mercury excretion was observed long-term in the urine“[<1005>].

Generally speaking, cannot totally guarantee the biological safety of amalgams or other restorative dental materials[<665>]. A randomised, double-blind study of the efficacy of amalgam removal is not feasible[<759>]. Everyone must decide for themselves[<446>].

7.3.3 Removal of amalgam and mobilisation therapy

A number of symptoms are associated with amalgam, often by patients themselves. Between 4 and 8% of the Swedish population believe that they are/were ill due to the side effects of amalgam fillings[<558>]. However, hardly any scientific investigations have been carried out[<441>] or reliable case histories have only been published for a few diseases.

Amalgam releases Hg, which is mainly absorbed as vapour, thus leading to a mercury burden in all persons with amalgam fillings. This chronic Hg exposure fluctuates in the low-dose range (micro mercuralism). The amalgam-induced Hg levels are mostly below the permissible levels and do not trigger clinical signs of poisoning. It can, thus be assumed, that not every person with amalgam fillings is affected[<182>]. However, certain individuals may be particularly sensitive. Immune reactions (allergies, autoimmune reactions or immunomodulation) may also occur[<172>]. According to amalgam opponents, every patient reacts differently[<442>]. There are no typical symptoms of amalgam intoxication[<866,1183,1268>]. Every person affected reacts with his own individual, constitutional weak points[<1183>].

It is difficult for doctors if the patient has a fixed idea that he is being poisoned by amalgam and does not accept any other explanation for his symptoms[<759,1381>]. The same also applies to doctors who see amalgam poisoning behind every disease. Not only can this lead to sometimes extensive, unnecessary dental procedures such as the extraction of healthy teeth, but it may also prevent or delay the diagnosis and treatment of the actual cause of the disease[<759,1381>]. Complementary medical test procedures are particularly controversial in this respect[<1381>]. Heavy metal exposure should, however, finally be considered if the symptoms appear shortly after insertion or removal of amalgam fillings or deteriorate[<558>] or if no organic causes or marked, psychological burden can be detected[<446,866,1268>]. Mercury excretion should at least be carried out in these cases[<11391>].

Seidel explains the problem very well: “Amalgam and DMPS remain an inconclusive topic for discussion in general practice as well as for patients. On the one hand, many doctors, who are known as specialists for assumed mercury intoxication to colleges as well as to lay persons, present successful case histories. On the other hand, doctors with large practices who specialise in environmental medicine state that they have not seen any patients in whom they have attributed the afore-mentioned symptoms clearly and exclusively to amalgam-induced mercury intoxication (i.e. raised mercury excretion in the urine with or without DMPS mobilisation)! This situation implicates scientific toxicology“[<1322>].

7.3.3.1 Prevention

Minimalisation generally applies in preventive environmental medicine: Avoidable exposure should, as its name implies, be avoided, based on the principle of proportionality[<193,380a,581,787,1380>]. “The presence of toxic metals in the mouth is basically undesirable. Minimisation should be attempted. Whether the constituents released by these metals are sufficient in order to trigger a toxic reaction in the body is a crucial question“[<548>]. As heavy metals are universally present, exposure cannot be totally avoided[<383a>].

7.3.3.2 Treatment necessity

In recent years, partly highly controversial discussions have focused on chronic and low-level heavy metal exposure from natural, industrial and “medicinal“ sources and the need for treatment.

In the one instance, a high mercury burden in the body due to amalgam fillings is not an indication for DMPS therapy[<1629>]. These are considered “unconventionally used treatment techniques in environmental medicine[<1555a>]. Use in “environmental medicine“ indications is rejected given the

lack of proof regarding efficacy and the fact that the risks of long-term therapy have not yet been clarified[<169,1232>]:

- "Overall, the fact remains that, with DMPS and DMSA we have available 2 antidotes that have become indispensable for the treatment of acute metal poisoning. Their use in supposedly chronic metal poisoning, as is partly the case in environmental medicine, cannot, however be justified based on the available data. According to view of the "Human-Biomonitoring" Commission, levels exceeding the HBM-II values are not generally an indication for chelate therapy. Lead intoxication during childhood is the only exception to the rule. In this instance, chelate therapy is indicated for a lead concentration of 450 µg/L of whole blood"[<1032>]. Others consider chelate therapy to be useful for patients with Hg levels > 20 µg/L in the urine[<988>].
- "According to the view of the poison information centres, the presumed load caused by dental amalgam is not an indication for DMPS therapy"[<573>].
- Their use in supposedly chronic metal poisoning, as is partly the case in environmental medicine, cannot, however be justified based on the available data. There are no limit values beyond which treatment is required"[1032>].

Others want treatment restricted to doctors specialising in environmental medicine: "Chelation therapy (used to remove metals from the body tissues) itself presents some health risks, and should be considered only when a licensed occupational or environmental health physician determines it necessary to reduce immediate and significant health risks due to high levels of mercury in the body"[<1030>].

Various case histories on the clinical effects of chronic heavy metal exposure, e.g. due to amalgam, have been published to date[<1291>]. In these cases histories, 60 – 90% of patients report an improvement or cure on removal of the amalgam fillings[<558,720>]. Ramak considers DMPS administration as the decisive therapeutic step in 12 of his patients[<1150>]. This is equivalent to approximately 8% of the 148 patients in whom heavy metal clearance was carried out and about 0.3% of the overall practice patient cohort[<1202a>]. Critics complain, and for some papers justifiably, that there are often very few items of data in some of these publications[<209,1509,1608>] and question the occasional fixation on amalgam as the sole cause[<1493>]. Many studies thus contain only measurements but fail to investigate any potential correlation between the symptoms and the heavy metal burden. Very few of the publications satisfy the recommendations to incorporate the environmental case histories memo issued by the Method and Quality Assurance in Environmental Medicine Commission of the Robert Koch Institute[<694>].

7.3.3.3 Clinical trials / non-intervention studies

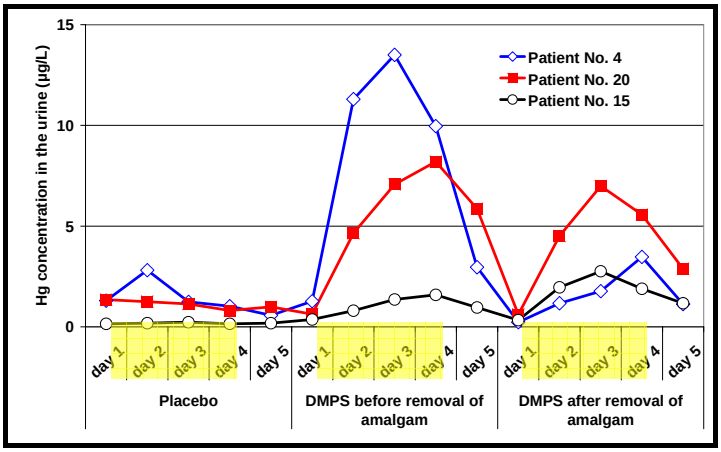
A marked rise in the urinary excretion of mercury was evident with DMPS in subjects with amalgam fillings, before and after amalgam removal. In contrast, subjects whose "fillings had been removed some time ago" exhibited only a minimal increase in mercury excretion as seen in the controls, who had never had amalgam fillings[<914>].

50 patients (35f,15m) with at least four occlusal fillings, who attributed their symptoms to amalgam and in whom other diseases potentially responsible for these symptoms had been ruled out, received either 30 mg DMSA/kg BW pr placebo for five days. The symptoms were recorded quantitatively with a pain index and personality structure questionnaire. In the DMSA group, the quantity of mercury excreted in the urine increased 4-fold and lead excretion 10-fold. The patients reported an improvement in symptoms. No difference could, however, be distinguished between DMSA and placebo[<515>].

Twenty patients (14f, 6m), who believed that they were suffering from the symptoms of amalgam-induced mercury poisoning, received either DMSA (20 mg/kg BW) or placebo for 2 weeks. The amalgam fillings were not removed. DMSA led to an increase in mercury excretion and a decrease in Hg levels in the blood. DMPS did not, however, display any advantage compared to placebo in terms of subjective symptoms. Three months after treatment, Hg levels in the blood had again risen to the baseline value.

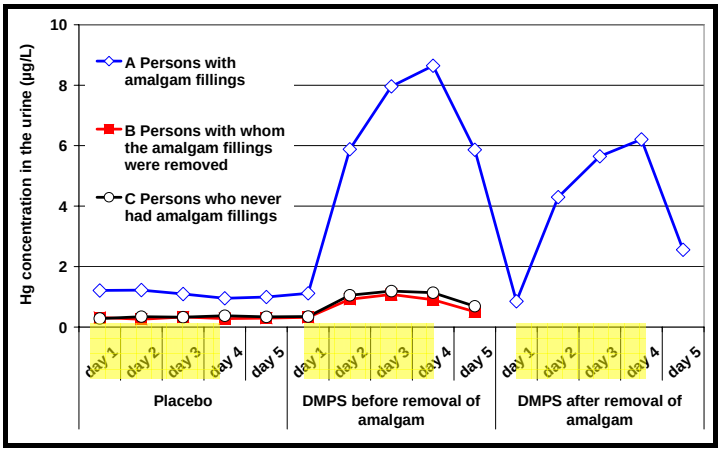
Twenty-four subjects (18f, 6m) attributed their symptoms to the presence of amalgam fillings. Sixteen were entered into a study. Prior to amalgam removal, they initially received placebo capsules for 3 days (days 2, 3 and 4, respectively) and thereafter DMPS capsules (100 mg t.i.d.). They received DMPS therapy for a further 3 days after removal of the amalgam fillings. In two participants in whom an allergy against amalgam had been confirmed, the removal of amalgam fillings and subsequent mobilisation therapy led to a permanent improvement in symptoms. No permanent improvement in symptoms was evident in the other subjects after amalgam removal and administration of DMPS. A transient, subjective improvement even sometimes occurred following placebo administration[<915>]. The short observation period should, however, be noted.

Fifty-nine patients who attributed their symptoms to amalgam-induced mercury intoxication were compared to 59 symptom-free subjects. The single oral dose of 300 mg DMPS increased Hg excretion in the urine compared to placebo. Neither DMPS nor the placebo altered the Hg levels in the plasma. Neither of the groups showed any differences in U(I), U(II) or in Hg levels in the plasma. The DMPS mobilisation test was not useful in terms of diagnosis. Neither of the groups differed in terms of symptom improvement or deterioration. According to the authors, the symptoms were presumably psychological and not mercury-induced. A slight rash with redness of the skin [<1311>] was observed in 2 of the original 120 patients following a single dose of 300 mg DMPS.



Mercury excretion in the 24-hour urine of three subjects receiving placebo or 3 x100 mg DMPS oral/day before and after removal of amalgam fillings[<915>]

No difference in the extent of mercury excretion was observed in 50 subjects who attributed their symptoms to amalgam, compared to healthy subjects. No correlation was found between the severity of the symptoms and the Hg values. Other, often psychological causes for the symptoms were established diagnostically[<589>].



Mercury excretion in 24-hour urine during administration of placebo or 3 x 100 mg DMPS oral/day
A Persons with amalgam fillings before and after removal of the fillings (n=19)
B Subjects who had already been amalgam-free for some time (n=10)
C Subjects who had never had amalgam fillings (n=10) [<914>]

Out of 300 patients in a practice specialising in dermatological environmental medicine and presenting with diffuse (e.g. headaches or fatigue) or manifest clinical symptoms (e.g. neurodermatitis) only 14 displayed a moderate (UII 16-35 µg Hg/g creatinine) and 17 a marked (UII > 35 µg/g creatinine) Hg burden in the DMPS test. Patients with a marked burden received 3 x 100 mg DMPS/week for 6 weeks in addition to zinc and selenium. Amalgam fillings were removed in some subjects. The Hg burden was then checked with the DMPS test and the treatment cycle was repeated, as required. All patients exhibited a mercury excretion of < 16 µg/g creatinine after the 3rd cycle at the latest and were symptom-free[<981>].

7.3.3.4 Recommendations for detoxification therapy

Even after removing amalgam fillings, mercury deposits are still initially present in the body[<182,307>] and these may persist for 1 – 2 years[<1133,1134>]. But rapid decomposition of the mercury deposits was also observed without DMPS administration[<914>]. The necessity for subsequent DMPS therapy is a matter of controversial discussion[<406>]. Some consider it essential only in severe cases[<361,1384>] whilst others consider it to be generally necessary[<182,442,477>], possibly even many years after amalgam removal[<325>]. A careful benefit-risk assessment should be carried out in every case[<752, 986,1635>]. "Give a trial of DMSA or DMPS, and measure the level of toxic metals in the urine before and after taking it. A large increase indicates that the metals are present, and that the medication is helpful in removing them"[<14>].

The recommendations for clearance therapy given in the literature are not based on any clinical trials, official authorisations or generally valid treatment recommendations. They are virtually always based on the individual experiences of the authors. This presupposes a number of various recommendations.

The results of amalgam cleaning with subsequent DMPS therapy varied. Some do not see any indication for such treatment[<573,1238>]. As far as they are concerned, amalgam fillings may increase the mercury load but would never, however, lead to mercury poisoning. "Therapeutic administration of Dimaval is not necessary following amalgam removal, but 2 – 3 Dimaval capsules may be administered as an option on the day after amalgam removal"[<729>].

Symptoms\References	1202a[1)]	1268[2)]	594[2)]	309[2)]	981[2)]
Allergies		65 %	52 %	45 %	0 %
Abdominal pain			63 %	73 %	
Depression			80 %	76 %	50 %
Memory disorders				85 %	
Hair loss (alopecia)	5	59 %			
Susceptibility to infections		80 %		61 %	
Headaches		73 %	78 %	85 %	50 %
Fatigue, loss of drive			70 %	88 %	17 %
Muscular/joint pains				71 %	
Nervousness, unrest	4		84 %	60 %	
Sleep disorders			77 %	71 %	
Dizziness			75 %	84 %	50 %
Tinnitus		48 %			
Tremor			71 %	85 %	
Dermatitis, eczema	17				33 %
Neurodermatitis	6				50 %
Candidiasis	21				50 %
Psoriasis	4				50 %
Metal taste					100 %
Dysmenorrhoea	6				
Rhinitis, conjunctivitis	10				
Asthma	3				
Acne	4				
Migraine	2				

Improvement of clinical symptoms after removal of amalgam and subsequent detoxification therapy (1) number of patients, 2) % of patients)

Others, however, report positive results even after many years of suffering[<971>]. "Everyone must make his personal evaluation of the dispute between the experts. It is always amazing how many diseases suddenly disappear when amalgam fillings are removed"[<444>]. "Correct amalgam removal has stopped the suffering of numerous chronically sick patients"[<1183>]. "There are many patients in my practice who are now healthy productive citizens instead of hopeless invalids, thanks to the use of DMPS administered in a safe manner"[<282>]. "In contrast to allergy sufferers, poisoning victims immediately feel much better after the injection"[<323>]. However, as DMPS has only a slight effect on Hg levels in the brain, other authors consider this as a placebo effect[<120>]. Spontaneous cures occasionally described immediately after amalgam removal are also difficult to explain as symptoms are initially expected to deteriorate due to the increase in the heavy metal load anticipated on removal of the fillings. Psychogenic causes may also be at play in such cases[<1383>]. As numerous measures (e.g. a change in diet, orthomolecular therapy, acupuncture and a change in lifestyle) are often implemented simultaneously, causality is generally impossible to establish.

The clinical symptoms of 10 patients disappeared after replacement of amalgam fillings and administration of chelate therapy. The mercury load after treatment was clearly below that of untreated patients with corresponding symptoms[<490>].

Otitis externa (inflammation of the auditory channel) in one female patient deteriorated during amalgam removal by a dentist (increase in mercury exposure through amalgam removal[<763>]). The woman became symptom-free on subsequent DMPS treatment[<448>]. The loss of hair (alopecia) in another female patient also deteriorated initially during amalgam removal. On completion of the DMPS treatment, there was no longer any hair loss[<448>].

The dose of DMPS, frequency of administration and duration of treatment depend on the individual level of the burden and the individual symptoms of poisoning[<182,637,638,1037>]. With heavy metal loads, DMPS is mostly administered at a smaller dose level than normal[<87>]. In the treatment of mercury overload, it is recommended to carry out interval therapy[<700>] with pauses because DMPS primarily binds to extracellular heavy metal[<194>]. The body should have time between the individual DMPS doses for redistribution of the mercury, e.g. from the brain into the emptied extracellular deposits, where it can then be mobilised by DMPS[<88>].

In severe cases, the administration of DMPS before removing the amalgam is recommended in order to empty the "long-standing stores"[<317,1506>]. Others recommend in these cases the removal of amalgam under DMPS protection, e.g. by administration of 100 mg DMPS 2 hours[<307,558>] before or 1 ampoule 20 minutes before boring[<973>] or one capsule each day before, during and after work on the amalgam[<1037>]. The start of treatment is normally recommended immediately after a visit to the dentist[<317,473,973>].

The dose of DMPS always depends on the nature and severity of the poisoning[<87>]. Depending on the patients, DMPS is administered every 4 – 8 weeks[<311,317,320,321,326,558,637,638,927,1184,1202a>] or every three months[<558,446,446,447>]. Other recommendations:

- With very high values (> 500 µg/g creatinine in the DMPS test), administration of 5 – 10 mg/kg BW[<473>] or 1 – 3 capsules DMPS[<88,315,558,969>] weekly;
- One DMPS capsule every second day or 300[<87,1037>] to 600 mg DMPS weekly with additional replacement of zinc, selenium and possibly iron[<481>];
- One ampoule every 6-8 weeks or one capsule per week[<1609>];
- 250 mg DMPS i.v. every 3 months, every 6 weeks in extreme cases[<352>];
- 250 mg DMPS i.v. every 4 weeks together with procaine[<720>];
- Slow, i.v. administration for 3 – 5 minutes every second week (a total of 5 to 10 injections)[<1114>];
- 100 mg DMPS per week for 3 months in patients exceeding the limit value[<183>];
- 100 mg DMPS every week for 9 weeks.

Hamre observed "a clinical effect in amalgam sickness" following the oral administration of 100 to 200 mg DMPS per week for one to three weeks after amalgam removal. Daunderer proposes individual dosage depending on the mercury burden measured by the DMPS mobilisation test[<314,325>]:

- For values over 1,000 µg/L urine, one DMPS capsule weekly
- For values over 100 µg/L urine, one DMPS ampoule every four weeks
- For values over 50 µg/L urine, one DMPS ampoule every three months.

Zinc	Copper	Mercury	Action
> 720 µg/g crea.	Irrelevant	Irrelevant	Repeat clearance after 3 months
< 720 µg/g crea.	> 1500 µg/g crea.	Irrelevant	Repeat clearance after 3 months
< 720 µg/g crea.	< 1500 µg/g crea.	> 50 µg/g crea.	Repeat clearance after 3 months
< 720 µg/g crea.	<1500 µg/g crea.	< 50 µg/g crea.	Completion of clearance

Clearance therapy with i.v. DMPS according to Friese[<441,558,973>]

Treatment was continued until all of the mercury values after DMPS mobilisation reached normal values[<87,88,324,326,1037,1184>]. Between 3 and 7 injections are normally required[<973>]. However others witnessed an improvement after just 2 to 5 injections[<1202a>]. Improvement was achieved in 80% of the patients within 3 to 6 months[<320,323,594>]. Sometimes the treatment was continued for one year or more[<309,312,321>]. A mother and daughter with suspected MCS, whose condition did not improved with orthodox medicine, were both completely free of symptoms following treatment with DMPS[<691a>].

147 patients with a "positive oral DMPS test" (no further details given) received 100 to 200 mg oral DMPS every day for 30 days as well as a food supplement. At the end of treatment, Hg levels in

the urine had fallen by 50 to 100% in 93 subjects (= 63%). The values for mercury levels in the urine are not known. Data on the course of treatment are also missing for the remaining 54 subjects[<351b>].

In contrast, Cutler rejected single doses of DMPS as they concealed the risk of redistribution of the heavy metal and thus a deterioration in symptoms. He preferred an incremental regimen. 50 – 100 mg DMPS are administered three times a day in the first stage of treatment. Treatment is administered in intervals. 4 to 14 days of DMPS therapy are followed by a treatment interval of 4 to 14 days. If the deposits that can be mobilised most quickly are emptied in this way (criteria for establishing this finding are not given), the additional recommendation of liponic acid is recommended. Treatment is continued for 6 months to 2 years. The heavy metal deposits in the brain should be mobilised in this way[<459>]. The approach to first of all empty the deposits that can be quickly mobilised in order to prevent redistribution of heavy metals in the brain following mobilisation seems logical. Unfortunately there are no clinical or laboratory data to confirm the effectiveness of this treatment regimen.

Conclusion:
Amalgam fillings continuously release mercury, which is partially absorbed. The risks associated with this exposure are subject to controversy. One the one hand, evidence to suggest that amalgam triggers no symptoms is not generally feasible (sufficient case numbers, appropriate choice of parameters, sensitivity of the methods or adequate observation periods can always be challenged). On the other hand, the cause-effect relationship with amalgam cannot be clearly confirmed (non-recognition of other sources, effects of other pollutants, change of lifestyle, random, simultaneous onset of symptoms). An individual assessment is, therefore, recommended in every individual case in order to assess whether amalgam cleaning together with clearance can be successful.

7.4 Biomonitoring and DMPS test

"Toxicity is not a substance property but a quantity problem"[<1636>]. As Paracelsus once said, every metal, even essential metals, can trigger toxic symptoms at a sufficiently high dose. During the period of evolution, the body has developed mechanisms in order to withstand lower doses[<666>].

What is not poisonous
Everything is poisonous
Nothing is without poisonous effect
Solely the dose makes a thing non-poisonous
Theophrastus Paracelsus von Hohenheim
(1493 - 1541)

7.4.1 Parameters for heavy metal exposure

Determination of the heavy metal content of the blood and urine are by far the most widely used techniques for investigating heavy metal loads[<19,1109>]. A steady-state theory between the heavy metals in the organs and the body fluids is assumed[<288>]. However, it takes 3 to 6 months for the steady-state to adjust[<380a>]. The correlation has proved to be more or less narrow, depending on the organ[<380a>]. On autopsy, Drasch found only a slight, linear dependency between the mercury content of the adrenal cortex or cerebellum and values in the blood, urine or hair[<360>].

7.4.1.1 Blood

"Mercury concentrations in the blood change depending on the level of mercury exposure shortly before. They are affected to considerable extent by the intake of mercury in a high fish diet."[<556>]. The Hg determination in the whole blood, therefore, reflects the inorganic and organic Hg loads in recent days[<192a>] to weeks[<83,89,121,577,843,985,1313>] or the internal load on continuous intake[<1033>]. Due to the relatively short half-life (1 to 2 days), low values do not rule out poisoning[<493,988>] (ethyl-Hg half-life = 7 days[<988>]). Determination of Hg concentrations in the plasma reflects the inorganic Hg burden, and in the erythrocytes, the organic Hg burden[<380a,1033>]. The erythrocyte/serum distribution quotient provides information on the proportion of organic Hg[<88,89,843>].

7.4.1.2 Urine

Urine measurements are the generally recognised method[<128,988>] used to determine Hg exposure and total body burden[<193>]. They reflect the exposure of previous weeks[<192a>] or months[<83,121,985>] and are thus suitable for establishing chronic exposure[<577>]. The inorganic Hg[<1033,1313>] load, primarily in the kidneys[<843>], is determined almost only in the urine. As up to approximately 90% of organic mercury is excreted via the faeces, the urine is not very suitable for the biomonitoring of organically bound mercury[<581>].

Urine values correlate with the number of amalgam fillings. Subjects with amalgam fillings have a higher mercury excretion in the urine than subjects without amalgam fillings. "On long-term exposure to mercury vapours, there is a clear correlation between the extent of the concentration in ambient air and the mercury concentration in the blood of exposed subjects. Likewise, a correlation exists between this blood concentration and the quantity excreted in the urine. Measurement of mercury concentration as spontaneous excretion in the urine of exposed subjects (best measured at the end of the working week) reflects the exposure load as confirmed by occupational medicine. If implemented correctly, the test method is highly accurate and is largely independent of influential external parameters"[<556>].

The urine should be measured over a period of 24 hours in order to take any fluctuations in mercury excretion into account[<493,577,988,1033>]. As this is feasible only with difficulty, the determination can alternatively be carried out in the morning urine[<1033>]. Spot samples can also be measured in emergency situations[<988>]. The normal values are 1-20 µg/L[<988>]. Values exceeding 10 to 20 µg/L are indicative of recent exposure. Neurological symptoms may develop at a value exceeding 100 µg/L and poisoning is assumed as from 300 µg/L[<988>]. "Urine samples with a creatinine content outside 0.3 – 3 g/l, cannot be evaluated"[<380a>].

7.4.1.3 Faeces

On the one hand, the faeces are used as the medium for the biomonitoring of orally ingested and intestinally only slightly absorbed metals (Cd, Hg, Mn, Ni, Pb). On the other hand, the selective determination of the organic mercury burden is feasible as up to approximately 90% of this is excreted via the faeces[<581>]. However, faecal analysis is only of limited relevance due to the individual fluctuations in the intestinal absorption and secretion of some metals[<1288>]. Determination of the heavy metal load through faecal analysis is not standardised scientifically[<556>] and does not yield rational values[<352>]. Standard values are missing[<988>]. 22 ng Hg/g dry weight were measured in 6 children[<988>].

7.4.1.4 Saliva

Saliva tests to measure the mercury load are not standardised scientifically[<556>]. The test is generally deemed to be unreliable[<1109>] or unsuitable[<380a>]. On average, the Hg content of the saliva increases with the number of amalgam fillings[<479>]. Amalgam particles released in the saliva and which are not absorbed[<380a>], may give a false result[<1018>].

7.4.1.5 Chewing gum test

The chewing gum test indicates the rate of release of mercury from amalgam fillings[<165,223,317,559,727,740,1134>] and thus the quality of the fillings[<1033>]. It provides evidence of individual Hg exposure[<970>]. The following estimates can be determined: the higher the mercury concentration in the saliva, the higher the exposure/load risk[<1289>].

Amalgam fillings	1 - 3	4 - 6	7 - 9	10 - 12	13 - 20
Smallest value (µg/day)	0.01	0.07	0.01	0.36	0.21
Biggest value (µg/day)	283	371	1.480	3.255	20.315
Mean (µg/day)	20	27	59	77	175
No. of subjects	61	183	330	442	373

The quantity of mercury measured in the saliva test (µg/day) depending on the number of amalgam fillings[<88>]

It is important that the test is carried out under standardised conditions (not immediately after cleaning the teeth or chewing gum,

drinking hot or acid drinks, or amalgam processing)[<89>]. Saliva is usually tested during the chewing gum test. In contrast to that, Hansen *et al*. recommend the determination of Hg in chewing gum, as this gives more reliable values[<559>].

The chewing gum test, however, does not provide any indication of the uptake of the heavy metal[<223>] and does not, therefore, allow any toxicologically justified assessment of the Hg intake by the body[<182,1313>], especially not via the crucial inhalation parameter[<1322>]. The "chewing gum test with subsequent saliva analysis is not suitable for diagnostic purposes as primarily non-absorbed mercury (alloy particles) is loosened and analysed"[<843>].

By way of comparison: According to the Drinking Water Decree (TrinkwV 2001), a mercury level not exceeding 1 µg/L is permissible in drinking water in Germany.

7.4.1.6 Hair

The analysis of hair indicates past Hg exposure[<1033>]. It reflects a mean exposure value over a longer period (growth period of the hair being studied)[<559,988,1033>]. "Later on it is possible to diagnose a poisoning by means of hair analyses, selecting corresponding area in view of the speed of hair growth"[<192a>]. Mercury levels in the hair correlate with those recorded in the blood or umbilical blood, in the erythrocytes and fish consumption[<581,1561>]. It highlights the organic Hg load in particular[<380a,1313>]. Inorganic mercury is only slightly incorporated in the hair matrix[<380a>]. Hair analysis can, therefore, be used for the biomonitoring of organic compounds.

It is important to obtain uncontaminated samples[<493>]. Problems mainly arise with external mercury contamination of the hair from the surroundings, which cannot always be removed through washing[<89,288,1561>]. "Given the defective method employed and the difficulty in interpreting the findings, hair analyses are not suitable for the objective assessment of mercury burden"[<843>]. "Hair analysis provides an opportunity to discover past exposure but frequently yields incorrect results due to exogenous contamination with heavy metals"[<1288>]. Based on data collated to date, determination of the mercury content of the hair does not highlight the mercury burden in the body[<1109>] and is unsuitable for assessing inorganic mercury and lead[<641>].

7.4.1.7 Breast milk

"Hg can also be determined quantitatively in breast milk. The concentration correlates with the number of amalgam fillings and is lower than that found in the maternal blood"[<380a>].

7.4.1.8 Porphyrin diagnosis

Patients with a higher Hg concentration in the urine also have a higher renal excretion rate of various porphyrins. The administration of DMPS increases the Hg excretion associated with a decrease in the raised porphyrin values in the urine[<1571>].

7.4.1.9 Respiratory volume

"Determination or mercury concentrations in the exhaled air may be appropriate for scientific studies but is not permissible for routine investigations due to cost. Basically, mercury released from amalgam fillings can be determined in the respiratory volume. However, mercury exposure over time is difficult to quantify under experimental conditions. A correlation between the mercury concentration in the urine or exhaled air and the number of amalgam fillings was found in a Norwegian study"[<380a>].

	1) Adult blood µg/L	2) urine µg/L Childrren	3) urine µg/L Adults	4) Saliva µg/L	5) Hair µg/g	6) Teeth mg/kg	7) Serum µg/L	8) Faeces µg/kg	9) House dust mg/kg	10) Urea µg/L
Ag	0.072	0.009	<0.008	<9.9		<0.25	<0.3		<1.2	<0.9
Al			<20*	<105	<20	<84.9	<8*	<287.000	<7.800	<20
As	0.93	25	34		<0.5		<10		<7.8	<25
Au	0.11	<0.024	0.027	<0.5	<0.25		<0.2	<50	<0.367	<0.6
B	42						<83		<58.6	<3.300
Ba	0.8	2.4	1.96				<2.9		<83.5	<5.7
Be	< 0.008	<0.009	<0.009				<0.3		<0.325	<0.8
Bi	< 0.008	0.01	<0.009			<0.25	<2.5	<10	0.99	<1.6
Ca							<112.000			<300.000
Cd	0.57	0.16	0.18	<3.3	<1.5	<0.25	<0.4	<60	<9.9	<1.3
Ce	< 0.008								<38.2	<12.1
Co	0.19	0.81	0.387	<2.5		<0.62	<0.4	<2.800	<2.7	<1.0
Cr		0.28	0.158				<0.4		<458.6	<1.5
Cs	3.6	4.4	4.7				<5.2		<0.409	<17.5
Cu	1.042	14	9	<72	<80	<10	<1.600	<23.000	<1.000	<50
Fe							<1.500	<253.000		
Ga	<0.2	<0.019	<0.019			<0.25	<1.1	<10	<3.2	<0.5
Ge									<0.111	
Hf	<0.006									<1.3
Hg	1.4			<2.7	<3.6	<0.2	<2.0	<10	<0.72	<1.4
In	< 0.009	<0.014	0.026		<0.25		<0.2	<10	<0.01	<0.2
Ir							<0.2		<0.01	<0.2
La	< 0.008						<1			<3.6
Li		77	35				<2.2		<2.2	<10
Mn	9	0.1	0.087		<2.0		<0.9		<340.5	<1.9
Mo	0.43	58	38				<1.2	<410	<7.8	<180
Ni	0.11	2.7	0.756	<9.9			<2.8	<3.620	116.3	<1.7
Pb	22	1.3	0.8	<23.1	<25	<22.3		<420	<816.7	<27
Pd	<0.02	<0.09	<0.09	<0.2	<0.02	<0.25	<0.2	<10	<0.8	<0.087
Pt		<0.009	0.011	<0.2		<0.25	<0.2		<0.01	<0.02
Rb	2.408	1.593	1.204				<317		<9.8	<4.096
Re							<0.2			<0.2
Rh	<0.006	<0.007	0.004				<0.2		<0.01	
Ru	0.007						<0.2		<0.01	<0.2
Sb	<0.013	0.063	0.063				<1.7		<10.5	<1.1
Se	133	17	14				<139		<3.4	<31
Si							<230			<12.100
Sn	0.18	1.2	8.6	<3.5		<2.36	<2	<640	<11.6	<2.0
Sr	20	154	166				<70		<202.5	<200
Ta							<0.2		<0.01	<0.2
Te	<0.14						<0.2		<0.01	<1.0
Ti							<7.7	<6.700	<113.6	<2.9
Th	<0.003									
Tl	0.019	0.018	0.15		<0.02	<0.25	<0.3	<10	<0.17	<0.7
U	<0.003	0.004	0.005				<0.2		<0.32	<0.2
V	0.052	<0.056	0.068				<1.1		<13.9	<1
W	<.011						<0.4		<2.7	<0.9
Y	<0.006									

	1) Adult blood µg/L	2) urine µg/L Childrren	3) urine µg/L Adults	4) Saliva µg/L	5) Hair µg/g	6) Teeth mg/kg	7) Serum µg/L	8) Faeces µg/kg	9) House dust mg/kg	10) Urea µg/L
Zn		482	269		<300	<265.5	<150	<69.000	<1.1	<850
Zr	0.033						<0.2		<1.4	<2

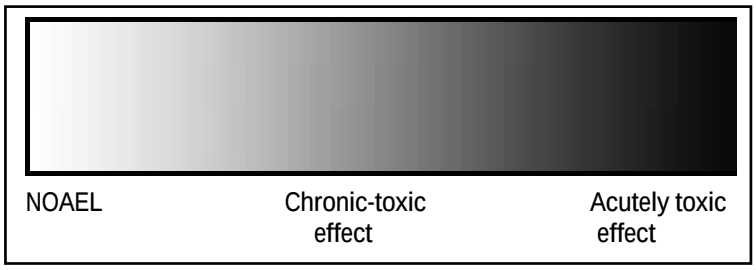
Normal and mean values of metals
1 Mean value in adult blood (n=130)[<574a>]
2 Mean value in children's urine (n=72)[<575b>]
3 Mean value in adult urine (n=87)[<575b>]
4-10 Normal values in various media
Measurements recorded by the Medicinal Laboratory, Bremen, Haferwende 12, D-28357 Bremen

7.4.2 Reference values

The statement, "mercury burden" is, first and foremost, an analytical result[<435>] that must be interpreted in each individual case. Various standard and limit values have been set to evaluate data.

These values are constantly adjusted in line with the current scientific state-of-the-art. The BAT values for lead in the blood virtually halved from 700 to 400 µg/L in the year 2,000[<1309>].

There are, however, also authors, who do not wish to set such values, "What is less clear is the dose of each form of mercury that presents little or no danger of adverse biologic effects"[<807>]. Gait ataxia were thus described in subjects with mercury levels below the HBM-II level whereas others with higher values did not exhibit these symptoms[<357>].



7.4.2.1 Human biomonitoring values (HBM I and HBM II)

In contrast the Human Biomonitoring Values (HBM values) are defined by the HBM Commission of the Umweltbundesamt (German Department of the Environment) and are toxicologically justified values for the assessment of internal hazardous substance load. They apply for subjects without occupational exposure, including both children and the elderly – subjected to external exposure, 24 hours a day, due to heavy metals in the environment or in the diet[<556>]. In values below HBM I [comparable with the NOAEL[<357>] (no observed adverse effect level)], no adverse effect on health is anticipated, based on the current state-of-the-art. There is, therefore, no toxicologically justifiable handling requirement. As regards the HBM I to HBM II range (test and control range), there is no scientific confirmation of a health hazard but similarly no sufficient evidence to substantiate that this substance is safe in terms of its effect on health. The "Human Biomonitoring" Commission recommends checking the values in the test range, initially through repetition. The person affected should be informed of the confirmation. It should be tested according to possible sources and removed at reasonable cost. If HBM II values are exceeded, it is comparable with the NOAEL[<357>], an effect on health cannot be ruled out. The HBM II value should be considered as an intervention value or measurement[<787>].

Neurological symptoms were, however, also detected below the HBM II value on mercury exposure[<357>]. A study carried out on gold diggers exposed to Hg in the Philippines showed that many patients displayed the clinical symptoms of mercury poisoning even below the HBM I value. The authors attribute this to the fact that the symptoms they observed were not taken into consideration when deducing the HBM values[<357>].

The reference values are purely statistically derived parameters and have no relevance per se on health. They show that measurements up to this reference value were recorded in 95% of the study population at the time of the test[<787>].

Heavy metal / Specimen material	Reference values		Human Biomonitoring Values		
	Group of people	Reference value	Group of people	HBM I	HBM II
Lead / whole blood	Children 6-12 years	60 µg/L	Children ≤ 12 years / Women ≤ 45 years	100 µg/L	150 µg/L
	Women 25-69 years	70 µg/L	Women > 45 years / men	150 µg/L	250 µg/L
	Men 25-69 years	90 µg/L			
Cadmium / whole blood	Children 6-12 years	0.5 µg/L	"N/A as based on the current state-of-the-art, there is no point deducing HBM I values for Cd in the blood"		
	Non-smoking adults 18-69 years	1.0 µg/L			
Cadmium / urine	Children 6-12 years	0.5 µg/L and 0.5 µg/g crea	Children and adults ≤ 25 years	1 µg/g crea	3 µg/g crea
	Non-smoking adults 25-69 years	0.8 µg/L and 1.0 µg/g crea	Adults ≥ 25 years	2 µg/g crea	5 µg/g crea
Mercury / whole blood With fish consumption up to three times a month	Children 6-12 years	1.5 µg/L	Children and adults	5 µg/L	15 µg/L
	Adults 25-69 years	2.0 µg/L			
Mercury / urine With fish consumption up to three times a month	Children 6-12 years and adults 25-69 years without amalgam fillings	1.4 µg/L and 1.0 µg/g crea	Children and adults	7 µg/L and 5 µg/g crea	25 µg/L and 20 µg/g crea

Reference and HBM values issued by the Human Biomonitoring Commission of the Umweltbundesamt (German Department of the Environment)[<787,1009,1033,1288>]

7.4.2.2 Other reference and limit values

The tolerance value for occupational exposure (MAK value up to Dec. 2004) is the time-weighted, average concentration of a substance in the air, which is not expected to acutely or chronically affect the health of the individual concerned. The calculation is generally based on eight hours' exposure over a five-day week throughout a person's working life. The tolerance value for occupational exposure is currently 0.1 mg/m^3 respiratory volume for elemental mercury and 10 µg/m³ for methyl mercury[<1110>].

The biological limit value (BAT value up to 2004) is the evaluation criterion for subjects with occupational exposure. This is the limit value for the toxicological concentration of a substance in the workplace, its metabolites or user indicator in corresponding biological material that does not generally adversely affect the health of an employee.

The Acceptable Daily Intake (ADI) describes the dose of a substance considered medically harmless on life-long daily ingestion. The value is mostly determined in feed tests in rats and mice. Various high dose levels of the test substance are given to these animals. This allows a dose level to be found at which no observable damage occurs [No Observable (Adverse) Effect Level (NOEL

Metal	BAT/BGW value	Test material
Aluminium	200 µg/L	Urine
Lead	400 µg/L 350 µg/L (women<45Y)	Blood
Lead, organic	50 µg/L	Urine
Aminolaevulinic acid (women < 45 years)	15 mg/L 6 mg /L	Urine
Manganese	20 µg/L	Blood
Mercury (inorganic and metallic	25 µg/L 100 µg/L	Blood Urine
Org. Mercury	100 µg/L	Blood

Biological Tolerance Value for Occupational Exposure (BAT) version 2004

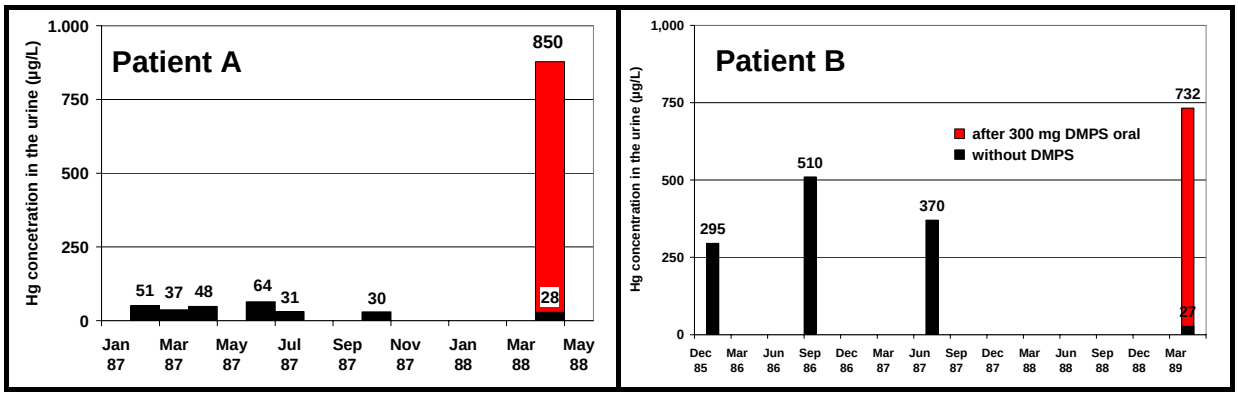
or NOAEL)]. The ADI is obtained by dividing with a safety factor. It is 3.6 µg/kg/day for lead, 1 µg/ kg/day for cadmium, 500 µg/kg/day for copper and 0.71 µg/kg/day for total mercury in adults and 0.35 µg/kg/day in children. Various USA authorities even set limit values of 0.1 to 0.5 µg/kg/day for daily mercury intake[<493>]. The WHO recommends a maximum daily mercury intake of 45 µg/ day[<121>] or 300 µg/week, not more than 200 µg of which must be methyl mercury[<352>].

The PTWI specifies the tolerable weekly intake. This is a toxicological limit value set by the WHO. The Hg value of 5 µg/kg/ week in adults and 2.5 µg/kg/week for children is currently being reassesssed[<1008a>]. 1.6 µg/kg/week of methyl mercury is permitted[<1004b>]. As regards Cd, the limit value is 7 µg/kg/week, for lead 25 µg/kg/week, for As 15 µg/kg/week[<1515a>] and for Al 1,000 µg/kg/week[<1004b>].

7.5 DMPS mobilisation test

Dimaval® and Dimaval® (DMPS) 100 mg hard capsules are licensed for the treatment of various types of heavy metal poisoning. Use as a diagnostic is not a licensed use for the two preparations.

The DMPS mobilisation test involves measuring the heavy metal content of the urine before and after oral, intramuscular and intravenous administration of DMPS[<121,352,1236>]. The mercury content of the liver can substantially increase up to 100-fold in the presence of mercury deposits in the body[<1104>]. Elevated values are indicative of storage[<121>]. This increase can be used as a parameter for the assessment of chronic Hg intoxication[<1102>].

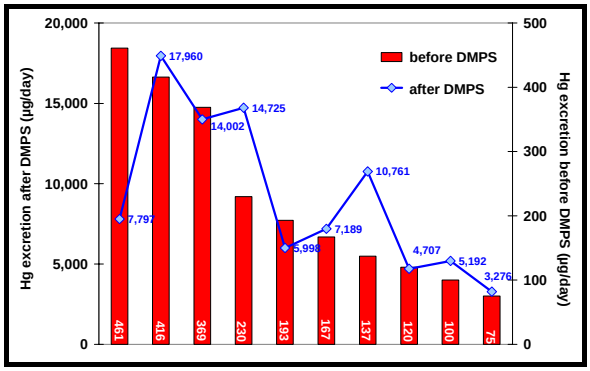


Mercury in the urine of two people with occupational Hg vapour exposure. They received a single oral dose of 300 mg DMPS in April 88 or 89[<1273>]

In mercury poisoning, administration of DMPS leads to a marked rise in Hg excretion in the urine. Contrastingly, a placebo does not increase excretion[<914,915,1311>]. The additional intake of potassium citrate had no synergistic effect on oral administration of DMPS[<587>].

Monitoring of the treatment of heavy metal intoxication with a chelating agent must always include monitoring of the heavy metal excretion in the urine[<288,1018>]. This means that every correctly performed treatment with chelating agents leads simultaneously to diagnostic information. Conversely, the DMPS test is simultaneously diagnosis and therapy[<170,182,294,383a,442,637>].

Higher Hg deposits were detected in 74 people with chronic occupational Hg vapour exposure without any typical clinical symptoms following administration of a single dose of DMPS[<1075>]. The DMPS test was recommended as far back as 50 years ago in the USSR to monitor employees in Hg factories[<1452>]. "Administration of a chelating agent capable of mobilizing the mercury bound in critical organs increases urinary excretion, and the excreted amount is considered to give a more realistic picture of the total body burden"[<985>]. "With the DMPS test according to Daunderer, we are now able to carry out the quantitative analysis of mercury poisoning in the urine"[<443>]. "Mercury excretion in the urine following administration of DMPS is thus a yardstick for determining the extent of the body deposit"[<69>]. High renal excretion rates are also mobilised on administration of DMPS with both palladium and copper[<637,638>].



Renal excretion of mercury before and after injection of 250 mg DMPS to persons with occupational Hg vapour exposure (µg/d)[<1075>]

7.5.1 Different parameters of the DMPS test

There are no standardised conditions for performing the DMPS test[<579>]. The various forms described in the literature differ in various parameters.

It is virtually impossible to evaluate the DMPS test as direct determination of the Hg concentrations in organ tissue is not feasible *in vivo* in man. Drasch *et al.* therefore attempted to verify the significance of the DMPS test on mercury using statistical methods. To this end, they compared the mercury concentrations measured in 149 human renal cortices at autopsy with the data recorded in the blood and urine of other living subjects. Hg levels in the adrenal cortices showed a significant dependency on the number of amalgam fillings, no difference being observed between men and women. Contrastingly, this dependency was not evident in the data recorded in blood and urine without DMPS administration – a fact that has been criticised by other people[<382>]. A correlation was also found after oral administration of DMPS and collection of 24-hour urine. No gender-specific difference was established. On i.v. administration of DMPS and 45-minute urine collection, Hg levels in the urine also correlated with the number of amalgam fillings in women, but not in men. This phenomenon could not be explained[<359>].

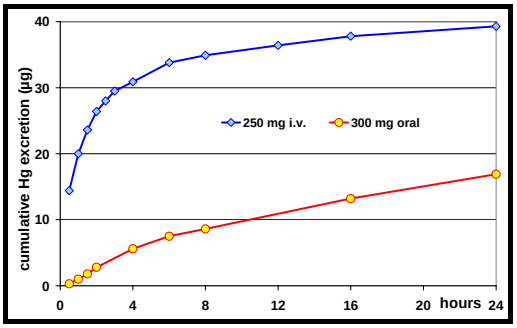
7.5.1.1 Choice of laboratory

There is no "test stick" for measuring heavy metal concentrations. Tests are carried out in appropriately equipped laboratories. As the quantities to be determined are relatively small and mercury analysis is prone to errors[<288>], measurements should be recorded only in qualified laboratories characterised, for instance, by participation in ring tests[<19,165,1278,1381>]. "However, the techniques involved in trace metal analysis in body fluids and tissues present certain difficulties, and such analysis should only performed in laboratories that are equipped for this purpose and that participate in external quality control"[<702>]. Specimen contamination must be avoided when collecting samples[<288,1277,1278>]. Only contamination-free, laboratory-tested test tubes must, therefore be used for collecting and dispatching samples[<19,1288>]. Analytical results with high values should be confirmed in a new sample obtained under optimal conditions[<1288>].

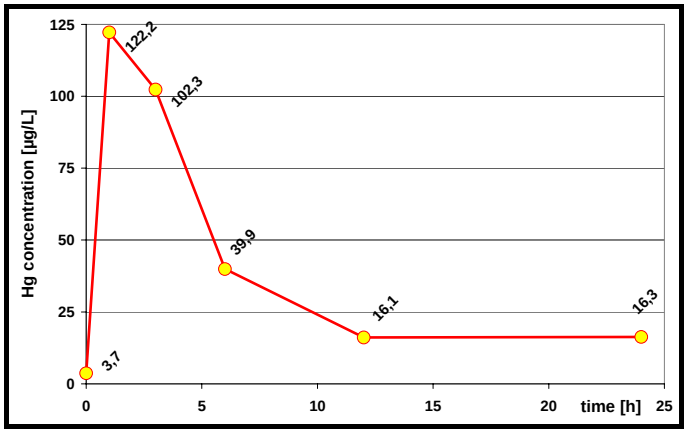
7.5.1.2 Type of administration (oral or parenteral)

The differences between oral and parenteral (i.v./i.m.) administration of DMPS were of a kinetic and quantitative nature. The i.v. administration led to a faster onset of action[<1273,1282,1283,1635>]. Fifty per cent of the mobilisable mercury was already excreted in the urine after 45 to 60 minutes[<1281,1635>]. Maximum excretion after i.v. administration was achieved after approximately 1½ hours[<174>] to 2 hours[<143>]. Possible absorption interference[<143>], e.g. through the formation of

gastrointestinal complexes[<143,381>], and thus difficulties in interpreting the measurements were excluded[<446,483>]. Otherwise, oral administration was as effective as the injection[<1281,1283>]. However, it must be taken into account that, after oral administration, generally less active substance is available, as only approximately 50% are absorbed[<435,1635>]. Hg excretion of 290 µg/24 hours was thus recorded after i.m. administration of DMPS, and 73.5 µg/24 hours after oral administration.



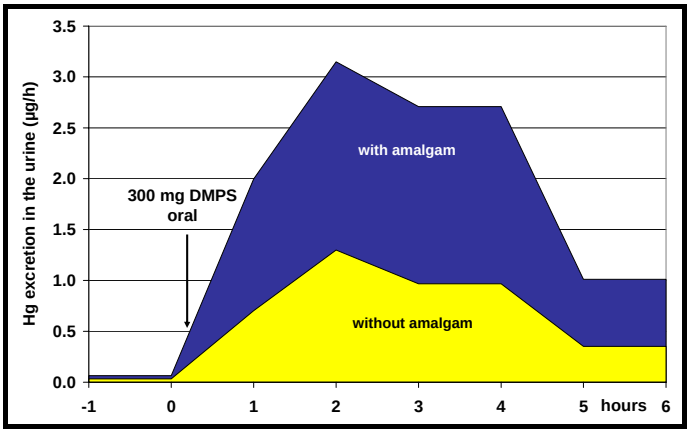
Cumulative renal Hg excretion after oral (300 mg) or i.v. administration (250 mg) of DMPS[<1273,1280,1282>]



Mercury concentration in the urine in 4 subjects following a single (i.v.) injection of 50 mg DMPS[<1150>]

The same peak concentrations were recorded in the urine[<472>] after administration of 10 mg oral DMPS/kg BW and 4 mg i.v. DMPS/kg BW. In contrast to i.m. administration, Hg excretion is still high 24 hours after oral administration[<985>].

The individual variation in absorption following oral administration of DMPS can lead to problems on interpreting the results[<440,985,1291,1482>]. An effective dose is guaranteed following i.v. administration[<1482>]. Parenteral administration is preferable to oral dosing in patients with known absorption problems[<1134>].



Hg excretion in the urine following single administration of DMPS (300 mg oral) to subjects with or without amalgam fillings[<54,58>]

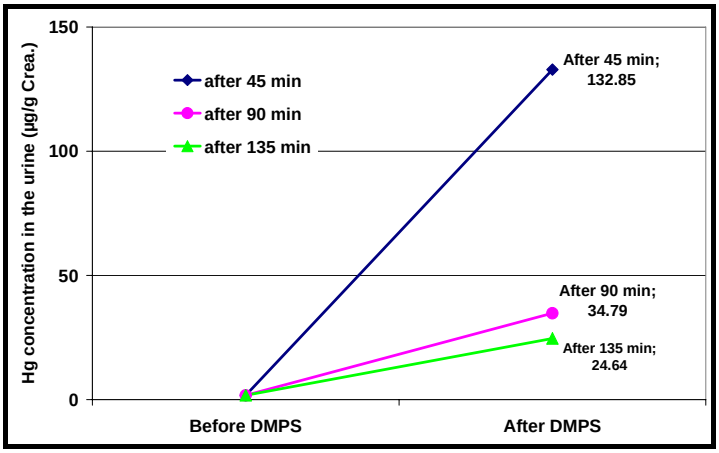
7.5.1.3 Dosage

3 to 4 mg/kg BW is mostly administered parenterally. For oral administration, the daily dose of 300 mg DMPS was mostly administered independently of body weight as a single dose, as with mobilisation tests with other chelating agents. Higher values may, however, be recorded in light patients than in heavy subjects as the relative dose is greater, calculated with reference to kg BW[<985>].

After it was found in laboratory animal experiments that the oral dose has to be 2.5 times the parenteral dose in order to obtain the same efficacy, Gerhard *et al.* introduced a mobilisation test with 10 mg DMPS/kg BW orally. This leads to similar excretion rates as in Daunderer's i.v. test[<473>].

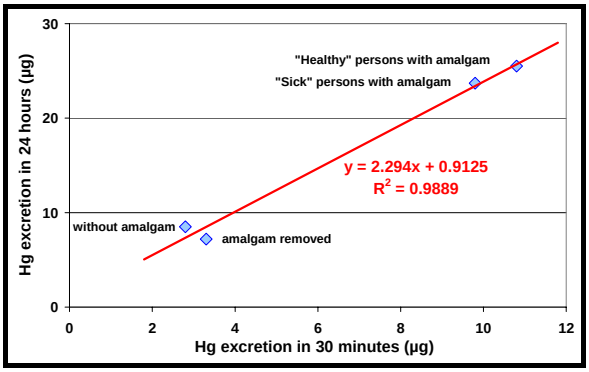
7.5.1.4 Collection from urine (spontaneous or 24-hour)

There is a lively debate on whether the urine should be collected over 24 hours or whether a shorter collection period or even the collection of spontaneous urine would suffice for the mobilisation test[<87,89,311,727,1493>]. In investigations with spontaneous urine, the mercury concentrations found in urine were considerably higher than those in 24-hour urine. Critics refer to "values that appear to be horrendously high"[<1110>].



Effect of the urine collection time on the Hg concentration after administration of 250 mg DMPS (n =26)<223>

The heavy metal-DMPS complex is excreted rapidly. Peak urinary excretion values in the urine were recorded two to three hours after ingestion or 45 to 90 minutes after i.v. injection of DMPS<174, 473,587,1290>. Elimination had returned to the baseline value after approximately 10 hours<173,174,1290>. The initially high concentration in the urine was thus diluted by the "late urine" with a considerably lower Hg content<174,313.473,1284>. The mean mercury concentration of 183 µg/g creatinine (collection time of 45 minutes) recorded in the urine of 261 women (250 mg DMPS i.v.) fell to 23 µg/L over a 10-hour collection period<472>.

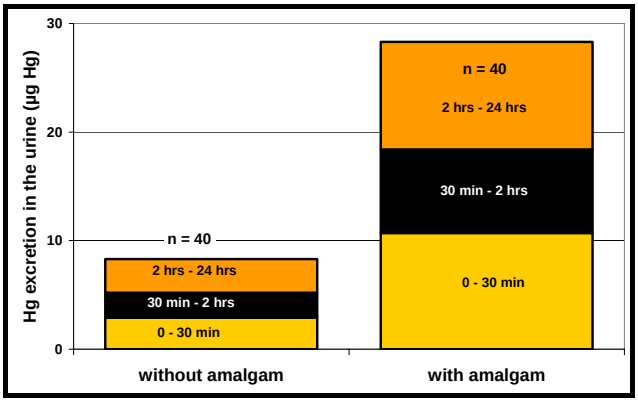


Comparison of Hg excretion 30 minutes and 24 hours after administration of 2 mg DMPS/kg BW i.v.<1482>

62% of the 24-hour excretion (oral 300 mg) was eliminated after 6 hours<1251>. After oral administration of DMPS, approximately 60%<947,1251> was excreted in the first 6 hours, 70 - 80 %<1273> in the first 8 hours and 25-32 %<1392> of the 24-hour excretion in the first 30 minutes. There was a significant correlation between urine excretion in the first 6 hours and the 24-hour value<947>. Measurements of the excretion time course showed that urine collection over 3<951> and 6<288,947> hours was sufficient for recognising mercury burden on oral administration of DMPS.

Following a single i.v. dose of DMPS (2 mg DMPS/kg BW i.v.), approximately 35 to 40% of the total 24-hour excretion were excreted in the urine within the first 30 minutes, around 70% within the first two hours<1482> and approximately 84 % in the first 8 hours<1273 >.

The good correlation between the mercury concentration (µg Hg/g creatinine) in the 45-minute spontaneous urine after i.v. DMPS and the mercury excretion in the 10-hour urine suggest that spontaneous urine is suitable for the assessment of the mercury deposit<472,473,1290>.

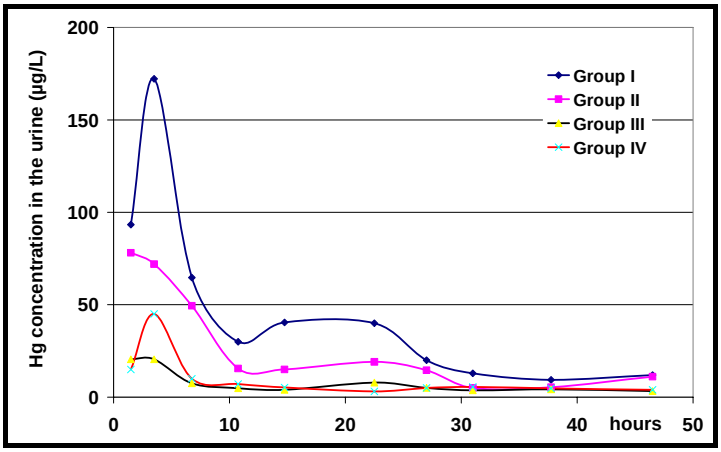


Hg excretion in the urine in patients with and without amalgam fillings after a single dose of 2 mg DMPS/kg BW i.v.<1482>

In 80% of patients, peak mercury levels in the urine were recorded between 0 and 3 hours after oral administration and, in 20, between 3 and 6 hours. The mercury level in the urine was still high after 24 hours. The excretion profile did not depend on the extent of the mercury load<985>. Regardless of the urine collection period of 1, 2, 4 or 9 hours, there was a correlation between mercury excretion after a single oral dose of DMPS and the amalgam score (surface area of all amalgam fillings)<54>.

The i.m. administration of DMPS increased the renal excretion of Hg in 7 workers with occupational phenyl mercury chloride exposure. 68% of the quantity excreted over 24 hours was already detected in 3-hour urine<497>.

Some authors nevertheless claim that the heavy metal content should be determined only in 24-hour urine[<382,549,550,728,729,1007>]. Determination of the mercury concentration in spontaneous urine is considered pointless[<1381>] as the result depends considerably on the volume of urine[<1380>]. However, the morning urine is suitable for determining the heavy metal content prior to administration of the chelating agent[<549,550,1007>]. Only in this way can the disruptive influences of the circadian rhythm and diuretically induced fluctuations in the quantity of urine be avoided[<87,89,1562>]. Not even standardisation to creatinine will suffice in this instance[<728,729>] as the urinary excretion of creatinine depends on the population (men, women and children have a different muscle mass and thus their creatinine excretion rate will vary), physical exercise and the time of day[<19>]. Thus lower creatinine excretion in children, for instance, is feigned by an increased pollutant burden[<1007>]. A shorter collection period gives a greater margin for errors[<406,947,1283>]. Although there is a linear correlation between µg Hg/24 hours and µg/g creatinine after stimulation[<581>], outlier values are nevertheless evident when the individual cases are considered[<729>]. A very high mercury concentration can be deceiving with a small quantity of urine[<87,89>].



Mercury excretion in the urine after oral administration of 300 mg DMPS[<1300>]
Group I only amalgam as the filling material (n=63)
Group II amalgam and other fillings (n=41)
Group III persons who previously had amalgam fillings(n=37)
Group IV persons who never had amalgam fillings (n=8)

Patient collection period	1 hour	2 hours	4 hours	9 hours	Amalgam score
1	47 x	53 x	50 x	31 x	45
2	25 x	26 x	26 x	15 x	29
3	11 x	9 x	7 x	14 x	3

Increase in Hg excretion in the urine after administration of DMPS (300 mg oral) compared to excretion before DMPS, depending on the urine collection time[<61>]

Long-term measurements, however, mask the problem of patient compliance (risk of contamination, collection error, greater expenditure)[<19,81,87,89,180,288,472,947,1033,1059,1251,1291,1562>]. Thus 9 out of 80 (11.25 %) of the 24-hour urine collections in a study must be discarded due to collection errors[<1482>]. Other studies report 1 in 7 = 14.3 %[<1251>] or 5 in 134 = 3.7 %[<581>] collection errors.

7.5.1.5 Urine or faeces

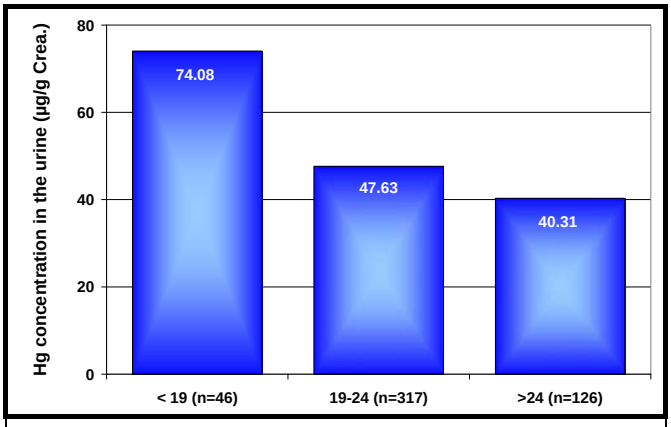
There have been occasional recommendations in the literature to determine the increase in heavy metal excretion after oral administration of DMPS not in the urine but in the faeces[<310,312,313,446>] or in the urine and faeces[<314>]. In these cases, a metabolic anomaly is assumed, whereby the heavy metal is excreted primarily in the faeces[<594>]. The supposed anomaly is not described in any greater detail. Similarly, there is no information as to how just the third bowel movement after administration of the antidote, for instance, should be examined.

Presumably mercury deposits other than those detected by investigation of the urine may be determined through faecal investigations. Up to approximately 50% of DMPS is absorbed after oral administration. This means that about 50% remains in the gastrointestinal tract. The unabsorbed DMPS can bind any mercury present in the stomach and intestines by interrupting[<435>] its enterohepatic circulation, for example[<1167>]. To determine the heavy metal deposited in the body, however, the heavy metal in the urine must be determined after oral administration of DMPS, as has been shown in numerous studies.

7.5.1.6 Calculation of heavy metal content in relation to creatinine concentration

The heavy metal content in the urine is often calculated with reference to the creatinine concentration in order to offset the diluting effect of the urine[<1482>]. "By determining the creatinine, highly concentrated (creatinine > 2 g/L) and markedly diluted (creatinine < 0.5 g/L) urine samples can be recognised"[<1033>]. With urine creatinine values of < 0.2 g/L, the values can no longer be meaningfully interpreted[<1277>].

It should, however, be borne in mind that renal creatinine excretion depends on the population and the time of day. In terms of average mg/L, women have a lower creatinine concentration, averaging 723 mg/L, compared to men with 975 mg/L[<83a>]. Creatinine is formed in the muscles and therefore depends on the muscle mass[<180>]. Thus the lower creatinine excretion in children, for instance, is feigned by an increased pollutant burden[<1007>]. Only minor fluctuations are normally observed in healthy subjects[<180>]. Details of the concentration, µg/L of urine and µg/g of creatinine can, in these cases, be equated approximately[<838>].



Dependency of mercury concentrations in the urine following oral mobilisation with DMPS from the body-mass index [<471>]

In a study involving 489 women, mercury excretion fell with increasing body mass index following single administration of 10 mg/kg oral DMPS[<471>]. One explanation is that the mercury deposited in fatty tissue is not mobilised. Increased excretion due to a higher muscle mass may also be the cause.

7.5.1.7 Order of the heavy metals

The following order for the excretion of heavy metals after mobilisation with DMPS has been given in various publications: Zn > Cu > As > Hg > Pb > Sn > Fe > Cd > Ni > Cr[<z. B. 128>]. According to this, zinc was the best mobilised. To what extent the authors have observed this themselves or how far they depend on the literature cannot be ascertained. Measurements that confirm the order are also missing.

This order contradicts the stability constants determined *in vitro* (see 3.7 Complex formation). The excretion of mercury, for example, is also increased even when zinc and copper are still present in the body. The authors probably mean the quantities excreted, not the order of metals[<1238>]. As zinc and copper are present in large quantities as trace elements in the body, a greater quantity of DMPS-metal complex is to be expected according to the law of mass action, even with lower binding constants.

Investigations in patients given zinc and selenium in addition to DMPS could not confirm that mercury mobilisation was more difficult due to high zinc and copper excretion[<981>].

Similarly, the data obtained with DMPS + Zn-DTPA or DMPS + Zn-DTPA + DMSA[<180>] combination therapies refute this order. The combination therapies must not exhibit greater excretion for the other heavy metals due to the addition of zinc.

7.5.1.8 Administration of DMPS with existing amalgam fillings

The administration of DMPS with existing amalgam fillings is subject to controversy[<952,1`114>]. There are occasional references in the literature that this should be avoided[<107>]. This applies to both oral[<315>] and i.v. administration[<737,927,973,1238>]. DMPS supposedly appears in the saliva and loosens mercury from the surface of the fillings[<927,1114,1238>]. This leads to acute heavy metal poisoning in the intestinal mucosa[<737,1238>] and other symptoms[<927>].

On the other hand, the same authors recommend that, in severe cases, DMPS should be administered before amalgam removal in order to empty the "long-standing stores"[<317,1591>]. Others recommend the removal of amalgam under DMPS protection, e.g. by administration of 100 mg DMPS 2 hours[<307,558>] before or 1 ampoule 20 minutes before boring[<973>] or one capsule each day before, during and after amalgam processing[<1037>].

To my knowledge, DMPS in the saliva has never been investigated. I do not consider it a problem even when small quantities of DMPS reach the saliva.

- DMPS only comes into contact with the surfaces of the amalgam fillings. DMPS cannot access the rest of the amalgam.
- DMPS reacts with Hg ions, not with metallic mercury, which is present in the amalgam alloy.
- No particular risk was evident in observations carried out on numerous patients following a DMPS test with existing fillings. Even long-term treatment in orthodox medicine has never indicated any problems in the presence of amalgam fillings.

"According to Dr. David Quig of Doctor's Data, there is little evidence that chelating with DMSA or DMPS causes an increase in mercury release from amalgam fillings. If that were the case, then adding the chelating agents would be an effective means of removing mercury amalgams. He believed it was safe to chelate with amalgams"[<1273a>].

7.5.1.9 Comparison of DMPS and DMSA

Both DMPS and DMSA are effective in the mobilisation of mercury[<952>]. DMPS appears to be a better chelating agent for Hg[<1121>], generating higher mercury levels in the urine[<637>]. "Typically a single dose of DMPS will provoke more mercury from the tissue than a single dose of DMSA"[<164>]. Following administration of 10 mg/kg p.o., 45 µg Hg/g creatinine was found in 6-hour urine with DMPS compared to just 4 µg Hg/g creatinine with DMSA[<1192>]. DMSA (30 mg/kg oral) increased Hg excretion from 4.98 to 13.11 µg/L in 65 patients, and DMPS (10 mg/kg oral) from 5.05 to 11.88 µg/L in 20 patients[<587>].

The information on DMSA-induced poisoning of the brain is inconsistent. In the literature, there is no evidence of a corresponding effect with DMSA, which numerous authors claim. Neither 'DMSA passes into the brain'[<927>] nor 'DMSA does not pass into the brain'[<738>] can be confirmed by corresponding clinical studies. Mercury concentrations in the brain cannot be measured on ethical grounds. Similarly, there is no evidence in humans to confirm the following statement: "In contrast to all of the previous complex-forming agents, DMPS lowers the concentration of mercury that has accumulated in the brain"[<325>].

7.5.1.10 Combination of complex-forming agents

"Even though DMPS enhances the excretion of a wide number of metals, many clinicians opt to combine chelating agents in the same challenge test. This remains a wide and relatively unexplored area of detoxification medicine"[<155a>]. More recent investigations show that heavy metal excretion can be increased with a suitable combination of chelating agents[<179a,180>]. They do not confirm that the antidotes have a synergistic effect. In combination therapy, the overall dose of chelating agent administered is higher. Whether a correspondingly higher dose of monotherapy would also generate this effect, has not been investigated.

The complexes of heavy metal and complex-forming agents are excreted primarily via the kidneys. If several chelating agents are administered concomitantly, then a particularly high burden can be expected in the kidneys. However, there have been no reports of kidney damage as a result of this to date. Based on experience gained in the interim, combination therapy with various chelating agents does not appear to pose any greater risks than corresponding monotherapy.

It is a well-known fact that DMPS also forms complexes with zinc, thus promoting its excretion. With a combination of Zn-DTPA and DMPS, there is therefore a possibility that DMPS will react primarily with the zinc and not be available for other metals. Comparison of zinc excretion during DMPS and DMPS/Zn-DTPA administration, highlights extremely high Zn excretion with the

combination[<180>]. Unfortunately, the values for Zn-DTPA monotherapy are not included in the following table.

95 percentile	Al	As	Ca	Cd	Cr	Cu	Hg	Ni	Pb	Sn	Zn
Basal urine n=550	124	132	245,000	0.87	21.4	56	2.4	11.5	4.1	4.17	650
DMSA n=614	324	235	269,000	1.24	39.8	308	24.4	17.5	74.23	11	2344
Na-EDTA n=22	236	190		3.92	20	193	2.04	21.5	30.22	16.73	22,491
EDTA+DMSA n=284	237	107	740,000	4	43.8	44	11.1	25.8	86.56	16.32	29,020
Ca-EDTA+DMSA n=31	146	82		3.14	28.5	740	22.1	21.3	158	34	27,930
Ca-EDTA+DMSA+DMPS n=58	348	91		2.26	22.5	1,245	82	33.4	81.3	40.8	39,530
Ca-EDTA+DMPS n=31	202	75		2	58.3	1,436	37.3	35	70.4	14.4	44,231
DMPS n=184	253	133	268,000	1.3	31.4	1,417	68	14.67	27.5	21	4,590
DMPS+Zn-DTPA n=512	266	266	269,000	2.84	31.1	1,444	107	23	75.03	25.5	746,000
DMPS+Zn-DTPA+DMSA n=216	262	209		2.82	27.7	1,199	120	17.1	119	21	520,000

Heavy metal excretion in the urine following the administration of various CA alone or in combination (µg/g crea), Measurements from the Micro Trace Minerals Laboratory, D-91217 Hersbruck[<179a,180>]

7.5.1.1 Variants of the DMPS mobilisation test

Variants of the DMPS mobilisation test are described in the literature. They differ in terms of DMPS administration, dose, urine collection period and mercury values (µg/L, µg/24h, µg/g creatinine). As a result, the measurements obtained are often incomparable[<559>].

A common factor to all variants of the mobilisation test is that urine is collected before and after administration of DMPS. Both urine samples are sent to suitably equipped laboratories for heavy metal determination[<727>]. Urinalysis prior to DMPS administration is occasionally dispensed with on financial grounds[<483>]. A uniform, standardised procedure must be used in order to obtain comparable, correct results[<87,89,549>]. Agreement between the doctor and the laboratory is important[<373>].

In addition, the patient must empty his bladder completely before administration of DMPS[<382,383a,472,1134>] and the urine must be collected correctly.

Where there are markedly raised zinc and/or copper values (copper > 2,500 µg/g creatinine[<1591>]) it must be borne in mind that there may possibly no longer be sufficient DMPS for mobilisation of other metals. The results may, therefore, be falsely negative[<182,195,321,440,444-446,1591>]. In these cases, repetition of the test after 4 to 12 weeks is recommended[<182,440,1308>].

Assessment of increased copper values poses a problem. Laboratory animal experiments have shown that where poisoning with arsenic[<885>], gold[<1424>] or mercury is present, the copper content of the kidneys is also significantly raised. Induction of the formation of metallothioneins, which then retain more copper, has been suggested as a mechanism of action[<1424>]. With DMPS therapy, not only the mercury, but also the copper levels fell. A similar situation was observed for zinc[<1424>].

7.5.1.11.1 Mobilisation test according to Daunderer (parenteral)

Based on experience with more than 6,000 patients, Daunderer recommended carrying out a mobilisation test at a mercury concentration in the urine of more than 5 µg/g creatinine or the corresponding clinical symptoms[<313,314,317,324>]. The patients do not need to fast[<472,473,476>].

❶ Creatinine is determined in addition to mercury in urine 1[<1291>].
Zinc is also measured in order to exclude mercury-induced zinc deficiency[<1633>] (the zinc level in the urine should be 400 – 600 µg/L[<315>]. Zn < 140 µg/g creatinine indicates zinc deficiency[<1591>], which should be replaced[<441>]).

❷ Slow i.v. administration of 3 – 4 mg DMPS/kg BW[<320,1568>].

❸ Get the patients to drink approximately 150 mL of tea, water or lemonade. Friese recommends a bottle of mineral water[<441>].

❹ Collection of spontaneous urine 45 minutes to 1 hour after administration of DMPS[<313,320>]. Birkmayer recommends the collection of urine after ½ to 1½ hours[<173,174>], Friese after 30 minutes[<441>].

❺ Creatinine and copper are determined in addition to mercury in urine II[<1291>]. If indicated, other heavy metals can also be determined[<313,1291>].

➲ A rise in the mercury in the urine after administration of DMPS to more than 50 µg/L or 50 µg/g creatinine shows accumulation of mercury[<310,320,324,327,441>]. A deposit is also present when the Hg concentration in the urine is increased more than 10-fold[<324>]. In contrast, Schiele considers values of up to 1,000 µg/g creatinine to be normal in persons with amalgam fillings[<1279>].

If the zinc level in urine I exceeds 720 µg/g creatinine, the test should be repeated after 3 months as copper and mercury may not be sufficiently mobilised due to the high zinc level. If the copper concentration in urine II exceeds 1,500 µg/g creatinine, the test should also be repeated after 3 months as the mercury excretion may be too low ("false negative result")[<441,446>].

The DMPS mobilisation test is also recommended for determination of the burden with other heavy metals, e.g. lead (in hypertension[<352,446>]), cadmium (in osteoporosis[<352,483,1591>]) or aluminium in Alzheimer's disease[<352>]. As the efficacy of DMPS is not confirmed for aluminium and cadmium (see Chapter 7.2.1 and 7.2.6), the final recommendations are dubious.

As	Cd	Cr	Cu	Hg	Mn	Ni	Pb	Sn	Zn
25	5		500	50	10		150	15	2.000

Limit values (µg/g creatinine) for the parenteral DMPS test according to Daunderer <87,89,313,316, 324,327,1633>

The Bremen Medical Laboratory detected copper excretions in the urine of up to 1,700 µg/g creatinine after DMPS administration in a group of 50 patients without amalgam fillings. According to Microtrace, the 95% percentile for copper is 1.417 µg/g creatinine[<180>].

Bonnet carried out this test in approximately 200 babies and young children. If possible, a spontaneous urine sample was initially collected. A urine collection bag was attached to the children after injection of 4 mg/kg DMPS i.m. The first urine collected after injection was used for the test. The fact that complete bladder emptying cannot be confirmed should be taken into account when interpreting the measurements[<195>].

7.5.1.11.2 Mobilisation test according to Schiele (oral)

Schiele[<1282>] recommends the following procedure for investigating the systemic load with mercury:

❶ Determination of the basal level for mercury
A spontaneous urine sample is normally sufficient to determine the baseline value. Preferably, a sample of the first morning urine should be used.

❷ After complete emptying of the bladder[<1557>], 300 mg Dimaval® (DMPS) are administered orally with water.

❸ Determination of the heavy metals in the 24-hour urine after administration of the complex-forming agent.

➲ "A rise of more than 10 times the basal level indicates above-average accumulation"[<208,1285>]. Schiele considers values of up to 100 µg/g creatinine to be normal in persons with amalgam fillings[<1279>]. Schuetz considers an increase of more than 3 times the basal level as an indication of a burden[<1307>]. According to Damrau, treatment is necessary if the BAT value of 200 µg/L is exceeded[<951>]. Kleber considers the upper limit of normal to be 30 µg/24 hours or from 30 µg/L in 24-hour urine[<728>].

7.5.1.11.3 Mobilisation test according to Aposhian (oral)

Aposhian describes a mobilisation test with 300 mg DMPS orally, regardless of body weight, for mercury, arsenic or lead[<57,187,502,890>]:

❶ Fasting and collecting of the urine overnight for determination of the baseline value.

❷ After complete emptying of the bladder, 300 mg Dimaval® (DMPS) are administered orally.

❸ Drinking sufficient water for approximately 500 mL of urine to be excreted in the next 6 hours.

❹ Light meal after 4 hours
❺ Collection of the urine up to 6 hours after administration of DMPS. Completely empty the bladder at the end.
➲ Excretion of ≥ 50 µg Hg/6-hour urine is a positive test for "patients with a significant history of Hg exposure"[<187>].

7.5.1.11.4 Mobilisation test according to Daunderer (oral)

Daunderer describes a mobilisation test with oral administration of DMPS [<319,322>] ("approximative quantity measurement"[<314>]):
❶ Determination of the basal level of mercury in the morning urine (zinc in addition to exclude deficiency[<1037>]). No fish during the week before as this can lead to high values[<987>].
❷ In adults, administration of 300 mg DMPS with ½ litre of mineral water on an empty stomach. Young children receive 100 mg and children of 12 years and over, 200 mg DMPS[<326>]. Then continue to fast for 1 - 2 hours[<86,87,970,981>]
❸ Collection of spontaneous urine 2 – 4 hours after administration of DMPS.
➲ A mercury concentration exceeding 16 µg/L[<86,314,352,981,1037>] or 20 µg/L[<1040>] in spontaneous urine or 20-30 µg/24h[<87,89>] indicates mercury burden. The limit value for copper is 500 and that for zinc, 2,000 µg/g creatinine[<89>].

7.5.1.11.5 Mobilisation test according to Gerhard (oral)

Gerhard carried out a mobilisation test with 10 mg DMPS/kg BW oral for mercury and other heavy metals such as As, Cd, Cu, Pb, Ni and Sn on more than 500 patients[<475>]:
❶ Collection of morning urine after 12 hours' fasting. Test for mercury, zinc and selenium.
❷ Ingestion of 10 mg DMPS/kg BW orally on an empty stomach
❸ Drink 1 to 2 litres of fluids in the following 3 hours.
❹ Collection of spontaneous urine 2 – 3 hours after administration of DMPS.
➲ The following concentrations are limit values: Hg 100, Pb 80, Cu 2.000, Cd 5 µg/g creatinine[<481>].

7.5.1.11.6 Mobilisation test according to Nerudova (oral)

The Prague scientists describe a mobilisation test for mercury involving two doses of 300 mg oral DMPS. In contrast to the spontaneous urine values, they found a better correlation between clinical findings and the measured values in exposed workers[<985,1472>]:
❶ After 7 hours' fasting, 4 mg DMPS/kg BW were administered on an empty stomach.
❷ The patients were instructed to drink at least two litres.
❸ 24 hours later, the patients received another dose of 4 mg oral DMPS/kg BW.
❹ Collection of urine over 24 hours
➲ No limit values

From comparing the clinical trials and laboratory animal experiments, Nerudova *et al*. concluded that 17 – 20% of the mercury deposited in the kidneys are mobilised and excreted in the urine[<985>] of workers presenting with occupational exposure following administration of 2 x 4 mg DMPS/kg BW oral, 24 hours apart, and 25 - 30% following administration of 2 x 4 mg DMPS/kg BW i.m.

7.5.1.11.7 Mercury triple test according to Hansen (oral)

As they considered the determination of only one parameter for the diagnosis of Hg to be too risky, the Luxembourg scientists developed the mercury triple test, which they tested out in more than 2,200 patients. In addition to the Hg concentration in the urine before and after administration of DMPS, the quantity of Hg was also determined in the hair and a chewing gum (not saliva!) after chewing for 30 minutes. The dose of DMPS administered depended on the body weight:
❶ Collection of urine I (morning urine) before eating or drinking anything

❷ Oral administration of DMPS with ½ L mineral water
200 mg DMPS for patients with a BW < 60 kg
300 mg DMPS for patients with a BW of 60 – 80 kg
400 mg DMPS for patients with a BW > 80 kg.
❸ Another ½ L mineral water after 2 hours
❹ Collection of the urine up to 4 hours after administration of DMPS.
➲ A higher Hg value in urine II and in the chewing gum indicates a Hg load due to amalgam fillings. However, the authors make no reference to limit values[<559>].

7.5.1.11.8 Mobilisation test according to D. Quig (oral)

The test, like the others, assumes intact excretory functions. Disturbances in the "nutritional and detoxification status" may lead to excessively low values.

❶ After 8 hours' fasting and complete emptying of the bladder, 10 mg DMPS/kg BW (up to a maximum of 500 mg) are administered to children (5 mg/kg)[<1117>].
❷ Drink 0.5 to 1 L or 1 to 1.5 L of water
❸ If necessary, eat a light meal (no fish) after 3 – 4 hours
❹ Collection of urine over 6 hours
➲ Limit values for women: < 4.1 µg/g creatinine – no burden
4.1 to 12 µg/g creatinine – raised values
> 12 µg/g creatinine – markedly raised values
Limit values for men: < 3.1 µg/g creatinine – no burden
3.1 to 9 µg/g creatinine – raised values
> 9 µg/g creatinine – markedly raised values[<967,1191,1192>].

7.5.1.11.9 Mobilisation test according to HP Bertram (oral)

❶ Collection of 24-hour urine
❷ Administration of 3 x 100 mg DMPS orally per day for 3 days and collection of 24-hour urine
➲ No reference to limit values[<165>].

7.5.1.11.10 Mobilisation test according to DAN! (Defeat Autism Now!)

❶ Oral administration 5 – 10 mg/kg, collection of urine over 6-12 hours or
❷ i.v. administration of 2-5 mg DMPS/kg, collection of urine over 6-8 hours or
❸ transdermal administration of 3 mg/kg, collection of urine over 12-24 hours or
❹ rectal administration of 10 mg/kg, whereby the suppositories must remain in place for at least 30 to 45 minutes, collection of urine over 8-12 hours
➲ No reference to limit values[<1231>].

7.5.1.11.11 Function test according to IFLB

Das Institut für Laboratoriumsmedizin Berlin IFLB (Berlin Institute for Laboratory Medicine) has described another version of the mobilisation test on its homepage:

❶ 1st day: Pass the first morning urine in the toilet as normal, but collect subsequent urine in bottle "No.I (before)" .
❷ 2. 2nd day: Collect the first morning urine in bottle "No. I (before)". Take one Dimaval® capsule at least one hour before breakfast. Then collect subsequent urine in bottle "No. 2 (after)".
❸ 3. 3rd day: Collect the first morning urine in bottle "No. II (after)".
➲ Elevated values indicate intoxication with mercury or the respective heavy metal[<1353a>].

Conclusion:
The list shows that there is no generally established DMPS test for mercury. There are, however, various techniques that differ in terms of dosage, method of administration of DMPS, collection period for urine and the units used to express the measurements. No generally acknowledged limit values are stipulated for the various heavy metals.

7.5.2 Results of mobilisation tests

In the first stage, the mobilisation test provides an analytical value[<435>] that must be interpreted and assessed in each individual case. “With the DMPS clearance test, the quantity of mercury is undisputedly stipulated, which is excreted from the body due to a defined quantity of the solvent, DMPS. There is a general convention from intensive medicine and from observations of natural medicine practitioners that at high clearance values, a high residual quantity of mercury is stored in the body. It has not, however, been clarified whether or not these high quantities of mercury have a considerable effect on the patient’s body“[<1490>]. Increased excretion is a sign of accumulation, but not of specific organ deposits[<460>]. A conclusion regarding total body burden is dubious as no dependencies have been established[<223>]. The DMPS test only facilitates recognition of a burden[<83,637,970>]. Intoxication [<83>] or particular sensitivity to mercury[<172,970>] is not detected in this way. Asymptomatic patients had similar mobilisation values to symptomatic patients[<874,1280>]. Patients who attributed their symptoms to amalgam exhibited the same values as healthy subjects with amalgam fillings[<1482>].

Only relatively rapidly available mercury deposits[<83,489,839,947>], essentially in the kidneys and bone marrow, are mobilised[<133,216,460,472,559,838,966,1134,1273,1283,1635>] through the DMPS test. This is borne out by the correlation between the concentration of coproporphyrin in the urine, a marker for mercury burden in the kidneys, and the Hg concentration in U(II)[<502>]. A correlation between the increase in mercury excretion in the urine following administration of DMPS and the existing total body load was evidenced in laboratory animal experiments.

As DMPS does not cross the blood-brain barrier, the test gave no results regarding the burden in the brain or the central nervous system[<223,359,382,446,460,973,1018,1133,1134,1236,1273, 1283,1322,1635>], where mercury has its main effect[<482,831,1557>]. Despite lower excretion values, loads may be present here[<444>]. This also applies to other poorly circulated compartments[<973>]. Information on the mercury load in the body overall is not to be anticipated[<1018>]. Even the statement, “Consideration of the concentrations of mercury before and after administration of Dimaval provides some indication of the heavy metals stored in the fat deposits of the body“[<1628>] presumably does not apply.

The increased Cu burden observed on Hg exposure does not mean that the body was also severely exposed to Cu but merely that increased quantities of Cu were stored in the kidneys. Laboratory animal experiments have shown that cadmium (see chapter 6.1.9.5) or mercury (see chapter 6.1.17.3.3.4) poisoning leads to higher copper deposits from food. Increased Cu excretion may, therefore, indicate a Hg burden[<179>].

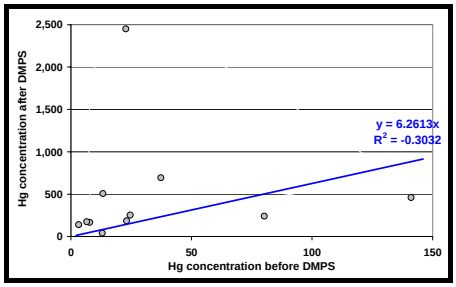
7.5.2.1 Theoretical mobilisation capacity of DMPS

The stability constant for the DMPS:Hg (1:1) complex is 27.05. It can, therefore, be assumed, that if sufficient mercury is present, no free DMPS is available. 250 mg DMPS (MW 210.27) can, therefore, bind a maximum of (250/210.27 * 200.59) = 238.5 mg mercury (MW 200.59) in aqueous solution. One mL of DMPS injection solution can then bind a maximum of 47.7 mg mercury. One 100 mg DMPS capsule (bioavailability of approximately 40%) can bind approximately 38 mg of mercury.

The value must, however, be lower *in vivo*, as the majority of DMPS is metabolised. Another part of the DMPS reacts with essential trace elements. These have lower binding constants but are present in higher concentrations. Part of the DMPS reacts with other heavy metals present in the body, such as lead.

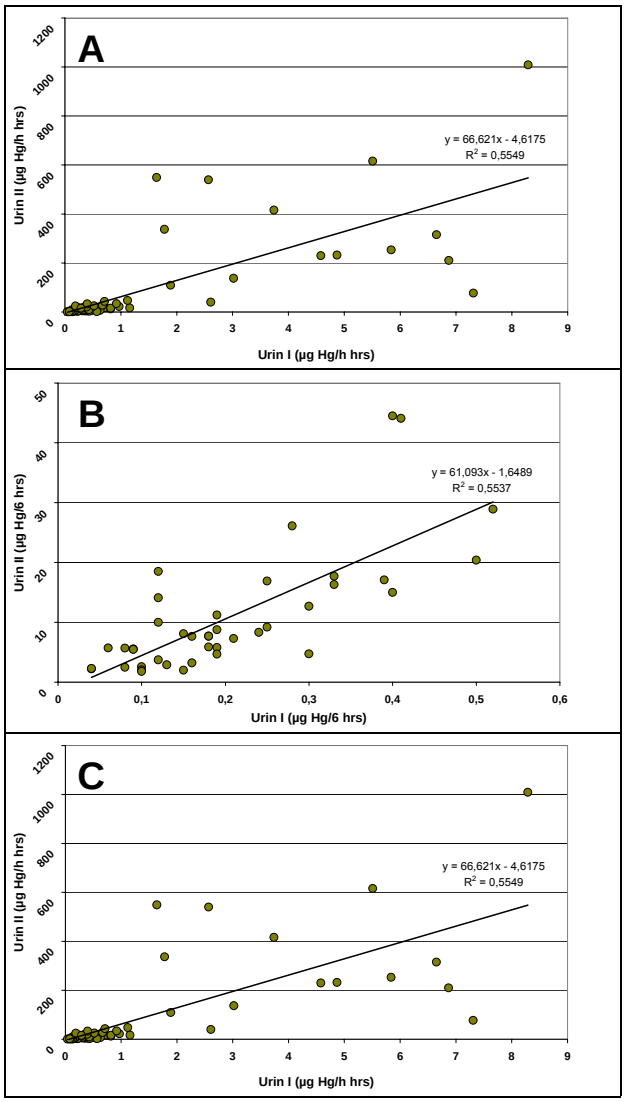
7.5.2.2 Necessity of a mobilisation test

The DMPS mobilisation test is nowadays offered by many laboratories as an IgeL (customised) service, essentially for determination of the mercury load from amalgam. In addition, it is also used for the recognition of heavy metal intoxication in people with occupational exposure[<925,985,1283,1385>]. The necessity of a mobilisation test is, however, a matter of dispute in clinical practice[<406>].



Mercury excretion in the urine 1 hour before and after administration of 3 mg DMPS/kg BW i.v.<1446>

Thus the Advisory Toxicology Committee of the Deutsche Gesellschaft für Pharmakologie und Toxikologie (German Society for Pharmacology and Toxicology), the Kommission Human Biomonitoring des Umweltbundesamtes (Human Biomonitoring Committee of the Department of the Environment)<380a,1032> and the BfArM (Federal Institute for Drugs and Medical Devices)<1006,1018> as well as other scientists do not consider the mobilisation test to be indicated for the determination of the mercury burden as it involves the unnecessary administration of a drug associated with a health risk<128,223,577,600,1232,1277> and does not produce any additional diagnostic information<209,382,546,550,577,581,583,588838,866.988,1059,1132,1313,1380,1562a>. It is only an "analytical magnifying glass"<382,1033>. As mercury does not, unlike arsenic<960> or lead<553>, have any marked tendency for accumulation in the body<1251>, measurements in the blood or urine are, in their view, sufficient<1322>. "This also applies to the so-called DMPS method. Administration of 300 mg of the complex-forming agent, 2,3-dimercapto-1-propane sulfonate sodium salt (DMPS, Dimaval), mobilises the mercury primarily stored in the renal tissue, and also allows it to be excreted in the urine. Urinary excretion is consequently increased 5- to 20-fold compared to spontaneous excretion. The method does not, however provide any better or additional information on the extent of external and internal burden or exposure through inorganic mercury. Similarly, the DMPS method does not provide any better, corroborated toxicological evaluation compared to test methods for the biological limit value. In contrast to spontaneous excretion, the excretion of mercury after DMPS administration depends on additional parameters (e.g. absorption rate and bioavailability). As the DMPS method does not provide any more information from a toxicological and occupational medicine standpoint than the measurement of spontaneous excretion of mercury in the urine (biological limit value) and since serious adverse reactions are to be anticipated on administration of the medicinal product, this method should be rejected for assessing occupational burden and exposure"<556>.



Heavy metal excretion in the urine before and after administration of DMPS<186>
A: Mercury, 300 mg DMPS oral
B: Mercury, 3 mg DMPS/kg BW i.v.
C: Arsenic, 300 mg DMPS oral

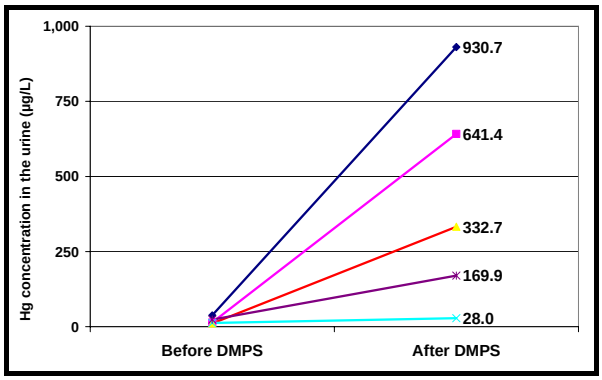
Even former supporters now, in the meantime, consider the test as unsuitable for routine, clinical diagnosis. "The test does not clarify whether the health of an individual female patient is at risk. Only a cautious estimate of the kidney burden seems feasible<233>. An excessively high DMPS test result alone does not qualify as an indication for the removal of amalgam. Patients with low values may be "very ill" whereas patients with high load values exhibit no symptoms<1490>. "A negative result in the mobilisation test cannot rule out former mercury poisoning"<1281>.

Other equally well-known scientists consider a mobilisation test to be meaningful where chronic mercury poisoning is suspected

because the mobilisable renal excretion is directly proportional to the total body burden[<475>]. The Untersuchungszentrum Füllungswerkstoffe der Zahnklinik Münster (Filling Substance Test Centre at the Münster Dental Clinic) also used the mobilisation test in addition to Hg determination in spontaneous urine[<1390>] "The mercury burden in living humans is best quantifiable with the Dimaval® test (urinalysis before and after administration)"[<1108>].

"As regards the relatively short biological half-life of mercury in the blood and urine of around 2 – 3 months, mercury analyses of urine and blood used within the scope of occupational medicine examinations and involving expert techniques should be assessed with reservation due to the fact that exposure often occurred a long time ago[<1273,1281>]. A mobilisation test with DMPS is "entirely appropriate for detecting mercury deposits in the body of living humans[<1283>]. "The mobilization of mercury by administration of DMPS … for evaluation of the mercury body burden has been successfully used at different exposure levels" [<273>]. "To assess mercury levels, a provoking or chelating agent is needed - one that has a high degree of binding affinity. DMPS … provides an excellent challenge substance because of its high degree of sulfhydryl bonds"[<155a>].

Statistical investigations showed, on average, a linear correlation between the excretion of Hg, arsenic[<480>] and tin[<197>] before and after administration of DMPS. There is no correlation with lead, cadmium or copper. Individually, there are, however, always deviations[<83,192,223,480,604,728,729,1280,1287,1290>]. In individual cases, the mobilisation values cannot be derived from the baseline values[<558,559,589,1280,1281>]. The tests always contain "outliers" – high excretion after DMPS with a relatively low baseline value[<729,1315>] or a high baseline value and a relatively low mobilisation value. "In individual cases, therefore, the value before Dimaval stimulation does not provide any indication of the approximate range of mercury values that may be found during stimulation"[<729>]. These specifics have hardly been broached in the literature to date.



Hg excretion in the urine before and after administration of DMPS in the mobilisation test according to Daunderer[<143>]

Hg may be mobilised from the various deposits[<729>]. Another explanation is that the value before administration of DMPS reflects more so the latest load after mobilisation than the earlier loads[<1472>]. It can thus be assumed that, in individual cases, the DMPS mobilisation test provides additional information on the determination of Hg in the urine and is therefore useful[<1472>].

"Furthermore, the DMPS test poses a considerable 'outlier problem[<382>], such that, in individual cases, it is not possible, to conclude between basal and stimulated values, and vice-versa"[<223>]. "A carefully conducted and statistically confirmed investigation of this type cannot provide any information about the effect in individual cases. It does, however, provide indicators and clues. We still need to take the reaction of the individual and his tolerance level into account". "With DMPS stimulation, groups of patients who may excrete considerably more during DMPS therapy, will differ from others in whom Hg excretion rises only slightly"[<89,728>]. "The measurement of the mercury excretion that can be mobilised with Dimaval® is thus not only to be interpreted as a toxicological magnifying glass for the body load, but also provides additional information about the quantities stored in the body"[<1280>]. An individual medical evaluation of these findings is, however, still questionable at the present time[<382>], as it does not provide any pathophysiological explanations for the difference in behavioural patterns such as various mercury deposits[<728>] or the varying types of mercury compounds.

The test is indicated in particular for patients with corresponding symptoms[<143,319>] when no organic damage is evident[<319>] and other treatment attempts prove ineffective. The mobilisation test is also recommended with increased values in the chewing gum test[<1167>]. "While the actual mercury load is determined primarily by determination in urine collections and serum, the mercury mobilisation test provides information on possible deposits in the body"[<208,604>] and thus offers a "simple method for confirmation of clinical diagnosis"[<490>] or for the exclusion of poisoning[<231,986>].

Conclusion:
The necessity of a mobilisation test is largely controversial. On average, there is a linear correlation between heavy metal excretion in the urine before and after administration of DMPS. In individual cases, however, there are occasionally discrepancies, which cannot be evaluated at the present time.

7.5.2.3 Limit values and special risk groups

Critics of the mobilisation test complain, amongst other things, that there are no toxicologically validated limit values available for a mobilisation test<83,223,382,406,546,866,1032,1110,1381,1399>. The measurements cannot, therefore, be sufficiently evaluated. This also applies to the "limit values according to DMPS", which often appears on laboratory tickets<550,1381>. The current limit values for the DMPS mobilisation test are derived predominantly from Daunderer, who has deduced these from his experience with over 800 patients<327>, but has only published a few facts about their determination<83,321>. Unstimulated limit values such as the BAT values<382,1279> must not be used as limit values according to mobilisation<288>.

The question of the level at which a long-term Hg load triggers the first adverse effect has so far been unanswered by scientists. "The major question which science has not been able to answer, is what effect does mercury in the food chain actually have on human health"<665>?

Limit values are mostly set only for individual substances<1548>. However, humans are nowadays exposed to various pollutants, which may interact because of their toxic effects (combination, summation or potentiation effects<1548>). Interactions with other environmental toxins must, therefore be taken into account when setting the limit value<83,195,310, 986,1134,1184,1605>.

This also applies to the potential long-term effects of low-level pollutants<1134>. "The long-term effect of small quantities of toxic substances is increasingly underestimated because they cannot be detected directly, but appear only later on or in subsequent generations"<1548>. A residual toxicological risk on chronic contact with even small quantities of mercury must not be ruled out, especially in pre-disposed patients, as there are still significant gaps in our scientific knowledge of the toxic effects of low-level exposure<966>.

7.5.2.3.1 Individual susceptibility

Limit values are mostly derived for healthy adults<83,201,1548>, but not, however, for "patients previously harmed" <313,966,1134>, children<313>, pregnant women<313> or allergy sufferers<313>. "Some populations are especially susceptible to mercury exposure, most notably the foetus, the newborn, and young children because of the sensitivity of the developing nervous system". Individual sensitivities should also be taken into account<270,443,577,986,1134>. There are individual reactions to all medicinal products, both in terms of treatment response and potential adverse reactions. The cytochrome-P450 system appears to play a role in this<270,797>. Many people appear to tolerate doses at which others already exhibit clinical symptoms<443>. There are still no tests to identify those people who are particularly highly sensitive<1384>.

7.5.2.3.2 Age-dependency

Children are particularly sensitive<63,195,201,310,313,352,443,966,1509,1510,1548>. Substantially greater susceptibility to Hg is sometimes reported in young children<1278>. For instance, they absorb 50% of orally ingested lead compared to just 8% in adults<63>. In addition, their excretion is lower<78,772>. Young rats displayed drastically higher total body loads than adult animals particularly following oral administration of inorganic mercury<696>. Elderly people are far more sensitive than healthy people between 20 and 40 years of age<1548>.

7.5.2.3.3 Gender-dependency

Gender-specific differences are also discussed in addition to age-dependency. Women are more sensitive to mercury[<446,1548>] or lead[<542>] than men. "Urinary mercury concentrations are highly correlated with both number of amalgam fillings and time since placement in children. Girls excrete significantly higher concentrations of mercury in the urine than boys with comparable treatment, suggesting possible sex-related differences in mercury handling and susceptibility to mercury toxicity"[<1570>].

7.5.2.3.4 Pregnant women

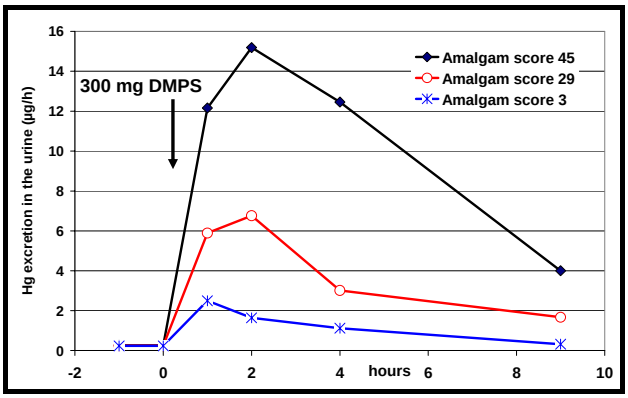
The WHO assumes that pregnant women are more sensitive to mercury than non-pregnant women[<966>].

7.5.2.3.5 Kidney damage

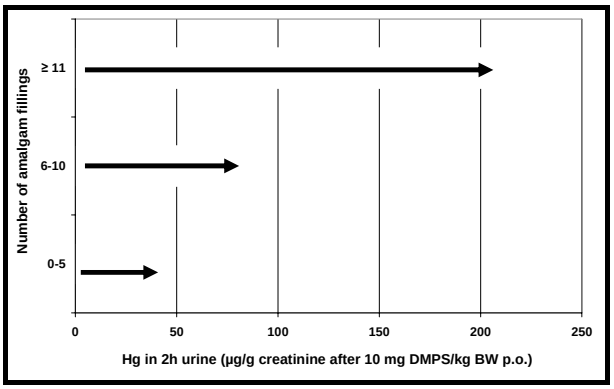
Correct functioning of the excretory system is a pre-requisite for a mobilisation test[<594,973>]. If the creatinine value exceeds 1.6 mg/dL, then kidney function is already impaired[<180>], with values over 2.5 mg/dL, the test is contraindicated[<352,1133>], in young children, values exceeding 1 mg/dL.

7.5.3 Results of DMPS mobilisation test

In mercury burden from amalgam, for instance, increased mercury excretion in the urine could be achieved by administration of DMPS. Mercury excretion before[<583,1273, 1283,1314>] and after mobilisation[<58,472,475,583,1273,1283,1291>] correlated on average with the number or the surface area of the amalgam fillings[<581,583>]. No correlation was found between the mercury level in the hair and the heavy metal level in the urine before or after mobilisation[<559,582>]. Similarly, no correlation was found between the mercury level in the hair and the number of amalgam fillings[<1314>].



Urinary excretion of Hg (µg/h) following mobilisation with 300 mg DMPS oral (amalgam score = total amalgam surface area)[<61>]

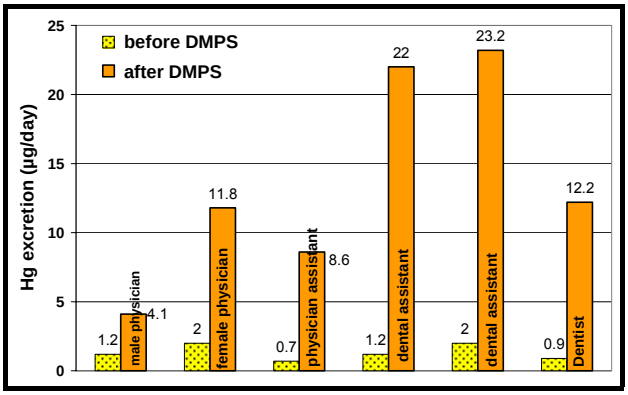


Increase in Hg concentration in 2-hour urine before and after DMPS administration (10 mg DMPS/kg BW oral) depending on the number of amalgam fillings[<476>].

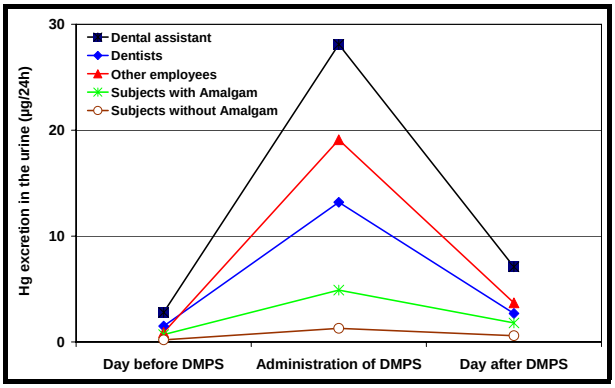
Persons with amalgam fillings, who attributed their symptoms to amalgam exhibited the same Hg levels in the DMPS test and in the blood as "healthy" subjects with amalgam fillings[<1481>].

If the mobilisation test was repeated after 3 to 18 months, women who meanwhile had had their amalgam fillings removed exhibited markedly lower values. If the amalgam fillings were still present, the mobilisation values were virtually unaltered[<472>].

A heavy metal burden was detected in 3 children during the DMPS test because of the mother's amalgam fillings[<445>]. The DMPS mobilisation test (4 mg DMPS/kg BW i.m., spontaneous urine) revealed especially high mercury and copper values on examination of 200 infants and toddlers when their mothers' teeth were treated with amalgam during pregnancy[<195>].



DMPS mobilisation test in six employees at a medical and dental practice<192>



Hg excretion in the urine (µg/24 h) of various groups before, during and after administration of DMPS (300 mg oral)<1604>

Investigations with the mobilisation test revealed that mercury excretion in the urine did not rise with homeopathic therapy<829> and the heavy metal load in the body was not reduced<182,313,442,483,829-831,1184,1345> although the symptoms at least improved in the interim<182,442,829-831,1184>. After mobilisation, one patient excreted 468 µg Hg/g creatinine after two courses of treatment with the entire potency series of homeopathic silver amalgam, and another excreted 126.5 µg/g creatinine<830>. Similarly, combination therapy with trace elements, minerals and high doses of vitamins did not trigger a statistically significant fall in Hg load<1345>.

	Before DMPS	After DMPS
Hg	2.4	109
As	3.4	14,0
Cd	0.4	0,7
Cu	39	1378
Pb	2.9	32

Renal heavy metal excretion (in µg/g crea) before and 2 hours after oral administration of DMPS (10 mg/kg BW) <471,476>

Employees of a dental practice had a higher burden because of their professional handling of amalgam<192,839,1604>. Dental assistants had higher values than the dentists<275,1604>. Slightly raised mercury values were found in students of dentistry after a 6-month phantom course in the insertion of amalgam fillings. The increase was, however, negligible in comparison with the background load from their own fillings<588>.

The highest values were exhibited by workers in mercury processing factories<582,1280>. In three former workers in a mercury refinery with normal mercury concentrations in the urine, a rise in mercury excretion to 25 – 59 µg/L indicated a mercury deposit<598>. Cabelkova *et al*. found a rise in mercury excretion of 200-fold in the urine following administration of two doses of 250 mg DMPS i.m. in 14 employees without any clinical symptoms and previously exposed to mercury, compared to a mere 20-fold increase in the controls. Urine concentrations exceeding 10,000 µg/L were recorded in exposed employees following administration of DMPS. Enzyme assays gave no indication of the kidney damage induced by DMPS or mercury<231>.

Stantschew examined 1,156 workers, previously exposed to mercury, with a spontaneous urinary mercury excretion of at least 20 µg/L. The values were determined in the overall nocturnal quantity of urine. A mercury deposit was assumed if the mercury elimination after the first injection of DMPS exceeded a value of 250 – 300 µg/L and if even higher concentrations of mercury were detected in the urine after a second injection. A peak urine value of 11,200 µg/L was reached. After a further 8 and, in exceptional cases, after 15 DMPS injections, even the largest mercury deposits were reduced/decorporated.

With the DMPS mobilisation test it was also possible to detect past exposure in the past. Even months after the cessation of exposure, the mercury concentration in the urine after administration of DMPS rose drastically in workers formerly exposed to mercury. In investigations of workers, the mercury elimination 7 to 56 months after leaving the work increased on mobilisation with DMPS from 4.3 to 34 µg/L<728>.

In investigations of patients with amalgam, the findings were non-uniform. Stenman *et al*. found higher excretion values in patients with severe symptoms<1392>. Some assume a linear correlation of mercury and copper correlation with the severity of the poisoning symptoms<323,489>. In contrast, others found no correlation<1280>. Patients with presumably subjective amalgam side effects displayed a not necessarily higher mobilisable mercury excretion than asymptomatic patients with

amalgam fillings[<874,1283>]. Hg exposure was generally markedly below the values triggered by occupational exposure[<1283>].

In ethyl mercury poisoning, there is no correlation between spontaneous mercury excretion in the urine, the clinical picture and the quantity of Hg absorbed. In contrast, a correlation was found between DMPS-induced mercury excretion and the severity of the clinical symptoms of poisoning[<1620>].

Classification of poisoning:	Number (n)	Spontaneous Hg excretion in the urine without DMPS (µg/L)		Hg excretion in the urine after administration of DMPS (µg/L)	
		Mean	Scatter	Mean	Scatter
Mild	26	28	0 - 60	95	10 – 260
Moderate	10	69	8 - 180	165	80 - 280
Severe	4	39	8 - 80	310	290 - 330

Correlation of the severity of the clinical symptoms of mercury poisoning with mercury excretion in the urine before and after administration of DMPS[<1620>]

Conclusion:
An increase in heavy metal excretion in the urine is measured with the DMPS mobilisation test. This confirms that heavy metals are stored in the body, are mobilised by DMPS and can be excreted. Whether this is a case of a tolerable load or clinically relevant poisoning, can generally be decided only by taking the entire clinical picture into account.

7.6 Other uses of DMPS

In the western world, DMPS is used almost exclusively as an antidote for heavy metal poisoning. In the Ukraine and other states of the former USSR, where DMPS has already been used therapeutically since 1957[<63,95,611,706>], and more recently, increasingly in the Peoples' Republic of China, there are many publications in which the use of DMPS has been reported for various other indications. The Redox properties of the active substance are used amongst other things. DMPS is used to treat over 40 diseases, syndromes and cases of poisoning[<1025>]. DMPS is thus often part of a treatment regimen comprising several types of medication. These indications have not been recognised to date outside these countries[<69>].

Some of the papers have only an English abstract so that the success cannot be assessed. The mechanism of action of DMPS cannot be evaluated particularly in these cases.

7.6.1 Alcoholism

Positive clinical effects were observed in the treatment of the effects of alcohol[<1606, 1613,1614>]. A combination of vitamins and DMPS improved alcohol polyneuritis[<632>]. Improvements were observed in biochemical and immunological parameters in 147 male patients (32 - 64 years old) with alcohol-induced liver disease following treatment with diuretics and DMPS[<718>]. Multiple medication containing DMPS amongst other substances, prevented complications on alcohol withdrawal in 169 patients[<1217>].

7.6.2 Alzheimer's disease

Ukrainian physicians assume that DMPS has a positive effect in patients in the initial stages of Alzheimer's disease presenting with mild to moderate symptoms through "depolymerisation" of amyloid deposits and "antedotally membrane-stabilising, antiradical" effects [<366,1025>].

7.6.3 Amyloidosis

26 patients with primary or secondary amyloidosis were treated with DMPS. Patients with nephritic syndrome showed a tendential improvement in serum proteins and serum cholesterol[<651>]. Proteinuria and chronic kidney failure did not, however improve[<1435>]. Improvements in secondary amyloidosis were observed in 32 out of 37 patients after 30 to 40 injections[<367>].

75 patients with secondary amyloidosis were treated with DMPS (250 mg i.m. daily, 15 – 20, in individual cases, up to 65 injections). 19 responded favourably to treatment. Proteinuria and oedema were reduced and SH- and protein levels in the blood increased. A satisfactory result was observed in 18 cases. 24 reported a subjective improvement and 14 no change or a deterioration. 3 patients developed an allergic rash, which disappeared when DMPS was withdrawn[<1175>].

7.6.4 Atherosclerosis

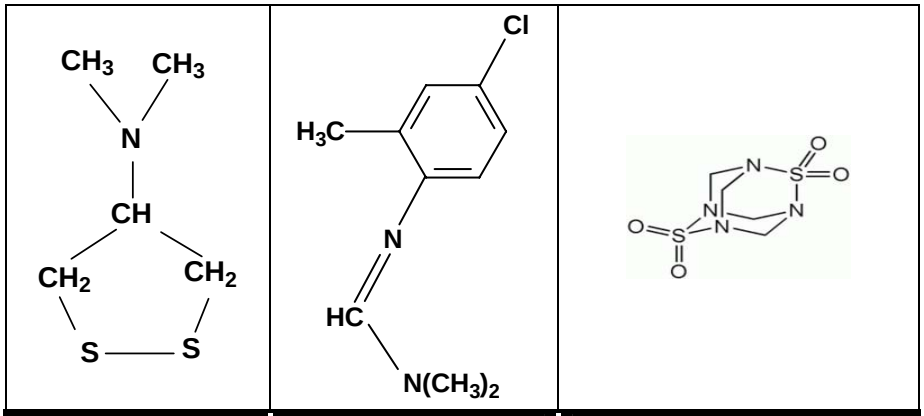
Treatment of atherosclerosis with DMPS showed positive clinical effects[<1606>]. DMPS therapy (250 mg DMPS i.m. daily) and a vitamin complex (2 x 2 tablets/day) led to an improvement in symptoms in 208 patients suffering from coronary atherosclerosis. Pain disappeared, often completely, and ECG parameters improved. The authors even recommended the therapy as prophylaxis in older and elderly patients[<810,813>]. In another study involving 119 patients, this treatment displays “a distinct therapeutic effect”[<812>]. ”Combination of unithiol with polyvitamins is indicated in the complex therapy of patients with hypertensive disease and initial stage of atherosclerosis“[<1641>].

The administration of DMPS before or during haemodialysis or haemofiltration should prevent an increase in homocysteine levels[<1357>].

7.6.5 Diabetes

A positive effect on diabetic ketoacidosis was found in 26 patients[<1606, 26,1614>]. The concentration of SH groups in the plasma returned to normal as well as the activity of AP and peroxidase[<1611>]. An improvement with a rise in SH concentrations in the serum and potentiation of the insulin effect has been described In patients with *Diabetes mellitus*[<1319>]. In 32 patients, symptoms of diabetic polyneuropathy improved through the additional administration of DMPS[<379>].

7.6.6 Insectides, pesticides, rodenticides, bactericides



Nereistoxin | Chlordimeform | TETS

There are various reports about the successful use of DMPS in poisonings with certain insecticides, pesticides, rodenticides and bactericides, especially in Chinese literature.

DMPS reduced the mortality rate caused by the insecticide SCS – a derivative of nereistoxin[<1194>]. In acute poisoning, 250 mg i.v. DMPS were initially administered followed by 250 mg DMPS i.m. every 6 hours. In one study, all 3 patients survived acute poisoning and in another, all 18[<253>]. In a further study, 96.7% of the 180 patients survived acute SCS poisoning through combination therapy with scopolamine and DMPS, whereas in 170 patients who received only scopolamine, the mortality rate was 89.4%[<253>].

DMPS helped in two poisonings with the insecticide chlordimeform (N'(4-chloro-o-tolyl)-N,N-dimethylformamidine; CDM). With the pesticide, bactericide 402 (ethyl thioethyl sulfonate), the symptoms disappeared faster and the length of time spent in hospital was shortened[<253>].

Various Chinese studies describe the positive effects of DMPS and vitamin B_6 on patients with acute poisoning due to the rat poison, TETS (tetramethylene disulfotetramine)[<331,1550>]. The poison generally leads to death within two days[<1172>]. During DMPS therapy, all 11 patients survived acute poisoning with TETS whilst 4 out of 5 people in the control group died[<131>]. In another study, 39 patients with acute poisoning were treated. They initially received 125 to 250 mg DMPS i.m. followed by 125 to 250 mg i.m. every ½ to 1 hour until the seizures were completely controlled[<253,1550>]. 72 children and three teachers survived TETS poisoning[<859>] thanks to the administration of DMPS and, if necessary, muscle relaxants.

In another investigation, DMPS did not have a positive effect on the mortality rate due to diazepam and sodium phenobarbital in patients with acute TETS poisoning[<112>]. "There was no significant difference in fatality between using unithol and not using patients (7.22% vs. 8.25%). CONCLUSION: Unithol has no significant influence of clinical therapeutic effect on tetramine poisoning patients and dose not reduce the fatality rate of patient with tetramine poisoning[<1531>].

7.6.7 Poisoning with cardiac glycosides

DMPS showed positive effects on poisoning with digitalis[<646>]. Improvements were observed under DMPS in 60 out of 68 patients on poisoning with cardiac glycosides[<905>]. In a further 18 patients, the toxic effects of the cardiac drugs (bradycardia and extrasystoles) disappeared within 3 to 5 days during DMPS therapy without treatment having to be interrupted. The SH concentration in the urine thus increased[<750>]. Concomitant administration of DMPS prevented the onset of toxic effects of the cardiac drugs[<403>] in 23 out of 25 patients with circulatory failure. DMPS therapy prevent toxic effects (extrasystoles and atrioventricular block) in 31 out of 35 patients presenting with cardiac glycoside overdose. K^+ and Na^+ levels reverted to normal in both the serum and erythrocytes in 16 of these patients[<906>]. Bradycardia disappeared in all 14 patients and ventricular extrasystoles in 9 out of 11 patients[<907>]. Bradycardia as a symptom of digitalis poisoning reverted to normal in one patient following administration of DMPS and potassium[<46>].

7.6.8 Circulatory failure, myocardial infarction

The additional administration of DMPS, ATP and vitamins (vitamin B_{12}, folic acid and panthenol) was more effective in patients with circulatory failure than administration of strophanthin alone[<747,748>]. The additional administration of DMPS also exhibited positive effects in patients with myocardial infarction[<746>].

7.6.9 Cystic fibrosis

In a study conducted in 98 children between 7 and 18 years of age[<1467>] and in 78 children between 5 and 15 years of age[<1468>], both the inhalation and oral administration of DMPS was inferior to the dose of mucosolvan in terms of the rheological properties of the sputum.

7.6.10 Scleroderma

Thirty patients with systemic scleroderma were treated with DMPS[<372>]. Positive effects of DMPS therapy were reported in 162 patients with systemic and 44 patients with focal scleroderma. The collagen structure and the elastin fibres returned to normal[<370>]. Another 168 patients (mainly women between 9 and 74 years of age) were observed for 10 years. They received 200 to 500 mg DMPS daily, i.m. as the sole therapy, sometimes for more than 780 days[<368,487>]. DMPS proved effective in both focal and systemic scleroderma[<368>]. Positive effects in five[<533>] patients and in one[<369>] patient are reported in other papers.

7.6.11 Miscellaneous

The various other uses of DMPS are reported in the literature:

- The administration of DMPS for 10 days had a marked effect on 89 patients with psoriasis, eczema or restricted neurodermatitis[<1461>]. Glutathione levels in the blood and lying outside the norm reverted to normal in 6 out of 20 patients following 10 days of treatment[<1323>]. The reduced plasma levels of p-phenylendiamine and histamine in patients with neurodermatitis and eczema increased again during DMPS therapy[<1335>].
- 80 % of examined patients with *Lupus erythematosus* showed positive reactions to DMPS therapy[<486>].
- Positive effects were observed in female patients with non-specific inflammation of the sex organs[<1187>].
- The administration of DMPS and penicillin improved hepatocerebral dystrophy in children[<897>].
- Streptomycin-induced hearing disorders were prevented in 25 patients by prophylactic administration of DMPS[<17>].
- 231 patients with hypertension were treated with a DMPS injection (i.m.) every day for 3 weeks[<494,811>].
- In 34 patients, one week's treatment with DMPS showed positive effects on the kallikrein-kinin system after kidney surgery[<980>].
- Positive clinical effects were also observed in the treatment of epilepsy, Parkinson's disease and schizophrenia[<494,1606>].
- DMPS was inferior to chlotazol in polyarthritis[<1337>].
- 37 patients with long-term schizophrenia, who were ineffectively treated with neuroleptics, received i.m. DMPS, B vitamins, iron preparations and drugs with a symptomatic mode of action for 20 to 25 days. A significant improvement, a less marked improvement and no improvement were observed in 26%, 43% and 31% of patients, respectively. 10 patients who developed serious complications during administration of neuroleptics, tolerated this medication after pre-treatment with DMPS[<1478>].
- 10-day, i.m. administration of DMPS as part of a multi-medication treatment regimen had positive effects on 35 patients with various porphyria diseases. Their clinical condition improved[<695>].
- 64 patients (18 to 58 years old, 36 males and 26 females) with acute, focal pneumonia were injected with 50 mg DMPS for 7 days. Laboratory parameters improved[<1182>]. Treatment with hyperbaric oxygen, vitamin E and DMPS led to good to excellent results in 75.8% of the 194 children (aged from 3 days to 3 years) with severe pneumonia[<1615>].
- Children with diffuse glomerulonephritis received 5 mg DMPS/kg for 15-25 days either alone or in combination with vitamin E. The antioxidants prevented deterioration and boosted the efficacy of other treatments[<801>]. DMPS lowered the peroxide concentration in the blood and urine of 115 children with glomerulonephritis[<1625>].
- Combination therapy with DMPS, magnesium sulfate and vitamin E reduced the duration of diarrhoea in patients with acute, intestinal infections due to Gram-negative micro-organisms and accelerated the return to normal function of the immune system[<528>].
- Additional administration of i.m. DMPS for 2 – 3 weeks had disadvantages in the treatment of patients with "vibration disease"[<371>]. DMPS was also effective in patients with fluorosis[<23>]. The administration of DMPS combined with haemodialysis was used in patients with thiol poisoning[<410>]. The additional administration of DMPS improved the efficacy of hypobaric hypoxia treatment in patients with osteochondrosis[<717>].
- The additional administration of DMPS for the first three days led to an improvement in the general well being of 9 patients with severe burns. Various biochemical parameters returned to normal[<25>].

Conclusion:
Both laboratory animal experiments and clinical studies indicated that DMPS can alsp help in the treatment of other diseases in addition to poisoning with heavy metals. No evaluation is carried out as this monograph focuses on the use of DMPS as an antidote.

7.7 Adverse drug reactions

As with all medicinal products, unwanted reactions may also occur during DMPS therapy. Most observations are potential, suspected cases. Only in a few cases has a causal relationship with DMPS been demonstrated (e.g. by re-exposure). Furthermore, it must be remembered that the unwanted adverse effects may also be the consequence of the heavy metal[<176>]. "It is often difficult to differentiate the adverse effects of DMPS from the toxicity of the metal under treatment"[<663a>]. This possibly accounts for the major differences in terms of adverse reaction rates in the various publications. Skin reactions as symptoms of mercury poisoning are mentioned several times[<185,944>]. Thus, for example, gingivitis and exanthema developed in a patient with thiomersal poisoning during DMPS therapy. These were not induced by DMPS[<1140>]. Leucopoenia is a symptom of mercuric chloride-induced disease. Copper poisoning is often associated with a reduction in leukocytes. The onset of fever (copper fever) was also described for this heavy metal. Nausea, headaches and changes of taste are side effects of various forms of heavy metal poisoning[<944>]. Zinc deficiency may also be a direct consequence of heavy metal poisoning[<1184>].

The symptoms may not be genuine side effects per se but the subjective sensitivity of the volunteers, which was also mentioned during administration of the placebo[<1311>].

There is occasional reference on the Internet and in printed articles[<293>] to fatalities during DMPS therapy. No details or examples are given to substantiate these claims. Such outcomes have never been reported to us. Neither the authorities (BfArM, FDA) nor the Drugs Commissions have contacted us about this matter. Similarly, relevant discussions with the authors did not shed any light on this.

DMPS is generally an effective[<401>], "very well tolerated"[<1202a>] active substance in the treatment of heavy metal intoxication[<31,200,401,625,1021,1117>] and triggers relatively few side effects. "DMPS is

Author(s)	Year	Ref.	Administration	No. of patients	Rate of side effects
Dubiinskii et. al.	1979	368		168	15.5 %
Oster et al.	1985	1104		7	0 %
MacLehose et al.	2001	881		5	20 %
Ashbel	1959	92	i.m.	22	9.1 %
Vainshtein	1972	1478	i.m.	37	2.7 %
Oginski et al.	1973	1069	i.m.	9	0 %
Bakir	1976	115	i.m.	26	0 %
Clarkson et al.	1981	281	i.m.	10	0 %
Cabelkova et al.	1984	231	i.m.	24	0 %
He et al.	1984	568	i.m.	84	1.2 %
Postnikov	1984	1175	i.m.	75	4 %
Bonnet e al.	1993	195	i.m.	200	0 %
Daunderer	1990	321	i.v.	6.000	ca. 5 %
Bannasch et al.	1991	123	i.v.	50	0 %
Stenman et al.	1991	1392	i.v.	58	0 %
Godfrey et al.	1992	490	i.v.	110	"Some"
Bittel	1995	176	i.v.	900	0 %
Lechner	1995	829	i.v.	600	3.3 %
Zinecker	1995	1633	i.v.	1.846	2.75 %
Dorfer	1997	352	i.v.	400	0 %
Ramsak	1998	1202a	i.v.	4	2.8 %
Busam	1999	223	i.v.	148	0.7 %
Vamnes et al.	2000	1482	i.v.	80	1.25 %
Siefert	2001	1345	i.v.	119	0.8 %
Wojcik et al.	2006	1568	i.v.	206	0 %
Hölzel	2000	600	i.v./ oral	46	26 %
Mant	1985	902	oral	7	28.6 %
Cuellar-Lopez	1987	290	oral	6	0 %
Cichini	1989	272	oral	12	0 %
Schiele	1990	1281	oral	>100	< 3 %
Molin	1991	947	oral	41	0 %
Aposhian et al.	1992	60	oral	20	15 %
Gerhard	1992	480	oral	490	0.6 %
Klobusch.	1992	740	oral	132	0 %
Zander	1992	1603	oral	29	0 %
Herrmann et al.	1993	581	oral	67	3 %
Zimmermann et al.	1993	1632	oral	20	0 %
Mayer	1995	914,915	oral	39	0 %
Gonzalez-Ramierez et al.	1995	502	oral	28	3.6 %
Torres-Alanis et al.	1995	1449	oral	10	10 %
Blume	1996	183	oral	41	2.4 %
Garza-Ocanas et al.	1997	463	oral	8	0 %
Nantel	2000	975a	oral	33	24.2 %
Nerudova	2000	985	oral	75	0 %
Heuchert et al.	2001	411,583	oral	36	2.8 %
Mazumder et al.	2001	917	oral	11	0 %
Böse-O'Reilly	2003	199	oral	95	1.1 %
Hansen et al.	2004	559	oral	2.223	0 %
NN	2004	1008	oral	50	0 %

Frequency of side effects during DMPS therapy

one of the safest and most effective chelating agents"[<480>]. "The oral administration of DMPS was a safe, simple and effective method for the removal of mercury from the body"[<1581>].

In 1999, the FDA included DMPS in the "List of Bulk Drug Substances that may be used in Pharmacy Compounding" and stipulated the following: "Dimercapto-1-propanesulfonic acid (DMPS), a chelating agent, is well characterized chemically. DMPS has been used to treat heavy metal poisoning. At doses reported in the literature for this indication, DMPS appears to be relatively non-toxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of DMPS's effectiveness for this indication is also reported in the literature"[<1031>]. It is a substance with very low systemic or local toxicity and is generally well tolerated[<26,30,87,324,401,446,657,706,1032,1438>], even during long-term administration[<70,350,1104,1141>]. Treatment is only rarely withdrawn[<30,31>]. DMPS has the advantage that only very small quantities reach the CNS[<1102>].

No adverse reactions have been reported with DMPS in most publications and unpublished case reports. There is generally explicit reference to the fact that the treatment is well tolerated and no undesirable reactions were reported:

- No evidence of ADR (side effect s) was found in 2,223 patients following mostly single doses of DMPS but sometimes also after repeated dosing[<559>].
- Single oral or i.v. administration of DMPS was tolerated without any complications by 1,000 patients[<326>].
- DMPS (i.v.) was tolerated without any problem by 90.5% of the 1,846 patients treated. Minor problems of intolerance were observed in 6.75% of cases. DMPS was subjectively poorly tolerated in 2.75 % of cases[<1633>].
- Only occasional, short-term nausea or mild allergic symptoms were observed during over 2,000 mobilisation tests[<446>].
- 1,000 physicians, who administer DMPS 15 – 20 times a day have not experienced any incidents in over 3 years[<738>].
- No serious complications were ever observed on injecting DMPS in over 6,000 patients[<321>].
- The administration of DMPS for 10 days was well tolerated by 89 patients with psoriasis, eczema or restricted neurodermatitis[<1461>].
- "Over 2,000 DMPS tests have been carried out in my practice over the last 10 years without any notable complications"[<221a>].
- No serious adverse reactions were observed during the i.v. test conducted in 206 patients[<1568>].

The following mild symptoms were observed whilst treating 27 patients with 250 mg DMPS. These symptoms generally disappeared after ½ to 4 hours. Dizziness, weakness, palpitations, tight chest, abdominal pain, loss of appetite, nausea and pruritus[<1620>].

Mild reactions occurred in 4 out of 147 treated patients during the first dose of DMPS. However, these quickly regressed without further treatment. Two patients reported nausea, increased salivation and headaches. One female patient presented with a local reaction accompanied by redness and pruritus. One developed mild dyspnoea, tachycardia and a fall in blood pressure to 90/60[<1202a>].

On interviewing 129 patients 48 hours after carrying out the DMPS test (300 mg DMPS, oral), 73% did not report any adverse reactions. Others complained of nausea, headaches, fatigue, joint pain, dizziness, diarrhoea, a fall in blood pressure or circulatory problems[<358>]. The study does not, however, contain any information as to whether these subjective observations can be medically explained.

7.7.1 Effects on mineral balance

Chelate formation by DMPS takes place not only with toxic heavy metals, but also with the physiological trace elements and can therefore lead to disorders[<87,472,666,706>]. It is, therefore, important to monitor copper and zinc levels in particular during DMPS therapy. Zinc replacement may be necessary[<637,1102>]. If possible, this should be replaced as soon as possible on the DMPS treatment-free days[<719>]. "DMPS slightly increases the excretion of some essential minerals, so a

basic mineral supplement is recommended to compensate for this loss"[<14>]. „DMPS increases the urinary excretion of copper and zinc, an effect that is not anticipated to be clinically significant in patients without pre-existing deficiency of these trace elements"[<770a>].

As the heavy metals can also have an effect on essential trace elements[<427>], it is advisable to monitor the trace elements before starting treatment, especially in chronic poisoning. This especially applies to zinc as chronic heavy metal poisoning can trigger zinc deficiency[<1184>]. Zinc deficiency manifests as impaired taste, impaired wound healing, dermatitides, exanthema or impaired immune function. Copper deficiency manifests in the form of connective tissue disorders, iron-resistant anaemias and osteopathy[<1041>].

7.7.1.1 Cu - Copper

The clinical use of DMPS increased the renal excretion of copper[<5,44,75,266,267,269,408,444,448,583,637,657,706,902,1251>]. In 11 volunteers, the excretion following i.v. administration of 3 mg/kg increased from 0.078 to 1.93 µg/g creatinine[<1446>], and, in 7 volunteers, values rose from 16 to 173 µg/24h[<1251>] after administration of 300 mg oral . An increase from 6.4 to 64 µg/day was recorded in 71 employees during administration of 500 mg DMPS i.v. A single oral dose increased copper levels from 16 to 173 µg/Tag (n = 7)[<269>]. Unchanged Cu excretion was also reported[<1605>]; hence no change in Cu^{2+} concentrations in the urine[<1577>] was observed in an investigation involving 100 patients.

A single dose of DMPS did not affect the deposits of copper in the body and blood levels remained unchanged[<411,583,597>]. The serum copper level did not increase during 14 days' treatment with DMPS (200 mg oral every 6 hours)[<872>] The serum copper level remained stable during 11 weeks' DMPS treatment (initially i.v., then oral)[<1443>] 4½ years' DMPS therapy (300 - 800 mg DMPS oral per day) did not lead to any effect on the plasma level despite increased copper excretion in the urine[<96>]. Administration of 300 mg/day for 6 months did not lead to any copper deficiency in the blood[<595>]. Copper concentrations in the plasma were virtually always unchanged even during long-term DMPS therapy[<166>] and no additional clinical measures were required[<657>].

In one study, Cu levels fell slowly after the 3rd injection of DMPS. A more marked decrease was observed after 5-7 injections but levels returned to normal, however, within 3-4 days following the withdrawal of DMPS[<408>].

Increased copper excretion in the urine was recorded in 85 patients during DMPS therapy. The erythrocyte count was not, however, consequently reduced. The copper ingested with the food is obviously sufficient in order to compensate for the increased excretion.

7.7.1.2 Fe - Iron

The published observations on the effect of DMPS on iron levels are inconsistent. One investigation involving 100 patients showed a change in the Fe^{+} concentration in the urine following administration of DMPS[<1577>]. Other studies noted that iron excretion was not increased during DMPS therapy[<70, 583, 657,1605>] or was within the normal range[<166>].

19 out of 20 volunteers had a higher concentration of iron in the serum following administration of a single dose of DMPS. In another study, a single dose of DMPS did not affect iron levels in the serum[<583>]. Iron concentrations in the plasma were virtually always unchanged even during long-term DMPS therapy[<166>]. Others found that iron substitution may be required following repeated administration of DMPS[<325>].

7.7.1.3 Mg - Magnesium

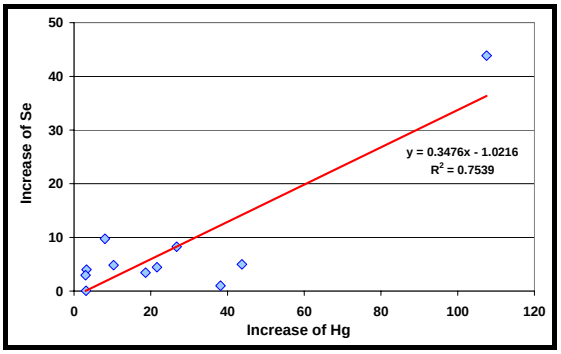
The concentration of Mg^{+} in the urine was "unchanged" following administration of DMPS in an investigation involving 100 patients[<1577>]. Following administration of 3 mg DMPS/kg BW i.v., magnesium levels in the urine increased in 9 out of 11 volunteers. In contrast, lower concentrations were found in the U(II) of two of the subjects. On average, excretion rose from 49.5 to 124.9 µg/g creatinine[<1446>]. It is, however, unclear whether magnesium excretion actually

increased or whether only the creatinine concentration is reduced due to increased diuresis. Other studies found no effect[<70,657,1605>]. From a chemical standpoint, it seems unlike that DMPS actively increases magnesium excretion through complex formation.

7.7.1.4 Mn - Manganese

Information on manganese excretion following DMPS administration varies. Whereas one investigation did not highlight any change[<70,657,1446,1605>], an increase in excretion from 5.0 to 8.3 µg/day was measured in 66 employees after injecting 500 mg[<1479>].

7.7.1.5 Se - Selenium



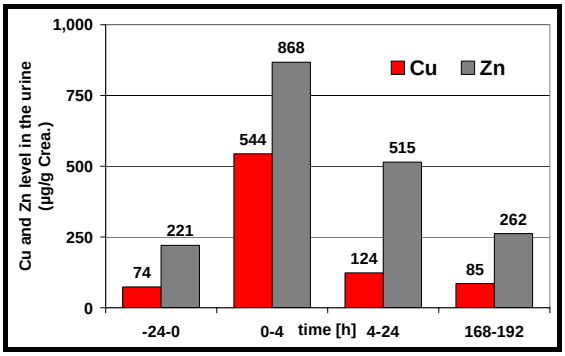
Correlation of the increase in Hg and Se excretion in the urine following administration of 3 mg DMPS/kg BW i.v. [<1446>]

The administration of 3 mg DMPS/kg BW i.v. increased selenium excretion in the urine from 0.02 to 0.133 µg/g creatinine in 11 volunteers[<1446>]. In other studies, the excretion remained unchanged[<70, 583,657,1605>]. However, whether the excretion was increased directly through DMPS was not discussed. It is a well-known fact that selenium reacts with mercury in the body to form mercury selenide[<1302>]. Comparison of the increase in the renal excretion of Hg and Se (concentration in 1-hour urine after DMPS divided by the concentration in 1-hour urine before DMPS) highlights a dependency. It can thus be concluded that DMPS does not react directly with selenium but increases mercury excretion, thus releasing the corresponding quantity of selenium for subsequent excretion.

A single dose of DMPS does not affect the deposits of selenium in the body and blood levels remain unchanged[<,597>]. 4½ years' DMPS treatment (300 - 800 mg DMPS oral per day) did not affect the selenium plasma level[<96>].

7.7.1.6 Zn - Zinc

In most cases, the administration of DMPS increased the renal excretion of zinc[<5,143,269,411,583,597,637, 902,1251,1577,1605>]. No effect was, however, reported[<657>]. A 15-fold increase in zinc excretion was observed during the clinical use of DMPS[<166>]. This effect disappeared on discontinuation of DMPS[<69>]. Following administration of 3 mg DMPS/kg BW i.v., zinc excretion in the urine increased from 1.03 to 7.11 µg/g creatinine in 11 subjects[<1446>], and from 441 to 2,653 µg/L in 40 subjects. After administration of 2 mg DMPS/kg BW i.v., excretion increased from 0.5 mg/L to 3.32 mg/L in 80 volunteers, and following administration of 300 mg oral, from 657 to 1,132 µg/24h in 7 volunteers[<143,1251>]. The excretions were, however, considerably lower than those observed with calcium edetate[<269,383a>].



Mean copper and zinc levels in the urine before and after oral administration of 300 mg DMPS[<411>]

A single dose of DMPS did not affect the zinc deposits in the body. Blood[<597>] and serum levels[<269>] were unchanged. The same applied in longer-term treatment[<166>]. No deficiency was observed[<293>]. Zinc levels in the serum and blood did not alter

- during 14 days' treatment with DMPS (200 mg oral every 6 hours)[<872>]
- during 11 weeks' DMPS treatment (initially i.v., then oral)[<1443>]

- during treatment with 300 mg/day for 6 months<596>
- during 4½ years of DMPS treatment (300 - 800 mg DMPS oral per day)<96>
- in a patient with acute mercury poisoning after approximately 600 ampoules of DMPS i.v. and around 400 capsules of DMPS oral<308>.
- with initially parenteral (4 days) and subsequently oral (3x100 mg/day) administration of DMPS for more than 3 months<1555>
- after more than one year's administration of 100 mg DMPS/day to a child<1141>.

The single oral administration of DMPS led to a lowering of the zinc level in the serum within the first 4 hours (78 → 67 µg/dL). The content increased once again to the baseline value over the next few days, but without substitution<411,583>. Zinc deficiency is thus not anticipated with DMPS therapy<973>, general Zn substitution is not required<182,352>. The trace elements ingested with the food generally suffice to compensate for increased excretion.

In a spontaneous report (1990), it was reported that, in one patient, the symptoms of existing zinc deficiency were potentiated by administration of DMPS. Substitution of the trace element produced a rapid improvement<586>.

Nevertheless, the trace elements should be monitored, especially on long-term therapy and during pregnancy and lactation, and the deficient trace element must be substituted<166,182,325,446,1104>. Zinc and DMPS should not, however, be given concomitantly<700>. "Zinc in conjunction with existing vitamin A should also be checked"<1104>.

7.7.1.7 Other elements

Chromium excretion was unchanged after administration of DMPS<1146> and cobalt excretion reduced<1605> or unchanged<70,657,1605>. The Ca^{2+} concentrations in the urine were "unchanged" following administration of DMPS in an investigation involving 100 patients"<1577>. A single i.v. dose of DMPS reduced the blood calcium level but had no clinical consequences<626>. DMPS had no effect or only a minimal effect on nickel levels<70,657,1805>. "It is unknown if it causes a loss of potassium"<14>. Increased potassium excretion is not anticipated during DMPS therapy. There is no laboratory animal experiment or clinical evidence in support of this.

Conclusion:
In addition to the excretion of toxic heavy metals, DMPS also increases the elimination of various trace elements. This does not, however, usually lead to a deficiency that has to be substituted. The quantity ingested with the food is mostly sufficient to compensate for increased excretion. Essential trace element levels should, however, be regularly monitored, especially during the long-term administration of DMPS.

7.7.2 Adverse drug reactions

The adverse drug reactions described in the literature or spontaneous reports are discussed below in the order of the various organ systems stipulated by MEDRA.

7.7.2.1 Influence on patient investigations

Apart from increased excretion of trace elements, no DMPS-induced effect on investigations is described.

7.7.2.2 Heart diseases, cardiovascular reactions

Cardiovascular reactions (hypotensive effect<52>) occurred virtually only after parenteral administration of DMPS, essentially following i.v. injection administered too rapidly<30,31,902,1506>. Where

possible, DMPS should, therefore, be administered orally. Injections should be administered slowly over 5 minutes[<418,663>] and only in acute poisoning[<52>].

The cardiovascular reactions manifested as dizziness, weakness, nausea, palpitation and a feeling of oppression in the chest[<70,368,586,1620,1633>]. Highly sensitive persons are mostly affected, as with every injection[<182>]. Two vegetatively highly labile patients out of 800 suffered collapse as a result of a transient fall in blood pressure[<323>]. In one spontaneous report, protracted collapse was also reported after parenteral DMPS administration[<586>]. A "reversible hypotonic circulatory reaction of a few minutes' duration occurred during i.v. injection in one out of 148 women"[<223>]. A transient drop in systolic blood pressure was observed during DMPS administration in two out of 5 volunteers. Pulse and diastolic blood pressure were unchanged[<626>]. Contrastingly, an increase in blood pressure and heart rate were reported in one paper[<1061>]. No evidence of hypotension was found in 95 volunteers following oral administration of 2 x 200 mg/day[<199>].

7.7.2.3 Disorders of the blood and lymph system

Intercurrent leucopenia towards the end of DMPS therapy for lead poisoning returned to normal after withdrawal of treatment[<171>]. Leucopenia was also observed during the treatment of mercury poisoning[<586>] and after administration of a test dose in one patient with Wilson's disease[<1521>]. Mild neutropenia is reported during DMPS therapy in one paper[<31>]. No haemolysis following the administration of DMPS has been reported to date in the case of glucose-6-phosphate-dehydrogenase deficiency[<573>].

7.7.2.4 Nervous system and behavioural disorders

Headaches[<501,1021,1061,1251,1311,1452>], fatigue or weakness[<290,368,501, 829,1311>] or dizziness[<368,600,829,1061>] are occasionally reported following administration of DMPS. These could be due to cardiovascular (see chapter 7.7.2.2) or allergic reactions (see chapter 7.7.2.13) to DMPS. Treatment withdrawal was not generally required[<368,829>]. Transient malaise, lethargy, paresthesia and a general sensation of weakness have also been reported[<1452>].

7.7.2.5 Eye diseases

The onset of conjunctival congestion during the treatment of one employee in a Hg-processing factory is mentioned in one paper. The authors provide no further information[<568>].

7.7.2.6 Disorders of the respiratory tracts, thorax and mediastinum

A mild allergic reaction with bronchospasm was observed in a 37 year-old man with allergic rhinitis, 5 minutes after the onset of DMPS injection. Broncholytic treatment was not required[<1482>].

7.7.2.7 Kidney and urinary tract disorders

In almost all cases, DMPS did not trigger any renal complications when administered at a therapeutic dose level[<295,369,663>]. The subacute renal toxicity of mercury is not potentiated by DMPS[<43>]. No changes in renal parameters were measured in ten patients given 100 mg DMPS t.i.d. for 5 days[<1449>]. A 10-year follow-up of 168 patients with scleroderma who received 1 – 2 ampoules of DMPS daily for up to 780 days, did not show any indications of kidney damage[<368,418,487>]. Enzyme assays carried out in 24 volunteers did not indicate any kidney damage following single i.m. administration of DMPS[<231>].

Only a few cases are described in which renal complications occurred during DMPS therapy.

A female patient who intravenously injected the contents of two thermometers with suicidal intent was only observed for almost four months as the mercury level in the urine did not exceed the BAT value of 200 µg/L. Oral treatment with 3 x 100 mg was then introduced when Hg levels reached

220 µg/L. Acute kidney failure with anuria developed just one day later warranting 14 days of haemodialysis. DMPS treatment was withdrawn. DMPS had obviously mobilised the stored mercury and flooded the kidneys in such quantities that acute renal failure was the consequence<564,1389>. In another report, one patient developed anuria and mental confusion over a period of 18 hours following DMPS injection. The symptoms spontaneously disappeared after injecting procaine<720>.

A transient increase in protein excretion in the urine was observed in one out of 7 patients<1251>. A transient disruption in kidney function was observed in one out of 37 patients with schizophrenia, but this did not recur as treatment progressed<1478>.

Increased micturition<ref. in 69 and 829> as well as reduced excretion, which disappeared following administration of diuretics, are also reported in the literature<907>.

7.7.2.8 Disorders of the skin and subcutaneous cell tissue

Skin reactions may be a sequelae of heavy metal poisoning. No direct, DMPS-induced skin disorders are described. Similarly, there is no evidence of diseases as a result of zinc deficiency with DMPS (as described with EDTA, for instance<1179>). Most of the skin reactions to DMPS are allergic reactions<902> (see chapter 7.7.2.13).

7.7.2.9 Metabolism and nutrition disorders

Individual cases of nausea were reported<60,290,368,501,829,1021,1311>. Nausea and vomiting occurred<60, 502,586,1061,1281> within 2 hours<60>, especially in patients with a delicate stomach, even after single<1281> oral administration of DMPS. Nausea and diarrhoea developed in one volunteer<502>.

Mild nausea was described in one patient with acute bismuth poisoning during both intravenous and oral administration of DMPS<1394>. Hölzel reports gastrointestinal disorders with a latency of 30 minutes to 3 hours post-dose, there being no significant difference between oral (300 mg) and parenteral (250 mg) administration<600>.

In some cases, impaired taste, e.g. metallic taste><1452> or the odour of hydrogen sulfide<368> were reported after administration of DMPS<501,600,1021,1311,1522,1523>. 20% of 148 patients reported a transient “putrid, sulphurous taste in the mouth“ immediately after i.v. administration of DMPS<223>. 4 patients lost their appetite<1620>.

7.7.2.10 Injury, poisoning and procedure-induced complications

Shock with seizures, respiratory arrest and excitation may occur after overdosing with more than 300 mg DMPS/kg<610>.

7.7.2.11 General disorders and discomfort at the site of administration

Local reactions such as transient redness<1345> or ulceration<625> are known to occur at the injection site following administration of DMPS<600>. Transient pain at the site of injection, persisting for not more than 1 hour, were reported<92>. In approximately 20 cases (with more than 600 i.v. doses), “skin changes at the site of injection“ were observed, but always without a dramatic clinical course<829>. Painful, local skin reactions were observed in 2 patients who received DMPS extravenously<490>. Skin necroses at the injection site are mentioned in one patient who was inadvertently given 100 mg/kg instead of 5 mg/kg<295,418,663>. Necroses and ulceration were also reported at the injection site following administration of high doses via the i.m. or s.c. route<69>. ”DMPS imparts a sulfur door to bodily excretions“<663a>.

7.7.2.12 Pregnancy, post-partum and perinatal disorders

DMPS is neither mutagenic nor carcinogenic[<1238>]. Teratogenic effects caused by the impact of essential trace elements, as reported with other chelating agents, have not been described in conjunction with DMPS[<902>].

7.7.2.13 Immune system disorders, allergic reactions

DMPS has a relatively high allergy potential[<472>], as reported with chelating agents containing sulfur[<666>]. This may be caused by an effect of the SH groups on the complement system[<1512>]. Most of the adverse reactions to DMPS were allergic reactions[<92,182,199,317,321,323,368,446,586,611,706,902, 975a,1175,1281,1449,1532,1633>], mostly of a mild nature[<446>] and transient[<182>] and occurring essentially during long-term treatment[<611,1304>]. "Self-limited, reversible allergic dermatological reactions, such as exanthemas or urticaria, have been most commonly reported adverse effect. Isolated cases of major allergic reactions, including erythema multiforme and Stevens-Johnson syndrome, have been reported"[<770a>].

- Allergic reactions in the form of skin and mucosal symptoms occurred in approximately 5% of cases after 4 to 10 injections[<321>].
- 1% of atopic subjects reacted with side effect s[<182,323>].
- A 10-year follow-up of 168 patients with scleroderma who received 250 to 500 mg DMPS i.m. revealed allergic reactions in 26 patients, depending on the various treatment periods. Intolerance against various other substances is known to occur in all these patients[<368,418,663>].
- "Allergic rash occurred in 3 patients of 75; it did not persist after drug withdrawal"[<1175>].
- One female patient with lead poisoning developed maculopapular exanthema on the face, trunk and arms after 14 days' treatment with DMPS. Treatment was, therefore, switched to DPA[<1286>].
- 8 out of 33 patients with acute arsenic poisoning developed Erythema multiforme of varying severity one week after the start of treatment. Four patients had to be admitted to hospital and Steven's-Johnson syndrome was diagnosed in 2 of them. All four patients recovered during administration of antihistamines and cortisone[<975a>].
- An erythematous, maculopapular rash developed on the lower legs of one patient with acute Hg intoxication during administration of DMPS (250 mg DMPS i.v., every 4 hours). DMPS therapy could be continued after reducing the dose (250 mg i.v. DMPS every 8 hours)[<299>].

Allergic skin reactions were also observed following the first dosing:

- in 2 out of 120 volunteers after administration of 300 mg DMPS oral[<1311>],
- in 1 of over 100[<1281>],
- in 1 of 95 after 200 mg[<199>],
- in 1 of 20 one week after administration (mild rash with redness of the skin)[<60>],
- in 1 of 45[<183>],
- in 1 of 36, 12 hours after DMPS (reversible exanthema)[<411>],
- in 2 of 168 scleroderma patients after the first injection[<368>],
- 3 of 490 volunteers (10 mg/kg BW oral) admitted having suffered from hot flushes and pruritus of the face or extremities during the day after taking DMPS[<480>].

The allergies are generally of a mild nature[<446>]. No cases of anaphylactic shock have so far been reported after administration of DMPS[<69,295,368,967>].

The allergic reactions mostly manifested as skin reactions[<31,92,313,542,902,1286>] with symptoms such as pruritus[<290,368,600,663,829,1021>], skin reactions (e.g. rash[<60,299,1021,1175>], exanthema[<290,411,542,1286>], erythema[<600>] or mucous membrane reactions[<902,1281>].

A Stevens-Johnson syndrome is reported to have occurred in six cases during DMPS therapy[<44,266,267,975a,1111,1506>]. One of these patients had initially milder symptoms of DMPS intolerance without having to interrupt drug intake. The intolerance increased and finally made hospital admission necessary, where Stevens-Johnson syndrome was suspected[<586>]. However, the data on all suspected cases are too view to allow any reliable correlation to be deduced. What is especially surprising is that the symptoms generally regressed within a very short time[<586>].

One patient presented with an intolerance reaction in the form of total body pruritus and exanthema. The symptoms quickly regressed during intravenous therapy with cimetidine as well as dimethindene and cortisone[<543>].

An allergic reaction manifested as bronchospasm in one other patient following i.v. administration of 2 mg DMPS/kg. Treatment was not, however, required[<1021,1482>].

Tremor[<154,1521,1523>], nausea, weakness, dizziness and fever[<154,368,1061,1521,1523>] were presumably also allergy-induced.

At the onset of side effect s, withdrawal of the medicinal product generally sufficed[<313,666,1175>]. The allergic reactions then regressed independently within 3 to 5 days[<368>]. The exanthema sometimes also disappeared spontaneously during subsequent treatment with DMPS[<368,586,829,1448>]. Anti-allergic treatment (antihistamines and corticosteroids) were required on massive reactions or prolonged treatment only in a few cases[<95,368,1304>]. Allergic dermatitis completely regressed without any residual damage following the withdrawal of DMPS under prednisolone[<1015>].

Treatment could also be continued in individual cases after a treatment pause[<368>] or corticosteroid protection[<95>]. A new treatment attempt at a lower dose can also be envisaged once symptoms regress[<1238>].

Normally, DMPS should no longer be administered following an allergic reaction[<558>]. DMPS is contraindicated in cases of known hypersensitivity[<539,973,1440>]. Life-threatening reactions may develop if DMPS is nevertheless continued[<1440>].

Proof can be obtained by carrying out a skin test[<1440>]. Sensitisation to DMPS can be detected by intracutaneous injection of DMPS[<368>]. Due to potential cross reactions, Aposhian recommended, on safety grounds, that DMPS or DMSA should not be administered to subjects with known hypersensitivity to penicillin, sulfonamides or other sulfur-containing medication[<52>]. One paper refers to potential cross reactions between various dithiol chelating agents[<1231>].

The risk of hypersensitivity is increased in subjects with allergic asthma[<31>]. An asthma attack may very occasionally occur in these patients during or immediately after injection[<586>].

7.7.2.14 Liver and gallbladder disorders

”DMPS has a small chance of increasing liver enzymes or decreasing blood cell count, so those should be monitored during treatment”[<14>]. In individual patients, increases in transaminases (GOT, GPT) were measured[<31,1506>].These sometimes returned to normal during subsequent DMPS treatment or at the end of therapy[<603>]. In some cases, the transaminases were already increased before starting therapy, so that the increase was not always associated with DMPS therapy[<153,269,586, 630,706>]. An increase in aminotransferase levels has also been reported[<663a>] but this can also be triggered by heavy metals[<91a>]. ”Elevated liver enzymes occurred in a patient receiving unithiol 400 mg/day. However, concomitant consumption of alcohol may have contributed to this effect”[<501>].

A transient increase in ALT values in the serum was measured in one out of 14 patients with Wilson’s disease, who received i.v. DMPS for 8 weeks (20 mg/kg/day in 500 mL of a 5% glucose solution). ALT levels in the serum increased on the 10th day of treatment with oral administration of 2.5 g DMPS/day. The increase was reversible[<5>].

A transient increase in liver enzymes was observed on treating employees at a mercury production plant with DMPS. The values reverted to normal a few days after treatment ended. It is, however, a well-known fact that even normal excretion of large quantities of mercury can lead to a transient effect on liver function.

7.7.2.15 Psychiatric disorders

Depression may occur during mercury poisoning, but will disappear as treatment progresses.

7.7.3 “Listed” side effects

The side effects probably associated with the administration of DMPS and which are currently listed in the Dimaval Patient Information Leaflet and Summary of Product Characteristics are presented in the following table:

Dimaval (Injection solution)	Dimaval DMPS 100 mg Hartkapseln
Tremor, fever or skin reactions presumably of an allergic nature such as itching (pruritus) or skin rash (exanthema, rash) may occasionally develop. These are, however, reversible on withdrawal of treatment. Serious, allergic skin reactions (e.g. Erythema exsudativum multiforme and Stevens-Johnson syndrome) have very occasionally been reported.	Tremor, fever or skin reactions presumably of an allergic nature such as itching (pruritus) or skin rash (exanthema, rash) may occasionally develop. These are, however, reversible on withdrawal of treatment. Serious, allergic skin reactions (e.g. Erythema exsudativum multiforme and Stevens-Johnson syndrome) have been reported in individual cases.
Dimaval can affect the mineral balance and especially the elements zinc and copper, primarily during long-term treatment.	Dimaval (DMPS) 100 mg Hartkapseln can affect the mineral balance and especially the elements zinc and copper, primarily during long-term treatment.
The mercury absorbed by the body is mobilised following administration of the preparation. Kidney failure as a clinical symptom of mercury poisoning can very rarely be triggered.	The mercury absorbed by the body is mobilised following administration of DMPS. The clinical symptoms of mercury poisoning can be triggered in individual cases.
Asthma patients may very occasionally experience an asthma attack immediately after injection.	
	Nausea seldom occurs following ingestion of Dimaval (DMPS) 100 mgHartkapseln.
Cardiovascular reactions may occur, especially if Dimaval is injected too rapidly, and can manifest as hypotension, nausea, dizziness and weakness usually shortly (5-10 minutes) after injection.	
An increase in transaminase levels may very occasionally be observed. The following have also very occasionally been reported: Pain at the injection site, unpleasant hydrogen sulfide odour, 50% reduction in leukocyte count, changes in taste, oppression of the chest, abdominal discomfort and loss of appetite.	An increase in transaminase levels may be observed in individual cases.

8 References

1 ***Aaseth J, Korkina LG, Afanasev IB***; Hemolytic activity of copper sulfate as influenced by epinephrine and chelating thiols; Acta Pharmacol. Sin. 19(3) 203-206 (1998)

2 ***Aaseth J, Jacobsen D, Andersen O, Wickstrom E***; Treatment of mercury and lead poisonings with dimercaptosuccinic acid and sodium dimercaptopropanesulfonate. A review; Hum. Analyst 120(3) 853-854 (1995)

3 ***Aaseth J, Benov L, Ribarov S***; Mercaptodextran-a new copper chelator and scavenger of oxygen radicals; Acta Pharmacol. Sin. 11(4) 363-367 (1990)

4 ***Aaseth J, Ribarov S, Bochev P***; The interaction of copper (Cu^{2+}) with the erythrocyte membrane and 2,3-dimercaptopropanesulfonate in vitro: a source of activated oxygen species; Pharmacol. Toxicol. 61(4) 250-253 (1987)

5 ***Aaseth, J, Halse J, Falch J***; Chelation of silver in argyria; Acta Pharmacol. Toxicol. 59(Suppl 7) 471-474 (1986)

6 ***Aaseth J***; Mobilization of copper by chelating agents; Plzen.Lek. Sborn. 49(Suppl.) 209-211 (1985)

7 ***Aaseth J, Skaug V, Alexander J***; Haemolytic activity of copper as influenced by chelating agents, albumine and chromium; Acta Pharmacol. Toxicol. 54(4) 304-310 (1984)

8 ***Aaseth J***; Recent advance in the therapy of metal poisonings with chelating agents; Hum. Toxicol. 2(2) 257-272 (1983)

9 ***Aaseth J, Alexander J, Raknerud N***; Treatment of mercuric chloride poisoning with dimercaptosuccinic acid and diuretics: preliminary studies; J. Toxicol. Clin. Toxicol. 19(2) 173-186 (1982)

10 ***Aaseth J, Alexander J, Deverill J***; Evaluation of methylmercury chelating agents using red blood cells and isolated hepatocytes; Chem. Biol. Interactions 36(3) 287-297 (1981)

11 ***Aaseth J, Friedheim AH;*** Treatment of methylmercury poisoning in mice with 2,3-dimercaptosuccinic acid and other complexing thiols; Acta Pharmacol. Toxicol. 42(4) 248-252 (1978)

12 ***Ablanova EK, Abykenov KK, Chuevskii AA, Ospanov KK***; Unithiol (sodium 2,3-dimercaptopropanesulfonate) complex formation with Fe(II)ions in solution; Izv. Nats. Akad. Nauk. Resp. Kaz. Ser. Khim. (4) 36-39 (1993) [Abstract]

13 ***Adam B, Felgenhauer N, Zilker T***; DMPS: The new chelating agent of choice in the treatment of arsenic poisoning; J. Toxicol. Clin. Toxicol. 41(4) 440 (2003)

14 ***Adams JB***; Summary of biomedical treatments for autism; www.eas.asu.edu/~autism/Additional/Summarybiomed07.pdf (2007)

15 ***Adams SR, Campbell RE, Gross LA, Martin BR, Walkup GK, Yao Y, Llopis J, Tsien RJ***; New biarsenical ligands and tetracysteine motifs for protein labeling in vitro and in vivo: synthesis and biological applications; J. Am. Chem. Soc. 124(21) 6063-6076 (2002)

16 ***Adveef A, Chemotti AR***; Cadmium binding by biological ligands. 4 Polynuclear complexes of cadmium with 2,3-dimercaptopropane-1-sulfonic acid; J. Chem. Soc. Dalton Trans. (5) 1189-1194 (1991)

17 ***Ageeva AN, Evstratova LI, Lantsov AA, Osherovich AM, Rozenblum AS***; Administration of unithiol in toxic lesions of the auditory analyzer; Vestn. Otorinolaringol. 33(4) 27-31 (1971) [Abstract]

18 ***Agocs M, Clarkson T, Ambre J, Becker C, Borak J, Canella J, Kipen H, Jackson RJ, Rodnick J, Wummer BA***; Mercury toxicity; Am. Fam Phys. 46(6) 1731-1744 (1992)

19 ***Aitio A, Bernard A, Fowler BA, Nordberg GF***; Biological monitoring and biomarkers; IN: Nordberg GF, Fowler BA, Nordberg M, Friberg LT (Eds.); Handbook on the Toxicology of Metals, 3rd Edition; Academic Press Inc. 65-78 (2007)

20 ***Al-Bayati MA***; A missed case of poisoning with arsenic; Veritas 4 1244-1250 (2007)

21 ***Al-Bayati MA***; A case of medically unjustified treatment with multiple mega doses of vitamin C with thyroid hormones that caused serious adverse reactions in a woman; Medical Veritas 1235-1243 (2007)

22 ***Al-Damluji SF, Murtadha M, Al-Abbasi AH, Amin-Zaki L, Bakir F, El-Hassani S, Al-Janabi K, Al-Omar K, Kuwaiti J, Audeau F, Mjid MA***; Intoxication due to alkylmercury-treated seed - 1971-72 outbreak in Iraq: Clinical aspects; Bull WHO 53 65-81 (1976)

23 ***Alekperov II, Melikzade TM,Shirinova SB, Kasianova KG***; Unithiol treatment in patients with fluorosis; Vrach. Delo. (10) 121-123 (1976) [Abstract]

24 ***Alexander J, Aaseth J***; Excretion of arsenic in rat bile-Role of complexing ligands containing sulfur and selenium; Nutr. Res. (Suppl.1) 515-519 (1985)

25 ***Alexeev AA, Ushakova TA, Lavrov VA***; Unithiol in combined therapy of burn toxemia; Russian Medical Journal (6) 50 (2000) [Abstract]

26 ***Ambrozic J, Logar D, Stajer D, Gorjup V, Golja M K, Horvat M***; Recurrent sepsis and seronegative arthritis in a patient with a selective IgG3 deficiency; Wien. Klin. Wochenschr. 112(15-16) 735-737 (2000)

27 ***Amler R, Amler S, Balk SJ, McLellan RK***; Pediatric environmental health - Case Studies in Environmental Medicine; ATSDR Publication No.: ATSDR-HE-CS-2002-0002 (2002)

28 ***Anatovskaya VS***; The use of Unithiol in the treatment of chronic lead intoxication; Gigieny Truda Profzabolevanii 29 50-56 (1962) [English Translation]

29 ***Andersen O, Aaseth J, Fischer AB***; Clinical chelation: Treatment of metal intoxications: Principles and recent developments; IN: Metals Essentiality, Toxicity and Selectivity, AB Fischer, R Prakash (Eds.), ABD Publishers, Jaipur, India, 48-113 (2005)

30 ***Andersen O***; Chemical and biological considerations in the treatment of metal intoxications by chelating agents; Mini Rev. Med. Chem. 4(1) 11-21 (2004)

31 ***Andersen O, Aaseth J***; Molecular mechanisms of in vivo metal chelation: Implications for clinical treatment of metal intoxications; Environ. Health Perspect. 110(Suppl.5) 887-890 (2002)

32 ***Andersen O***; Principles and recent developments in chelation treatment of metal intoxication; Chem. Rev. 99(9) 2683-2710 (1999)

33 ***Andersen O***; Oral cadmium exposure in mice: Toxicokinetics and efficiency of chelating agents; Crit. Rev. Toxicol. 20(2), 83-112 (1989)

34 ***Andersen O***; Choice of chelating antidotes for acute cadmium intoxication; Toxicol. Environ. Chem. 23 105-120 (1989)

35 ***Andersen O, Nielsen JB***; Oral cadmium chloride intoxication in mice: Effects of penicillamine, dimercaptosuccinic acid and related compounds; Pharmacol. Toxicol. 63(5) 386-389 (1988)

36 ***Anderson RA, McAllister WAC, Taylor A;*** Acute mercuric iodide poisoning; Ann. Clin.Biochem. 33(5) 468-470 (1996)

37 ***Anderson WJ***; Intravenous mercury: a three year follow-up; Ulster Med. J. 62(2) 180-183 (1993)

38 ***Angelova E, Stoytchev T***; Experimental studies on the antidotal and copper-decorporating effects of unithiol upon acute poisoning with copper sulfate and the influence acidosis and alkalosis on these effects; Bull. Inst. Physiol. 15 179-186 (1973)

39 ***Anghileri LJ, Ottaviani M, Ricard S, Raynaud C***; Radioruthenium-2,3-dimercaptopropanesulfonic acid complex. A potentially useful radiocompound for kidney studies; Eur. J. Nucl. Med. 6(9) 403-405 (1981)

40 ***Anghileri LJ, Ottaviani M, Raynaud C***; Etude comparative de la fixation renale de plusieurs complex chez le rat; Int. J. Biol. Med. 7 211-212 (1980)

41 ***Angle CR, Manton WI;*** Prolonged half life of childhood blood lead after termination of environmental exposure (EAPCCT XIX Int. Congress); J. Toxicol. Clin. Toxicol. 37 401 (1999)

42 ***Angle CR***; Chelation therapies for metal intoxication; IN: LW Chang (Ed.), Toxicology of Metals; CRC Lewis Publishers Boca Raton, 487-504 (1996)

43 ***Angle CR***; Organ-specific therapeutic intervention; IN: Organ Specific Metal Toxicology; Academic Press, San Diego; pp 71 - 110 (1995)

44 ***Angle CR***; Childhood lead poisoning and its treatment; Annu. Rev. Pharmacol. Toxicol. 33 409-434 (1993)

45 ***Anner BM, Moosmayer M, Imesch E***; Mercury blocks Na-K-ATPase by a ligand-dependent and reversible mechanism; Am. J. Physiol. Renal Fluid Electrolyte Physiol. 262(5) F830- F836 (1992)

46 ***Anshelevich YV, Sorokina TA, Orlova VP, Kalvelis AD, Sporan VG, Ozolin MA***; The effecttiveness of digoxin in the emergency therapy of paroxysmal supraventricular tachyarrhythmia; Klin. Med.(Moscow) 61(3) 31-35 (1983) [Abstract]

47 ***Antikainen PJ, Rossi VMK***; Oxyanion chelates of α-dithiols and α-mercaptoalcohols. II. Ionization and chelate formation ability of sodium 2,3-dimercaptopropanesulfonate; Suomen Kemistilehti B36(7-8)132-135 (1963) [Abstract]

48 ***Apfel B, Csef H***; Angst vor Umweltgiften-berechtigte Realangst oder psychische Störung?; Psychother. Psychosom. Med. Psychol. 45 90-96 (1995)

49 ***Aplin A, Wonnacott S***; Interaction of p-aminophenyldichloroarsine, an arsenical with specificity for vicinal cysteines, with (^{3}H)cytisine binding sites in rat brain membranes; Biochem. Pharmacol. 48(3) 473-477 (1994)

49a ***Aposhian HV***; Polonium-210 and sulfhydryl chelating agents; Bethesda Symposium (2007)

50 ***Aposhian HV, Aposhian MM***; Arsenic toxicology: five questions; Chem. Res. Toxicol. 19(1) 1-15 (2006)

51 ***Aposhian HV, Morgan DL, Queen HLS, Maiorino RM, Aposhian MM***; Vitamin C, glutathione, or lipoic acid did not decrease brain or kidney mercury in rats exposed to mercury vapour; J. Toxicol. Clin. Toxicol. 41(4) 339-347 (2003)

52 ***Aposhian HV, Aposhian MM***; Arsenic mobilization by DMPS; IN: Arsenic Exposure and Health Effects, WR Chappell, CO Abernathy, RL Calderon (Eds.), Proc. Int .Conf, 4th, Elsevier Science Ltd., Oxford, UK, P: 397-406 (2001)

53 ***Aposhian HV, Zheng B, Aposhian MM, Le XC, Cebrian ME, Cullen W, Zakharyan RA, Ma M, Dart RC, Cheng Z, Andrewes P, Yip L, O'Malley GF, Maiorino RM, van Voorhies W, Healy SM, Titcomb A***; DMPS-arsenic challenge test. II. Modulation of arsenic species, including monomethylarsonous acid (MMA(III)), excreted in human urine; Toxicol. Appl. Pharmacol. 165(1) 74-83 (2000)

54 ***Aposhian HV***; Mobilization of mercury and arsenic in humans by sodium 2,3-dimercapto-1-propane sulfonate (DMPS); Environ. Health Perspect. 106(Suppl.4) 1017-1025 (1998)

55 ***Aposhian HV***; Enzymatic methylation of arsenic species and other new approaches to arsenic toxicity; Annu. Rev. Pharmacol. Toxicol. 37 397-419 (1997)

56 ***Aposhian HV, Arroyo A, Cebrian ME, Del Razo LM, Hurlbut KM, Dart RC, Gonzalez-Ramirez D, Kreppel H, Speisky H, Smith A, Gonsebatt ME, Ostrosky-Wegman P, Aposhian MM***; DMPS-arsenic challenge test. I Increased urinary excretion of monomethylarsonic acid in humans given dimercaptopropane sulfonate; J. Pharmacol. Exp. Ther. 282(1)192-200 (1997)

57 ***Aposhian HV, Gonzalez-Ramirez D, Maiorino RM, Zuniga-Charles M, Hurlbut KM, Aposhian MM, Dart RC***; DMPS (Dimaval) as a challenge test to assess the mercury and arsenic body/kidney load in humans and as a treatment of mercury toxicity; Pacific Basen Conference on Hardous Waste; Malaysia (1996)

58 ***Aposhian HV, Maiorino RM, Gonzalez-Ramirez D, Zuniga-Charles M, Xu Z, Hurlbut KM, Junco-Munoz P, Dart RC, Aposhian MM***; Mobilization of heavy metals by newer, therapeutically useful chelating agents; Toxicology 97(1-3) 23-38 (1995)

59 ***Aposhian HV, Hurlbut KM, Maiorino RM, Dart R, Aposhian MM***; DMPS as a challenge test for mercury and other heavy metals and metaloids; J. Toxicol. Environ. Health 40 (2-3) 445 (1993)

60 ***Aposhian HV, Bruce DC, Alter W, Dart RC, Hurlbut KM, Aposhian MM***; Urinary mercury after administration of 2,3-dimercaptopropane-1-sulfonic acid: correlation with dental amalgam score; FASEB. J. 6(7) 2472-2476 (1992)

61 ***Aposhian HV, Maiorino RM, Rivera M, Bruce DC, Dart RC, Hurlbut KM, Levine DJ, Zheng W, Fernando Q, Carter D, Aposhian MM***; Human studies with the chelating agents DMPS and DMSA; J. Toxicol. Clin. Toxicol. 30(4) 505-528 (1992)

62 ***Aposhian HV, Maiorino RM, Dart RC, Perry DF***; Urinary excretion of meso-2,3-dimercaptosuccinic acid in human subjects; Clin. Pharmacol. Ther. 45(5) 520-526 (1989)

63 ***Aposhian HV***; The biological fate of heavy metals and metalloids; IN: Why chemicals are toxic, Chemical pathology and toxicology; Amer. Chemical Soc. & Lewis publishers, 1988

64 ***Aposhian HV, Dart RC, Aposhian MM, Dawson BV***; Tissue decorporation of polonium-210 in rats by DMPA; Res. Commun. Chem. Pathol. Pharmacol. 58(2) 157-171 (1987)

65 ***Aposhian HV, Maiorino RM, Weber GL, Aposhian MM, Kelvie DH, Wilson SE***; Water soluble dithiol metal binding agents - efficacies and biotransformation; Acta Pharm. Tox. 59(Suppl.7) 467-470 (1986)

66 ***Aposhian HV***; Development of new methods for dithiol analysis and urinary excretion of DMPS and DMSA; Unpublished results 1986

67 ***Aposhian HV, Maiorino RM, Aposhian MM, Hsu CA, Stine ER***; Water soluble dithiol metal binding agents - efficacies and additional modes of action; Plzen. Lek. Sborn 49(Suppl.) 47-51 (1985)

68 ***Aposhian HV, Carter DE, Hoover TD, Hsu CA, Maiorino RM, Stine E***; DMSA, DMPS, and DMPA - as arsenic antidotes; Fundam. Appl. Toxicol. 4(2 Pt 2) s58-s70 (1984)

69 ***Aposhian HV***; DMSA and DMPS-water soluble antidotes for heavy metal poisoning; Annu. Rev. Pharmacol. Toxicol. 23 193-215 (1983)

70 ***Aposhian HV***; Biological chelation: 2,3-dimercapto-propanesulfonic acid and meso-dimercaptosuccinic acid; Adv. Enzyme Regul. 20 301-319 (1982)

71 ***Aposhian HV, Mershon MM, Brinkley FB, Hsu CA, Hackley BE***; Anti-lewisite activity and stability of meso-dimercaptosuccinic acid and 2,3-dimercapto-1-propanesulfonic acid; Life Sci. 31(19) 2149-2156 (1982)

72 ***Aposhian HV, Tadlock CH, Moon TE***; Protection of mice against lethal effects of sodium arsenite - a quantitative comparison of a number of chelating agents; Toxicol. Appl. Pharmacol. 61(3) 385-392 (1981)

73 ***Aposhian HV, Aposhian MM***; Newer developments in arsenic toxicity; J. Amer. Coll. Toxicol. 8(7) 1297-1305 (1980)

74 ***Aposhian MM, Maiorino RM, Xu Z, Aposhian HV***; Sodium 2,3-dimercapto-1-propane-sulfonate (DMPS) treatment does not redistribute lead or mercury to the brain of rats; Toxicology 109(1) 49-55 (1996)

75 ***Aposhian MM, Aposhian HV, Domingo JL, Llobet JM. Zheng W, Dart RC***; Radon decay products: DMPS decreases tissue polonium-210; Plzen. Lek. Sborn. 56(Suppl.) 99-101 (1988)

76 ***Araya M, Olivares M, Pizarro F, Mendez MA, Gonzalez M, Uauy R***; Supplementing copper at the upper level of the adult dietary recommended intake induces detectable but transient changes in healthy adults; J. Nutr. 135(10) 2367-2371 (2005)

77 ***Arbusow SJ***; Die Schutzwirkung einiger pharmakologischer Mittel bei Strahlenschäden; Arch. Exp. Path. Pharmacol. 236 265-272 (1959)

78 ***Arezina R, Kargacin B, Kostial K, Landeka M***; The effect of oral chelation therapy with DMPS, DMSA or ZnDTPA on retention of ingested mercury-203 in rats; IN: Trace Elem. Man Anim. 7: Monogr, Proc, Round Tables Discuss Int Symp, 7th, Inst. Med. Res. Occup. Health Univ. Zagreb, Yugoslavia, P: 24/5-24/6 (1991)

79 ***Aripov AN, Akbarova NM***; Changes in the adenylate cyclase system of rat liver cells in acute experimental hepatitis and ways of correcting them; Vopr. Med. Khim. 40(4) 31-33 (1994) [Abstract]

80 ***Arkhipova OG, Roschin IV***; Use of chelating agents for protection against molybdenum poisoning); Nov. Danny Toksikol. Redk. Zh. Farmakol. Khim. Sredstva Toksiol. Abst. No. 7.54.387 (1968) [Abstract]

81 ***Arkhipova OG, Roschin IV, Kuzmicheva MN***; Use of chelating agents for protection against vanadium poisoning; Nov. Danny Toksikol. Redk. Zh. Farmakol. Khim. Sredstva Toksiol. Abst. No. 7.54.753 (1967) [Abstract]

82 ***Arkhipova OG***; Iron metabolism during experimental administration of complexons; Bull. Exp. Biol. Med. 62(1) 782-785 (1966)

83 ***Arndt A***; Diagnostik und Therapie der chronischen Quecksilberbelastung durch Zahnamalgam-Füllungen unter besonderer Berücksichtigug der Quecksilber-Mobilisation mit 2,3-Dimercaptopropane-1-sulfonsäure (DMPS); Dissertation Technische Universität München (1995)

83a ***Arndt T***; Urin-Kreatininkonzentration: Kenngröße zur Prüfung auf Probenverwertbarkeit? Kritische Überlegungen aus ca. 25000 Urin-Kreatininbestimmungen in einem klinisch-chemischen Labor; Toxichem. Krimtech. 74(2) 94-99 (2007)

84 ***Arnold AP, Canty AJ, Reid RS, Rabenstein DL***; Nuclear magnetic resonance and potentiometric studies of the complexation of methylmercury(II) by dithiols; Can. J. Chem. 63(9) 2430-2436 (1985)

85 ***Arnold AP, Canty AJ, Moors PW, Deacon GB***; Chelation therapy for methylmercury(II) poisoning. Synthesis and determination of solubility properties of MeHg(II) complexes of thiol and dithiol antidotes; J. Inorg. Biochem. 19(4) 319-327 (1983)

86 ***Arnold-von Versen B***; Buntes klinisches Bild. Schwermetallbelastungen; Z. Umweltmedizin 9(1) 24-25 (2001)

87 ***Arnold B***; Eigenschaften und Einsatzgebiete des Chelatbildners Dimercaptopropanesulfonsäure (DMPS); Z. Umweltmedizin 5(1) 38-41 (1997)

88 ***Arnold B***; Diagnose und Therapie von Schwermetallbelastungen; Erfahrungsheilkunde 46(5) 267-275 (1997)

89 ***Arnold B***; Diagnostik und Monitoring von Schwermetallbelastungen. I+II; ZWR 105(10) 586-589; (11) 665-669 (1996)

90 ***Arnold LL, Cano M, Cohen SM***; Dimethylarsinous acid (DMA^{III}) in the urine of female F344 rats treated with dimethylarsinic acid (DMA); 5th International Conference on Arsenic Exposure and Health Effects, San Diego, 2002

90a ***Arnold RG, Carpenter DO, Kirk D, Koh D, Armour MA, Cebrian M, Cifuentes L, Khwaja M, Ling B, Makalinao I, Paz-y-Mino C, Peralta G, Prasad R, Singh K, Sly P, Tohyama C, Woodward A, Zheng B, Maiden T***; Meeting

Report: Threats to Human Health and Environmental Sustainability in the Pacific Basin; Environ Health Perspect. 115(12) 1770-1775 (2007)

91 ***Aronow R***; Heavy metals and inorganic agents: Mercury; IN: Clinical management of poisoning and drug overdose; 2nd ed.; LM Haddad, JF Winchester (Eds.); WB Saunders Co; Philadelphia; 1002-1009 (1990)

91a ***Aronson JK***; Side effects of drugs annuak 27, p.234 (2004)

92 ***Ashbel SI***; Unithiol in Prophylaxe und Therapie berufsbedingter Vergiftungen mit Quecksilber und dessen organischen Verbindungen; IN: "Tiolovye soedineniya v meditsine; NI Luganskii, VE Petrunkin, PV Rodionov, AI Cherkes (Eds.); Meditsinskoe Izdatel'stvo USSR Kiev, S.161-168 (1959)

93 ***Ashizawa N, Okumura H, Kobayashi F, Aotsuka T, Takahashi M, Asakura R, Arai K, Matsuura A***; Inhibitory activities of metal chelators on endothelin-converting enzyme. I In vitro studies; Biol. Pharm. Bull. 17(2) 207-211 (1994)

94 ***Ashizawa N, Okumura H, Kobayashi F, Aotsuka T, Takahashi M, Asakura R, Arai K, Matsuura A***; Inhibitory activities of metal chelators on endothelin-converting enzyme. II In vivo studies; Biol. Pharm. Bull. 17(2) 212-216 (1994)

95 ***Ashton CE, Hla KK, Mant T, Volans G***; 2,3-Dimercaptopropane-1-sulfonate (DMPS) in the treatment of heavy metal poisoning, an effective and potentially life saving treatment?; Annual Meeting of European Association of Toxicology and Poison Control Centres Meeting, Istanbul 1992

96 ***Ashton CE, House I, Volans G***; A case of severe intravenous metallic poisoning managed successfully with prolonged Dimercapto-1-propanesulfonate therapy; Annual Meeting of European Association of Toxicology and Poison Control Centres Meeting, Istanbul 1992

97 ***Ashton CE***; A case of severe intravenous metallic poisoning managed successfully with prolonged Dimercapto-1-propanesulfonate therapy; Annual Meeting of European Association of Poison Control Centres, Münster 1989

98 ***Ashton CE, House I***; Two cases of severe inorganic mercury ingestion treated with Dimercapto-1-propane sulfonate; Annual Meeting of European Association of Poison Control Centres, Münster 1989

99 ***Astorga BO, Pelis RM, Wright SH***; Interaction of mercapto-containing sulfonates with human, rabbit and mouse orthologs of OAT1 and OAT3; FASEB J. 20 A1239 (2006)

100 ***Aubakirova KK, Ospanova AK, Ospanov KK, Shabikova GK, Seilkhanova GA***; Synthesis and physicochemical study of the properties of the chromium(V) complex with unithiol; Izv. Nats. Akad. Nauk. Resp. Kaz., Ser. Khim (1) 59-64 (1995) [Abstract]

101 ***Auer C, Ducrey N, Uffer S, Othenin-Girard P, Herbort CP***; Self-mutilating intraocular injection of metallic mercury; Arch. Ophthalmol. 115 (4) 556 - 557 (1997)

102 ***Autenrieth T, Schmidt T, Haberscheid W***; Bleivergiftung durch griechische Keramiktasse; Dtsch. Med. Wochenschr. 123(12) 353-358 (1998)

103 ***Avdeef A, Chemotti AR***; Cadmium binding by biological ligands. 4 Polynuclear complexes of cadmium with 2,3-dimercaptopropane-1-sulfonic acid; J. Chem. Soc. Dalton Trans. (5) 1189-1194 (1991)

104 ***Aymaz S, Groß O, Krakamp B, Ortmann M, Diener HP, Weber M***; Membranous nephropathy from exposure to mercury in the fluorescent-tube-recycling industry; Nephrol. Dial. Transplant. 16 2253-2255 (2001)

105 ***Bader T, Hoffmann HM***; Letter to the Editor - Dimercapto-1-propanesulfonic Acid (DMPS);Townsend Letter 2/2006

106 ***Baert A, Danel V***; Armes chimiques: EMC Toxicologie Pathologie 1(3) 117-123 (2004)

107 ***Baga KM*** ; Taking a bite out of the harmful effects of mercury in dental fillings: Advocating for national legislation for mercury amalgams ; J. Law Health 20(7) 169-197 (2006)

108 ***Bagiyan GA, Koroleva IK, Soroka NV, Ufimtsev AV***; Complexes of copper(I) with dimercapto compounds as catalysts for oxidation of mercaptans and hydrogen sulfide with molecular oxygen in aqueous solutions; Russ. J. Appl. Chem. 76(1) 88-94 (2003)

109 ***Bagiyan GA, Koroleva IK, Soroka NV, Ufimtsev AV***; Oxidation of thiol compounds by molecular oxygen in aqueous solutions; Russ. Chem. Bull. 52(5) 1135-1141 (2003)

110 ***Bahn A, Knabe M, Hagos Y, Rödiger M, Godehardt S, Graber-Neufeld DS, Evans KK, Burckhardt G, Wright SH***; Interaction of the metal chelator 2,3-dimercapto-1-propanesulfonate with the rabbit multispecific organic anion transporter 1 (rbOAT1); Mol. Pharmacol. 62(5) 1128-1136 (2002)

111 ***Bai H, Zhang S, Sun C***; Observation of clinical symptom of acute tetramethylene disulfotetramine poisoning and evaluation of therapeutic effects of sodium dimercaptopropanesulfonate on poisoning; Xiandai Yufang Yixue 33(6) 868-869 (2006) [Abstract]

112 ***Bai H, Zhang S, Zhang H, Ji J, Ma P, Wang H, Bai Y, Zhou X, Ding M, Lu X, Sun C***; Evaluation of therapeutic project on acute tetramethylene disulfotetramine poisoning and effects on intelligence in children; Zhonghua Yufang Yixue Zazhi 39(2) 95-98 (2005) [Abstract]

113 ***Bakhishev GV***; Cysteine activity in the poisoning of animals by various aliphatic series halogenated hydrocarbons; Farmakol. Toksikol. 41(3) 342-344 (1978) [Abstract]

114 ***Bakir F, Al-Khalidi A, Clarkson TW, Greenwood MR***; Clinical observations on treatment of alkylmercury poisoning in hospital patients; Bull. WHO 53 87-92 (1976)

115 ***Bakir F***; Methylmercury poisoning in Iraq; J. Kwt. Med. Assoc. 8(4) 223-226 (1974)

116 ***Bakka A, Aaseth J, Rugstad HE***; Influence of certain chelating agents on egress of cadmium from cultured epithelial cells containing high amounts of metallothionein: a screening of Cd-releasing and toxic effects; Acta Pharmacol. Toxicol. 49(5) 432-437 (1981)

117 ***Bakka A, Aaseth J***; Cadmium excretion in mice given dimercaptopropanesulfonate and some other complexing dithiols; Arh. Hig. Rada Toksikol. 30(Suppl.) 183-189 (1979)

118 ***Balan GM, Yurchenko IV, Ignatenko LI, Prodanchuk GN, Gil LN, Stahovich VI, Golovanova NN***; To clinical aspect and treatment of neurologic and abdominal disturbances with the chronic lead intoxication; Modern Problems of Toxicology (4) (2003)

119 ***Balatskii KP***; Use of unithiol and dicaptol in arsenic poisoning of cattle; Materialy 8-01 (Vos'mos) Nauchn. Konf. po Farmakol., Moscow, Sb. 1963, 158-159 [Abstract]

120 ***Balatskii KP***; The effect of unithiol on biochemical changes in the blood of rabbits and dogs with experimental arsenic poisoning; Nauk. Pratsi. Vet. Fak. L'vivs'k. Zoovet. Inst. 12 20-23 (1963) [Abstract]

121 ***Baldwin DR, Marshall WJ***; Heavy metal poisoning and its laboratory investigation; Ann. Clin. Biochem. 36(3) 267-300 (1999)

122 ***Balykin NS, Sedov KR, Kovaleva VS***; Verfahren zur Entfernung von Quecksilber aus dem Abwasser; Patent UdSSR 660 942 vom 15.5.1979 [Deutsche Übersetzung]

123 ***Bannasch L, Schleicher P***; Immunstatus vor und nach Quecksilbermobilisation; Natur & Ganzheitsmedizin (4) 53 - 56 (1991)

124 ***Barceloux DG***; Cobalt; J. Toxicol. Clin. Toxicol. 37(2) 201-206 (1999)

125 ***Barceloux DG***; Copper; J. Toxicol. Clin. Toxicol. 37(2) 217-230 (1999)

126 ***Barceloux DG***; Zinc; J. Toxicol. Clin. Toxicol. 37(2) 279-292 (1999)

127 ***Barceloux DG***; Manganese; J. Toxicol. Clin. Toxicol. 37(2) 293-307 (1999)

128 ***Bartram F, Höhne I, von Baehr V, Thill R, Meisch JP***; Umweltmedizinischer Anamnesepfad in der Zahnmedizin /Umwelt-ZahnMedizin - Empfehlungen des Arbeitskreises Zahnmedizin des Deutschen Berufsverbandes der Umweltmediziner e.V.; Umwelt-Medizin-Gesellschaft 20(2) 89-98 (2007)

129 ***Baruthio F***; Toxic effects of chromium and its compounds; Biol. Trace Elem. Res. 32145-153 (1992)

130 ***Basinger MA, Jones MM, Holscher MA, Vaughn WK***; Antagonists for acute oral cadmium chloride intoxication; J. Toxicol. Environ. Health 23(1) 77-89 (1988)

131 ***Basinger MA, Gibbs SJ, Forti RL, Mitchell WM, Jones MM***; Antidotes for gold(sodium bis (thiosulfato)gold(I)) intoxication in mice; J. Rheumatol. 12(2) 274-278 (1985)

132 ***Basinger MA, Jones MM, McCroskey SA***; Antidotes for acute bismuth intoxication; J. Toxicol. Clin. Toxicol. 20(2) 159-165 (1983)

133 ***Basinger MA, Jones MM, Shinobu LA***; Structural requirements for chelate antidotes for acute cadmium intoxication; J. Inorg. Nucl. Chem. 43(11) 3039-3042 (1981)

134 ***Basinger MA, Casas JS, Jones MM, Weaver DD, Weinstein NH***; Structural requirements for Hg(II) antidotes; J. Inorg. Nucl. Chem. 43 1419-1425 (1981)

135 ***Basinger MA, Jones MM***; Structural requirements for chelate antidotal efficacy in acute antimony(III) intoxication; Res. Commun. Chem. Pathol. Pharmacol. 32(2) 355-363 (1981)

136 ***Basinger MA, Jones MM***; Chelate antidotal efficacy in acute zinc intoxication; Res. Commun. Chem. Pathol. Pharmacol. 33(2) 263-272 (1981)

137 ***Basinger MA, Jones MM, Tarka MP***; Relative efficacy of chelating agents as antidotes for acute nickel(II)acetate intoxication; Res. Commun. Chem. Pathol. Pharmacol. 30(1) 133-141 (1980)

137a ***Bateman DN***; The epidemiology of poisoning; Medicine 35(10) 537-539 (2007)

138 ***Batora I, Teply I, Ulicna O, Kostolanska K, Urbanova E, Plackova S, Kresanek J***; Intrabronchial aspiration of elemental mercury: A 14 month follow-up; XXI Int. Congress EAPCCI, Barcelona (2001)

139 **Batora I, Mrazova J, Ulicna O, Plackova S, Kresanek J, Urbanova E**; Intravenous elemental mercury intoxication in a drug addict; J. Toxicol. Clin. Toxicol. 38(2) 254 (2000)

140 ***Battistone GC, Miller RA, Rubin M***; The use of 2,3-dimercaptopropane sodium sulfonate (DMPS) in mercury chelation therapy; IN: Clinical chemistry and chemical toxicology of metals; SS Brown (Ed.), Amsterdam, Elsevier Press/North-Holland, pp. 221-224 (1977)

141 ***Baud FJ, Borron SW, Bismuth C***; Modifying toxicokinetics with antidotes; Toxicol. Lett. 82/83 785-793 (1995)

142 ***Baum CR***; Treatment of mercury intoxication; Curr. Opin. Pediatr. 11(3) 265-268 (1999)

143 ***Bayer W***; Harnausscheidung der Elemente Quecksilber, Kupfer und Zink bei Amalgamträgern vor und nach Behandlung mit einem Komplexbildner (DMPS); Erfahrungsheilkunde 41(10) 628-633 (1992)

144 ***Bearer CF***; How are children different from adults?; Environ. Health Perspect. 103(Suppl.6) 7-12 (1995)

145 ***Behari JR, Gupta S, Srivastava S, Srivastava RC***; Use of liposome encapsulated sodium 2,3-dimercaptopropanesulfonate (DMPS) in the treatment of mice loaded with cadmium; J. Environ. Sci. Health A25(6) 597-610 (1990)

146 ***Behnke W, Schulz JH***; Allergische Reaktionen auf Hilfsstoffe von Arzneimitteln am Beispiel einer Quecksilberallergie; Umwelt-Medizin-Gesellschaft 13(3) 248-252 (2000)

147 ***Behnke W, Schulz JH***; Kopfschmerz und Migräne: Schon mal an Amalgam gedacht?; Der Allgemeinarzt 17(11) 1222-1223 (1995)

148 ***Belgova IN***; Effect of unithiol on the toxicity of embitol in mice of different age groups; Farmakol. Toksikol. 33(2) 216-219 (1970) [Abstract]

149 ***Belgova IN***; The effect of ethylenediamineactetates and sodium dimercaptopropane-sulfonate upon hemolytic activity of the clostridium perfringens α-Toxin; Farmakol. Toksikol. 32(6) 707-710 (1969)

150 ***Belgova IN***; Action of mercapto compounds on novembichin poisoning in mice of different ages; Farmakol. Toksikol. 31(6) 738-741 (1968) [Abstract]

151 ***Belgova IN***; Sodium dimercaptopropanesulfonate (unithiol) as antidote in novembichin poisoning; Tr. Leningrad Pediat. Med. Inst. 32 25-28 (1965) [Abstract]

152 ***Belgova IN***; A study of the effect of sodium dimercaptopropanesulfonate (Unithiol) and EDTA on the activity of streptolysin O; Farmakol Toksikol. 27(2) 231-234 (1964) [Abstract]

153 ***Belonozhko GA, Vitte-Drozdovskaya VI, Kefili EI, Shchepotin BM***; The administration of a new antidote - Unithiol - for poisonings caused by arsenic and mercury compounds; Vrach. Delo (1) 87 (1957) [Abstract]

154 ***Belyaeva LN, Klyushina LV***; Biochemical indexes in intoxication with chromium compounds and clinical and experimental treatment with Unithiol; Vopr. Gigieny Prof. Patol. Toksikol. Sb. Sverdlovsk 413-417 (1964) [Abstract]

155 ***Bennett DW, Huang L, Dill K;*** Semiempirical self-consistent field (CNDO) calculation of arsenical-antidotes adducts; Chem. Res. Toxicol. 5(1) 5-7 (1992)

155a ***Bennett P***; Working up the toxic patient: Practical intervention and treatment stategies; 13th International Symposium of The Institute for Functional Medicine (2006)

156 ***Bennett TA, Edwards BS, Sklar LA, Rogelj S***; Sulfhydryl regulation of L-selectin shedding: Phenylarsine oxide promotes activation-independent L-selectin shedding from leukocytes; J. Immunol. 164 4120-4129 (2000)

157 ***Benov LC, Ribarov SR, Monovich OH***; Study of activated oxygen production by some thiols using chemi-luminescence; Gen. Physiol. Biophys. 11(2) 195-202 (1992)

158 ***Benov LC, Benchev IC, Monovich OH***; Thiol antidotes effect on lipid peroxidation in mercury-poisoned rats; Chem. Biol. Interact. 76(3) 321-332 (1990)

159 ***Benov LC, Monovich OH, Benchev IC*****;** Effect of DMPS and D-penicillamine on the level of lipid peroxidation products in metal-poisoned rats; Plzen. Lek. Sborn. 56(Suppl.) 177 (1988)

160 ***Berger J***; Erste Hilfe im Betrieb; BGI Information 509 - (Oktober 2004)

161 ***Bernal J, Lee JH, Cribbs LL, Perez-Reyes E***; Full reversal of Pb^{++} block of L-type Ca^{++} channels requires treatment with heavy metal antidotes; J. Pharmacol. Exp. Ther. 282(1) 172-180 (1997)

162 ***Berisha A, Buznikov GA, Malchenko LA, Rakic L***; Action of heavy metal salts on the development of sea urchin embryos and on protein synthesis by the cells of transplantable mouse tumors; Ontogenez 14(2) 173-179 (1983) [Abstract]

163 ***Berlin M, Zalups RK, Fowler BA***; Mercury; IN: Nordberg GF, Fowler BA, Nordberg M, Friberg LT (Eds.); Handbook on the Toxicology of Metals, 3rd Edition; Academic Press Inc. 675-729 (2007)

164 ***Bernard S, Enayati A, Roger H, Binstock T, Redwood L, McGinnis W***; Autism: a novel form of mercury poisoning; www.nomercury.org/science/documents/ A_unique_type_of_mercury_poisonig_2000.pdf (2000)

165 ***Bertram HP***; Amalgam - Toxikologische Aspekte; www.lanisa.de/umweltmedizin/amalgam.htm (1994)

166 ***Bertram HP***; Spurenelemente-Analytik, ökotoxikologische und medizinisch-klinische Bedeutung; Urban & Schwarzenberg (1992)

167 ***Bertram HP, Kemper FH, Jekat FW, Winterberg B***; Clinical application of DMPS in intoxications with inorganic compounds; Annual Meeting of European Association of Poison Control Centres, Münster 1989

168 ***Bertram HP, Kemper FH, Khayyal MT***; Verwendung von Alkalisalzen der Dimercaptopropane-1-sulfonsäure bei der Behandlung von Schistosomiasis; Offenlegungsschrift DE 29 01 350 (1980)

169 ***Bertsche T, Schulz M***; Succimer zur Ausleitungstherapie?; Pharm. Ztg. 148(25) 2274-2276 (2003)

170 ***Beuse W***; Sammlung Patienteninformationen; www.akdoc.de/download/allg_info.pdf (2004)

171 ***Bialonczyk C, Partsch H, Donner A***; Bleivergiftung durch Langzeitanwendung von Diachylonsalbe; Z. Hautkr. 64(12) 1118-1120 (1989)

172 ***Bieger WP, Noppeney H, Mayer W, von Baehr R***; Immuntoxikologie der Dentalmetalle; Z. Umweltmedizin 5(4) 232-238 (1997)

173 ***Birkmayer JGD***; Ein Brief an die Helden der Amalgamdiskussion; Forum Prakt. Allgem. Arztes 29(1) 23-24 (1990)

174 ***Birkmayer JGD, Daunderer M, Reschenhofer E***; Quecksilberdepots im Organismus korrelieren mit der Anzahl der Amalgamfüllungen; Biol. Zahnmedizin 6(2) 57-61 (1990)

175 ***Bismuth C, Borron SW, Baud FJ, Barriot P***: Chemical weapons: Documented use and compounds on the horizon; Toxicol. Lett. 149(1-3) 11-18 (2004)

176 ***Bittel GI, Wrbitzky R***; Amalgam: Ich habe Hunderte entgiftet; Medical Tribune (1995)

177 ***Blair W***; Arsenic Poisoning and McGuff Compounding Pharmacy http://www.mcguffpharmacy.com/News%20Room/arsenic_poisoning_in_main.htm (2003)

178 ***Blanusa M, Varnai VM, Piasek M, Kostial K***; Chelators as antidotes of metal toxicity: Therapeutic and experimental aspects; Curr. Med. Chem. 12(23) 2771-2794 (2005)

179 ***Blanusa M, Prester L, Radic S, Kargacin B***; Inorganic mercury exposure, mercury-copper interaction, treatment in rats; Environ. Health Perspect. 102(Suppl. 3) 305-307 (1994)

179a ***Blaurock-BuschE, VanderSchaar P***; Chelating corner; Townsend Letter June 2007

180 ***Blaurock-Busch E***; Antidota - Chelattherapie-Handbuch mit Anwendungsbeispielen und wichtigen Hinweisen; 1. Auflage, MICRO TRACE MINERALS (2006)

181 ***Blaurock-Busch E***; Tabak - Medizin, Genussmittel oder Gift deines Lebens?; Comed (10) 58-59 (2005)

182 ***Bleul G***; Anleitung zur Ausleitung-oder: Sinn und Unsinn von Drainagemitteln, potenzierten Giften und standardisierter Begleittherapie; Allg. Homöopath. Z. 241(5) 188-197 (1996)

183 ***Blumer W, Epper M***; Detection of amalgam-induced mercury poisoning by DMPS-elimination test; Plzen. Lek. Sborn. 71(Suppl.) 41-42 (1996)

184 ***Böckers M, Wagner R, Oster O***; Nageldyschromie als Leitsymptom einer chronischen Quecksilberintoxikation durch ein kosmetisches Bleichmittel; Z. Hautkr. 60(10) 821-829 (1985)

185 ***Böckers M, Schönberger W, Oster O, Neumann P***; Inhalative Quecksilbervergiftung unter dem klinischen Bild einer Akrodynie (Selter-Swift-Feer); Dtsch. Med. Wochenschr. 108(21) 825-828 (1983)

186 ***Bogdan GM, Dart RC***; Summary report: Clinical experience with DMPS; Unpublished Results (2001)

187 ***Bogdan GM, Aposhian HV, Aposhian MM, Hurlbut KM, Dart RC***; Diagnostic use of 2,3-dimercpato-1-propane sulfonate (DMPS) to assess mercury exposure; SOT Annual Meeting (1999)

188 ***Bogle RG, Shanmugalingham S, Ross S, Oyenubi A, House I, Jones AL, Volans G;*** A case of serious bismuth poisoning treated with early DMPS without sequela of renal failure; J. Toxicol. Clin. Toxicol. 38(2) 253-254 (2000)

189 ***Bogomilskii MR, Diakonova IN, Poliakov VG, Rakhmanova IV, Stakhovskaia OA, Tikhomirov AM***; Ototoxic effect and its prevention in administration of cisplatin; Vestnik Otorinolaringologii (2) 7-10 (2002) [Abstract]

190 ***Bogumil R, Namgaladze D, Schaarschmidt D, Schmachtel T, Hellstern S, Mutzel R, Ullrich V***; Inactivation of calcineurin by hydrogen peroxide and phenylarsine oxide. Evidence for a dithiol–disulfide equilibrium and implications for redox regulation; Eur. J. Biochem. 267 1407-1415 (2000)

191 ***Bogush TA, Donenko FV, Saprykina VS***; Unithiol and thymidine influence on toxicity and therapeutic effect of adriamycin; Vopr. Onkol. 32(5) 58-63 (1986) [Abstract]

192 ***Böhmer G, Hahn B***; Quecksilber-Mobilisation mit dem Komplexbildner DMPS (Dimaval) bei ärztlichem und zahnärztlichem Personal im Vergleich; Der Artikulator (30) 11-12 (1989)

192a ***Bolshoy DV, Pykhteeva EG, Shafran LM, Burlak GF***; Poisonings with mercury - A lasting problem; Toxicol. Lett. 164S s102-s103 (2006)

193 ***Bolt HM, Greim H, Marquardt H, Neumann HG, Oesch F, Ohnesorge FK***; Stellungnahme der Beratungs-kommission Toxikologie der Deutschen Gesellschaft für Pharmakologie und Toxikologie DGPT zur Toxizität von Zahnfüllungen aus Amalgam; Schweiz. Rundschau Med. 79(9) 186-187 (1990)

194 ***Bonnet E***; Diaplazentarer Schadstofftransfer belastet Feten; Mineraloscop 1 16 (1996)

195 ***Bonnet E, Bonnet M***; Amalgamauswirkungen bei Säuglingen - Beziehungen zum SIDS; IN: Prävention, Diagnose und Therapie von Umwelterkrankungen, Kongressband vom VI. Stuttgarter Mineralstoff-Symposium S.123-131 (1993)

195a ***Borges VC, Nogueira CW***; The role of thiol-reducing agents on modulation of glutamate binding induced by heavy metals in platelets; Toxicol In Vitro in press (2008)

196 ***Borges VC***; Modulation of glutamatergic system in platelets: Effect of heavy metals and organochalcogens; Dissertation Universität Santa Maria, RS, Brasil (2007)

197 ***Borho K***; Zinn und das weibliche Endokrinum - Zinnkonzentrationen im Urin und Speichel bei Frauen mit Fertilitätsproblematik und anderen endokrinen Störungen; Dissertation Universität Heidelberg (2001)

198 ***Borokhov AI, Gurichev VV***; Adrenal Cortex function in patients suffering from chronic mercury poisoning and in mercury carriers; Gig.Tr.Prof.Zabol. 14(8) 22-25 (1970) [Abstract]

199 ***Böse-O'Reilly S, Drasch G, Beinhoff C, Maydl S, Vosko MR, Roider G, Dzaja D***; The Mt. Diwata study on the Philippines 2000 - Treatment of mercury intoxicated inhabitants of a gold mining area with DMPS (2,3-Dimercapto-1-propane-sulfonic acid, Dimaval); Sci. Total Environ. 307(1-3) 71-82 (2003)

200 ***Böse-O'Reilly S***; Multiple manifestations of mercury intoxication; Environmental Threats to the Health of Children: Hazards and Vulnerability, Bangkok, Thailand, 3-7 March 2002 [Abstract]

201 ***Böse-O'Reilly S, Drasch G, Eife R, Laub MC***; Chronische Metallintoxikationen als Ursache neuropädiatrischer Erkrankungen; Pädiatr. Praxis 45 183-197 (1993)

202 ***Bosque MA, Domingo JL, Paternain JL, Llobet JM, Corbella J***; Evaluation of the developmental toxicity of 2,3-dimercapto-1-propanesulfonate (DMPS) in mice. Effect on mineral metabolism; Toxicology 62(3) 311-320 (1990)

203 ***Bottei EM, Gottsch SG***; Minimal local availability of DMPS: A cause of concern in cases of severe arsenic poisoning; Clin. Toxicol. 44(5) 674-675 (2006)

203a ***Bradberry SM***; Copper; Medicine 35(11) 608 (2007)

203b ***Bradberry SM***; Mercury; Medicine 35(12) 632 (2007)

203c ***Bradberry SM, Vale A***; Management of poisoning: antidotes; Medicine 35(10) 562-564 (2007)

203d ***Bradberry SM***; Mercury; Medicine 31(10) 59-60 (2003)

204 ***Bradberry SM, Vale JA***; Mercury vapour intoxication: Features and management; XXI Int. Congress EAPCCI, Barcelona (2001)

204a ***Bradstreet J***; Advanced biomedical treatments using new biomarkers; 2nd Asian Autism Conference, Hong Kong 2007

205 ***Brandao R, Santos FW, Farina M, Zeni G, Bohrer D, Rocha JB, Nogueira CW***; Antioxidants and metallothionein levels in mercury-treated mice; Cell. Biol. Toxicol. 22(6) 429-438 (2006)

206 ***Brandao R, Santos FW, Zeni G, Rocha JBT, Nogueira CW***; DMPS and N-acetylcysteine induced renal toxicity in mice exposed to mercury; Biometals 19(4) 389-398 (2006)

207 ***Brawer-Tschernobilskaja B, Belonoschka E***; Unithiol in derTherapie von Schwermetallintoxikationen; IN: Tiolovye Soyedineniyav Meditsine, NN Luganskii, VE Petrunkin, PV Radionov, AJ Cherkes (Eds.); Gos. Med. Idz. Ukrain, SSR, Kiev, pp.139-143 (1959) [Deutsche Übersetzung]

208 ***Brehler R, Panzer B, Forck G, Bertram HP***; Quecksilbersensibilisierung bei Amalgamfüllungen - Beurteilung aus dermatologischer Sicht; Dtsch. Med. Wochenschr. 118(13) 451-456 (1993)

209 ***Brent J***; Mysteries of the mysterious metal – When and if mercury should be chelated; Clin. Toxicol. 44 473-475 (2006)

210 ***Breslavets VI, Durnev VI***; Use of unithiol in acute blood losses; Farmakol. Toksikol. 34(5) 598-601 (1971) [Abstract]

211 ***Bridges BA, Koch R***; Radiation protection by some sulfhydryl derivatives of pyridoxine and a new BAL preparation; Int. J. Rad. Biol. 3(1) 49-58 (1961)

211a ***Bridges CC, Joshee L, Zalups RK***; Multidrug resistance proteins and the renal elimination of inorganic mercury mediated by DMPS or DMSA; J. Pharmacol. Exp. Ther. 324(1) 383-390 (2008)

212 ***Brock N, Pohl J, Stekar J***; Studies on the urotoxicity of oxazaphosphorine cytostatics and its prevention. 2 Comparative study of the uroprotective efficacy of thiols and other sulfur compounds; Eur. J. Cancer Clin. Oncol. 17(11) 1155-1163 (1981)

213 ***Brockmann J, Maus S, Haberkorn U, Rösch F***; Darstellung verschiedener Nitrophenyl-Dithiarsinanyl-Strukturen zur Markierung rekombinanter Proteine für die Gentherapie; Jahresbericht Institut für Kernchemie, Universität Mainz (1999)

214 ***Brodkin E, Copes R, Mattman A, Kennedy J, Kling R, Yassi A***; Lead and mercury exposures: Interpretation and action; Can. Med. Assov. J. 176(1) 59-63 (2007)

215 ***Brockstedt M, Oberdisse U***; Acute childhood lead encephalopathy can be treated effectively with DMPS alone - Report of 4 cases; Meeting of the European Poison Control Centers, Oslo (1997)

216 ***Buchet JP, Lauwerys RR***; Influence of 2,3-dimercaptopropane-1-sulfonate and dimercaptosuccinic acid on the mobilization of mercury from tissues of rats pretreated with mercuric chloride, phenylmercury acetate or mercury vapors; Toxicology 54(3) 323-333 (1989)

217 ***Buchet JP, Lauwerys R***; Role of thiols in the in-vitro methylation of inorganic arsenic by rat liver cytosol; Biochem. Pharmacol. 37(16) 3149-3153 (1988)

218 ***Bulman RA***; The chemistry of chelating agents in medical sciences; IN: Structure and Bonding 67 91-141 (1987)

219 ***Burckhardt BC, Drinkuth B, Menzel C; König A, Steffgen J, Wright SH, Burckhardt G***; The renal Na^+-dependent dicarboxylate transporter, NaDC-3, translocates dimethyl- and disulfhydryl-compounds and contributes to renal heavy metal detoxificafion; J. Am. Soc. Nephrol. 13(11) 2628-2638 (2002)

220 ***Burckhardt G***; Physiology and pathophysiology of renal organic anion transporters 1 and 3 (OAT1 and OAT3); Leopoldina Symposium „Epithelial Transport of Ions Health and Disease", Halle (2003)

221 ***Burckhardt G, Wolff NA, Bahn A***; Molecular characterization of the renal organic anion transporter 1; Cell Biochem. Biophys. 36(2-3) 169-174 (2002)

221a ***Burtscher E***; Aktuelle Aussagen und Richtlinien in der modernen AK; Med. J. Appl. Kinesiology 19 5-7 (2003)

222 ***But TS***; Role of thiols in amyloidogenesis; Vestn. Akad. Med. Nauk. SSSR (8) 31-41 (1980) [Abstract]

223 ***Busam A***; Die Quecksilberausscheidung im Urin nach intravenöser DMPS-Gabe bei Frauen mit Amalgamfüllungen; Dissertation Universität Heidelberg (1999)

224 ***Butler AR, Elkins-Daukes S, Parlin D, Williams DLH***; Direct NO group transfer from S-nitrosothiols to iron centres; Chem. Commun. 7(18) 1732-1733 (2001)

225 ***Buttar R***; Transdermal delivery systems and transdermal chelation preparations; WO Patent 2005/107 723 A3 (2006)

226 ***Buttar R***; Buttar Autism Treatment Protocol - Advanced Concepts in Medicine / Center for Advanced Medicine; http://defeatautismyesterday.com/tddmpspro.pdf (2004)

227 ***Butz JA, Burritt MF***; Heavy Metals - Toxicity and Testing for Today's Labs; Clinical Laboratory News 12-14 (September 2005)

228 ***Butz S, Gerhard I, Krähe J, Waldbrenner A***; Chlorkohlenwasserstoffe (CKW) und Schwermetallbelastung bei Frauen mit Abortanamnese; Arch. Gynecol. Obstet. 254(1-4) 1294-1296 (1993)

229 ***Bystryakov VP, Lanin SN, Arzamastsev AP***; Use of dual detectors for the determination of aliphatic sulfhydryl compounds by HPLC; Pharm. Chem. J. 25(2) 136-139 (1991)

230 ***Bystryakov VP, Lanin SN***; Dependence of the retention of biologically active derivatives of aliphatic thiols on their nature and composition of mobile phase in reversed-phase HPLC; Zh. Anal. Khim. 45(10) 1955-1959 (1990) [Abstract]

231 ***Cabelkova Z, Mencik M, Cikrt M, Lukas E, Urban P, Musil J, Krombholzova L, Madlo Z, Svobodova M, Roth Z***; Mobilization of mercury from the organism by sodium 2,3-dimercaptopropane-1-sulfonate in persons exposed to mercury; Pracov. Lek. 36(5) 158-162 (1984) [Abstract]

232 ***Caisova D, Eybl V***; The effect of cadmium and chelating agents on CuZn-Superoxidedismutase activity in liver of mice; Plzen. Lek. Sborn. 56(Suppl.) 137-139 (1988)

233 ***Caisova D, Eybl V***; The influence of chelating agents on lipid peroxidation and glutathione level in liver of mice; Plzen. Lek. Sborn. 49(Suppl.) 243-246 (1985)

234 ***Calderon RL, Abernathy CO, Thomas DJ***; Consequences of acute and chronic exposure to arsenic in children; Pediatr. Ann. 33(7) 461-466 (2004)

235 ***Campbell JR, Clarkson TW, Omar MD***; The therapeutic use of 2,3-dimercaptopropane-1-sulfonate in two cases of inorganic mercury poisoning; JAMA 256(22) 3127-3130 (1986)

236 ***Canty AJ, Moors PW, Deacon GB***; Octanol/water partition coefficients as a model for assessing antidotes for methylmercury(II) poisoning and for studying mercurials with medicinal applications; J. Inorg. Biochem. 22 65-72 (1984)

237 ***Cao BJ.; Chen ZK; Chi ZQ***; Antidotal effects of sulfhydryl compounds on acute poisonings by sodium ammonium dimethyl-2-(propane-1,3-dithiosulfate) monohydrate, nereistoxin and cartap; Chung. Kuo. Yao. Li. Hsueh. Pao. 11(2) 180-184 (1990) [Abstract]

237a ***Caravati EM, Erdman AR, Christianson G, Nelson LS, Woolf AD, Booze LL, Cobaugh DJ, Chyka PA, Scharma EJ, Manoguerra AS, Troutman WG***; Elemental mercury exposure: an evidence-based consensus guideline for out-of-hospital management; Clin. Toxicol. 46(1) 1-21 (2008)

238 ***Carranza-Rosales P, Guzman-Delgado NE, Cruz-Vega DE, Balderas-Renteria I, Gandolfi AJ***; DMPS reverts morphologic and mitochondrial damage in OK cells exposed to toxic concentrations of $HgCl_2$; Cell Biol. Toxicol. 23(3) 163-186 (2007)

239 ***Carvalho MC, Franco JL, Ghizoni H, Kobus K, Nazari EM, Rocha JB, Nogueira CW, Dafre AL, Müller YM, Farina M***; Effects of 2,3-dimercapto-1-propanesulfonic acid (DMPS) on methylmercury-induced locomotor deficits and cerebellar toxicity in mice; Toxicology 239(3) 195-203 (2007)

240 ***Casa JS, Jones MM***; Mercury(II) complexes with sulfhydryl containing chelating agents; Stability constant in consistencies and their resolutions; J. Inorg. Nucl. Chem. 42 99-102 (1980)

241 ***Cascorbi IC, Knorr U, Schiele R, Petschelt A***; Ergebnisse aus dem Erlanger Untersuchungszentrum Amalgam; Dtsch. Zahnärztl. Z. 49(11) 936-939 (1994)

242 ***Catsch A, Harmuth-Hoene AE***; Pharmacology and applications of agents used in heavy metal poisoning; Pharmac. Ther. A1 1-118 (1976)

243 ***Catsch A, Harmuth-Hoene AE***; New developments in metal antidotal properties of chelating agents; Biochem. Biopharmacol. 24(17) 1557-1562 (1975)

244 ***Catsch A***; Dekorporierung radioaktiver und stabiler Metallionen-Therapeutische Grundlagen; Karl Thiemig-Verlag, München; (1968)

245 ***Catsch A***; Der Einfluß von Chelatbildnern auf das Verhalten von Blei im Organismus; Arzneim.-Forsch. 12 924-930 (1962)

246 ***Chadha IA***; Poisoning; Indian J. Anaesth. 47(5) 402-411 (2003)

247 ***Chakchir BO, Trokhimchuk VV***; Spectrophotometric determination of unithiol; Farm. Zh. Kiev (3) 42-45 (1985) [Abstract]

248 ***Chan CK, Chan YC***; Antidotes for tetramine poisoning; Hong Kong Med. J. 12(1) 87 (2006)

248a ***Chan NWC, Wang Y, Tenn CC, Weiss T, Hancock JR, Chenier CL, Lee WE, Dickinson-Laing T, Gebremedhin MG, Mah DCW***; Rational design of therapeutic and diagnostic against Botulinum Neurotoxin; DRDC Suffield TM 2006-233. Defence R&D Canada – Suffield (2006)

249 ***Chang SG, Pham E, Littlejohn D, Shi Y***; Development of a metal chelate additive for use in wet limestone systems to remove simoultaneously SO_2 and NO_x from flue gas; Annual Coal Prep., Util. Environ. Control Contract Conf., Proc. 10th National Technical information Service, Springfield, Va, P: 207-214 (1994)

250 ***Chavdarova V, Stoytchev T***; Influence of 2-mercaptopropionyl-glycine (Thiola), 2,3-dimercaptopropane-1-sulfonate and dehydrocholic acid (Decholine) on the toxicity of copper sulfate and on the distribution of copper in certain organs; Bull. Inst.Physiol. Bulg. Acad. Sci. 16 297-303 (1974)

251 ***Chen F, Zhao Q***; Improved synthesis of unithiol; Zhongguo. Yiyao. Gongye. Zazhi. 22(11) 487-488 (1991) [Abstract]

252 ***Chen WY, Wang YC, Kuo MS***; Determination of total mercury and methylmercury in human hair by graphite-furnace atomic absorption spectrophotometry using 2,3-dimercaptopropane-1-sulfonate as a complexing agent; Anal. Sci. 18(3) 255-260 (2002)

253 ***Chen ZK, Lu ZQ***; Sodium dimercaptopropane sulfonate as antidote against non-metallic pesticides; Acta Pharmacol. Sin. 25(4) 534-544 (2004)

254 ***Cherian MG, Miles EF, Clarkson TW, Cox C***; Estimation of mercury burdens in rats by chelation with dimercaptopropane sulfonate; J. Pharmacol. Exp. Ther. 245(2) 479-484 (1988)

255 ***Cherian MG***; Unpublished results (1987)

256 ***Cherian MG***; Estimation of renal burden of metals by chelation with DMPS; Plzen. Lek. Sborn 49(Suppl.) 43-46 (1985)

257 ***Cherian MG***; Chelation of cadmium without increased renal cadmium deposition; Environ. Health Perspect. 54 243-248 (1984)

258 ***Cherian MG, Onosaka S, Carson GK, Dean PA***; Biliary excretion of cadmium in rat. V Effects of structurally related mercaptans on chelation of cadmium from metallothionein; J. Toxicol. Environ. Health 9(3) 389-399 (1982)

259 ***Cherian MG***; Biliary excretion of cadmium in rat. IV Mobilization of cadmium from metallothionein by 2,3-dimercapto-propaneol; J. Toxicol. Environ. Health 6(2) 393-401 (1980)

260 ***Cherkes AI, Braver-Chernobulskaya, BS***; Unithiol-ein Antidot gegen Kobalt; Farmakol. Toksikol. 21(3) 59-63 (1958) [Deutsche Übersetzung]

261 ***Chesnokova NP, Kulyash, GY***; On the mechanism of energy dependent ion transport across biochemical membrane in botulinum toxin poisoning; Biull. Eksp. Biol. Med. 94(9) 29-31 (1982) [Abstract]

262 ***Chetty CS, Cooper A, McNeil C, Rajanna B***; The effects of cadmium in vitro on adenosine triphosphatase system and protection by thiol reagents in rat brain microsomes; Arch. Environ. Contam. Toxicol. 22(4) 456-458 (1992)

263 ***Chetverikov GN, Smirnova VV, Demidova MA***; The effect of sulfur-containing preparations on the development of immediate allergisation; Farmakol. Toksikol. 54(1) 43-46 (1991) [Abstract]

264 ***Chigaev A, Zwartz GJ, Buranda T, Edwards BS, Prossnitz ER, Sklar LA***; Conformational regulation of the α4ß1-integrin affinity by reducing agents: "inside-out" signaling is independent and additive to reduction-regulated integrin activation; J. Biol. Chem. 279(31) 32435-32443 (2004)

265 ***Chin CC***; Detoxification of antimony potassium tartrate by Na-dimercaptopropanesulfonate; Acta Physiol. Sinica 22 323-328 (1958) [Abstract]

266 ***Chisolm JJ***; BAL, EDTA, DMSA and DMPS in the treatment of lead poisoning in children; J. Toxicol. Clin. Toxicol. 30(4) 493-504 (1992)

267 ***Chisolm JJ***; Evaluation of the potential role of chelation therapy in treatment of low moderate lead exposure; Environm. Health Perspect. 89 67-74 (1990)

268 ***Chisolm JJ, Thomas DJ***; The role of DMPS and other chelating agents in the management of childhood poisoning; IN: Orphan Diseases and Orphan Drugs; IH Scheinberg, JM Walshe (Eds.); Fulbright Papers; pp.86-97 (1986)

269 ***Chisolm JJ, Thomas DJ***; Use of 2,3-dimercaptopropane-1-sulfonate in treatment of lead poisoning in children; J. Pharmacol. Exp. Ther. 235(3) 665-669 (1985)

270 ***Christen U***: Toxikologie und Vergiftungen; Pharmakurs: Allgemeine Pharmakologie und Toxikologie WS 2006/07, Klinikum der Johann-Wolfgang-Goethe-Universität Frankfurt (2007)

271 ***Chu CC, Huang CC, Ryu SJ, Wu TN***; Chronic mercury induced peripheral neuropathy; Acta Neurol. Scand. 98(6) 461-465 (1998)

272 ***Cichini GM, Petzl DH, Zeitlhofer J, Wolf C, Meisinger V, Strasser K, Schuster E, Jahn O***; Effekt von DMPS und D-Penicillamin bei inhalativer Intoxikation mit metallischem Quecksilber; Intensivmed. Notf. Med. 26(6) 303-306 (1989)

273 ***Cikrt M, Urban P***; Center for Occupational Health at the National Institute of Public Health - WHO Collaborating Center for Occupational Health; Cent. Eur. J. Publ. Health 13(3) 107-111 (2005)

274 ***Cikrt M, Nerudova J, Cabelkova Z, Frantik E***; Biological monitoring of Hg exposure using DMPS; IN: Met-Ions-Biol-Med, 4th Proc-Int-Symp, 411-413, 1996; P. Collery (Ed.), Philippe Publisher: Libbey Eurotext, Montrouge, Fr, CODEN: 64OOAC. (1996)

275 ***Cikrt M, Cabelkova Z, Lukas E, Urban P, Suckova B, Volf J, Tucek M***; Mobilization of mercury with sodium 2,3-dimercaptopropane sulfonate in dental assistants; Plzen Lek. Sborn. 62(Suppl.) 205 (1990)

276 ***Cikrt M, Lepsi P, Cabelkova Z, Jones MM, Tichy M***; Biliary excretion of metals: A model for testing an efficacy of chelating agents; Plzen Lek. Sborn. 49(Suppl.) 153-160 (1985)

277 ***Cikrt M, Lenger V***; Distribution and excretion of $^{203}Hg^{2+}$ in rats after unithiol, spironolactone and polythiol resin treatment; Toxicol. Lett. 5(1) 51-54 (1980)

278 ***Cikrt M, Tichy M***; Effect of some chelating agents on biliary excretion of mercury. 1 Excretion kinetics and distribution of mercury in the organism; J. Hyg. Epidemiol. Microbiol. Immunol. 24(3) 346-355 (1980)

279 ***Cikrt M***; The influence of unithiol and spironolactone on the biliary excretion of ^{203}Hg in rat; Arch. Toxicol. 39(3) 219-223 (1978)

280 ***Clarkson TW***; The toxicology of mercury: Crit. Rev. Clin. Lab. Sci. 34(3) 369-403 (1997)

281 ***Clarkson TW, Magos L, Cox C, Greenwood MR, Amin-Zaki L, Majeed MA, Al-Damluji SF***; Tests of efficacy of antidotes for removal of methylmercury in human poisoning during the Iraq outbreak; J. Pharmacol. Exp. Ther. 218(1) 74-83 (1981)

282 ***Cline JC***; Mercury toxicity and the use of DMPS chelation; www.karlloren.com/ultrasound/p18.htm (1998)

283 ***Cohen SM, Arnold LL, Uzvolgyi E, Cano M, St. John M, Yamamoto S, Lu X, Le XC***; Possible role of dimethylarsinous in dimethylarsinic acid-induced urothelial toxicity and regeneration in the rat; Chem. Res. Toxicol. 15(9) 1150-1157 (2002)

284 ***Connett PH, Wetterhahn KE***; In vitro reaction of the carcinogen chromate with cellular thiols and carboxylic acids; J. Am. Chem. Soc. 107(14) 4282-4288 (1985)

285 ***Connett PH, Wetterhahn KE***; Metabolism of the carcinogen chromate by cellular constituents; Structure Bonding 54 93-124 (1983)

286 ***Copeland RL***; Heavy metals and heavy metal antagonists; www.med.howard.edu/pharmacology/handouts/HEAVY%20METALS%20new.ppt (2006)

287 ***Coveny JR, Robbins MS***; Biodistribution of radiomercury in rabbits and efficacy of dimercaptopropanesulfonic acid (DMPS) and dimercaprol (BAL) to reduce tracer-level kidney burden of radiomercury in rats; Fed. Proceed. 45 (3) 440 (1986)

288 ***Cranton EM***; Testing for toxic elements and chelation mercury; Clin. Pract. Alternative Med. 2(1) 56-58 (2001)

289 ***Crinnion WJ***; Environmental medicine. III: Long-term effects of chronic low-dose mercury exposure; Altern. Med. Rev. 5(3) 209-223 (2000)

290 ***Cuellar-Lopez JA***; Natrium-2,3-Dimercaptopropane-1-Sulfonat-Behandlung bei akuten anorganischen Quecksilber-vergiftungen; Dissertation, Universität Münster (1987)

291 ***Cummings RT, Walsh CT***; Interaction of Tn501 mercuric reductase and dihydroflavin adenine dinucleotide anion with metal ions: Implications for the mechanism of mercuric reductase mediated Hg(II) reduction; Biochemistry 31(4) 1020-1030 (1992)

292 ***Cüppers HJ, Hein D, Pudill R, Schubert GE, Köbberling J***; Kaliumbichromat-Intoxikation – Klinisch-Toxikologischer Case Report; Intensivmedizin 25(7) 370 (1988)

293 ***Cutler AH***; Amalgam illness - diagnosis and treatment. What you can do better. How your doctor can help you; ISBN 0-9676168-0-8 (1999)

294 ***Dallmann P***; Welche Gefahren können durch Quecksilber entstehen? Amalgam - eine endlose Geschichte; PeDa-Eigenverlag (1995)

295 ***Dally S***; Les chelateurs; IN: FJ Baud, P Barriot and B Riou (Eds.); Les Antidotes; Masson, Paris; pp. 43-62 (1992)

296 ***Dambite GR***; Successful treatment of lead atrophy of the optic nerve with unithiol; Oftalmol. Zh. 21(5) 329-331 (1966) [Abstract]

297 ***Danilenko VS, Kotii VN***; Ionizing radiation as a possible physical factor of the effect on the biological activity of thiolic compounds; Farmakol. Toksikol. 6 106-108 (1971) [English Translation]

298 ***Dargan P, Dines A, Nash S, Dev S, Thomson J, Greene S, Jones A, Gillies M, Wood D, Black J, Collignon U, Clarke S, Burchett N***; Guideline on Antidote Availability for Accident and Emergency Departments; www.emergencymed.org.uk/ BAEM/Clinical%20Effectiveness%20Committee/downloads/Antidote_list-Intro_and_Explanation.pdf (2006)

299 ***Dargan PI, Giles L, House IM, Murphy N, Wallace CI, Jones AL, Beale R, Thomson AH***; A case of severe mercuric sulfate ingestion treated with 2,3- dimercaptopropane-1-sulfonate (DMPS) and hi-flow hemodiafiltration Crit Care 7(3) R1-6 (2003)

300 ***Dargan PI, Bailey CA, Greene SL, Murray SA, Jones AL***; A case of severe iatrogenic bismuth poisoning; J. Toxicol. Clin. Toxicol. 41(5) 738 (2003)

301 ***Dargan PI, Jones AL, O Neill S, Sinnamon DG***; A case of serious bismuth poisoning treated with 2,3-dimercaptopropane-1-sulfonate (DMPS); J. Toxicol. Clin. Toxicol. 39(5) 555 (2001)

302 ***Darte L, Oginski M, Persson RB***; ^{99m}Tc-unithiol complex, a new radiopharmaceutical for kidney scintigraphy. III Studies of labelling unithiol with ^{99m}Tc; Nuklearmedizin 18(1) 26-35 (1979)

302a ***Daschner F, Mutter J***; Sondervotum zu „Amalgam: Stellungnahme aus umweltmedizinischer Sicht“, Mitteilung der Kommission „Methoden und Qualitäts sicherung in der Umwelt medizin“ des Robert Koch-Instituts, Berlin; Bundesgesundheitsbl. Gesundheitsforsch. Gesundheitsschutz 50(11) 1432-1433 (2007)

303 ***Daunderer M***; Säuglingstod durch mütterliches Amalgam; Dt. Ärzteblatt 102(11) 764 (2005)

304 ***Daunderer M***; Handbuch der Amalgamvergiftung-Diagnostik, Therapie, Recht; Ecomed-Verlag, Landsberg (1992-1996)

305 ***Daunderer M***; Handbuch der Umweltgifte-Klinische Umwelttoxikologie für die Praxis; Ecomed-Verlag, Landsberg (1990-2007)

306 ***Daunderer M***; Metallvergiftungen-Diagnostik und Therapie; Ecomed-Verlag, Landsberg (1995)

307 ***Daunderer M***; Amalgam; Ecomed-Verlag, Landsberg (1995)

308 ***Daunderer M***; Kasuistik einer schwersten akuten Quecksilbervergiftung; Persönliche Mitteilung 1994

309 ***Daunderer M***; Toxikologische Erfahrungen am Menschen; Quecksilber in der Umwelt-Hearing zum Amalgamproblem, Niedersächsisches Umweltministerium (1991)

310 ***Daunderer M***; Amalgam-Grenzwerte gelten nur für Gesunde!; Dtsch. Z. Biol. Zahnmed. 7(1) 37-38 (1991)

311 ***Daunderer M***; Amalgamteste; Forum Prakt. Allgem. Arzt 30(2) 64-66 (1991)

312 ***Daunderer M***; Therapie der Amalgamvergiftung; Forum Prakt. Allgem. Arzt 30 47-49 (1991)

313 ***Daunderer M***; Die Amalgamvergiftung und ihre medizinische Folgen; Forum Prakt. Allgem. Arzt 30(2) 44-66 (1991)

314 ***Daunderer M***; Quecksilber-Thermometer zerbissen: Gibt es Nachwirkungen?; Ärztliche Praxis (1991)

315 ***Daunderer M***; Der amalgamvergiftete Zahnarzt; Dtsch. Zschr. F. Biol. Zahnmedizin 7(2) 70-72 (1991)

316 ***Daunderer M***; Jugendlicher starb an Amalgam; Forum Prakt. Allgem. Arzt 29(11) 294 (1990)

317 ***Daunderer M***; Amalgamteste; Forum Prakt. Allgem. Arzt 29(8) 213-214 (1990)

318 ***Daunderer M***; Kupfervergiftung; Forum Prakt. Allgem. Arzt 29(5) 142 (1990)

319 ***Daunderer M***; Schwermetallvergiftungen: Mobilisationstest weist uralte Intoxikationen nach; Forum Prakt. Allgem. Arzt 29(4) (1990)

320 ***Daunderer M, Gossweiler B, Bolt HM, Nirschl M, Till TT***; Amalgam - falscher Alarm?; Selecta 32(3-4) 118-121 (1990)

321 ***Daunderer M***; Besserung von Nerven- und Immunschäden nach Amalgamsanierung; Dtsch. Zschr. f. Biologische Zahnmedizin 6(4) 152-157 (1990)

322 Daunderer M; Amalgamversorgung aus toxikologischer Sicht; Vortrag in der Zahnklinik Süd Berlin (1990)

323 ***Daunderer M***; Therapieerfahrungen bei Quecksilber-Amalgamentgiftung; Forum Prakt. Allgem. Arzt 28(8) 262 (1989)

324 ***Daunderer M***; Mobilisationstest bei Umweltmetallvergiftungen; Forum Prakt. Allgem. Arzt 28(6) 208-209 (1989)

325 ***Daunderer M***; Quecksilbervergiftung durch Amalgam-Leitsymptom Kopfschmerzen; Forum Prakt. Allgem. Arzt 28(3) 89-91 (1989)

326 ***Daunderer M***; Antidot eliminiert Schwermetalle aus dem Körper - Durch Umweltgifte drohen Osteoporose und Polyneuropathie; Selecta 31(27-28) 1616-1617 (1989)

327 ***Daunderer M***; Amalgamfüllungen - ein Kunstfehler?; Vita. Min. Spur. 4(4) 179-182 (1989)

328 ***De Kimpe J, Cornelis R, Vanholder R***; In vitro methylation of arsenite by rabbit liver cytosol: effect of metal ions, metal chelating agents, methyltransferase inhibitors and uremic toxins; Drug Chem. Toxicol. 224(4) 613-628 (1999)

329 ***De Kimpe J, Cornelis R***; Methylation of inorganic arsenic by liver cytosol: effect of arsenic compounds, inorganic ions, chelating agents, methyltransferase inhibitors and uremic toxins; IN: 18th Mengen-Spurenelem., Arbeitstag., 100-107 (1998), M Anke (Ed.), Verlag Harald Schubert, Leipzig, Germany (1998)

330 ***De Toranzo EGD, Castro JA***; Reaction of 4-hydroxynonenal with some thiol-containing radioprotective agents or their active metabolites; Free Rad. Med. 16(7) 605-607 (1994)

331 ***Dehua G, Daxi J, Honglang X, Bin X, Yun L, Leishi L***; Sequential hemoperfusion and continuous venovenous hemofiltration in treatment of severe tetramine poisoning; Blood Purif. 24(5-6) 524-530 (2006)

332 ***Dejbod N, Townsend LS, Chapman BD, Seidler GT, Cullen WR, Mandoli DF***; Acetabularia Acetabulum: A Novel model for arsenic toxicity; 5th International Conference on Arsenic Exposure and Health Effects, San Diego (2002)

333 ***Demirhan I, Chandra A, Sarin PS, Hasselmayer O, Hofmann D, Chandra P***; Inhibition of tat-mediated HIV-1-LTR transactivation and virus replication by sulfhydryl compounds with chelating properties; Anticancer Res. 20(4) 2513-2517 (2000)

334 ***Densow D, Demirdag Y, Hädinger T, Helms E, Kay M, Klausmann C, Koch M, Oesten K, Özeker M, Rall M, Rieg T, Schwille U***; Aufbau und Ablauf der Dekontamination und Notfallversorgung Verletzter bei Zwischenfällen mit chemischen Gefahrstoffen; Zivilschutz-Forschung - Schriftenreihe der Schutzkommission beim Bundesminister des Inneren, Band 56 (2005)

335 ***Desel H***; Paradigmenwechsel bei der Giftentfernung - Evidence based medical toxicology; Toxichem. Krimtech. 74(1) 20-21 (2007)

336 ***Desel H***; Antidote - Übersichtsliste über aktuell und früher verwandte Gegenmittel; www.giz-nord.de/php/index.php?option=com_content&task=view&id=104&Itemid=85 (2007)

337 ***Diamond GL, Klotzbach JM, Stewart JR***; Complexing activity of 2,3-dimercapto-1-propanesulfonate and its disulfide auto-oxidation product in rat kidney; J. Pharmacol. Exp. Ther. 246(1) 270-274 (1988)

338 ***Dittmann V, Pribilla O***; Suizid durch intravenöse Injektion von Sublimatlösung; Z. Rechtsmed. 94(4) 301-307 (1985)

339 ***Doja A, Roberts W***; Immunizations and autism: A review of the literature; Can. J. Neurol. Sci. 33(4) 341-346(2006)

340 ***Domenico P, Salo RJ, Novick SG, Schoch PE, van Horn K, Cunha BA***; Enhancement of bismuth antibacterial activity with lipophilic thiol chelators; Antimicrob. Agents Chemother. 41(8) 1697-1703 (1997)

341 ***Domingo JL***; Developmental toxicity of metal chelating agents; Reprod. Toxicol. 12(5) 499-510 (1998)

342 ***Domingo JL***; Prevention by chelating agents of metal-induced developmental toxicity; Reprod. Toxicol. 9(2) 105-113 (1995)

343 ***Domingo J***L; Metal-induced developmental toxicity in mammals: A review; J. Toxicol. Environ. Health 42(2) 123-141 (1994)

344 ***Domingo JL, Bosque MA, Llobet JM, Corbella J***; Amelioration by BAL (2,3-dimercapto-1-propaneol) and DMPS (sodium 2,3-dimercapto-1-propanesulfonic acid) of arsenite developmental toxicity in mice; Ecotoxicol. Environ. Safety 23(3) 274-281 (1992)

345 ***Domingo JL, Ortega A, Bosque MA, Corbella J***; Evaluation of the developmental effects on mice after prenatal, or pre- and postnatal exposure to 2,3-dimercaptopropane-1-sulfonic acid (DMPS); Life Sci. 46(18) 1287-1292 (1990)

346 ***Domingo JL, Ortega A, Llobet JM, Paternain JL, Corbella J***; Comparison of the antidotal efficacy of chelating agents upon acute toxicity of strontium in mice; Plzen. Lek. Sborn. 56(Suppl.) 65-67 (1988)

347 ***Domingo JL, Llobet JM, Paternain JL, Corbella J***; Acute zinc intoxication: Comparison of the antidotal efficacy of several chelating agents; Vet. Hum. Toxicol. 30(3) 224-228 (1988)

347a ***Domres B, Becker HD***; Aufbau und Ablauf der Dekontamination und Notfallversorgung Verletzter bei Zwischenfällen mit chemischen Gefahrstoffen; ZIVILSCHUTZFORSCHUNG Neue Folge Band 56 (2003)

348 ***Donenko FV***; Unithiol effect on toxicity of some antitumor agents; Vopr. Onkol. 31(7) 101-105 (1985) [Abstract]

349 ***Donner A, Hruby K, Pirich K, Kahls P, Schwarzacher K, Meisinger V***; Dimercaptopropanesulfonate (DMPS) in treatment of acute lead poisonig; Vet. Hum. Toxicol. 29 (Suppl.2) 37 (1987)

350 ***Donner A, Meisinger V, Scholtz I, Pirich K, Hruby H***; Dimercapto-propane-sulfonic acid (DMPS) in the treatment of an acute copper and an acute chromium poisoning; Toxicol. Lett. 31(Suppl.) 154 (1986)

351 ***Donner C, Valet O, Yang Y, Baumgärtel H***; The chemisorption of 2,3-dimercapto-n-propane sulfonate at the Au<111> electrode; Z. Phys. Chem. 217(10) 1319-1330 (2003)

351a ***Donoso A, Cruces P, Camacho J, Ríos JC, Paris E, Mieres JJ***; Acute respiratory distress syndrome resulting from inhalation of powdered copper; Clin. Toxicol. 45(6) 714-716 (2007)

351b ***Doolan BR, Wojcik DP, Godfrey M, Smith L, Corish R, Moench B, Rudhall J***; The detection and reduction of mercury in humans using oral DMPS (2,3-dimercaptopropane-1-sulfonate) with support nutritionals; 4th Malaysian Conference SAAAMM (2007)

352 ***Dorfer L***; Aktuelles Amalgam-Review; Akupunktur Aurikulomedizin (2) 13-20, (3) 26-31, (4) 13-27 (1997)

353 ***Dörffer U***; Anorexia Hydragyra - ein Fallbericht aus der Praxis; Monatsschr. Kinderheilkd. 137(8) 472 (1989)

354 ***Dou Y, McHugh T, Lane WV, Rossant CJ, Loring RH***; Interactions of dithiols with p-aminophenyldichloroarsine and nicotinic acetylcholine receptors; J. Biol. Chem. 269(32) 20410-20416 (1994)

355 ***Drasch G, Boese-O'Reilly S, Illig S***; Increase of renal excretion of organo-mercury compounds like methlymercury by DMPS (2,3-Dimercapto-1-propanesulfonic acid, Dimaval); Clin. Toxicol. 45(3) 266-269 (2007)

356 ***Drasch G, Böse-O'Reilly S***; Increase of the renal excretion of 0rgano-mercury compounds like methlymercury by DMPS (2,3-Dimercapto-1-propanesulfonic acid, Dimaval ®); Mercury 2006, 8th International Conference on Mercury as a Global Pollutant (2006)

357 ***Drasch G, Böse-O'Reilly S, Maydl S, Roider G***; Scientific comment on the German human biological monitoring values (HBM values) for mercury; Int. J. Hyg. Environ. Health 205(6) 509-512 (2002)

358 ***Drasch G, Muss C***; Diagnose von Metallbelastungen (Quecksilber, Gold und Palladium) aus zahnärztlichen Werk-stoffen durch das Mobilisationsverfahren mit Dimercaptopropanesulfonsäure; www.praxis-dr-muss.de/html/diagnose_von_schwermetallbelas.html (1998)

359 ***Drasch G, Scharl K, Roider G, Schiwara HW, Zilker T, Steiner M, Schümann M***; Aussagekraft des DMPS-Test auf Quecksilber; Umweltmed Forsch. Prax. 2(1) 2-10 (1997)

360 ***Drasch G***; Aussagekraft von Quecksilberspiegeln in Blut, Urin, Haaren und Speichel; Konferenz Humantoxikolo-gische Aspekte von Amalgamzahnfüllungen, Freiburg (1997)

361 ***Drasch G, Roider G***; Zahnamalgam und Schwangerschaft; Geburtshilfe Frauenheilkd. 55(6) M63-M65 (1995)

362 ***Drasch G, Schupp I, Riedl G, Günther G***; Einfluß von Amalgamfüllungen auf die Quecksilberkonzentration im menschlichen Organismus; Dtsch. Zahnärztl. Z. 47(8) 490-496 (1992)

363 ***Drexler H, Göen T***; Interpretation von toxikologischen Daten in der Umweltmedizin; Dtsch. Med. Wochenschr. 123(25/26) 807-813 (1998)

364 ***Drexler H, Schaller KH***; The mercury concentration in breast milk resulting from amalgam fillings and dietary habits; Environ. Res. 77(2) 124-129 (1998)

365 ***Dubinina LK, Sheikkh MA, Ospanov KK, Germanova LN***; Physicochemical analysis of the interaction between zinc and cadmium ions and unithiol in aqueous solutions; Russ. J. Coord. Chem. 21(1) 21-23 (1995)

366 ***Dubinski AA, Merzalow WS, Guida PP***; Die Antiamyloidtherapie bei den Alterungskrankheiten und der Demenz; www.univer.kharkov.ua/main/medic/de/vvedenie.html (2002)

367 ***Dubinskii AA, Bondarenko IP, Iakovtsova AF, Liss ND, Postnikov AV***; Unithiol therapy of patients with secondary amyloidosis; Ter. Arkh. 52(8) 122-124 (1980) [Abstract]

368 ***Dubinskii AA, Guida PP***; Side-effects of the donator of sulfhydryl groups, unithiol; Vrach. Delo. (2) 68-71 (1979) [English Translation]

369 ***Dubinskii AA, Guida PP***; Case of Buschke's sclerodema successfully treated with unithiol; Vestn. Dermatol. Venerol. (8) 49-51 (1978) [Abstract]

370 ***Dubinskii AA, Tseraidis GS, Guida PP, Petrusenko EA, Babykina EA***; Morphological changes in the skin in scleroderma in the process of treatment with unithiol; Vrach. Delo. (10) 112-114 (1978) [Abstract]

371 ***Dubinskii AA, Abramovich-Poliakov DK, Dynnik VI, Mikailov AI***; Treatment of vibration disease using sulfhydryl group donors; Gig. Tr. Prof. Zabol. (5) 17-20 (1978) [Abstract]

372 ***Dubinskii AA, Guida PP***; Treatment of scleroderma with unithiol; Vopr. Revm. (2) 54-58 (1974) [Abstract]

373 ***Dunemann L, Begerow J;*** Möglichkeiten und Grenzen des Biomonitoring; Der Kassenarzt (46) 44-48 (1996)

374 ***Dutczak WJ, Ballatori N***; Transport of the glutathione-methylmercury complex across liver canalicular membranes on reduced glutathione carriers; J. Biol. Chem. 269(13) 9746-9751 (1994)

375 ***Dutkiewicz T, Oginski M***; Use of BAL (2,3-dimercapto-1-propaneol) and Unithiol (sodium 2,3-dimercapto-1-propanesulfonate) in the removal of mercury from living organisms; Farm. Pol. 24(4) 283-287 (1968) [Abstract]

376 ***Dutkiewicz T, Oginski M***; Dislokation und Ausscheidung des Quecksilbers bei den Ratten nach Applikation von Unithiol; Int. Arch. Arbeitsmed. 23(3) 197-201 (1967)

377 ***Echeverria D, Aposhian HV, Woods JS, Heyer NJ, Aposhian MM, Bittner AC, Mahurin RK, Cianciola M***; Neurobehavioral effects from exposure to dental amalgam Hg degree: New distinctions between recent exposure and Hg body burden; FASEB J. 12(11) 971-980 (1998)

378 ***Edwards BS, Southon EA, Curry MS, Salazar F, Gale JM, Robinson MK, Graf LH, Born JL***; Oxidant inhibition of αLß2 integrin adhesion: evidence for coordinate effects on conformation and cytoskeleton linkage; J. Leukoc. Biol. 63(2) 190-202 (1998)

379 ***Efimov AS,Tkach SN***; Unithiol in the treatment of diabetic polyneuropathies; Sov. Med. (9) 59-63 (1981) [Abstract]

380 ***Efimova AN, Vorobev AM, Khodyreva MA, Izergina AG***; Efficiency of skin decontamination from polonium-210; Gig. Sanit. 3(5) 114-116 (1968) [Abstract]

380a ***Eis D, Wolf U***; Amalgam: Stellungnahme aus umweltmedizinischer Sicht; Bundesgesundheitsbl. Gesundheitsforsch. Gesundheitsschutz 50(10) 1304-1307 (2007)

381 ***Eis D***; Methoden und Qualitätssicherung in der Umweltmedizin - Einrichtung einer Umweltmedizin-Kommission am RKI; Bundesgesundheitsbl. Gesundheitsforsch. Gesundheitsschutz 43(5) 336-342 (2000)

382 ***Eis D, Ewers U, Schweinsberg F, Wilhelm M***; Pro and contra DMPS-Mobilisations-Test; Umweltmed. Forsch. Prax. 2(3) 161-164 (1997)

383 ***Eldeib MMR, Dove CR, Parker CD, Veum TL, Zinn GM, White AA***; Reversal of the biological activity of Escherichia coli heat-stable enterotoxin by disulfide-reducing agents; Infect. Immun. 51(1) 24-30 (1986)

383a ***Eliaz I, Weil E, Wilk B***; Integrative medicine and the role of modified citrus pectin/alginates in heavy metal chelation and detoxification – Five case reports; Forsch. Komplementärmed. 14(6) 358-364 (2007)

384 ***Elliott DJS, Neale EJ, Dunham JP, Munsey TS,Hunter M, Sivaprasadarao A***; Molecular mechanism of voltage sensor movements in a potassium channel; EMBO J. 23(24) 4717–4726 (2004)

385 ***Ellis JP, Camper ND***; In vitro cultured cocklebur (Xanthium strumarium L.) responses to dimercaptopropanesulfonic acid and monosodium methanearsonate; J. Plant. Growth. Regul. 14(1) 9-13 (1995)

385a ***Ellithorpe R, Mazur P, Gum G, Button G, Le J, Pfadenhauer EH, Settineri RA, Nicolson G***; Comparison of the absorption, brain and prostate distribution, and elimination of CaNa2 EDTA of rectal chelation suppositories to intravenous administration; J. Am. Nutraceut. Assoc. 10(2) 38-44 (2007)

386 ***Elsenhans B, Hunder G, Schümann K***; Stoichiometry between Hg^{2+} and thiol antidota in restoring Hg^{2+} - inhibited lactase activity: 1:1 Complexes are the most protective ones; Naunyn Schmiedebergs Archives of Pharmacology 357 (4 Suppl.). R130 (1998)

386a ***Enderle G, Seidel HJ***; Arbeitsmedizin; Elsevier GmbH Deutschland, S.424 (2004)

387 ***Erleskova EV***; Pecularities of distribution and excretion of polonium in animals subjected to unithiol administration; Med. Radiol. 4(8) 54-60 (1959) [Abstract]

388 ***Ershov YA, Pleteneva TV, Merisov YI, Vanivskaya EN***; Complexation of copper(II)ions by 2,3-dimercaptopropane-sulfonate; Koord. Khim. 15(9) 1240-1245 (1989) [Abstract]

389 ***Erstenyuk HM, Gubsky YI***; Influence of Unithiol on red blood and oxyhemoglobin level under cadmium intoxication; Sovrem. Probl. Toksikol. (2) 30-32 (2004) [Abstract]

390 ***Erstenyuk HM***; Oxidation modifications of proteins and lipids during cadmiosis and their correction by unithiol; Modern Problems of Toxicology (4) (2003) [Abstract]

391 ***Essex DW, Li M***; Redox control of platelet aggregation; Biochemistry 42(1) 129-136 (2003)

392 ***Ewan KBR, Pamphlett R***; Increased inorganic mercury in spinal motor neurons following chelating agents; NeuroToxicology 7(2) 343-349 (1996)

393 ***Ewers U***; Human Exposure to Mercury - Effect of Amalgam Fillings; 3. European Meeting of Environmental Hygiene, Düsseldorf (1991)

394 ***Eybl V, Koutensky J, Sykora J, Mertl F***; Interaction of chelating agents, ferric dextran and zinc with indium in mice; Acta Pharmacol. Toxicol. 59(Suppl.7) 475-477 (1986)

395 ***Eybl V, Koutensky J, Koutenska M, Sykora J, Melsova H, Majerova S, Mertl F***; The interaction of CaDTPA, DMPS and DMSA with zinc, cadmium, mercury and cobalt in acute experiments in mice; Plzen. Lek. Sborn. 49(Suppl.) 53-57 (1985)

396 ***Eybl V, Sykora J, Drobnik J, Mertl F, Svec F, Benes M, Stamberg J, Peska J***; Influence of metal-complexing polymers on the retention and distribution of cadmium and mercury in mice; Plzen. Lek. Sborn 49(Suppl.) 169-172 (1985)

397 ***Eybl V, Sykora J, Koutensky J, Caisova D, Schwartz A, Mertl F;*** Interaction of chelating agents with cadmium in mice and rats; Environ. Health Perspect. 54 267-273 (1984)

398 ***Eybl V, Sykora J. Koutensky J. Svacinova J, Mertl F***; The influence of the combination of sodium 2,3-dimercaptopropane-1-sulfonate and thiomestrone on the retention and distribution of mercury; 7th Congress of the Polish Pharmacological Society, Poznan 1980

399 ***Eyer F, Felgenhauer N, Pfab R, Drasch G, Zilker T***; Neither DMPS nor DMSA is effective in quantitative elimination of elemental mercury after intentional i.v. injection; Clin. Toxicol. 44(4) 395-397 (2006)

400 ***Eyer F, Felgenhauer N, Pfab R, Kreymann B, Zilker T***; Extracorporeal albumin dialysis: An option in treating fulminant hepatic failure due to intoxication; J. Toxicol. Clin. Toxicol. 40(3) 285 (2002)

401 ***Fabricius W, Heinemeyer G, Keyser D (Eds.)***; Allgemeine Maßnahmen bei Vergiftungen und Drogennotfällen; Max von Pettenkofer-Institut des Bundesgesundheitsamtes (1991)

402 ***Falnoga I, Kobal AB, Stibilj V, Horvat M***; Selenoprotein P in subjects exposed to mercury and other stress situations such as physical load or metal chelation treatment, Biol. Trace Elem. Res. 89(1) 25-33 (2002)

403 ***Federova TA***; Effect of unithiol on toxic effect of cardic glycosides; Farmakol. Toksikol. 30(3) 315-318 (1967) [Abstract]

404 ***Felgenhauer N, Pfab R, Stier A, Schramel P, Zilker T***; Acute potassium dichromate poisoning treated with extracorporeal limination procedures and liver transplantation; XXI Int. Congress EAPCCI, Barcelona (2001)

405 ***Felgenhauer N, Zilker T***; Akute Vergiftungen - Rasch reagieren; Der Hausarzt 13(1) 30-33 (2001)

406 ***Felgenhauer N, Zilker T***: Einsatz von Chelatbildnern in der Klinischen Toxikologie und Umweltmedizin; Umweltmed. Forsch. Prax. 5(1) 5-10 (2000)

407 ***Ferguson CL, Cantilena LR***; Mercury clearance from human plasma during in vitro dialysis: Screening systems for chelating agents; J. Toxicol. Clin. Toxicol. 30(3) 423-441 (1992)

408 ***Fesenko IT***; The effect of unithiol on the body's excretion of copper in the treatment of mercury poisoning; Vrach. Delo. 12 99-101 (1969) [Abstract]

409 ***Fichtl B, Kreppel H, Reichl FX, Forth W***; Lack of effectiveness of D-penicillamine in experimental arsenic poisoning; Plzen. Lek. Sborn. 56(Suppl) 85-87 (1988)

410 ***Firsov NN, Shimanko II***; Possibility of use of unithiol dialysis in treatment of acute poisonings with thiol poisons; Farmakol. Toksikol. 32(6) 742-744 (1969) [Abstract]

411 ***Fischer AB, Heuchert A, Herr C, Harpel S, Eikmann T***; Metal concentrations in blood and urine following treatment with the chelating agent DMPS; IN: Metals Essentiality, Toxicity and Selectivity, AB Fischer, R Prakash (Eds.), ABD Publishers, Jaipur, India, 200-208 (2005)

412 ***Fischer AB, Hess C, Neubauer T, Eikmann T***; Testing of chelating agents and vitamins against lead toxicity using mammalian cell cultures; Analyst 123(1) 55-58 (1998)

413 ***Fischer AB, Neubauer T***; The effect of chelating agents on cellular uptake, lead toxicity and mobilization of lead from preloaded cells - in vitro studies with mammalian cell cultures; Plzen. Lek. Sborn. 71(Suppl.) 87-88 (1996)

414 ***Fischer AB***; Studies of cadmium chelator efficacy using mammalian cell cultures; Analyst 120(3) 975-978 (1995)

415 ***Fischer AB, Falk A, Seibold G***; Testing of chelator efficacy using mammalian cell cultures; Plzen. Lek. Sborn. 62(Suppl.) 35-36 (1990)

416 ***Fischer AB, Seibold G***; Antidotal effects of chelating agents against cadmium induced cytotoxicity tested in vitro; IN: Heavy Met. Environ., T Lekkas (Ed.), CEP Consult, Edinburgh; pp.110-112 (1985)

417 ***Fisher P, House I, Belon P, Turner P***; The influence of the homoeopathic remedy plumbum metallicum on the excretion kinetics of lead in rats; Hum. Toxicol. 6(4) 321-324 (1987)

418 ***Flanagan RJ, Jones AL***; Antidotes; Taylor & Francis, London, New York (2001)

419 ***Flora SJS, Flora G, Saxena G, Mishra M***; Arsenic and lead induced free radical generation and their reversibility following chelation; Cell. Mol. Biol. 53(1) 26-47 (2007)

420 ***Flora SJS, Bhadauria S, Kannan GM, Singh N***; Arsenic induced oxidative stress and the role of antioxidant supplementation during chelation: A review; J. Environmental Biol. 28(2 Suppl) 333-347 (2007)

421 ***Flora SJ, Bhadauria S, Pant SC, Dhaked RK***; Arsenic induced blood and brain oxidative stress and its response to some thiol chelators in rats; Life Sci. 77(18) 2324-21092 (2005)

422 ***Flora SJS, Tripathi N***; Treatment of arsenic poisoning: An update; Indian J. Pharm. 30(4) 209-217 (1998)

423 ***Flora SJS, Kumar P***; Biochemical and immunotoxicological alterations following repeated gallium arsenide exposure and their recoveries by meso-2,3-dimercaptosucciic acid and 2,3-dimercaptopropane-1-sulfonate administration in rats; Environ. Toxicol. Pharmacol. 2(4) 315-320 (1996)

424 ***Flora SJS, Seth PK, Kannan GM, Pant BP, Malhotra PR***; Combined therapeutic efficacy of few thiols with calcium disodium versenate during acute lead intoxication in mice; Trace Elem. Electrolytes 13(1) 33-36 (1996)

425 ***Flora SJS, Mathur S; Mathur R***; Effects of meso-2,3-dimercaptosuccinic acid or 2,3-dimercaptopropane-1-sulfonate on beryllium-induced biochemical alterations and metal concentration in male rats; Toxicology 95(1-3) 167-175 (1995)

426 ***Flora SJS, Dube SN, Arora U, Kannan GM, Shukla MK, Malhotra PR***; Therapeutic potential of meso 2,3-dimercaptosuccinic acid or 2,3-dimercaptopropane-1-sulfonate in chronic arsenic intoxication in rats; Biometals 8(2) 111-116 (1995)

427 ***Flora SJS, Tandon SK***; Adjuvants for therapeutic chelating drugs in lead intoxication; Trace Elem. Electrolytes 12(3) 131-140 (1995)

428 ***Flora SJS, Pant SC, Sachan AS***; Mobilization and distribution of lead over course of combined treatment with thiamine and meso 2,3-dimercaptosuccinic acid or 2,3-dimercaptopropane sulfonate in rats; Clin. Chem. Enzym. Commun. 6(4) 207-216 (1994)

429 ***Flora SJS, Kumar P***; Biochemical and immunotoxicological evaluation of metal chelating drugs in rats; Drug Invest. 5(5) 269-273 (1993)

430 ***Flora SJS***; Influence of simultaneous supplementation of zinc and copper during chelation of lead in rats; Hum. Exp. Toxicol. 10(5) 331-336 (1991)

431 ***Flora SJS, Tandon SK***; Chelation in metal intoxication. XV Influence of dimercaptopropane sulfonate (DMPS) on lead poisoned rats with normal or damaged kidneys; Ind. Health 23(1) 17-24 (1985)

432 ***Fluri F, Lyrer P, Gratwohl A, Raetz-Bravo AE, Steck AJ***; Lead poisoning from the beauty case: Neurologic manifestations in an elderly woman; Neurology 69(9) 929-930 (2007)

433 ***Foderman VM***; The experimental grounds of antidotal inhalation prophylaxis of micromercurialism; Zh. Ushn. Nos. Gorl. Bolezn. (3) 50-54 (1977) [Abstract]

434 ***Fombonne E, Zakarian R, Bennett A, Meng L, McLean-Heywood D***; Pervasive developmental disorders in Montreal, Quebec, Canada: Prevalence and links with immunizations; Pediatrics 118(1) e139-e150 (2006)

435 ***Forth W***; Toxikologie von Quecksilberverbindungen; IN: Quecksilber in der Umwelt-Hearing zur Amalgam-problematik; Niedersächsisches Umweltministerium (1991)

436 ***Forth W***; Chelatbildner: Pharmakologie, Toxikologie und therapeutsiche Anwendung; Dt. Ärtzeblatt 84(48) 2306-2307 (1987)

437 ***Forth W, Rummel W***; Gastrointestinal absorption of heavy metals; IEPT Sect 39B, Pharmacology of intestinal absorption-gastrointestinal absorption of drugs; W Forth, W.Rummel (Eds.); Pergamon Press, Oxford Vol.II; pp.599-746 (1975)

438 ***Francesconi KA, Kuehnelt D***; Determination of arsenic species: A critical review of methods and applications, 2000–2003; Analyst 129(5) 373-395 (2004)

439 ***Frenet M, Vincent F, Boiteau HL***; Dissolution In Vitro des Oxydes Metalliques dans le Plasma Humain et Fixation Des Metaux sur les Proteines Plasmatiques-Influence des Chelateurs; Toxicol. Eur. Res. 5(3) 131-139 (1983)

440 ***Friese KH***; Homöopathie in der HNO-Heilkunde; Hippokrates-Verlag, Stuttgart; S.115-120 (1998)

441 ***Friese KH***; Alternative Behandlungsverfahren in der HNO-Heilkunde 45(8) 593-607 (1997)

442 ***Friese KH***; Homöopathische Behandlung der Amalgamvergiftung; Erfahrungsheilkunde (4) 251-253 (1996)

443 ***Friese KH***; Amalgamvergiftung-möglicher Zusammenhang mit angeborener Schwerhörigkeit; Der Naturarzt 135(8) 13-15 (1995)

444 ***Friese KH***; Polemik und Wirklichkeit; Allgemeine Homöopathische Zeitschrift 239(6) 225-233 (1994)

445 ***Friese KH***; Können Amalgamplomben angeborene Innenohrschäden verursachen?; Therapeutikon 7(11) 492-496 (1993)

446 ***Friese KH***; Amalgam-Problem für Ärzte und Zahnärzte; Panta 3(3) 63-68 (1992)

447 ***Friese KH***; Amalgam-Chronische Vergiftung durch Amalgam-Zahnplomben; Mabuse 77 58-61 (1992)

448 ***Friese KH***; Gift im Mund - Ratschläge für die Praxis bei Amalgambelastung; Natura Med. 7(4) 295-306 (1992)

449 ***Gabard B***; Removal of internally deposited gold by 2,3-dimercaptopropane sodium sulfonate (Dimaval); Br. J. Pharmacol. 68(4) 607-610 (1980)

450 ***Gabard B, Walser R***; Note on the metabolism of the mercury chelating agent sodium 2,3-dimercaptopropane-1-sulfonate; J. Toxicol. Environ. Health 5(4) 759-764 (1979)

451 ***Gabard B, Planas-Bohne F, Regula G***; The excretion of trace elements in rat urine after treatment with 2,3-dimercaptopropane sodium sulfonate; Toxicology 12(3) 281-284 (1979)

452 ***Gabard B***; Distribution and excretion of the mercury chelating agent sodium 2,3-dimercaptopropane-1-sulfonate in the rat; Arch. Toxicol. 39(4) 289-298 (1978)

453 ***Gabard B***; The excretion and distribution of inorganic mercury in the rat as influenced by several chelating agents; Arch. Toxicol. 35(1) 15-24 (1976)

454 ***Gabard B***; Improvement of oral chelation treatment of methyl mercury poisoning in rats; Acta Pharmacol. 39(2) 250-255 (1976)

455 ***Gabard B***; Treatment of methylmercury poisoning in the rat with sodium 2,3-dimercaptopropane-1-sulfonate: influence of dose and mode of administration; Toxicol. Appl. Pharmacol. 38(2) 415-424 (1976)

456 ***Gaber W***; Bio/chemical - terrorism - Threats, responses and impact; www.eagosh.com/articlesandusefulinformations/bioterrorism/gaber/gitverlagnov01.pdf (2001)

457 ***Gabor S, Botoc M, Kovats A***; Effect of DMPS and DMSA on lead-induced lipid peroxidation in rat liver and kidney; Plzen. Lek. Sborn. 56(Suppl.) 133-136 (1988)

458 ***Gailer J, Lindner W***; On-column formation of arsenic-glutathione species detected by size- exclusion chromatography in conjunction with arsenic-specific detectors; J. Chromatogr. B Biomed. Sci. Appl. 716(1-2) 83-93 (1998)

459 ***Gale GR, Smith AB, Jones MM, Singh PK***; Meso-2,3-dimercaptosuccinic acid monoalkyl esters: effects on mercury levels in mice; Toxicology 81(1) 49-56 (1993)

460 ***Ganzer C, Gerhard I***; Amalgamfüllungen und Dentallegierungen als Auslöser oraler Beschwerden? Die Bestimmung von Metallkonzentrationen in Speichel und Urin von Frauen; Umwelt-Medizin-Gesellschaft 17(1) 57-67 (2004)

461 ***Gao Y***; Glycopeptide antibiotics and development of inhibitors to overcome vancomycin resistance; Nat. Prod. Rep. 19(1) 100-107 (2002)

462 ***Garifzyanov AR, Toropova VF, Budnikov GK, Gainutdinova DF***; New indicator reactions involving sulfur-containing organic compounds for the kinetic determination of selenium; J. Anal. Chem. 56(5) 485-488 (2001)

463 ***Garza-Ocanas L, Torres-Alanis O, Pineyro-Lopez A***; Urinary mercury in twelve cases of cutaneous mercurous chloride (calomel) exposure: Effect of sodium 2,3-dimercaptopropane-1- sulfonate (DMPS) therapy; J. Toxicol. Clin. Toxicol 35(6) 653-655 (1997)

464 ***Gebel T***; Genotoxicity of arsenical compounds; Int. J. Hyg. Environ. Health 203(3) 249-262 (2001)

465 ***Gebel T, Dunkelberg H***; Einfluß des Kaugummikonsums sowie einer dentalen Nachbarschaft von Amalgamfüllungen zu metallischen Restaurationen anderer Art auf den Quecksilberuringehalt; Zentralbl. Hyg. Umweltmed. 199(1) 69-75 (1996)

466 ***Gebhardt M, Welker D, Knopf B***; Gesundheitliche Risiken von Amalgamfüllungen aus dermatologischer und zahnärztlicher Sicht; Z. Dermatologie 181(1) 6-15 (1995)

467 ***Geier DA, Geier MR***; A case series of children with apparent mercury toxic encephalopathies manifesting with clinical symptoms of regressive autistic disorders; J. Toxicol. Environ. Health A 70(10) 837-851(2007)

468 ***Georgadze II, Chigogidze NS, Topuriia NV, Khasenova ZK, Bukhnikashvili I***L; Stabilization of antiviral activity of porcine leukocytic interferon; Vopr. Virusol. 34 (6) 720 - 723 (1989) [Abstract]

469 ***George GN, Prince RC, Gailer J, Buttigieg GA, Denton MB, Harris HH, Pickering IJ***; Mercury Binding to the Chelation Therapy Agents DMSA and DMPS, and the Rational Design of Custom Chelators for Mercury; Chem. Res. Toxicol. 17(8) 999-1006 (2004)

470 ***Gerhard I, Waibel S, Daniel V, Runnebaum B***; Impact of heavy metals on hormonal and immunological factors in women with repeated miscarriages; Hum. Reprod. Update 4(3) 301-309 (1998)

471 ***Gerhard I, Monga B, Waldbrenner A, Runnebaum B***; Heavy metals and fertility; J. Toxicol. Environ. Health 54(8) 593-611 (1998)

472 ***Gerhard I, Frick A, Monga B***; Diagnostik der chronischen Quecksilberbelastung; Clin. Lab. 43(7+8) 637-647 (1997)

473 ***Gerhard I, Kühn A***; Fertilitätsstörungen durch Quecksilber und andere Metalle; IN: NATUM Naturheilkunde und Umweltmedizin in der Frauenheilkunde, W Behrendt, I Gerhard (Eds.) Hippokrates Verlag, Stuttgart, 57-65 (1996)

474 ***Gerhard I, Monga B, Runnebaum B***; Endometriose und Umwelt; Der Frauenarzt 36(2) 215-219 (1995)

475 ***Gerhard I***; Amalgam aus gynäkologischer Sicht; Der Frauenarzt 36(6) 627-628 (1995)

476 ***Gerhard I, Runnebaum B***; Umweltbelastungen und Infertilität; IN: Gynäkologische Endokrinologie und Fortpflanzungsmedizin, B Runnebaum, T Rabe (Eds.), Springer Verlag Berlin; S. 209-251 (1994)

477 ***Gerhard I***; Ganzheitliche Diagnostik und Therapie bei Infertilität; Erfahrungsheilkunde 42(3) 100-106 (1993)

478 ***Gerhard I***; Unfruchtbarkeit bei Frauen durch Umweltgifte; IN: Prävention, Diagnose und Therapie von Umwelterkrankungen, JD Kruse-Jarres (Ed.), pp. 51-68)(1993)

479 ***Gerhard I***; Reproductive risks of heavy metals and pesticides in women; IN: Reproductive Toxicology, M. Richardson (Ed.), VCH Weinheim, 167-183 (1993)

480 ***Gerhard I, Waldbrenner P, Thuro H, Runnebaum B***; Diagnostik von Schwermetallbelastungen mit dem peroralen DMPS-Test und dem Kaugummitest; Klin. Lab. 39(9) 404-411 (1992)

481 ***Gerhard I, Runnebaum B***; Schadstoffe und Fertilitätsstörungen. Schwermetalle und Mineralstoffe; Geburtshilfe Frauenheilkd. 52(7) 383-396 (1992)

482 ***Gersl V, Hrdina R, Vavrova J, Holeckova M, Palicka V, Voglova J, Mazurova Y, Bajgar J***; Effects of repeated administration of dithiol chelating agent-sodium 2,3-dimercapto-1-propanesulfonate (DMPS) on biochemical and haematological parameters in rabbits; Acta Med. (Hradec Kralove) 40(1) 3-8 (1997)

483 ***Gerz W, Schlett S***; Ganzheitliche Therapiemöglichkeiten bei Schwermetallbelastung am Beispiel des Quecksilbers/Amalgam; IN: Anregungen aus der Nutritionalen Medizin; Centropa Pharma Vertriebs eG (Ed.); München (1993)

484 ***Gesheva M, Stankova E, Hubenova A, Mechkarska B***; Acute poisoning with arsenic – A case report; Clin. Toxicol. 45(4) 363 (2007)

485 ***Giganova T, Stepanov K, Diachuk G, Vishnevetskaya T, Afanasiev V***; Voluntary ethanol intake following ethanol deprivation rats: Effect of calcium channel blockers and unithiol; Alcoholism Clinical Experimental Research 22(3 Abstr. Suppl) 177a (1998)

486 ***Glavinskaia TA, Grube SB, Pavlova LT, Shutov AN***; Complexons in the treatment of lupus erythematosus; Dermatol. Venerol. (12) 24-28 (1980) [Abstract]

487 ***Glukharev AG***; Effect of unithiol on the functional capacity of the kidney; Farmakol. Toksikol. 28(1) 87-89 (1965) [Abstract]

488 ***Godfrey ME, Wojcik DP, Krone CA***; Apolipoprotein E genotyping as a potential biomarker for mercury neurotoxicity; J. Alzheimers Dis. 5(3) 189-195 (2003)

489 ***Godfrey M, Campbell N***; Confirmation of mercury retention and toxicity using 2,3-dimercapto-1-propane-sulfonic acid sodium salt (DMPS); J. Adv. Med. 7(1) 19-30 (1994)

490 ***Godfrey M, Campbell N***; Investigation of 2,3-dimercapto-1-propane-sulfonic acid, Na salt (DMPS) as a diagnostic test to confirm chronic accumulation of mercury; IN: Trace Elements: Roles, Risks Remedies, Proc NZ Trace Elem. Group Conf., AG Research, Palmerston North NZ, P:161-165 (1992)

491 ***Goebel HH, Schmidt PF, Bohl J, Tettenborn B, Kramer G, Gutmann L***; Polyneuropathy due to acute arsenic intoxication: biopsy studies; J. Neuropathol. Exp. Neurol. 49(2) 137-149 (1990)

492 ***Golbs S, Fuchs V, Pfüller U, Ebert E, Pfeifer D***; Beeinflussung des Spurenelementhaushaltes der Ratte durch das Schwermetallantidot "Unithiol" (Natrium-2,3-dimercaptopropanesulfonat); Arch. Exp. Veterinärmed. 34(3) 373-381 (1980)

493 ***Goldman LR, Shannon MW, Balk SJ, Gitterman BA, Miller MD, Shea KM, Weil WB***; Technical report: Mercury in the environment: Implications for pediatricians; Pediatrics 108(1) 197-205 (2001)

494 ***Golota LG***; Therapeutic and antidotal properties of Unithiol; Farm. Zh. 1 18-22 (1980) [English Translation]

495 ***Golota LG***; Effect of unithiol on the toxicity of cardiac glycosides; Vrach. Delo. 3 41-42 (1972) [Abstract]

496 ***Golota LG***; Comparative effect of Unithiol and sodium 2-(ß,γ-dimercaptopropoxy) ethanesulfonate on the bile-secreting function of the liver; Farmakol. Toksikol. (4) 80-83 (1968) [Abstract]

497 ***Gombos B, Merva M, Sekula F, Koci M***; Phenylmercury and its mobilization in the organism by a metal complex-forming substance: 2,3-dimercapto-1-propane sodium sulfonate; Med. Lav. 87 (4) 297 - 304 (1996)

498 ***Gomez M, Sanchez DJ, Colomina MT, Domingo JL, Corbella J***; Evaluation of the protective activity of 2,3-dimercaptopropaneol and sodium 2,3-dimercaptopropane-1-sulfonate on methylmercury-induced developmental toxicity in mice; Arch. Environ. Contam. Toxicol. 26(1) 64-68 (1994)

499 ***Goncharenko LE, Kozyreva OI***; The results of histological study of the brain in rabbits poisoned by stibine and treated with Unithiol; Farmakol. Toksikol. 35(5) 173-178 (1970) [Abstract]

500 ***Gong Z, Jiang G, Cullen WR, Aposhian HV, Le XC***; Determination of arsenic metabolic complex excreted in human urine after administration of sodium 2,3-dimercapto-1-propane sulfonate; Chem. Res. Toxicol. 15(10) 1318-1323 (2002)

501 ***Gonzalez-Ramirez D, Zuniga-Charles M, Narro-Juarez A, Molina-Recio Y, Hurlbut K, Dart RC, Aposhian HV***; DMPS (2,3-dimercaptopropane-1-sulfonate, Dimaval) decreases the body burden of mercury in humans exposed to mercurous chloride; J. Pharmacol. Experiment. Ther. 287(1) 8-12 (1998)

502 ***Gonzalez-Ramirez D, Maiorino RM, Zuniga-Charles M, Xu Z, Hurlbut KM, Junco-Munoz P, Aposhian MM, Dart RC, Diaz-Gama JH, Echeverria D, Woods JS, Aposhian HV;*** Sodium 2,3-dimercaptopropane-1-sulfonate challenge test for mercury in humans. II Urinary mercury, porphyrins and neurobehavioral changes of dental workers in Monterrey, Mexico; J. Pharmacol. Exp. Ther. 272(1) 264-274 (1995)

503 ***Gopinath E, Kaaret TW, Bruice TC;*** Mechanism of mercury(II)reductase and influence of ligation on the reduction of mercury(II) by a water soluble 1,5-dihydroflavin; Proc. Natl. Acad. Sci. USA 86(9) 3041-3044 (1989)

504 ***Gopinath E, Bruice TC***; Assistance of protodemercuration by bis-thiol ligation and nucleophilic catalysis: A model study which relates to the organomercurial lyase reaction; J. Am. Chem. Soc. 109 7903-7905 (1987)

505 ***Gorshkov ES, Shapovalov SN, Sokolovskii VV, Troshichev OA***; Gravitational cause of fluctuations of the rate of oxidation of unithiol by nitrite ion; Biofizika 45(4) 631-635 (2000) [Abstract]

506 ***Goyer RA, Cherian MG, Jones MM, Reigart JR***; Role of chelating agents for prevention, intervention, and treatment of exposures to toxic metals; Environ. Health Perspect. 103(11) 1048-1052 (1995)

507 **Gracia RC, Snodgrass WR**; Lead toxicity and chelation therapy; Am. J. Health Syst. Pharm. 64(1) 45-63 (2007)

508 ***Grachev SA, Sverdlov AG, Nikanorova NG, Timoshenko SI***; Effect of unithiol on cystamine toxicity in dogs; Radiats. Biol. Radioecol. 39(2-3) 261-263 (1999) [Abstract]

509 ***Grachev SA, Sverdlov AG, Nikanorova NG, Timoshenko SI***; Increased efficacy of radiation protection against fission neutrons using unithiol; Radiats. Biol. Radioecol. 39(2-3) 258-260 (1999) [Abstract]

510 ***Grachev SA, Sverdlov AG***; Chemical protection against X-ray, gamma, and neutron Radiation; AFRRI Contract Report 97-1: Published by Armed Forces Radiobiology Research Institute, USA (1997)

511 ***Grachev SA, Sverdlov AG, Nikanorova NG, Bolshakova OI, Koroleva IK***; Decrease of toxic effects of aminothiol radiation-protective agents and increase of chemical protection action against ionizing radiation by the use of unithiol; Radiat. Biol. Radioecol. 34(3) 424-429 (1994) [Abstract]

512 ***Graeme KA, Pollack CV***; Heavy metal toxicity, part II: Lead and metal fume fever; J. Emerg. Med. 16(2) 171-177 (1998)

513 ***Graeme KA, Pollack CV***; Heavy metal toxicity; part I: Arsenic and mercury; J. Emerg. Med. 16(1) 45-56 (1998)

514 ***Graevskii EY, Konstantinova MM***; The mechanism of the protective action of dithiols against radiation; Dokl. Akad. Nauk. 136 1219-1222 (1961) [Abstract]

515 ***Grandjean P, Guldager B, Larsen IB, Jorgensen PJ, Holmstrup P***; Placebo response in environmental disease. Chelation therapy of patients with symptoms attributed to amalgam fillings; J. Occup. Environ. Med. 39(8) 707-714 (1997)

516 ***Gray BH, Porvaznik M, Flemming C, Lee LH***; Tri-n-Butyltin: a membrane toxicant; Toxicology 47(1-2) 35-54 (1987)

517 ***Gray BH, Porvaznik M, Lee LH, Flemming C***; Inhibition of tributyltin mediated hemolysis by mercapto compounds; J. Appl. Toxicol. 6(5) 363-370 (1986)

518 ***Graziano C, Hamilton RJ***; Toxicity: Arsenic; http://www.emedicine.com/med/topic168.htm: eMedicine Journal 3(4) (2002)

519 ***Graziano JH***; Role of 2,3-dimercaptosuccinic acid in the treatment of heavy metal poisoning; Med. Toxicol. 1(3) 155-162 (1986)

520 ***Green TA***; Gold electrodeposition for microelectronic, optoelectronic and microsystem applications; Gold Bulletin 40(2) 105-114 (2007)

521 ***Greenwalt DE, Tandon NN***; Platelet shape change and Ca^{2+} mobilization induced by collagen, but not thrombin or ADP, are inhibited by phenylarsine oxide; Br. J. Haematol. 88(4) 830-838 (1994)

522 ***Gregus Z, Nemeti B***; Purine nucleoside phosphorylase as a cytosolic arsenate reductase; Toxicol. Sci. 70(1) 13-19 (2002)

523 ***Grinshtein YI, Grinshtein AB, Danilova TD, Kalyuzhnyi IA***; Acute poisoning by spirits of thallium; Klin. Med. 66(3) 118-120 (1988) [Abstract]

524 ***Gritsenko VG***; Biochemical changes of blood in experimental poisoning with copper salts and the treatment with unithiol and dicaptol; Nauk. Pratsi. Vet. Fak. Lvovsk. Zoovet. Inst. 12 27-30 (1963) [Abstract]

525 ***Gromov LA, Sereda PI, Syrovatskaya LP, Ovinova GV, Filonenko MA***; Free radical mechanisms of memory disturbances of toxic genesis and experimental therapy of this abnormality; Patol. Fiziol. Eksp. Ter. (4) 24-26 (1993) [Abstract]

526 ***Groszkowski S, Ochoki Z***; Determination of drugs containing mercapto-groups with N-bromsuccinimide; Farmacia Polska 36 (5) 273-275 (1980) [Abstract]

527 ***Grutman MI, Persidskii IV, Frolov VM, Nagornaia-Persidskaia RN, Gushla EP***; Protective effect of unithiol and its combination with magnesium sulfate in endotoxin poisoning and in infection by gram-negative bacteria; Patol. Fiziol. Eksp. Ter. (1) 23-26 (1992) [Abstract]

528 ***Grutman MI, Frolov VM, Peresadin NA, Pshenichnyi I, Nagornaia-Persidskaia NA, Varich V***; The antioxidant treatment of patients with acute intestinal infections due to gram-negative microorganisms; Vrach. Delo. (6) 122-124 (1992) [Abstract]

529 ***Grutman MI, Persidskiiy IV, Frolov VM; Nagornaia-Persidskaia RN, Gushla EP***; Neutralization of toxic action of endotoxins of gram-negative bacteria by unithiol and magnesium sulfate; Bull. Exp. Biol. Med. 110(3) 1193-1195 (1990)

530 ***Gubrelay U, Mathur R, Flora SJS***; Beneficial effects of combined administration of thiamine, methionine or zinc with few chelating agents in preventing acute cadmium toxicity in mice; Indian J. Pharmacol. 30(1) 21-24 (1998)

531 ***Gubsky YI, Erstenyuk HM, Briuzgina TS, Zadorina OV***; Fatty acid composition of erythrocytes and blood plasma lipids in cadmium intoxication and its correction with unithiol; Ukr. Biokhim. Zh. 75(5) 103-105 (2003) [Abstract]

532 ***Gülden JW, Christ F, Hauser E, Kramer HJ***; Zirkulatorische Verteilung von intravenös injiziertem, metallischen Quecksilber; Röntgenblätter 40(12) 401-405 (1987)

533 ***Guida PP, Dubinskii AA***; Therapeutic efficacy of unithiol in Buschke's scleroderma; Vrach. Delo. (8) 36-38 (1983) [Abstract]

534 ***Gundorova RA***; Clinical and biochemincal changes in the vitreous body of the eye containing foreign particles of iron and copper; Vestn. Oftalmol. 79(5) 21-26 (1966) [Abstract]

535 ***Guryanov BM, Tarnavskaya MI***; The therapeutic and prophylactic action of Unithiol under the prolonged action of lead according to data from patamorphological studies; Farmakol. Toksikol. 5 166-169 (1970) [Abstract]

536 ***Guryanov BM***; Curative effectiveness of sodium 2,3-dimercapto-1-propane sulfonate (Unithiol); Fiziol. Aktiv. Veschestva (2) 82-84 (1969) [Abstract]

537 ***Guryanov BM***; Effect of Unithiol on the coproporphyrin in the urine during chronic lead poisoning; Farmakol. Toksikol. (4) 176-178 (1968) [Abstract]

538 ***Guryanov BM***; The effect of Unithiol on the elimination of lead via urine during subacute form of saturnism; Farmakol. Toksikol (4) 175-176 (1965) [English Translation]

538b ***Gussow L***: Five things every toxicologist should know about polonium; EMN p. 22, February 2007

538a ***Guzzi GP, La Porta CAM***; Molecular mechanisms triggered by mercury; Toxicology 244(1) 1-12 (2008)

539 ***Habal R***; Toxicity: lead; Emedicine J. 3(1) January 11 (2002)

540 ***Habernig SM, Kau T, Rogatsch H, Hausegger K***; Intravenöse Selbstapplikation von elementarem Quecksilber; Fortschr. Röntgenstr. 179(4) 424-425 (2007)

541 ***Hackel R, Mattern R, Miksch T***; Eine medizinale Quecksilber-Vergiftung; Beitr. Gerichtl. Med. 47 111-114 (1989)

542 ***Hahn A, Michalak H, Begemann K, Preußner K, Engler A, Brehmer W, Heinemeyer G, Gundert-Remy U***; Ärztliche Mitteilungen bei Vergiftungen nach §16e Chemikaliengesetz 2003

543 ***Hahn A, Michalak H, Begemann K, Preußner K, Engler A, Rüdiger T, Heinemeyer G, Gundert-Remy U***; Ärztliche Mitteilungen bei Vergiftungen nach §16e Chemikaliengesetz 2002; In Bericht der "Zentralen Erfassungsstelle für Vergiftungen, gefährliche Stoffe und Zubereitungen, Umweltmedizin" im Bundesinstitut für Risikobewertung für das Jahr 2002

544 ***Hahn A, Michalak H, Begemann K, Heinemeyer G, Gundert-Remy U***; Ärztliche Mitteilungen bei Vergiftungen nach § 16e Chemikaliengesetz 1997; Vierter Bericht der „Dokumentations- und Bewertungsstelle für Vergiftungen“ im Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin (1997)

545 ***Hahn A, Michalak H, Noack K, Heinemeyer G***; Ärztliche Mitteilungen bei Vergiftungen nach § 16e Chemikaliengesetz 1990-1995; Zweiter Bericht der „Dokumentations- und Bewertungsstelle für Vergiftungen“ im Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin, S. 26 (1995)

545a ***Halbach S***; Ausleiten von Quecksilber; Arzneimittel Therapie Kritik 39(4) 785-787 (2007)

546 ***Halbach S***; Amalgam: Gesundheitsrisiko und interdisziplinäres Problem?; Pädiat. Prax. 58(3) 377-386 (2000)

547 ***Halbach S***; Quecksilberbelastung aus Amalgam-Zahnfüllungen vor und nach ihrer Entfernung; IN: Jahresbericht 1996/GSF-Forschungszentrum für Umwelt und Gesundheit, S. 31-34 (1997)

548 ***Halbach S***; Statement anlässlich der Pressekonferenz über Amalgam der Bundeszahnärztekammer am 14.05.1996 in Bonn (1996)

549 ***Halbach S***; Fakten und Zahlen: Quecksilber aus Amalgamfüllungen; Pharm. Ztg. 140(12) 1001-1005 (1995)

550 ***Halbach S***; Amalgamfüllungen: Belastungen oder Vergiftung mit Quecksilber?; Dt. Ärzteblatt 91(8) 399-402 (1994)

551 ***Halbach S***; Thiol chelators and mercury effects on isolated heart muscle; Plzen. Lek. Sborn 62(Suppl.) 39-41 (1990)

552 ***Halbach S***; Sulhydryl-induced restoration of myocardial contractility after alteration by mercury; Arch. Toxicol. 63(Suppl. 13) 349-352 (1989)

553 ***Halbach S***; Amalgamfüllungen aus toxikologischer Sicht; Zahnärztl. Mitteilungen 79(20) 2335-2336 (1989)

554 ***Halbach S***; Indirect sympathomimetic action of thiols; Arch. Pharmacol. 334(Suppl.) R18 (1986)

554a ***Haley BE***; The relationship of the toxic effects of mercury to exacerbation of the medical condition classified as Alzheimer's disease; Medical Veritas 4 1510-1524 (2007)

555 ***Hall AH***; Chronic arsenic poisoning; Toxicol. Lett. 128(1-3) 69-72 (2002)

556 ***Halsen G, Eickmann U, Wegscheider W***; Quecksilber in Zahnarztpraxen; Berufsgenossenschaft für Gesundheitsdienst und Wohlfahrtspflege – BGW (2007)

557 ***Hamada T***; A new experimental system of using fertile chick eggs to evaluate vanadium absorption and antidotal effectiveness to prevent vanadium uptake; J. Nutr. Biochem. 5(8) 382-388 (1994)

558 ***Hamre HJ, Friese KH***; Amalgam - Probleme und Lösungen in der naturheilkundlichen Praxis! Hippokrates Verlag (1997)

559 ***Hansen G, Victor R, Engeldinger E, Schweitzer C***; Evaluation of the mercury exposure of dental amalgam patients by the Mercury Triple Test; Occup. Environ. Med. 61(6) 535-540 (2004)

560 ***Hansson M. Abedi-Valugerdi M***; Mercuric chloride induces a strong immune activation, but does not accelerate the development of dermal fibrosis in tight skin 1 mice; Scand. J. Immunol. 59(5) 469-477 (2004)

561 ***Hargreaves RJ, Evans JG, Janota I, Magos L, Cavanagh JB***; Persistent mercury in nerve cells 16 years after metallic mercury poisoning: Neuropathol. Appl. Neurobiol. 14 443 - 452 (1988)

562 ***Harhammer R***; Zur Risikobewertung des zahnärztlichen Füllungswerkstoffes Amalgam; Bundesgesundheitsbl. Gesundheitsforsch. Gesundheitsschutz 44(2) 149-154 (2001)

563 ***Hartmann M***; HELPP-Syndrom - eine klinische Studie; Dissertation TU München (1995)

564 ***Hasenhöller A***; Suizidale Vergiftung durch intravenöse Injektion von metallischem Quecksilber mit akutem Nieren-versagen nach Therapie mit Dimaval. Kasuistik und Übersicht über die Weltliteratur; Dissertation, Universität Kiel (1993)

565 ***Haskell SRR, Payne M, Webb A, Riviere J, Craigmill AL***; Antidotes in food animal practice; J. Am. Vet. Med. Assoc. 22(6) 884-887 (2005)

566 ***Hauser W, Weger N***; Treatment of arsenic poisoning in mice with sodium-dimercaptopropane-1-sulfonate (DMPS); 7th International Congress of Pharmacology Paris (1978)

567 ***Hayden J, Pires J, Roy S, Hamilton M, Moore GJ***; Discovery and design of novel inhibitors of botulinus neurotoxin A: Targeted 'hinge' peptide libraries; J. Appl. Toxicol. 23(1) 1-7 (2003)

568 ***He FS, Zhow XR, Lin BX, Xiung YP, Chen SY, Zhang SL, Ru JY, Deng MH***; Prognosis of mercury poisoning in mercury refinery workers; Ann. Acad. Med. Singapore 13(2 Suppl) 389-393 (1984)

569 ***Hein D, Daldrup T, Passlick J, Königshausen T, Grabensee B***; Möglichkeiten und Grenzen extrakorporaler Detoxifikationsverfahren bei schwerster akuter Quecksilberdampfintoxikation; Intensivmedizin 18(3) 177-180 (1981)

570 ***Heinemeyer G, Begemann K, Gundert-Remy U***; Toxicokinetics of lead and mercury in man and animals with special respect to renal clearance and its impact to chelation treatment; XXI Int. Congress EAPCCI, Barcelona (2001)

571 ***Heinemeyer G, Begemann K, Scharmann W, Wolff D, Palavinskas R, Gundert-Remy U***; Effects of DMPS on kinetics of lead in rabbits; J. Toxicol. Clin. Toxicol. 38(2) 222-223 (2000)

572 ***Heinemeyer G, Palavinskas R, Begemann K, Donbavand B, Hahn A, Michalak H***; Vergiftungen mit Blei, ein alter Hut?; Tätigkeitsbericht des BgVV 227-230 (1997)

573 ***Heinemeyer G, Fabian U (Eds.)***; Der Vergiftungs- und Drogennotfall; Ullstein-Mosby Verlag, Berlin, Wiesbaden, 3. Auflage, S.82-85 (1990)

574 ***Heinrich-Ramm R, Schaller KH, Horn J, Angerer J***; Arsenic species excretion after dimercaptopropanesulfonic acid (DMPS) treatment of an acute arsenic trioxide poisoning; Arch. Toxicol. 77(1) 63-68 (2003)

574a ***Heitland P, Köster HD***; Biomonitoring of 37 trace elements in blood samples from inhabitants of northern Germany by ICP-MS; J. Trace Elem. Med. Biol. 20 253-262 (2006)

574b ***Heitland P, Köster HD***; Biomonitoring of 30 trace elements in urine of children and adults by ICP-MS; Clin. Chim. Acta 365 310-318 (2006)

575 ***Held KD, Sylvester FC, Hopcia KL, Biaglow JE***; Role of Fenton chemistry in thiol-induced toxicity and apoptosis; Radiat. Res. 145(5) 542-553 (1996)

576 ***Held KD, Biaglow JE***; Mechanisms for the oxygen radical-mediated toxicity of various thiol-containing compounds in cultured mammalian cells; Radiat. Res. 139(1) 15-23 (1994)

577 ***Hentschel***; Faltblatt Amalgam; http://www.gesundheitsamt.de/umwelt/noxenchemisch/met.../amalgamfaltblatt.htm (1998)

577a ***Henschler D***; Bedrohung durch biologische und chemische Substanzen; Zivilschutz-Forschung 55 135-140 (2005)

578 ***Hermann W, Kühn HJ, Merle U, Stremmel W***; Leitlinien für Diagnostik und Therapie in der Neurologie: Morbus Wilson Leitlinien für Diagnostik und Therapie in der Neurologie; 3. überarbeitete Auflage 2005, ISBN3-13-132413-9; Georg Thieme Verlag Stuttgart http://www.uni-duesseldorf.de/WWW/AWMF/ll/030-091.htm (2005)

579 ***Herr CEW, Kopka , Mach J, Runkel B, Schill WB, Gieler U, Eikmann T***; Interdisciplinary diagnostics in environmental medicine - findings and follow-up in patients with chronic medically unexplained health complaints; Int. J. Hyg. Environ. Health 207(1) 31-44 (2004)

580 ***Herrmann M, Schweinsberg F***; Biomonitoring zur Beurteilung einer Quecksilberbelastung aus Amalgamfüllungen. Quecksilberbestimmungen in Urin vor und nach oraler Gabe von 2,3-Dimercapto-1-propanesulfonsäure (DMPS) und in den Haaren; IN: Beiträge zur Umweltmedizin Umwelt und Gesundheit, Frankfurt am Main: Mabuse-Verlag, Vol. 6, S. 9-34 (1999)

581 ***Herrmann M, Schweinsberg F***; Biomonitoring zur Beurteilung einer Quecksilberbelastung aus Amalgamfüllungen. Quecksilberbestimmung in Urin vor und nach oraler Gabe von 2,3-Dimercapto-1-propanesulfonsäure (DMPS) und in Haaren; Zentralbl. Hyg. Umweltmed. 194(3) 271-291 (1993)

582 ***Herrmann M, Widon B, Schweinsberg F, Holzapfel G, Brückner C***; Quecksilber in Boden, Luft, Blut, Urin und Haaren: Belastung durch Amalgamfüllungen und am Arbeitsplatz in einem Betrieb in der DDR; GSF Symposium, Berlin (1990)

583 ***Heuchert A, Fischer AB, Herr C, Harpel S, Eikmann T***; Human biomonitoring of metal concentrations in blood and urine following application of the complexing agent DMPS-assessment of the diagnostic DMPS mobilization test; Biomarkers Environ. 4(Suppl.1) 49-52 (2001)

584 ***Heyl E, Parr W***; Use of dimercaptopropanesulfonic acid and dimercapto-propanesuccinic acid for the preparation of pharmaceutical compositions and a method of treatment; US Patent 4.720.379 (1988)

585 ***Heyl E, Parr W***; Verwendung von Dimercaptopropanesulfonsäure und Dimercaptobernsteinsäure zur Herstellung von pharmazeutischen Mitteln; Offenlegungsschrift DE 31 11 770 A1 (1982)

586 ***HEYL***; Unveröffentlichte Fallberichte aus der klinischen Prüfung von Dimaval zur Behandlung von Schwermetall-vergiftungen und Berichte über unerwünschte Begleitreaktionen von DMPS

587 ***Hibberd AR, Howard MA. Hunnisett AG***; Mercury from dental amalgam fillings: Studies on oral chelating agents for assessing and reducing mercury burdens in humans; J. Nutr. Environ. Med. 8(3) 219-231 (1998)

588 ***Hickel R, Wild J, Martus P, Schiele R***; Die Quecksilberbelastung von Zahnmedizinstudenten nach beruflicher Amalgamexposition; Dtsch. Zahnärztl.Z. 50(7) 506-510 (1995)

589 ***Hickel R, Meier C, Schiele R, Raab W, Petschelt A***; Nebenwirkungen von Amalgam? Eine interdisziplinäre Studie; Dtsch. Zahnärztl. Z. 46(8) 542-544 (1991)

590 ***Higgins MA, Evans R***; Antidotes - Inappropriate timely availability; Hum. Exp. Toxicol. 19(9) 485-488 (2000)

591 ***Hirsch M, Jöchle W, Spahr A***; Quecksilbervergiftung durch Merbromin; Münch. Med. Wochenschr. 139(46) 39-40 (1997)

592 ***Hla KK, House I, Henry JA***; Use of DMPS in bismuth intoxication; XIV. Int. Congress of European Association of Poison Control Centres, Mailand (1990)

593 ***Ho BSJ, Lin JL, Huang CC, Tsai YH, Lin MC***; Mercury vapor inhalation from Chinese Red (Cinnabar); J. Toxicol. Clin. Toxicol. 41(1) 75-78 (2003)

594 ***Hofmann U***; Krank durch Amalgam - und was dann?; Institut für Naturheilverfahren, Marburg (1996)

595 ***Hofmann U, Segewitz G***; Influence of chelation therapy on acute lead intoxication in rats; Arch. Toxicol. 34(3) 213-225 (1975)

596 ***Hohage H, Otte B, Westermann G, Witta J, Welling U, Zidek W, Heidenreich S;*** Elemental mercurial poisoning; Southern Med. J. 90(10) 1033-1036 (1997)

597 ***Hol PJ, Vamnes JS, Gjerdet NR, Eide R, Isrenn R***; Copper, zinc, and selenium in human blood and urine after injection of sodium 2,3-dimercaptopropane-1-sulfonate: A study on subjects with dental amalgam; Biol. Trace Elem. Res. 91(1) 19-31 (2003)

598 ***Hol JP, Vamnes JS, Gjerdet NR, Eide R, Isrenn R***; Dental amalgam affects urinary selenium excretion; Biol. Trace Elem. Res. 85(2) 137-147 (2002)

599 ***Hol JP, Vamnes JS, Gjerdet NR, Eide R, Isrenn R***; Dental amalgam and selenium in blood; Environ. Res. 87(3) 141-146 (2001)

600 ***Hölzel C, Staehle HJ, Triebig G***; Zur Frage von Nebenwirkungen des "DMPS-Mobilisationstestes“; 40. Jahrestagung der Deutschen Gesellschaft für Arbeitsmedizin und Umweltmedizin e.V., Berlin, P37 (2000)

601 ***Hoover TD, Aposhian H***; BAL increases the arsenic-74 content of rabbit brain; Toxicol. Appl. Pharmacol. 70(1) 160-162 (1983)

602 ***Hopkins S***; 2,3-Dimercaptopropane sodium sulfonate; Drugs of the Future 6(2) 75-77 (1981)

602a ***Hoppe HW, Heinrich-Ramm R***; Methylmercury; The MAK-Collection Part IV: Biomonitoring Methods, Vol. 10, 169-190 (2006)

603 ***Horn J, Eichler H, Mühlberg W, Platt D***; Akute Arsentrioxid-Intoxikation - blander Verlauf nach hochdosierter Chelattherapie; Intensivmed. 39(3) 246-253 (2002)

604 ***Horn J***; Akute Vergiftungen. 4 Antidottherapie; Fortschr. Med. 113(12) 36-38 (1995)

605 ***Hörstadt-Bindslev P, Magos L, Holmstrup P, Arenholt-Bindslev D***; Amalgam - Eine Gefahr für die Gesundheit?; Deutscher Ärzte-Verlag, Köln (1993)

606 ***Hrdina R, Gersl V, Klimtova I, Simunek T, Mazurova Y, Machackova J, Adamcova M***; Effect of sodium 2,3-dimercaptopropane-1-sulfonate (DMPS) on chronic daunorubicin toxicity in rabbits: comparison with dexrazoxane; Acta Med. (Hradec Kralove) 45(3) 99-105 (2002)

607 ***Hrdina R, Gersl V, Klimtova I, Simunek T, Machackova J, Holeckova M***; Effects of chelating agent DMPS on chronic daunorubicin cardiotoxicity in rabbits; Biomark. Environm. 3 P7 (2000)

608 ***Hrdina R, Gersl V, Vavrova J, Holeckova M, Palicka V, Voglova A, Mazurova Y,Bajgar J***; Myocardial elements content and cardiac function after repeated i.v. administration of DMPS in rabbits; Hum. Exp. Toxicol. 17(4) 221-224 (1998)

609 ***Hrdina R, Gersl V***; Effect of unithiol on acute adriamycin cardiotoxicity in rat; Pharmacol. Res. 31(Suppl.) 76 (1995)

610 ***Hruby K, Schiel H;*** Antidotarium International 2002/2003; Medizinisch-pharmazeutische Verlagsgesellschaft, Pukersdorf bei Wien (2003)

611 ***Hruby K, Donner A***; 2,3-Dimercapto-1-propanesulfonate in heavy metal poisoning; Med. Toxicol. 2(5) 317-323 (1987)

612 ***Hruschka E***; Eine chronische Wismutvergiftung; Forum Prakt. Allgem. Arzt 29(11) 305 (1990)

613 ***Hruschka, M***; Zinnvergiftung bei einer Zahnarzthelferin; Forum Prakt. Allgem. Arzt 29(10) 275 (1990)

614 ***Hruz P, Mayr M, Huber G, Drewe J***; DMPS (sodium-2,3-dimercapto-propanesulfonate): A highly effective agent for the elimination of colloidal bismuth in bismuth intoxication-induced acute renal failure; Ther. Drug Monit. 25(4) 492 (2003)

615 ***Hruz P, Mayr M, Loew R, Drewe J, Huber G***; Fanconi's syndrome, acute renal failure, and tonsil ulcerations after colloidal bismuth subcitrate intoxication; Am. J. Kidney Dis. 39(3) E18 (2002)

616 ***Hsieh CJ, Yen CH, Kuo MS***; Determination of trace amounts of arsenic(III) and arsenic(V) in drinking water and arsenic(III) vapor in air by graphite-furnace atomic absorption spectrophotometry using 2,3-dimercaptopropane-1-sulfonate as a complexing agent; Anal. Sci. 15(7) 669-673 (1999)

617 ***Hsu CA, Aposhian HV, Heydolph S, Parr W***; Optical isomers of 2,3-dimercapto-1-propanesulfonate: antidotal activity, in vitro and in vivo, against sodium arsenite; J. Pharmacol. Exp. Ther. 224(2) 314-318 (1983)

618 ***Hsu MF, Chen YS, Huang LJ, Tsao LT, Kuo SC, Wang JP***; GEA3162, a nitric oxide-releasing agent, activates non-store-operated Ca^{2+} entry and inhibits store-operated Ca^{2+} entry pathways in neutrophils through thiol oxidation; Eur. J. Pharmacol. 535(1-3) 43-52 (2006)

619 ***Hu H***; Exposure to metals; Prim. Care Clin. Off. Pract. 27(4) 983-996 (2000)

620 ***Hu H, Möller G, Abedi-Valugerdi M***; Thiol compounds inhibit mercury-induced immunological and immuno-pathological alterations in susceptible mice; Clin. Exp. Immunol. 107(1) 68-75 (1997)

621 ***Hu J, Wang G, Cheng N, Wang X, Hong M, Han Y, Yang R***; Clinical study on manifestation of hepatolenticular degeneration complicated with epilepsy and therapeutic effect of integrative Chinese and Western medicine treatment; Zhongguo Zhong Xi Yi Jie He Za Zhi 24(9) 793-797 (2004) [Abstract]

622 ***Huang LE, Zhang H, Bae SW, Liu AY***; Thiol reducing reagents inhibit the heat shock response. Involvement of a redox mechanism in the heat shock signal transduction pathway; J. Biol. Chem. 269(48) 30718-30725 (1994)

623 ***Hubskyi II, Erstenyuk HM, Briuzhina TS, Zadorina OV***; Fatty acid composition of lipids in erythrocytes and blood plasma in cadmium intoxication and its correction with unitiol; Ukr. Biokhim. Zh. 75(5) 103-105 (2003) [Abstract]

623a ***Hummel A***; Arzneimittellehre; Verlag Vincentz Network GmbH & Co. KG, S.348 (2004)

624 ***Hunder G, Schümann K, Elsenhans B, Fichtl B, Forth W***; In situ effects of arsenite on intestinal absorptive functions in rats-efficiency of dithiols; Naunyn Schmiedebergs Archives of Pharmacology 357 (4 Suppl.) R130 (1998)

625 ***Hurlbut KM, Tong TG, Sullivan JB***; Pharmacotherapy for the toxicity of hazardous materials; Clin. Occup. Environ. Med. 2(2) 299-312 (2002)

626 ***Hurlbut KM, Maiorino RM, Mayersohn M, Dart RC, Bruce DC, Aposhian HV***; Determination and metabolism of dithiol chelating agents. XVI Pharmacokinetics of 2,3-dimercapto-1-propanesulfonate after intravenous administration to human volunteers; J. Pharmacol. Exp. Ther. 268(2) 662-668 (1994)

627 ***Hursh JB, Clarkson TW, Nowak TV, Pabico RC, McKenna BA, Miles E, Gibb FR***; Prediction of kidney mercury content by isotope techniques; Kidney Int. 27(6) 898-907 (1985)

628 ***Hurst CG, Newmark J, Romano JA, Biederbick W, Fock R;*** Terrorismus mittels toxischer Chemikalien; IN: Harrisons Innere Medizin, 16. Auflage, Deutsche Ausgabe, ABW Wissenschaftsverlag, Berlin, 1382-1384 (2005)

629 ***Hussain S, Meneghini E, Moosmayer M, Lacotte D, Anner BM***; Potent and reversible interaction of silver with pure Na,K-ATPase and Na,K-ATPase-liposomes; Biochim. Biophys. Acta 1190(2) 402-408 (1994)

630 ***Iffland R, Bösche G***; Therapie und klinisch-toxikologische Verlaufskontrolle einer Brechweinstein-Vergiftung durch ein Ameisenvernichtungsmittel bei einem Kind; Monatsschr. Kinderheilkd. 135(4) 227-230 (1987)

631 ***Iglesia-Turino S, Febrero A, Jauregui O, Caldelas C, Araus JL, Bort J***; Detection and quantification of unbound phytochelatin 2 (PC2) in plant extracts of Brassica napus grown with different levels of mercury; Plant. Physiol. 142(2) 742-749 (2006)

632 ***Iliash TI***; Treatment of alcoholic polyneuritis; Vrach. Delo. (9) 93-96 (1979) [Abstract]

633 ***Ilin LA, Arhangelskaya GV, Norets TA***; Comparative effectiveness of some substances inducing formation of complexes in the speeding of ^{65}Zn excretion from the organism; Radiobiologiya (4) 926-927 (1964) [Abstract]

634 ***Imesch E, Moosmayer M, Anner BM;*** Mercury weakens membrane anchoring of Na-K-ATPase; Am. J. Physiol. 262(5 Pt.2) F837-F842 (1992)

635 ***Inns RH, Rice P***; Efficacy of dimercapto chelating agents for the treatment of poisoning by percutaneously applied dichloro(2-chlorovinyl)arsine in rabbits; Hum. Exp. Toxicol. 12(3) 241-246 (1993)

636 ***Inns RH, Rice P, Bright JE, Marrs TC***; Evaluation of the efficacy of dimercapto chelating agents for the treatment of systemic organic arsenic poisoning in rabbits; Hum. Exp. Toxicol. 9(4) 215-220 (1990)

637 ***Ionescu G***; Schwermetallbelastung durch Dentallegierungen. Ausleitungsverfahren bei Neurodermitis- und Psoriasispatienten; Z. Umweltmedizin 5(3) 163-171 (1997)

638 ***Ionescu*** *G*; Korrosions- und Biokompatibilitätsprüfung dentaler Legierungen. Therapieansätze bei Amalgamträgern mit atopischer Dermatitis und Psoriasis vulgaris; Ärztezeitschrift für Naturheilverfahren 38(2) 119-139 (1997)

639 ***Ionescu G***; Schwermetallbelastung bei atopischer Dermatitis und Psoriasis-Diagnose und Therapie; Biol. Med. (2) 65-68 (1996)

640 ***Ionescu G***; Amalgambelastung bei atopischem Ekzem – Diagnose und Ausleitungsverfahren; Erfahrungsheilkunde 41(10a) 745-746 (1992)

641 ***Ip P, Ko P, Lam C, Nelson T, Wong V, Keung TCY, Kumana CR***; Hong Kong College of Paediatricians: Position paper on Exposure to lead and mercury in children and chelation therapy; HK J. Paediatr. 9 103-108 (2004)

642 ***Islinger F***; Untersuchungen zum Wirkmechanismus des klinisch angewandten Schwermetallchelators 2,3-Dimercapto-1-Propanesulfonsäure (DMPS); Dissertation, Universität Würzburg (2002)

643 ***Islinger F, Gekle M, Wright SH***; Interaction of 2,3-Dimercapto-1-propane sulfonate with the Human Organic Anion Transporter hOAT1; J. Pharmacol. Exp. Ther. 299(2) 741-747 (2001)

644 ***Ivannikov AI***; The influence of unithiol on the course of acute uranium intoxication; Med. Radiol. 9(5) 45-50 (1964)

645 ***Ivanov N, Zhelyaskov D, Mangarova M, Belceva A, Kalicin I, Popdimitrov I, Keneva Z***; Organ-dependent reduction of the sulfhydril groups in acute intoxication, caused by mercury, and its treatment with mono- and dithiol antidotes and protein hydrolysate “Hydroprot"; Eksp. Med. Morfol. 24(2) 45-49 (1985) [Abstract]

646 ***Ivanov VV, Klimatskaia LG***; Use of antioxidants for preventing the hepatotoxic effect of acrylonitrile; Farmakol. Toksikol. 47(5) 96-100 (1984) [Abstract]

647 ***Jacobi C, Obieglo S, Hermanns-Clausen M***; Akzidentelle Chromat-Vergiftung durch Künstlerfarbe; 99. Jahrestagung der Deutschen Gesellschaft für Kinderheilkunde und Jugendmedizin, Bonn (2003)

647a ***Jacobsen D, Haines JA***; The relative efficavy of antidotes: The International Programme on Chemical Safety (IPCS) evaluation series; Arch. Toxicol. 19(Suppl.) 305-310 (1997)

648 ***Jaggi JS, Kappel BJ, McDevitt MR, Sgouros G, Flombaum CD, Cabassa C, Scheinberg DA***; Efforts to control the errant products of a targeted in vivo generator; Cancer Res. 65(11) 4888-4895 (2005)

649 ***Jahn O, Meisinger V, Mulac K, Carniel M, Zwieauer K, Hruby K, Dorda W***; Chrom in Serum und Harn nach akuter Chromsäureintoxikation; IN: Verhandlungen der Dt. Gesellschaft für Arbeitsmedizin; S Zadkowski (Ed.); Gentner-Verlag, Stuttgart; pp. 377-375 (1985)

650 ***Jan KY, Wang TC, Ramanathan B, Gurr JR***; Dithiol compounds at low concentrations increase arsenite toxicity; Toxicol. Sci. 90(2) 432-439 (2006)

651 ***Jansing PJ, Zurhorst C, Prager HM***; Quecksilberexposition im Leuchtstoffröhrenrecycling; Arbeitsmed. Sozialmed. Umweltmed. 35(7) 334-339 (2000)

652 ***Jaroni HW***; Umed Info 16 - Umwelt und Kind; Landesgesundheitsamt Baden-Württemberg (2004)

653 ***Jarrett PS, Ni Dhubhghaill OM, Sadler PJ***; Amphiphilic bis(thiolato)-nickel(II), -palladium(II) and -platinum(II) complexes with diphosphine or phosphinoarsine ligands: J. Chem. Soc. Dalton Trans. 1863-1870 (1993)

654 ***Jauhiainen M, Stevenson KJ, Dolphin PJ***; Human plasma lecithin-cholesterol acyltransferase. The vicinal nature of cysteine 31 and cysteine 184 in the catalytic site; J. Biol. Chem. 263(14) 6525-6533 (1988)

655 ***Jeitner TM, Delikatny EJ, Bartier WA, Capper HR, Hunt NH***; Inhibition of drug-naive and-resistant leukemia cell proliferation by low molecular weight thiols; Biochem. Pharmacol 55(6) 793-802 (1998)

656 ***Jeitner TM, Kneale CL, Christopherson BI, Hunt NH***; Thiol-bearing compounds selectively inhibit protein kinase C-dependent oxidative events and proliferation in human T cells; Biochim. Biophys. Acta Mol. Cell. Res. 1223(1) 15-22 (1994)

657 ***Jekat FW, Kemper FH***; The oral application of DMPS in metal intoxication: Case Reports; Plzen. Lek. Sborn. 62(Suppl.) 47-48 (1990)

657a ***Jepson B***; Changing the course of autism: A scientific approach for parents and physicians; Sentient Puplications, p.232 (2007)

658 ***Johansson L, Chen C, Thorell JO, Fredriksson A, Stone-Elander S, Gafvelin G, Arner ES***; Exploiting the 21st amino acid-purifying and labeling proteins by selenolate targeting; Nat. Methods 1(1) 61-66 (2004)

659 ***Johary NS, Owen LN***; Dithiols. 18 Some water-soluble derivatives containing the sulfonic acid group; J. Chem. Soc. 1307-1311 (1955)

660 ***Johri S, Shrivastava S, Sharma P, Shukla S****;* Analysis of time-dependent recovery from beryllium toxicity following chelation therapy and antioxidant supplementation; Indian J. Exp. Biol. 42(8) 798-802 (2004)

661 ***Johri S, Shukla S, Sharma P***; Role of chelating agents and antioxidants in beryllium induced toxicity; Indian J. Exp. Biol. 40(5) 575-582 (2002)

662 ***Jones AL***; GTPU Annual Report 2005-2006; http://www.medtox.org/info/GTPU.pdf

663 ***Jones AL***; Side effect s to poison antidotes: Part 2; Adverse Drug React. Bull. No. 229 (2004)

663a ***Jones AL, Flanagan RJ***; Dimercaptopropanesulfonic acid (DMPS); IN: Medical Toxicology, R Dart (Ed.), Lippincott Williams & Wilkins, pp 193-194 (2004)

664 ***Jones DC, Smith GL, May PM, Williams DR***; Assessment of pharmaceutical agents for removing cadmium from humans using chemical speciation models; Inorganica Chimica Acta 93 93-100 (1984)

665 ***Jones DW***; A Canadian perspective on the dental amalgam issue; Brit. Dent. J. 184(12) 581-586 (1998)

666 ***Jones MM***; Introduction to chelation chemistry and therapies; American College for Advancement in Medicine (1999)

667 ***Jones MM***; Chemistry of chelation: Chelating agent antagonists for toxic metals; IN: Handbook of Experimental Pharmacology, Vol.115, Toxicology of Metals: Biochemical Aspects; RA Goyer, MG Cherian (Eds.); Springer Verlag, Berlin; pp.279-304 (1995)

668 ***Jones MM***; Chelating agent mobilization of cadmium from its aged intracellular deposits; Plzen. Lek. Sborn. 68(Suppl) 7-9 (1993)

669 ***Jones MM, May PM***; The effect of kinetic factors on the thermodynamic evaluation of therapeutic chelating agents; Inorg. Chim. Acta 138(1) 67-73 (1987)

670 ***Jones MM***; Heavy-metal detoxification using sulfur compounds; Sulfur Rep. 4 119-156 (1985)

672 ***Jones MM***; An alternative model for the selection of therapeutic chelating agents; Inorg. Chim. Acta 107 235-241 (1985)

672 ***Jones MM***; Antagonists for toxic heavy metals; Proc. West. Pharmacol. 27 163-167 (1984)

673 ***Jones MM***; Therapeutic chelating agents; IN: Metal Ions in Biological Systems; H Siegel (Ed.); Vol. 16,3; Marcel Dekker, New York, pp 47-83 (1983)

674 ***Jones MM, Basinger MA***; Chelate antidotes for sodium vanadate and vanadyl sulfate intoxication in mice; J. Toxicol. Environm. Health 12(4-6) 749-756 (1983)

675 ***Jones MM, Basinger MA***; A hypothesis for the selection of chelate antidotes for toxic metals; Med. Hypotheses 9(5) 445-453 (1982)

676 ***Jones MM. Weaver AD, Basinger MA***; Characteristics of chelate antidotes for acute Cu(II) intoxication; J. Inorg. Nucl. Chem. 43 2175-2181 (1981)

677 ***Jones MM, Basinger MA, Weaver AD***; Chelate antidotes for acute Ni(II) intoxication; J. Inorg. Nucl. Chem. 43 1705-1710 (1981)

678 ***Jones MM, Basinger MA, Tarka MP***; The relative effectiveness of some chelating agents in acute copper intoxication in the mouse; Res. Commun. Chem. Pathol. Pharmacol. 27(3) 571-577 (1980)

679 ***Jones MM, Basinger MA, Weaver AD, Davis CM, Vaughn WK***; Comparison of standard chelating agents for acute mercuric chloride poisoning in mice; Res. Commun. Chem. Pathol. Pharmacol. 27(2) 363-372 (1980)

680 ***Jones MM, Basinger MA***; Restrictions on the applicability of mixed ligand chelate therapy (MLC) in acute cadmium intoxication; Res. Commun. Chem. Pathol. Pharmacol. 24(3) 525-531 (1979)

681 ***Jones MM, Weaver AD, Weller WL***; The relative effectiveness of some chelating agents as antidotes in acute cadmium poisoning; Res. Commun. Chem. Pathol. Pharmacol. 22(3) 581-588 (1978)

682 ***Jones MM, Pratt TH***; Therapeutic chelating agents; J. Chem. Educ. 53(6) 342-347 (1976)

683 ***Jones SB, Jones-Tiffany L, Garnestani K, Gansow OA, Kozak RW***; Evaluation of dithiol chelating agents as potential adjuvants for anti-IL-2 receptor lead or bismuth alpha radioimmunotherapy; Nucl. Med. Biol. 23(2) 105-113 (1996)

684 ***Jornod P, Vannotti M, Dascal DR, Auer C, Savolainen H, Buclin T, Nicod P, Waeber G***; Intoxication volontaire au mercure: consequences biologiques et signification psychiatrique; Schweiz. Rundsch. Med. Prax. 86(22) 946-951 (1997)

685 ***Jouglard J, Aquaron R, Arditti J, Jean P, Bourdon JH, David JM***; Saturnisme et Porphyries; Sem. Hop. 63(34) 2767-2772 (1987)

686 ***Juresa D, Blanusa M, Kostial K***; Simultaneous administration of sodium selenite and mercuric chloride decreases efficacy of DMSA and DMPS in mercury elimination in rats; Toxicol. Lett. 155(1) 97-102 (2005)

687 ***Kachru DN, Tandon SK***; Chelation in metal intoxication. XX Effect of pre-treatment with chelators on the distribution of mercury; Res. Commun. Chem. Pathol. Pharmacol. 52(3) 399-402 (1986)

688 ***Kaliman PA, Barannik T, Strelchenko E, Inshina N, Sokol O***; Intracellular redistribution of heme in rat liver under oxidative stress: the role of heme synthesis; Cell Biol. Int. 29(1) 9-14 (2005)

689 ***Kamysbaev DK, Utegulov RN, Ospanov KK***; The thermodynamics of complex formation of metals(II) with unithiol in aqueous solution; Russ. J. Inorg. Chem. 38(2) 288-290 (1993)

690 ***Kamysbaev DK, Utegulov RN, Ospanov KK***; Thermodynamic characteristics of formation of transition metal unithiolato complexes; Russ. J. Coord. Chem. 18(2) 135-138 (1992)

691 ***Kamysbaev DK, Butinchieva TS, Shestakova VA, Ospanov KK***; Complexation of platinum(II) with unithiol solution; Koord. Khim 18(8) 880-881 (1992) [(Abstract]

691a ***Kannengießer C***; Mutter und Tochter – ein interessanter Fall: Karies- und amalgamfrei und dennoch amalgambelastet?; Med. J. Appl. Kinesiology 18 26-29 (2003)

692 ***Kanyuka AI***; Effect of unithiol and calcium disodium EDTA on the morphological profile of the blood; Nauk. Pr.-Ukr. Sil's'kogospod. Akad. 156(2) 64-65 (1976) [Abstract]

693 ***Kapahi P, Takahashi T, Natoli G, Adams SR, Chen Y, Tsien RY, Karin M***; Inhibition of NF-κB activation by arsenite through reaction with a critical cysteine in the activation loop of IκB kinase; J. Biol. Chem. 275(46) 36062-36066 (2000)

694 ***Kappos AD, Beyer A, Hahn A***; Vorschlag zur Gliederung von umweltmedizinischen Kasuistiken Mitteilung der Kommission „Methoden und Qualitätssicherung in der Umweltmedizin"; Bundesgesundheitsbl. Gesundheitsforsch. Gesundheitsschutz 49(5) 485-486 (2006)

695 ***Kapralov IK***; Use of Unithiol and CaNa2EDTA in combined therapy of porphyria; Vestn. Dermatol. Venerol. 38(9) 21-25 (1964) [Abstract]

696 ***Kargacin B, Kostial K***; Methods for decreasing ^{203}Hg retention in relation to age and route of exposure; Advances in Mercury Toxicology, T Suzuki et al. (Eds.), Plenum Press, New York, 135-152 (1991)

697 ***Karpinski H, Markoff C***; Quecksilbervergiftungen im Kindesalter; Monatssch. Kinderheilkd. 145(3) 262-265 (1997)

698 ***Karpov LM, Brown II, Poltavtseva NV, Ershova ON, Karakis SG, Vasileva TV, Chaban IL***; The postradiation use of vitamin-containing complexes and a phytocyanin extract in a radiation lesion in rats; Radiats. Biol. Radioecol. 40(3) 310-314 (2000) [Abstract]

699 ***Kassabova T, Russanov E***; Decorporation of copper from liver subcellular fractions after alimentary loading of rats; Acta Physiol. Pharmacol. Bulg. 4(2) 13-19 (1978)

700 ***Kaupp M, Kleine-Homann D***; Chelating agents; Heavy Metal Bulletin 2(1) 19-21 (1995)

701 ***Kawaguchi M, Yamashita N, Maehashi H***; Enhanced antitumor activity of cisplatin by combination with dimercapto-compounds in a mouse model; Jpn. J. Pharmacol. 49(Suppl.) 72p (1989)

702 ***Kazantzis G***; Diagnosis and treatment of metal poisoning – general aspects; IN: Nordberg GF, Fowler BA, Nordberg M, Friberg LT (Eds.); Handbook on the Toxicology of Metals, 3rd Edition; Academic Press Inc. 303-317 (2007)

703 ***Kehe K, Szinicz L***; Chemische Gefahren; IN: Handbuch "Biologische Gefahren. Beiträge zum Bevölkerungsschutz" Bundesamt für Bevölkerungsschutz und Katastrophenhilfe, Bonn - Bad Godesberg (2004)

704 ***Kehe K, S, Krebs G, Kreppel H, Reichl FX, Liebl B, Szinicz L***; Effects of Lewisite on cell membrane integrity and energy metabolism in human keratinocytes and SCL II cells; Toxicology 163(2-3) 137-144 (2001)

705 ***Keith RL, Setiarahardjo I, Fernando Q, Aposhian HV, Gandolfi AJ***; Utilization of renal slices to evaluate the efficacy of chelating agents for removing mercury from the kidney; Toxicology 116 (1-3) 67-75 (1997)

706 ***Kemper FH, Jekat FW, Bertram HP, Eckard R***; IN: Basic Science in Toxicology; Proceedings of the 5th International Congress of Toxicology; England 1989; GN Volans, J Sims, FM Sullivan, P Turner (Eds.); Taylor & Francis Publishers Ltd, London; pp.523-546; (1990)

707 ***Kemper FH, Müller C, Winterberg B***; Clinical experiences with DMPS in acute intoxications with heavy metal other than mercury; Annual Meeting of European Association of Poison Control Centres, Münster (1989)

708 ***Kenar L, Karayilanoglu T***; Prehospital management and medical intervention after a chemical attack; Emerg. Med. J. 21(1) 84-88 (2004)

708a ***Kennish S, Curie S***; Polonium-210 poisoning; Student Br. Med. J. 15 324-325 (2007)

709 ***Keppler S***; Bleiausleitung mit Dimaval (DMPS) bei Pferden; www.tierheilpraxis-keppler.de (2003)

710 ***Kern JK, Grannemann BD, Trivedi MH, Adams JB***; Sulfhydryl-reactive metals in autism; J. Toxicol. Environ. Health A 70(8) 715-721 (2007)

711 ***Kew J, Morris C, Aihie A, Fysh R, Jones S, Brooks D***; Arsenic and mercury intoxication due to Indian ethnic remedies; Brit. Med. J. 306 (6876) 506 - 507 (1993)

712 ***Khandelwal S, Kachru DN, Tandon SK***; Influence of metal chelators on metalloenzymes; Toxicol. Lett. 37(3) 213-219 (1987)

713 ***Khanina NI, Desnitskaia MM***; Lipidogram, isoenzyme spectrum and summary activity of the nonspecific esterases in the blood serum of rats subjected to the action of a permanent magnetic field; Patol. Fiziol. Eksp. Ter. (2) 26-29 (1986)

714 ***Kharitonov YY, Ospanov KK, Bigalieva M***; Potentiometric study of complexation of rhodium(III) with unithiol in solutions; Koordinatsionnaya Khimiya 11(4) 525-527 (1985) [Abstract]

715 ***Kharitonov YY, Sholtyrova UI, Ospanov KK***; Potentiometric study of complex formation by platinum(II) with unithiol in solution; Russ. J. Inorg. Chem. 23(10) 1510-1513 (1978)

716 ***Khayyal MT, Kemper FH, Bertram HP, Renhof M***; The effect of DMPS, a thiol compound, in modifying the action of antimonials in experimental schistosomiasis; 7th International Congress of Pharmacology, Paris 1978

717 ***Khmara NF, Gavrilova AR, Misnikova VA, Belikov VG, Shalkevich VB***; Lipid peroxidation and the antioxidant system in the therapeutic effect of hypobaric hypoxia in patients with neurologic manifestations of lumbar osteochondrosis; Zh. Nevropatol. Psikhiatr. 91(4) 32-35 (1991) [Abstract]

718 ***Khvorostinka VN, Pasieshvili LM, Teslenko VG, Aleksandrova NK***; Out-Patient treatment of patients with chronic alcoholic liver diseases; Ter. Arkh. 63(8) 115-117 (1991)

719 ***Kidd PM***; Autism, an extreme challenge to integrative medicine. Part II: Medical management; Altern. Med. Rev. 7(6) 472-499 (2002)

720 ***Kidd RF***; Results of dental amalgam removal and mercury detoxification using DMPS and neural therapy; Altern. Ther. Health Med. 6(4) 49-55 (2000)

721 ***Kidess L***; Behandlung von Arsenik-Vergiftungen bei Mäusen mit Dimercaptopropane-1-sulfonat; Dissertation Uni München, 1980

722 ***Kiehl R***; Regulation of IgE-synthesis and proliferation: Stress protein IgE as early warning signal for our body; www.rki-i.com/doc/books/09__IGEwarningS.pdf; (1994)

723 ***Kim Y, Lust MR, Kreimer-Kirnbaum M***; 2,3-Dimercaptopropane-1-sulfonate (DMPS) in the treatment of lead-poisoning; FASEB J. 2(6) 1820 (1988)

724 ***Kirchgatterer A, Rammer M, Knoflach P, Schute L***; Gewichtsverlust, Bauchschmerzen und Anämie als Folgen einer Urlaubsreise - Fallbericht einer Bleiintoxikation; Dtsch. Med. Wochenschr. 130(40) 2253-2256 (2005)

725 ***Kirichenko YG, Vilkov GA, Bardakchyan EA***; Effect of unithiol on myocardial and adrenal ultrastructure in endotoxin shock; Farmakol. Toksikol. 48(3) 49-52 (1985)

726 ***Kirova A, Stoytchev T***; Effect of some thiol compounds on the content of carbon tetrachloride in the liver and brain in cases of acute poisoning of rats; Acta. Physiol. Pharmacol. Bulg. 3(1) 70-76 (1977)

727 ***Kistner A***; Quecksilbervergiftung durch Amalgam: Diagnose und Therapie; ZWR 104(5) 412-417 (1995)

728 ***Kleber JJ, Ganzert N, Zilker T***; Quecksilberkonzentration im Urin nach DMPS-Gabe: Korrelation zur Anzahl der Amalgamfüllungen; IN: Status Quo and Perspectives of Amalgam and other Dental Materials; LT Friberg, GN Schrauzer (Eds.); Georg-Thieme Verlag, Stuttgart, New York; pp.61-69 (1995)

729 ***Kleber JJ, Ganzert M, Pfab R, Heppe H, Felgenhauer N, Zilker T***; Zahn-Amalgam: Wie hoch ist die Quecksilber-belastung?; Therapiewoche 44(2) 94-100 (1994)

730 ***Klemm M, Schüttig R, Demant T***; Two cases of lead poisoning; Toxichem. und Krimtech. 69(2) 86 (2002)

731 ***Klimmek R, Krettek C, Werner HW***; Acute effects of the heavy metal antidotes DMPS and DMSA on circulation, respiration, and blood homoeostasis in dogs; Arch. Toxicol. 67(6) 428-434 (1993)

732 ***Klimmek R, Szinicz L, Weger N***; Chemische Gifte und Kampfstoffe-Wirkung und Therapie; Hippokrates-Verlag, Stuttgart (1983)

733 ***Klimmer OR***; Schwermetallantidote; Arch. Toxicol. 24(1) 15-29 (1968)

734 ***Klimova LK***; Material zur Pharmakologie von Unithiol; IN: Tiolovye Soyedineniyav Meditsine, NN Luganskii, VE Petrunkin, PV Radionov, AJ Cherkes (Eds.); Gos. Med. Idz. Ukrain, SSR, Kiev, pp.135-138 (1959) [Deutsche Übersetzung]

735 ***Klimova LK***; Pharmacology of the new antidote Unithiol; Farmakol. i Toksikol. 21(3) 53-59 (1958) [English Translation]

736 ***Klimtova I, Gersl V, Simunek T, Hrdina R, Machackova J, Ponka P, Adamcova M, Palicka V***; The effects of pyridoxal-isonicotinoyl-hydrazone and 2,3-dimercaptopropane- 1-sulfonate on biochemical and haematological parameters in rabbits; Fundam. Clin. Pharmacol. 15(Suppl.1) 152 (2001)

737 ***Klinghardt D***; Amalgamvergiftung – Das Handbuch, Rezension in Zahnarztmagazin 12(4) 26-30 (1997)

738 ***Klinghardt D***; Schwermetalle – Vergiftung und Entgiftung; Vortrag auf Schloß Elmau (1996)

739 ***Klobusch J, Rabe T, Gerhard I, Runnebaum B***; Schwermetallbelastungen bei Patientinnen mit Alopezie; Arch. Gynecol. Obstet. 254(1-4) 278-280 (1993)

740 ***Klobusch J, Rabe T, Gerhard I, Runnebaum R***; Alopezie und Umweltbelastungen; Klin. Lab. 38(9) 469-476 (1992)

741 ***Klöckner A***; Einstellung und Verhalten zur Mundgesundheit bei Amalgamträgern; Dissertation Medizinischen Fakultät der Rheinisch-Westfälischen Technischen Hochschule Aachen (2007)

742 ***Kloczkowski K, Oginski M***; Use of unithiol for reducing radiation hazard of renal scintigraphy with chlormerodrin ^{203}Hg. II Scintigraphic estimation; Int. Urol. Nephrol. 5(4) 377-382 (1973)

743 ***Klotzbach JM, Diamond GL***; Complexing activity and excretion of 2,3-dimercapto-1-propane sulfonate in rat kidney; Am. J. Physiol. 254(6 Pt 2) F871-F878 (1988)

744 ***Klotzbach JM***; Studies on the mechanism of action of 2,3-dimercaptopropane sulfonate (DMPS): A mercurial complexing agent; Thesis: Dep. of Pharmacology, University of Rochester (1987)

745 ***Klyachina KN, Belyaeva LN***; Effect of Unithiol on the inclusion of chromium-51 in erythrocytes of peripheral blood; Klin. Patog. Profil. Proftabol. Khim. Etiol. Predspr. Tsvet. Chern. Met., pp. 102-106 (1967) [Abstract]

746 ***Klykov NV, Byta VA***; Treatment of patients with myocardial infarct; Vrach. Delo. (12) 50-53 (1979) [Abstract]

747 ***Klykov NV***; Results of complex treatment of patients with chronic circulatory insufficiency using strophanthin, ATP, vitamin B_{12}, folic acid, calcium pantothenate and unithiol; Kardiologiia 12(1) 126-131 (1972) [Abstract]

748 ***Klykov NV***; Use of ATP, cofactors of synthesis and precursors of nucleic acids and unithiol in the treatment of chronic cardiac insufficiency; Kardiologiia 9(5) 72-76 (1969) [Abstract]

749 ***Klykov NV;*** Role of sulfhydryl groups in preventing and overcoming the toxic effect of strophanthin on the dog's heart; Bull. Exp. Biol. Med. 63(6) 627-629 (1967)

750 ***Klykov NV***; Use of unithiol for eliminating the toxic effects of cardiac glycosides; Ter. Arkh. 38(7) 121-123 (1966) [Abstract]

750a ***Koch WH***; Oft übersehen: Zahnersatz als Ursache für Allergien; Naturarzt (2) 15-17 (2007=

751 ***Koch WH, Weitz M***; Amalgam-Belastungen - eine Realität: Was raten Sie Ihrem Patienten? I Amalgam-Belastungen, Entfernen von Amalgamfüllungen, Therapiehinweise; Therapiewoche 41(23) 1501-1504 (1991)

752 ***Koch WH, Weitz M***; Amalgam-Belastungen - eine Realität: Was raten Sie Ihrem Patienten? II Die verschiedenen Therapiemöglichkeiten zur Amalgam-Eliminierung; Therapiewoche 41(25) 1669-1677 (1991)

753 ***Koh AS, Simmons-Willis TA, Pritchard JB, Grassl SM, Ballatori N***; Identification of a mechanism by which the methylmercury antidotes N-acetylcysteine and dimercaptopropanesulfonate enhance urinary metal excretion: Transport by the renal organic anion transporter-1; Mol. Pharmacol. 62(4) 921-926 (2002)

754 ***Köhler W, Linde K, Halbach S, Zilker T, Kremers L, Saller R, Melchart D***; Prognos® in the diagnosis of amalgam hypersensitivity - a diagnostic case-control study; Forsch. Komplementärmed. 14(1) 18-24 (2007)

755 ***Kölfen W, Treiss I***; Enzephalopathie im Kindesalter - ausgelöst durch eine chronische Bleivergiftung; Pädiat. Prax. 58(3) 425-430 (2000)

756 ***Kolganova DN, Kryukova YI, Yurevich V***; Sodium 2,3-dimercapto-propane-sulfonate synthesis method - by decomposing predried lead dimercapto-propane-sulfonate derivative with solution of hydrogen chloride in solvent mixture, then cooling mass; SU Patent 1036005 (1996)

757 ***Koller U, Halbach S***; Amalgam – so schlecht wie sein Ruf?; www.gsf.de/flugs/Amalgam.pdf (2004)

758 ***Köppel C, Baudisch H, Fahron G***: Mercury excretion in patients with mercury deposits; Proceedings of the International Conference on Human Health Effects of Mercury Exposure, Torshavn, Faroe Islands (1997)

759 ***Köppel C***; Mercury concentrations, clinical and neurophysiological findings in patients suspecting mercury poisoning from amalgam fillings; IN: Status Quo and Perspectives of Amalgam and other Dental Materials; LT Friberg, GN Schrauzer (Eds.); Georg-Thieme Verlag, Stuttgart, New York; pp.70-74 (1995)

760 ***Köppel C, Baudisch H, Keller F***; Methoxyethylmercury chloride poisoning: Clinical findings and in vitro experiments; J. Toxicol. Clin. Toxicol. 19(4) 391-400 (1982)

761 ***Köppel C, Keller F, von Keyserling HJ, Schulze G***; Hemoperfusion for organic mercury detoxification?; Klein. Wochenschr. 59(15) 865-866 (1981)

762 ***Köstler W***; Beeinflussung der zellulären Immunabwehr durch Quecksilberfreisetzung; Forum Prakt. Allgem. Arzt 30(2) 62-63 (1991)

763 ***Köstler W***; Immunologische und spektralanalytische Veränderungen durch Quecksilbermobilisierung aus Amalgamfüllungen; Dtsch. Zschr. f. Biol. Zahnmed. 7(1) 27-32 (1991)

764 ***Kohl-Himmelseher M***; Reaktionen der alkylierenden Zytostatika Cyclophosphamid und Tris-(2-chlor-ethyl)-amin mit biologischen Makromolekülen von Leberzellen; Disseration Universität Erlangen (1985)

765 ***Kojima S, Takahashi Y, Kiyozumi M, Funakoshi T, Shimada H***; Characterization of gold in urine and bile following administration of gold sodium thiomalate with chelating agents to rats; Toxicology 74(1) 1-8 (1992)

766 ***Kojima S, Takahashi Y, Kiyozumi M, Tagawa Y***; Protective effects of chelating agents against renal toxicity of gold sodium thiomalate in rats; Arch. Toxicol. 65(7) 532-536 (1991)

767 ***Kolesov OE, Cherepanova VN***; Antitdote action of cobalt mercaptides against cyanide intoxication; Farmakol. i. Toksikol. (1) 167-173 (1964) [Abstract]

768 ***Koriakov VV, Goldfarb IS***; Acute grey mercury ointment poisoning (Abstract); Anesteziol. Reanimatol. (3) 59-60 (1995)

769 ***Koshtoyants KS, Bunkina LS***; The effect of sulfhydril groups on veratrine sensitization of muscle to the action of potassium; Bull. Exp. Biol. Med. 47(3) 270-271 (1959) [Abstract]

770 ***Kosnett MJ, Wedeen RP, Rothenberg SJ, Hipkins KL, Materna BL, Schwartz BS, Hu H, Woolf A***; Recommendations for medical management of adult lead exposure; Environ. Health Perspect. 15(3) 463-471 (2007)

770a ***Kosnett MJ***; Unithiol (DMPS); IN: Poisoning & Drug Overdose, KR Olson (Ed.), McGraw-Hill Professional, 506-507 (2004)

771 ***Kosnett MJ***; Unanswered questions in metal chelation; J. Toxicol. Clin. Toxicol. 30(4) 529-547 (1992)

772 ***Kostial K, Blanusa M, Maljkovic T, Kargacin B, Piasek M, Momcillovic B, Kello D***; Age and sex influence the metabolism and toxicity of metals; IN: Trace Elem Man Anim. 7: Monogr, Proc, Round Tables Discuss Int Symp, 7th , Inst. Med. Res. Occup. Health Univ. Zagreb, Yugoslavia, P: 11/1-11/5 (1991)

773 ***Kostial K, Kargacin B, Arezina R, Landeka M, Simonovic I***; Factors influencing the efficiency of chelation therapy; J. Hyg. Epidemiol. Microbiol. Immunol. 35(4) 1092-350 (1991)

774 ***Kostial K, Kargacin B, Landeka M***; Gut retention of metals in rats; Biol. Trace. Elem. Res. 21 213-218 (1989)

775 ***Kostial K, Kargacin B, Landeka M***; 2,3-Dimercaptopropane-1-sodium sulfonate for reducing retention of ingested ^{203}Hg in suckling rats; Bull. Environ. Contam. Toxicol. 41(2) 185-188 (1988)

776 ***Kostial K, Kargacin B, Blanusa M, Landeka M***; The effect of 2,3-dimercaptopropane sodium sulfonate on mercury retention in rats in relation to age; Arch. Toxicol. 55(4) 250-252 (1984)

777 ***Kostigov NM***; The action of mercaptosuccinic acid and Unithiol as mercury antidotes; Farmakol. Toksikol. 21(3) 64-69 (1958) [English Translation]

778 ***Koutenska M, Eybl V, Koutensyk J, Mertl F, Sykora J***; Interaction of chelating agents with vanadium; Plzen. Lek. Sborn. 49(Suppl.) 63-66 (1985)

779 ***Koutensky J, Eybl V, Koutenska M, Mertl F, Sykora J, Kotyzova D***; Antidotal efficacy of some chelating agents on the acute toxicity and distribution of Ni(II) in mice; Plzen. Lek. Sborn. 49(Suppl) 187-189 (1985)

780 ***Koutsarova T, Shkenderov S***; Activating papain with unithiol in the ferment treatment of erythrocytes; Dokl. Bulg. Akad. Nauk. 20(3) 249-252 (1967)

781 ***Koval IV***; Synthesis, structure, and physicochemical characteristics of thiols; Russian J. Org. Chem. 41(5) 631-648 (2005)

782 ***Kovanicova O, Gombos B, Moscovicova E***; Mercury development in the working environment and our experience in the treatment of chronic professional intoxications; Acta Hygienica, Epidemiologica et Microbiologica Praha, 16-27 (1983) [zitiert in 497]

783 ***Koyun M, Akman S, Güven AG***; Mercury intoxication resulting from school barometers in three unrelated adolescents; Eur. J. Pediatr. 163(3) 131-134 (2004)

784 ***Kozyreva OI***; Morphological and histochemical studies of the liver of animals poisoned with stibine and treated with Unithiol; Farmakol. Toksikol. (4) 164-168 (1968) [Abstract]

785 ***Kozlov EI; L'vova MS***; Reaction of dehydroascorbic acid with unithiol and some of its kinetic regularities; Pharm. Chem. J. 10(5) 643-648 (1976)

786 ***Kraus T, Anders M, Weber A, Hermer P, Zschiesche W***; Zur Häufigkeit umweltbezogener Stomatisierungsstörungen; Arbeitsmed. Sozialmed. Umweltmed. 30 147-152 (1995)

787 ***Krause C***; Zur umweltmedizinischen Beurteilung von Human-Biomonitoring-Befunden in der ärztlichen Praxis. Kommission „Human-Biomonitoring" des Umweltbundesamtes; Umweltmed. Forsch. Prax. 5(3) 177-180 (2000)

788 ***Kremers L,Halbach S, Mehl A, Willruth H, Wack FX, Hickel R***; Quecksilberkonzentrationen bei der Entfernung von Amalgamfüllungen mit und ohne Kofferdamm; Dtsch. Zahnärztl. Z. 51(10) 617-619 (1996)

789 ***Kreppel H, Reichl FX, Szinicz L, Fichtl B, Forth W***; Efficacy of various dithiol compounds in acute As_2O_3 poisoning in mice; Arch. Toxicol. 64(5) 387-392 (1990)

790 ***Kreppel H, Reichl FX, Szinicz L, Hunder G, Forth W, Fichtl B***; Arsenic content in organs of mice acutely poisoned with arsenic trioxide and treated with BAL, DMPS, or DMSA; Plzen. Lek. Sborn. 62(Suppl.) 57-58 (1990)

791 ***Kreppel H, Knebel R, Reichl FX, Fichtl B, Mückter H, Forth,W***; Influence of dithiol compounds and the newly synthesized compound 2,3-bis(acetylthio)propanesulfonamide on tissue content and elimination of arsenic in mice; 6th International Trace Element Symposium, Leipzig, VOL. 4, pp. 1046-1052 (1989)

792 ***Kreppel H, Reichl FX, Mückter H, Fichtl B, Forth W***; Influence of oral treatment with dithiol compounds on the survival rate of mice poisonend with arsenic; 6th International Trace Element Symposium, Leipzig, VOL. 4, pp. 1039-1045 (1989)

793 ***Kreppel H, Reichl FX, Forth W, Fichtl B***; Lack of effectiveness of D-penicillamine in experimental arsenic poisoning; Vet. Hum. Toxicol. 31(1) 1-5 (1989)

794 ***Kreppel H, Knebel R, Mückter H, Reichl FX***; Influence of dithiol compounds on tissue content and elimination of arsenic in mice; Naunyn Schmiedeberg's Arch. Pharmacol. 1092(Suppl.) R26 No. 104 (1988)

795 ***Kreppel H, Szinicz L***; Reduction of toxicity of arsenic by 2,3-dimercapto-1-propaneol (BAL), 2,3-dimercaptopropane-1-sulfonate sodium (DMPS) and 2,3-dimercaptosuccinic acid (DMSA) in mice; Naunyn Schmiedeberg's Arch. Pharmacol. 332(Suppl.) R27 No. 106 (1986)

796 ***Kreppel H, Fichtl B, Forth W***; Effectiveness of various thiol compounds in reducing the arsenic content of tissues in acute arsenic poisoning; Naunyn Schmiedeberg's Arch. Pharmacol. 332(Suppl.) R17 No. 70 (1986)

797 ***Kroemer HK***; Neues über Cytochrom-P450-Enzyme: Folgen für die Pharmakotherapie? Pharmazeutische Ztg, 142(5) 301-306 (1997)

798 ***Krüger M***; Chemische Kampfstoffe (C-Waffen) 2; Derm. Beruf. Umwelt. 39(6) 179-193 (1991)

799 ***Kruse-Jarres JD***; Klinische Relevanz essentieller Mikroelemente; GIT Labor-Medizin 11(12) 704-712 (1988)

800 ***Kruszewska S, Wiese M, Kolacinski Z, Mielczarska J***; The use of haemodialysis and 2,3-propanesulfonate (DMPS) to manage acute oral poisoning by lethal dose of arsenic trioxide; Int. J. Occup. Med. Environ. Health 9(2) 111-115 (1996)

801 ***Krylov VI, Petrushina AD, Zhmurov VA***; Clinical pharmacology of membrane-destabilizing processes in nephropathies in children; Farmakol. Toksikol. 49(5) 114-116 (1986) [Abstract]

802 ***Künzel G, Kirchdörfer U, Klobusch J, Rabe T, Gerhard I, Runnebaum B***; Welchen Einfluß hat Quecksilber auf die zelluläre Immunität bei Frauen mit Alopezia areata und Alopezia diffusa?; Arch. Gynecol. Obstet. 254 277-278 (1993)

803 ***Kuchmerovskaia TM, Donchenko GV, Klimenko AP, Chichkovskaia GV, Pakirbaeva LV, Kozitskii ZI, Efimov AS***; Role of aldose reductase inhibitors in the development of peripheral neuropathy in experimental diabetes; Ukrainskii Biokhimicheskii Zhurnal 69(3) 77-82 (1997)

804 ***Kufner W***; Osteoporose und Polyneuropathie; Selecta 31(35) 1918 (1989)

805 ***Kuhn A***; Einfluß von Chelaten auf den Stoffwechsel von Mangan; Report KFK 775, Kernforschungszentrum Karlsruhe, Mai 1968

806 ***Kulichenko AN, Popov YA***; Development of the method of nitrosoguanidine inactivation in the mutagenic treatment of bacteria; Zh. Mikrobiol. Epidemiol. Immunobiol. (8) 5-7 (1989) [Abstract]

807 ***Kulig P***; A tragic reminder about organic mercury; New Engl. J. Med. 338(23) 1693-1694 (1998)

808 ***Kumagai Y, Koide S, Taguchi K, Endo A, Nakai Y, Yoshikawa T, Shimojo N***; Oxidation of proximal protein sulfhydryls by phenanthraquinone, a component of diesel exhaust particles; Chem. Res. Toxicol. 15(4) 483-489 (2002)

809 ***Kummer A, Michot F***; Ein Fall von iatrogener Quecksilber-Inkorporation durch Ballonruptur einer Miller-Abbot-Sonde bei Dünndarmsubileus; Schweiz. Med. Wochenschr. 114(6) 210-212 (1984)

810 ***Kurliandchikov VN***; Treatment of patients with cerebral forms of hypertensive disease by combination of decamevit with unithiol in conditions of biotron; Vrach. Delo. (8) 66-69 (1976) [Abstract]

811 ***Kurliandchikov VN***; Use of decamevit and unithiol in the treatment of patients with cerebral form of hypertensive disease in usual conditions and in the Biotron; Vrach. Delo. (1) 38-41 (1975) [Abstract]

812 ***Kurliandchikov VN***; Complex decamevit and unithiol treatment of patients with hypertensive disease in conditions of the biotron; Vrach. Delo. (7) 25 - 29 (1974) [Abstract]

813 ***Kurliandchikov VN***; Treatment of patients with coronary arteriosclerosis with unithiol in combination with Decamevit; Vrach. Delo. 6 8-12 (1973) [English Translation]

814 ***Lai MW, Boyer EW, Kleinman ME, Rodig NM, Ewald MB***; Acute arsenic poisoning in two siblings; Pediatrics 116(1) 249-257 (2005)

815 ***Lammers HJ***; Autismus durch Quecksilberbelastung?; Z. Umweltmed. 11(2) 70-75 (2003)

816 ***Lapin IP***; The comparative efficacy of rhodanase activators (cysteine and Unithiol) during cyanide poisoning; Farmakol. Toksikol. 25 361-364 (1962) [English Translation]

817 ***Lapin IP, Grande NV***; Increase of the rhodanese activity under the influence of dimercaptopropanesulfonate sodium (unithiol); Farmakol. Toksikol. 24 604-610 (1961) [Abstract]

818 ***Larsen RH, Slade S, Zalutsky MR***; Blocking [^{211}At]Astatide accumulation in normal tissues: Preliminary evaluation of seven potential compounds; Nucl. Med. Biol. 25(4) 351-357 (1998)

819 ***Lash LH, Putt DA, Zalups RK***; Influence of exogenous thiols on inorganic mercury-induced injury in renal proximal and distal tubular cells from normal and uninephrectomized rats; J. Pharmacol. Exp. Ther. 291(2) 492-502 (1999)

820 ***Lash LH, Putt DA, Zalups RK***; Role of extracellular thiols in accumulation and distribution of inorganic mercury in rat renal proximal and distal tubular cells; J. Pharmacol. Exp. Ther. 285(3) 1039-1050 (1998)

821 ***Lash LH, Zalups RK***; Mercuric chloride-induced cytotoxicity and compensatory hypertrophy in rat kidney proximal tubular cells; J. Pharmacol. Exp. Ther. 261(2) 819-829 (1992)

822 ***Laskavaya FP,Lastkov OA, Liubomudrov VE, Stoyanova TM, Shaparenko BA, Kovalyov EZ***; Effect of unithiol inhalations on the development and course of micromercurialism in the experiment; Vrach. Delo. 12 115-118 (1971) [Abstract]

823 ***Lauer R***; Amalgam - Diagnose und Therapie der chronischen Quecksilbervergiftung; www.amalgam.homepage.t-online.de/diag_ther.htm (2006)

824 ***Lazareva VI, Lazarev AI***; Spectrophotometric determination of ruthenium with unithiol; Industrial Laboratory USSR 51(12) 1075-1080 (1986)

825 ***Lazaris JA, Bavelsky ZE***; Dithisone diabetes in rabbits and its prevention by sulfhydryl and imidazole containing compounds; Endocrinol. Exp. 18(3) 157-167 (1984)

826 ***Lazaris JA, Bavelsky ZE***; Prevention of dithizone diabetes by compounds containing sulfhydryl groups; Bull. Exp. Biol. Med. 67(3) 257-259 (1969)

827 ***Le XC, Ma M, Lu X, Cullen WR, Aposhian HV, Zheng B***; Determination of monomethylarsonous acid, a key arsenic methylation intermediate, in human urine; Environ. Health Perspect. 108(11) 1015-1018 (2000)

828 ***Le XC, Lu X, Ma M, Cullen WR, Aposhian HV, Zheng B***; Speciation of key arsenic metabolic intermediates in human urine; Anal. Chem. 72 5172-5177 (2000)

829 ***Lechner J***; Zur Wirkung von DMPS und DMSA - Erweiterte Aspekte zur Amalgamausleitung; Dtsch. Zschr. f. Biol. Zahnmed. 11(4) 140-151 (1995)

830 ***Lechner J***; Regulation und Information; Hüthig Verlag (1993)

831 ***Lechner J***; Quecksilberbelastung, Strommessung und Nosodentherapie - eine kritische Gegenüberstellung; Dtsch. Z. Biol. Zahnmed. 8(1) 8-14 (1992)

832 ***LeClerc GM, Grahame DA***; Methylcobamide:coenzyme M methyltransferase isozymes from Methanosarcina barkeri. Physicochemical characterization, cloning, sequence analysis, and heterologous gene expression; J. Biol. Chem. 271(31) 18725-18731 (1996)

833 ***Ledovskikh VM***; Goal-directed synthesis of surfactants of the thiourea series for electrodeposition of lustrous copper from a sulfuric acid electrolyte; Zashch. Met. 21(5) 741-752 (1985) [Abstract]

834 ***Lee SH, Kellner L, Zilker T, Drasch G, Berweck S, Döhlemann C***; Neurological and psychiatric symptoms due to mercury intoxication in a family from Iraq; Neuropediatrics 36 (2) P100 (2005)

835 ***Lee SH, Lee KT, Lee JH, Lee JK, Rhee PL, Kim JJ, Koh KC, Paik SW, Rhee JC, Choi KW***; Effects of chelators on liver cadmium contents in chronic cadmium intoxication rats; Korean J. Hepatol. 4(1) 59-68 (1998)

836 ***Lee V, Oberdörster G***; Effect of chelating agents on cadmium retention in rats after inhalation exposure; 8th Annual Report - Environmental Health Sciences Center at the University of Rochester 85-87 (1983)

837 ***Lee YW, Rhim KH***; A study on the histopathological change of placenta and protective effects of DMPS in the pregnant rat treated with cadmium; J. Pub. Health Assoc. 13(2) 31-42 (1987) [Abstract]

838 ***Legrum W***; Quecksilber-„Belastung“ durch Amalgamfüllungen; Dtsch. Med. Wochenschr. 118(4) 398 (1993)

839 ***Legrum W, Stachniss V***; Wie problematisch ist der Dentalwerkstoff Amalgam?; Dtsch. Med. Wochenschr. 115(39) 1490-1494 (1990)

839a ***Leikin JB, McFee RB***; Handbook of nuclear, biological and chemical agent exposures; CRC Press (2007)

840 ***Leistevuo J, Leistevuo T, Helenius H, Pyy L, Osterblad M, Huovinen P, Tenovuo J***; Dental amalgam fillings and the amount of organic mercury in human saliva; Caries Res. 35(3) 163-166 (2001)

841 ***Leuschner F***; Mutagenicity evaluation of Ames Salmonella/Microsome plate test; Unpublished results (1981)

842 ***Li W, Chien PK, Furst A***; Evaluation of three antidotes on arsenic toxicity in the common earthworm (Lumbricus terrestris); J. Appl. Toxicol. 14(3) 181-183 (1994)

843 ***Lichtnecker H, Weihrauch M***; Umweltmedizinische Leitlinien der Deutschen Gesellschaft für Arbeitsmedizin und Umweltmedizin e.V.: Quecksilber; Arbeitsmed. Sozialmed. Umweltmed. 38(4) 210-212 (2003)

844 ***Liebl B, Mückter H, Doklea E, Fichtl B, Forth W***; Antidotal efficacies of BAL and DMPS alone and in combination in oxophenylarsine (PhAsO)-exposed MDCK cells; Naunyn Schmiedebergs Archives of Pharmacology 357 (4 Suppl.) R130 (1998)

845 ***Liebl B, Mückter H, Doklea E, Fichtl B, Forth W***; Reversal of oxophenylarsine-induced inhibition of glucose uptake in MDCK cells; Fundam. Appl. Toxicol. 27(1) 1-8 (1995)

846 ***Lin CC, Ger J, Yang CC, Wu ML, Tsai WJ, Deng JF***; Acute chromium poisoning after extensive dermal exposure to dichromate; 5th Congress of APAMT - 6th to 8th August, Cinnamon Grand Hotel, Colombo (2006)

847 ***Lindner J***; Rettungseinsatz in einem industriellen Großbetrieb; Der Notarzt 16(4) 124-129 (2000)

848 ***Liniecki J, Surma M, Mlodkowska E, Oginski M***; ^{99m}Technetium-Unithiol complex, a new pharmaceutical for kidney scintigraphy. II Comparison of renal scintigrams in man, obtained by means of ^{197}Hg-chlormerodrin or ^{99m}Tc-Unithiol complex; Nuklearmedizin 16(4) 179-182 (1977)

849 ***Link B***; Richtwerte für die Innenraumluft - Quecksilber; Bundesgesundhbl. Gesundheitsforsch. Gesundheitsschutz 42(2) 168-174 (1999)

850 ***Liu J, Zheng B, Aposhian HV, Zhou Y, Chen ML, Zhang A, Waalkes MP***; Chronic arsenic poisoning from burning high-arsenic-containing coal in Guizhou, China; Environ. Health Perspect. 110(2) 119-122 (2002)

851 ***Liu W, Jiang C, Hu Z, Zhang C, Xu Q, Zhou G***; Mercury concentration in cerebrospinal fluid in patients with chronic mercury poisoning; Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi 24(7) 403-405 (2006) [Abstract]

852 ***Liu Y, Holmgren M, Jurman ME, Yellen G***; Gated access to the pore of a voltage-dependent K channel; Neuron 19(1) 175–184 (1997)

853 ***Llobet JM, Domingo JL, Paternain JL, Corbella J***; Treatment of acute lead intoxication. A quantitative comparison of a number of chelating agents; Arch. Environ. Contam. Toxicol. 19(2) 185-189 (1990)

854 ***Llobet JM, Domingo JL, Corbella J***; Antidotes for zinc intoxication in mice; Arch. Toxicol. 61(4) 321-323 (1988)

855 ***Llobet JM, Bosque A, Colomina MT, Domingo JL, Corbella J***; The protective action of chelating agents in experimental zinc poisoning; Plzen Lek. Sborn 56(Suppl.) 61-63 (1988)

856 ***Loan ND, Quyen NB, Phuc NH***; The treatment of padan poisoning by unithiol in experimental animals; www.oshvn.net/en/Tu%20lieu/TAPSANYHLD/THANG9-1996/DieuT riNhiemDocPadanBangUnithiolTrenDongVat ThucNghiem-en.htm (1996)

857 ***Lobner D, Asrari M***; Neurotoxicity of dental amalgam is mediated by zinc; J. Dent. Res. 82(3) 243-246 (2003)

858 ***Loring RH, Dou YM, Lane W, Jones GS***, Stevenson KJ; Aromatic trivalent arsenicals: covalent yet reversible reagents for the agonist binding site of nicotinic receptors; Brain Res. Mol. Brain Res. 15(1-2) 113-120 (1992)

859 ***Lowell JA, Burgess S, Shenoy S, Curci JA, Peters M, Howard TK***; Mercury poisoning associated with high-dose hepatitis-B immune globulin administration after liver transplantation for chronic hepatitis B; Liver Transplant. Surg. 2(6) 475-478 (1996)

860 ***Lu C, Chen Z, Lin Z, Xing Y, Xu H, Zhang Y***; Tetramine poisoning of children: First-Aid, emergency department treatment, and intensive care ; Prehospital Dis. Med. 2002; 17(Suppl.2) s24-s25

861 ***Lu X, Arnold LL, Cohen SM, Cullen WR, Le XC***; Speciation of dimethylarsinous acid and trimethylarsine oxide in urine from rats fed with dimethylarsinic acid and dimercaptopropane sulfonate; Anal. Chem. 75(23) 6463-6468 (2003)

862 ***Lu Z, Liu X, Hu G, Liang H, Qiu Q, Li H, Chen S***; A study about bromoxynil toxity and the protective effects of Na-DMPS in mouse during acute toxicity of bromoxynil; Chin. J. Emerg. Med. 15(2) 124-127 (2006) [Abstract]

863 ***Lu ZQ, Qiu QM, Miao XJ, Hu GX***; Experimental study on detoxication effect of sulfhydryl compounds in acute poisoning of dimethylformamide; Chin. Crit. Care Med. 19(4) 233-235 (2007) [Abstract]

864 ***Lu ZQ, Hu GX, Chen ZK***; Antidotal effects of 2,3-dimercaptopropane-1-sulfonate sodium (DMPS) and combined with diazepam on acute poisoning caused by sodium ammonium-dimethyl-2-propaneo-1,3-dithiosulfate monohydrate (SCD); Chemical Abstracts 118-13-118 437 (1993)

865 ***Lu ZQ, Chen ZK***; Dose-effect relationship of DMPS on acute poisoining caused by SCD; Chemical Abstracts 116-03-016 887 (1992)

866 ***Lübbe J, Wüthrich B***; Amalgamallergie und Amalgamkontroverse; Schweiz. Med. Wochenschr. 126(16) 661-665 (1996)

867 ***Luchese C, Zeni G, Rocha JBT, Nogueira CW, Santos FW***; Cadmium inhibits delta-aminolevulinate dehydratase from rat lung in vitro: Interaction with chelating and antioxidant agents; Chem. Biol. Interact. 165(2) 127-137 (2007)

868 ***Luganskii NI, Loboda YI***; Experimental data on peroral administration of unithiol; Farmakol. Toksikol. Sb. (Kiev) (1) 161-166 (1964) [Abstract]

869 ***Luganskii NI, Loboda YI***; Effect of unithiol and its analoges on SH-groups of rabbit serum during arsenic intoxication; Ukrain. Biokhim. Zhur. 33 315-324 (1961) [Abstract]

870 ***Luganskii NI, Loboda YI***; Umwandlung vom Unithiol im Organismus; Farmakol. Toksikol. 23(4) 349-355 (1960) [German Translation]

871 ***Luganskii NI, Loboda YI;*** The effect of unithiol in distribution, accumulation and elimination of radioactive arsenic-76 in rabbits; Med. Radiobiol. Moscow 392-397 (1957) [Abstract]

872 ***Lund ME, Banner W, Clarkson TW, Berlin M***; Treatment of acute methylmercury ingestion by hemodialysis with N-acetylcysteine (Mucomyst) infusion and 2,3-dimercaptopropane sulfonate; J. Toxicol. Clin. Toxicol. 22(1) 31-49 (1984)

873 ***Lungkaphin A, Chatsudthipong V, Evans KK, Groves CE, Wright SH, Dantzler WH***; Interaction of the metal chelator DMPS with OAT1 and OAT3 in intact isolated rabbit renal proximal tubules; Am. J. Physiol. Renal Physiol. 286(1) f68-f76 (2004)

874 ***Lussi A, Buser D***; Amalgamproblematik: Empfehlungen zur Patientenabklärung; VSAO ASMAC Journal (7) 10-16 (2001)

875 ***Lynch E, Braithwaite R***; A review of the clinical and toxicological aspects of 'traditional' (herbal) medicines adulterated with heavy metals; Expert Opin. Drug Saf. 4(4) 769-778 (2005)

876 ***Lynn S, Yu GL, Kun, Yan J***; Vicinal-thiol-containing molecules enhance but mono-thiol-containing molecules reduce nickel-induced DNA strand breaks; Toxicol. Appl. Pharmacol. 160(2) 198-205 (1999)

877 ***Lysenko NM***; Reactions of dithiols with tetramethylthiuram disulfide and with carbon disulfide; Zh. Obs Zh. Obshch. Khim. 44(1) 157-161 (1974)

878 ***Maas C; Bruck W; Haffner HT; Schweinsberg F***; Untersuchung zur Bedeutung einer cerebralen Quecksilberbelastung aus Amalgamfüllungen durch direkten Mund- und Nase- Hirn-Transport; Zentralbl. Hyg. Umweltmed. 198(3) 275-279 (1996)

879 ***MacDonald JR, Gandolfi AJ, Sipes IG***; Structural requirements for cytoprotective agents in galactosamine-induced hepatic necrosis; Toxicol. Appl. Pharmacol. 81(1) 17-24 (1985)

880 ***MacGregor JT, Clarkson, TW***; Treatment of mercury poisoning; IN: "Protein-Metal interactions", M. Friedman (Ed.), Plenum Press, New York, 490 - 495 (1974)

881 ***MacLehose R, Pitt G, Will S, Jones A, Duane L, Flaherty S, Hannant D, Stuttard B, Silverwood A, Snee K, Murray V, Syed Q, House I, Bellis MA***; Mercury contamination incident; J. Public Health Med. 23(1) 18-22 (2001)

882 ***Madejczyk MS, Aremu DA, Simmons-Willis TA, Clarkson TW, Ballatori N***; Accelerated urinary excretion of methylmercury following administration of its antidote N-acetylcysteine requires Mrp2/Abcc2, the apical multidrug resistanceassociated protein; J. Pharmacol. Exp. Ther. 322(1) 378-384 (2007)

883 ***Maehashi H, Murata Y, Miyazawa T***; Treatment of arsenic poisoning with DMSA or DMPS in the rat; Chemical Abstracts 119-19-197 399 (1993)

884 ***Maehashi H, Murata Y***; Arsenic excretion after treatment of arsenic poisoning with DMSA or DMPS in mice; Jpn. J. Pharmacol. 40(1) 188-190 (1986)

885 ***Maehashi H, Yamaguchi Y***; Treatment of arsenic poisoning with heavy-metal antagonists in mice; Matsumoto Shigaku 9(1) 47-51 (1983)

886 ***Maehashi H, Yamaguchi Y, Tsutsumi S***; Arsenic and copper excretion after treatment of arsenic poisoning in rats with heavy-metal antagonists; Dev. Toxicol. Environ. Sci. 11 325-328 (1983)

887 ***Maehashi H, Yamaguchi Y, Tsutsumi S;*** Arsenic and copper excretion after treatment of arsenic poisoning in rats with heavy-metal antagonists; Toxicol. Lett. 18(Suppl.) 116 (1983)

888 ***Maiorino RM, Aposhian HV***; Determination and metabolism of dithiol chelating agents. XVIII Comparison of the biotransformation of sodium 2,3-dimercapto-1-propanesulfonate in humans after intravenous and oral administration; Unpublished results (1997)

889 ***Maiorino RM, Xu ZF, Aposhian HV***; Determination and metabolism of dithiol chelating agents. XVII In humans, sodium 2,3-dimercapto-1-propanesulfonate is bound to plasma albumin via mixed disulfide formation and is found in the urine as cyclic polymeric disulfides; J. Pharmacol. Exp. Ther. 277(1) 375-384 (1996)

890 ***Maiorino RM, Gonzalez-Ramirez D, Zuniga-Charles M, Xu Z, Hurlbut KM, Aposhian MM, Dart RC, Woods JS, Ostrosky-Wegman P, Gonsebatt ME, Aposhian HV***; Sodium 2,3-dimercaptopropane-1-sulfonate (DMPS) challenge test for mercury in humans: III Urinary mercury, and porphyrins after exposure to mercurous chloride; J. Pharmacol. Exp. Ther. 277(2) 938-944 (1996)

891 ***Maiorino RM, Dart RC, Carter DE, Aposhian HV***; Determination and metabolism of dithiol chelating agents. XII Metabolism and pharmacokinetics of sodium 2,3-dimercaptopropane-1-sulfonate in humans; J. Pharmacol. Exp. Ther. 259(2) 808-814 (1991)

892 ***Maiorino RM, Weber GL, Aposhian HV***; Determination and metabolism of dithiol chelating agents. III Formation of oxidized metabolites of 2,3-dimercaptopropane-1-sulfonic acid in rabbit; Drug Metab. Dispos. 16(3) 455-463 (1988)

893 ***Maiorino RM, Barry TJ, Aposhian HV***; Determination and metabolism of dithiol-chelating agents: electrolytic and chemical reduction of oxidized dithiols in urine; Anal. Biochem. 160(1) 217-226 (1987)

894 ***Maiorino RM, Weber GL, Aposhian HV***; Fluorometric determination of 2,3-dimercaptopropane-1-sulfonic acid and other dithiols by precolumn derivatization with bromobimane and column liquid chromatography; J. Chromatogr. 374(2) 297-310 (1986)

895 ***Maiorino RM, Aposhian HV***; Dimercaptan metal-binding agents influence the biotransformation of arsenite in the rabbit; Toxicol. Appl. Pharmacol. 77(2) 240-250 (1985)

896 ***Mairgünther R, Scheuber T, Hamm G***; Normale und provozierte Hg-Freisetzung aus unterschiedlichen Amalgamen; Schweiz. Monatsschr. Zahnmed. 102(4) 419-423 (1993)

897 ***Malyshev II***; Hepato-cerebral dystrophy in children; Pediatriia (12) 30-33 (1975) [Abstract]

898 ***Manatauov TD, Ospanov KK, Mansurov GN***; Investigation of the adsorption of unithiol on a thin-film platinum electrode by resistometry; Elektrokhimiya 26(6) 782-783 (1990) [Abstract]

899 ***Mandoli DF, Townsend LS, Cullen WR; Dejbod N***; Acetabularia acetabulum: A novel model for arsenic toxicity; www.aspb.org/meetings (2001)

900 ***Mangir M, Ruprecht J, Bunte T***; Untersuchungen zur Reversibilität von Quecksilberintoxikationen durch Dimaval (DMPS) in vitro; unveröffentlichte Ergebnisse (1990)

901 ***Manolov K, Boyadjiev S***; On the possibilities to increase the effectiveness of protection from lethal intoxication with methyldichlordiethylamine (Embichin); Folia Med. 21(3) 25-29 (1979)

902 ***Mant TGK***; Clinical studies with dimercapto sulfonate in mercury poisoning; Human Toxicology 4 346 (1985)

903 ***Martin JC, Lacombe D, Lefebvre D, Bonafe JL, Taieb A, Maleville J***; Erythromelalgie: Une observation familiale. Discussion sur le role du mercure; Ann. Dermatol Venerol. 121(4) 309-314 (1994)

904 ***Mashkovskii MD, Shvarts GI***; Experimental study of the antihypertensive activity of unithiol, D-penicillamine and cysteine; Farmakol. Toksikol. 46(6) 24-28 (1983) [Abstract]

905 ***Masliuk VI, Fedorova TA***; Unithiol in the therapy of poisoning caused by cardiac glycosides; Kardiologiia 7(10) 125-127 (1967) [Abstract]

906 ***Masliuk VI, Burmistrova LD, Pogosian AA***; The effect of unithiol on the electrocardiogramm and some indices of electrolyte exchange in therapy of overdosage of cardic glycosides; Sov. Med. 29(5) 62-67 (1966) [Abstract]

907 ***Masliuk VI, Pogosian AA***; Elimination of the toxic action of cardiac glycosides by Unithiol (dimercaptopropane-sulfonate); Sov. Med. 27(11) 89-92 (1964) [Abstract]

908 ***Mathur S, Flora SJS, Mathur R, Kannan GM, Das Gupta S***; Beryllium-induced biochemical alterations and their prevention following co-administration of meso-2,3-dimercaptosuccinic acid or 2,3-dimercaptopropane sulfonate in rats; J. Appl. Toxicol. 14(4) 263-267 (1994)

909 ***Matts RL, Schatz JR, Hurst R, Kagen R***; Toxic heavy metal ions activate the heme-regulated eukaryotic initiation factor-2α kinase by inhibiting the capacity of hemin-supplemented reticulocyte lysates to reduce disulfide bonds; J. Biol. Chem. 266(19) 12695-12702 (1991)

910 ***Maximov JN, Krasniuk EP, Ovrutzki VM, Grygoryeva TM, Lubianova IP, Danova IV***; Antidotal effectiveness of resynthesized Unithiol; Modern Problems of Toxicology (1) (2000) [Abstract]

911 ***May PA, Bulman RA***; The present status of chelating agents in medicine; IN: "Progess in Medicinal Chemistry", GP Ellis, GB West (Eds.), Elsevier Science Publishers, pp. 225-336 (1983)

912 ***May PM, Smith GL, Williams DR***; Specification studies for cadmium in vivo and an assessment of cadmium chelating drugs; Proc. Int. Conference on Heavy Metal in the Environment, Amsterdam, 632-634 (1981)

913 ***Mayer AF, Weyland B, von Issendorf WD, Rommens PM***; Chirurgische Therapie einer Quecksilbervergiftung durch Sportunfall beim Bogenschießen; Sportorthopädie Sporttraumatologie 15(3) 153-154 (1999)

914 ***Mayer K***; Risikobestimmung der Amalgambelastung, Teil 1+2; ZWR 105(4) 213-218; (5) 280-283 (1996)

915 ***Mayer K***; Amalgam: Zeitbombe im Mund?; ZWR 104(3) 209-214 (1995)

916 ***Mazumder DNG***; Chronic arsenic toxicity: Clinical features, epidemiology, and treatment: Experience in West Bengal; J. Environ. Sci. Health - Part A: Toxic Hazard. Subst. Environ. Eng. 38(1) 141-163 (2003)

917 ***Mazumder DNG, De BK, Santra A, Ghosh N, Das S, Lahiri S, Das T***; Randomized placebo-controlled trial of 2,3-dimercapto-1-propanesulfonate (DMPS) in therapy pf chronic arsenicosis due to drinking arsenic contaminated water; Clin. Toxicol. 39(7) 665-674 (2001)

918 ***Mazumder DNG, Ghoshal UC, Saha J, Santra A, De BK, Chatterjee A, Dutta S, Angle CR, Centeno JA***; Randomized placebo-controlled trial of 2,3-dimercaptosuccinic acid in therapy of chronic arsenicosis due to drinking arsenic contaminated subsoil water; Clin. Toxicol. 36(7) 683-690 (1998)

919 ***McGown EL, Tillotson JA, Knudsen JJ, Dumlao CR***; Biological behavior and metabolic fate of the BAL analogues DMSA and DMPS; Proc. West. Pharmacol. Soc. 27 169-176 (1984)

920 ***McKay CA, Holland MG, Nelson LS***; Call to arms for medical toxicologists: The dose, not the detection, makes the poison; Int. J. Med. Toxicol. 6(1) 1 (2003)

921 ***Mehta A, Flora SJ***; Possible role of metal redistribution, hepatotoxicity and oxidative stress in chelating agents induced hepatic and renal metallothionein in rats; Food Chem. Toxicol. 39(10) 1029-1038 (2001)

922 ***Mehta A, Flora SJS***; Chelating agents induced metallothionein and oxidative stress in male rats; Indian J. Pharmacol. 33(1) 53-54 (2001)

923 ***Meier-Abt PJ, Kupferschmidt H***; Dekontamination und wichtigste Antidote; Schweiz. Med. Forum (16) 402-405 (2001)

924 ***Meinel K, Deuber HJ, Osten B***; Quecksilberinduzierte Glomerulopathie infolge Amalgam-Belastung; Umweltmed. Forsch. Prax. 3(4) 256-257 (1998)

925 ***Meisinger V, Jahn O;*** AAS als Anwendungstechnik der Spurenanalytik bei medizinischer Routineuntersuchung; GIT Labor Medizin 10(6) 265-268 (1987)

926 ***Melchart D, Köhler W, Halbach S, Zilker T, Kremers L, Linde K***; Can biomonitoring of mercury distinguish between patients with complaints attributed to dental amalgam and healthy amalgam carriers? A diagnost case-control study; Clin. Toxicol. 45(4) 362 (2007)

927 ***Mercola J, Klinghardt D***; Mercury toxicity and systemic elimination agents; J. Nutr. Environ. Med. 11(1) 53-62 (2001)

928 ***Meredith TJ, Haines JA, Berger JC***; IPCS/CEC-evaluation of clinical efficacy of chelating agents used in the treatment of poisoning; Plzen. Lek. Sborn. 62(Suppl.) 13-15 (1990)

929 ***Merkord J, Weber H, Kröning G, Hennighausen G***; Antidotal effects of 2,3-dimercaptopropane-1-sulfonic acid (DMPS) and meso-2,3-dimercaptosuccinic acid (DMSA) on the organotoxicity of dibutyltin dichloride (DBTC) in rats; Hum. Exp. Toxicol. 19(2) 132-137 (2000)

930 ***Merkord J, Henninghausen G, Kröning G***; Interactions of dimercaprol, DMSA and DMPS with dialkyl-tin compounds; Plzen. Lek. Sborn. 62(Suppl.) 59-61 (1990)

931 ***Merkulova NN, Khromova EA, Mineeva NV***; A comparative assessment of using sulfide reducers for detection of IgG antibodies to antigens of ABO erythrocytes; Gematol. Transfuziol. 49(3) 16-18 (2004) [Abstract]

932 ***Meulenbelt J, van Dijk A, Ververs FFT, de Vries I***; Dimercapto-1-propane sulfonate (DMPS) The chelator of choice in mercury intoxication (DMPS); European Association of Poison Control Centers and Clinical Toxicologist, Oslo, June 1997

933 ***Miao X, Lu Z, Qiu Q, Hu G, Yu F;*** Study on toxicity of dimethylformamide administered by gavage and treatment effect of sodium dimercaptopropanesulfonate; Shiyong Yixue Zazhi 22(12) 1367-1369 (2006) [Abstract]

934 ***Micheva M, Stoichev T***; Effect of thiol compounds on aniline toxicity and aniline metabolism; Eksp. Med. Morfol. 19(1) 36-40 (1980) [Abstract]

934a ***Midtdal K, Solberg K, Stenehjem A, Lierhagen S, Jacobsen D***; Chronic arsenic poisoning: Probably no effect from chelating therapy using DMSA; J. Toxicol. Clin. Toxicol. 40(3) 385-386 (2002)

935 ***Miller DM, Woods JS***; Redox activities of mercury-thiol complexes: Implications for mercury-induced porphyria and toxicity; Chem. Biol. Interact. 88(1) 23-35 (1993)

936 ***Min W, Desheng W, Xiaoyuan L, Xiaolin Y***; Regeneration of functionally active rat brain muscarinic receptor in vitro after inhibition with methylmercury chloride; J. West. China Univ. Med. Sci. 28(2) 140-143 (1997) [Abstract]

937 ***Mitchell WM, Basinger MA, Jones MM***; Antagonism of acute copper(II)-induced renal lesions by sodium 2,3-dimercaptopropanesulfonate; Johns Hopkins Med. J. 151(6) 283-285 (1982)

938 ***Miyazawa T; Naito M; Maehashi H***; The effects of DMSA and DMPS on arsenate excretion in mice; Matsumoto Shigaku 26(2-3) 102-105 (2000)

939 ***Miyazawa T; Maehashi H***; The effect of chelating agents on the excretion of sodium arsenate and sodium monomethylarsonic acid in mice; Jpn. J. Pharmacol. 49(Suppl) 336 (1989)

940 ***Mizyukova IG, Petrunkin VE***; Unithiol and mercaptid as antidotes in poisoning with arsenic-containing substances; Vrach. Delo. (2) 126-129 (1974) [Abstract]

941 ***Mizyukova IG, Petrunkin VE, Lysenko NM***; Antidotal potency of a series of thiol compounds as a function of their structure; Farmakol. Toksikol. 34(1) 70-74 (1971) [Abstract]

942 ***Mizyukova IG, Lokantsev DS***; A comparative essay of toxic and antidotal activity of some mercaptoalkanesulfonate derivatives; Farmakol. Toksikol. 23 355-361 (1960)

943 ***Moaddel R, Sharma A, Huseni T, Jones GS, Hanson RN, Loring RH***; Novel biotinylated phenylarsonous acids as bifunctional reagents for spatially close thiols: Studies on reduced antibodies and the agonist binding site of reduced Torpedo nicotinic receptors; Bioconjugate Chemistry 10(4) 629-637 (1999)

943a ***Moecke H, Bey T, Koenig KL, Rechenbach P, Schallhorn J***; Polonium-210 - eine Kurzinformation; Notfall Rettungsmedizin 10(1) 37-40 (2007)

944 ***Moeschlin S***; Klinik und Therapie der Vergiftung; Georg-Thieme Verlag Stuttgart, New York (1980)

945 ***Mokrzan EM, Kerper LE, Clarkson TW***; Methyl-mercury uptake into cultured brain capillary endothelial cell on amino acid system; J. Pharmacol. Exp. Ther. 272(3) 1277-1284 (1995)

947 ***Molin M, Schütz A, Skerfving S, Sällsten G***; Mobilized mercury in subjects with varying exposure to elemental mercury vapour; Int. Arch. Occup. Environ. Health 63(3) 187-192 (1991)

947 ***Monov A***; Mass Poisonings by Chemical Toxic Substances; IN: Chemical Terrorism and Traumatism, Alexander Monov A, Dishovsky C (Eds.), Sofia, Publishing House of the Union of Scientists in Bulgaria (2005)

948 ***Moore DF, O'Callaghan CA, Berlyne G, Ogg CS, Davies HA,House IM, Henry A***; Acute arsenic poisoning: absence of polyneuropathy after treatment with 2,3-dimercaptopropanesulfonate (DMPS); J. Neurol. Neurosurg. Psychiatry 57(9) 1133-1135 (1994)

949 ***Moore G, Hayden J, Pires J, Hamilton MG***; Rational Design of botulinus neurotoxin therapies; In. Chemical and Biological Medical Treatments Symposium, May 2000

950 ***Moracevskij JV, Volf LA***; Zur Maskierung von Kationen bei komplexometrischen Titrationen; Anal. Bioanal. Chem. 183(4) 301-302 (1961)

951 ***Morgenstern J, Burk G, Damrau J, Franzen E***; Kriterien für Diagnostik und Therapie von Quecksilberdepots bei Hg-Exponierten; 32. Jahrestagung der Deutschen Gesellschaft für Arbeitsmedizin, Köln (1992)

952 ***Moss J***; A viewpoint on mercury - Part V: Methods and controversies concerning treatment; http://www.nutritioncouncil.com/newsletter.html (2002)

953 ***Mraz L, Sykora J, Eybl V***; Palladium and chelating agents; Plzen. Lek. Sborn. 49(Suppl.) 143-145 (1985)

654 ***Mückter H, Doklea E, Hopfer C***; Cytotoxicity of some cyclic trithiocarbonates; Naunyn Schmiedebergs Arch. Pharmacol. 371(Suppl.1) r126-r127 (2005)

955 ***Mückter H, Wedekind S***; Arsen: Mörderisch und heilsam zugleich; Pharm. Ztg. 149(43) 3784-3785 (2004)

956 ***Mückter H, Liebl B, Reichl FX, Hunder G, Walther U, Fichtl B***; Are we ready to replace dimercaprol (BAL) as an arsenic antidote?; Hum. Exp. Toxicol. 16 (8) 460 - 465 (1997)

957 ***Mückter H, Islambouli S, Doklea E, Hopfer C, Szinicz L, Fichtl B, Forth W***; Isolated rat kidney tubules as a screening system for arsenic antidotes; Toxicol. Appl. Pharmacol. 121(1) 118-128 (1993)

958 ***Mückter H, Islambouli S, Fichtl B, Forth W***; Different efficacies of thiol antidotes against organic and anorganic arsenic compounds. An in-vitro study using isolated rat kidney tubules; Plzen. Lek. Sborn. 62(Suppl.) 63-64 (1990)

959 ***Mückter H, Islambouli S, Szinicz L***; Isolated rat kidney tubules as a screening system for arsenic antidotes; Naunyn Schmiedeberg's Arch. Pharmacol. 339(Suppl.) R78 (1989)

960 ***Mückter H***; Zur Behandlung der Arsenvergiftung mit geschützten Dithiolen; Dissertation, Uni München (1988)

961 ***Mulkey JP, Oehme FW***; Are 2,3-dimercapto-1-propanesulfonic acid or prussian blue beneficial in acute thallotoxicosis in rats? Vet. Hum. Toxicol. 42(6) 325-329 (2000)

962 ***Mulkey JP***; Thallium toxicity: The problem - An analytical approach - An antidotal study; Thesis, Department of Clinical Sciences, College of Veterinary Medicine; KANSAS STATE UNIVERSITY, Manhattan (1993)

963 ***Müller C, Bertram HP, Rau W, Morandini T***; Diagnosis and DMPS-treatment of accidental cobalt chloride ingestion. Case report; Annual Meeting of European Association of Poison Control Centres, Münster (1989)

964 ***Müller K, Krone O, Göbel T, Brunnberg L, Hofer H***; Akute Bleiintoxikation bei zwei Seeadlern (Haliaeetus albicilla); Tierärztl. Prax. 29(K) 209-213 (2001)

965 ***Müller KE***; Generalisierter Pruritus, Fieberschübe, Myalgien und Arthralgien durch chronische Bleiresorption aus Schrotkugeln; Z. Umweltmedizin 6(1) 46-48 (1998)

966 ***Müller L***; Quecksilber und Amalgam; Band 1 Schriftenreihe Umweltbezogener Gesundheitsschutz; Freie Hansestadt Bemen, Senator für Gesundheit, Jugend und Soziales (1994)

967 ***Muran PJ***; Mercury elimination with oral DMPS, DMSA, vitamin C, and glutathione: an observational clinical review; Altern. Ther. Health Med. 12(3) 70-75 (2006)

968 ***Murray V***; Chemical Incident Report Number 28, produced by the Division of Chemical Hazards and Poisons, London (2003)

969 ***Muss C, Mellinghoff J***; Therapie und Prophylaxe von Metallbelastungen aus Dentallegierungen; GZM Praxis und Wissenschaft 8(3) 12-17 (2003)

970 ***Muss C***; Labordiagnostik bei Metallbelastungen durch Dentallegierungen in der Praxis; GZM Praxis und Wissenschaft 8(2) 18-21 (2003)

971 ***Mutter J, Naumann J, Guethlin C***; Xenobiotikaausleitung bei einer Patientin mit Fibromyalgia, chronischer Erschöpfung und stammbetonter Adipositas; Forsch. Komplementärmed. 14(1) 39-44 (2007)

971a ***Mutter J, Naumann J, Guethlin C***; Comments on the Article "The Toxicology of Mercury and Its Chemical Compounds" by Clarkson and Magos (2006); Crit. Rev. Toxicol. 37(6) 537-549 (2007)

972 ***Mutter J, Naumann J, Walach H, Daschner F***; Amalgam: Eine Risikobewertung unter Berueckichtigung der neuen Literatur bis 2005; Gesundheitswesen 67(3) 204-216 (2005)

973 ***Mutter J***; Amalgam – Risiko für die Menschheit: Quecksilbervergiftungen richtig ausleiten; Fit fürs Leben Verlag in der NaturaViva Verlags GmbH, Weil der Stadt (2001)

974 ***Nadig J, Knutti R, Hany A***; DMSP-Behandlung bei einer akuten Sublimat-(Quecksilberchlorid)-Vergiftung; Schweiz. Med. Wochenschr. 115(15) 507-511 (1985)

975 ***Naidis FB, Plotnikova NA***; Utilization of lead chloride - A by-product of unithiol production; Pharm. Chem. J. 3(3) 540-541 (1969)

975a ***Nantel A***; A high incidence of adverse effects to DMPS in the treatment of a group acute poisoning by arsenic; Unpublished Report (2000)

976 ***Nazarenko VA, Rybalka VB, Medinets VI, Lepeshkin V***I; Heteroligand thiol-thiol complexes of arsenic(III) and their ionic associates with basic dyes; Zh. Anal. Khim. 39(8) 1449-1454 (1984) [Abstract]

977 ***Nazarenko VA, Rybalka VB***; Study of ion associates of unithiol complexes of arsenc with basic dyes; Zh. Anal. Khim. 38(7) 1251-1256 (1983) [Abstract]

978 ***Nazaretian RA, Babayan EA***; The materials to the reason of unithiole, methionine and aminanaloge usage for treatment and prophylaxis of the intoxications by molybdenum xanthogenate compounds; Z. Eksp. Klin. Khim. 27(4) 359-364 (1987) [Abstract]

979 ***Neale EJ, Elliott DJS, Hunter M, Sivaprasadarao A***; Evidence for intersubunit interactions between S4 and S5 transmembrane segments of the shaker potassium channel; J. Biol. Chem. 278(31) 29079-29085 (2003)

980 ***Neimark AI***; Changes in the kallikrein-kinin system of the blood and kidneys and their correction with unithiol in operations on the kidneys; Urol. Nefrol. (3) 38-41 (1983) [Abstract]

981 ***Nekwasil J, Dawczynski H, Arnold B***; Diagnose und Therapie von Quecksilberbelastungen: Ein Praxisbericht; Z. Umweltmedizin 6(3-4) 172-177 (1998)

982 ***Nemeti B, Csanaky I, Gregus Z***; Arsenate reduction in human erythrocytes and rats - testing the role of purine nucleoside phosphorylase; Toxicol. Sci. 74(1) 22-31 (2003)

983 ***Nemeti B, Gregus Z, Waalkes MP, Liu J***; Reduction of arsenate to arsenite in hepatic cytosol; Toxicol. Sci. 70(1) 4-12 (2002)

984 ***Nerudova J, Frantik E, Cabelkova Z, Hornychova M, Cikrt M***; Factors affecting mercury concentration in brain tissue of rats exposed to mercury vapours; Biomarkers Environ. 4(Suppl.1) 82-86 (2001)

985 ***Nerudova J, Cabelkova Z, Frantik E, Lukas E, Urban P, Blaha K, Pelclova D, Lebedova J. Cikrt M***; Mobilization of mercury by DMPS in occupationally exposed workers and in model experiments on rats: Evaluation of body burden; Int. J. Occup. Med. Environ. Health 13(2) 131-146 (2000)

986 ***Neuburger N, Arend V, Guzek B***; Kompendium Umweltmedizin; MediVerlagsgesellschaft, Hamburg (1996)

987 ***Neustadt J, Pieczenik S***; Heavy-metal toxicity - with emphasis on mercury; Integr. Med. 6(2) 26-32 (2007)

988 ***Ng DKK, Chan CH, Soo MT, Lee RSY***; Low-level chronic mercury exposure in children and adolescents: Meta-analysis; Pediatr. Int. 49(1) 80-87 (2007)

989 ***Nguyen PT, Liebl B, Doklea E, Mückter H, Fichtl B***; The cytotoxicity of mono-substituted organic arsenicals in MDCK monolayers; IN: 35th Spring Meeting of the German Society for Experimental and Clinical Pharmacology and Toxicology, Mainz,1994. Naunyn-Schmied-Arch-Pharmacol 349(Suppl.) R116 (1994)

990 ***Nielsen JB, Andersen O***; Effect of four thiol-containing chelators on disposition of orally administered mercuric chloride; Hum. Exp. Toxicol. 10(6) 423-430 (1991)

991 ***Nielsen JB, Andersen O***; Thiol-containing chelators change the disposition of orally administered mercuric chloride; Plzen. Lek. Sborn. 62(Suppl.) 65-66 (1990)

992 ***Niemeier B***; Der Einfluß von Chelatbildnern auf Verteilung und Toxizität von Cadmium; Int. Archiv Gewebepathol. Gewebehyg. 24 160-168 (1967)

993 ***Nigrovic V***; Der Einfluß von Chelatbildnern auf das Verhalten von Quecksilber im Organismus; Arzneim. Forsch. 13 787-792 (1963)

994 ***Nigrovic V***; Untersuchungen über den Einfluß von Chelatbildnern auf die Verteilung von Radioquecksilber im Organismus der Ratte; Dissertation Universität Heidelberg (1962)

995 ***Nilius M***; Schweres Gift – Die erhöhte Bindung von Schwermetallen an Hirngewebe durch die Entgiftung mit BAL, DMSA und DMPS; Tectum Verlag, Marburg (2005)

996 ***Nilius M, Walter U***; Dithiole erhöhen die Bindung von Arsenit an Proteine des ZNS; Dtsch. Zahnärztl. Z 56(3) 197-200 (2001)

996a ***NN***; Interpreting and managing blood lead levels <10 µg/dL in children and reducing childhood exposures to lead: Recommendations of CDC's advisory committee on childhood lead poisoning prevention; MMWR Recomm. Rep. 56(RR-8) 1-20 (2007)

997 ***NN***; 2,3-Dimercapto-1-Propanesulfonic acid; CA Registry File (2007)

998 ***NN***; Arsen und Arsenverbindungen – Wiederkäuer; www-vetpharm.uzh.ch/clinitox/toxdb/WDK_035.htm?clinitox/wdk/toxiwdk.htm (2007)

999 ***NN***; Antidote bei Vergiftungen 2007; Bull. Bundesamt für Gesundheit (5) 77-89 (2007)

1000 ***NN***; C-Waffen; Faltblatt "Eigenschaften und Wirkungen chemischer Kampfstoffe", OWR AG (2007)

1001 ***NN***; Arsen und Quecksilber in Nahrungsergänzungsmitteln gefunden; Pressenotiz der Fachgesellschaft für Ernährungstherapie und Prävention e.V, 2007

1002 ***NN***; Traditional Indian (Ayurvedic) and Chinese medicines associated with heavy metal poisoning; Aust. Adverse Drug Reac. Bull. 26(1) 1 (2007)

1002a ***NN***; Schon über 50 Bleivergiftungen in Leipzig; www.eve-rave.net/abfahrer/presse/presse07-11-19.pdf (2007)

1002b ***NN***; Bleiintoxikation-Therapieempfehlung; Faltblatt Universitätsklinikum Leipzig (2007)

1003 ***NN***; Fachinformation Tauredon® (2006)

1004 ***NN***; WHO UNEP: Sound management of pesticides and diagnosis and treatment of pesticide poisoning - A resource tool; World Health Organization (2006)

1004a ***NN***; RANET Technical Guidelines - Interim Technical Guidelines for National Assistance Capabilities; EPR-RANET, ATTACHMENT 3, International Atomic Energy Agency (2006)

1004b ***NN***; Summary and conclusions of the sixty-seventh meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (2006)

1005 ***NN***; Mittelfristige neurobiologische Effekte von Amalgam-Zahnfüllungen bei Kindern; Der Arzneimittelbrief 40(9) 69-70 (2006)

1006 ***NN***; Amalgame in der zahnärztlichen Praxis; Informationsschrift des BfArM (2005)

1007 ***NN***; Normierung von Stoffgehalten im Urin - Kreatinin. Stellungnahme der Kommission "Human-Biomonitoring" des Umweltbundesamtes; Bundesgesundheitsbl. Gesundheitsforsch. Gesundheitsschutz 48(5) 616-618 (2005)

1008 ***NN***; DMPS; www.generationrescue.org/pdf/heyl.pdf (2004)

1008a ***NN***; Opinion of the Scientific Panel on Contaminants in the Food Chain on a request from the Commission related to mercury and methylmercury in food; The EFSA Journal 34 1-14 (2004)

1009 ***NN***; Aktualisierung der Referenzwerte für Blei, Cadmium und Quecksilber im Blut und Urin von Erwachsenen; Bundesgesundheitsbl. Gesundheitsforsch. Gesundheitsschutz 46(12) 1112-1113 (2003)

1010 ***NN***; Stoffmonographie Arsen – Referenzwert für Urin; Bundesgesundheitsbl. Gesundheitsforsch. Gesundheitsschutz 46(12) 1098-1106 (2003)

1011 ***NN***; EMEA/CPMP Guidance Document on the Use of Medicinal Products for the Treatment of Patients Exposed to Terrorist Attacks with Chemical Agents; EMEA/CPMP/1255/03, 25. April 2003

1012 ***NN***; Bundestagsdrucksache 15/1312: Antwort der Bundesregierung auf eine kleine Anfrage zur Zukunft des Sanitätsdienstes der Bundeswehr (2003)

1013 ***NN***; Fachinformation Angass® (2003)
1014 ***NN***; De-NOL™, Information for Health Professionals (2003)
1015 ***NN;*** On suspected adverse effect of Unithiol (5% solution for injections in 5 ml ampoules), produced by Chemical & Pharmaceutical "Oktyabr" JSC, Russian Federat; www.pharma-center.kiev.ua/vigilance/2003/871_1096_a.html#921 (2003)
1016 ***NN***; DMPS-Challenge Test; http://www.naturalhealinghouse.com/pages/hm_dmps.html
1017 ***NN***; ZMK Münster, Poliklinik für Zahnerhaltung – Untersuchungszentrum Füllungswerkstoffe; http://medweb.uni-muenster.de/institute/zmk/einrichtungen/kons/ueberblick/untagam (2002)
1018 ***NN, Müller KE***; BfArM: „Keine Gesundheitsgefahr durch Amalgam" + Stellungnahme; Z. Umweltmed. 10(3) 122-133 (2002)
1019 ***NN***; Giftinfo der Uni Mainz; http://www.giftinfo.uni-mainz.de/Deutsch/antidotarium/alphabetische_liste_der_speziell.htm (2002)
1020 ***NN***; Neue Arzneistoffe: Arsentrioxid Trisenox® Injection (Cell Therapeutics); www.pharmazeutische-zeitung.de/86-02.htm (2002)
1021 ***NN***; Unithiol; www.micromedex.com/products/drugdex/updates/unith.htm (2002)
1022 ***NN***; Verordnung zur Novellierung der Trinkwasserverordnung vom 21. Mai 2001
1023 ***NN***; Solubility of active pharmaceutical compounds (APCs) in USP grade dimethylsulfoxide (DMSO); Gaylord Chemical Bulletin #124 (2001)
1024 ***NN***; Global mercury assessment - United Nations Environment Programme Chemicals; http://www.unep.org/GoverningBodies/GC22/Document/UNEP-GC22.INF3.pdf
1025 ***NN***; Die Antimyloidtherapie bei den Alterungskrankheiten und der Demenz - Die Bibliothek der Charkower Staatlichen Medizinischen Universität; http://www.univer.kharkov.ua/main/medic/de/vvedenie.html
1026 ***NN***; Health aspects of chemical, biological and radiological (CBR) hazards; Australian Emergency Manuals Series Part III: Emergency Management Practice - Volume 2 - Specific Issues (2000)
1027 ***NN***; Technische Regeln für Gefahrstoffe TRGS 907: BarBl. Heft 2/2000
1028 ***NN***; EMEA position statement: Recent developments concerning thiomersal in vaccines; http://www.emea.eu.int/pdfs/human/press/pos/157800en.pdf (2000)
1029 ***NN***; Draft Toxicological profile for arsenic; Agency for Toxic Substances and Disease Registry ATSDR (USA); http://www.atsdr.cdc.gov/toxprofiles/tp2.pdf (2005)
1030 ***NN***; Toxicological profile for mercury; Agency for Toxic Substances and Disease Registry ATSDR (USA); http://www.atsdr.cdc.gov/toxprofiles/tp46.html (1999)
1031 ***NN***; Dimercapto-1-propanesulfonic acid; Federal Register 64(4) 998 (1999)
1032 ***NN***; Einsatz von Chelatbildnern in der Umweltmedizin? Stellungnahme der Kommission 'Human-Biomonitoring' des Umweltbundesamtes; Bundesgesundheitsbl. Gesundheitsforsch. Gesundheitsschutz 42(10) 823-824 (1999)
1033 ***NN***; Stoffmonographie Quecksilber- Referenz- und Human-Biomonitoring-Werte (HBM); Bundesgesundheitsbl. Gesundheitsforsch. Gesundheitsschutz 42(9) 522-532 (1999)
1034 ***NN***; Komission Human-Biomonitoring des Umweltbundesamtes: Quecksilber-Referenzwerte; Bundesgesundhbl. (6) 271 (1998)
1035 ***NN***; Guidelines for Poison Control; World Health Organization, Geneva (1997)
1036 ***NN***; γ2-freie Amalgame als zahnärztliche Füllungswerkstoffe-Bescheid des BfArM vom 21.7.95; PZ 140(30) 2656,2726 (1995)
1037 ***NN***; Therapie der Schwermetallbelastung; Mineraloscope (1) 22-23 (1996)
1038 ***NN***; Fachinformation Telen®; Yamanouchi (1994)
1039 ***NN***; Monographie: Dimercaptopropanesulfonsäure mit Ergänzung; Bundesanzeiger 5.1.1991 und 13.10.1994,
1040 ***NN***; DMPS Mittel der Wahl bei der Diagnose von Schwermetallbelastungen; APIS (01) 16 (1994)
1041 ***NN***; Mineralstoffe und Spurenelemente-Leitfaden für die ärztliche Praxis; Verlag Bertelsmann-Stiftung, Gütersloh (1992)
1042 ***NN***; Environmental Health Criteria 118, Inorganic mercury; World Health Organization, Geneva (1991)
1043 ***NN***; Environmental Health Criteria 101, Methylmercury; World Health Organization, Geneva (1990)
1044 ***NN***; Indicative list of antidotes; Official J. Europ. Communities No.294 19-23 (1989)
1045 ***NN;*** Die Gefahr kommt aus der Konservendose: Chronische QuecksilberintoxikationM Selecta (52) 4345-4346 (1984)
1046 ***NN;*** www.periodensystem.info
1047 ***Nogue S, Culla S****;* Burton's line; N. Engl. J. Med. 354(20) e21 (2006)
1048 ***Nogueira CW, Santos FW, Soares FA, Rocha JB***; 2,3-Dimercaptopropaneol, 2,3-dimercaptopropane-1-sulfonic acid, and meso-2,3-dimercaptosuccinic acid inhibit (delta)-aminolevulinate dehydratase from human erythrocytes in vitro; Environ. Res. 94(3) 254-261 (2004)
1049 ***Nogueira CW, Soares FA, Nascimento PC, Muller D, Rocha JBT***; 2,3-Dimercaptopropane-1-sulfonic acid and meso-2,3-dimercaptosuccinic acid increase mercury- and cadmium-induced inhibition of δ-aminolevulinate dehydratase; Toxicology 184(2-3) 85-95 (2003)
1050 ***Nogueira CW, Rotta LN, Tavares RG, Souza DO, Rocha JBT***; BAL modulates glutamate transport in synapto-somes and synaptic vesicles from rat brain; NeuroReport 12(3) 511-514 (2001)

1051 ***Nogueira CW, Rocha JBT, Souza DO***; Effect of dithiol chelating agents on (3H)MK-801 and (3H) glutamate binding to synaptic plasma membranes; Neurochem. Res. 26(12) 1305-1310 (2001)

1052 ***Nordberg GF, Gerhardsson L, Broberg K, Mumatz M, Ruiz P, Fowler BA***; Interactions in metal toxicity; IN: Nordberg GF, Fowler BA, Nordberg M, Friberg LT (Eds.); Handbook on the Toxicology of Metals, 3rd Edition; Academic Press Inc. 117-145 (2007)

1053 ***Novak VP, Bogovina VI, Bedovik SS, Maltsev VI***; Photometric determination of molybdenum in steels and alloys based on nickel in the form of molybdenum-unithiol complex; Ind. Laboratory USSR 37(10) 1495-1496 (1971)

1054 ***Nriagu J, Becker C***; Volcanic emissions of mercury to the atmosphere: global and regional inventories; Sci. Total Environ. 307(1-3) 3-12 (2003)

1055 ***Nukhin AN***; Interaction of 2,3-dimercaptopropanesulfonic acid with silver(I) in aqueous solutions; Russ. J. Coord. Chem. 21(2) 145-146 (1995)

1056 ***Nukhin AN***; Thermochemistry of unithiolate mercury (II) complexes in aqueous solution; Russ. J. Inorg. Chem. 40(4) 610-611 (1995)

1057 ***Nukhin AN, Ospanova FK, Kamysbaev DK***; Interaction of copper (I) with 2,3-dimercaptopropanesulfonic acid in aqueous solutions; Russ. J. Inorg. Chem. 40(1) 107-108 (1995)

1058 ***Nukhin AN, Ospanov KK, Vasilev VP, Garavin VY***; Thermodynamics of lead(II) unithiol complexes in aqueous solution; Russ. J. Inorg. Chem. 37(5) 571-573 (1992)

1059 ***Nuttall KL***; Interpreting mercury in blood and urine of individual patients; Ann. Clin. Lab. Sci. 34(3) 235-250 (2004)

1060 ***Nwokolo CU, Pounder RE***; D-penicillamine does not increase urinary bismuth excretion in patients treated with potassium dicitrato bismuthate; Br. J. Clin. Pharmac. 30(4) 648-650 (1990)

1061 ***Oberdisse E, Hackenthal E, Kuschinsky K (Eds.)***; Pharmakologie und Toxikologie; Springer Verlag Berlin, Heidelberg, New York, S. 780-787 (2002)

1062 ***O'Connor RJ, McGown EL, Dill K, Hallowell SF***; Relative binding constants of arsenical-antidote adducts determined by NMR spectroscopy; Res. Commun. Chem. Pathol. Pharmacol. 69(3) 365-368 (1990)

1063 ***O'Connor RJ, McGown EL, Dill K***; Two-dimensional NMR studies of arsenic-sulfhydryl adducts; Magn. Reson. Chem. 27(7) 669-675 (1989)

1064 ***Ochi T, Kinoshita K, Suzuki T, Miyazaki K, Noguchi A, Kaise T***; The role of glutathione on the cytotoxic effects and cellular uptake of diphenylarsinic acid, a degradation product of chemical warfare agents; Arch. Toxicol. 80(8) 486-491 (2006)

1065 ***Ochi T, Suzuki T, Isono H, Kaise T***; In vitro cytotoxic and genotoxic effects of diphenylarsinic acid, a degradation product of chemical warfare agents; Toxicol. Appl. Pharmacol. 200(1) 64-72 (2004)

1066 ***Oehme P, Krause W, Michael N, Göres E***; Amalgam-kontrovers diskutiert; Pharmazie 49(5) 361-363 (1994)

1067 ***Oginski M, Giryn I, Piatek T***; ^{99m}Tc-unithiol complex, a new radiopharmaceutical for kidney scintigraphy. IV Autoradiographic localisation of its cellular distribution in the kidney; Nuklearmedizin 19(2) 91-92 (1980)

1068 ***Oginski M, Rembelska M***; ^{99m}Technetium-unithiol complex, a new pharmaceutical for kidney scintigraphy; Nuklearmedizin 15(6) 282-286 (1976)

1069 ***Oginski M, Kloczkowski K***; Use of unithiol for reducing radiation hazard of renal scintigraphy with chlormerodrin-^{203}Hg. I Estimation of the urinary excretion of ^{203}Hg; Int. Urol. Nephrol. 5(4) 371-376 (1973)

1070 ***Oginski M***; Use of Unithiol for speeding up renal excretion of chlormerodrin ^{203}Hg; Int. Urol. Nephrol. 3(2) 203-208 (1971)

1070a ***Ökten Z***; Single molecule mechanics and the myosin family of molecular motors; Dissertation Freie Universität Berlin (2005)

1071 ***Okun I, Malarchuk S, Dubrovskaya E, Khvat A, Tkachenko S, Kysil V, Kravchenko D, Ivachtchenko A***; Screening for caspase-3 inhibitors: effect of a reducing agent on identified hit chemotypes; J. Biomol. Screen. 11(6) 694-703 (2006)

1072 ***Oleinik PN***; Use of Unithiol and dicaptol in experimental granosan and mercuric chloride intoxications; Materialy 8-oi (Vosmoi) Nauchn.Konf. pro farmakol. Moscow SB 162-163 (1963) [Abstract]

1073 ***Omelyanenko ZP***; The effect of dithiols on some variables of the functional condition of the cardiovascular system; Farmakol. Toksikol. Resub. Mezhedom. Sb. 4 47-50 (1968) [Abstract]

1074 **Opitz H, Schweinsberg F, Großmann T, Wendt-Gallitelli MF, Meyermann R**; Demonstration of mercury in the human brain and other organs 17 years after metallic mercury exposure; Clin. Neuropathol. 15(3) 139-144 (1996)

1075 ***Osinska J, Trojanowska B***; The clinical state of persons with the mercury deposits detected by the use of the unithiol test; Przegl. Lek. 38(8) 595-598 (1981) [Abstract]

1076 ***Osipova EA, Shapovalova EN, Ofitserova MN, Podlesnykh SV***; Amperometric detection of unithiol complexes of heavy metals in high-performance liquid chromatography; J. Anal. Chem. 55(1) 52-57 (2000)

1077 ***Ospanov K, Utegulov R, Nukhuly A, Kamysbayev D***; The rules of formation of unithiolate metal complexes; Sci. Isr. Technol. Advantages 3(1-2) 163-173 (2001)

1078 ***Ospanov KK, Bakenov ZB, Nukhin AN;*** The thermodynamics of thallium(III)unithiolate complexes in aqueous solutions; Russ. J. Coord. Chem. 21(2) 92-93 (1995)

1079 ***Ospanov KK, Razimbekova GK, Aubakirova KK***; Formation of cobalt(II) unithiol complexes in aqueous solutions; Koord. Khim. 16(6) 843-845 (1990) [Abstract]

1080 ***Ospanov KK, Sholtyrova UI, Kamysbaev DK, Nurpeisova ND, Butinchieva TS***; Calculation of equilibrium constant of platinum(II) unithiol nuclear complexes; Koordinatsionnaya Khimiya 16(2) 271-273 (1990) [Abstract]

1081 ***Ospanov KK, Kamysbaev DK, Fatkin AY, Kaipov MD, Baimakhanova GM***; Preparation of unithiol (triethylenetetramine)rhodium(III) chloride hydrate; Koord. Khim. 15(10) 1377-1379 (1989) [Abstract]

1082 ***Ospanov KK, Shabikova GK, Nukhin AN***; Study of interaction of unithiol with copper salts by the solubility method; Izvestiya Vysshikh Uchebnykh Zavedenii, Khimiya i Khimicheskaya Tekhnologiya 32 (8) 22-25 (1989) [Abstract]

1083 ***Ospanov KK, Shabikova GK, Ospanova AK***; Solubility in the sodium tungstate-unithiol-water system at 25 and 50 ºC; Russ. J. Inorg. Chim, 32(8) 1200-1202 (1987)

1084 ***Ospanov KK, Shabikova GK, Nukhin AN***; Lead nitrate-unithiol-water and lead acetate-unithiol-water systems; Russ. J. Inorg. Chem. 32(8) 1194-1195 (1987)

1085 ***Ospanov KK, Mirkin VA, Urazalina GS***; Stability of copper(I) unithiolate in ammoniacal solutions; Russ. J. Inorg. Chem. 32(7) 1062-1063 (1987)

1086 ***Ospanov KK, Sholtyrova UI, Fedosov SN, Ospanova AK***; Spectrophotometric study of a pentavalent rhenium complex with unithiol in a solution; Izvestiya Akademii Nauk Kazakhskoi SSR, Seriya Khimicheskaya (1) 18-21(1987) [Abstract]

1087 ***Ospanov KK, Sholtyrova UI, Kharitonov YY***; Spectrophotometric study of the kinetics of complexing of platinum with unithiol in solutions; Russ. J. Coord. Chem. 28(8) 1130-1135 (1983)

1088 ***Ospanov KK, Sholtyrova UI, Kharitonov YY***; Spectrophotometric study of the complexing of platinum(II) with unithiol in aqueous solutions; Zhurnal Neorganicheskoi Khimii, 23(10), 2724-2727 (1978) [Abstract]

1089 ***Ospanov KK, Fedosov SN, Songina OA, Sarmurzina RG***; Spectrophotometric study of the composition and stability of cobalt(II), nickel(II), and iron(II) unithiolates; Izvestiya Akademii Nauk Kazakhskoi SSR, Seriya Khimicheskaya 22(1) 4-9 (1972) [Abstract]

1090 ***Ospanov KK, Fedosov SN; Rozhdestvenskaya ZB***; Composition and stability of a complex copper unithiolate in relation to its analytical use; Zhurnal Analiticheskoi Khimii 23(2) 175-180 (1968) [Abstract]

1091 ***Ospanov KK, Makletsova NE, Tember NI***; Rapid photometric determination of iron by means of unithiol; Zhurnal Analiticheskoi Khimii 22(3) 444-445 (1967) [Abstract]

1092 ***Ospanov KK, Rozhdestvenskaya ZB***; Electrooxidation of unithiol; Izvestiya Vysshikh Uchebnykh Zavedenii, Khimiya i Khimicheskaya Tekhnologiya 10(12) 1349-1353 (1967) [Abstract]

1093 ***Ospanov KK, Rozhdestvenskaya ZB***; Reaction of iron ions with unithiol; Sb. Statei Aspir. Soiskatelei, Min. Vyssh. Sredn. Spets. Obrazov. Kaz. SSR, Khim. Tekhnol. (3-4) 216-17 (1965) [Abstract]

1094 ***Ospanov KK, Rozhdestvenskaya ZB, Songina OA***; Polarographic study of unithiol on a dropping mercury electrode; Anal. Bioanal. Chem. 208(6) 444 (1965) [Abstract]

1095 ***Ospanova AK, Ospanov KK, Seilkhanova GA, Abilov ZA***; The peculiarities of interactions in the system containing polyethyleneimine and unithiol; Eurasian Chem. Tech. J. 3(1) 45-48 (2001)

1096 ***Ospanova AK, Aubakirova KK, Ospanov KK, Shabikova GK***; Spectrophotometric study of chromium(III) complexation with unithiol; Izv. Akad. Nauk. Kaz. SSR, Ser. Khim. (4) 28-32 (1991) [Abstract]

1097 ***Ospanova AK, Ospanov KK, Shabikova GK, Khachaturova TG***; The synthesis and physicochemical study of properties of complexes ot rhenium(V) with unithiol; Russ. J. Inorg. Chem. 35(10) 1458-1460 (1990)

1098 ***Ospanova AK, Ospanov KK, Shabikova GK, Khachaturova TG;*** The synthesis and physicochemical study of the properties of unithiolate complexes of tungsten(V) ; Russ. J. Inorg. Chim. 34(1) 41-44 (1989)

1099 ***Ospanova AK, Ospanov KK, Shabikova GK, Khachaturova TG***; Preparation and physicochemical study of the properties of molybdenum (V) complexes with unithiol; Koord. Khim. 15(6) 782-787 (1989) [Abstract]

1100 ***Ostapenko YN, Luzhnikov EA, Nechiporenko SP, Petrov AN***; Clinical and institutional aspects of antidote therapy in Russia; Przegl.Lek. 58(4) 290-292 (2001)

1101 ***Ostapkevich NA, Naidis FB, Kulbitskii GN, Kulaeva LV***; Electrochemical preparation of sodium 2,3-dibromopropanesulfonate in unithiol production; Pharm. Chem. J. 7(10) 634-635 (1969)

1102 ***Oster O***; Therapie der Quecksilber-Intoxikation; IN: Spurenelemente - Bedarf, Vergiftungen, Wechselwirkungen und neuere Meßmethoden, I Lombeck (Ed.), Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, S. 21-29 (1997)

1103 ***Oster O, Prellwitz W***; Metall- und Metalloid-Intoxikation; IN: W.Kaufmann, W.Siegenthaler (Eds.); Innere Medizin in Praxis und Klinik; Georg-Thieme-Verlag S. 18.94-18.107 (1992)

1104 ***Oster O, Prellwitz W***; Die Pathobiochemie, Diagnose und Therapie der Metall- und Metalloidintoxikation - 2. Die Quecksilberintoxikation; Intensivmed. 22(3) 130-139 (1985)

1105 ***Oster O. Prellwitz W***; Die Notwendigkeit der Bestimmung von Spurenelementen im klinisch-chemischen Laboratorium; Ärztl. Lab. 30(4) 119-127 (1984)

1106 ***Otiko G, Razi MT, Sadler PJ, Isab AA, Rabenstein DL***; A ^{1}H-NMR study of the interaction of aurothiomalate ("Myocrisin") with human red blood cells in vitro; J. Inorg. Biochem. 19(3) 227-235 (1983)

1107 ***Ott KHR***; Untersuchungszentrum Füllungswerkstoffe; http://medweb.uni-muenster.de/institute/zmk/einrichtungen/kons/ueberblick/untagam/index.html (1. Januar 2000)

1108 ***Ott, KHR***; Die Messung der Quecksilber-Belastung im Speichel; Dtsch. Zahnärztl. Z. 48(3) 154-157 (1993)

1109 ***Otterbach I, Bergold M, Beyer M, Eikmann T, Herr C***; Individuelle Gesundheitsleistungen (IGeL) in der Umweltmedizin; Umweltmed. Forsch. Prax. 11(3) 173-182 (2006)

1110 ***Otto M***; Quecksilber-Informationsblatt; www.gesundheitsamt.de/umwelt/noxen/ noxen_chemisch/metalle/quecksilber_informationsblatt.htm (1998)

1111 ***Pagliuca A, Mufti GJ, Baldwin D, Lestas AN, Wallis RM, Bellingham AJ***; Lead poisoning: Clinical, biochemical, and haematological aspects of a recent outbreak; J. Clin. Pathol. 43(4) 277-281 (1990)

1112 ***Pai P, Thomas S, Hoenich N, Roberts R, House I, Brown A***; Treatment of a case of severe mercuric salt overdose with DMPS (dimercapo-1-propane sulfonate) and continuous haemofiltration; Nephrol. Dial. Transplant. 15(11) 1889-1890 (2000)

1113 ***Pakhmurnyi BA***; The effect of unithiol and cysteine on the renal effect of strophanthin; Bull. Exp. Biol. Med. 63(7) 59-61 (1967) [English Translation]

1114 ***Pangborn J***; Mechanism of detoxification and procedures of detoxification; Doctor's Data Inc. and Bionostics Inc. 137-140 (1994)

1115 ***Panova EN, Ablanova EK, Ospanov KK***; Complexing of unithiol with manganese(II)chloride; Russ. J. Inorg. Chem. 44(5) 718-720 (1999)

1116 ***Pant SC, Vijayaraghavan R, Kannan GM, Gansean K***; Sulfur mustard induced oxidative stress and its prevention by sodium 2,3-dimercapto propane sulfonic acid (DMPS) in mice; Biomed. Environ. Sci. 13 225-232 (2000)

1117 ***Parcell SW***; Clinical pearls - Part I of the 39th Annual Meeting of the Academy of Environmental Medicine; Integr. Med. 4(2) 42-45 (2005)

1118 ***Parr W***; Process for producing of 2,3-dimercaptopropane-1-sulfonic acid and its salts; US Patent 4382 040 (1983)

1119 ***Parr W***; Verfahren zur Herstellung der 2,3-Dimercaptopropane-1-sulfonsäure und ihrer Salze; Europäisches Patent 0 024 562 (1981)

1120 ***Parr W***; Verfahren zur Herstellung der 2,3-Dimercaptopropane-1-sulfonsäure und ihrer Salze; Deutsches Patent 29 33 027 (1981)

1121 ***Parzefall W***; Toxikologie von Metallen - Beispiele: Blei und Quecksilber; www.univie.ac.at/Toxikologie/TU172071/6Metalle.pdf (2002)

1122 ***Pasovskaja GB***; Eine schnelle konduktometrische Bestimmung von Calcium in Kalkgesteinen; Anal. Bioanal. Chem. 199(2) 156 (1964)

1123 ***Paternain JL, Folch J, Bosque MA;*** Zinc, copper and metallothionein content in mice treated with 2,3-dimercapto-1-propanesulfonate (DMPS) during embryogenesis; Rev. Toxicol. 10(3) 146-150 (1993)

1124 ***Paul M, Mason R, Edwards R***; Effect of potential antidotes on the acute toxicity, tissue disposition and elimination of selenium in rats; Res. Commun. Chem. Pathol. Pharmacol. 66(3) 441-450 (1989)

1125 ***Paul PC, Chattopadhyay A, Dutta SK, Mazumder DN, Santra A***; Histopathology of skin lesions in chronic arsenic toxicity-grading of changes and study of proliferative markers; Indian J. Pathol. Microbiol. 43(3) 257-264 (2000)

1126 ***Pelclova D, Lukas E, Urban P, Preiss J, Rysava R, Lebenhart P, Okrouhlik B, Fenclova Z, Lebedova J, Stejskalova A, Rizdon P***; Mercury intoxication from skin ointment containing mercuric ammonium chloride; Int. Arch. Occup. Environ. Health 75(Suppl.) s54-s59 (2002)

1127 ***Pelis RM, Dangprapai Y, Wunz TM, Wright SH***; Inorganic mercury interacts with cysteine residues (C451 and C474) of hOCT2 to reduce its transport activity; Am. J. Physiol. Renal. Physiol. 292 F1583-F1591 (2007)

1128 ***Peramo B, Martinez de Maria J, Nunez R, Pedro C***; High levels of mercury in blood can impair normal ovarian function: A case report; Fertil. Steril. 86(3 Suppl.1) s284 (2006)

1129 ***Perez M, Carr Z***; Development of stockpiles for radiation emergencies; Report of the Radio-Nuclear Working Group - WHO Consultation meeting on Development of Stockpiles for Radiation and Chemical Emergencies, Editors: M Perez and Z Carr, 14-16 February 2007, WHO Headquarters, Geneva Switzerland (2007)

1130 ***Pertel-Ashouwak P***; Chemical Poisoning Case: Attempted Mass Murder?; On The Edge 11(3) 4-8 (2005)

1131 ***Peschanskaya IV, Golovko LA, Suprunovich VI***; Different-metal and thiol-thiol complexes of copper (indium) with 8-mercaptoquinoline (unithiol); Zh. Anal. Khim. 47(4) 587-597 (1992) [Abstract]

1132 ***Petereit-Haack G, Künzel M, Kreck HC, Mellmann K, Bacher-Zeller I, Bösel G, Bunk W, Dietz-Magel B, Dornow R, Freund-Hoffmann U, Gloßmann V, Kämpfer R, Kafurke H, Kater U, Leimbeck M, Linn M, Mumenthaler W, Nölling P, Schmitz D, Wzatek J, Herr C, Eikmann T***; Patienten mit abklärungs- und gegebenenfalls therapiebedürftigen Gesundheitsstörungen bei Verdacht auf „Amalgambelastung"; Umweltmed. Forsch. Prax. 5(2) 63, 120-123 (2000)

1133 ***Peters U, Schmidt H, Huber H***; Organbelastungen aufspüren? Mit dem DMPS-Mobilisationstest kein Problem; Heilpraxis-Magazin (5) 40 (1996)

1134 ***Peters U, Keiner K, Schmidt H***; Umweltmedizinische Diagnostik am Beispiel der Schwermetallbelastung; Biol. Med. (4) 172-176 (1996)

1135 ***Pethran A, Szinicz L***. Forth W; Effect of various dithiols on acute toxicity of different metals in mice; Plzen. Lek. Sborn. 62(Suppl) 69-70 (1990)

1136 ***Pethran A***; Wirkung verschiedener Dithiole auf die akute Toxizität von Metallen; Dissertation Universität München, (1985)

1137 ***Petrovnin MG***; Mechanism of action and certain conditions of effective use of unithiol in polonium intoxication; Polonii (Moscov. Med.) SB 179-188 (1964) [Abstract]

1138 ***Petrunkin VE***; Synthese und Eigenschaften der Dimerkaptoderivate von Alkansulfonsäuren; Ukrain. Khim. Zhur. 22 603-611 (1956) [Deutsche Übersetzung]

1139 ***Petrusenko RI;*** The treatment of arsenical periodontitis; Stomatologiya 46(2) 32-35 (1967) [Abstract]

1140 ***Pfab R, Mückter H, Roider G, Zilker T***; Clinical course of severe poisoning with thiomersal; Clin. Toxicol, 34(4) 453-460 (1996)

1141 ***Pfenningsdorf S, Küppers G, Münnich S, Lieb WE***; Behandlung von metallischem Quecksilber in der Orbita - Fallvorstellung einer Verletzung mit einem Thermometer; 24.Tagung der Deutschen Ophtalmologischen Gesellschaft (1996)

1142 ***Pham EK, Chang SG***; Removal of NO from flue gases by absorption to an iron(II) thiochelate complex and subsequent reduction to ammonia; Nature 369 139-141 (1994)

1143 ***Pietrek UA***; Medizinische und toxikologische Erkenntnisse aus der Analyse zweier Umweltkatastrophen; Dissertation Medizinischen Fakultät der Universität Ulm (2006)

1144 ***Pike A, Loring RH***; Effects of p-aminophenyl pichloroarsine on reduced high-affinity [^{3}H]nicotine binding sites from chick brain: A covalent, yet reversible, agent for neuronal nicotinic receptors; Eur. J. Neurosci. 4 1362-1368 (1992)

1145 ***Pilipenko AT, Ryabushko OP***; Instability constants of complexes formed by zinc with some dimercatoalkanesulfonic acids; Ukr. Khim. Zh. 33(4) 52-56 (1973)

1146 ***Pilipenko AT, Ryabushko OP, Makarenko TK***; The application of thiols in analysis of instability constants of lead complexe with several dimercaptoalkanesulfonacids; Ukr. Khim. Zh. 34 (8) 59-61 (1968)

1147 ***Pilipenko AT, Ryabushko OP***; Use of thiols in analysis of instability constants of mercury(II) with some dimercaptoalkane sulfonic acids; Ukr. Khim. Zhur. 32(6) 622-626 (1966) [Abstract]

1148 ***Pingree SD, Simmonds PL, Rummel KT, Woods JS***; Quantitative evaluation of urinary porphyrins as a measure of kidney mercury content and mercury body burden during prolonged methylmercury exposure in rats; Toxicol. Sci. 61(2) 234-240 (2001)

1149 ***Pingree SD, Simmonds PLm Woods JS***; Effects of 2,3-dimercapto-1-propanesulfonic acid (DMPS) on tissue and urine mercury levels following prolonged methylmercury exposure in rats; Toxicol. Sci. 61(2) 224-233 (2001)

1150 ***Pirker C, Petzl D H, Rodinger G, Wekkeli M, Rosenkranz A R, Koller D, Jarisch R, Götz M***; Therapy-resistant mercury contacteczema: A treatment trial with 2,3-dimercaptopropane-1-sulfonate; Arch. Dermatol. Res. 283(1) 25 (1991)

1151 ***Pirmanova NS, Ablanova EK, Ospanov KK***; Stability of Ni(II)unithioloate complexes in aqueous solution; Izv. Nats. Akad. Nauk. Kaz, Ser. Khim (4) 39-44 (1993) [Abstract]

1152 ***Planas-Bohne F***; Verteilungskoeffizient verschiedener Metallchelate; Unveröffentlichte Ergebnisse (1991)

1153 ***Planas-Bohne F***; Removal of cadmium by chelating agents; Plzen. Lek. Sborn. 49(Suppl.) 13-17 (1985)

1154 ***Planas-Bohne F, Lehmann M***; Influence of chelating agents on the distribution and excretion of cadmium in rats; Toxicol. Appl. Pharmacol. 67(3) 408-416 (1983)

1155 ***Planas-Bohne F, Shand E, Taylor DM***; The effects of dimercaptosuccinic acid and other chelating agents on the retention of platinum in the rat kidney after treatment with cisplatin; Cancer Chemother. Pharmacol. 9(2) 120-121 (1982)

1156 ***Planas-Bohne F, Taylor DM, Volf V***; Neue Möglichkeiten der Dekorporationstherapie; KFK-Nachrichten 13(1-2) 112-115 (1981)

1157 ***Planas-Bohne F, Olinger H***; The interaction of chelating agents with methylmercuric chloride bound to erythrocytes; Biochem. Pharmacol. 30 667-699 (1981)

1158 ***Planas-Bohne F***; The effect of 2,3-dimercaptorpropane-1-sulfonate and dimercaptosuccinic acid on the distribution and excretion of mercuric chloride in rats; Toxicology 19(3) 275-278 (1981)

1159 ***Planas-Bohne F***; The influence of chelating agents on the distribution and biotransformation of methylmercuric chloride in rats; J. Pharmacol. Exp. Ther. 217(2) 500-504 (1981)

1160 ***Planas-Bohne F, Gabard B, Schäffer EH***; Toxicological studies on sodium 2,3-dimercaptopropane-1-sulfonate in the rat; Arzneimittelforschung 30(8) 1291-1294 (1980)

1161 ***Planas-Bohne F***; Chelate treatment in acute cadmium poisoning; Experientia 36 1001-1002 (1980)

1162 ***Planas-Bohne F***; Dekorporation von Schwermetallen, insbesondere Quecksilber; Umweltchemikalien (Vortragsveranstaltung der AGF), Bonn (1979)

1163 ***Planas-Bohne F***; Influence of several chelating agents on the excretion and organ concentration of copper in the rat; Toxicol. Appl. Pharmacol. 50(2) 1092-345 (1978)

1164 ***Planas-Bohne F***; The effect of mercuric chloride on the excretion of two urinary enzymes in the rat; Arch. Toxicol. 37(3) 219-225 (1977)

1165 ***Planas-Bohne F***; The excretion of two renal enzymes as influenced by mercuric chloride and DMPS; IN: Clinical chemistry and chemical toxicology of metals, SS Brown (Ed.) Amsterdam, Elsevier/North-Holland, pp 119-122 (1977)

1166 ***Playford RJ, Matthews CH, Campbell MJ, Delves HT, Hla KK, Hodgson HJ, Calam J***; Bismuth induced encephalopathy caused by tri potassium dicitrato bismuthate in a patient with chronic renal failure; Gut 31(3) 359-360 (1990)

1167 ***Pleva J***; Dental mercury-a public health hazard; Rev. Environ. Health 10(1) 1-27 (1994)

1168 ***Pochinok TV, Tarakhovsky ML, Portnyagina VA, Denisova MR,Vonsyatsky VA, Aleksandrova AN***; A rapid method for the determination of the antioxidant activity of drugs; Khim. Farm. Zh. 19(5) 565-569 (1985) [Abstract]

1168a ***Podosinovikova NP, Petrov VV, Belyaev VA, Bespalova AY, Trefilov VV, Dolgo-Saburov VB***; Daphnia Magna (Straus) a new test object for modeling dopaminergic neurotransmission deficiency induced by the selective neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; Eksp. Klin. Farmakol. 70(4) 20-22 (2007) [Abstract]

1169 ***Poltabekova GP, Tusupbekova, AS; Ospanov KK; Nitalina AS, Ivanova EV***; Reaction of bismuth(III)halides with unithiol in hydrogen halides; Koord. Khim. 18(9) 927-929 (1992) [Abstract]

1170 ***Poluboyarinova ZI, Streltsova VN***; The mechanism of functional and morphological changes of the kidneys in rats treated with unithiol for radiation sickness ^{210}Po; Med. Radiol 9(7) 22-27 (1964) [Abstract]

1171 ***Poluboyarinova ZI***; The effect of unithiole on the renal function of dogs affected with ionizing radiation; Med. Radiol (6) 44-50 (1963) [Abstract]

1172 ***Poon WT, Chan K, Lo MH, Yip KK, Lee T, Chan AYW***; A case of tetramine poisoning: a lethal rodenticide; Hong Kong Med. J. 11(6) 507-509 (2005)

1173 ***Porru S, Alessio L***; The use of chelating agents in occupational lead poisoning; Occup. Med. 46(1) 41-48 (1996)

1174 ***Portnyagina VA, Fedorova IP, Pochinok TV,Tarahovskii ML, Zadorozhnaya TD, Yatsenko KV***; Microcapsules of sodium 2,3-dimercaptopropane sulfonate (unithiol); Farmatsiya (2) 24-27 (1991) [Abstract]

1175 ***Postnikov AV***; Unithiol in the treatment of secondary amyloidosis patients; Ter. Arkh. 56(10) 115-116 (1984) [Abstract]

1176 ***Pöthig J***; Orientierende Untersuchungen auf dem Gelände der ehemaligen Heeresmunitionsanstalt St. Georgen; Tiefbau (2) 81-86 (2006)

1176a ***Pouls G, Pouls M***; The chelation controversy: How to safely detoxify; Basic Health Publications, Inc., p.23 (2005)

1177 ***Probst T, Probst A, Judmaier G, Vogel W***; Morbus Wilson; Dtsch. Med. Wochenschr. 121(9) 280-284 (1996)

1178 ***Prochazkova J, Sterzl I, Kucerova H, Bartova J, Stejskal VD***; The beneficial effect of amalgam replacement on health in patients with autoimmunity; Neuro Endocrinol. Lett. 25(3) 211-218 (2004)

1179 ***Proksch E, Kölmel K***; Zinkmangelsyndrom als Nebenwirkung von Chelatbildnem; Dtsch. Med. Wochenschr. 110(25) 1001-1003 (1985)

1180 ***Pronczuk de Garbino J, Haines JA, Jacobsen D, Meredith T***; Evaluation of antidotes: Activities of the international programme on chemical safety; J. Toxicol. Clin. Toxicol. 35(2) 125-126 (1997)

1181 ***Proskuryakov SY, Fedorovskaya EO, Ryabchenko NI, Poverenny AM***; The effect of unithiol on the antineoplastic and antimetastatic activity of N-methylformamide; Vopr. Med. Khim. 39(3) 32-34 (1993) [Abstract]

1182 ***Provotorov VM. Zizemskaia EV***; The clinical efficacy of treating patients with acute pneumonias by using drug and quantum correction of the lipid peroxidation-antioxidant system; Ter. Arkh. 64(3) 29-32 (1992) [Abstract]

1183 ***Pscheidl H***; Amalgam und andere Zahnmetalle: Versuch einer kritischen Darstellung aus ganzheitlicher Sicht; http://people.freenet.de/amalgam/spiegel/heinz.htm (1997)

1184 ***Pscheidl H***; Amalgamvergiftung - eine chronische Krankheit und ihre Therapie; ACD 3(4) 153-166 (1994)

1185 ***Pscheidl H***; Verträglichkeit zahnärztlicher Werkstoffe aus homöpathischer Sicht; ACD 3(3) 145-147 (1994)

1186 ***Pudill R, Siebeck HJ, Köbberling J, Schubert GE***; Therapie und klinisch-toxikologische Verlaufskontrolle einer tödlich verlaufenden Kaliumbichromat-Vergiftung; GIT Labor-Medizin 12(10) 469-473 (1989)

1187 ***Pzheusskaia LD***; Disintoxication therapy of patients with nonspecific inflammatory diseases of the female genital organs; Akush. Ginekol. (4) 30-34 (1977) [Abstract]

1188 ***Qiu Z, Lan H, Zhang S, Xia Y, Huang S***; Antidotal effects of vitamin B_6 and sodium dimercaptopropane sulfonate on acute poisoning with tetramethylene disulfotetramine in animals; Zhonghua Nei Ke Za Zhi 41(3) 186-188 (2002) [Abstract]

1189 ***Qiu Q, Miao X, Lu Z, Hu G***; Influences of sodium dimercaptopropane sulfonate on superoxide dismutase, xanthine oxidase, and catalase in acute dimethyl formamide poisoning mice; Zhongguo Jijiu Yixue 26(5) 354-356 (2006) [Abstract]

1190 ***Quig DW***; Assessment of toxic metal body burden: Ammunition, hot topics, and food for thought; Townsend Letter June 2007

1191 ***Quig DW***; Basic pharmacology of DMSA, DMPS and Ca-EDTA; www.autismone.com/uploads/David%20Quig%20PhD%20AO%202007%20presentation.ppt (2007)

1192 ***Quig DW***; Heavy metal toxicity. Environmental sources and their pathophysiology in illness; 3rd International Medical Convention for Complementary/Alternative Medicine, Niagara Falls (2002)

1193 ***Quintans LN, Castro GD, Castro JA***; Effects of several plant polyphenols and sulfur containing chemicals in the rat testicular microsomal biotransformation of ethanol to actealdehyde; Biocell 27(Suppl.1) 112 (2003)

1194 ***Quondamatteo F, Krick W, Hagos Y, Kruger MH, Neubauer-Saile K, Herken R, Ramadori G, Burckhardt G, Burckhardt BC***; Localization of the sulfate-anion exchanger (SAT-1) in rat liver; Am. J. Physiol. Gastrointest. Liver Physiol. 290(5) g1075-g1081 (2006)

1195 ***Rabenstein DL, Arnold AP, Guy RD***; ^{1}H-NMR study of the removal of methylmercury from intact erythrocytes by sulfhydryl compounds; J. Inorg. Biochem. 28(2-3) 279-287 (1986)

1196 ***Rabenstein DL, Isab AA, Kadima W, Mohanakrishnan P***; A proton nuclear magnetic resonance study of the interaction of cadmium with human erythrocytes; Biochim. Biophys. Acta 762 531-541 (1983)

1197 ***Rabenstein DL, Reid RS, Isab AA***; ^{1}H-NMR study of the effectiveness of various thiols for removal of methylmercury from hemolyzed erythrocytes; J. Inorg. Biochem. 18(3) 241-251 (1983)

1198 ***Rabenstein DL, Isab AA***; A proton nuclear magnetic resonance study of the interaction of mercury with intact human erythrocytes; Biochim. Biophy. Acta 721 374-384 (1982)

1199 ***Radabaugh TR, Sampayo-Reves A, Zakharyan RA, Aposhian HV***; Arsenate reductase II. purine nucleoside phosphorylase in the presence of dihydrolipoic acid is a route for reduction of arsenate to arsenite in mammalian systems; Chem. Res. Toxicol. 15(5) 692-698 (2002)

1200 ***Rael LT, Ayala-Fierro F, Carter DE***; The effects of sulfur, thiol, and thiol inhibitor compounds on arsine-induced toxicity in the human erythrocyte membrane; Toxicol. Sci. 55(2) 468-477 (2000)

1200a ***Rahde AF, Bates N, Dargan PI***; Monograph: Lead, inorganic; International Programme on Chemical Safety Evaluation (2007)

1201 ***Rajagopalan PTR, Datta A, Pei D;*** Purification, characterization, and inhibition of peptide deformylase from Escherichia coli; Biochemistry 36(45) 13910-13918 (1997)

1202 ***Ramirez AV***; El cuadro clinico de la intoxicacion ocupacional por plomo; An. Fac. Med. Lima 66(1) 57-70 (2005) [Abstract]

1202a ***Ramsak I***; Schwermetallausleitung mit DMPS (Praxiserfahrung); Med. J. Appl. Kinesiology 4 16-17 (1998)

1203 ***Rau W, Planas-Bohne F, Taylor DM***; Two models for screening chelating agents for cadmium removal; Cell Biol. Toxicol. 5(1) 91-99 (1989)

1204 ***Rau W, Planas-Bohne F;*** Enhancement of the kidney Cd burden by SH-containing chelating agents; Biol. Trace Elem. Res. 21 227-231 (1989)

1205 ***Rau W, Planas-Bohne F, Taylor DM***; Influence of several chelating agents on the distribution and binding of cadmium in rats; Hum. Toxicol. 6(6) 451-458 (1987)

1206 ***Rau W;*** Die Bedeutung der biochemischen Bindung von Cadmium in der Zelle für seine Mobilisierung; Dissertation Universität Heidelberg (1986)

1207 ***Reichl FX, Wigger K, Kreppel H, Durner J, Schumann K, Singh P, Jones MM, Forth W***; Effect of new synthesized antidotes on the biliary and enteric excretion of arsenic in guinea pigs after injection with oxophenylarsine (PhAsO);IN: 18th Mengen-Spurenelem., Arbeitstag., 17-23 (1998), M Anke (Ed.), Verlag Harald Schubert, Leipzig, Germany (1998)

1208 ***Reichl FX, Wigger K, Hunder G, Liebl B, Kreppel H, Kauth I, Forth W***; Effects of dimercaptopropanesulfonate (DMPS) and adsorbents on fecal excretion of arsenic in guinea-pigs after injection with As_2O_3 or phenylarseneoxide; Naunyn Schmiedeberg Arch. Pharmacol. (Suppl.) R130 (1996)

1209 ***Reichl FX, Hunder G, Liebl B, Fichtl B, Forth W***; Effect of DMPS and various adsorbents on the arsenic excretion in guinea-pigs after injection with As_2O_3; Arch. Toxicol. 69(10) 712-717 (1995)

1210 ***Reichl FX, Kreppel H, Szinicz L, Mückter H, Fichtl B, Forth W***; Effect of various antidotes on the biliary and intestinal excretion of arsenic in situ and into the feces in vivo in guinea-pigs after injection of As_2O_3; Arch. Toxicol. 69(1) 35-38 (1994)

1211 ***Reichl FX, Mückter H, Kreppel H, Forth W***; Effect of various antidotes on biliary excretion of arsenic in isolated perfused livers of guinea pigs after acute experimental poisoning with As_2O_3; Pharmacol. Toxicol. 70(5 Pt 1) 352-356 (1992)

1212 ***Reichl FX, Kreppel H, Forth W***; Pyruvate and lactate metabolism in livers of guinea pigs perfused with chelating agents after repeated treatment with As_2O_3; Arch. Toxicol. 65(3) 235-238 (1991)

1213 ***Reichl FX, Kreppel H, Szinicz L, Mückter H, Fichtl B, Schumann K, Forth W***; Effect of chelating agents on biliary excretion of arsenic in perfused livers of guinea pigs pretreated with As2O3; Vet. Hum. Toxicol. 32(3) 223-226 (1990)

1214 ***Reichl FX, Kreppel H, Szinicz L, Mückter H, Fichtl B, Schumann K, Forth W***; Effect of antidotes on pyruvate metabolism in perfused livers of guinea pigs after repeated As_2O_3-injections; Plzen. Sborn. 62(Suppl.) 79-80 (1990)

1215 ***Reichl FX, Mückter H, Kreppel H, Fichtl B, Schümann K, Forth W***; Effect of metal binding agents on biliary excretion of arsenic in perfused livers of guinea pigs after As_2O_3 inextions; 6th International Trace Element Symposium, Leipzig, Vol. 4, pp.1032-1038 (1989)

1216 ***Reigart JR, Roberts JR***; Arsenical Pesticides; Recognition and Management of Pesticide Poisonings", 5th Edition United States Environmental Protection Agency, Chapter 14, p. 126-136 (1999)

1217 ***Remennik AG, Nepomnyashchikh LM, Remennik VI***; Progressive toxemia with acetaldehyde in a reactive form of alcohol withdrawal syndrome; Bull. Exp. Biol. Med. 139(6) 732-734 (2005)

1218 ***Ren MS, Hu WB, Zhang Z, Ju SW, Fan YX, Wang GQ, Yang RM***; Copper-chelating therapeutic effect in Wilson disease with different clinical phenotypes and polymorphisms of ATP7B gene; World Journal of Gastroenterology 4(4) 530-532 (1998)

1219 ***Rencova J, Vlkova A, Curik R, Holusa R, Vesela G***; Influence of heavy metals upon the retention and mobilization of polonium-210 in rats; Int. J. Radiat. Biol. 80(10) 769-776 (2004)

1220 ***Rencova J, Volf V, Jones MM, Singh PK***; Decorporation of polonium from rats by new chelating agents; Radiat. Prot. Dosim. 53(1-4) 311-313 (1994)

1221 ***Rencova J, Volf V, Jones MM, Singh PK***; Relative effectiveness of dithiol and dithiocarbamate chelating agents in reducing retention of polonium-210 in rats; Int. J. Radiat. Biol. 63(2) 223-232 (1993)

1222 ***Rengby O, Johansson L, Carlson LA, Serini E, Vlamis-Gardikas A, Karsnas P, Arner ES***; Assessment of production conditions for efficient use of Escherichia coli in high-yield heterologous recombinant selenoprotein synthesis; Appl. Environ. Microbiol. 70(9) 5159-5167 (2004)

1223 ***Renner G, Kramer HJ***; Studies on the oxygen toxicity after administration of chelate-forming agents in mice; Int. J. Clin. Pharmacol. Ther. Toxicol. 21(3) 115-117 (1983)

1224 ***Rennie AC, McGregor-Schuerman M, Dale IM, Robinson C, McWilliam R;*** Mercury poisoning after spillage at home from a sphygmomanometer on loan from hospital; Br. Med. J. 319(7206) 366-367 (1999)

1225 ***Reuther H, Wildenauer DB, Weger N***; Interactions of the chelating agent 2,3-dimercaptopropane-1-sulfonate with red blood cells in vitro. II. Effects on metalloproteins; Chem. Biol. Interact. 42(2) 179-194 (1982)

1226 ***Reuther H, Wildenauer D, Weger N***; Effects of DMPS on erythrocytes; unpublished results (1981)

1227 ***Reuther H***; Erythrozyten als Modell für Wechselwirkungen von Pharmaka mit biologischen Membranen: 1 Aufnahme des Schwermetallantidots 2,3-Dimercaptopropane-1-sulfonat Natrium in Erythrozyten und Auswirkungen auf zytoplasmatische Proteine. 2 Reaktion des alkylierenden Zytostatikums Tris (2-chloräthyl)amin mit der Membran und Einfluß auf die Gestaltänderung von Erythrozyten; Universität Universität München (1982)

1228 ***Riba-Adell M, Ballin L, Lafon M, Amourette-Martin C, Pasquier C, Fatome M***; Essais therapeutiques du DMPS administre per os chez radiocontamine par polonium-210; IN: SSA-1983-TS-4 [1983] 132/5, INIS Atomindex 15 No. 052 480 (1984)

1229 ***Richardson GM***; Assessment of mercury exposure and risks from dental amalgam; Final Report Medical Devices Bureau, Environmental Health Directorate, Health Canada (1995)

1230 ***Richter M, Cantin AM, Beaulieu C, Cloutier A, Larivee P***; Zinc chelators inhibit eotaxin, RANTES, and MCP-1 production in stimulated human airway epithelium and fibroblasts; Am. J. Physiol. Lung Cell. Mol. Physiol. 285(3) L719-L729 (2003)

1231 ***Rimland B***; Background and Introduction to the Position Paper of the Consensus Conference On The Mercury Detoxification of Autistic Children; Autism Research Institute (2005)

1232 ***Risher JF, Amler SN***; Mercury exposure: Evaluation and intervention. The inappropriate use of chelating agents in the diagnosis and treatment of putative mercury poisoning; NeuroToxicology 26(4) 691-699 (2005)

1233 ***Robinson JPP, Cosivi O***; WHO guidance - Public health response to biological and chemical weapons; Second edition of Health aspects of chemical and biological weapons: report of a WHO Group of Consultants, World Health Organization, Geneva (20049

1234 ***Roessler G, Guilmette RA***; Why 210Po?; Health Phys. News 35(2) 1-9 (2007)

1235 ***Romanov SS***; Unithiol as an antidote in pulmonary edema secondary to intravenous injection of silver nitrate; Farmakol. Toksikol. 30 237-238 (1967) [Abstract]

1236 ***Rooney JPK***; The role of thiols, dithiols, nutritional factors and interacting ligands in the toxicology of mercury; Toxicology 234(3) 145-156 (2007)

1237 ***Rossant CJ, Lindstrom J, Loring RH***; Effects of redox reagents and arsenical compounds on (^{3}H)-cytisine binding to immunoisolated nicotinic acetylcholine receptors from chick brain containing $\alpha_4ß_2$ subunits; J. Neurochem. 62(4) 1368-1374 (1994)

1238 ***Rozema TC***; The protocol for the safe and effective administration of EDTA and other chelating agents for vascular disease, degenerative disease and metal toxicity; J. Adv. Med. 10(1) 5-100 (1997)

1239 ***Rothberg BS, Shin KS, Yellen G***; Movements near the gate of a hyperpolarization-activated cation channel; J. Gen. Physiol. 122(5) 501-510 (2003)

1240 ***Rothberg BS, Shin KS, Phale PS, Yellen G***; Voltage-controlled gating at the intracellular entrance to a hyperpolization-activated cation channel; J. Gen. Physiol. 119(1) 83-91 (2002)

1241 ***Routledge PA, Bialas MC, Babar I, Smith SC, Hutchings AD, Lazarus JH***; Blood arsenic and chromium concentrations after dermal exposure to tannalysing fluid and the use of DMPS; J. Toxicol. Clin. Toxicol. 36(5) 494-495 (1998)

1242 ***Ruble G, Chuanchu W, Squire RA, Gansow OA, Strand M***; The use of ^{212}Pb-labeled monoclonal antibody in the treatment of murine erythroleukemia; Int. J. Radiation Oncology Biol. Phys. 34(3) 609-616 (1996)

1243 ***Rudnitskaia EI***; Pathological changes in the organs of dogs during intravenous administration of high doses of unithiol; Farmakol. Toksikol. 31(1) 110-111 (1968) [Abstract]

1244 ***Rukhadze R, Sanikidze T, Mirtskhulava M, Papava M***; Effect of Plaferon LB in ischemia/reperfusion of the pancreas; Ann. Biomed. Res. Edu. 3(2) 145-148 (2003)

1245 ***Runow KD***; „Edelmetall“ Palladium als Zahnlegierungsbestandteil umstritten; Mineraloscope (1) 19-20 (1996)

1246 ***Runow KD, Weber KM***; Gesundheitliche Störungen durch Schwermetalle in Dentallegierungen (Zinn, Palladium, Quecksilber, Blei, Cadmium); X. Int. Symposium für Umweltmedizin; Bad Emstal (1995)

1247 ***Ruprecht J***; Problems in the supply of antidotes-A view from the pharmaceutical industry; Toxicology 233(1-3) 20-22 (2007)

1248 ***Ryabushko OP, Pilipenko AT, Krivokhizina LA***; Instability constants of mercury(II) complexes with unithiol and its analogs; Ukr. Khim. Zh. 39(12) 93-94 (1973)

1249 ***Ryabykh LD, Trokhimchuk VV***; Methods for quantitative determination of unithiol; Farmatsiya 32(3) 63-66 (1983) [Abstract]

1250 ***Rysava R, Merta M, Tesar V, Hochmanova K, Pelclova D, Stejskalova A***; Membranous nephropathy in young diabetic man with mercury intoxication: Case report; Nephrol. Dialysis Transplant. 16(6) a54 (2001)

1251 ***Sällsten G, Barregard L, Schütz A***; Clearance half life of mercury in urine after the cessation of long term occupational exposure: Influence of a chelating agent (DMPS) on excretion of mercury in urine; Occup. Environ. Med. 51(5) 1092-342 (1994)

1252 ***Sabirova RA, Inoiatova FK, Gapparov OS***; Effects of SH-compounds on changes in the antioxidant enzyme activity in various tissues during acute pancreatitis; Eksp. Klin. Farmakol. 63(3) 33-35 (2000) [Abstract]

1253 ***Saha KC***; Cutaneous malignancy in arsenicosis; Br. J. Dermatol. 145(1) 185 (2001)

1254 ***Saha JC, Dikshit AK, Bandyopadhyay M, Saha KC***; A review of arsenic poisoning and its effects on human health; Crit. Rev. Environ. Sci. Technol. 29(3) 281-313 (1999)

1255 ***Samoilov NN, Kublenko VG, Popov VG;*** Experimental therapy of acute and subacute lithium chloride poisonings; Farmakol. Toksikol. 37(1) 102-105 (1974)

1256 ***Sampayo-Reyes A, Radabaugh TR, Zakharyan RA, Aposhian HV***; Arsenate reductase II. Purine nucleoside phosphorylase in the presence of dihydrolipoic acid is a route for reduction of arsenate to arsenite in mammalian systems; 5th International Conference on Arsenic Exposure and Health Effects, San Diego, July 14-18 (2002)

1257 ***Sandborgh-Englund G, Elinder CG, Johanson G, Lind B, Skare I, Ekstrand J***;The absorption, blood levels, and excretion of mercury after a single dose of mercury vapor in humans; Toxicol. Appl. Pharmacol. 150(1) 146-153 (1998)

1258 ***Sandborgh-Englund G, Dahlqvist R, Lindelöf B, Söderman E, Jonzon B, Vesterberg O, Larsson KS***; DMSA administration to patients with alleged mercury poisoning from dental amalgams: a placebo-controlled study; J. Dent. Res. 73(3) 620-628 (1994)

1259 ***Sanotsky VA, Zotova MG, Efimov VI, Rudnitskaia EI, Fedorovskii LL, Furaeva LP***; On the possibility of intravenous use of unithiol in high doses; Farmakol. Toksikol. 30(4) 480-482 (1967) [Abstract]

1260 ***Santos FW, Rocha JB, Nogueira CW***; 2,3-Dimercaptopropaneol, 2,3-dimercaptopropane-1-sulfonic acid and meso-2,3-dimercaptosuccinic acid increase lead-induced inhibition of delta-aminolevulinate dehydratase in vitro and ex vivo; Toxicol. In Vitro 20(3) 317-323 (2006)

1261 ***Santos FW, Goncales CE, Rocha JB, Nogueira CW***; 2,3-Dimercaptopropaneol, 2,3-dimercaptopropane-1-sulfonic acid and meso-2,3-dimercaptosuccinic acid acute administration differentially change biochemical parameters in mice; Basic Clin. Pharmacol. Toxicol. 96(4) 331-334 (2005)

1262 ***Santos FW, Zeni G, Rocha J, do Nascimento PC, Marques MS, Nogueira CW***; Efficacy of 2,3-dimercapto-1-propanesulfonic acid (DMPS) and diphenyl diselenide on cadmium induced testicular damage in mice; Food Chem Toxicol. 43(12) 1723-1730 (2005)

1263 ***Saravu K, Jose J, Bhat MN, Jimmy B, Shastry BA***; Acute ingestion of copper sulfate: A review on its clinical manifestations and management; Indian J. Crit. Care Med. 11(2) 74-80 (2007)

1264 ***Sarc L, Jasek M***; DMPS in the treatment of chronic lead poisoning; J. Toxicol. Clin. Toxicol. 38(2) 252-253 (2000)

1265 ***Saxe SR, Wekstein MW, Kryscio RJ, Henry RG, Cornett CR, Snowdon DA, Grant FT, Schmitt FA, Donegan SJ, Wekstein DR, Ehmann WD, Markesbery WR***; Alzheimer's disease, dental amalgam and mercury; J. Am. Dent. Assoc. 130(2) 191-199 (1999)

1266 ***Saxena G, Flora SJS***; Lead-induced oxidative stress and hematological alterations and their response to combined administration of calcium disodium EDTA with a thiol chelator in rats; J. Biochem. Mol. Toxicol. 18(4) 221-233 (2004)

1267 ***Scarmoutzos LM, Boyd OE***; Environmental and toxiclogical concerns of dental amalgam and mercury; www.mvssolutions.com/mercury.pdf (2003)

1268 ***Schaeffer M, Schöllmann C***; Risikofaktor Amalgam – Ein Problemstoff in der aktuellen Diskussion; Schriftenreihe Umweltmedizin, Forum Medizin Verlagsgesellschaft (1996)

1269 ***Schäfer B***; Untersuchung zur Eignung von Dithiolen zur Ausschleusung von Arsen aus verschiedenen Organen bei der Maus; Dissertation, Tierärztliche Fakultät der Ludwig-Maximilians-Universität München (1993)

1270 ***Schäfer B, Kreppel H, Reichl FX, Fichtl B, Forth W***; Effect of oral treatment with Bal, DMPS or DMSA arsenic in organs of mice injected with arsenic trioxide; Arch. Toxicol. 14(Suppl.) 228-230 (1991)

1271 ***Schäfer SG***; Treatment of methlmercury poisoning by subchronic administration of sodium 2,3-dimercaptopropane-1-sulfonate (DMPS); 2nd Int. Symp. Chelating Agents in Pharmacology Toxicology and Therapeutics, Pilsen (1987)

1272 ***Schäfer SG, Storp M, Richter E***; Subchronic treatment with sodium 2,3-dimercaptopropane-1-sulfonate in methylmercury poisoning; Bull. Environ. Contam. Toxicol. 29(4) 416 - 421 (1982)

1273 ***Schaller KH, Schiele R;*** Experiences with the antidote 2,3-dimercapto-1-propane sulfonic acid for the mobilization of mercury depots in the human organism as a diagnostic tool; 23rd Congress on Occupational Health, Montreal (1990)

1273a ***Schauss MA***; How to assess environmental toxicity loads in your clientele; http://www.markschauss.com/wp-content/uploads/2007/10/sacramento-nanp-presentation.pdf (2007)

1274 ***Scheuhammer AM, Cherian MG***; Effects of heavy metal cations, sulfhydryl reagents and other chemical agents on striatal D_2 dopamine receptors; Biochem. Pharmacol. 34(19) 3405-3413 (1985)

1275 ***Scheurmann T***; Abklärung von chronischen Quecksilberintoxikationen bei Trägern von Amalgamfüllungen; Dokumentation Institut Dr. Viollier, Basel (1996)

1276 ***Schiele R***; Berufskrankheiten - Durch chemische Einwirkungen verursachte Krankheiten: Metalle und Metalloide (Blei, Quecksilber, Arsen, Thallium ...); IN: Arbeitsmedizin - Handbuch für Theorie und Praxis, G Triebig, M Kentner, R Schiele (Eds.), Gentner Verlag, Stuttgart, 163-202 (2003)

1277 ***Schiele R***; Arbeitsmedizinische Bewertung der Ergebnisse biomonitorischer Analysen; IN: Biomonitoring in der Praxis - Tb 140 "Schriftenreihe der Bundesanstalt für Arbeitsschutz und Arbeitsmedizin" 32-38 (2002)

1278 ***Schiele R***; Arbeitsbedingte Quecksilber-Intoxikation - Arbeiten unter Einwirkung von Quecksilber und seinen Verbinfungen; Leitlinien Deutsche Gesellschaft für Arbeitsmedizin und Umweldmedizin e.V. (DGAUM); www.uni-duesseldorf.de/WWW/AWMF/ll/quecksi (1998)

1279 ***Schiele R***; Amalgamfüllungen - Umweltgift im Mund? Zum aktuellen Stand der Diskussion; IN: Bericht über die 33. Jahrestagung der Deutschen Gesellschaft für Umweltmedizin e.V. - G Triebig, O Stelzer (Eds.) - Genter Verlag Stuttgart - 105-109 (1993)

1280 ***Schiele R***; Toxikologische Aspekte der Amalgam-Füllungen; IN: Neue Füllungsmaterialien, Indikation und Verarbeitung, Hrsg. Akademie Praxis und Wissenschaft in der DGZMK, Hanser Verlag München S. 9-19 (1990)

1281 ***Schiele R, Schaller KH***; Einsatz des Komplexbildners DMPS (Dimaval) zur Feststellung von Quecksilber-Speicherungen; IN: Berufskrankheiten, Krebserzeugende Arbeitsstoffe, Biological Monitoring, Verhandlungen der Deutschen Gesellschaft für Arbeitsmedizin e.V., 30. Jahrestagung, F Schuckmann, S.Schopper-Jochum (Eds.), Gentner Verlag Stuttgart, 379 – 382 (1990)

1282 ***Schiele R, Schaller KH, Welte D***; Mobilisation von Quecksilber-Speicherungen im Organismus mittels DMPS (Dimaval); Arbeitsmed. Sozialmed. Präventivmed. 24(11) 249-251 (1989)

1283 ***Schiele R, Kröncke A***; Quecksilber-Mobilisation durch DMPS (Dimaval®) bei Personen mit und ohne Amalgamfüllungen; Zahnärztl. Mitt. 79(17) 1866-1868 (1989)

1284 ***Schiele R, Kröncke A***; Stellungnahme; Die Zahnarztwoche (45) 13 (1989)

1285 ***Schiele R***; Toxikologie metallischer Werkstoffe in der Zahnheilkunde; IN: "Umwelt, Arbeitswelt, Gesundheit", Hrsg. Akademie Praxis und Wissenschaft in der DGZMK, Hanser Verlag München, S. 25-37 (1988)

1286 ***Schilling U, Mück R, Heidemann E***; Bleiintoxikation durch Einnahme ayurvedischer Arzneimittel; Med. Klinik 99(8) 476-480 (2004)

1287 ***Schirren C***; Bedeutung von Umwelteinflüssen in der Andrologie und Reproduktionsmedizin; Hautnah Dermatologie 13(6) 394-400 (1997)

1288 ***Schiwara HW***; Rationelle Diagnostik bei Umweltbelastung mit toxischen Schwermetallen; Z. Umweltmed. 7(5) 285-291 (1999)

1289 ***Schiwara HW***; Schwermetallbelastungen durch Amalgamfüllungen und andere Dentallegierungen; IN: NATUM Naturheilkunde und Umweltmedizin in der Frauenheilkunde, W Behrendt, I Gerhard (Eds.) Hippokrates Verlag, Stuttgart, 57-65 (1996)

1290 ***Schiwara, HW, Gerhard I;*** Korrelation der Quecksilberausscheidung vor und nach DMPS-Gabe; Öffentliche Expertenanhörung BfArM, Berlin (1994)

1291 ***Schiwara HW, Daunderer M, Kirchherr H, Heß C, Harders B, Hoppe HW, Molsen C, Engler J, Scholze M, Buchterkirche B, Buchterkirche C***; Bestimmung von Kupfer, Quecksilber, Methylquecksilber, Zinn, Methylzinn und Silber in Körpermaterial von Amalgamträgern; Klin. Labor 38(9) 391-403 (1992)

1292 ***Schleicher P, Bannasch L, Kistner A, Schrauzer GN***; Immunologischer Status bei quecksilberbelasteten Patienten - Der Status vor und nach Detoxifikationstherapie mit den Spurenelementen Zink und Selen; Notabene Medici 23(12) 426-431 (1993)

1293 ***Schleicher P, Bannasch L***; Immunschäden durch Toxine; Argumente + Fakten der Medizin 05 (1992)

1294 ***Schleicher W***; Untersuchungen zur Verteilung und Dekorporation von anorganischem Quecksilber. In-vivo-Versuche mit Ratten, in-vitro-Experimente mit Humanserum; Dissertation Universität Karlsruhe (1977)

1295 ***Schmid I, Paulweber B, Pechböck W, Oberkofler H, Patsch W***; Eine spät erkannte Bleiintoxikation; Toxichem. Krimtech. 67(3) 96-97 (2000)

1296 ***Schmidt E, Becker HD, Domres B***; Aktivitäten auf Bundesebene zur Vorsorge von bioterroristischen Anschlägen; Bundesgesundheitsbl. Gesundheitsforsch. Gesundheitsschutz 46(11) 997-1000 (2003)

1297 ***Schmidt I, van Spanning RJ, Jetten MS***; Denitrification and ammonia oxidation by Nitrosomonas europaea wild-type, and NirK- and NorB-deficient mutants; Microbiology 150(Pt 12) 4107-4114 (2004)

1298 ***Schmidt I, Steenbakkers PJM, op den Camp HJM, Schmidt K, Jetten MSM***; Physiologic and proteomic evidence for a role of nitric oxide in biofilm formation by nitrosomonas europaea and other ammonia oxidizers; J. Bacteriol. 186(9) 2781-2788 (2004)

1299 ***Schmidt I, Zart D, Bock E***; Gaseous NO_2 as a regulator for ammonia of Nitrosomonas eutropha; Antonie van Leeuwenhoek 79(3-3) 311-318 (2001)

1300 ***Schöllhorn SV***; Amalgamstudie über den zeitlichen Verlauf der Quecksilberausscheidung nach Gabe des Medikamentes DMPS bei Personen mit und ohne Amalgamfüllungen; Dissertation Johannes-Gutenberg-Universität, Mainz (1995)

1300a ***Scholz H***: Amalgam und (k)ein Ende? Ein Update auf dem Weg zur metallfreien Zahnmedizin; Co'med (10) 1-3 (2007)

1301 ***Schott K***; Toxisch-metabolische Enzephalopathien; IN: Neurologische Therapieb, Dickgans, Brandt, Diener (Eds.) Kohlhammer-Verlag (1987)

1302 ***Schrauzer GN***; Quecksilber-Selen-Wechselwirkungen und das Zahnamalgam-Problem; IN: Status Quo and Perspectives of Amalgam and other Dental Materials; LT Friberg, GN Schrauzer (Eds.); Georg-Thieme Verlag, Stuttgart, New York; pp.106-118 (1995)

1303 ***Schroth R***; „Schleichende Quecksilbervergiftung"-Möglichkeiten und Grenzen der kausalen Ursachenzuschreibung; Pressekonferenz: Quecksilberbelastung durch Amalgam-Zeit zum Handeln, Bühl/Baden-Baden (1996)

1304 ***Schrott E***; Aus der täglichen Praxis: Amalgamvergiftung - ayurvedische Behandlung linderte Leiden: Der Naturarzt (5) 26-29 (1994)

1305 ***Schubert J***; Therapy of plutonium and cadmium poisoning by combinations of chelating agents; IN: Biological Aspects of Metals and Metal-related Disesases B Sarkar (Ed.); Raven Press, New York, pp. 279-307 (1983)

1306 ***Schubert J, Derr SK***; Mixed ligand chelate therapy for plutonium and cadmium poisoning; Nature 275(5678) 311-313 (1978)

1307 ***Schuetz A, Molin M, Nilsson A, Skerfving S, Sällsten G***; Does a mobilization with 2,3-dimercaptopropane sulfonate reflect the body burden of mercury; 23rd Congress on Occupational Health, Montreal (1990)

1308 ***Schulte-Uebbing C***; Umweltbedingte Frauenkrankheiten; Sonntag-Verlag, Stuttgart (1996)

1308a ***Schulz A, Höfler M***; Monoble metal dithiolates preparations containing them and their use; US Patent 5705664 (1998)

1309 ***Schulz M, Drath C, Ihrig A, Triebig G***; Zur Frage einer Bleiintoxikation als Berufskrankheit bei Korrosionsschutz-arbeitern; Arbeitsmed. Sozialmed. Umweltmed. 40(1) 4-10 (2005)

1310 S***chulz M, Ihrig A, Zimmer H, Triebig G***; Untersuchung zum diagnostischen Stellenwert der Bleimobilisation nach einer mehrwöchigen hohen Bleibelastung; Arbeitsmed. Sozialmed. Umweltmed. 40(3) 173-174 (2005)

1311 ***Schuurs A, Exterkate R, ten Cate JM***; Biological mercury measurements before and after administration of a chelator (DMPS) and subjective symptoms allegedly due to amalgam; Europ. J. Oral Sciences 108(6) 511-522 (2000)

1312 ***Schweinsberg F, Wascher E, Dietz K, Heinzow B***; Umgang mit Kritik an wissenschaftlichen Publikationen; Umweltmed. Forsch. Prax. 5(2) 65-66 (2002)

1313 ***Schweinsberg F***; Gesundheitliche Bewertung von Quecksilber in der Umweltmedizin durch Human-Biomonitoring; Umweltmed. Forsch. Prax. 3(4) 211 (1998)

1314 ***Schweinsberg F***; Risk estimation of mercury intake from different sources; Toxicol. Lett. 72 345-351 (1994)

1315 ***Schweinsberg F, Herrmann M, Widon B, Ostertag A, Pickert A, Wiethölter H***; Quecksilberbelastung durch Amalgam und Beruf - Messen und Bewerten, Forum Städte Hyg. 43(2) 73-76 (1992)

1316 ***Schweisfurth H, Schmidt M, Leppert R, Brugger E, Maiwald L***; Value of determination of kininase II in bronchoalveolar lavage fluid; Adv. Exp. Med. Biol. 198(A) 523-528 (1986)

1317 ***Schwenk M, Kluge S, Jaroni H***; Toxicological aspects of preparedness and aftercare for chemical-incidents; Toxicology 214(3) 232-248 (2005)

1318 ***Schwohl T, Schroeder B, Müller-Esch G, Djongalic H***; Zur Quecksilberelimination mittels Hämofiltration und Hämoperfusion bei akuter Sublimatintoxikation; Intensivmedizin 25 198-201 (1988)

1318a ***Scott BR***; Health risk evaluations for ingestion exposure of humans to Polonium-210; Dose Response; 5 94-122 (2007)

1319 ***Sedov KR, Bobovskaia LG***; Correction of sulfhydryl group level in patients with diabetes mellitus; Klin. Med. 56(8) 61-65 (1978) [Abstract]

1320 ***Seidel A***; Metabolism and toxicology of polonium and its removal from the body; IN: Gmelin Handbook of Inorganic and Organometallic Chemistry, 8th Edn., Polonium Supplement Vol. 1; KC Buschbeck, C Keller (Eds.), Springer Verlag Berlin, Heidelberg, New York, pp. 251-274 (1990)

1321 ***Seidel D, Catsch A, Schweer KH***; Dekorporation von Radionukliden (Untersuchungen an Radioruthenium); Strahlentherapie 122 595-610 (1963)

1322 ***Seidel HJ***; Praxis der Umweltmedizin. Grundlagen, Fakten und Informationen für einen verantwortungsvollen Umgang mit Umwelt und menschlicher Gesundheit; Thieme Verlag, Stuttgart, New York (1998)

1323 ***Seropyan KA***; Amounts of gluthathione in the blood of patients with psoriasis and Unithiol treatment; Vestn. Dermatol. Venerol. 37(11) 33-35 (1963) [Abstract]

1324 ***Shafer TJ***; Effects of Cd2+, Pb2+ and CH3Hg+ on high voltage-activated calcium currents in pheochromocytoma (PC12) cells: Potency, reversibility, interactions with extracellular Ca2+ and mechanisms of block; Toxicol. Lett. 99(3) 207-221 (1998)

1325 ***Shakhnazarov AM***; On the effective use of unithiol in combination with ephedrine in acute enteral sodium bichromate poisoning; Gig. Tr. Prof. Zabol. (8) 38-43 (1978) [Abstract]

1326 ***Shander D, Ahluwalia GS, Marks-Del Grosso D***; Method of reducing hair growth employing sulfhydryl active compounds; US Patent 6743419 (2004)

1327 ***Shannon M***; Lead poisoning treatment - A continuing need (commentary); J. Toxicol. Clin. Toxicol. 39(7) 661-663 (2001)

1328 ***Shapovalova EN, Ofitserova MN, Savostyanova EV, Shpigun OA***; Ion-pair chromatography of metal complexes of unithiol in the presence of quaternary phosphonium salts; J. Anal. Chem. 56(2) 160-165 (2001)

1329 ***Shareeff M, Bhat YM, Adabala R, Raoof S***; Shortness of breath after suicide attempt; Chest 118(3) 837-838 (2000)

1330 ***Sharkawy AA, Abd-Elghaffar SK, Omar HM***; Efficacy of 2,3-dimercaptopropaneol (BAL) and 2,3-dimercapto-1-propane sulfonate (DMPS) on long-term mercuric chloride exposure in rats: Toxicological and pathological studies; Environmental Encyclopedia for Assiut University (2000)

1331 ***Sharma BL, Khandelwal S, Kachru DN, Singh S, Tandon SK***; Chelation in metal intoxication. XXV Mercapto-acrylic acids as antidotes of lead and nickel toxicity; Jpn. J. Pharmacol. 45(3) 295-302 (1987)

1332 ***Shemanova LP***; Use of unithiol for prophylaxis of the ototoxic effect of corrosive mercuric chloride; Zh. Ushn. Nos. Gorl. Bolezn. (4) 8-11 (1975) [Abstract]

1333 ***Shi Y, Littlejohn D, Chang SG***; Kinetics of NO-absorption in aqueous iron(II)-bis(2,3-dimercapto-1-propane-sulfonate solutions using a stirred reactor; Ind. Eng. Chem. Res. 35(5) 1668-1672 (1996)

1334 ***Shinobu LA, Jones MM, Basinger MA, Mitchell WM, Wendel D, Razzuk A***; In vivo screening of potential antidotes for chronic cadmium intoxication; J. Toxicol. Environ. Health 12(4-6) 757-765 (1983)

1334a ***Shiri R, Ansari M, Ranta M, Falah-Hassani K***; Lead poisoning and recurrent abdominal pain; Ind. Health 45(3) 494-496 (2007)

1335 ***Shleikin AG, Gorkova LB, Pozhilenkova KS, Zvezdochkin AG***; Mechanism of changes in amine binding to plasma proteins during allergy; Vopr. Med. Khim. 35 (2) 86 - 89 (1989) [Abstract]

1336 ***Shleikin AG, Zubzhitskii IN, Baskovich GA, Kolmakov VN, Rodionova LP***; Effect of unithiol and acetylcysteine on lipid peroxidation and the erythrocyte antioxidant system in sensitized guinea pigs; Bull. Exp. Biol. Med. 103 (5) 548 - 550 (1987) [Abstract]

1337 ***Shtelmakh NI, Sidorov AP, Leonteva FS, Riabkova LP, Gulida TI***; Comparative treatment effectiveness with chlotazol and unithiol preparations in rheumatoid arthritis; Vrach. Delo. (1) 49-52 (1982) [Abstract]

1338 ***Shvarts GI, Paskhina TS, Egorova TP, Eliseeva YE, Pavlikhina LV***; Molecular-biological problems of the creation of drugs and study of the mechanism of their action; Pharm. Chem. J. 15 537-541 (1982)

1339 ***Shvarts GI***; Action of parmidin and drugs influencing kinin metabolism on painful reactions in mice; Farmakol. Toksikol. 44(5) 606-611 (1981) [Abstract]

1340 ***Shvarts GI***; Comparative evaluation and analysis of the bradykinin-potentiating properties of D-penicillamine and other thiol and non-thiol kininase inhibitors; Farmakol. Toksikol. 44(3) 327-330 (1981) [Abstract]

1341 ***Shymanskyy I, Kuchmerovska T, Donchenko G, Veliky M, Kuchmerovskyy M, Pakyrbaeva L***; Nicotinamide and aldose reductase inhibitors in correction of diabetes-related oxidative stress; Diabetologia 45(Suppl.2) A324 (2002)

1342 ***Siblerud RL, Kienholz E, Motl J;*** Evidence that mercury from silver dental fillings may be an etiological factor in smoking; Toxicol. Lett. 68(3) 307-310 (1993)

1343 ***Siddiqi NJ, Alhomida AS***; Effect of mercuric chloride on urinary excretion of free hydroxyproline; Med. Sci. Monit. 12(3) BR95-101 (2006)

1344 ***Siddiqi NJ, Alhomida AS***; Effect of mercuric chloride on various hydroxyproline fractions in rat serum; Mol. Cell. Biochem. 271(1-2) 159-165 (2005)

1345 ***Siefert K***; Veränderungen der Quecksilberausscheidung im Dimercaptopropion-sulfonsäure-Mobilisationstest durch Einnahme von Vitaminen und Spurenelementen oder von organotropen Homöopathika im Vergleich mit einer Kontrollgruppe; Dissertation Universität Heidelberg (2001)

1346 ***Siemann S, Clarke AJ, Viswanatha T, Dmitrienko GI***; Thiols als classical and slow-binding inhibitors of IMP-1 and other binuclear metallo-ß-lactamases; Biochemistry 42 1673-1683 (2003)

1347 ***Siems WG, Krämer K, Grune T***; Störungen im Glutathionsystem und klinische Konsequenzen; Pharm. Ztg. 141(46) 11-22 (1996)

1348 ***Simkiss D***; Traditional remedies in lead poisoning; J. Trop. Pediatr. 49(1) 2-3 (2003)

1349 ***Simmons-Willis TA, Koh AS, Clarkson TW, Ballatori N***; Transport of a neurotoxicant by molecular mimicry: The methylmercury-L-cysteine complex is a substrate for human L-type large neutral amino acid transporter (LAT) 1 and LAT2; Biochem. J. 367(1) 239-246 (2002)

1350 ***Simson TF, Rozhdestvenskaya ZB***; Electrochemical studies of sulfide and oxide minerals; Zh. Anal. Khim. 36 1933-1938 (1981) [Abstract]

1351 ***Simunek T, Hrdina R, Klimtova I, Gersl V, Machackova J, Ponka P, Kaplanova J, Mazurova Y***; 2,3-Dimercapto-propane-1-sulfonate and pyridoxal-isonicotinoyl-hydrazone: comparison of cardiovascular effects of two metal-chelating agents in rabbits; Fundam. Clin. Pharmacol. 123(Suppl.1) 15 (2001)

1352 ***Skakun NP, Moroz GS, Tsilyurik IT, Volkova LA, Oleinik AV, Kovalchuk SF, Kudin IT***; Excretory function of the liver with an allyl alcohol lesion and the antioxidant correction of the disorders; Farmakol. Toksikol. 50(1) 100-103 (1987) [Abstract]

1353 ***Skakun NP; Kovalchuk SF***; Effectiveness of antioxidants in a combined carbon tetrachloride and ethanol lesion of the liver; Farmakol. Toksikol. 50(3) 97-99 (1987) [Abstract]

1353a ***Skoblo RM, Lätzsch I***; Funktionsteste; www.iflb.de/files/PDF/Aerzte/funktionsteste_x.pdf (2007)

1354 ***Skomorokhova TN, Prokhorova II, Eidelshtein SI, Borisov VP, Seletskaia LI***; Effect of complexons on the function of ciliary epithelium; Vestn. Otorinolaringol. (3) 65-68 (1976) [Abstract]

1355 ***Slikkerveer A, Noach LA, Tytgat GNJ, Van der Voet GB, De Wolff FA***; Comparison of enhanced elimination of bismuth in humans after treatment with meso-2,3-dimercaptosuccinic acid and D,L-2,3- dimercaptopropane-1-sulfonic acid; Analyst 123(1) 91-92 (1998)

1356 ***Slikkerveer A, Jong HB, Helmich, RB, de Wolff FA***; Development of a therapeutic procedure for bismuth intoxi-cation with chelating agents; J. Lab. Clin. Med. 119(5) 529-537 (1992)

1357 ***Smirnov AV, Dobronravov VA, Zhloba AA, Golubev RV***; Method for the treatment of hyperhomocysteinemia in patients with chronic renal insufficiency and treated by hemo-dialysis or hemo-filtration; PATENT RU 2281090 (2005) [Abstract]

1358 ***Smith PG;*** Arsenic biotransformation in terrestrial organisms - A study of the transport and transformation of arsenic in plants, fungi, fur and feathers, using conventional speciation analysis and X-ray absorption spectroscopy; Thesis Biology Department of Queen's University Kingston, Ontario, Canada (2007)

1359 ***Smith PG, Koch I, Gordon R, Mandoli DF, Chapman BD, Reimer KJ***; X-ray absorption near-edge structure analysis of arsenic species for application to biological environmental samples; Environ. Sci. Technol. 39(1) 248-254 (2005)

1360 ***Smith RM, Martell AE***; Critical stability constants, Volume 6: Second supplement; Plenum Press, New York, London

1361 ***Smrz P***; Amalgam - ein unnötiger Krankheitsherd; Dtsch. Zschr. Biologische Zahnmedizin (5) 109-115 (1989)

1362 ***Soares FA; Farina M; Santos FW; Souza D; Rocha JB; Nogueira CW***; Interaction between metals and chelating agents affects glutamate binding on brain synaptic membranes; Neurochem. Res. 28(12) 1859-1865 (2003)

1363 ***Sobolevsky AI, Yelshansky MV, Wollmuth LP***; The outer pore of the glutamate receptor channel has 2-fold rotational symmetry; Neuron 41(3) 367-378 (2004)

1364 ***Sobolevsky AI, Rooney LA, Wollmuth LP***; Staggering of Subunits in NMDAR Channels; Biophys. J. 83(6) 3304-3314 (2002)

1365 ***Softova E, Belcheva A, Mangarova M;*** Comparative study of the influence of mono- and dithiol antidotes upon renal structural changes and urea level in acute mercury intoxication; Scr. Sci. Med. 21 13-17 (1984)

1366 ***Softova E, Mangarova M, Belcheva A***; Influence of unithiol upon the progress of renal regenerative process of subchronic mercury intoxication; Scr. Sci. Med. 20 28-32 (1983)

1367 ***Sokolovskii VV, Danchia II, Avetisyan TK***; Poisoning of a platinum catalyst during liquid-phase hydrogenation under hydrogenation pressure; Zh. Prikl. Khim. 56(11) 2460-2463 (1983)

1368 ***Sokolovskii VV, Belozerova LA, Ogurtsova RE***; Quantitative determination of tissue disulfide groups by reverse amperometric titration; Vopr. Med. Khim. 23(5) 709-712 (1977) [Abstract]

1369 ***Soli NE, Froslie A, Aaseth J***; The mobilization of copper in sheep by chelating agents; Acta Vet. Scand. 19(3) 422-429 (1978)

1370 ***Song Y, Li A***; Massive elemental mercury ingestion; Clin. Toxicol. 45(2) 193 (2007)

1371 ***Songina OA, Ospanov KK, Fedosov SN***; Composition and strength of silver, palladium, and gold unithiolates; Izvestiya Akademii Nauk Kazakhskoi SSR, Seriya Khimicheskaya 19(4) 20-26 (1969) [Abstract]

1372 ***Songina OA, Ospanov KK, Rozhdestvenskaya ZB***; Amperometric titration of mercury(I) and mercury(II) with unithiol; Anal. Bioanal. Chem. 215(1) 56 (1965) [Abstract]

1373 ***Songina OA, Ospanov KK, Rozhdestvenskaya ZB***; Polarographic study of electrolytic oxidation of unithiol on a platinum electrode; Anal. Bioanal. Chem. 208(6) 444-445 (1965) [Abstract]

1374 ***Soroka VR, Sorokina AA***; The effect of unithiol and $CaNa_2EDTA$ on the urinary elimination of trace elements in the dog; Gig. Tr. Prof. Zabol. 13(6) 40-41 (1969) [Abstract]

1375 ***Southgate HJ, Ward A, Taylor A, Carr P***; Lessons to be learned: a case study approach. An unusual case of alveloar deposition from swallowing metallic mercury in an attempt at self-poisoning; J. Roy. Soc. Health 118(5) 305-308 (1998)

1376 ***Spähni-Su P***; Comparative efficacy of chelators to remove renal cadmium burden in isolated perfused rat kidneys; Dissertation Universite de Lausanne (2002)

1377 ***Spranger H, Fibbe C, Layer P***; Eine ungewöhnliche Ursache für ein akutes Abdomen; Der besondere gastroenterologische Fall - Norddeutscher Gastroenterologentag, Hannover (2007)

1378 ***Srivastava RC, Gupta S, Ahmad N, Hasan SK, Farookh A, Husain MM;*** Comparative evaluation of chelating agents on the mobilization of cadmium: A mechanistic approach; J. Toxicol. Environ. Health 47(2) 173-182 (1996)

1379 ***Staab HA***; Einführung in die theoretische Chemie; Verlag Chemie, Weinheim; pp.192-194 (1970)

1380 ***Städtler P, Ebeleseder K***; Amalgam; Dermatosen in Beruf und Umwelt 43(4) 163-171 (1995)

1381 ***Stähle HJ***; Unverträglichkeit gegenüber Dentalmaterialien – Bei Verdacht ist interdisziplinäre Abstimmung erforderlich; Dt. Ärzteblatt 97(49) A 3344-3351 (2000)

1382 ***Stähle HJ, Gerhard I***; Konsensuspapier zur Verträglichkeit von Zahnfüllmaterialien; Zahnmedizin 89(8) 958-959 (1999)

1383 ***Stähle HJ;*** Gesundheitsrisiken durch zahnärztliche Materialien?; Dt. Ärzteblatt 91(8) 394-399 (1994)

1384 ***Stähle HJ***; Zahnärztliche Materialien-Überblick und Diskussion möglicher Wirkungen; IN: Praktische Umweltmedizin-Klinik, Methoden, Arbeitshilfen; Springer Loseblatt Systeme (1994)

1385 ***Stantschew S***; Bestimmung und Dekorporation der Quecksilberdepots bei Quecksilberexponierten; Z. Gesamte. Hyg. 29(7) 388-390 (1983)

1386 ***Stark AM, Barth H, Grabner JP, Mehdorn HM***; Accidental intrathecal mercury application; Eur. Spine J. 13(3) 241-243 (2004)

1387 ***Starshinova AE***; Experimental study of the anti-arrhythmia action of unithiol; Farmakol. Toksikol. 38(2) 168-170 (1975) [Abstract]

1388 ***Steens W, Loehr JF, von Foerster G, Katzer A***; Chronische Kobaltvergiftung in der Endoprothetik - Ein Fallbericht; Orthopäde; 35(8) 860-864 (2006)

1389 ***Steffen C***; The dilemma of approving antidotes; Toxicology 233(1-3) 13-19 (2007)

1390 ***Steinmann F, Ott K***; Studie über die Beschwerdebilder von Patienten mit Verdacht auf eine Amalgam-Unverträglichkeit; Dtsch. Zahnärztl. Z. 53(2) 152-155 (1998)

1391 ***Stenman S, Grans L***; Symptoms and differential diagnosis of patients fearing mercury toxicity from amalgam fillings; Scand. J. Work Environment Health 23(Suppl.3) 59-63 (1997)

1392 ***Stenman S, Grans L***; The use of 2,3-dimercapto-1-propanesulfonic acid (DMPS) to evaluate the Hg-burden in amalgam patients; Unpublished results (1991)

1393 ***Stevens E, Ectors M, Cornil A***; Acute intoxication by ingestion of inorganic mercury salts; Acta Clin. Belg. Suppl.13 105-106 (1990)

1394 ***Stevens PE, Moore DF, House IM, Volans GN, Rainford DJ***; Significant elimination of bismuth by haemodialysis with a new heavy-metal chelating agent; Nephrol. Dial. Transplant. 10(5) 696-698 (1995)

1395 ***Stewart JR, Diamond GL***; In vivo renal tubular secretion and metabolism of the disulfide of 2,3-dimercaptopropane-1-sulfonate; Drug Metab. Dispos. 16(2) 189-195 (1988)

1396 ***Stewart JR, Diamond GL***; Renal tubular secretion of the alkanesulfonate 2,3-dimercapto-1-propanesulfonate; Am. J. Physiol. 252(5 Pt 2) F800-F810 (1987)

1397 ***Stier U***; Radiologische Langzeitbeobachtung einer intravenösen Quecksilberapplikation; Akt. Radiol. 8(2) 98-100 (1998)

1398 ***Stoll R***; Arbeitsbedingte Cadmium-Intoxikation - Gefährdung, Diagnostik, Therapie und Prävention; Leitlinien Deutsche Gesellschaft für Arbeitsmedizin und Umweltmedizin e.V. (DGAUM) (2005)

1399 ***Stoll S***; Allergien in aller Munde? Eine Untersuchung der Epikutantests der Zahn-, Mund- und Kieferklinik Freiburg von 1993 bis 2001; Dissertation Albert-Ludwig-Universität Freiburg i. Br. (2007)

1400 ***Storp M, Schäfer SG, Weger N***; Die subchronische Wirkung von DMPS (2,3-Dimercaptopropane-1-sulfonat) auf die Ausscheidung und Organverteilung von Methylquecksilber bei Ratten; Mainzer Frühjahrstagung der DPhG (1983)

1401 ***Stoytchev TS, Kirova A***; Effect of ethylxanthogenate, diethyldithiocarbamate and unithiol on carbon tetrachloride poisoning; Acta Physiol. Pharmacol. Bulg. 3(1) 61-69 (1977)

1402 ***Stoytchev TS***; Antidotal effect of some thiol compounds on acute copper sulfate poisoning; Proc. Eur. Soc. Toxicol. 16 252-257 (1975)

1403 ***Stoytchev TS, Koleva M, Kirova A***; The effect of unithiol (2-mercapto-propane sulfonate sodium) on the motor activity stimulated by amphetamine, on evipan anesthesia and on the activity of dopamine-ß-hydroxylase; Eksp. Med. Morfol. 13(2) 118-123 (1974) [Abstract]

1404 ***Stoytchev TS, Koleva M, Kirova A***; Influence of ethylxanthogenate and unithiol on the amphetamine-induced locomotor activity, hexobarbital sleeping time and dopamine hydroxylase activity Proc. Eur. Soc. Study Drug Toxicity, Amst.-New York, p.345-349 (1974)

1405 ***Stoytchev TS***; Experimental studies on the antidotal treatment of acute copper sulfate poisoning; Bull. Inst. Physiol. Bulg. Acad. Sci. 15 173-178 (1973)

1406 ***Strassner W***; Testung von Strahlenschutzsubstanzen am DNS-Gehalt von Knochenmarkzellen bestrahlter Meerschweinchen; Rad. Ther. 2(1) 117-123 (1961)

1407 ***Stücklin-Utsch A, Seidel C, Lentze MJ***; Iatrogene Quecksilbervergiftung bei einem Zweijährigen durch Verwechslung im OP; Deutscher Kinderärztekongreß, Freiburg (2001)

1408 ***Sun P, Han J, Weng Y***; The antidotal effects of high-dosage gamma-aminobutyric acid on acute tetramine poisoning as compared with sodium dimercaptopropane sulfonate; J. Huazhong Univ. Sci. Technolog. Med. Sci. 27(4) 419-421 (2007) [Abstract]

1409 ***Sun W, Liu R, Cao X, Hu Y***; Flotation separation of marmatite from pyrrhotite using DMPS as depressant; Transact. Nonferrous Metals Soc. China 16(3) 671-675 (2006)

1410 ***Sun W, Liu R, Hu Y***; Research on depression mechanism of jamesonite and pyrrhotite by organic depressant DMPS; Kuangye Gongcheng 25(6) 31-34 (2005) [Abstract]

1411 ***Sundermann A***; Lehrbuch der inneren Medizin, Band III; Gustav-Fischer-Verlag, Jena, p.807 (1989)

1412 ***Surovikina MS, Fomina EE***; A method for detection of blood plasma kallikrein inhibitors in man and animals; Biull. Eksp. Biol. Med. 91(5) 623-626 (1981) [Abstract]

1413 ***Surovkina MS***; Biological methods of determining free kinins in peripheral blood; Biull. Eksp. Biol. Med. 91(2) 241-243 (1981) [Abstract]

1414 ***Susa N, Ueno S, Furukawa Y***; Protective effects of thiol compounds on chromate-induced toxicity in vitro and in vivo; Environ. Health Perspect. 102(Suppl. 3) 247-250 (1994)

1415 ***Susa N, Ueno S, Furukawa Y***; Protective effects of thiol compounds on chromate-induced cytotoxicity in HeLa cells; J. Vet. Med. Sci. 54(2) 281-288 (1992)

1416 ***Sutton DJ, Tchounwou PB***; Mercury induces the externalization of phosphatidyl-serine in human renal proximal tubule (HK-2) cells; int. J. Environ. Res. Public Health 4(2) 138-144 (2007)

1417 ***Suzuki S, Niwa O, Takamura S, Sugiki K, Imai M***; Protection of mercuric chloride-induced acute inhibition of enzymes in rat duodenal mucosa and kidney cortex by DMPS; J. Toxicol 86(1-2) 29-48 (1994)

1418 ***Swarovsky B, Eissele R, Doss M, Lorenz-Meyer H***; Oberbauchbeschwerden und Alkoholkonsum bei einem Maschinenbauarbeiter; Internist 36(8) 828-832 (1995)

1419 ***Szinicz L, Mückter H, Felgenhauer N, Zilker T***; Toxicodynamic and toxicokinetic aspects of the treatment of arsenical poisoning; J. Toxicol.Clin. Toxicol. 38(2) 214-216 (2000)

1420 ***Szinicz L, Wiedemann P, Häring H, Weger N***; Effects of repeated treatment with sodium 2,3-dimercaptopropane-1-sulfonate in beagle dogs; Arzneimittelforschung. 33(6) 818-821 (1983)

1421 ***Szinicz L, Hauser W, Hell U, Weger N***; Reduction of toxicity of arsenic in suspensions of isolated rat kidney tubules and in vivo in mice by 2,3-dimercapto-1-propane sulfonate (DMPS) and 2,3-Dimercapto succinic acid (DMSA); Unpublished results (1981)

1422 ***Szinicz L, Weger N***; Wirkung von 2,3-Dimercaptopropanesulfonat auf die Toxizität von Arsenik in isolierten Nieren-tubuli der Ratte und in vivo in Mäusen; Unveröffentlichte Ergebnisse (1981)

1423 ***Tadlock CH, Aposhian HV***; Protection of mice against the lethal effects of sodium arsenite by 2,3-dimercapto-1-propane-sulfonic acid and dimercaptosuccinic acid; Biochem. Biophys. Res. Commun. 94(2) 501-507 (1980)

1424 ***Takahashi Y, Funakoshi T, Shimada H, Kojima S***; The utility of chelating agents as antidotes for nephrotoxicity of gold sodium thiomalate in adjuvant-arthritic rats; Toxicology 97(1-3) 151-157 (1995)

1425 ***Takahashi Y, Funakoshi T, Shimada H, Kojima S***; Comparative effects of chelating agents on distribution, ex-cretion, and renal toxicity of gold sodium thiomalate in rats; Toxicology 90(1-2) 39-51 (1994)

1426 ***Takahashi Y, Funakoshi T, Shimada H, Kiyozumi M, Kojima S***; Effect of repeated administration of chelating agents on distribution, excretion, and renal toxicity of gold sodium thiomalate in rats; Res. Commun. Chem. Pathol. Pharmacol. 76(2) 253-256 (1992)

1427 ***Tandon SK, Prasad S, Singh S***; Chelation in metal intoxication: influence of cysteine or N-acetylcysteine on the effi-cacy of 2,3-dimercaptopropane-1-sulfonate in the treatment of cadmium toxicity; J. Appl. Toxicol. 22(1) 67-71 (2002)

1428 ***Tandon SK, Singh S, Prasad SM, Flora GJS, Seth PK, Flora SJS***; Influence of methionine administration during chelation of cadmium by $CaNa_3$DTPA and DMPS in the rat; Environ. Toxicol. Pharmacol. 3(3) 159-165 (1997)

1429 ***Tandon SK. Singh S, Jain VK, Prasad S***; Chelation in metal intoxication. XXXVIII Effect of structurally different chelating agents in treatment of nickel intoxication in rat; Fundam. Appl. Toxicol. 31(2) 141-148 (1996)

1430 ***Tandon SK, Singh S, Jain VK***; Efficacy of combined chelation in lead intoxication; Chem. Res. Toxicol. 7(5) 585-589 (1994)

1431 ***Tandon SK. Singh S, Flora SJS***; Influence of methionine and zinc supplementation during chelation of lead in rats; J. Trace Elem. Electrolytes Health Dis. 8(2) 75-77 (1994)

1432 ***Tandon SK, Chandra SV, Singh J, Husain R, Seth PK***; Chelation in metal intoxication. I. In vivo effect of chelating agents on liver and testis of manganese administered rats; Environm. Res. 9 18-25 (1975)

1433 ***Tarakhovskii ML, Tsypkun AG, Shmuter GM***; Effect of L-DOPA and unithiol on the functional state of the central nervous system in rabbits that have sustained chronic intrauterine hypoxia; Fiziol. Zh. 24(2) 202-206 (1978) [Abstract]

1434 ***Tarakhovskii ML***; Role of sulfhydryl groups in the mechanism of utrine concentraction in response to stimulation of cholinergic and serotinergic receptors; Bull. Exp. Biol. Med. 77(4) 359-361 (1974)

1435 ***Tareev EM, Vinogradova OM, Kochubei LN, Chegaeva TV***; Approaches to the treatment of amyloidosis; Urol. Nefrol. (6) 56-63 (1983) [Abstract]

1436 ***Teepker M, Hamer HM, Knake S, Bandmann O, Oertel WH, Rosenow F***; Myoclonic encephalopathy caused by chronic bismuth abuse; Epileptic Disord. 4(4) 229-233 (2002)

1437 ***Thomas DJ, Chisolm JJ***; Lead, zinc and copper decorporation during calcium-disodium-ethylenediamine-tetra-acetate treatment of lead poisoned children; J. Pharmacol. Exper. Ther. 239(2) 829-835 (1986)

1437a ***Thomas S***; Clinical aspects of poisoning with polonium 210; North American Congress of Clinical Toxicology, New Orleans (2007)

1438 ***Thompson N, Lowe-Ponsford F, Mant TGK, Volans, GN***; Button battery ingestion: A review; Adverse Drug React. Acute Poisoning Rev. 9(3) 157-182 (1990)

1439 ***Thorn KS, Naber N,Matuska M, Vale RD, Cooke R***; A novel method of affinity-purifying proteins using a bis-arsenical fluorescein; Protein Science 9 213-217 (2000)

1440 ***Tian YR, Sun LL, Wang W, Du F, Song AX, Ni CY, Zhu Q, Wan Q***; A case of acute thallotoxicosis successfully treated with double-filtration plasmapheresis; Clin. Neuropharmacol. 28(6) 292-294 (2005)

1441 ***Tichy M, Horejsi M, Cikrt M***; Effect of some chelating agents on the biliary excretion of mercury. 2 Relationship between the excretion of mercury and its binding to bile fractions; J. Hyg. Epidemiol. Microbiol. Immunol. 24(3) 309-323 (1980)

1442 ***Tikhonova LI, Razbitnaya LM***; Physicochemical (Chromatographic) investigation of the effectiveness of certain complex-forming compounds; Khim.Zashchita Organizma ot Ioniziruyushchikh Izluchenii 112-116 (1960) [Abstract]

1443 ***Toet AE; van Dijk A, Savelkoul TJ, Meulenbelt J***; Mercury kinetics in a case of severe mercuric chloride poisoning treated with dimercapto-1-propane sulfonate (DMPS); Hum. Exp. Toxicol. 13(1) 11-16 (1994)

1444 ***Tomassoni AJ***; Response to a covert chemical threat; http://www.oemc.us/necoem/0405Tomassoni.pdf (2003)

1445 ***Tonkopii VD***; Effect of cystamine, unithiol and glutaminic acid on methemoglobin formation in xylidine poisoning; Farmakol. Toksikol. 30 (3) 358 - 361 (1967) [Abstract]

1446 ***Torres-Alanis O, Garza-Ocanas L, Bernal MA, Pineyro-Lopez A***; Urinary excretion of trace elements in humans after sodium 2,3- dimercaptopropane-1-sulfonate challenge test; J. Toxicol. Clin. Toxicol. 38(7) 697-700 (2000)

1447 ***Torres-Alanis O, Garza-Ocanas L***; Evaluation of the effect of 2,3-dimercaptopropane-1-sulfonate (DMPS) against mercury cytotoxicity in primary liver and kidney cell cultures; Abstract 1774A SOT 2000 Annual Meeting (2000)

1448 ***Torres-Alanis O, Garza-Ocanas L, Pineyro-Lopez A***; Intravenous self-administration of metallic mercury: Report of a case with a 5-year follow-up; J. Toxicol. Clin. Toxicol. 35(1) 83-87 (1997)

1449 ***Torres-Alanis O, Garza-Ocanas L, Pineyro-Lopez A***; Evaluation of urinary mercury excretion after administration of 2,3-dimercapto-propane sulfonic acid to occupationally exposed men; J. Toxicol. Clin. Toxicol. 33(6) 717-720 (1995)

1450 ***Torres-Alanis O, Garza-Ocanas L, Pineyro-Lopez A***; Protective effect of 2,3-dimercaptopropane sodium sulfonate (Dimaval) against mercury cytotoxicity in primary liver cell cultures; Fundam. Clin. Pharmacol. 7(7) 383 (1993)

1451 ***Townsend LS, Cullen WR, Dejbod N, Mandoli DF***; Poster heavy metals: Acetabularia acetabulum: A novel model for arsenic toxicity; http://rycomusa.com/aspp2001/public/P35/0473.html (2001)

1452 ***Trakhtenberg IM***; Chronic effects of mercury on organisms; U.S. Dept. of Health, Education, and Welfare, Public Health Service, National Institutes of Health; for sale by the Supt. of Docs., U.S. Govt. Print. Off., Washington (1974)

1453 ***Trakhtenberg IM, Kulik GI***; Materials for substantiating the prophylactic application of Unithiol in work with organic mercury compounds; Gigiyena i Toksikologiya Novykh Pestisidov i Klinika Otravleniy, Moskau 451-458 (1962)

1454 ***Triebig G, Baur X, Brüning T, Schiele*** **R, *Stoll R;*** Arbeit unter Einwirkung von Blei und seinen Verbindungen; Leitlinien Deutsche Gesellschaft für Arbeitsmedizin und Umweldmedizin e.V. (DGAUM) (2005)

1455 ***Trinus FP, Luik AI, Braver-Chernobulskaya BS, Novikova NV, Lukyanchuk VD, Tkachuk VV, Chubenko AV***; Penetration and binding strength of cadmium and its complexes with dithiols in cells; Farmakol. Toksikol. 47(3) 104-108 (1984) [Abstract]

1456 ***Trinus FP, Riabukha TK, Chubenko AV, Fedotenko OI***; Thiol compounds in the combined therapy of proserine poisonings; Farmakol. Toksikol. 46(6) 67-69 (1983) [Abstract]

1457 ***Tripathi N, Flora SJS***; Effects of some thiol chelators on enzymatic activities in blood, liver and kidneys of acute arsenic (III) exposed mice; Biomed. Environ. Sci. 11(1) 38-45 (1998)

1458 ***Tripathi N, Kannan GM, Pant BP, Jaiswal DK, Malhotra PR, Flora SJS***; Arsenic-induced changes in certain neurotransmitter levels and their recoveries following chelation in rat whole brain; Toxicol. Lett. 92(3) 201-208 (1997)

1459 ***Trofimov BA, Morozova LV, Mikhaleva ABI, Markova MV, Oparina LA, Scotheim TA***; Hybrid polyalkylene oxide-polyalkylene sulfide copolymers from divinyl ethers and sodium 2,3-dimercaptopropane-1-sulfonate; Sulfur Lett. 23(3) 121-130 (2000)

1460 ***Troshichev OA, Gorshkov ES, Shapovalov SN, Sokolovskii VV, Ivanov VV, Vorobeitchikov VM***; Variations of the gravitational field as a motive power for rhythmics of biochemical processes; Adv. Space Res. 34(7) 1619-1624 (2004)

1461 ***Tsyganok SS***; Unithiol in the treatment of dermatoses; Vestn. Dermatol. Venerol. (9) 67-69 (1978) [Abstract]

1462 ***Tusupbekova AS, Polatbekova GP, Ospanov KK, Fedina LV***; Interaction of bismuth(III) with unithiol in perchloric acid; Koord. Khim. 18(9) 930-932 (1992) [Abstract]

1463 ***Twarog T, Cherian MG***; Chelation of lead by dimercaptopropane sulfonate and a possible diagnostic use; Toxicol. Appl. Pharmacol. 72(3) 550-556 (1984)

1464 ***Twarog T, Cherian MG***; Chelation of lead with sodium dimercaptopropane sulfonate and estimation of renal lead burden; IN: "Chemical Toxicology and Clinical Chemistry of Metals"; SS Brown, J Savory (Eds.), Academic Press, pp.377-380 (1983)

1465 ***Twarog TA, Cherian MG***; Chelation of lead with DMPS and BAL in rats injected with lead; Bull. Environ. Contam. Toxicol. 30(2) 165-169 (1983)

1466 ***Ueno S***; Protective effects of thiol containing chelating agents against liver injury induced by hexavalent chromium in mice; Kitasato. Arch. Exp. Med. 65(2-3) 87-96 (1992)

1467 ***Uglitskikh AK, Khan MA, Sharapov SV, Kapranov NI, Plisko LF***; Inhalation and peroral mucolytic therapy in mucoviscidosis in children; Vopr. Kurortol. Fizioter. Lech. Fiz. Kult. (5) 15-18 (1996) [Abstract]

1468 ***Uglitskih AK, Kapranov NI, Simonova OI, Stycalova AI, Semikin SU***; Comparison value efficacy of some mucolytics drugs in CF children; Eur. Resp. J. 7(Suppl.18) 455s (1994) [Abstract]

1469 ***Uliyaninsky LS, Gritsak AV; Zhdanova NF***; Effect of sulfhydryl compounds on the automatism of the pacemakers; Bull. Exp. Biol. Med. 82(4) 1454-1457 (1976)

1470 ***Urban P, Gobba F, Nerudova J, Lukas E, Cabelkova Z, Cikrt M***; Color discrimination impairment in workers exposed to mercury vapor; Neurotoxicology 24(4-5) 711-716 (2003)

1471 ***Urban P, Nerudova J, Cabelkova Z, Krajca V, Lukas E, Cikrt M***; EEG photic driving in workers exposed to mercury vapors; Neurotoxicology 24(1) 23-33 (2003)

1472 ***Urban P, Lukas E, Nerudova J, Cabelkova Z, Cikrt M***; Neurological and electrophysiological examinations on three groups of workers with different levels of exposure to mercury vapors; Eur. J. Neurol. 6(5) 571-577 (1999)

1473 ***Usatenko YI, Klimovich EA, Loshkarev YM***; Amperometric titration of mercury using a unithiol solution; Ukr. Khim. Zh. 27(6) 823-827 (1961)

1474 ***Uspenskaya MS, Izergina AG***; Effects of Unithiol on excretion of chemical compounds in urine of rats injured by ^{210}Po; Radiobiologiya 3 762-765 (1963)

1475 ***Utegulov RN***; Protolytic equilibria in aqueous solutions of dithiols; Russ. J. Phys. Chem. 77(5) 755-760 (2003)

1476 ***Utegulov RN, Komyshaev DK, Spanov KK, Kozilowskii CV***; Spectrophotometric study of the complexation of osmium(VI) with sodium 2,3-dimercaptopropanesulfonate; Koord. Khim. 14(11) 1529-1530 (1988) [Abstract]

1477 ***Vaernes MH, Chen LH, Chien YW***; The sieving characteristics of intestinal transport and effect of chelating agents.; Pharm. Res. 14(11 Suppl.) S647 (1997)

1477a ***Vahidnia A, van der Voet GB, de Wolff FA***; Arsenic neurotoxicity A review; Hum. Exp. Toxicol. 26(10) 823-832 (2007)

1478 ***Vainshtein IA***; Unithiol and D-penicillamine as psychic energizers and corrective agents in treatment with neuroleptics; Vrach. Delo. 7 115-118 (1972) [Deutsche Übersetzung]

1479 ***Vakhnitsky AS***; The influence of unithiole and $CaNa_2EDTA$ on the excretion of trace elements; Gig. Tr. Prof. Zabol. 9(9) 54-56 (1965) [English Translation]

1480 ***Valet OK***; Bildung und Eigenschaften von 2,3-Dimercaptopropaneosulfonat-Schichten auf Gold(111); Dissertation FU Berlin (1999)

1481 ***Vamnes JS, Eide R, Isrenn R, Hol PJ, Gjerdet NR***; Blood mercury following DMPS administration to subjects with and without dental amalgam; Sci. Total Environ. 308(1-3) 63-71 (2003)

1482 ***Vamnes JS, Eide R, Isrenn R, Hol PJ, Gjerdet NR***; Diagnostic value of a chelating agent in patients with symptoms allegedly caused by amalgam fillings; J. Dent. Res. 79(3) 868-874 (2000)

1483 ***van den Bergh A, Willems L***; Intoxicatie met arsenicum; Pharmakon 34(4) 13-17 (2002)

1484 ***Vanlic-Razumenic N, Johannsen B, Spies H, Syhre R, Kretzschmar M, Berger R;*** Preparation and characterization of pure ^{99m}Tc-complex of 2,3-dimercaptopropanesulfonate as a potential radiopharmaceutical; IN: Nuklearmedizin-Die klinische Relevanz der Nuklearmedizin; HE Schmidt, G.Riccabona (Eds.); FK Schattauer Verlag, Stuttgart; pp.142-145 (1980)

1485 ***Vanlic-Razumenic N, Johannsen B, Spies H, Syhre R, Kretzschmar M, Berger R***; Complex of technetium(V) with 2,3-dimercaptopropanesulfonate (Unithiol): preparation and distribution in the rat; Int. J. Appl. Radiat. Isot. 30(11) 661-667 (1979)

1486 ***Vantroyen B, Meulemans A, Sabbe M, Heilier JF, Michels A, Buchet JP, Vanderschueren S, Haufroid V***; Survival after a lethal dose of arsenic trioxide; J. Toxicol. Clin. Toxicol. 42(6) 889-895 (2004)

1487 ***Vasilev VP, Utegulov RN, Ramenskaya LM, Kamysbaev DK, Ospanov KK***; Thermodynamic dissociation characteristics of unithiol in water; Zh. Obshch. Khim. 59(1) 210-215 (1989)

1488 ***Vasilev VP, Garavin VY, Nukhin AN, Ospanov KK***; Thermodynamics of the successive ionisation of unithiol in aqueous solution; Russ. J. Phys. Chem. 62(4) 460-462 (1988)

1489 ***Velvart J, Nisoli A***; Antidot-Therapie bei Vergiftungen; Therapeutische Umschau 43(4) 250-258 (1986)

1489a ***Venkatesh T***; Effect of environmental lead on the health status of women and children in developing countries; INCHES Vienna June 2007

1490 ***Vill P***; Amalgambelastung - BFD-Test = DMPS-Test; Erfahrungsheilkunde 47(4) 237-242 (1998)

1491 ***Vishnevetskaya T, Ciganova G, Strepetova I, Dyachuck G, Afanasiev V***; A comparative study of unithiol and verapamil treatment for acute alcohol intoxication in rodents; J. Toxicol. Clin. Toxicol. 33(5) 500 (1995)

1492 ***Visser H***; Quecksilberexposition durch Amalgamfüllungen; Hüthig-Verlag (1993)

1493 ***Visser H***; Diagnoseverfahren in der Auseinandersetzung um die Amalgame; IN: Quecksilber in der Umwelt-Hearing zur Amalgamproblematik; Niedersächsisches Umweltministerium (1991)

1494 ***Vissonov VV***; Application of tetoxacin and Unithiol in ^{144}Ce-induced radiation sickness; Patogenez Eksp. Profil, Ter. Luchevykh Porazhenii Sb. Statei 267-275 (1964) [Abstract]

1495 ***Vlkova A, Routa V, Rencova J, Volf V***; In vitro studies on decorporation of polonium-210 from blood cells; Biomark. Environm. 3(3-4) P22 (2000)

1496 ***Volf LA***; Die Verwendung von Natrium-2,3-dimercaptopropanesulfonat (Unithiol) zur volumetrischen Bestimmung von Zink; Analyt. Bioanalyt. Chem. 179(5) 362 (1961)

1497 ***Volf LA***; Masking of zinc, cadmium, mercury, lead, and tin by unithiol during the complexometric determination of strontium and barium; Zavodskaya Lab. 26 1353-1354 (1960) [Abstract]

1498 ***Volf LA***; The use of unithiol as a masking reagent in the complexometric determination of calcium and magnesium; Ind. Laboratory USSR 25(12) 1507-1508 (1959)

1499 ***Volf V, Rencova J, Jones MM, Singh PK***; Combined chelation treatment for polonium after simulated wound contamination in rat; Int. J. Radiat. Biol. 68(4) 395-404 (1995)

1500 ***Volf V, Rencova J, Jones MM, Singh PK***; Preliminary data on treatment of simulated wounds contaminated with polnium; Plzen. Lek. Sborn. 63(Suppl.) 59-61 (1993)

1501 ***Volf V***; Dekorporierung von Radionukliden (Untersuchung an Polonium); Strahlentherapie 145(1) 101-115 (1973)

1502 ***Volf V***; The effect of chelating agents on the distribution of ^{210}Po in rats; Experientia 29 307-308 (1973)

1503 ***von Baehr R***; Ist die Füllung schuld? Wie wahrscheinlich sind Unverträglichkeitsreaktionen auf Zahnersatzstoffe? Das Magazin Diabetes heute 10(1) 43-45 (2004)

1504 ***Von Burg R, Smith JC***; Biliary mobilization of cadmium by 2,3-dimercaptopropaneol and some related compounds; J. Toxicol. Environ. Health 6(1) 75-85 (1980)

1505 ***von Mach MA, Weilemann LS***; Aktuelle Therapie von Intoxikationen; Dtsch. Med. Wochenschr 128(34-35) 1779-1781 (2003)

1506 ***von Mühlendahl KE, Oberdisse U, Bunjes R, Brockstedt M***; Vergiftungen im Kindesalter; Thieme Verlag, Stuttgart (2003)

1507 ***Von Mühlendahl KE, Schulte-Wissermann H, Grips M***; Hautveränderungen bei Feer'scher Krankheit; Kinderarzt und Umwelt - Jahrbuch 1995/1996; KE von Mühlendahl (Ed.); Alete Wissenschaftlicher Dienst; pp. 133-138 (1996)

1508 ***von Mühlendahl KE***; Bleibelastung bei Kindern: Wahrscheinlich auch in Deutschland ein gravierendes Problem; IN: Kinderarzt und Umwelt Jahrbuch 1991/92; KE von Mühlendahl (Ed.); Alete Wissenschaftlicher Dienst; pp.62-64 (1992)

1509 ***von Mühlendahl KE***; Toxizität von Quecksilber in Amalgam-Zahnfüllungen; Pädiatr. Grenzgeb. 31(1) 21-25 (1992)

1510 ***von Mühlendahl KE***; Die Feer'sche Krankheit; Monatsschr. Kinderheilkunde 139(4) 224-227 (1991)

1511 ***von Mühlendahl KE***; Intoxication from mercury spilled on carpets; The Lancet 336(8730) 1578 (1990)

1512 ***von Zabern I, Nolte R***; Activation of the alternative pathway of human complement by sulfhydryl compounds of analytic and therapeutic use; Int. Arch. Allergy Appl. Immunol. 84(2) 178-184 (1987)

1513 ***Voronkov MG, Knutov VI, Shevko ON***; Polyfunctional macroheterocycles 6. Crown ethers containing n and s with exocyclic methoxycarbonylethyl, hydroxy-, or sulfonatomethyl groups; Chemistry of Heterocyclic Compounds 28(5) 596-599 (1992)

1514 ***Vosyliene MZ, Kazlauskiene N, Svecevicius G***; Effect of a heavy metal model mixture on biological parameters of rainbow trout Oncorhynchus mykiss; Environ. Sci. Pollut. Res. Int. 10(2) 103-107 (2003)

1515 **Vozdvizhenskii VF, Ospanov KK, Sholtyreva UI, Ospanova AK, Kharitonov YY***;* Spectrophotometric study of the interaction of unithiol with palladium(II) and silver(I); Izvestiya Akademii Nauk Kazakhskoi SSR, Seriya Khimicheskaya (4) 1-3 (1983) [Abstract]

1515a ***Vracko P, Tuomisto J, Grad J, Kunseler E***; Exposure of children to chemical hazards in food; Fact Sheet No. 4.4, World Health Organization - Regional Office for Europe, May 2007

1516 ***Waelti S***; Pharmakokinetik der uroprotektiven Sulfhydrylgruppen im Urin gesunder Probanden nach peroraler Gabe von Na-Merkaptoethansulfonat (Uromitexan®) und Na-Dimercaptopropanesulfant (Dimaval®); Dissertation Universität Bern (1992)

1517 ***Wagner W***; Vergiftungen und Antidota; Kat. Med. 3(1) 6-10 (2007)

1518 ***Wagner W***; Arzneimittelberatung für die Katastrophenmedizin; Intensiv- und Notfallbehandlung 29(2) 84–93 (2004)

1519 ***Waldbrenner A, Gerhard I, Krähe J, Runnebaum B***; Umwelttoxikologische Belastungen bei Frauen mit Uterusmyomen und/oder Endometriose; Arch. Gynecol. Obstet. 254 588-590 (1993)

1520 ***Waller EA, Stodilka RZ, Leach K, Prud'homme-Lalonde L***; Literature survey on décorporation of radionuclides from the human body; Defence R&D Canada - Ottawa TECHNICAL MEMORANDUM DRDC Ottawa TM 2002-042 April 2002

1521 ***Walshe JM, Yealland M***; Chelation treatment of neurological Wilson's disease; Q. J. Med. 86(3) 197-204 (1993)

1522 ***Walshe JM***; Tetrathiomolybdate (MoS_4) as an 'anti-copper' agent in man; IN: "Orphan Drugs and Orphan Diseases"; JH Scheinberg, JM Walshe (Eds.), Fulbright Papers, pp.76-85 (1986)

1523 ***Walshe JM***; Unithiol in Wilson's disease; Br. Med. J. 290(6469) 673 - 674, 1213 (1985)

1524 ***Walt H, Busch R, Molzahn I***; Fragen und Beschwerden der "Amalgam-Patienten" – Ergebnisse der Exploration und Untersuchung; 9. Arbeits- und umweltmedizinisches Kolloquium des ZAUM Berlin (1997)

1525 ***Walther SC, Walther UL, Reichl FX, Mückter H***; Efficiency of complexing compounds in reversion of zinc-mediated toxic reactions in lung cells; Biomarkers Environ. 4(Suppl.1) 107-110 (2001)

1526 ***Walther UI, Mückter H, Fichtl B, Forth W***; Efficiency of chelators in reversal of zinc-mediated cellular reactions in cultured lung cells; J. Trace Elem. Exp. Med. 13(2) 215-226 (2000)

1527 ***Wan W, Xu M, Zou H, Lu A, Shen X, Chen Y***; The activity of blood cholinesterase in rats exposed to dimehypo after drug intervention; Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi 20(6) 419-421 (2002) [Abstract]

1528 ***Wang C***; Preparation and purification of dimercaptopropanesulfonic acid sodium salt; Patent No. CN 1432566 (2003) [Abstract]

1529 ***Wang HC, Hwang YC, Hsieh CJ, Kuo MS***; Determination of total mercury in drinking ester and of methylmercury in air by graphite-furnace atomic absorption spectrophotometry using 2,3-dimercaptopropane-1-sulfonate as a complexing agent; Anal.Sci. 14(5) 983-986 (1998)

1530 ***Wang JP, Tsai JJ, Chen YS, Hsu MF***; Stimulation of intracellular Ca^{2+} elevation in neutrophils by thiol-oxidizing phenylarsine oxide; Biochem. Pharmacol. 69(8) 1225-1234 (2005)

1531 ***Wang L, Xian M, Geng W, Qin Z, Li Y***; Logistic regression analysis of factors influencing clinical therapeutic effect on acute tetramine poisoning; Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi 22(1) 26-28 (2004) [Abstract]

1532 ***Wang SJ, Liu SY, Shi Z***; Chelators in the treatment of occupational metal intoxication in China; 2nd Internat. Symposium "Chelating Agents, Pharmacology, Toxicology and Therapeutics", Pilsen, 1987

1533 ***Wang XP, Yang RM, Ren MS, Sun BM***; Anticopper efficacy of captopril and sodium dimercaptosulfonate in patients with Wilson's disease; Funct. Neurol. 18(3) 149-153 (2003)

1534 ***Wang Y***; Mechanisms for cadmium lumen-to-cell transport by luminal membrane of the rabbit proximal tubule; Thesis, Georgia State University 2007

1534a ***Wang Y, Zalups RK, Barfuss DW***; Cadmium transport mechanisms in the proximal tubule; FASEB J. 21(5) Abstract 605.13 (2007)

1535 ***Wannag A, Aaseth J***; The effect of immediate and delayed treatment with 2,3-dimercaptopropane-1-sulfonate on the distribution and toxicity of inorganic mercury in mice and in foetal and adult rats; Acta Pharmacol. Toxicol. 46(2) 81-88 (1980)

1536 ***Watson WA, Litovitz TL, Klein-Schwartz W, Rodgers GC, Youniss J, Reid N, Rouse WG, Rembert RS, Borys D***; 2003 annual report of the American Association of Poison Control Centers (AAPCC) Toxic Exposure Surveillance System / Case 191; Am. J. Emerg. Med. 22(5) 335-404 (2004)

1537 ***Wax PM, Thornton CA***; Recovery from severe arsenic-induced peripheral neuropathy with 2,3- dimercapto-1-propanesulfonic acid; J Toxicol. Clin. Toxicol. 38(7) 777-780 (2000)

1538 ***Weber I***; Tierexperimentelle Untersuchungen über den Einfluß von Chelaten auf den Stoffwechsel von Radiozink; Report KFK 785, Kernforschungszentrum Karlsruhe, 1968

1539 ***Webster SM, del Camino D, Dekker JP, Yellen G***; Intracellular gate opening in Shaker K1 channels defined by high-affinity metal bridges; Nature 428(6985) 864-868 (2004)

1540 ***Wedekind G, Beyer D***; Multiple Mikroembolisationen durch elementares Quecksilber; Radiologe 34 483-486 (1994)

1541 ***Weger N***; Arsenhaltige Hautkampfstoffe (Dichlorarsine); IN: Helm U, Weger N; Grundzüge der Wehrtoxikologie; IN: Wehrmedizin - Ein kurzes Handbuch mit Beiträgen zur Katastrophenmedizin, pp. 272-275 (1980)

1542 ***Wegner R, Baur X***; Erkrankungen durch Metalle und Metalloide; Allergologie 28(1) 26-38 (2005)

1543 ***Wegner R***; Vergiftungen durch Schwermetalle und Arsen; Internist 43(7) 818-827 (2002)

1544 ***Wehner-Caroli J, Scherwitz C, Schweinsberg F, Fierlbeck G***; Exazerbation einer Psoriasis pustulosa bei Quecksilber-Intoxikation; Hautarzt. 45(10) 708-710 (1994)

1545 ***Weide R, Engelhart S, Färber H, Kaufmann F, Heymanns J, Köppler H***; Chronische Bleivergiftung durch ayurvedische Heilpillen; Dtsch. Med. Wochenschr. 128(46) 2418-2420 (2003)

1546 ***Weilemann LS***; Wichtige Antidote - Update; Monatsschr. Kinderheilkd. 152(10) 1069-1074 (2004)

1547 ***Weisser K, Bauer K, Volkers P, Keller-Stanislawski B***; Thiomersal und Impfungen; Bundesgesundheitsbl. Gesundheitsforsch. Gesundheitsschutz 47(12) 1165-1174 (2004)

1548 ***Wemmer U***; Grenzwerte und Richtwerte von Umweltschadstoffen; IN: Prävention, Diagnose und Umwelt-erkrankungen; JD Kruse-Jarres (Ed.); Kongreßband vom VI. Stuttgarter Mineral-Stoff-Symposium; pp.13-24 (1993)

1549 ***White MA, Sabbioni E***, Trace element reference values in tissues from inhabitants of the European Union. X. A study of 13 elements in blood and urine of a United Kingdom population; Sci. Total Environ. 216(3) 253-270 (1998)

1550 ***Whitlow KS, Belson M, Barrueto F, Nelson L, Henderson AK***; Tetramethylenedisulfotetramine: Old agent and new terror; Ann. Emerg. Med. 45(6) 609-613 (2005)

1551 ***Wichmann HE, Schlipköter HW, Füllgraff G***; Handbuch der Umweltmedizin; Ecomed-Verlag, Landsberg (1992-2007)

1552 ***Wie M, Wu D, Liu X, Yang X***; Regeneration of functionally active rat brain muscarinic receptor in vitro after inhibition with methylmercury chloride; Hua-Hsi-I-Ko-Ta-Hsueh-Hsueh-Pao 28(2) 140-144 (1997) [Abstract]

1553 ***Wieczorek H, Oberdörster G***; Effects of selected chelating agents on organ distribution and excretion of manganese after inhalation exposure to $^{54}MnCl_2$. I Injection of chelating agents; Pol. J. Occup. Med. 2(3) 261-267 (1989)

1554 ***Wiedemann P, Fichtl B, Szinicz L***; Pharmacokinetics of ^{14}C-DMPS (sodium-1,3 ^{14}C-2,3-dimercaptopropane-1-sulfonate) in beagle dogs; Biopharm. Drug Dispos. 3(3) 267-274 (1982)

1555 ***Wieseler B, Leng G, Lenz S, Schultz C, Wilhelm M***; Fallbericht: Chronische Bleiintoxikation; Umweltmed. Forsch. Praxis 4(1) 13-17(1999)

1555a ***Wiesmüller GA, Konteye C***; Umweltmedizinischer Wegweiser des Kreises Aachen; www.gesundheitskonferenz.de/Wegweiser.pdf (2002)

1556 ***Wigzell K, Rehnqvist N***; Chemical Accidents and Disasters - Medical Care - Planning Guidance; Socialstyrelsen – The National Board of Health and Welfare, Sweden (2000)

1557 ***Wild J***; Untersuchungen über die Quecksilberbelastung bei Zahnmedizinstudenten unter Verwendung von DMPS (Dimaval); Dissertation Universität Erlangen-Nürnberg (1993)

1558 ***Wildenauer DB, Reuther H, Weger N***; Interactions of the chelating agent 2,3-dimercaptopropane-1-sulfonate with red blood cells in vitro. I Evidence for carrier mediated transport; Chem. Biol. Interact. 2(2) 165-177 (1982)

1559 ***Wildenauer DB, Oehlmann CM***; In vitro studies of the reactivity of metabolites of cyclophosphamide: Reaction of acrolein with membrane proteins of microsomes and erythrocytes; Naunyn Schmiedeberg's Arch. Pharmakol. 316(Suppl.) R8 (1981)

1560 ***Wilhelm M***; Toxikologie; IN: G. Kojda, Pharmakologie / Toxikologie systematisch, Deutsche Bibliothek Bremen, 901-946 (1997)

1561 ***Wilhelm M, Müller F, Idel H***; Biological monitoring of mercury vapour exposure by scalp hair analysis in comparison to blood and urine; Toxicol. Lett. 88(1-3) 221-226 (1996)

1562 ***Wilhelm M, Koep J, Müller F***; Überwachung der Quecksilberbelastung; IN: Prävention, Diagnose und Umwelterkrankungen (JD Kruse-Jarres (Ed.); Kongreßband vom VI. Stuttgarter Mineral-Stoff-Symposium; pp.111-121 (1993)

1562a ***Williams D; de Jong W, Dekant W, Hensten A, Goldberg M, Jansen JA, Ladefoged O, Wilson N***; Safety of dental amalgam and alternative dental restoration materials; Preliminary Report Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), EU Commission (2007)

1563 ***Williams DR, Halstead BW***; Chelating agents in medicine; J. Toxicol. Clin. Toxicol. 19(10) 1081-1115 (1982)

1564 ***Willig RP, Drohn W, Stegner H***; Quecksilberintoxikation: Erfolgreiche Behandlung im Säuglingsalter mit DMPS (Dimaval®); Monatschr. Kinderheilkd. 132(9) 701 (1984)

1565 ***Winker R, Schaffer AW, Konnaris C, Barth A, Giovanoli P, Osterode W, Rüdiger HW, Wolf C***; Health consequences of an intravenous injection of metallic mercury; Int. Arch. Occup. Environ. Health 75 581-586 (2002)

1566 ***Winski SL, Carter DE***; Interactions of rat red blood cell sulfhydryls with arsenate and arsenite; J. Toxicol. Environ. Health 46(4) 379-397 (1995)

1566a ***Wirth H***; Therapie akuter Arsenvergiftungen mit Dimaval® (DMPS) 100 mg Hartkapseln und Dimaval® Injektionslösung; Unveröffentlichter Bericht (2003)

1567 ***Wiskamp V, Proske W***; Modellversuche zur Therapie bei Schwermetallvergiftungen; Chemie in Labor und Biotechnik 48(9) 371-372 (1997)

1568 ***Wojcik DP, Godfrey ME, Christie D, Haley BE***; Mercury toxicity presenting as chronic fatigue, memory impairment and depression: Diagnosis, treatment, susceptibility, and outcomes in a New Zealand general practice setting (1994–2006); Neuro Endocrinol Lett. 27(4) 415-423 (2006)

1569 ***Woolf AD, Goldman R, Bellinger DC***; Update on the clinical management of childhood lead poisoning; Pediatr. Clin. North Am. 54(2) 271-294 (2007)

1570 ***Woods JS, Martin MD, Leroux BG, DeRouen TA, Leitao J, Bernardo MF, Luis HS, Simmonds PL, Kushleika JV, Huang Y***; The contribution of dental amalgam to urinary mercury excretion in children; Environ. Health Perspect. 115(10) 1527–1531 (2007)

1571 ***Woods JS***; Altered porphyrin metabolism as a biomarker of mercury exposure and toxicity; Can. J. Physiol. Pharmacol. 74 (2) 210 - 215 (1996)

1572 ***Wortberg W***; Intrauterine Fruchtschädigung durch Schwermetallbelastung der Mutter; Umwelt-Medizin-Gesellschaft 2006; 19(4) 274-280

1573 ***Wozniak L, Oginski M, Karasek M, Piatek T***; Histologische und histochemische Untersuchungen an Rattennieren nach Verabreichung von Chlormerodrin ^{203}Hg und Unithiol; Fortschr. Geb. Röntgenstr. Nuklearmed. 119(5) 603-609 (1973)

1574 ***Wroblewski N, Schill WB, Henkel R***; Metal chelators change the human sperm motility pattern; Fertil. Steril. 79(Suppl.3) 1584-1589 (2003)

1575 ***Wroblewski N***; Beeinflussung der Motilität humaner Spermatozoen mittels verschiedener Chelatbildner in vitro; Inaugural-Dissertation Universität Gießen (2000)

1576 ***Wronski M***; Electrophoresis of thiols in cellulose gels. IV. Estimation of molecular weight; J. Chromatogr. 288(1) 206-211 (1984)

1577 ***Wu P, Du SF, Zhang ZX, Wang Y, Zhang H, Chai DL***; The mercury was removed and the microelements in human body were retained by compound pellet of soil and gold; Pharm. Care Res. 4(4) 342-344 (2004) [Abstract]

1578 ***Wu XQ, Ce XC, Zhou HF, Rao YW, Li AF, Zhang WJ***; The antagonistic effect of selenium on the toxicity of mercury; Trace Elem. Med. 7(1) 40-44 (1990)

1579 ***Wu Z, Walsh C***; Dithiol compounds: Potent, time-dependent inhibitors of VanX, a zinc-dependent D,D-Dipeptidase required for Vancomycin resistance in Enterococcus faecium; J. Am. Chem. Soc. 118(7) 1785-1786 (1996)

1579a ***Xu Z, Li J, He A***; Relationship between chemical structure and cadmium-eliminating ability of chelators; Zhongguo Gongye Yixue Zazhi 19(1) 13-17 (2006) [Abstract]

1580 ***Xu Z, Yang J, Yin Z, Yu J, Sun W, Li J***; Effects of several materials on oxidative damage induced by mercury in rat kidney; Zhongguo Zhiye Yixue 32(3) 5-8 (2005) [Abstract]

1581 ***Xu Z; Aposhian HV***; The distribution of oral sodium 2,3-dimercapto-1-propanesulfonate and challenge test for mercury; J. China Med. University 28(4) 266-268 (1999) [Abstract]

1582 ***Xu ZF, Jones MM***; Comparative mobilization of lead by chelating agents; Toxicology 53(2-3) 277-288 (1988)

1582a ***Xue BC, Yang RM, Hu JY***; Effect of Gandou decoction IV combined with short-term decoppering therapy with sodium dimercapto-sulfonate on serum indexes of hepatic fibrosis in patients with Wilson' s disease; Zhongguo Zhong Xi Yi Jie He Za Zhi. 27(9) 785-788 (2007) [Abstract]

1583 ***Yakovlev NA, Slyusar TA, Zalevskii LK*** ; Endonasal electrophoresis of unithiol in the treatment of patients with early symptoms of chronic chromium poisoning; Gig. Tr. Prof. Zabol. (2) 13-16 (1985) [Abstract]

1584 ***Yamaguchi Y, Maehashi H***; Arsenic Excretion after Treatment of Arsenic Poisoning in Rats and Mice with DMSA or DMPS; Jpn. J. Pharmacol. 36(Suppl.) 217P (1984)

1585 ***Yanev S, Janku I, Stoytchev T, Havlik I, Krebs V***; Effects of potassium ethylxanthogenate and 2,3-dimercapto-propane sulfonate sodium on the pentobarbital pharmacokinetics and metabolism in male mice; Eur. J. Drug Metab. Pharmacokinet. 7(1) 21-29 (1982)

1586 ***Yang Y, Valet OK, Donner C, Baumgärtel H***; The adsorption of 2,3-dimercaptopropanesulfonate at the Au<111> electrode in alkaline solution; Z. Phys. Chem. 217(5) 493-512 (2003)

1587 ***Yannai S, Budman E, Taitelman U***; Efficiency of lead clearance by chelating agents; Plzen. Lek. Sborn. 62(Suppl.) 107-110 (1990)

1588 ***Yurkiv VA, Melikhov VI***; Sodium 2,3-dithiopropanesulfate blockade of the effect of cholera enterotoxin on adenylate cyclase and the concentration of cyclic 3',5'-adenosine monophosphate in the small intestine mucosa of the rabbit; Bull. Exp. Biol. Med. 91(10) 432-434 (1981)

1589 ***Zabrodskii PF, Germanchuk VG, Nodel ML***; Unithiol modifies the immunotoxicity of 2-chloroethenyldichloroarsine; Eksp. Klin. Farmakol. 65(5) 53-55 (2002) [Abstract]

1590 ***Zahn V, Schulte-Uebbing C***; Umweltmedizinische Fibel-Praktische Umweltmedizin; UMGEWE Straubing (1993)

1591 ***Zahn V, Schulte-Uebbing C***; Umweltmedizin-Angewandter Umweltschutz; UMGEWE Straubing (1991)

1592 ***Zak VI***; Mechanism of the goitrogenic action of cobalt; Bull. Exp. Biol. Med. 65(3) 283-286 (1968) [Abstract]

1593 ***Zakharov VA, Songina OA, Ospanov KK***; Oscillopolarographic behavior of unithiol on the platinum electrode; Izvestiya Akademii Nauk Kazakhskoi SSR, Seriya Khimicheskaya 18(6) 21-27 (1968) [Abstract]

1594 ***Zakharyan RA, Aposhian HV***; Arsenite methylation by methylvitamin B_{12} and glutathione does not require an enzyme; Toxicol. Appl. Pharmacol. 154(3) 287-291 (1999)

1595 ***Zalups RK, Ahmad S;*** Transport of N-acetylcysteine S-conjugates of methylmercury in madin-darby canine kidney cells stably transfected with human isoform of organic anion transporter 1; J. Pharmacol. Exp. Ther. 314(3) 1158-1168 (2005)

1596 ***Zalups RK***; Molecular interactions with mercury in the kidney; Pharmacol. Rev. 52(1) 113-143 (2000)

1597 ***Zalups RK, Parks LD, Cannon VT, Barfuss DW***; Mechanisms of action of 2,3-dimercaptopropane-1-sulfonate and the transport, disposition, and toxicity of inorganic mercury in isolated perfused segments of rabbit proximal tubules; Mol. Pharmacol. 54(2) 353-363 (1998)

1598 ***Zalups RK, Lash LH***; Binding of mercury in renal brush-border and basolateral membrane- vesicles: Implication of a cysteine conjugate of mercury involved in the luminal uptake of inorganic mercury in the kidney: Biochem. Pharmacol. 53 (12) 1889-1900 (1997)

1599 ***Zalups RK, Lash LH***; Advances in understanding the renal transport and toxicity of mercury; J. Toxicol. Environ. Health 42(1) 1-44 (1994)

1600 ***Zalups RK***; Influence of 2,3-dimercaptopropane-1-sulfonate (DMPS) and meso-2,3-dimercaptosuccinic acid (DMSA) on the renal disposition of mercury in normal and uninephrectomized rats exposed to inorganic mercury; J. Pharmacol. Exp. Ther. 267(2) 791-800 (1993)

1601 ***Zalups RK, Gelein, RM, Cernichiari E***; DMPS as a rescue agent for the nephropathy induced by mercuric chloride; J. Pharmacol. Exp. Ther. 256(1) 1-10 (1991)

1602 ***Zalups RK, Gelein, RM, Cernichiari E***; 2,3-dimercapto-1-propanesulfonic acid as a rescue agent for the nephropathy induced by mercuric chloride; Toxicologist 10(1) 13-16 (1990)

1603 ***Zander D, Ewers U, Freier I, Brockhaus A***; Untersuchungen zur Quecksilberbelastung der Bevölkerung. III Quecksilbermobilisation durch DMPS (Dimaval) bei Personen mit und ohne Amalgamfüllungen; Zentralbl. Hyg. Umweltmed. 192(5) 447-454 (1992)

1604 ***Zander D, Ewers U, Freier I, Brockhaus A***; Untersuchungen zur Quecksilberbelastung der Bevölkerung. IV Quecksilberbelastung von Zahnärzten, Zahnärztinnen und Zahnarzthelferinnen; Zentralbl. Hyg. Umweltmed. 193(4) 318-328 (1992)

1605 ***Zapadniuk VI, Kurliandchikov VN, Neiko EM***; Urinary excretion of sulfur compounds and certain microelements in patients with hypertensive disease treated by combination of unithiol and decamevit under biotron conditions; Vrach. Delo. (12) 26-28 (1974) [Abstract]

1606 ***Zapadniuk VI, Kurliandchikov VN***; Pharmacological activity of unithiol and its use in clinical practice; Vrach. Delo. 8 122-125 (1973) [Abstract]

1607 ***Zart D, Schmidt I, Bock E***; Significance of gaseous NO for ammonia oxidation by Nitrosomanas eutropha; Antonie van Leeuwenhoek 77(1) 49-55 (2000)

1608 ***Zaun H***; Amalgam und Effluvium bei Frauen; Hautarzt 44(9) 602-603 (1993)

1609 ***Zehenter C***; Quecksilber, Cadmium, Blei - reduzieren Sie Ihre Schwermetallbelastung; Der Naturarzt 144(11) 13-15 (2004)

1610 ***Zeitlhofer J, Petzl DH, Cichini G, Meisinger V, Schuller W, Wimberger D, Mayr N, Strasser K, Jahn O***; Neurologische Symptome bei Inhalationsvergiftung mit metallischem Quecksilber; Nervenarzt 59(7) 426-429 (1988)

1611 ***Zelinskii BA, Goncharov LI, Gamarnik LV***; Use of sulfhydryl-group donors in the complex treatment of diabetic ketoacidosis; Ter. Arkh. 53(4) 132-133 (1981) [Abstract]

1612 ***Zemlyanoy A, Lupachyov YU, Tyaptin A, Torkounov P, Varlashova M, Novosyolova N***; The treatment of ammonia poisoning by taurine in combination with a broncholytic drug; Adv. Exp. Med. Biol. 483 627-630 (2000)

1613 ***Zenovich SM, Strelets BK***; Physiologically active agents containing vicinal dithioglycols and use thereof in various branches of economy; United States Patent 7229637 (2007)

1614 ***Zenovich SM, Strelets BK***; Curing and prophylactic agent applied during the use of alcohol and psychoactive substances; US Patent 2006148898 (2006)

1615 ***Zhdanov GG, Nechaev VN, Alipov PA***; Hyperbaric oxygenation and antioxidants in the complex intensive therapy of severe forms of pneumonia in children; Anesteziol. Reanimatol. (2) 54-58 (1991) [Abstract]

1616 ***Zhang X, Groves CE, Bahn A, Barendt WM, Prado MD, Rodiger M, Chatsudthipong V, Burckhardt G, Wright SH***; Relative contribution of OAT and OCT transporters to organic electrolyte transport in rabbit proximal tubule; Am. J. Physiol. Renal. Physiol. 287(5) F999-F1010 (2004).

1617 ***Zhang CY, Zhu TJ, Chen XY, Hu GX, Chen ZK***; Actions of sodium dimercaptopropanesulfonate against convulsions induced by tetraethylenedisulfotetramine; Chin. Pharm. J. China 36(11) 736-738 (2001) [Abstract]

1618 ***Zhang CY, Zhu TJ, Hu GX, Chen XY, Liu DX, Chen ZK***; Effect of sodium dimercaptopropanesulfonate on antagonism of tetramethylenedisulfotetramine to GABA receptor; Acta Pharmacol. Sin. 22(5) 435-439 (2001)

1619 ***Zhang H, Zhou J, Zhang S, Sun C, Wu Y***; Effect of sodium dimercaptopropane sulfonate on excretion of tetramine in rabbits; Zhongguo Gongye Yixue Zazhi 17(5) 277-279 (2004) [Abstract]

1620 ***Zhang J***; Clinical observations in ethyl mercury chloride poisoning; Am. J. Ind. Med. 5(3) 251-258 (1984)

1621 ***Zhao Y, Wan J, Liu F***; Appliance of $Fe_?(DMPS)_2$ in flue gas denitrifecation and desulfurization; Jiangsu Environmental Science and Technology 18(12) 7-9 (2005) [Abstract]

1622 ***Zhao-Fa X, Jing-Hua Y, Jia-Ming Y, Zhong-Wei Y***; Experimental study on the effects of BSO, GSH, vitamin C and DMPS on the nephrotoxicity induced by mercury; Wei Sheng Yan Jiu 34(5) 533-536 (2005) [Abstract]

1623 ***Zheligovskaya NN, Kamysbaev DK, Butinchieva TS, Ospanov KK***; Mixed ligand platinum unithiolate complexes; Koord. Khim. 18(2) 176-177 (1992) [Abstract]

1624 ***Zheng W, Maiorino RM, Brendel K, Aposhian HV***; Determination and metabolism of dithiol chelating agents. VII Biliary excretion of dithiols and their interactions with cadmium and metallothionein; Fundam. Appl. Toxicol. 14(3) 598-607 (1990)

1625 ***Zhmurov VA, Krylov VI, Petrushina AD***; Effect of antioxidants and miscleron on destabilization of cell membranes during nephritis in children; Vopr. Med. Khim. 33(1) 40-43 (1987) [Abstract]

1626 ***Zhou GY, Jauhiainen M, Stevenson K, Dolphin PJ***; Human plasma lecithin:cholesterol acyltransferase. Preparation and use of immobilized p-aminophenylarsenoxide as a catalytic site-directed covalent ligand in enzyme purification; J. Chromatogr. 568(1) 69-83 (1991)

1627 ***Ziegler A, Mucska H, Schalko B***; Unfälle mit gefährlichen Stoffen: Feuerwehreinsatz und medizinische Erstversorgung; NOTFALLMEDIZIN - Leitfaden für Notärzte 3. Auflage (1998/99)

1628 ***Ziegler B***; Dimaval-Test; http://www.medizin-links.de/ziegler/fachinformationen/ umweltmedizin.htm [accessed November, 2005}

1629 ***Zilker T***; Antidotarium Rote Liste S.471-490 (2007)

1630 ***Zilker T, Felgenhauer N, Pfab R, Drasch G, Roider G, Roos G***; Little effect of haemodialysis and CAVHDF in the elimination of arsenic compared to DMPS treatment; J. Toxicol. Clin. Toxicol. 37 400-401 (1999)

1631 ***Zimmermann F, Friedrich L***; Untersuchungen zur bindegewebsbeeinflussenden Wirkung von 2,3-Dimercaptopropanesulfonsäure-Na und D-ß,ß-Dimethycystein; unveröffentlichte Ergebnisse (1976)

1632 ***Zimmermann M, Mairgünther R, Scheuber, T, Hamm, G***; Normale und provozierte Hg-Freisetzung aus unterschiedlichen Amalgamen; Schweiz. Monatsschr. Zahnmed. 103(4) 419-423 (1993)

1633 ***Zinecker S***; Praxisproblem Amalgam: 5-Jahres-Beobachtung bei über 1800 Patienten mit dem chronischen Bild einer Schwermetallvergiftung; Der Allgemeinarzt 17(11) 1215-1221 (1995)

1634 ***Zinke T***; Gibt es neue Erkenntnisse zur Amalgamproblematik?; IN: Status Quo and Perspectives of Amalgam and Other Dental Materials; LF Friberg, GN Schrauzer (Eds.); Georg-Thieme-Verlag, Stuttgart, New Yorl, pp.1-7 (1995)

1635 ***Zinke T***; Amalgame aus der Sicht des Bundesgesundheitsamtes; IN: Quecksilber in der Umwelt-Hearing zur Amalgamproblematik; Niedersächsisches Umweltministerium (1991)

1636 ***Zirngiebl***; Industrielle Verwendung und Emission von Quecksilber; IN: Quecksilber in der Umwelt-Hearing zur Amalgamproblematik; Niedersächsisches Umweltministerium (1991)

1637 ***Zlotkowska R, Zajac-Nedza M***; Occupational acute mercury intoxication. A case report; Medycyna Pracy 53(4) 315-317 (2002) [Abstract]

1638 ***Zolotova MG***; Effects of unithiol on excretion of ^{210}Po from the body; Med. Radiol. USSR 3(6) 67-68 (1958) [Abstract]

1639 ***Zotova MG***; Penetration of ^{210}Po through wounds into the organism; Raspredelenie i Biologicheskoe Deistvie Radioaktivnykh Izotopov, Atomizdat, Moscow, pp 83 - 88 (1966) [Abstract]

1640 ***Zotova MG***; Effect of unithiol on the rate of absorption of polonium administered subcutaneously in animals; Radiobiologiya 2 705-708 (1962) [Abstract]

1641 ***Zozulia IS, Kurliandchikov VN***; Electrical activity of the brain in patients with the cerebral form of hypertension under the effect of combined unithiol and dekamevit treatment under biotron conditions; Vrach. Delo. (1) 35-39 (1974) [Abstract]

1642 ***Zuber KH, Griese H, Müller J, Schmidt R***; Development of environmentally sound gold plating and recycling processes; IEEE International Symposium on Electronics and Environment 190-195 (2002)

9 Abbreviations

24h	24 hours
ABDA	Bundesvereinigung Deutscher Apothekerverbände (Federal Union of German Associations of Pharmacists)
Ac	Actinium
ADA	American Dental Association
ADI	Acceptable daily intake
ALD	Delta Aminolaevulinic acid
ALA	Aminolaevulinic acid
ALAD	δ-aminolaevulinic acid dehydratase
ALAU	Urine concentration of delta aminiolaevulinic acid
ALP	Alkaline leukocyte phosphatase
ALT	Alanine aminotransferase
AMP	Adenosine monophosphate
AP	Alkakine phosphatase
AST	Aspartate aminotransferase (previously SGOT = Serum-glutamate-oxalacetate-transaminase)
BAL	British anti-lewisite = 2,3-dimercaptopropaneol
BAT	Biological tolerance value for occupational exposure
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
BgVV	Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin (Federal Institute for Health Protection of Consumers and Veterinary Medicine)
BGW	Biological limit value (BLV)
BLL	Blood lead level
BUN	Blood-urea-nitrogen
BW	Body weight
Ca-DTPA	Calcium ditripentate (acid)
CAS	Chemical Abstracts Service
CAVHDF	Continuous arteriovenous haemodiafiltration
CA	Chelating agent
CHO	Chinese Hamster Ovary
CPK	Creatinine phosphokinase
CPMP	Committee for Proprietary Medicinal Products (Scientific committee of the EMEA)
CVVHD	Continuous veno-venous haemodialysis
DGAUM	Deutsche Gesellschaft für Arbeitsmedizin und Umweltmedizin German Society for Occupational and Environmental Medicine
dL	Decilitre
DMA	Dimethylarsenic
DMPA	N-(2,3-Dimercaptopropyl)-Phtalamidic Acid
DMPS	2,3-Dimercaptopropane-1-sulfonic acid
DMSA	2,3-Dimercaptobernsteinsäure (Dimercaptosuccinic acid)
DMSO	Dimethylsulfoxide
DTPA	Diethylene triamine pentaacetate
DTT	Dithiothreitol
DPA	D-Penicillamine
DTA	(ADI) permissible daily intake
EDTA	Ethylene diamine tetraacetic acid
EKA	Exposure equivalent of carcinogenic materials in the workplace
EMEA	European Agency for the Evaluation of Medicinal Products
EP	Erythrocytes Porphyrin
FDA	U. S. Food and Drug Administration
GABA	γ-Aminobutyric acid
GFR	Glomerular filtration rate
GOT	Glutamate oxalacetate transaminase
GPT	Glutamatpyruvate transaminase
GSH	Glutathione
GSSG	Oxidised glutathione
γ-GT	γ-Glutamyltranspeptidase
h	Hours
HBM	Human Biomonitoring
HeLa	Henrietta Lacks cervical carcinoma cells
HPLC	High Pressure Liquid Chromatography
i.m.	Intramuscular
i.p.	intraperitoneal

i.v.	intravenous
IC_{50}	Inhibitory concentration
IGeL	Individuelle Gesundheitsleistung (Individual, customised health service)
IPCS	International Programme on Chemical Safety der WHO
Crea	Creatinine
L-A	Murine fibroblast cell line
LAP	Lucien amino peptidase
$LD_{50/100}$	Lethal dose
LDH	Lactate dehydrogenase
LOAEL	Lowest observed adverse effect level
LQL	Air quality guidelines (AQG)
MAK	Maximum occupational concentration
MCS	Multiple Chemical Sensitivity
MDA	Malondialdehyde
MDCK	Madin-Darby Canine Kidney cells
MEDRA	Medical Dictionary for Regulatory Activities
MIK	Maximal emission concentration
Min	Minutes
MMA	Monomethylarsonate
mL	Millilitre
MPTP	N-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRK	Maximum indoor air concentration
MT	Metallothionein
NAC	N-Aceytcysteine
NAPA	N-Acetyl-DL-Penicillamine
NEL	No effect level
NOAEC	No observed adverse effect concentration
NOAEL	No observed adverse effect level
NOEL	No observable effect level
OAT	Ornithinaminotransferase
PAO	Phenylarsenic oxide
PEG	Polyethylene glycol
PAH	Para amino hippuric acid
PH	Hydrogen ion concentration (pondus hydrogenii [L])
PTWI	Provisional tolerable weekly intake
ROS	Reactive oxygen species
s.c.	subcutaneous
SCD	Sodium ammonium dimethyl-2-propaneo-1,3-dithiosulfate
SF	Safety factor
SH-Gruppe	Sulfhydryl group
SOD	Superoxide dismutase
TBD	Tripotassium-bismuth(III)-dicitrate
TEQ	Toxicity equivalents
TETS	Tetramethylene disulfotetramine
TDI	Tolerable daily intake
TMAO	Trimethyl arsenic oxide
TRK	Technical target concentration
ADR	Side effect
USSR	United States of Soviet Russia
UNIDO	United Nations Industrial Development Organization
VLD	Very low density lipoproteins
WHO	World Health Organization
XOD	Xanthin Oxidase
Zn-DTPA	Zinc Ditripentate (acid)
CNS	Central nervous system
ZPP	Zinc protoporphyrin

10 Summary

Dimaval® und ***Dimaval***® ***(DMPS) 100 mg Hartkapseln*** contain the sodium salt of (RS)-2,3-bis(sulfanyl)propane-1-sulfonic acid, monohydrate – formerly known as (R,S)-2,3-dimercaptopropane-1-sulfonic acid (DMPS), is a chelating agent that belongs to the vicinal dithiol group with two sulfhydryl groups and one sulfonate group. DMPS has a high affinity for many heavy metals and forms stable complexes with these. It also has a reducing effect.

DMPS can be administered both orally and parenterally (i.m., i.v.). Orally, it is absorbed relatively quickly. The peak concentration is reached in the plasma after 3.4 hours. The bioavailability is 50% in man. The highest concentrations are detected in the plasma and the kidneys. Up to 90% bind loosely to proteins. Excretion is primarily via the kidneys. The elimination half-life after i.v. administration is $t_{½}\alpha$ = 1.1 and $t_{½}\beta$ = 27.6 hours. No accumulation of the active substance is observed after repeated dosing.

DMPS is not decomposed in the body. It is mainly oxidised to cyclic and acyclic Di- and higher sulfides.

DMPS is only slightly toxic. Acute toxicity depends on the animal species and ranges from 150 (dogs, cats) to 2,000 (mice) mg/kg BW. Mainly cardiovascular reactions, characterised predominantly by a fall in blood pressure, occur following injection of high doses. Chronic toxicity studies do not reveal any significant biochemical or haematological changes. No mutagenic effects are observed with DMPS in the Ames test. Teratogenicity studies conducted to date have not indicated any changes.

DMPS has proved to be an effective antidote for poisoning with various heavy metals in laboratory animal experiments. It binds heavy metals and promotes their excretion. The renal elimination of the heavy metals is particularly high. However, the faecal excretion of heavy metals is often also increased. The heavy metal concentration in the organs, and particularly in the kidneys, is lowered. Heavy metal accumulation in the brain could be ruled out during DMPS therapy. The biological half-life of the heavy metals in the body is reduced. The SH groups in proteins are protected from blockage by the poisons or existing blockade is abolished. The enzymes retain or recover their ability to function.

Due to the asymmetrical carbon, DMPS can be present in two different optic isomers (R or S) and as a racemate (R,S). No significant differences in terms of absorption, toxicity or efficacy are observed between the various isomers in laboratory animal experiments. No racemate separation is thus required.

Both pharmaceutical forms have been granted marketing authorisations (licences) in Germany by the BfArM (Federal Institute for Drugs and Medical Devices). The active substance is available only on prescription. It is also licensed in Taiwan. No marketing authorisation application has been submitted in the USA to date. Therefore, DMPS has not been granted a marketing authorisation by the FDA.

Dimaval® is licensed for the treatment of mercury poisoning and Dimaval® (DPS) 100 mg Hartkapseln for mercury or lead poisoning. The chelating agent has also been used effectively on several occasions, especially in the treatment of arsenic and bismuth poisoning. Use as a diagnostic is not a licensed indication for the two preparations.

Measurement of heavy metal excretion in the urine can monitor treatment efficacy. This means that every correctly performed treatment with DMPS leads simultaneously to diagnostic information about the heavy metal burden in the body.

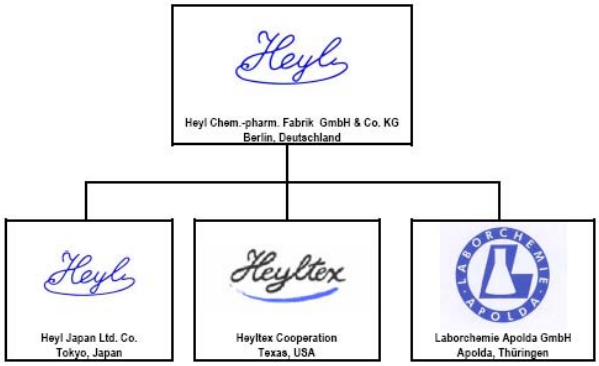
DMPS is a substance with very low systemic or local toxicity and is generally well tolerated, even during long-term treatment. In addition to the increased excretion of essential trace elements (particularly zinc), allergic reactions in the form of skin reactions have mainly been observed.

11 Company Profile

The HEYL Chemisch-pharmazeutische Fabrik Gmbh & Co.KG Company is an independent, separate, family-based company with headquarters in Berlin, which, nowadays, is probably Germany's liveliest city. The company was founded on 16.12.1926. At the time, it focused primarily on the acquisition and processing of cod-liver oil using its own, patented methods and handling vitamin preparations, which were novel at the time.

Today, we focus our strengths on specialist areas and niche markets and are committed to promoting the advance of medicine. As a niche specialist, we approach new areas of activity and focus on products that are too small for major companies or too demanding for smaller companies. Over the last 30 years, we have developed a range of antidotes through our collaboration with national and international research institutes and universities. Our products are highly effective drugs that are used to counteract poisoning due to thallium, arsenic, heavy metals (mercury, lead) or radioactive isotopes such as radiocaesium or plutonium. Demands from all continents confirm the unique approach and medical significance of these medicinal products.

In conjunction with our international subsidiaries, our strengths lie in the licensing and marketing of medicinal products and in the sale of pharmaceutical active substances and speciality chemicals. In order to consolidate our position in the key foreign markets such as the USA and Japan, the Heyltex Corporation in Texas/ USA was founded in 1979 followed in 1983 by the creation of the Heyl Japan Co. Ltd. in Tokyo/Japan.



Since its creation, the HEYL Company has strived to independently manufacture important active substances for its pharmaceutical preparations. In order to improve production facilities in the field of chemical syntheses, the Apolda GmbH chemical laboratory was privatised in 1993 and acquired as a 100% subsidiary of the Heyl Company.

Experience in regulatory affairs coupled with long-term marketing competence and medical-scientific know-how are consolidated in the Company's German and international headquarters.


Güte-Gewähr

Wir erklären hiermit die Herstellungscharge
Nr.
DEUTSCHER ARZNEITRAN Heyl
nach den gesetzlichen Vorschriften des Deutschen Arzneibuches ferner auf Vitamingehalt geprüft zu haben.
Nach den Untersuchungsergebnissen entspricht diese Charge hinsichtlich ihrer chemischen Konstanten den Anforderungen des Deutschen Arzneibuches und der Güteklasse AA der Verfügung der Reichsstelle für Milcherzeugnisse. Öle und Fette vom Mai 1932.
Auf Grund der Vitaminprüfung leisten wir Gewähr für einen Gehalt von mindestens 1000 internationalen Einheiten Vitamin A und 100 internationalen Einheiten Vitamin D.
Wir erklären weiterhin, die sachgemäße Abfüllung in Einzelpackungen überwacht und geprüft zu haben.
Berlin-Wedermünde
Wissenschaftliches Laboratorium der
HEYL & CO
Chemisch-pharmazeutische Fabrik

Diese Güte-Gewähr hat nur Gültigkeit bei unversehrtem Verschluß dieser Packung.

The management team and employees concentrate on maintaining our competitive edge at the German site through competence and a disciplined pricing strategy. In this way we endeavour to satisfy our customers' expectations and fulfil our responsibility both now, and in the future, to our family of employees and our investors.

The HEYL Company will also strive in the future to provide both the prescribers and users of its medicinal products with the highest standards in terms of therapeutic efficacy and safety. We offer our customers high-quality benefits and a reliable partnership: We talk to them, focus on their requirements and fulfil their expectations. We offer them quality products and guarantee an excellent service.

Dimaval®, injection solution. **Active pharmaceutical ingredient:** (RS)-2,3-Bis(sulfanyl)propane-1-sulfonic acid, 1 H_2O sodium salt; available only on prescription. **Composition**: 1 ampoule with 5 ml injection solution contains: ml/L, pH 1: 271.4 mg (RS)-2,3-Bis(sulfanyl)propane-1-sulfonic acid, sodium salt 1 H_2O (DMPS-sodium salt 1 H_2O) equivalent to 250 mg (RS)-2,3-Bis(sulfanyl)propane-1-sulfonic acid, sodium salt, excipient: water for injection. **Indications**: Acute poisoning with mercury (metallic, vapour, inorganic and organic compounds), when oral treatment or treatment via a gastric catheter is not feasible; **Contraindications**: DMPS must not be administered to patients who are hypersensitive to the active substance or its salts. Use of the preparations is feasible only with concomitant dialysis in cases of severely limited kidney function (kidney failure). Particular caution must be exercised in patients with allergic, asthmatic symptoms. **Pregnancy and lactation**: There is insufficient experience on the use of Dimaval in human pregnancy. The laboratory animal experiments carried out have shown no evidence of embryotoxic/teratogenic effects. Basically, the preparation should not be administered during pregnancy. If the administration of DMPS is essential during pregnancy on the grounds of a vital indication, then minerals and trace elements (especially copper and zinc) should be monitored in order to ensure that children receive essential trace elements because it is a well-known fact that zinc deficiency caused by a chelating agent can have teratogenic effects. Lactation should generally be avoided in the presence of heavy metal poisoning. **Side effects**: Tremor, fever or skin reactions presumably of an allergic nature such as itching (pruritus) or skin rash (exanthema, rash) may occasionally develop. These are, however, usually reversible on withdrawal of treatment. Serious, allergic skin reactions (e.g. Erythema exsudativum multiforme and Stevens-Johnson syndrome) have very occasionally been reported. Dimaval can affect the mineral balance and especially the elements zinc and copper, primarily during long-term treatment. The mercury absorbed by the body is mobilised following administration of the preparation. Kidney failure as a clinical symptom of mercury poisoning can very occasionally be triggered. Asthma patients may very occasionally experience an asthma attack immediately after injection. Cardiovascular reactions may occur, especially if Dimaval is injected too rapidly, and can manifest as hypotension, nausea, dizziness and weakness usually shortly (5-10 minutes) after injection. An increase in certain enzymes (transaminases) may very occasionally be observed. The following have also very occasionally been reported: Pain at the injection site, unpleasant hydrogen sulphide odour, 50% reduction in leukocyte count, changes in taste, oppression of the chest, abdominal discomfort and loss of appetite. **Heyl** Chem-pharm. Fabrik GmbH & Co. KG, Goerzallee 253, D-14167 Berlin

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Dimaval® (DMPS) 100 mg Hartkapseln. Active pharmaceutical ingredient: (RS)-2,3-Bis(sulfanyl)-propane-1-sulfonic acid, 1 H_2O sodium salt; available only on prescription. **Composition:** One hard capsule contains 108.56 mg (RS)-2,3-Bis(sulfanyl)propane-1-sulfonic acid, sodium salt $1H_2O$ equivalent to 100 mg DMPS-sodium, Other ingredients: Copovidone, gelatine, maize starch, sodium dodecylsulfate, titanium dioxide, water for injection; **Indications**: clinically manifest (recognisable) chronic and acute poisoning with mercury (inorganic and organic compounds, vapour, metallic mercury), chronic poisoning with lead. **Contraindications:** Dimaval (DMPS) 100 mg hard capsules must not be administered to patients who are hypersensitive to DMPS or its salts. **Pregnancy and lactation:** No teratogenic effects were observed with DMPS in laboratory animal experiments. Although there is no adequate experience in humans to date, pregnant women must not fundamentally be excluded from DMPS therapy. The risk of poisoning and the risk of medicinal treatment should be carefully considered. If DMPS is administered during pregnancy, mineral levels, especially zinc, should be closely monitored. It is a well known fact that zinc deficiency due to a chelating agent can have teratogenic effects. Lactation should basically be avoided in the presence of heavy metal poisoning. **Side effects:** Tremor, fever or skin reactions presumably of an allergic nature such as itching (pruritus) or skin rash (exanthema, rash) may occasionally develop. These are, however, reversible on withdrawal of treatment. Serious, allergic skin reactions (e.g. Erythema exsudativum multiforme and Stevens-Johnson syndrome) have been reported in individual cases. Dimaval (DMPS) 100 mg hard capsules can affect the mineral balance and especially the elements zinc and copper, primarily during long-term treatment. The mercury absorbed by the body is mobilised following administration of DMPS. The clinical symptoms of mercury poisoning can be triggered in individual cases. Nausea very occasionally occurs following ingestion of Dimaval (DMPS) 100 mg hard capsules. Increased levels of certain enzymes (transaminases) can be observed in individual cases. **Heyl** Chem-pharm. Fabrik GmbH & Co. KG, Goerzallee 253, D-14167 Berlin

Not approved by the FDA!