7. Clinical use

The increased excretion or reduction of blood or plasma levels are usually used for assessing the clinical efficacy for chelating agents. It would, however, be more important to take into account the reduced burden of critical target organs and recovery from pathological changes. Thus, the organs can be emptied without any change in the blood level. The danger of redistribution of the heavy metal in critical organs (e.g. brain), which has been demonstrated for other chelating agents but not for DMPS, must also be taken into account.

7.1 Therapeutic use in heavy metal poisoning

Poisoning with heavy metals is nowadays a fairly rare form of poisoning in Europe. As a result, clinical experience with DMPS is restricted to a limited number of patients. Comparative clinical studies on the therapeutic use of DMPS and other chelating agents have only occasionally been published and most publications are single case reports.

Summary of the fields of use for DMPS mentioned in the literature

DMPS is nowadays recommended for both oral (chronic poisoning) and parenteral therapy (acute poisoning, oral intake of poison) for poisoning with metals and metalloids. It is given in the EU list as an antidote for organic and inorganic mercury poisoning and for intoxication with lead and should be available within 2 hours. In larger hospitals in Switzerland, it should be kept in stock.

In the Monograph Dimercaptopropane sulfonic acid of the BfArM the following indications are given for DMPS:

- Clinically manifested chronic and acute poisoning with mercury (inorganic and organic compounds, vapor, metallic mercury).
- Chronic poisoning with lead.
There are also indications that DMPS is suitable for increased elimination in poisoning with
- Arsenic (apart from poisoning with arsine)
- Copper
- Antimony
- Chromium
- Cobalt.

In chronic poisoning the dosage is normally 3 - 4 capsules per day. The daily dose can also be increased in case of severe chronic poisoning. The daily dose should be divided into partial doses of 1-2 capsules and should be distributed evenly across the day.

<table>
<thead>
<tr>
<th>Day of treatment</th>
<th>Individual dose</th>
<th>Number</th>
<th>Daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>250 mg</td>
<td>6</td>
<td>1500 mg</td>
</tr>
<tr>
<td>2</td>
<td>250 mg</td>
<td>4</td>
<td>1000 mg</td>
</tr>
<tr>
<td>3, 4, ...</td>
<td>250 mg</td>
<td>1-3</td>
<td>250 - 750 mg</td>
</tr>
</tbody>
</table>

Treatment with DMPS should be started as early as possible and be monitored in the laboratory by determining the metal in the urine.

<table>
<thead>
<tr>
<th>Metal</th>
<th>1st choice</th>
<th>2nd choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mercury</td>
<td>DMPS</td>
<td>DMSA</td>
</tr>
<tr>
<td>- metallic</td>
<td></td>
<td>DMSA</td>
</tr>
<tr>
<td>- organic</td>
<td>DMPS, DMSA, DMPS</td>
<td></td>
</tr>
<tr>
<td>- inorganic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lead</td>
<td>DMSA</td>
<td>DMPS</td>
</tr>
<tr>
<td>Arsenic</td>
<td>DMPS, DMSA</td>
<td>BAL</td>
</tr>
<tr>
<td>Chromium</td>
<td>DMPS</td>
<td></td>
</tr>
<tr>
<td>Antimony</td>
<td>DMPS</td>
<td></td>
</tr>
</tbody>
</table>

7.1.1 Antimony

Antimony is one of the non essential metalloids. Symptoms of intoxication are: vomiting, diarrhea, abdominal pain, coughing, hypoxia, liver failure, oliguria, weakness, EEG changes, dermatitis, thrombophlebitis and disorders of the electrolyte balance. DMPS is a suitable antidote for antimony poisoning in adults and children as well.
In three children (1 year 4 months to 4½ years) who were suffering from poisoning with antimony potassium tartrate, the renal antimony excretion was increased by oral administration of 50 mg DMPS every 8 or 12 hours. No side effects were observed.<ref>15,460</ref>

A three-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 diarrhea, exsiccosis and a rapid flat pulse. The child developed increased apathy. First of all, forced diuresis was initiated. After the diagnosis "severe antimony potassium tartrate poisoning" was made, 65 mg DMPS was administered initially i.v. 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 to the 20th day. In addition, blood exchange was undertaken 39 hours after swallowing the poison. When the DMPS therapy was withdrawn, there was, especially on the arms and hands, punctate papulous generalized exanthema with severe itching. The effects on heart and liver described for antimony poisoning, such as ECG disorders and changes in immunoglobulin values, did not occur<ref>29,661</ref>.

DMPS has been tested for reducing the toxicity of antimony compounds during schistosomiasis treatment with good results<ref>474</ref>.

### 7.1.2 Arsenic

Arsenic is one of the non-essential metalloids<ref>45,489</ref>. It is a constituent of insecticides, herbicides, fungicides, color pigments and wood preservatives<ref>45,115,255</ref>.

On acute poisoning, reactions of the gastrointestinal tract predominate. Vomiting, sometimes blood stained diarrhea and development of a shock state as the result of massive loss of liquid with collapse are typical symptoms. This state can be aggravated by cardiovascular disorders and frequently leads to death<ref>646</ref>.

In chronic exposure, late and long-term sequelae through accumulation of the arsenic predominate. These can lead to increased damage in the lungs (malignoma), skin (hyperkeratoses, malignoma), cardiovascular system (myocardial damage, disorders of peripheral circulation), kidneys (kidney failure) and the nervous system (peripheral neuropathy, impairment of sight and hearing), tiredness, fatigue, loss of appetite, Mee's lines in the nails, salivation, apathy or alopecia<ref>45,66,646</ref>. In animal experiments it has also been shown that arsenite and arsenate have embryotoxic actions<ref>255</ref>. The WHO has defined the tolerable daily dose as 2 µg inorganic arsenic per kg body weight<ref>646</ref>.

DMPS is given by various authors as the drug of choice for acute and chronic arsenic poisoning.

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**Arsenic excretion (µg/2h) after administration of 300 mg DMPS orally**

- **A** Volunteers with a highly contaminated drinking water (≈ 593 µg As/l)
- **B** Volunteers with low contamination of drinking water (≈ 21 µg As/l)<ref>34</ref>

The following treatment is recommended for intoxication with arsenic containing warfare gases[487]:

⇒ Mild absorptive poisoning: 200 mg DMPS t.i.d. p.o.
⇒ Severe absorptive poisoning: 200 mg DMPS i.v. or 400 mg DMPS orally

Every 2 hours 100 - 200 mg DMPS i.v.
or 200 - 400 mg DMPS orally
slow reduction of the daily dose

Successful treatment of arsenic poisoning by parenteral administration of DMPS was described by Wax[977,978]:

July 1994 Peripheral neuropathy of uncertain origin was diagnosed in a 32-year-old woman.
August 1994 - spring 1995 Neuropathy improved, but there were repeated skin reactions.
September 1995 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 1030 µg/l. Oral treatment with DMSA was initiated. The arsenic excretion did not increase. The clinical symptoms of progressive neuropathy deteriorated further. Finally, the patient had to be inspired and could no longer move her limbs.

16.11.95 Start of parenteral administration of DMPS (250 mg i.v. slowly over 5 minutes, distributed into 9 doses per day). The arsenic level in the urine rose from 101 to 300 µg/l.
Within 72 hours after starting DMPS therapy improvement of 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 and fell in the course of the treatment to 56 µg/l.
The injections were tolerated without adverse reactions. There were no indications 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 He patient can walk again without aid.

A similar long-term history was suffered by a 41-year-old wine-grower who swallowed 8 - 9 g of arsenic with suicidal intent[362].
February 84 Poisoning by ingestion of 8 - 9 g arsenic. Within a few hours, nausea and diarrhea developed. 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 in the feet.
14th day  The arsenic level had fallen in the urine to 0.2 mg/l.
7th week  Mee's 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 biopsies of the nerves. Slow improvement of
          neurological symptoms.
9th month  Completion of DMPS therapy.
3rd year   Renewed nerve biopsy. Arsenic was no longer detectable. Regeneration of
          the nerves was observed morphologically.
February 88 The neurological findings were still not in the normal range. In spite of this
          there is no longer any weakness of the leg muscles, so that walking with
          crutches was no longer necessary.

In another patient an arsenic level in the urine of 63 µg/l and of 20 µg/g in the hair
          (normal < 1 µg/g) were measured. Mee's lines were visible in the finger nails and in
          addition there was hyperkeratosis. Various reflexes could not be induced. After 6
          weeks, weakness of the limbs and difficulties in walking appeared. Treatment with 100
          mg DMPS t.i.d. for 3 weeks and 400 mg DMSA t.i.d. for 2 weeks produced no
          improvement. The symptoms were still present after 2 years.<sup>475</sup>

Two case histories from the Poisons Unit, Guy Hospital, London<sup>70,640</sup>, show that timely
          treatment with high doses of DMPS can prevent arsenic induced polyneuropathy.

A 21 year old man took 4 g of arsenic (toxic dose 120 - 200 mg)
            3rd hour  Abdominal pain, nausea, vomiting
            6th hour  Creatinine level of 160 µmol/l (normal < 100 µmol/l) which increased to
                      280 µmol/l. Simultaneously, urine excretion fell. Fall in blood pressure.
            26th hour Arsenic level in the blood 400 µg/l (toxic > 50 µg/l).
            32nd hour Intubation because of onset of dyspnoea.
                      Successful reanimation of cardiac arrest.
                      Start of DMPS treatment with 5 mg/kg BW i.v. every 4 hours.
                      Increase in blood pressure and quantity of urine.

After 2½ days  Extubation
            7th day   Investigations with EMG and nerve velocity studies did not show any
                      indications of arsenic induced neuropathies. Conversion of treatment to
                      DMPS orally 400 mg every 4 hours.
            13th day  Discharge of the patient.
            6th week  Normal renal function and no indication of neurological disfunction.

In the 19 year old brother who had taken 1 g of arsenic, an arsenic concentration in the
          blood of 98 µg/l was measured after 36 hours. He was treated initially for 24 hours with
          DMPS i.v. (5 mg/kg BW every 4 hours) and then for 5 days with 400 mg DMPS orally
          every 4 hours. He, too, did not show any signs of neurological disfunction.

A 33-year-old woman accidentally
          took an ointment containing 1.850
          mg arsenic trioxide, which was
          several times the lethal dose. Within
          3 hours she had burning sensations
          in the mouth, nausea, dizziness,
          diarrhea and abdominal pain. 100

![Arsenic excretion in the urine under DMPS + hemodialysis<sup>548</sup>](image)
hours after swallowing the poison she was admitted to the hospital. She was given DMPS in addition to active charcoal (2 days 250 mg i.v. four times daily, 2 days 250 mg i.v. three times daily, 23 days 250 mg i.v. twice daily). At the same time hemodialysis was carried out. The patient recovered completely and the occurrence of severe neurological symptoms could be avoided.

Five unpublished case reports also confirm the positive effect of DMPS on arsenic poisoning. Two patients who had taken lethal doses of arsenic with suicidal intent were treated a short time after swallowing the poison. As DMPS was not immediately available in the hospital and because of the acute situation, a parenterally administerable chelating agent was preferred, so dimercaprol was first used but was then replaced by DMPS. In addition to drug therapy, the patients were treated simultaneously with hemodialysis and hemoperfusion to remove the poison. Both cases recovered without complications.

One patient with acute arsenic poisoning was given DMPS from the start. Because of the uncertainty about the quantity of arsenic swallowed (initial arsenic concentration in the urine of 200 µg/l was known only with some delay), the patient was given 14 g (!) each on the first two days orally distributed throughout the day. This case, too, recovered without complication.

One patient exhibited typical symptoms of arsenic poisoning 5½ weeks after taking the arsenic. After recovering from the acute phase, a slow improvement of the clinical state was found on approximately 4 weeks' DMPS treatment with slowly falling arsenic concentrations in the urine.

Two patients suffered from chronic arsenic poisoning through use of an "alternative" medicine. The arsenic was eliminated with DMPS and the neuropathy improved. In one further case the neuropathy was already irreversible.

90 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.

7.1.3 Bismuth

Bismuth is a non essential metalloid. DMPS is a possible antidote to poisoning with bismuth. After administration of 250 mg DMPS i.v. the bismuth excretion in the urine of the female patient was increased from 0.1 to 4.1 µg/l. A sixty eight year old man with restricted renal function inadvertently took twice the quantity of a bismuth-containing antacid TBD (tripotassium bismuth(III) dicitrate, 864 mg Bi/day) for two months. 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. By oral administration of 100 mg DMPS daily the renal clearance could be increased tenfold to 2.4 ml/min in spite of limited renal function. The bismuth level fell within 50 days from 880 to 46 µg/l, whereby the fall at the time of the DMPS therapy was steeper. The cerebral disfunction improved and the EEG returned to normal.

A forty four year old patient developed renal 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 hemodialysis. Symptoms of encephalopathy did not occur<sup>70,414</sup>.

**Bismuth excretion in the urine during treatment with DMPS (µg Bi/day)<sup>884</sup>**

A twenty one year old man developed anuria with a serum creatinine of 837 µmol/l 48 hours after an overdose of TBD. Further symptoms were nausea, diarrhea, vomiting and fatigue. The bismuth level in the blood was 590 µg/l (normal range 1 - 15 µg/l). After initial treatment with active charcoal and polyethylene glycol orally as well as BAL i.m. and dialysis, treatment was switched to DMPS:
- Initially: 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 orally every 12 hours for 14 days.

The daily hemodialysis (1 hour after the 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 6 days, the bismuth level in the blood was reduced to less than 50 µg/l<sup>884</sup>.

From the experience gained with this patient, Stevens et al. suggest the following treatment for overdose with colloidal bismuth<sup>884</sup>:

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), hemodialysis (membrane with large pores), dialysis for at least 6 hours, continue dialysis until renal function is again normal.
4. Continuation of DMPS therapy with 500 mg daily orally for 14 days (subdivided into two doses).

7.1.4 Cadmium

Cadmium is a non essential heavy metal<sup>445</sup>. It is used in color pigments, batteries and corrosion protection agents<sup>445</sup>. It is also used in large quantities in the tobacco industry<sup>485,534,1009</sup>.

The critical organs for cadmium exposure are the kidneys, lungs and bones<sup>455</sup>. In addition, embryotoxic effects have been demonstrated<sup>455</sup>. The half-life in humans is between 16 and 33 years<sup>445,960</sup>. Symptoms of chronic cadmium poisoning are: exanthema, proteinuria, disorders

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**Cadmium (µg/l creatinine)**

Hours after DMPS administration

---

Bismuth excretion in the urine during treatment with DMPS (µg Bi/day)<sup>884</sup>
of mineral balance, osteoporosis (Itai-Itai disease), gingivitis and central nervous disorders<sup>66,115</sup>.

Cadmium can be mobilized only to a low degree by DMPS<sup>975</sup> because of its intra-cellular<sup>65, 350,354</sup> and especially firm binding to metallothioneins<sup>379</sup>. Thus, the heavy metal level in the urine rose under DMPS from 0.4 to 0.7 µg/g creatinine<sup>340,344,349,351, 493,666</sup>. A women who had worked for many years in a cadmium processing factory exhibited various symptoms of cadmium poisoning. Cadmium excretion in the urine rose from 1.8 to 4.2 µg/l after administration of DMPS<sup>203,202</sup>.

### 7.1.5 Chromium

Chromium is an essential heavy metal<sup>255</sup>. It is important for the release of insulin from the islets of Langerhans<sup>667</sup>.

Administration of DMPS is a possibility for treating poisoning with chromium<sup>262,421,438, 629,755</sup>, especially on acute poisoning<sup>203</sup>.

A twenty 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. In spite of rapid admission to the hospital 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<sup>192,755</sup>.

A worker fell into the chromic acid bath of an electroplating firm and swallowed some of the liquid. High dosed oral treatment with DMPS was initiated within an hour in addition to forced diuresis. The dose was slowly reduced (5 days 12 x 2 capsules/day, 5 days 4 x 2 capsules/day, 14 days 2 x 2 capsules/day). The excretion of chromium in the urine rose drastically and was 13,614 µg/ml 12 hours after start of therapy. The patient survived in spite of a serum level of 5,850 µg Cr/l and short-term anuria (dialysis). Normally, approximately half is considered to be the fatal limit<sup>435</sup>.

<table>
<thead>
<tr>
<th>Day</th>
<th>Serum (µg/l)</th>
<th>Urine (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5,859</td>
<td>39.7</td>
</tr>
<tr>
<td>2</td>
<td>2,349</td>
<td>25.4</td>
</tr>
<tr>
<td>3</td>
<td>1,447</td>
<td>12.2</td>
</tr>
<tr>
<td>4</td>
<td>1,196</td>
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<td>905</td>
<td>9.1</td>
</tr>
<tr>
<td>10</td>
<td>370</td>
<td>1.8</td>
</tr>
<tr>
<td>20</td>
<td>109</td>
<td>0.2</td>
</tr>
<tr>
<td>40</td>
<td>87</td>
<td>0.3</td>
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<tr>
<td>77</td>
<td>43</td>
<td>0.2</td>
</tr>
<tr>
<td>201</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>
Effect of DMPS therapy on the serum level and chromium excretion in the urine

From their experience with this patient, Pudill et al. suggest the following treatment for acute poisoning with dichromates:

1. Poison elimination by gastric lavage
2. Administration of active charcoal and magnesium oxide
3. Starting of antidote therapy with DMPS as soon as possible
   * Initial dosage 250 mg i.v.
   * then 250 mg i.v. every 4 hours for 24 hours
   * then 250 mg i.v. every 6 hours
4. Continuous arteriovenous hemofiltration

67 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.

7.1.6 Cobalt

Cobalt is an essential heavy metal (vitamin B	extsubscript{12}). However, in too high a quantity it is toxic. Fetotoxicity has also been suggested.

DMPS is recommended as an antidote to cobalt poisoning. After cobalt poisoning, it increased the cobalt excretion.

Two children aged 2 years 9 months and 5 years that suffered acute cobalt poisoning through swallowing cobalt compounds from a chemical experiment kit were first of all treated with 25 mg D-penicillamine/kg body weight. From the 5th day treatment was changed to 50 mg DMPS t.i.d. orally. The cobalt level in the serum rose slightly initially, presumably as the result of increased mobilization of the heavy metal from its depots. Treatment was continued until the cobalt excretion in the urine was again in the normal range. The children survived the acute intoxication without complications and without myocardial damage.

DMPS was administered to a fourteen year old body 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. There were no symptoms of intoxication.

7.1.7 Copper

Copper is an essential heavy metal. Symptoms of chronic copper intoxication are: disorders of concentration, ataxia, marked tremor, headaches, depression and liver damage.

DMPS is a possible antidote for copper poisoning. It has been successfully used for hepatolenticular degeneration. It increased copper excretion in the urine.
A thirteen 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.d.). Copper excretion was increased as a result from 2000 to 3000 µg day and the plasma level fell. The cupuresis was comparable with that with treatment with D-penicillamine or trientine. 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 treatment with D-penicillamine or trientine. Clinically the child was well during the observation period of two years. In further patients, good copper excretion could be achieved by administration of test doses of DMPS. In 2 further patients, good cupuresis was also achieved. In these cases, however, the treatment had to be stopped because of adverse reactions.

<table>
<thead>
<tr>
<th>Hours</th>
<th>Copper in urine</th>
<th>µg/l</th>
<th>µg/g Crea</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>118</td>
<td>181</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>144</td>
<td>533</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>144</td>
<td>1,600</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>423</td>
<td>3,021</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>640</td>
<td>4,267</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>3,116</td>
<td>3,180</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>1,212</td>
<td>1,865</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>167</td>
<td>69</td>
<td></td>
</tr>
</tbody>
</table>

Copper excretion during treatment with DMPS

A three year old boy swallowed more than 3 g of copper sulfate. The initial copper concentration in the urine was 118 µg/l. Treatment was started immediately with gastric lavage and DMPS. 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 the toxicologically alarming level. It was possible to discharge the child from hospital after two days.

7.1.8 Gold

Gold intoxication damages in particular the kidneys (nephrotic syndrome), skin (allergic reactions, dermatitides) and bone marrow. DMPS is recommended as an antidote for gold poisoning. In one patient with iatrogenic gold poisoning, the DMPS therapy produced an increase in gold excretion, but in spite of this the patient died of heart failure.

7.1.9 Lead
Lead is a non-essential heavy metal\(^{45,46}\). It is used in leaded pigments and was also an additive to motor fuels for many years\(^{45}\). The daily lead intake in the food is, according to estimates by the WHO, 100 - 300 µg\(^{115}\). Symptoms of chronic lead poisoning are: anaemia, fatigue, weakness, colics, swollen liver, headaches, dizziness, depressions, sleeplessness, epileptic fits, nervous disorders, tremor, lead encephalopathy, delirium and even coma\(^{46,115,787}\).

Lead inhibits various enzymes which are necessary for the synthesis of hem\(^{45,115}\). It can have neurotoxic effects even at concentrations at which no toxic effects are visible\(^{827}\). Thus children with blood levels of more than 25 µg/dl may be expected to have CNS disorders (irreversible learning disorders and changes in behaviour)\(^{45}\). Lead can also impair the growth of children. A negative correlation has been found between the blood lead level and the height of children\(^{28}\). It is known to cross the placenta\(^{962}\). Embryotoxic actions have not been demonstrated in humans\(^{286}\), but are not unlikely\(^{654}\).

The administration of DMPS is a possible treatment in patients with lead poisoning\(^{27,38,47,149,189,203,310,351,470,728,755,787,837,915,961,975}\). After administration of the antidote, the excretion of the heavy metal increases in the urine\(^{350,352,354}\). Thus the lead concentration in the urine of women with a history of abortion rose after administration of 10 mg DMPS per kg body weight orally by 14 times from 2.25 to 31 µg/g creatinine\(^{152}\). Because of the quantities of lead that are often stored in the bones (half-life \(\approx 20\) years\(^{45}\)) longer-term treatment is generally necessary\(^{203,310}\).

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 were excreted in the urine over 24 hours. Without treatment there was no reduction in the lead concentration detectable within 4 weeks. Interval therapy with Dimaval
(800 mg/day for 2 weeks, followed by a 2 weeks' pause) was initiated. In spite of increased lead excretion, the lead concentration in the blood fell slowly, possibly caused by continuous release of lead from the skeletal stores. The laboratory parameters improved in parallel to the treatment. Side effects of the treatment were not observed.<sup>905</sup> It is striking that DMPS increased the lead excretion by almost 10-fold, even after treatment for 1½ years.

<table>
<thead>
<tr>
<th>Day</th>
<th>Blood (mg/l)</th>
<th>Urine (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.18</td>
<td>0.4</td>
</tr>
<tr>
<td>1</td>
<td>0.8</td>
<td>2.4</td>
</tr>
<tr>
<td>2</td>
<td>0.6</td>
<td>7.9</td>
</tr>
<tr>
<td>3</td>
<td>0.8</td>
<td>3.9</td>
</tr>
<tr>
<td>4</td>
<td>0.9</td>
<td>3.9</td>
</tr>
</tbody>
</table>

A 64 year old woman exhibited symptoms of lead poisoning with weakness, fatigue, loss of weight, anaemia, hypotension and neuropathy after 1 year's use of a lead containing ointment. Oral treatment with Dimaval (DMPS) capsules was initiated. Initially, 16 capsules were given in 12 hours. Subsequently the patient was 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 the treatment, the lead level in the blood fell from 1150 µg/l to 570 µg/l. Peak lead excretion in the urine of about 7300 µg/l was achieved on the 3rd day. Treatment led within 9 weeks to almost complete emptying of the lead depot in the body, to a disappearance of the symptoms of intoxication and to normalization of blood formation.<sup>120,261,421</sup>.

In a case of optic nerve atrophy caused by lead deposition in the eye, DMPS treatment (parenteral and local, two 5-day treatment cycles) improved visual acuity, visual field and dark adaptation.<sup>194</sup>.

A fall in 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.<sup>661</sup>.

In a female patient with acute lead poisoning the lead level in the blood rose slowly again after 5 days' treatment with CaNa₂EDTA. 5 days' administration of DMPS lowered the blood level from 800 to 500 µg/l.<sup>704</sup>.
250 mg DMPS i.m. were administered daily to 60 men with chronic lead poisoning in comparison with a patient group that only received 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 anemia disappeared. Hematological parameters, porphyria and liver function improved after treatment in more patients of the DMPS group than in patients with symptomatic treatment. The clinical picture of chronic lead poisoning improved during DMPS therapy more rapidly than in controls, so that the DMPS patients could be discharged from the hospital up to 6 weeks earlier<20,51>. The symptoms of lead encephalopathy improved within a few days in two children (aged 2½ years and 4 months)<961>.

Children aged 31 to 53 months that were still asymptomatic but had chronic lead poisoning (lead concentration in the blood initially 400 - 600 µg/l) were treated for 5 days with DMPS at a daily dose of 200 mg/m² body surface orally (= 4 x 30 mg/d)<175,178>. To make it easier for the children to take the substance, the active ingredient was dissolved in cold orange or apple juice and immediately administered<175,178>. After 5 days, the lead level had fallen to 72 % of the starting value. Doubling of the DMPS daily dose produced a reduction of the lead level in the blood to 68 % of the initial value. The activity of DMPS on the blood concentration of lead was thus comparable with that of calcium disodium edetate CaNa₂EDTA (reduction to 60 %)<920>. DMPS had the advantage over EDTA that the blood level of zinc and copper was practically unaffected. The cumulative excretion of lead in the urine after 5 days' DMPS therapy was two to six times the excretion before therapy<177,178>.

7.1.10 Mercury

Mercury is a non-essential heavy metal<45,59,193,489,516>. It is used in the electrolytic production of alkalis, batteries, drugs and dental products, fungicides, catalysers, protective paints and electronic products<400>. The clinical consequences of mercury poisoning depend on the dose and the type of mercury compound<488,816,930>. In acute poisoning with inorganic mercury (Hg²⁺, Hg⁺), the kidneys are the primary target organ<499,1010>. Nephrotoxicity therefore predominates (breakdown of renal function, mercuric chloride nephrosis, anuria)<46,311,818,862>.

Organic mercury compounds (R-Hg⁺, R-Hg-R) can spread further in the body because of the lipophilic nature. In addition, they can cross the placenta<699> and are also able to
overcome the blood brain barrier. They affect primarily the hematopoietic and nervous systems (Minamata disease, central nervous disorders)<ref>. Fetotoxic effects have also been confirmed<ref>. Organic mercury compounds may, however, also be dealkylated<ref> and then accumulate like inorganic mercury in the kidneys<ref>.

On poisoning with mercury vapor damage to the respiratory tract (dyspnoea, irritant cough, lung oedema, lung necroses) predominate in the clinical picture<ref>. Stomatitis, salivation and tremor (mercury induced erethism) develop on chronic intoxication<ref>. Symptoms of chronic mercury poisoning have in contrast to acute poisoning an insidious character<ref>. Damage to the CNS generally predominates<ref>. On exposure to low levels of mercury, in particular, the symptoms are extremely diffuse<ref>. In addition to general complaints about fatigue, poor concentration, headaches and dizziness, loss of appetite, pressure in the stomach, nausea, salivation, alopecia, sweating and unsteady gait have been mentioned<ref>. The first objective symptoms is a fine tremor, especially of the hands, followed by tremor in the area of the eyelids and tongue. In addition, there is increased salivation which in some cases is accompanied by stomatitis. Later-on, the patients are easily irritable and suffer from sleeplessness with a constant feeling of tiredness and loss of energy and depressive mood. Psychological changes in the form of anxious shyness and indecisiveness are characteristic<ref>. DMPS is used or recommended by many authors as an antidote for mercury poisoning<ref>. This also applies to children<ref> or prophylactically for workers in mercury-handling factories<ref>. DMPS produces an acceleration of mercury excretion in the urine independently of the type or severity of the mercury poisoning<ref>. The mercury concentration rose markedly after DMPS administration, even when the basal values before treatment were in the normal range in spite of the presence of clinical symptoms<ref>. It generally reached a peak during the course of treatment in a few days.

In individual investigations mercury concentrations were measured in the blood<ref>, serum or plasma<ref>. A generally slow reduction of concentration of mercury in the blood was found overall. In some cases, a unique transient increase of concentration was found at the start of treatment<ref> or several peaks were observed during the course of treatment<ref>. This "rebound" phenomenon has been attributed to mobilization (dissolution of mercury from its bindings in the organs) and redistribution of the mercury from the tissues to the blood.

In the treatment of acute mercury poisoning, other measures (gastric lavage, hemodialysis, peritoneal dialysis, hemofiltration, hemoperfusion, plasma exchange, forced diuresis)<ref> were often used in addition to administration of DMPS. With DMPS therapy twice as high a clearance could be achieved with peritoneal dialysis in comparison with that of dimercaprol therapy. With hemodialysis the mercury clearance was even 5 to 10 times higher than with dimercaprol<ref>.
In acute life-threatening poisoning, parenteral administration was generally preferred, where available. Administration of DMPS i.v. is characterised by a more rapid onset of action in comparison with oral administration. After a single dose, about 50% of the total daily dose was already excreted within the first hour, while with oral administration this lasted several hours\textsuperscript{806,809}. 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 the excretion and the clinical symptoms.

To avoid irreversible damage, it is generally important that the therapy starts with a suitable chelating agent as early as possible at a suitable dosage and under laboratory monitoring\textsuperscript{699,961}. Thus, for example, proteinuria of those exposed to mercury should be treated as rapidly as possible with complexing agents\textsuperscript{1879}.

For chronic mercury poisoning, oral dosage forms are preferred because of the simpler procedure for long-term therapy. Generally, the preparation was given at a dose of 100 mg t.i.d.\textsuperscript{665}, and in small children at 50 mg t.i.d.\textsuperscript{469}. The longest period of treatment with DMPS reported was 4½ years\textsuperscript{471}. Occasionally, DMPS treatment was carried out as an interval therapy\textsuperscript{128,699}.

Some papers describe the parenteral administration of DMPS for chronic mercury poisoning\textsuperscript{15,67,76,620,1022}. DMPS was given over three to seven 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 insomnia, nervousness, headaches, paraesthesia, arthralgia, increased salivation and sweating were reported during DMPS therapy\textsuperscript{87,108,128,129,156,234,259,402,1022}. In children, the clinical symptoms of mercury induced Feer's disease (acrodynia) was improved with DMPS\textsuperscript{129,965,966}.

Even without treatment with a chelating agent slow improvement of clinical symptoms in patients with mild to moderate chronic mercury intoxication was observed after removal of the source of poisoning\textsuperscript{76,328}. However, without additional therapy\textsuperscript{156} deterioration of the clinical state in spite of removing the patient from the source of poisoning has been described. The neurological symptoms of poisoning that persisted in patients who received DMPS treatment were less marked than in patients without this therapy\textsuperscript{402}. During the course of two months' observation the symptoms in the patients treated with DMPS improved more rapidly than in patients without DMPS treatment\textsuperscript{1022}.

Because of these observations and on the basis of experience that severe neurological disorders can scarcely ever be corrected with treatment\textsuperscript{78,106,402}, DMPS treatment should be started as early as possible after recognition of mercury poisoning and before the occurrence of severe central nervous damage\textsuperscript{823}.

\textbf{7.1.10.1 Poisoning with inorganic mercury}

\textbf{7.1.10.1.1 Acute poisoning}
On acute poisoning fatal outcome could often be prevented by DMPS therapy and intensive medical care. An intermediate rise in mercury in the serum may occur as the result of mobilization from depots. It was possible to manage a normally fatal mercury intoxication with rapid high-dose DMPS therapy (initially i.v., then oral). The clinical symptoms showed a relatively mild course. A thirty eight year old patient drank 100 ml of a mercury chloride solution of unknown concentration. Nausea, blood-stained feces and blood-stained vomiting developed. After admission to a hospital and gastric lavage, active charcoal was given and a single dose of BAL. Tubular necroses and oliguria developed.

8 hours Transfer of the patient to a specialized hospital. The urine output was less than 10 ml/h. Mercury concentration in blood was 14,300 µg/l (!). A concentration of more than 220 µg/l is normally considered to be fatal. Hypovolemic 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 over 48 hours.

12 hours Hemodialysis was initiated because of total renal failure with anuria while continuing high-dose DMPS therapy. The biological half-life of the mercury was 2.5 days (normally 40 - 60 days).

2nd day Gastrointestinal endoscopy showed massive ulcerative changes. The pH of the stomach was adjusted to ≥ 4 with drugs.

3rd day Blood transfusion because of the anemia induced by the blood losses. Administration of DMPS i.v. every 6 hours for 48 hours.

5th day Administration of DMPS i.v. every 8 hours.

6th day The mercury level in the blood was still above 2000 µg/l. In spite of this the kidneys were again functioning and the mercury was excreted renally. Hemodialysis was stopped. Biological half-life of mercury: 8.1 days.

21st day Mercury concentration in the blood 700 µg/l.

4th week Conversion 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, in the urine < 300 µg/l. Copper and zinc were not affected by the DMPS therapy.

6th month Complete recovery of the patient, no rise in mercury values in the blood or urine.

A forty two year old chemistry teacher with severe acute mercury poisoning (HgCl₂) was given 2 g DMPS i.v. on the first day, distributed in 8 individual doses. In the following two days the dose was reduced to 1.5 g i.v. distributed as 6 individual doses. Because of short-term unavailability of parenteral DMPS, 2 days' treatment with 0.8 g/day orally was carried out. This was followed by 9 days' treatment with 0.75 g/day i.v. and 19 days' treatment with oral DMPS 0.1 g/day. In addition, hemodialysis, hemoperfusion and plasma exchange were carried out. The patient was saved.

A nineteen 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 hemodialysis, hemofiltration and plasma exchange. The patient survived acute poi-
sioning (mercury concentration in the blood initially 12,000 µg/l), which normally would have been fatal within a few hours because of multiple organ failure.<sup>729</sup>

One hour after ingestion of 1 g mercuric chloride, a nineteen year old female patient exhibited nausea, retching and difficulties in swallowing (Hg in blood 805 µg/l, Hg in urine 6,625 µg/l). Hemodialysis, forced diuresis and DMPS therapy (300 mg initially, 300 mg/day orally) were started immediately. The mercury level in the blood and urine fell continuously. Renal function remained normal.<sup>191</sup>

A nineteen year old women was admitted to hospital about ½ hour after an attempted suicide (3 g mercuric chloride) with vomiting, and here gastric lavage was carried out immediately. Complete anuria developed already 1 hour later, so that peritoneal dialysis had to be started. In addition, hemodialysis was carried out.

DMPS was also administered (up to 1,800 mg orally or 400 mg i.v.). In between, BAL was also tried. After 10 days, urine excretion restarted and after 20 days there was a polyuric phase.<sup>649</sup> 100 days after intoxication, the creatinine clearance was again normal.

A seventeen year old patient was saved with DMPS after ingestion of 10 g inorganic mercury in spite of 10 days' acute renal failure.<sup>70</sup>

In small children also, rapid DMPS therapy was able to prevent damage of acute mercury poisoning. A 1-year-old child vomited twice after ingestion of inorganic mercury compounds. One hour after ingestion of the toxin, lavage was carried out and active charcoal and sodium sulfate administered. The mercury level in the blood was about 400 µg/l and in the urine 2,500 µg/l. DMPS was administered as a short-term infusion. On the fourth day of treatment, there was motor restlessness and on the fifteenth 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 after eleven days were thirteen µg/l in the blood and 55 µg/l in the urine.<sup>465</sup>

In another one year old child, vomiting and cyanosis developed 30 minutes after swallowing an ointment containing 0.5 g inorganic mercury. On admission to the hospital after an hour the mercury levels in the blood were 368 in the blood and in the urine 8260 µg/l. Oral treatment with DMPS was initiated (initially 15 mg/kg BW, followed by 2 x 2.5 mg/kg BW/day. After 4 days, the levels had fallen to 107 µg/l in the blood and 195 µg/l in the urine. After 7 days, 38 µg/l were found in the blood and 27 µg/l in the urine. No adverse reactions of the treatment were observed.<sup>997</sup>

In some cases of acute mercury poisoning fatal outcome could not be prevented in spite of therapeutic efforts.<sup>70,661</sup> In one case there was massive intraperitoneal poisoning through abdominal irrigation with mercury oxy cyanide. About 12 hours after the irrigation the patient already had marked shock symptoms and marked heavy metal induced peritonitis and extensive measures for removal of the poison were initiated. While the blood mercury level could be reduced within twenty days from 2.4 mg/l to 0.2

<table>
<thead>
<tr>
<th>Day</th>
<th>1: 6 x 5 mg DMPS/kg BW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 2-3:</td>
<td>4 x 5 mg DMPS/kg BW</td>
</tr>
<tr>
<td>Days 4-9:</td>
<td>2 x 2.5 mg DMPS/kg BW</td>
</tr>
<tr>
<td>Days 10-15:</td>
<td>2 x 2.5 mg DMPS/kg oral</td>
</tr>
</tbody>
</table>

Mercury clearance under DMPS:
Peritoneal dialysis: 0.39 - 0.45 ml/min
Hemodialysis: 3.5 - 5 ml/min

Mercury clearance under DMPS:
Peritoneal dialysis: 0.39 - 0.45 ml/min
Hemodialysis: 3.5 - 5 ml/min

**Day**

1: 6 x 5 mg DMPS/kg BW
2 - 3: 4 x 5 mg DMPS/kg BW
4 - 9: 2 x 2.5 mg DMPS/kg BW
Days 10-15: 2 x 2.5 mg DMPS/kg oral
mg/l, the development of intestinal necroses, progressive intestinal disintegration and putrefaction of the abdominal cavity could no longer be prevented. Another patient died 48 hours after instillation of HgCl₂ on surgical treatment of colonic carcinoma with acute renal failure (blood mercury level 560 µg/l)<sup>210</sup>. In a further case, unconsciousness, anuria and complete hemolysis were already present after intravenously administered mercuric chloride and initial dimercaprol treatment and dialysis before the DMPS therapy was started one day after poison ingestion. The patient died on the 2nd day after mercuric chloride injection.

Because the parenteral form of DMPS was temporarily not available, another case of severe mercuric chloride poisoning was treated orally with DMPS (2 days 1.2 g/day in 12 individual doses, subsequently 0.4 g/day for 2 days). After 3 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 DMPS orally<sup>649</sup>.

The treatment of acute mercury poisoning by oral administration of DMPS has been described many times<sup>179,188,511,555,588,702,997,1020</sup>. In most cases other measures to accelerate poison elimination were carried out simultaneously with the antidote therapy. The DMPS dosing schedules and duration of treatment were variable.

In some cases of acute mercury poisoning, no symptoms of poisoning occurred as the result of the DMPS therapy in spite of quite high blood mercury levels of up to 2.4 mg/l<sup>188,511,555</sup>. Even patients with anuria after ingestion of inorganic mercury compounds and mercury concentrations in the blood of up to 12 mg/l recovered with DMPS<sup>840</sup>.

A complication free course was reported in the treatment of an acute mercuric chloride poisoning. The patient was treated initially for 6 days with 1.2 g DMPS per day i.v. 12 individual doses. Subsequently, treatment was switched for 38 days to oral DMPS at 2.4 g/day in 12 individual doses<sup>661</sup>.

In a fifty three year old man who had taken 50 g of mercuric iodide with suicidal intent, the treatment with DMPS was started 8 hours after taking the poison. Initially, 250 mg DMPS were administered i.v. every 4 hours for 60 hours. In addition, NaCl and dextrose solution were administered. Thereafter, treatment was continued orally for 18 days. A largely complication free course was achieved with this "aggressive" DMPS therapy. In particular, no signs of renal damage were observed<sup>228</sup>.

**7.1.10.1.2 Subacute poisoning**

Through treatment with an inadvertently high dosed homeopathic mercury preparation (3 x 206 mg HgCl₂ daily) the psoriasis of a 68-year-old female patient that existed for 4 years 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 the renal excretion by a factor of 20. This produced rapid removal of the heavy metal associated with a continual improvement of the skin findings<sup>906</sup>. 
A one year old girl developed diarrhea 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 on the second day of treatment to 590 µg/l. After treatment the serum level fell to 16 µg/l. Two further children were also treated with DMPS after swallowing batteries.<ref>{521}</ref>

Psoriasis which had been known 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. Treatment with 200 mg DMPS orally daily was started and after 4 months the dose was reduced to 100 mg DMPS weekly and continued for a further eight months. Tachyarrhythmia which had developed before the DMPS treatment remained.<ref>{128}</ref>

After four years' use of a mercury containing cosmetic bleaching cream, the finger nails of a 56-year-old female patient turned greenish-black. The toe-nails were unaffected. In addition, she developed difficulties in staying asleep, nervousness and marked nocturnal sweating. 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 1660 µg/l on the 10th day of treatment. On completing the treatment, the mercury level in the serum rose again, probably through release of the mercury from the facial skin, so that a second treatment series lasting three weeks was necessary. The dyschromia of the nails disappeared.<ref>{128}</ref>

56 patients suffered mercury poisoning after dermal use of a mercury containing ointment (Hg in blood up to 800 µg/l; gastro-intestinal disorders, nephropathies, hepatopathies, fever, dermatitides) and they were treated with DMPS.<ref>{521}</ref>

### 7.1.10.2. Poisoning with organic mercury compounds
The mercury half-life in the blood after chronic methyl mercury intoxication was reduced from 61 - 65 days on treatment with placebo or without treatment to ten days on treatment with DMPS. DMPS was thus the most effective in comparison with treatment with D-penicillamine (mercury half-life of 26 days), N-acetyl-penicillamine (24 days) and thioresins (20 days). The excretion of mercury in the urine with DMPS was also superior to that with D-penicillamine.

A twenty year old patient was treated with hemodialysis and D-penicillamine after swallowing, amongst other things, a methyl mercury-containing fungicide with suicidal intent. After three days, the treatment was converted to 200 mg DMPS orally every 6 hours. The patients survived the poisoning without any major symptoms of intoxication.

A fort 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 sent to a university hospital. There, blood-stained gastritis was also diagnosed. In addition to DMPS orally, DMPS was administered parenterally and DMSA orally.

1st day  Start of acute polyuric renal failure which improved on conservative therapy within 40 days.
4th day  Fever of up to 40°C without infection.
6th day  Gingivitis and exanthema, development of polyneuropathy.
11th day  Delirium with coma, changes in the EEG.
16th day  Start of mechanical respiration.
19th day  Improvement of the neurological symptoms; the blood level fell to less than 100 µg/l.
148th day  The patient largely recovered.

The maximum blood level was 14 mg/l in blood, 1.7 mg/l in serum, and in cerebrospinal fluid 25 µg/l and in urine 10.7 mg/l. There was no correlation between the concentration in the blood and the CSF. In the first three days of treatment, more heavy metal was excreted than in the remaining 140 days. The half-life of the mercury was $t_{\alpha} = 2.2$ days and $t_{\beta} = 40.5$ days. Although the patient survived this massive thiomersal poisoning, no clear effect of DMPS and DMSA could be detected in this case on the renal mercury excretion.

A fifteen year old boy was admitted to hospital because of swallowing an unknown quantity of Fusariol (cyanoethylmercury). After gastric lavage, active charcoal and sodium thiosulfate were administered and forced diuresis started. Initially, treatment was with BAL before switching to DMPS, with which a marked increase in the mercury excretion was achieved. During the DMPS administration, nausea, retching and headaches developed, but these were controllable. No changes in the blood picture or in transaminases or in serum electrolytes were observed.
A forty nine year old women was admitted to hospital two hours after ingestion of an organic mercury compound with suicidal intent. In spite of vomiting and gastric lavage, 700 to 1000 mg mercury were absorbed of which 11 mg were removed by hemoperfusion. The blood level was thereby halved. In addition, forced diuresis and alternating therapy with 3 x 300 mg D-penicillamine/day and 3 x 100 mg DMPS orally/day was initiated. This led to renal excretion of 500 mg Hg. The patient was discharged after four weeks without toxic symptoms in the kidneys or central nervous system occurring.<ref>611</ref>

For five months a previously healthy girl (9 ½ years) complained of abdominal pains. Within three months, a shaky script absorbed as the 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 2200 mg) was initiated. The mercury levels fell and the symptoms improved. The source of the poison was identified as mercury treated seeds on which the child had frequently chewed.<ref>132</ref>

Compounds with radioactive mercury were used for renal scintigraphy as this heavy metal accumulates in this organ. The nuclide elimination was promoted by subsequent administration of DMPS (by 35 % in comparison with controls) and the radiation dose of the kidneys thus rapidly reduced.<ref>494, 685</ref>

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 twenty seven patients and DMSA (2 x 500 mg i.v.) in thirteen patients for three days. After four days' treatment pause, another three days' treatment was carried out. The patients went through up to eight treatment cycles. DMPS was found to be slightly superior to DMSA. There was a correlation between the severity of the symptoms and the mercury levels under DMPS therapy.<ref>1022</ref>

### 7.1.10.3 Poisoning with mercury vapor

Mercury in the vapor form is very readily absorbed because of its lipophilic nature and high diffusion capacity (absorption rate in the lungs: 80 %<ref>14</ref>). Poisoning with mercury vapor may occur at workplaces where it is processed.<ref>231, 688, 807, 879</ref>

In a 14 year old girl who suffered from unrecognized chronic mercury poisoning for three months, the apparent psychological and neurological symptoms were interpreted for a long time as a neurotic anxiety syndrome. Some time later she suffered from marked sweating and insomnia at night. As the investigations that were carried out did not show any pathological findings, the symptoms were interpreted as an expression of psychological disorder. Tremor at rest, loosening of the teeth and exanthema with generalized itching developed before the diagnosis of chronic mercury intoxication was finally made. The cause was spilt mercury which could not be removed from the carpeting with a vacuum cleaner. Treatment with DMPS 100 mg every other day was initiated. The urine excretion was increased by more than 14 times. The symptoms of the illness regressed slowly as the serum level fell.<ref>129</ref>
84 employees of a mercury refinery were treated for four weeks with DMPS. The mercury level in the urine fell from 224 to 41.3 µg/l. The clinical symptoms also improved partially. Two workers who had intoxication with mercury vapor were treated for 60 days with DMPS. The biological half-life was reduced from an average of 33 days to 11 days.

10 workers in a mercury processing factory who had urine levels of over 50 µg Hg/g creatinine were treated for 5 days with 100 mg DMPS t.i.d. orally. The urine excretion of the heavy metal was significantly increased. It is striking that with similar mercury excretion before DMPS (workers 6-10) the excretion in the first 24 hours after starting DMPS therapy differed by up to a factor of 15.

<table>
<thead>
<tr>
<th>Worker</th>
<th>Before DMPS</th>
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<tr>
<td>1</td>
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</tr>
<tr>
<td>10</td>
<td>50</td>
<td>201</td>
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Mercury excretion in the urine (µg/g creatinine) in 10 workers before, 24 hours after and 3 days after the last administration of 100 mg DMPS t.i.d. orally.

22 workers with occupationally induced intoxication (organic Hg, Hg vapor) exhibited increased fatigue, sexual impotency, neuralgia, polyneuritis and pathological changes of internal organs. They were treated with DMPS i.m. 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. The mercury excretion in urine and feces rose markedly as the result of DMPS administration and the subjective well-being of the workers improved. In six of them there was short-term deterioration of the symptoms because of marked mercury mobilization from the depots.
Because the heavy metal is predominantly inhaled via the lungs, the DMPS was administered in 9 workers as an aerosol. The treatment was well tolerated. The symptoms of intoxication improved. Mercury excretion in feces and urine rose. Even in workers with no mercury detectable before treatment, excretion of the heavy metal was detected

DMPS was also administered by inhalation as prophylaxis for mercury vapor poisoning

19 underground railway building workers were exposed without noticing to mercury vapor 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 mucous membrane, tiredness, headaches and jaw pain, insomnia, tremor, hypersalivation, dyspnoea and speech disorders developed. The patients were treated either with 600 mg/d DMPS (n=6), 300 mg/d DMPS (n=6) or 450 mg/day D-penicillamine (n=7). The mercury level fell in all groups during the 7 day treatment. The highest excretion in the urine was achieved in the high-dose DMPS group. D-penicillamine showed only an inadequate action at the dose used.

A man wanted to destroy wasps with liquid mercury. During the process, the container broke and the majority of the heavy metal spread on the carpet. The parents attempted to remove the mercury with a vacuum cleaner. The mother exhibited symptoms of poisoning such as headaches and nausea already on the next day. The four children developed severe bronchitis during the next week. They were immediately treated with 100 mg DMPS/day subdivided into two doses. After four weeks, they could be discharged in good condition without any symptoms of mercury poisoning.

<table>
<thead>
<tr>
<th>Day</th>
<th>A</th>
<th>B</th>
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<th>D</th>
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</tr>
<tr>
<td>12</td>
<td>615</td>
<td>1370</td>
<td>947</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>189</td>
<td>233</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>615</td>
<td>472</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mercury excretion in the urine of four children during DMPS (100 mg/day)
A 2½-year-old girl (S.K.) suffered from a weeping eczema for four months until a diagnosis of chronic mercury poisoning was made. Later she developed loss of appetite, diarrhea and photosensitivity. 8 months previously a mercury thermometer had broken in the children's bedroom (wall-to-wall carpeting, underfloor heating). Two siblings (R.K. 1½ years, J.K. 7 years) were also found to have symptoms of mercury intoxication (Feer's disease). Treatment with 30 mg DMPS b.i.d. was initiated and continued for 4 months. It was noted in particular in patient RK that the mercury concentrations before the administration of DMPS were still in the normal range in spite of clinical symptoms. Only after administration of the chelating agent was the mercury intoxication visible in the urine.<ref><sup>965,966</sup></ref>

### 7.1.10.4 Poisoning with metallic, liquid mercury

In poisoning with metallic mercury the toxic effects develop mainly through the mercury ions produced<ref><sup>203,383</sup></ref>. Metallic mercury can therefore form a depot that leads to chronic absorption mercury intoxication<ref><sup>383</sup></ref>. There is some dispute whether poisoning with metallic mercury must be treated in every case. When taken orally, some people consider it to be non-toxic<ref><sup>14,952</sup></ref> (absorption from the gastrointestinal tract < 0.01 %<ref><sup>115</sup></ref>), while others consider the treatment is necessary<ref><sup>555,699</sup></ref>. „Metallic mercury in fatty tissue is, however, highly toxic because of its lipid solubility and needs treatment with chelating agents“<ref><sup>499</sup></ref>. Thus, treatment was carried out for 6 months in one case with s.c. mercury incorporation<ref><sup>116</sup></ref>.

In a 2½ year old boy a depot of metallic mercury developed in the eye socket after an accident with a thermometer. As complete surgical removal of the heavy metal was impossible, additional treatment with DMPS (100 mg/day) was initiated. At the start of treatment, there was a rise in mercury concentration in the 24-h urine from 24 µg/l to 443 µg/l. The treatment, which was carried out more than a year, was well tolerated without side-effects and will be continued as mercury depots are still detectable by X-ray and the mercury level in the urine is still slightly raised<ref><sup>725</sup></ref>.

In a twenty three year old man the mercury level in the blood rose following i.v. injection of mercury to 294 µg/l. 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. Side-effects did not occur and the plasma levels of copper, zinc and selenium were not reduced<ref><sup>71,72</sup></ref>.

In a thirty two year old female patient who had injected mercury from a thermometer i.v., long-term therapy with N-acetyl penicillamine and DMPS showed positive results. The heavy metal excretion in the urine was increased by DMPS from 560 to 3,700 µg daily<ref><sup>115,116,118</sup></ref>. In a 21 year old female patient the renal mercury excretion after
administration of DMPS increased from 484 to 1,304 µg/l more than one year after the heavy metal injection<sup>383</sup>.

A sixty one year old man inadvertently aspirated metallic mercury into his lungs. After 8 months it was determined by isotope investigations that organic mercury had formed and concentrated in the kidneys. 6 days' treatment with DMPS reduced the renal level from 28.1 to 19.6 mg<sup>426</sup>. A thirty five year old man ingested metallic mercury through rupture of the balloon of a Miller-Abbot probe. A raised mercury level of 940 µg/l was detected in the blood after about 24 h. DMPS treatment was therefore started immediately. The blood level fell rapidly and the urine levels rose briefly to 700 µg/l. There were no clinical symptoms in the patient of mercury poisoning<sup>555</sup>. An increased mercury excretion in the urine or an increased mercury concentration of blood after incorporation of metallic mercury makes the administration of DMPS essential<sup>555</sup>.

7.1.11 Nickel

Nickel is a constituent of some metalloenzymes. It also acts as an enzyme activator<sup>68,69</sup>. On the other hand, it is a potent carcinogen<sup>255</sup> and fetotoxic effects are also known<sup>255</sup>. DMPS may be considered as an antidote after poisoning with nickel<sup>203, 246</sup>. Administration of DMPS increased nickel excretion<sup>470</sup>.

7.1.12 Palladium

DMPS increases renal elimination of palladium<sup>203,916</sup>. The palladium excretion in urine before and after administration of DMPS (oral or i.v.) was determined in 50 volunteers<sup>790,791</sup>. The elimination rose from 0.3 to 38 µg/g creatinine. No difference was observed between the oral and parenteral administration<sup>790,791</sup>. In another investigation, DMPS increased the palladium excretion in the urine on average from 12 to 49 µg/g creatinine<sup>440</sup>.

7.1.13 Platinum

DMPS is recommended as an antidote for platinum poisoning<sup>755</sup>.

7.1.14 Selenium

Selenium is an essential trace element<sup>45,255</sup>. In excess, however, it is toxic<sup>255</sup>. Fetotoxic effects are known for high doses<sup>255</sup>. DMPS is given as an antidote for selenium poisoning<sup>203</sup>. An accelerated selenium excretion was observed after administration of DMPS<sup>242</sup>.

7.1.15 Silver
DMPS increases the renal silver excretion and offers a possible means of treatment for silver poisoning.

A sixty year old man treated erosion of the gums topically with a 3% silver nitrate solution. Three years later his hair turned silver grey, and 5 years later the skin began to darken. In particular, areas exposed to the sun were bluish-grey. Biopsies showed a 100-fold increase in silver level and a tenfold increase in selenium. 15 years after exposure, treatment with various chelating agents was attempted and of these only DMPS showed an effect in that it increased the silver excretion in the urine. In the course of two treatment cycles with up to 2500 mg DMPS, however, only 1% of the total quantity of silver was removed from the body. Because 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 therapy was unable to mobilize the silver selenide.

In a patient with silver poisoning (argyrosis) the silver excretion in the urine during treatment with DMPS (300 mg orally per day) was up to 100 times higher than that during treatment with D-penicillamine.

### 7.1.16 Technetium

$^{99m}$Tc-DMPS complex accumulated after i.v. administration especially in the kidneys. The content in the liver and blood, in contrast, fell rapidly. Thus renal scintigrams could be recorded with a γ-camera in four patients up to 180 min after administration of the complex.

### 7.1.17 Tin

DMPS increases the renal excretion of tin. A dental assistant suffered from marked tin exposure through kneading of amalgam in the unprotected palm of the hand. The tin excretion in the urine could be increased by administration of DMPS to 1,094.4 µg/l. The clinical symptoms of tiredness, lack of drive, migraine, dizziness and tremor improved.

In another female patient, the tin excretion in the urine increased threefold after DMPS injection from 6.2 to 20.3 µg/l. In fifty volunteers an increase from 4.9 to 5.3 µg/g creatinine was observed.
7.1.18 Zinc

Zinc is an essential trace element (constituent of more than 100 enzymes\(^{115}\))\(^{45,255,489}\). Its content within the human body is between 1.3 and 2 g\(^{467}\). Excretion in the urine could be increased by up to thirteefold by administration of DMPS\(^{201}\)\(^{105}\).

7.2 Heavy metals from the environment and amalgam

A major environmental catastrophe with mercury took place between 1953 and 1960 in Minamata, Japan. Waste water containing organic mercury compounds were fed into the bay without monitoring. The heavy metal accumulated in the course of the food chain in fish. Mass poisoning with forty deaths\(^{818}\) and 200 - 800 partially irreversible disabilities\(^{368,1035}\) developed through eating the poisoned fish. Those affected suffered from "wooden-doll" disease and were no longer able to move their arms and legs. In addition, teratogenic effects were observed\(^{17,270,834}\).

Between 1965 and 1970, 53 people living along a river in Japan became ill after a company discharged organic mercury compounds. 6 people died\(^{591}\).

In 1971 in Iraq, eating of grain that had been treated with methyl mercury led to mass poisoning of more than 6500 persons\(^{17,279}\). In 1961, more than 100 Pakistanis became ill from chronic mercury poisoning from a mercury containing fungicide\(^{193}\).

In 1955 in Japan, grain, rice and vegetable fields were contaminated with cadmium containing waste water from a mine. Consumption of the foodstuffs led to Itai-Itai disease in 350 Japanese with pains in the back and thighs as well as a tendency to spontaneous fractures due to osteomalacia. 100 patients died as the result of the poisoning\(^{834,1031}\).

Environmental burden is being increasingly discussed as part of a multifactorial event in the development of chronic diseases\(^{836}\). Pollutants can accumulate in the body until the metabolic functions and the immune system are overloaded, which finally leads in the course of time to clinical symptoms\(^{493,534,552,788}\). This is the last straw\(^{150}\).

Various mechanisms have been proposed whose clinical effects cannot always be separated:

- Intoxication = increased heavy metal levels\(^{198,127,143,326,338,357,448,582,798}\)
- Allergy = positive epicutaneous test\(^{127,143,326,338,357,582,798}\)
- Intolerance = action at homeopathic doses\(^{127,357,582,798}\)
- Reaction blockade for healing stimuli\(^{127,711}\)

7.2.1 DMPS mobilization test
DMPS-HEYL® and Dimaval® (DMPS) 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.

Monitoring of the treatment of heavy metal intoxication with a chelating agent must always include monitoring of the heavy metal excretion in the urine<sup>665</sup>. This means that every correctly performed treatment with chelating agents leads simultaneously to diagnostic information. Conversely, the DMPS test is simultaneously diagnosis and therapy<sup>127,193,316,348</sup>.

Chronic poisoning frequently does not have any typical symptoms. Diagnosis of chronic intoxications with mild disorders of well-being is therefore among the most difficult tasks in medicine<sup>896</sup>. Patients with chronic heavy metal intoxication therefore often have a long history of complaints before the correct diagnosis is made and suitable treatment is initiated<sup>129,969,1022</sup>.

In mercury poisoning, administration of DMPS leads to a marked rise in mercury excretion in the urine<sup>130,639,687,688,699,718,806,838,1028</sup>. In exposed persons in whom the mercury concentration in the blood and urine was already largely within the normal range, marked increases in mercury excretion in the urine could be provoked with DMPS<sup>602</sup>. This was attributable primarily to mobilization of the heavy metal stored in the kidneys<sup>148,197,201,545,569,1034</sup>. In animal experiments it was possible to show a correlation between the rise in mercury excretion in the urine after administration of the DMPS and the existing whole body burden<sup>166,374</sup>. The mobilization test therefore permits conclusion to be draw about the whole body burden from the heavy metal concentration in the urine<sup>666</sup>.

**7.2.1.1 Necessity of a mobilization test**

The DMPS mobilization test is used primarily for the 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<sup>629,879</sup>. The necessity of a mobilization test is, however, a matter of dispute in clinical practice.

Thus the Advisory Committee of the Deutsche Gesellschaft für Pharmakologie und Toxikologie [German Society for Pharmacology and Toxicology]<sup>227</sup> and other scientists do not consider the mobilization test to be indicated for the determination of mercury burden as it is an unnecessary administration of a drug and does not produce any additional information<sup>133,134,312,392,596,405,469,503,549,569,582,639,666,750,806,838,877,953,993,1001,1033</sup>. As mercury does not, unlike arsenic<sup>648</sup> or lead<sup>936</sup>, have any marked tendency for accumulation in the body<sup>793</sup>, measurements in blood or urine are in their view sufficient. In addition, mainly the rapidly mobilizable mercury in the kidneys and bone marrow is mobilized by DMPS<sup>669,684,715,718,892,1033</sup>, but not the heavy metal in the CNS, so that the mobilization test
cannot provide any information about the heavy metal load in the CNS and brain because the mobilizable renal excretion is directly proportional to total body burden. Performance is especially indicated in patients with corresponding symptoms, if no pathological damage of organs can be detected and other trial treatments have been abortive. The mobilization test is also recommended with increased values in the chewing gum test. The mercury load of living humans is best quantifiable with the Dimaval® Test (analysis of urine before and after administration) as only by mobilization with the chelating agent does the heavy metal deposited in various tissues appear in the urine or blood. While the actual mercury load is determined primarily by determination in twenty four hour urine and serum, the mercury mobilization test provides information on possible deposits in the body and thus offers a „simple method for confirmation of a clinical diagnosis“ or for the exclusion of poisoning.

In combination with the saliva test, the DMPS test permits conclusions about the source of the mercury in the human body.

Statistical investigations showed on average a linear correlation between the mercury excretion before and after administration of DMPS. Individually, there are, however, always deviations. In the individual case therefore the value before the DMPS stimulation does not provide any indication of the approximate range of mercury values that may be found after stimulation. The measurement of the mercury excretion mobilizable 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. The same also applies for arsenic, lead, cadmium and copper.

7.2.1.2 Limits

Critics of the mobilization test criticize, amongst other things, that there are no scientifically recognized limits available. The current limits for the DMPS mobilization test are derived predominantly from Daunender, who has only published a few facts about their determination.

The question of the level at which long-term mercury load produces the first adverse effect has so far been unanswered by scientists. What is certain so far is that there is no physiological need for Hg as a trace element and that therefore any Hg intake is unnecessary and may be classified as potentially pathological.

Setting of a limit is difficult, if not impossible. Up to now, there are no precise dose response relationships.
available for mercury. An LOAEL (lowest observed adverse effect level), LOEL (lowest observed effect level) or NOAEL (no observed adverse effect level) is unknown. There are no limit concentrations for mercury in the human body. Only a few values have been determined, especially for occupational medicine. The WHO regards 20 µg/l in blood and 50 µg/l in urine as limits up to which non specific early symptoms of poisoning with inorganic mercury can be ruled out. According to the criteria of the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) [German Federal Institute for Drugs and Medicinal Products] endangerment of health cannot be ruled out from a mercury concentration of 20 µg/l urine or 10 µg/l (inorganic) or 30 µg/l (organic) in blood.

When answering the question what concentration of the metal has toxicological risks, various factors must be taken into account.

⇒ Previous illness
  Limit values apply generally to healthy humans, but not to "predisposed" patients. Thus it is known for instance that people suffering from allergy can react more sensitively.

⇒ Possible deficits of zinc or selenium
  Zinc and selenium are natural antagonists to mercury. People with sufficient selenium tolerate more mercury than those with a selenium deficiency.

⇒ Individual sensitivity
  There are individual reactions to all medicaments, both with respect to response to treatment and possible side effects. The cytochrome P450 system appears to play a role.

  The individual sensitivity to heavy metals varies. Some people appear to tolerate doses that already produce clinical symptoms in others. There are no tests that can be used to filter out people with possibly especially high individual sensitivity.

  In addition, sex specific differences have been suggested.

⇒ Children
  Children frequently react sensitively. They absorb, for example, about 50 % of orally administered lead, while adults absorb only 8 %. In addition, their excretion rate is lower.

⇒ Pregnant women
  "The WHO assumes that pregnant women react more sensitively to mercury."

⇒ Interactions with other environmental poisons
  Humans are exposed to various stresses which can occur in interactions with respect to their toxic effects (combination effect). Thus, a mercury burden increases, for example, sensitivity to formaldehyde, lindane or PCP.

⇒ Possible long-term effects of low loads
  "A residual toxicological risk of the chronic effects of small mercury doses cannot be ruled out, especially in predisposed patients" as there are still extensive gaps in our knowledge about the toxic effects of low level exposure.
DMPS does not touch the mercury in the brain, so that in spite of lower excretion values toxic levels may be present.<sup>320</sup>

Renal damage
A prerequisite for the mobilization test is functioning of the excretion system<sup>414</sup>.

### 7.2.1.3 Different parameters of the mobilization test

There are no standardized conditions for performing the mobilization test with DMPS. The various forms described in the literature differ in various parameters.

#### 7.2.1.3.1 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 rapid onset of action<sup>809,1033,1034</sup>. 50 % of the mobilizable mercury was already excreted in the urine after 45 to 60 min<sup>806,1033,1034</sup>. Maximum excretion after i.v. administration was achieved after approx. 1½ hours<sup>123</sup>. Absorption interference, e.g. through the formation of gastrointestinal complexes<sup>98,357</sup> were excluded<sup>322,326,357</sup>. Otherwise, oral administration was as effective as the injection<sup>806,809</sup>. However, it must be taken into account that on oral administration there is generally less active material available as only about 50 % is absorbed<sup>311,1033</sup>.

#### 7.2.1.3.2 Dosage

Parenterally 3 to 4 mg/kg BW is mostly administered. For oral administration, the daily dose of 300 mg DMPS was administered independently of body weight as a single dose as with mobilization tests with other chelating agents.

After it was found in animal experiments that the oral dose has to be 2.5 times the parenteral dose to obtain the same efficacy, Gerhard et al. introduced a mobilization test with 10 mg DMPS/kg BW orally<sup>230</sup>.

#### 7.2.1.3.3 Collection of urine (spontaneous or 24-h urine)

There is a particularly lively discussion on whether for the performance of the mobilization test the urine should be collected over 24 hours or whether a shorter collecting period or even obtaining spontaneous urine would be sufficient<sup>65,66,213,480,953</sup>. In
investigations with spontaneous urine, the mercury concentrations found in urine were considerably higher than those in the 24-h urine. The excretion of heavy metal-DMPS complexes takes place rapidly. The mercury excretion reached a peak in the urine two hours after ingestion of the DMPS<sup>493</sup>, and after 10 hours the elimination had returned to the initial values<sup>121</sup>. The initially high concentration in the urine was thus diluted by the "late urine" with considerably lower content of mercury<sup>201,217,810</sup>.

Many make a strong plea for determination of the heavy metals only in the 24-h urine<sup>309,392,393,482,483</sup>. If necessary, the morning urine is suitable for heavy metal determination before administration of the chelating agent<sup>392,393</sup>. Only in this way can the interfering effects of diurnal rhythm and diuretically induced fluctuations in the urine be avoided<sup>65,66,994</sup>. For these people, standardization in terms of creatinine is also insufficient<sup>482,483,1034</sup>. A short collection period thus produces a greater source of error<sup>439,809</sup>. For long-term measurements, on the other hand, there is the problem of patient compliance (contamination risk, collecting errors, greater effort)<sup>65,66,994</sup>.

On oral administration of DMPS about 60 %<sup>639,793</sup> was excreted in the first 6 hours, 70-80 % in the first 8 hours of the 24-h excretion<sup>802</sup>. The urine excretion in the first 6 hours correlates with the 24-h value<sup>639</sup>. Measurement of the time course of excretion showed that collection of the urine for 3 hours was sufficient for recognizing mercury burden on oral administration of DMPS<sup>196</sup>.

<table>
<thead>
<tr>
<th>Collection period</th>
<th>1 hour</th>
<th>2 hours</th>
<th>4 hours</th>
<th>9 hours</th>
<th>Amalgam score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>47 x</td>
<td>53 x</td>
<td>50 x</td>
<td>31 x</td>
<td>45</td>
</tr>
<tr>
<td>Patient 2</td>
<td>25 x</td>
<td>26 x</td>
<td>26 x</td>
<td>15 x</td>
<td>29</td>
</tr>
<tr>
<td>Patient 3</td>
<td>11 x</td>
<td>9 x</td>
<td>7 x</td>
<td>14 x</td>
<td>3</td>
</tr>
</tbody>
</table>

Increase of mercury excretion in the urine by administration of DMPS (300 mg orally) depending on the collection period for the urine<sup>441</sup>

The good correlation between the mercury concentration (µg/g creatinine) in the 45-min spontaneous urine after DMPS i.v. and the mercury excretion (µg absolute) in the 10-hour urine suggest that the spontaneous urine is quite suitable for assessment of the mercury depot<sup>812</sup>.

### 7.2.1.3.4 Urine or feces

There have been various recommendations in the literature to determine the increase in mercury excretion after oral administration of DMPS not in the urine but in the feces<sup>209,210,215,217,248,322</sup>. In these cases, a metabolic anomaly is assumed, whereby the heavy metal is excreted primarily in the feces<sup>414</sup>.

However, other possible mercury depots may be determined than those that are detected by investigation of the urine. DMPS is absorbed to about 50 % after oral administration. That means that about 50 % remains in the gastrointestinal tract. The unabsorbed DMPS can bind any mercury present in the stomach and intestines by interrupting its enterohepatic circulation<sup>317,746</sup>. To determine the heavy metal deposited
in the body, the heavy metal in the urine must also be determined after oral administration of DMPS, as has been shown in numerous studies.

7.2.1.3.5 Order of heavy metals

The following order for the excretion of heavy metals after mobilization with DMPS has been given in various publications: Zn > Cu > As > Hg > Pb > Fe > Cd > Ni > Cr<sup>98,127,137,204,228,229,318,320,321-324,326,357,715,716</sup>. According to this, zinc was the best mobilized. To what extent the authors have observed this themselves or how far they depend on the literature cannot be ascertained.

This order contradicts the stability constants determined in vitro (see 3.5. Complex formation). The excretion of mercury, for example, is increased even when zinc and copper are still present in the body. The authors probably mean the quantities excreted not the order of the metals. As zinc and copper are present in large quantities in the body as essential trace elements, a greater quantity of DMPS-metal complex is to be expected according to the law of mass action, even with lower binding constants.

7.2.1.4 Variants of the DMPS mobilization test

There are so far no standardized conditions for performance of the mobilization test with DMPS. The variants of the test described in the literature differ in various parameters.

A common factor to all variants of the mobilization 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<sup>480</sup>. A uniform procedure must be used in order to obtain comparable and correct results<sup>485,992</sup>. Agreement between the doctor and the laboratory is important<sup>274</sup>. In addition, the patient must empty his bladder completely before administration of the DMPS<sup>716</sup>.

Where there are markedly raised zinc and/or copper values (copper > 2500 µg/g creatinine<sup>910</sup>) it must be borne in mind that there may possibly no longer be sufficient DMPS for mobilization of other metals. The results may be falsely negative<sup>127,228,229,293,320-323,332,326,1008</sup>. In these cases, repetition of the test after 4 - 12 weeks is recommended<sup>127,834</sup>.

Assessment of increased copper values is problematical. Animal experiments have shown that where poisoning with arsenic<sup>695</sup>, gold<sup>910</sup> and mercury<sup>127</sup> is present, the copper content of the kidneys is also significantly raised. The induction of the formation of metallothioneins, which then retain more copper<sup>127,910</sup>, has been suggested as a mechanism of action. With DMPS therapy not only the mercury, but also the copper levels fell<sup>127</sup>. A similar situation was observed for zinc<sup>910</sup>.

7.2.1.4.1 Mobilization test according to Daundrer (parenteral)

Daundrer recommended the performance of a mobilization test at a mercury concentration in the urine of more than 5 µg/g or the corresponding clinical symptoms<sup>218,233,565</sup>.
Determination of the basal level for mercury
(Additionally of zinc to exclude zinc deficiency\textsuperscript{1029}, (Zn < 140 µg/g creatinine indicates zinc deficiency\textsuperscript{1008}), and possibly also copper)

1. Slow i.v. administration of 3 - 4 mg DMPS/kg BW
2. Get the patient to drink about 150 ml tea, water or lemonade
3. Collection of spontaneous urine 45 minutes to 1 hour after administration of DMPS. Birkmayer recommends the collection of the urine from ½ to 1½ hours\textsuperscript{121,122}.

\[ \text{A rise in the mercury in urine after administration of DMPS to more than 50 µg/l or 50 µg/g creatinine shows accumulation of mercury.} \textsuperscript{210,229,233,238,239}\]

The DMPS mobilization test is also recommended for determination of burden with other heavy metals, e.g. lead (in hypertension)\textsuperscript{322,326} or cadmium in osteoporosis\textsuperscript{357,1008}.

<table>
<thead>
<tr>
<th>As</th>
<th>Cd</th>
<th>Cr</th>
<th>Cu</th>
<th>Hg</th>
<th>Mn</th>
<th>Ni</th>
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<td>3</td>
<td>500</td>
<td>50</td>
<td>10</td>
<td>8</td>
<td>50</td>
<td>15</td>
<td>2,000</td>
</tr>
</tbody>
</table>

\textit{Limits (µg/g creatinine) for parenteral DMPS test according to Daungerer}\textsuperscript{65,203,211,220,233,237-239,1029}

\subsection{7.2.1.4.2 Mobilization test according to Schiele}

Schiele\textsuperscript{807} recommends the following procedure for investigating the systemic load with mercury:

1. Determination of the basal level for mercury
   A spontaneous urine sample is normally sufficient to determine the basal level. Preferably a sample of the first morning urine be used.
2. After complete emptying of the bladder, 300 mg Dimaval\textsuperscript{®} (DMPS) are administered orally with water.
3. Determination of the heavy metals in the 24-hour urine after administration of the chelating agent.

\[ \text{"A rise of more than 10-fold of the basal level indicates above average accumulation."} \textsuperscript{143,811,831} \]

Schuetz considers an increase of more than 3 times the basal level as an indication of a burden\textsuperscript{833}. According to Damrau, treatment is necessary if the BAT value of 200 µg/l is exceeded\textsuperscript{196}. Kleber considers the upper limit of normal to be 30 µg/24h\textsuperscript{483}.

\subsection{7.2.1.4.3 Mobilization test according to Aposhian (oral)}

Aposhian describes a mobilization test with 300 mg DMPS orally, independently of the body weight, for mercury, arsenic or lead\textsuperscript{35,36,602}:

1. Fasting and collecting of the urine overnight for determining the basal level.
2. After completely emptying the bladder, administration of 300 mg Dimaval\textsuperscript{®} (DMPS) orally.
3. Drinking sufficient water for about 500 ml urine to be excreted in the next 6 hours.
4. Light meal after 4 hours.
5. Collection of the urine up to 6 hours after administration of DMPS. Completely empty the bladder at the end.

\[ \text{Limits are not given by Aposhian.} \]
7.2.1.4.4 Mobilization test according to Daunnderer (oral)

Daunnderer describes a mobilization test with oral administration of DMPS:

1. Determination of the basal level of mercury in the morning urine (in addition zinc to exclude deficiency).
2. Administration of 300 mg DMPS on a fasting stomach with ½ l mineral water.
3. Collection of spontaneous urine 2 - 4 hours after administration of DMPS.
4. A mercury concentration of more than 16 µg/l or 20 µg/l in the spontaneous urine indicates a mercury overload.

7.2.1.4.5 Mobilization test according to Gerhard (oral)

Gerhard describes a mobilization test with 10 mg DMPS/kg BW orally for mercury and other heavy metals such as As, Cd, Cu, Pb:

1. Collection of morning urine after 12 hours’ fasting
2. Ingestion of 10 mg DMPS/kg body weight orally on an empty stomach
3. Drink 1 - 2 liter fluids in the following 3 hours
4. Collection of spontaneous urine 2 - 3 hours after administration of DMPS
5. The values given by Daunnderer for the i.v. test are proposed as limits. According to Schulte-Uebbing, the following limits apply: Hg 100, Pb 80, Cu 2000, Cd 5 µg/g creatinine.

7.2.1.5 Results of the DMPS mobilization test

In mercury burden from amalgam, an increased mercury excretion in the urine could be achieved by administration of DMPS. The mercury excretion before and after mobilization correlated with the number or the surface area of the amalgam fillings. Coproporphyrin in the urine (a measure of Hg burden of the kidneys) correlated with the excretion of DMPS, but not before mobilization. No correlation was found between the mercury level in the hair and the heavy metal in the urine before or after mobilization. Similarly, no correlation was found between the mercury level in the hair and the number of amalgam fillings.

<table>
<thead>
<tr>
<th>Urine I</th>
<th>Hg</th>
<th>Zn</th>
<th>Cu</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest value</td>
<td>0.1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Highest value</td>
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<td>1180</td>
</tr>
<tr>
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<tr>
<td>n</td>
<td>154</td>
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</table>

<table>
<thead>
<tr>
<th>Urine II</th>
<th>oral</th>
<th>i.v.</th>
</tr>
</thead>
</table>

Urine excretion of Hg (µg/h) after mobilization with 300 mg DMPS orally (Amalgam score = sum of amalgam surfaces).
<table>
<thead>
<tr>
<th></th>
<th>Hg</th>
<th>Zn</th>
<th>Cu</th>
<th>Hg</th>
<th>Zn</th>
<th>Cu</th>
</tr>
</thead>
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<tr>
<td>Lowest value</td>
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<td>12.5</td>
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<td>13</td>
<td>25</td>
<td>13</td>
</tr>
<tr>
<td>Highest value</td>
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<td>3610</td>
<td>1450</td>
<td>1755</td>
<td>32540</td>
<td>10150</td>
</tr>
<tr>
<td>Mean</td>
<td>21.8</td>
<td>944</td>
<td>350</td>
<td>267</td>
<td>8595</td>
<td>1545</td>
</tr>
<tr>
<td>n</td>
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<td>36</td>
<td>36</td>
<td>83</td>
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</tbody>
</table>

The mercury, zinc and copper levels in the urine before (Urine I) and after (Urine II) administration of DMPS (µg/g creatinine)<66>

Investigations with the mobilization test showed that with homeopathic therapy the heavy metal load of the body is not reduced<127,215,317,357,565,566,753>, although the symptoms improved at least temporarily<127,316,317,565,566,753>. One patient excreted 468 µg Hg/g creatinine after two cycles with the entire potency series of homeopathic silver amalgam and another 126.5 µg/g creatinine<565>. 
<table>
<thead>
<tr>
<th></th>
<th>DMPS</th>
<th>Number (n)</th>
<th>Before DMPS</th>
<th>After DMPS</th>
<th>Unit</th>
<th>Increase</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Without amalgam</td>
<td>300 mg orally</td>
<td>15</td>
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<td>2.8</td>
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<td>28</td>
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<td>1.3</td>
<td>1</td>
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<td>1015</td>
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<td></td>
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<td>5.1</td>
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<td>43</td>
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<td>2.6</td>
<td>1</td>
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<td>405</td>
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<td>1</td>
<td>6</td>
<td>3</td>
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<td>5</td>
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<tr>
<td></td>
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<td>1</td>
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<td>809</td>
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<td>1</td>
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<td></td>
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<td>1.1</td>
<td>3.9</td>
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</tr>
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<td></td>
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<td>39.1</td>
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<td>22</td>
<td>361</td>
</tr>
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<td>Amalgam removed</td>
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<td>1.4</td>
<td>10.7</td>
<td>4</td>
<td>8</td>
<td>361</td>
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<td>41.3</td>
<td>4</td>
<td>30</td>
<td>881</td>
</tr>
<tr>
<td>With amalgam</td>
<td>300 mg orally</td>
<td>10</td>
<td>0.7</td>
<td>17.2</td>
<td>2</td>
<td>25</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21</td>
<td>0.7</td>
<td>4.9</td>
<td>1</td>
<td>7</td>
<td>1016</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18</td>
<td>0.8</td>
<td>4.4</td>
<td>6</td>
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<td>639</td>
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<tr>
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<td>0.9</td>
<td>6.4</td>
<td>1</td>
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<td>13</td>
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<td>8.2</td>
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<td>19.5</td>
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<tr>
<td></td>
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<td>Hg cream user</td>
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<td>708</td>
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<tr>
<td>Dentist</td>
<td>300 mg orally</td>
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<td>1.5</td>
<td>13.2</td>
<td>1</td>
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<td>130</td>
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<td>19.1</td>
<td>1</td>
<td>21</td>
<td>1016</td>
</tr>
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<td>Workers</td>
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<td>6.4</td>
<td>134.2</td>
<td>5</td>
<td>21</td>
<td>806</td>
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<td></td>
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<td>125</td>
<td>175</td>
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<td>639</td>
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<tr>
<td></td>
<td></td>
<td>11</td>
<td>333</td>
<td>4282</td>
<td>4</td>
<td>13</td>
<td>602</td>
</tr>
</tbody>
</table>

**Mercury excretion in the urine before and after administration of DMPS**

(Unit: 1 = µg Hg/24h; 2 = µg Hg/9h; 3 = µg Hg/6h; 4 µg Hg/l; 5 µg Hg/g creatinine; 6 = µMol Hg/g creatinine)

Conversion factors for mercury$^{84+}$:
- 1 µg = 4.985 nmol; 1 µg/l = 4.985 nmol/l;
- 1 ppb = 4.985 nmol/l; 1 µg/dl = 49.85 nmol/l; 1 µg/g Creatinine = 0.564 nmol/mmol Creatinine
A lead overload could be demonstrated by means of the DMPS test in a woman who had a stall on the street with high traffic density<sup>469</sup>.

A heavy metal burden because of the amalgam in the mother was detected in three children<sup>52,31</sup>. The DMPS mobilization test (4 mg DMPS/kg BW i.m., spontaneous urine) showed especially high mercury and copper values on examination of 200 infants and toddlers when their mothers' teeth were treated with amalgam during pregnancy<sup>136,137</sup>.

Employees of a dental practice had a higher burden because of their professional handling of amalgam<sup>121,130,218,570</sup>. Dental assistants had higher values than the dentist<sup>181,756</sup>. In students of dentistry slightly raised mercury values were found after 6 months' phantom course in the placing of amalgam fillings. The increase was, however, negligible in comparison with the background load from their own fillings<sup>413</sup>.

The highest values were exhibited by workers in a mercury processing factory<sup>408,805</sup>. 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 depot<sup>402</sup>.

Cabelkova et al.<sup>153</sup> found a rise in mercury excretion of 200-fold after a single dose of DMPS i.m. in previous mercury exposed persons in comparison with controls who only had an increase of 20-fold.

Stantschew<sup>879</sup> investigated 1156 former mercury-exposed workers with a spontaneous mercury excretion in the urine of at least 20 µg/l. The determination was carried out on the total overnight urine. A mercury depot was assumed if the mercury elimination after the first DMPS injection exceeded a value of 250 - 300 µg/l and after a second injection even higher mercury concentrations were found in the urine. A maximum urine value of 11,200 µg/l was achieved in the urine. After a further 8 and in exceptional cases after 15 DMPS injections even the largest mercury depots were decorporated. With the DMPS mobilization test it was also possible to detect exposure in the past. Even months after the cessation of exposure, the mercury concentration in the urine after administration of DMPS rose drastically in mercury exposed workers<sup>482</sup>. In investigations of workers the Hg elimination 7 to 56 months after leaving the work increased on mobilization with DMPS from 4.3 to 34 µg/day<sup>482</sup>. Autopsy investigations in a previous mercury worker confirmed that mercury loads are retained for a very long time in the body. 17 years after mercury poisoning through an accident (treated with D-penicillamine) and 14 years after leaving the company, raised mercury values could be found in the brain, lungs and kidneys after he had died<sup>687</sup>.

While no relationship between spontaneous mercury excretion in the urine, clinical picture or absorbed quantity of mercury existed on poisoning with ethyl mercury, there
was a correlation between DMPS provoked mercury excretion and the severity of the clinical symptoms of poisoning.<ref>1022</ref>

<table>
<thead>
<tr>
<th>Classification of poisoning</th>
<th>Number (n)</th>
<th>Spontaneous excretion in the urine without DMPS (µg/l)</th>
<th>Hg excretion in the urine after administration of DMPS (µg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>Scatter</td>
</tr>
<tr>
<td>Mild</td>
<td>26</td>
<td>28</td>
<td>0 - 60</td>
</tr>
<tr>
<td>Moderate</td>
<td>10</td>
<td>69</td>
<td>8 - 180</td>
</tr>
<tr>
<td>Severe</td>
<td>4</td>
<td>39</td>
<td>8 - 80</td>
</tr>
</tbody>
</table>

**Correlation of severity of clinical symptoms and mercury poisoning with mercury excretion in the urine before and after administration of DMPS<ref>1022</ref>**

In investigations of patients with amalgam the findings were non-uniform. Stenman et al. found higher excretion in patients with severe symptoms.<ref>881</ref> Daunderer assumes a linear correlation of mercury excretion and severity of the poisoning.<ref>232</ref> Others, in contrast, found no relationship.<ref>805</ref> Patients without symptoms had the same mobilization values as patients with symptoms.<ref>805</ref>

No significant relationship was found in women with endometriosis between the occurrence of the disease and heavy metal burden.<ref>341</ref>

<table>
<thead>
<tr>
<th>Element</th>
<th>With endometriosis</th>
<th>Without endometriosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>As</td>
<td>30</td>
<td>71</td>
</tr>
<tr>
<td>Cd</td>
<td>32</td>
<td>74</td>
</tr>
<tr>
<td>Cu</td>
<td>29</td>
<td>73</td>
</tr>
<tr>
<td>Hg</td>
<td>31</td>
<td>75</td>
</tr>
<tr>
<td>Pb</td>
<td>30</td>
<td>73</td>
</tr>
</tbody>
</table>

**Heavy metal excretion in the urine before (Urine I) and after (Urine II) administration of DMPS (mobilization test according to Gerhard) <ref>341</ref>**

Higher mercury levels in blood, urine and hair were measured in patients with idiopathic Parkinsonism.<ref>776</ref> In patients with Alzheimer’s disease, in addition to raised mercury levels there were lower zinc and selenium levels (the natural antagonists of mercury).<ref>776</ref> In patients with increased fractures due to osteomalacia an increased cadmium content was found.<ref>237</ref>

In children with congenital hearing deficiencies a heavy metal burden via the mother (amalgam work during pregnancy) was demonstrated.<ref>318</ref>

### 7.2.2 Release of mercury from amalgam

About 35 million amalgam fillings, equivalent to 20 tons of mercury, are implanted per year in Germany<ref>668,648,817</ref>, and in the USA it is 160 million fillings<ref>114,335</ref>. The average number of fillings for German citizens is about 12<ref>316</ref>. People with amalgam fillings have
up to 10 g of mercury in their mouth which is bound only via the crystal structure of the amalgam<sup>104,414</sup>.

### 7.2.2.1 Composition of amalgam fillings

Amalgam is the name for liquid or solid alloys of mercury with metals. It is derived from the Arabic almalgam and means "emollient ointment". All the amalgams used in dentistry, even the new non-γ<sub>2</sub>-containing amalgams, are a mixture of about 50 % liquid mercury and about 50 % "alloy powder" or "filings"<sup>35,66,98,104,127,228,229,240,265,327,338,357,468,482,854</sup>. The alloy powder varies in composition according to supplier<sup>327</sup>. It usually consists of about 34 % silver, 9 % tin, 5 % copper and 2 % other constituents<sup>240,716</sup>.

After mixing the two components, a plastic material is first produced which can be readily molded. It hardens rapidly through the formation of an amalgam between the mercury and alloy powder and the formation of mercury containing crystalline metal phases<sup>240,338,681,745,859,952</sup> and is then capable of withstanding the relatively high chewing pressure in the molar region. Nowadays, practically only non-γ<sub>2</sub>-amalgams are used, in which the especially corrosion sensitive γ<sub>2</sub>-phase does not develop during hardening<sup>338,482,648,654,876,952</sup>.

To reduce environmental pollution by mercury from amalgam, all dental practices were required at the start of the 90s to install amalgam separators as part of the Waste Water Regulations according to Section 7a of the "Wasserhaushaltsgesetz" [Water Conservation Act]. In this way, a reduction of amalgam burden in waste water of at least 95 % was to be achieved<sup>570,644,845</sup>.

### 7.2.2.2 Release of mercury from amalgam

It was assumed until about 15 years ago that the mercury was firmly bound on hardening of the amalgam<sup>115,265,701</sup>, whereas it is nowadays generally recognized that amalgam fillings continuously release mercury and contribute to a measurable extent of the mercury load in humans<sup>45,265,480,505,681,753,859,876,1032</sup>. “In this respect, it should be especially remembered that when an amalgam filling is placed, a source of mercury is implanted which releases mercury continuously throughout the entire period of retention, i.e. generally for many years”<sup>268</sup>.

γ<sub>2</sub>-containing amalgams release more mercury than γ<sub>2</sub>-free products<sup>1028</sup> and unpolished fillings more than polished fillings because of the much greater surface area<sup>17</sup>. Furthermore, amalgam was previously inserted without any basal filling, which favored uptake of the mercury by the body<sup>209</sup>.
The mercury is released as vapor and also passes into the saliva in a metallic and ionized form<sup>405</sup>. In the body, elementary mercury can be partially oxidized<sup>17,203,392</sup> and inorganic mercury partially reduced<sup>372,570,627</sup>. It is disputed whether bacteria in the mouth or intestines is capable of converting inorganic mercury to organic methylated mercury<sup>664</sup>. While some workers assume that this is so<sup>203,204,206,226,228,229,311,344,348,364,414,744,821,929</sup>, others do not find any evidence<sup>392,396</sup>. The release of the heavy metal is increased:

- **mechanically** by chewing, bruxism and teeth cleaning<sup>123,228,405,480,654,744,753,798</sup>. While 1.9 µg Hg/m<sup>3</sup> was measured in the expired air with intact amalgam fillings, the value after teeth cleaning rose to 8 and after chewing gum to 13.7 µg Hg/m<sup>3</sup><sup>663,964</sup>. Without mechanical load, 9 ng were released per minute and on chewing gum 76 - 98 ng mercury per minute<sup>682</sup>. The mercury content in the saliva after 10 minutes chewing gum increased from 4.9 to 12.95 µg/l. In patients without amalgam fillings only 0.4 µg Hg/l was measured in the saliva<sup>668a</sup>. On drinking hot lemon juice, the mercury level in the blood rose from 0.19 to 0.53 µg/l<sup>516</sup>. 

- **chemically** by acids, hot meals or drinks<sup>123,228,480,654,744,798</sup>, and fluorine containing toothpaste<sup>744,798</sup>. The mobilization test also showed higher values<sup>666</sup>. The daily release rate of fresh amalgam fillings is 1 - 5 µg Hg/cm<sup>2</sup>. After 5 days this falls to 0.1 - 0.3 µg Hg/cm<sup>2</sup><sup>338</sup> (passivation<sup>413</sup>). 

- **electrochemically** through contact of amalgam with noble metals<sup>123,480,627,744,798</sup>. Especially large quantities of mercury are released on insertion and polishing of new fillings and on boring out of old fillings<sup>232,480,644</sup>. 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 even as high as 4 µg/l<sup>668a</sup>. The mobilization test also showed higher values<sup>666</sup>. After removal of amalgam fillings, the mercury level of the blood fell<sup>682</sup>. 

Increased mercury and silver levels were detected in the feces after insertion and removal of amalgam fillings<sup>744</sup>. The cofferdam provided only partial protection against mercury uptake<sup>258,535</sup>. The load can also be kept lower by processing well, extracting vapor, underfilling, polishing and avoidance of various metals in the mouth<sup>127</sup>. After removal of amalgam fillings, the mercury level of the blood fell<sup>392,393</sup>. 

Indications of the release rate of mercury from amalgam fillings is provided by the chewing gum or saliva test<sup>345,348,375,480,493,716,718,798,993</sup>. It is important that the test is carried out under standardized conditions (not directly after cleaning the teeth, chewing gum, drinking hot or acid drinks or amalgam processing)<sup>668</sup>. The chewing gum test, however, does not provide any indication of the uptake of mercury from the saliva by the body<sup>480</sup>. 

<table>
<thead>
<tr>
<th>Amalgam fillings</th>
<th>Minimum value (µg/day)</th>
<th>Maximum value (µg/day)</th>
<th>Mean (µg/day)</th>
<th>Number of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>0.01</td>
<td>283</td>
<td>20</td>
<td>61</td>
</tr>
<tr>
<td>4-6</td>
<td>0.07</td>
<td>371</td>
<td>27</td>
<td>183</td>
</tr>
<tr>
<td>7-9</td>
<td>0.01</td>
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<td>59</td>
<td>330</td>
</tr>
<tr>
<td>10-12</td>
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<td>3,255</td>
<td>77</td>
<td>442</td>
</tr>
<tr>
<td>13-20</td>
<td>0.21</td>
<td>20,315</td>
<td>175</td>
<td>373</td>
</tr>
</tbody>
</table>

**Quantities of mercury (µg/day) measured in the saliva in relation to the number of amalgam fillings**<sup>65</sup>
For comparison: the limit for mineral and table waters in 1984 was 1 µg/l and in 1986 the limit for drinking water was reduced from 4 to 1 µg/l.<ref>281</ref>

### 7.2.2.3. Uptake of mercury in the body

The mercury released from amalgam is partially absorbed and deposited in the body. The BGA writes, „Amalgam fillings release mercury and thus contribute to the overall load of the body with mercury as well as by foodstuffs, water and air<sup>289</sup>“. The heavy metal is not continuously accumulated, but a steady state develops between uptake and excretion. The depots in the body depend on the number of amalgam fillings<sup>392,393</sup>.

Various routes have been suggested for the uptake of mercury from amalgam.

- Via the lungs
  by inhalation of vapor (absorption rate > 80 %<sup>133,405,480,798,963,964</sup>) or dust<sup>127</sup>.

- Via the gastrointestinal tract
  Swallowing of the mercury released by wear, corrosion or chemically released mercury<sup>98,127,343,414,627,716,744,753</sup>. Inorganic mercury is absorbed at a rate of 2 - 50 % in the intestines<sup>133,405,480,627,965,966</sup>.

- Via the tooth roots
  Direct transport of the mercury from the amalgam via the tooth root and the jaw bones has been suggested, especially in the absence of underfilling<sup>98,127,716,744,753</sup>.

- Via the olfactory nerve
  Some people suggest retrograde axonal transport of the mercury along the olfactory nerve directly into the brain<sup>98,227,344,414,480,744,753</sup>. For others, there is insufficient evidence for direct transport of mercury into the brain<sup>684</sup>.

By adding radioactive mercury to amalgam fillings it could be shown in sheep that mercury from the tooth amalgam is taken up in the body and is deposited especially in the liver and kidneys<sup>390</sup>. Similarly results were obtained with guinea pigs<sup>315</sup> and monkeys<sup>199,389</sup>. Autopsies of corpses have shown a significant relationship between the concentration of inorganic mercury in the renal cortex, liver and brain areas and the number of teeth filled with amalgam<sup>265,480,766</sup>. The mercury found in the occipital cortex consisted of 77 % inorganic Hg<sup>776</sup>. In pregnant women, the mercury passes from the mothers’ fillings to the fetus<sup>265,480,1032</sup>. For this reason, amalgam fillings should not be inserted during pregnancy<sup>480,1034</sup>. Increased values were found in the dental pulp<sup>811</sup>. In teeth without amalgam fillings, 0.75 µg/g were found and in teeth with amalgam fillings 25.7 µg/g<sup>688a</sup>.

In the meantime it is known that amalgams can contribute considerably more to the overall load than other sources (food, beverages)<sup>265,378,805,904,1015</sup>. In addition to mercury, the amalgam fillings also release silver, tin and copper<sup>228,229,664</sup>.

<table>
<thead>
<tr>
<th>Source</th>
<th>Hg vapor</th>
<th>Inorganic Hg</th>
<th>Organic Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>0.03</td>
<td>0.002</td>
<td>0.008</td>
</tr>
<tr>
<td>Fish</td>
<td>0</td>
<td>0.6</td>
<td>2.4</td>
</tr>
<tr>
<td>Other foods</td>
<td>0</td>
<td>3.6</td>
<td>0</td>
</tr>
<tr>
<td>Drinking water</td>
<td>0</td>
<td>0.05</td>
<td>0</td>
</tr>
<tr>
<td>Amalgam</td>
<td>3.8 - 21</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Especially high levels of mercury (increased by 5- to 10-fold) were found in various organs of members of the staff of dental practices. This is confirmed by dust measurements in dental practices. The heavy metal content of the dust increased with the number of processed fillings. Even 15 years after retiring from the profession, high values were still found in autopsies of dentists.

The individual mercury loads fluctuate very markedly. Women exhibited higher levels than men after the mobilization test according to Daunderer. In contrast, no sex specific dependency was found on autopsy. This discrepancy cannot at present be explained.

Generally, the mercury load from amalgam is less than that which is measured in workers from mercury processing facilities. No pathological changes could be detected in many workers occupationally exposed to mercury.

The amount of mercury released increases on average with the number of amalgam fillings. In individual cases, however, there may be marked differences. Thus, individual patients with many fillings may have lower mercury levels than patients with few fillings. The mercury load for the same number of amalgam fillings varies by more than a factor of 10. In a group of 643 patients, 51% of those with amalgam fillings had values of less than 50 µg Hg/g creatinine in the DMPS mobilization test.

7.2.2.4. Effects of absorbed mercury

"Toxicity is not a substance property, but a quantity problem." The statement "mercury burden" is also in the first place an analytical result. The question must therefore be: is the amount of mercury taken up overall by humans sufficient to initiate toxic reactions? In addition to the mercury from amalgam, the background load from food and the environment must also be taken into account. In addition, other constituents of the amalgam or environmental burdens may cause symptoms. The synergistic effects of various toxins must also be considered.

Controversy about the possible harm of amalgam began soon after this medicinal product started to be used (1826 in the USA) and has lasted in the meantime for more than a 100 years.
It is undisputed that amalgam can cause impairment of taste as well as allergic and lichenoid reactions with various clinical symptoms.\(^{227,480,482,648,668a,876}\). In contrast, the possible toxic consequences of this permanent burden are a matter of very controversial discussion.\(^{66,98,141,322,376,480,627,716,819,993}\). The WHO has ascertained that there is no value that can be given up to which mercury load is harmless.\(^{670}\). The BfArM has deleted the sentence, „This is not associated with any risk to health“ in its notice on the 21st July 1995 from the previous data sheet on \(\gamma\)2-free amalgams. „For reasons of prophylactic health protection“ the mercury uptake in the body should be kept as low as possible.\(^{480,1032}\).

Many people consider amalgam to be at present the best available filling material and to be toxicologically safe.\(^{333,391,701,805}\). The mercury levels found are below the toxicological limits.\(^{14,115,411,809,1028}\). For them there are no scientific investigations which demonstrate an unjustifiable risk from amalgam fillings.\(^{314,413,469,627,681,878,1032,1033,1034}\). Opponents to amalgam are often accused of "playing on anxiety".\(^{150}\). The symptoms described by the patients have been diagnosed as psychiatric findings or psychological symptoms.\(^{32,321,411,413,510,511,533,627,1000}\). The positive effects of amalgam removal are interpreted as psychoso-matic or placebo effects.\(^{480}\). An exchange of intact amalgam fillings is not necessary from the toxicological point of view.\(^{391,628}\). Mercury poisoning is only rarely observed in dentists.\(^{811}\).

Others in contrast call amalgam "poisonous waste" that should be removed in every case.\(^{513}\). "Damage to health is not uncommon".\(^{993}\). Even deaths have been attributed to amalgam.\(^{217,220}\).

Every patients reacts differently.\(^{516,317}\). There are no typical symptoms of intoxication.\(^{582,798,993,1030}\). Many syndromes have been associated in the literature with amalgam, but logical case histories have been published for only a few syndromes.

- Allergies\(^{123,193,210,222,234,316-318,414,618,716,834,1029}\)
- Alzheimer's disease\(^{216,227,480,776,798}\)
- Anaemia\(^{222,654}\)
- Antibiotic resistance\(^{480}\)
- Aphthous ulcers\(^{121,320,627,654,798}\)
- Loss of appetite\(^{414,798}\)
- Asthma, bronchitis\(^{123,316-318,320-323,654,798}\)
- Abdominal pain, diarrhea, ulcerative colitis, gastroenteritis, nausea\(^{123,234,204,219,226,236,316,357,414,483,682,753,798,834,1029,1030}\)
- Disorders of gait, ataxia\(^{123,228}\)
- Depression, anxiety\(^{123,127,193,204,210,227,238,234,238,295,316-318,320-323,357,414,483,654,715,716,753,798,1029,1030}\)
- Skin reactions, eczema, exanthema, neurodermatitis\(^{123,193,316-318,320-323,414,483,682,654,682,798,1029}\)
- Loss of hair, alopecia\(^{123,193,316-318,320-323,439,551,654,798,1040}\)
- Hormone disorders, menstruation problems, infertility\(^{340,343,346,347,351,480,708,834,835,993}\)
- Hearing disorders, inflammation of the auditory channel, otitis\(^{193,204,222,238,318,321,323,357,654,834}\)
- Susceptibility to infections, effects on the immune system\(^{123,127,204,210,227,222,227,238,234,238,316,317,320-323,357,414,514,551,618,716,753,798,834,916,929,1029}\)
- Cardiovascular reactions, cardiac arrhythmias\(^{123,222,316,317,414,480,798}\)
- Poor concentration, disorders of memory, forgetfulness\(^{193,204,210,222,227,228,234,239,318,321,322,357,361,414,566,798,916,1029,1030}\)
- Headaches, migraine\(^{65,104,123,140,193,204,210,222,227,228,234,238,318,321,322,357,361,414,566,798,916,1029,1030}\)
- Multiple sclerosis (MS)\(^{216,228,232,234,328,357,480,798}\)
• Cancer, malignoma<207,228,232,357>
• Paralyses<123,193,222,654>
• Metallic taste<316,317,320,322,323,361,414,484,798,1029>
• Parkinson's disease<480,776>
• Tiredness, weakness, loss of drive<123,193,204,210,222,228,238,316,317,322,357,361,414,484,566,763,798,1029,1030>
• Complaints in the muscles and joints<123,193,204,210,222,227,228,239,357,753,798,834,916,1029,1030>
• Nervousness<123,193,204,210,222,227,234,316,317,753,916,993>
• Neuralgia<113,654,916>
• Kidney damage<316,317,322,323,480,993>
• Parodontosis, gingival bleeding<204,414,654,753>
• Chronic pharyngitis<320>
• Mycoses<210,916>
• Sudden child death<136,137>
• Irritability, aggressiveness, restlessness<127,193,222,654,716,716,798>
• Rheumatic diseases<252,414,798>
• Insomnia<123,193,234,204,210,222,227,228,239,316,317,357,654,715,716,798,993,1029>
• Chronic rhinitis<119,320,322,323,798>
• Dizziness<85,204,210,222,228,316,317,320,322,323,375,414,798,834,1030>
• Sweating<65>
• Visual disorders<123,193,204,222,228,316,317,357,414,654,798,834,993>
• Selenium and zinc deficiency<229,320,325,480,712,753,929>
• Chronic sinusitis<123,316-318,320-323,654,798>
• Salivation<65,484,753>
• Speech disorders<127,193,316,317,715,716>
• Tetany<123,316,317,320,323,654>
• Tinnitus, ringing in the ears<316,317,320,323,361>
• Chronic tonsillitis<127,318,320-323,654,798>
• Shakiness, tremor<85,123,127,193,204,210,222,227,228,234,716,753,798,834,1029,1030>
• Burning tongue<484,798>

It can be assumed that not everyone is affected by amalgam fillings<85,127>. Often it is only a subclinical load<85>. Thus, patients tolerate amalgam if sufficient glutathione-S-transferase (GST) is present<204>. If clinical symptoms occur, then amalgam is not always the sole cause<217,582>. Psychosomatic involvement has been suggested<204,338,582>. The heavy metal load may also be combined with a deficiency in trace elements (zinc and selenium), which in turn can cause symptoms<204,320,325,618,712,929>.

The claim that uncertain symptoms are caused by amalgam can in the last resort neither be clearly proven nor rejected<66>. In children, too, there is no confirmed evidence that increased mercury load can lead to disorders of development and damage<265,649,676,677>. In children, too, there is no confirmed evidence that increased mercury load can lead to disorders of development and damage<265,649,676,677>. The reason for this is the long latency period<217>. "As a result of the wide scatter in sensitivity of people with amalgam fillings, the WHO does not rule out at the individual level (i.e. on considering the individual case) that there may be a relationship to disorders of well-being and health"<648>. In this situation, only careful follow up of patients by the family doctor can help<65>. Everyone must decide for themselves<322>.

It is problematical 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<150,878>. The same applies to doctors who see amalgam poisoning behind every disease and neglect other necessary treatments<150,878>. The possibility of heavy metal poisoning should, however, be considered if no other organic or psychological cause can be found<322,582,798>. 

It is problematical 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<150,878>. The same applies to doctors who see amalgam poisoning behind every disease and neglect other necessary treatments<150,878>. The possibility of heavy metal poisoning should, however, be considered if no other organic or psychological cause can be found<322,582,798>. 

- I 20 -
7.2.3. Cleaning up of amalgam and mobilization therapy

So far only occasional case reports have been published on the clinical effects of chronic poisoning with heavy metals, e.g. from amalgam. Critics complain, and for some papers justifiably, that there are often very few pieces of data in some of these publications and occasional fixation on amalgam as the sole cause.

Even after removing amalgam fillings, there are still mercury depots in the body and these may persist for 1 - 2 years. But rapid removal of the mercury depot was also observed without DMPS administration. The necessity for subsequent DMPS therapy is a matter of controversial discussion. Some consider it only necessary for severe cases, others consider it to be generally necessary. Careful risk benefit assessment should take place in every case.

In severe cases, the administration of DMPS before removing the amalgam is recommended to empty the "long standing stores". Others recommend in these cases the removal of amalgam under DMPS protection, e.g. by administration of 100 mg DMPS 2 hours before boring or 1 capsule each on the day before, during and after the work on the amalgam.

The results of removing amalgam with subsequent DMPS therapy varied. In one study with 24 subjects (6 men and 18 women) first placebo capsules and then DMPS capsules were administered before and after amalgam removal. In two participants in whom allergy to amalgam was demonstrated, permanent improvement of the symptoms was achieved by removing the amalgam fillings and mobilization therapy. In the other subjects, no permanent improvement of the symptoms was detectable on amalgam removal and administration of DMPS (1 capsule t.i.d. for 3 days). In some there was even a temporary subjective improvement of symptoms after placebo.

Other authors, in contrast, found positive results. "It's amazing how many diseases suddenly disappear when amalgam fillings are removed".

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.

The inflammation of the auditory channel in one female patient deteriorated during amalgam removal by a dentist (increase in mercury exposure through amalgam removal). The woman became free of symptoms on subsequent DMPS treatment. The loss of hair in another female patient also deteriorated initially during amalgam removal. On completion of the DMPS treatment there was no loss of hair any longer.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>References</th>
<th>798</th>
<th>414</th>
<th>209</th>
</tr>
</thead>
<tbody>
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<td>Allergies</td>
<td>65 %</td>
<td>52 %</td>
<td>45 %</td>
<td></td>
</tr>
<tr>
<td>Abdominal pains</td>
<td>63 %</td>
<td></td>
<td>73 %</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>80 %</td>
<td></td>
<td>76 %</td>
<td></td>
</tr>
<tr>
<td>Memory disorders</td>
<td>85 %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of hair</td>
<td>59 %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Susceptibility to infections</td>
<td>80 %</td>
<td></td>
<td>61 %</td>
<td></td>
</tr>
<tr>
<td>Headaches</td>
<td>73 %</td>
<td>78 %</td>
<td>85 %</td>
<td></td>
</tr>
<tr>
<td>Symptom</td>
<td>Before</td>
<td>After</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------</td>
<td>-------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiredness, loss of drive</td>
<td>70 %</td>
<td>88 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscular/joint pains</td>
<td>84 %</td>
<td>60 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervousness</td>
<td>77 %</td>
<td>71 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>75 %</td>
<td>84 %</td>
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<td></td>
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<td>Dizziness</td>
<td>48 %</td>
<td>71 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>71 %</td>
<td>85 %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Improvement of clinical symptoms after removal of amalgam and subsequent clearance therapy (as % of patients)**

Occasionally observed spontaneous cures directly after removal of the amalgam are difficult to explain as potentiation of the symptoms is rather to be expected, because of the increased heavy metal burden on boring out the fillings. In these cases, there are possibly psychogenic causes.

The doses of DMPS, frequency of administration and duration of the treatment depended on the individual level of the burden and the individual symptoms of poisoning. In the treatment of mercury overload it is advisable to carry out interval therapy with pauses because DMPS primarily binds the extracellular heavy metal. The body should have time between the individual DMPS doses for redistribution of the mercury (e.g. from the brain into the extracellular depots).

Depending on the patients, DMPS is administered every 4 - 8 weeks or every three months. The dose is generally 250 mg DMPS parenterally or 300 mg DMPS orally. Other authors recommend for the treatment of mercury burden arising from amalgam fillings a dose of 1 capsule DMPS every other day or 3 capsules a week.

Daunderer proposes individual dosage depending on the mercury burden measured by the DMPS mobilization test:

- For values over 1000 µg/l urine 1 capsule Dimaval® (DMPS) weekly
- For values over 100 µg/l urine 1 ampoule DMPS every four weeks
- For values over 50 µg/l urine 1 ampoule DMPS every three months

The treatment is continued until the mercury levels after DMPS mobilization reached normal values. Improvement was achievable in 80 % of the patients within 3 - 6 months. Sometimes the therapy was necessary for one year and more.

**7.2.3.1. Pregnancy disorders**

In addition to other pollutants (e.g. chlorinated hydrocarbons) heavy metals such as Hg, As, Cd or Pb may influence fertility. Knowledge of the toxin is important for individual therapy. Amalgam is „a pollutant that may be assumed to be responsible for or contribute to many female complaints, but especially for sterility“. Women with hormonal disorders had, on average, a higher heavy metal burden. In many women with idiopathic disorders of the cycle, a burden with mercury could be demonstrated. Higher lead values were found in women with primary sterility. Women with a history of abortion exhibited higher lead and cadmium values, which possibly play a role via hormonal or immunological effects in
repeated miscarriages. A higher cadmium level was found in patients with uterine myomatosis. An influence on steroid metabolism has been suggested.

Gerhard et al. were able to show by investigations in 490 women that with high heavy metal loads (in the mobilization test > 500 µg Hg/g creatinine) spontaneous pregnancies no longer occurred. After clearance of the heavy metals, many women were spontaneously pregnant, even after 12 to 14 years all attempted therapy had been ineffective.

7.2.3.2. Headaches, migraine

Mercury induced headaches sometimes improved rapidly after DMPS treatment. In two female patients without psychological problems, as the authors explicitly emphasized, the headache regressed after removal of amalgam and clearance with DMPS.

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, the dizziness disappeared completely and the migraine is now only weakly present.

An incorrectly performed dental treatment with amalgam (absence of underfilling in five fillings) led in a previously healthy 15-year-old girl to diffuse symptoms such as headaches and joint pain, dizziness, forgetfulness and tiredness. 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. The appetite, body weight and activity of this teenager improved.

7.2.3.3. Loss of hair

147 women with alopecia diffusa and 132 women with alopecia areata were investigated with the DMPS mobilization test for heavy metal depots. An increased mercury load was found in 87 and 49 % respectively. The chewing gum test indicated the amalgam fillings as the cause of the heavy metal load. 9 % had arsenic, 2 % cadmium and 1 % lead burdens. In 80 % of the patients, changes in cellular immune response were diagnosed. The authors assume that the heavy metal load in addition to a burden of chlorinated hydrocarbons is one of the multifactorial causes of alopecia.
In female patients with alopecia, the amalgam fillings were removed after unsuccessful prior treatment. In 13 there was a regression of the alopecia, partially accompanied by regrowth of new hair\(^{44b}\). However, this study was criticized 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\(^{1019}\).

Other papers also reported new growth of hair after removal of amalgam\(^{1030}\). In a 28-year-old female patient alopecia developed about 2 months after removal of three amalgam fillings. Amalgam allergy was demonstrated in addition to mercury intoxication. After removal of the amalgam and mobilization therapy with DMPS the hair grew again\(^{713}\).

A 22-year-old women suffered from alopecia, migraine and "colds". The DMPS test showed mercury load of 496.2 µg/g creatinine. During removal of the amalgam the alopecia increased. The mercury level fell to 42.4 µg/g creatinine as the result of subsequent DMPS therapy. Alopecia, colds and migraine disappeared. The patient is free of symptoms\(^{323}\).

7.2.3.4. Immune system, allergies, skin reactions

Mercury from amalgam influences the immune system\(^{815-817,1029}\). In 14 students, increased mercury release was induced by chewing gum or drinking hot lemon drinks. The Hg level in the blood rose from 0.19 to 0.53 µg/l. The immune system showed clear reactions, e.g. the natural killer cells, T-helper cells and T-lymphocytes fell\(^{114}\). An improvement of the immune status could be demonstrated after DMPS administration\(^{819}\). Sometimes zinc and selenium were also administered\(^{815-817}\).

In 77 patients, positive effects on various parameters of the immune system that were altered by the mercury load were achieved by mobilization with DMPS and additional administration of zinc and selenium\(^{816}\).

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\(^{320}\).
A 6-year-old girl with asthmatic bronchitis and multiple allergies was completely free of symptoms after amalgam removal and clearance therapy.

A 33-year-old female patient with recurrent inflammation of the auditory canal showed a mercury load of 401.5 µg/g creatinine in the DMPS test. After amalgam removal and two clearance cycles with DMPS the value fell to 25.4 µg/g creatinine. The female patient is subjectively free of symptoms.

A 38-year-old business woman suffered since 1972 from hay-fever and since 1973 from allergies on the hands. In 1983 she developed a permanently itching skin eruption in the face and on both arms which did not improve in spite of dermatological treatment. In 1990, she developed a sun allergy. One year later the severely itching skin eruption spread slowly over the entire body. Allergies to various substances were diagnosed. In spite of antiallergic treatment and cortisone ointments, the state of the skin deteriorated. In January 1992, DMPS was injected for the first time. Thereafter, amalgam was removed and the DMPS therapy continued. The mercury level after DMPS fell from 810 to 14.1 µg/l. The extensive disfiguring eczema over the entire body including the face slowly disappeared. Only a slight, scarcely noticeable skin sensitivity has remained. The allergic symptoms are almost no longer detectable.

A 15-year-old girl suffered since childhood from hay-fever and allergies to house mite dust, flower pollen, rye, wheat, oats and cats' hair. A 3-year desensitization treatment had been without any notable success. Between 10 and 14 she began to have sneezing attacks with inflammations of the nasal sinuses, which were treated continuously with antibiotics. Throughout the year she had difficulties in concentration, headaches, indefinite feelings of anxiety, tiredness and fatigue. The patient was "irritated, grumpy and irate". Her mother was of the opinion that you could no longer talk to her. At 15 she developed dyspnoea for the first time. Two months later, in July 1995, the first DMPS mobilization therapy was carried out. This revealed a marked mercury burden. The allergic symptoms disappeared in a few days after the first treatment, "her mood was super" and the physical symptoms disappeared completely. Subsequently, the amalgam fillings were removed and renewed DMPS therapy carried out. The patient is free of symptoms to the present day.

<table>
<thead>
<tr>
<th></th>
<th>Number (n)</th>
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<th>Hg U2</th>
<th>Cu U1</th>
<th>Cu U2</th>
<th>Pb U1</th>
<th>Pb U2</th>
<th>Pd U1</th>
<th>Pd U2</th>
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<td>5</td>
<td>27</td>
<td>16</td>
<td>55</td>
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</tr>
</tbody>
</table>

**Heavy metal content of the urine before (U1) and after DMPS (U2) (5 ml i.v., U2 45 min after injection)**

In patients with atopic dermatitis or psoriasis, a burden of mercury, copper, lead and palladium was detected with the aid of the DMPS test. Through removal of amalgam and subsequent clearance treatment (administration of DMPS every 5 - 6 weeks) a significant improvement was achieved in most cases.

### 7.3. Other uses of DMPS

In the Western world, DMPS is used almost exclusively as an antidote for heavy metal poisoning. In the previous USSR, in particular, where DMPS has already been used
therapeutically since 1957, there are many publications in which the use of DMPS has been reported for various other indications. Most of the papers have only an English abstract, so that assessment of the success is not possible.

7.3.1. Scleroderma

30 patients with systemic scleroderma were treated with DMPS. 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. Another 168 patients were observed for 10 years. They were given 250 to 500 mg DMPS daily i.m. as the sole therapy, sometimes for more than 780 days. Positive effects in five and one patient are reported in further papers.

7.3.2. Alcoholism

Positive clinical effects were observed in the treatment of the effects of alcohol with DMPS. The combination of vitamins and DMPS produced improvement in alcoholic polyneuritis.

7.3.3. Atherosclerosis

Treatment of atherosclerosis with DMPS showed positive clinical effects. In 208 patients with coronary atherosclerosis, treatment with DMPS and a vitamin complex led to improvement of the symptoms, the pain often disappeared completely and the ECG parameters improved. The authors even recommended the treatment as prophylaxis in older and elderly patients.

7.3.4. Circulatory failure

The additional administration of DMPS, ATP and vitamins (vitamin B₁₂, folic acid, dexpantenol) was more effective in patients with circulatory failure than administration of strophanthin alone. The additional administration of DMPS also exhibited positive effects in patients with myocardial infarction.

7.3.5. Poisoning with cardiac glycosides

DMPS showed positive effects on poisoning with digitalis. Improvement was observed under DMPS in 68 patients with poisoning with cardiac glycosides. In a further 18, DMPS reduced the toxic action of cardiac drugs.

7.3.6. Diabetes

A positive effect on diabetic ketoacidosis was found in 26 patients. The concentration of SH groups in the plasma returned to normal as well as the activity of AP and
peroxidase^1021^*. In patients with diabetes mellitus an improvement with rise in SH concentration in the serum and potentiation of the insulin effect has been reported^842^.

7.3.7. Amyloidosis

26 patients with primary or secondary amyloidosis were treated with DMPS. Patients with nephrotic syndrome showed a tendential improvement of the serum proteins and of serum cholesterol. Proteinuria and chronic renal failure did not, however, improve^915^*. In 32 of 37 patients, improvement of secondary amyloidosis was found after 30 to 40 injections of DMPS^268^.

7.3.8. Miscellaneous

The administration of DMPS showed marked effects in 89 patients with psoriasis, eczema or limited neurodermatitis^693^.

80 % of patients with lupus erythematosus who were examined showed positive reactions to DMPS therapy^358^.

Positive effects were also observed in female patients with non specific inflammations of the genital organs^793^.

The administration of DMPS and penicillin improved hepatocerebral dystrophy in children^610^.

Streptomycin induced hearing disorders were prevented in 25 patients by prophylactic administration of DMPS^13^.

In 34 patients, one week’s treatment with DMPS showed positive effects on the kallikrenin-kinin system after renal operations^653^.

231 patients with hypertension were treated for 3 weeks with a DMPS injection (i.m.) daily^564,566^.

Positive clinical effects were also seen in the treatment of epilepsy, Parkinsonism, schizophrenia and polyarthritis^364,855,1018^.

7.4. Side effects

DMPS is a substance with low systemic and local toxicity and is generally well tolerated^45,237,286,310,322,440,469,883,927^, even on long-term use^52,262^.

No adverse drug reactions to DMPS are reported in most publications and unpublished case reports. Generally it is often explicitly pointed out that in the course of treatment no adverse drug reactions were observed. Adverse effects during DMPS therapy have only been reported occasionally. The following summary of adverse drug reactions include

- the adverse drug reactions described in the literature
- the adverse drug reactions given in unpublished case reports
- the spontaneous reports received by the HEYL company.
In addition to adverse effects that may occur because of the pharmacodynamic mode of action of DMPS, such as increased excretion of essential trace elements and cardiovascular reactions, skin reactions have been reported in particular.

In the adverse reactions reported during treatment, 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 adverse effects may also be the consequence of the heavy metal. Skin reactions have frequently been described as symptoms of mercury poisoning\(^{<125,129,614,638>}\). Thus, for example, gingivitis and exanthema developed in a patient with thiomersal poisoning during the course of the DMPS therapy which were not triggered off by the DMPS\(^{<723>}\).

Leucopenia is a symptom of mercuric chloride induced disease. A fall in leucocytes is also known for copper poisoning. The occurrence of fever (copper fever) has also been reported for this heavy metal. Nausea, headaches and changes of taste are side effects of various heavy metal intoxications\(^{<638>}\). Zinc deficiency may also be a direct consequence of heavy metal poisoning\(^{<753>}\).

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Ref.</th>
<th>Administration</th>
<th>Patients</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gerhard, I.</td>
<td>1992</td>
<td>353</td>
<td>oral</td>
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<tr>
<td>Schiele, R.</td>
<td>1990</td>
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<td>oral</td>
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<td>&lt; 3 %</td>
</tr>
<tr>
<td>Zander, D.</td>
<td>1992</td>
<td>1015</td>
<td>oral</td>
<td>29</td>
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<tr>
<td>Bannasch, L.</td>
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<td>Bittel, G.</td>
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<td>Lechner, J.</td>
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<tr>
<td>Zinecker, S.</td>
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<td>1029</td>
<td>i.v.</td>
<td>&gt;1,800</td>
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<tr>
<td>Bakir, F.</td>
<td>1976</td>
<td>78</td>
<td>i.m.</td>
<td>26</td>
<td>0.0 %</td>
</tr>
</tbody>
</table>

**Frequency of side effects to DMPS**

**7.4.1. Effects on mineral balance**

Chelate formation by DMPS takes place not only with toxic heavy metals, but also with physiological trace elements and can therefore lead to disorders\(^{<65,150,469>}\). As in animal experiments, increased zinc and copper excretion\(^{<4,101,115,118,178,291,320,323,324,440,469,516>}\) were found during the clinical use of DMPS. The excretion was, however, considerably less than with calcium edetate\(^{<178>}\). After withdrawal of the DMPS the effect stopped\(^{<51>}\).

Concentrations of zinc and copper in the plasma remained almost unchanged, however, during the course of DMPS therapy. No deficiency was observed\(^{<178,300,568,737>}\). 4½ years' DMPS therapy (300 to 800 mg DMPS orally per day) did not lead to any effect on the mineral balance\(^{<1,72>}\). Administration of 100 mg DMPS daily for more than a year in a child did not produce any trace element deficiency\(^{<725>}\). In a patient with acute mercury poisoning the zinc level remained in the normal range without substitution after about 600 ampoules of DMPS i.v. and about 400 capsules of DMPS orally\(^{<206>}\). The trace elements taken in with the food generally suffice to compensate for the increased excretion.
Either no or only minimum effects of DMPS were observed on iron, cobalt, manganese, magnesium, nickel or selenium<sup>52,204,440,599,1017</sup>. In a spontaneous report (1990) it was reported that in a patient in whom there were already symptoms of existing zinc deficiency they were potentiated by administration of DMPS. Substitution of the trace elements produced rapid improvement<sup>661</sup>. For this reason, the zinc level in particular should be monitored, especially on long term therapy. If necessary, the deficient trace element must be substituted in individual cases<sup>115,127,237,322,662,699</sup>. The zinc and DMPS should not, however, be given simultaneously<sup>667</sup>. General zinc administration is not necessary for DMPS therapy<sup>127</sup>. As the heavy metals can also have an effect on essential trace elements<sup>303</sup>, it is advisable to monitor the trace elements before starting treatment, especially in chronic poisoning. This applies especially to zinc as chronic heavy metal poisoning can produce zinc deficiency<sup>753</sup>. Zinc deficiency is noticeable through changes in taste, disorders of wound healing, dermatitides, exanthema or disorders of immune function. Copper deficiency is apparent in the form of connective tissue disorders, iron resistant anemia and osteopathy<sup>667</sup>.

7.4.2. Allergic reactions

Most of the adverse reactions to DMPS were allergic reactions<sup>127,222,226,228,229,232,269,322,421,469,614,681,806,926,975,1029</sup>, which occurred especially on long-term therapy<sup>421,815</sup>. This is possibly caused by an effect of the SH groups on the complement system<sup>967</sup>. They are generally of a mild nature<sup>322,421</sup> with symptoms such as itching, nausea, dizziness, fever, weakness, skin reactions (e.g. rash, urticaria) and mucous membrane reactions<sup>614,806</sup>. Raised body temperature<sup>269</sup> or shivering and fever<sup>109,972,974</sup> were probably allergically based. The occurrence of erythema exsudativa multiforme has been reported in individual cases<sup>704</sup>.

A Steven's-Johnson syndrome is reported to have occurred in four cases during DMPS therapy<sup>28,175,176,704</sup>. One patient had initially mild symptoms of DMPS intolerance without having to interrupt drug intake. The intolerance increased and finally made hospital admission necessary, where Steven's-Johnson syndrome was suspected<sup>665</sup>. However, the data on all four suspected cases are too few to enable any reliable relationship to be deduced. What is especially surprising is that the symptoms generally recovered within a very short time<sup>661</sup>. No cases of anaphylactic shock have so far been reported after administration of DMPS<sup>617</sup>.

The allergic reactions generally regressed after withdrawal of DMPS within 3 to 5 days without treatment<sup>699</sup>. Sometimes the exanthema also disappeared during continued treatment with DMPS<sup>681</sup>. Treatment could be continued in some cases after a pause in therapy<sup>269</sup> or under corticosteroid protection<sup>70</sup>. Massive reactions or longer duration of illness that made antiallergic treatment necessary (antihistamines and corticosteroids) occurred in only a few cases<sup>70,269</sup>.

7.4.3. Cardiovascular reactions
Cardiovascular reactions occurred only after parenteral administration of DMPS (especially on too rapid injection). It was seen as dizziness, weakness, nausea, palpitation and a feeling of oppression in the chest\(^{62,269,661,815,1022,1029}\). Two very labile patients out of 800 suffered collapse as the result of a transient fall in blood pressure\(^{232}\). In one spontaneous report, protracted collapse was reported after parenteral DMPS administration\(^{661}\).

### 7.4.4. Effect on the kidneys

The subacute renal toxicity of mercury is not potentiated by DMPS\(^{26}\). No changes in the renal parameters were measured in 10 patients given 100 mg DMPS t.i.d. for five days\(^{626}\). A 10-year follow up of 168 patients with scleroderma who received 1 - 2 ampoules DMPS daily for up to 780 days did not show any indications of renal toxicity\(^{269,359}\).

Up to now, one cases is known in which renal complications developed during DMPS therapy. A female patient who injected the contents of two thermometers i.v. with suicidal intent was only observed for 4 months as the mercury level did not exceed the BAT level of 200 µg/l in the urine. At an Hg level of 220 µg/l, treatment with 100 mg DMPS orally t.i.d. was started. One day later, acute renal failure developed with anuria and this required 14-days' hemodialysis. The DMPS therapy was withdrawn. Apparently, the DMPS had mobilized the stored mercury and flooded it into the kidneys in such quantities that acute renal failure was the consequence\(^{460}\). “In order to avoid renal sequelae it therefore appears necessary to carry out therapy with chelating agents (e.g. Dimaval) also in patients with low injection dose and absence of symptoms”\(^{383}\).

### 7.4.5. Other side effects

In isolated cases there was nausea and vomiting\(^{661,807}\), especially in patients with a delicate stomach on oral administration of DMPS.

In isolated patients, slight increases in transaminases were measured, which sometimes occurred for short periods or returned to normal values at the end of therapy. In some cases, the transaminases were already increased before starting therapy, so that the increase was not always associated with DMPS therapy\(^{108,178,429,469,661}\).

Intercurrent leucopenia towards the end of DMPS therapy for lead poisoning returned to normal after withdrawal of the therapy\(^{120}\). Leucopenia was also observed during treatment of poisoning with mercury\(^{861}\) and in a patient with Wilson’s disease\(^{972,974}\).

In one case each, headaches\(^{793}\), reversible rise in albumin in the urine\(^{793}\) and taste disorders\(^{974}\) were reported during DMPS therapy.

Further reactions during DMPS therapy have been reported especially in Russia and China: transient pain at the site of injection\(^{67}\), odor of hydrogen sulfide in two patients\(^{269}\), congestion of the conjunctiva\(^{420}\), loss of appetite in 4 patients\(^{1022}\) and changes in taste\(^{973}\).
7.5. DMPS in daily practice

7.5.1. When is DMPS indicated

As with all medicaments, careful risk-benefit considerations are necessary before administration of DMPS. The licensed fields of use for Dimaval® (DMPS) and DMPS-Heyl® are:

- Clinically manifest, chronic and acute poisoning with mercury (inorganic and organic compounds, vapor and metallic mercury).
- Chronic poisoning with lead.

The source of the heavy metals is irrelevant.

7.5.2. Contraindications and precautions

Dimaval®(DMPS) and DMPS-Heyl® should not be used in the presence of hypersensitivity to DMPS or its salts.

Special care is necessary when injections of DMPS-Heyl® are administered to patients with allergic or asthmatic symptoms. There is a higher risk of side-effects in these patients.

As the kidneys are the most important site of excretion for DMPS and its complexes, an especially careful risk-benefit consideration must be undertaken in patients with impaired renal function (creatinine in the serum > 2.5 mg/dl). This also applies in patients with acute infections because of the influence of DMPS on the zinc metabolism, since zinc plays an important role in the body's defenses.

7.5.3. Use in pregnancy and lactation

There is insufficient experience on the use of DMPS during pregnancy and lactation. Investigations in animals did not provide any indication of embryotoxic or teratogenic actions. If anything, DMPS reduces the teratogenic effects of various heavy metals.

There are so far no known reports of DMPS having teratogenic consequences in pregnant women. For reasons of safety, however, therapy with DMPS should not be carried out, where possible, during pregnancy and lactation.

If the use of DMPS during pregnancy and lactation is necessary for vital indications, then the mineral balance and essential trace elements (especially zinc) should be monitored in order to ensure provision of the child with essential trace elements.

7.5.4. Mode of administration

DMPS should only be administered parenterally if oral administration is not possible.
Parenteral administration of DMPS is recommended

- in acute cases,
- in oral poisoning in order to avoid possibly increased poison resorption due to oral administration,
- erosion of the gastrointestinal tract.

Intravenous administration must take place slowly over 5 min (1 ml/min).

DMPS ampoules should not be added to other infusion solutions. Combination therapy with various chelating agents is not recommended.

During DMPS therapy the patient should drink a lot in order to support renal elimination of the poison.

7.5.5. Use in small children

If necessary, DMPS can also be given to small children. Thus, a 2½-year-old boy was treated for more than a year without complications with 100 mg DMPS daily.

However, DMPS has also already been used in children less than 1 year. Bonnet has treated approx. 200 infants and small children.

7.5.6. Invoicing

In the supplement "Die KV-Abrechnung 3/94" to the journal "Der Kassenarzt" (Journal for doctors supplying services under State Health Insurance Scheme) it is stated, "The chelating agent DMPS is licensed under the name Dimaval® (capsule form) and DMPS-Heyl® (injection solution) as an antidote for the fields of chronic and acute poisoning with mercury and chronic poisoning with lead according to the German Medicines Act. If DMPS is administered according to the indication for the treatment of mercury or lead poisoning, then corresponding determinations of the concentrations of these metals before and during therapy are indicated and can be paid for as standard services. In contrast, DMPS is not yet licensed for diagnostic purposes. Therefore, it should be only administered for treatment of existing poisoning and not for the clarification of uncertain symptoms or vague suspicion of poisoning".

As the position of amalgam as a cause of various diseases is at present still disputed, reimbursement for mobilization therapy depends on the individual case decision of the pertinent clerk. Some refuse to pay and others pay without objection.