IPCS EVALUATION OF ANTIDOTES
IN POISONING BY METALS AND METALLOIDS

Unithiol
(2,3-Dimercapto-1-propanesulphonic acid, DMPS)

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1. Introduction

Unithiol (2,3-dimercapto-1-propanesulphonic acid, DMPS) was developed and first used in Russia in the 1950s (Petrunkin, 1956; Klimova, 1958), and later used in China (He et al., 1984). It only became more widely used in America and Western Europe since the mid-1970s (Hruby & Donner, 1987), and particularly since the late 1970s when the Heyl Company in Germany began production (Aposhian, 1982; Aposhian et al., 1984).

Both unithiol and succimer (2,3-dimercaptosuccinic acid, DMSA) are derivatives of dimercaprol (2,3-dimercapto-1-propanol, British Anti-Lewisite, BAL), and they are replacing dimercaprol as the main antidote used in the management of heavy metal poisoning (Hruby & Donner, 1987; Aposhian et al., 1995; Andersen, 1999). These derivatives have several advantages over dimercaprol including lower toxicity, increased solubility in water and lower lipid solubility. It is due to these properties that they are effective by oral administration (Hruby & Donner, 1987). Succimer is less toxic than unithiol and where these two drugs appear to have similar efficacy as an antidote for a particular metal, succimer is generally preferred.

Unithiol has been used in the management of acute and chronic poisoning with a number of different metals and metalloids, and is particularly useful for arsenic, bismuth and mercury. Unithiol can be given parenterally or orally depending on the clinical situation and severity of poisoning. It is well tolerated and adverse effects are relatively rare. Most common adverse effects are skin reactions such as rashes, pruritis and blistering which are allergic in origin. Most resolve within a few days and generally no treatment is required, but antihistamines and/or corticosteroids may be given if necessary.

2. Name and chemical formula

International non-proprietary name: Unithiol

Synonyms: DMPS, sodium (DL)-2,3-dimercaptopropane-1-sulphonate, sodium 2,3-dimercaptopropanesulphonate

IUPAC name: Sodium D,L-2,3-dimercapto-1-propanesulphonic acid

CAS No.: 4076-02-2

Chemical formula: $\text{H}_2\text{C(SH)-HC(SH)-H}_2\text{CSO}_3\text{H} \cdot \text{Na}_2\text{H}_2\text{O}$
Relative molecular mass: 228.28 (monohydrate)

Commercial Names: Dimaval®

Conversion:

- $1 \text{ g} = 4.4 \text{ mmol}$
- $1 \text{ mmol} = 228.3 \text{ mg}$
- $1 \text{ g/L} = 4.4 \text{ mmol/L}$
- $1 \text{ mmol/L} = 0.228 \text{ g/L}$

3. Physico-chemical properties

Physical condition: White crystalline powder

Melting point: $235^\circ C$ (decomposes)

Boiling point: Not applicable

Solubility: Readily soluble in water (350 mg/ml); not readily soluble in ethanol; not soluble in apolar solvents

Optical properties: Not applicable as the racemate is used

Acidity: pH 4.5-5.5 of an 1% aqueous solution

$pK_a$: Not known

Stability in light: No specific advice with respect to storage is necessary

Thermal stability: Stable (e.g., aqueous solution may be sterilized and the substance may also be heated for drying)

Refractive index and specific gravity: Not applicable

Loss of weight on drying: 6-8% when dried to constant weight at $100^\circ C$

4. Pharmaceutical formulation and synthesis

4.1 Routes of Synthesis

Procedures for the synthesis of unithiol were first described in the 1950s (Johary & Owen, 1955; Petrunkin, 1956). A short description of possible ways of synthesis for unithiol is also given in Hopkins (1981): sodium 2-propanesulphonate is brominated in acetic acid with bromine which gives sodium 2,3-dibromopropanesulphonate. The latter may either be treated with sodium hydrosulphide to give unithiol or may be treated with acetylthiopropane sulphonate which is then hydrolysed with hot aqueous acetic acid thus leading to unithiol.
4.2 Manufacturing Process

The Heyl company uses a patented manufacturing process which involves precipitation of unithiol as the lead salt, after which unithiol is released by addition of hydrogen sulphide. The unithiol is subsequently recrystallised from alcohol (Ruprecht, 1997).

4.2.1 Parenteral Solution

The crystalline unithiol is diluted in freshly distilled water suited for injection. The sterile filtered solution is then filled into ampoules. All steps have to be performed in an atmosphere of sterile nitrogen in order to protect the sensitive compound against oxidation. For the same reason only non-metallic working materials should be used. A complex-forming agent such as sodium edetate (1% of the amount of unithiol) may be added to the solution (water for injection) in order to bind ions eventually released from working materials. The ampoules are then sterilized.

4.2.2 Capsules

The active compound is thoroughly mixed with the filling aid until homogeneity is achieved. Thereafter the mixture is filled into commercially available hard gelatine capsules.

4.3 Presentation and formulation

At an analytical grade unithiol is available from several manufacturers. The pharmaceutical product is available from Heyl Chemisch-pharmazeutische Fabrik GmbH & Co. KG, Berlin, Germany, both for oral and parenteral administration. The sodium salt of a racemic mixture is used for medical purposes.

Unithiol is available in a pharmaceutical preparation as capsules and a parenteral injection. The capsules contain 100 mg unithiol and the ampoules 250 mg as a 5% solution. The injection can be administered either intravenously or intramuscularly.

5. Analytical methods

5.1 Quality control procedures for the antidote

The quality control procedures listed below are oriented towards national and supranational pharmacopoeial standards. Quality control parameters for the antidote include

- **Identity**
- **Purity**
  - By-products (mainly disulphides) are assayed by high performance liquid chromatography (HPLC) and should not amount to more than 5% of total peak area.
  - Bromide content: maximum 0.5% (as potassium bromide).
  - Heavy metals: maximum 20 ppm (as lead).
  - Loss of weight on drying: 6.0-8.0%.
• pH of an 1% aqueous solution: 4.5-5.5.

• The content may be assayed by iodometric titration. The assay by HPLC is preferred however, because of its specificity. At least 95% is set for requirements. The method has been validated formerly possessing a variation coefficient of 1.5% and a recovery rate of 99.7%.

The pharmaceutical preparations are additionally controlled for

• Ampoules
  • Sterility.
  • Filling volume.
  • Optical appearance (colour, clarity of the solution, particulate matter).
  • Testing for leaks.

• Capsules
  • Uniformity of filling weight.
  • Disintegration time (maximum 30 minutes in water).
  • Optical appearance.

5.2 Methods for identification of the antidote

Several methods are available to identify the antidote including HPLC, infrared spectroscopy, colour reaction with sodium nitroprusside and flame spectroscopy specifically for the sodium in the molecule.

5.3 Methods for identification of the antidote in biological samples

Methods for qualitative and quantitative determination of unithiol and its metabolites are published by Maiorino et al. (1987; 1988; 1991) and Hurlbut et al. (1994). The urine is treated with sodium borohydride and analysed by HPLC with fluorescence detection.

5.4 Analysis of the toxic agent in biological samples

Heavy metals should be analysed in blood and urine before, during and after antidotal therapy. Sensitive methods, such as atomic absorption spectroscopy (AAS) or inductively coupled plasma-atomic emission spectroscopy (ICP-AES), can be used (Berman, 1980; Bertram, 1983).

6. Shelf-life

The shelf life for the commercial available pharmaceutical preparations Dimaval® is 5 years for the capsules and 4 years for the ampoules. The expiry date is stated on each package. Although no special advice for storage is given, it is recommended that capsules are stored in a dry place.

7. General properties
Unithiol, like succimer and dimercaprol, owes its metal-binding properties to the presence of two adjacent thiol groups. Unithiol is a water-soluble dithiol, a derivative of dimercaprol and is capable of forming complexes with a number of metals and metalloids. The advantages of unithiol over dimercaprol are:

- Lower local and systemic toxicity.
- Better solubility in water.
- Active by oral administration.

It should be noted that unithiol is not a true chelating agent; a chelator is a molecule which binds a metal or metalloid ion by at least two functional groups to form a stable ring complex known as a chelate. For mercury, it has been shown that unithiol (and succimer) do not form a true chelate and as such both could be considered suboptimal as metal antidotes (George et al., 2004). However, there are currently no other substances available with the advantages of these two drugs (high water solubility with relatively low toxicity).

The mechanism of action of unithiol has not been fully elucidated. Most studies on this subject have focused on its interaction with arsenic and mercury. In addition to increasing urinary elimination of arsenic, unithiol has also been shown to alter the relative urinary concentrations of organoarsenic metabolites by interfering with arsenic methylation (Aposian et al., 1997; Gong et al., 2002; Heinrich-Ramm et al., 2003).

Unithiol also promotes mercury excretion and is effective in inhibiting mercury accumulation in renal proximal and distal tubular cells, and protecting against mercury-induced renal damage. Studies in chickens (Stewart & Diamond, 1987) and rat kidneys (Klotzbach & Diamond, 1988) have demonstrated that urinary excretion of unithiol is blocked by both the substrate p-aminohippurate (PAH) and the inhibitor probenecid of the organic transport process. In the in vitro study by Zalups et al., (1998) using isolated perfused segments of rabbit proximal tubules the removal of mercury from proximal tubules by unithiol was blocked by the addition of PAH. Islinger et al. (2001) postulated on the transport of unithiol in renal proximal cells. Unithiol enters the cells across the basolateral membrane from the blood, via the organic anion transporter (OAT). Both oxidised and reduced unithiol interact with the transporter, but the majority of unithiol entering cells is probably oxidised since this is present in the blood in a greater concentration. Once in the cell the unithiol is reduced by a glutathione-dependent thiol-disulphide exchange reaction in the proximal tubule cell (Stewart & Diamond, 1988). Unithiol then binds mercury within the cell and the complex exits the cell, presumably via an export pump. The unithiol-mercury complex is not reabsorbed and is excreted in the urine.

Owing to its high hydrophilicity unithiol is relatively ineffective at clearing metals from the brain (unlike its lipophilic parent compound, dimercaprol) and excretion by the organic anion transporter (expressed in the apical membrane of the choroid plexus) may further reduce the efficacy of unithiol in the brain (Islinger et al., 2001). Of the organic anion transporters expressed in the basolateral proximal tubule cells determined in animal studies (Kojima et al., 2002), recent work has identified (OAT1) as the transporter involved in movement of unithiol into cells; it is a comparatively poor substrate of OAT3 (Koh et al., 2002).
Recently, multidrug resistance protein 2 (MRP2 or ATP-binding cassette, sub-family C [ABCC2]) has been showed to be involved in the renal proximal tubular elimination of unithiol complexes of methylmercury (Zalups & Bridges, 2009).

It is often assumed, that clinical effectiveness of a metal-binding agent is linked to the stability constant in vitro where the greater the stability constant of a metal-binding agent, the greater the mobilisation of that ion following administration of the metal-binding agent. However, Jones et al. (1980) found no correlation in an in vivo study in mercury-poisoned mice. Therefore data on stability constants are not given in this monograph, but may be found elsewhere (Casa and Jones, 1979).

8. Animal studies

8.1 Pharmacodynamics

There are numerous studies on the effect of unithiol in animals with experimental metal poisoning. Many studies compare the effect of a number of different metal-binding agents and in some cases the antidotes are given immediately or sometimes before dosing with the metal. Administration of the antidote with or before exposure does not reflect the clinical situation in human metal poisoning. In addition, the effect of antidotes are measured in a variety of ways including changes in survival rates, urinary excretion, faecal excretion, metal concentrations in organs, body burden and biochemical parameters in target organs. Many studies give conflicting results and this is probably a reflection of a variety of factors including differences in doses of metal and antidote, routes and times of administration and methods of determining elimination and retention. Furthermore, direct extrapolation from animal studies to humans is not possible because of the potential differences in the kinetics of both heavy metals and metal-binding agents such as unithiol between animals and humans.

8.1.1 Antimony

Unithiol has been shown to reduce antimony toxicity in animals.

In a study comparing survival rates of different antidotes in antimony poisoning, mice were given intraperitoneal antimony potassium tartrate 120 mg/kg (LD$_{50}$ 54.6 mg/kg). The antidotes were given by the same route 1 hour later at a dose of 10:1 mole ratio of antidote to antimony (except for dimercaprol which was given at a 1:1 ratio). Succimer and unithiol were found to be the most efficacious antidotes for antimony potassium tartrate poisoning, with succimer the superior of the two (Basinger & Jones, 1981a).

In an earlier study administration of unithiol was shown to reduce the LD$_{50}$ of subcutaneous antimony potassium tartrate by a factor of 8 compared to controls (Chih-Chang, 1958).

8.1.2 Arsenic

Unithiol has been shown to be of benefit in poisoning with several arsenic
compounds including lewisite (β-chlorovinyl-dichloroarsine). Mückter et al. (1997) argue that unithiol and succimer have advantages over dimercaprol in the treatment of arsenic poisoning since they are more effective in preventing arsenic from crossing epithelial boundaries and entering cells and they enhance the excretion of arsenic more rapidly and completely. In addition, unithiol and succimer are less toxic than dimercaprol. However, dimercaprol appears to be more effective in restoring cellular function to tissues which are poorly penetrated by unithiol or succimer. Dimercaprol also has the disadvantage of increasing arsenic concentrations in the brain; this is not the case with unithiol or succimer.

Aposhian et al. (1982) demonstrated the effectiveness of unithiol in rabbits exposed to subcutaneous lewisite. Unithiol increased survival when given orally or subcutaneously. Similarly, in mice injected with sodium arsenite (0.14 mmol/kg subcutaneously), intraperitoneal unithiol (0.25 mmol/kg) was a potent antidote, even when given 2 hours later (Tadlock & Aposhian, 1980).

In rabbits poisoned with dermal lewisite dimercaprol, succimer and unithiol were all shown to reduce the incidence and severity of liver changes. There was no difference between the three agents at the dose of 40 µmol/kg. Compared to dimercaprol, succimer and unithiol may have prolonged survival time and the relatively low toxicity of unithiol and succimer allowed high doses (160 µmol/kg) to be given (Inns & Rice, 1993). In a study of intravenous lewisite poisoning in rabbits there was no difference between the level of protection provided by the three antidotes (Inns et al., 1990).

In mice poisoned with sodium arsenite (0.129 mmol/kg subcutaneously) unithiol (0.8 mmol/kg intraperitoneally) given 90 minutes later was found to increase the LD50 by 4.2 fold (Aposhian et al., 1981).

In rabbits poisoned with sodium arsenite (1 mg subcutaneously) given either succimer, unithiol or N-(2,3-dimercaptopropyl) phthalamidic acid (DMPA; 0.2 mmol/kg intramuscularly) 1 hour later, the urinary excretion of total arsenic between 0 and 24 hours was elevated after antidote administration. However, urinary excretion of total arsenic between 24 and 48 hours was significantly lower than controls. The three antidotes differed in the proportion of arsenic metabolites in the urine. All increased arsenic excretion by decreased dimethylarsinate excretion. Unithiol and DMPA increased methylarsonate excretion but succimer did not. Both succimer and unithiol increased arsenate excretion. Of the three antidotes used, unithiol was the most effective at removing arsenic from the body (Maiorino & Aposhian, 1985). Unithiol and succimer (both at 50 mg/kg) also significantly increased renal arsenic excretion in rats with chronic arsenic poisoning (sodium arsenate 1 mg/kg orally 6 days a week of 3 weeks). Both also restored arsenic-induced inhibition of δ-aminolevulinic acid dehydratase activity and hepatic glutathione concentrations. Although both antidotes reduced arsenic-induced histopathological lesions, succimer was more effective (Flora et al., 1995a).

Kreppel et al. (1989) compared the effectiveness of D-penicillamine, dimercaprol, unithiol and succimer as antidotes in acute arsenic intoxication using different controlled experimental settings. In one study mice and guinea pigs were injected subcutaneously with 8.4 mg/kg arsenic trioxide (containing a tracer dose of arsenic-74). An antidote (0.7 mmol/kg intraperitoneally) was given 30 minutes later. As
determined 4 and 12 hours after the arsenic injection, D-penicillamine was unable to reduce the arsenic-74 content in any organ investigated (blood, liver, kidneys, lungs, heart, brain, testes, spleen, skeletal muscle, and skin). In contrast, dimercaprol, unithiol and succimer markedly reduced the tissue content of arsenic-74 compared to controls. Finally, the ability of the antidotes to reverse biochemical effects of arsenic was investigated in vitro using suspensions of isolated renal tubule cells. The marked inhibition of gluconeogenesis induced by 30 μmol/L arsenic trioxide was almost completely reversed upon addition of 90 μmol of dimercaprol, unithiol or succimer. In this experimental model, too, D-penicillamine was ineffective.

In mice given arsenic trioxide, intraperitoneal administration of unithiol (0.7 mmol/kg) 0.5 minutes later was less effective than the same dose of succimer. When the antidote was given 30 minutes after the arsenic, succimer and unithiol showed reduced but similar efficacy. The efficacy of the antidotes for reducing arsenic organ concentrations was investigated in mice and guinea pigs. Animals received 8.4 mg/kg (0.043 mmol/kg) of radiolabelled arsenic trioxide subcutaneously and an antidote (0.7 mmol/kg intraperitoneally) 30 minutes later. Both unithiol and succimer and the two in combination were more effective as reducing organ concentrations of arsenic than dimercaprol. In addition, dimercaprol increased arsenic concentrations in the brain, whereas succimer and unithiol did not. Succimer increased the arsenic content of bile but unithiol and the two in combination did not (Kreppel et al., 1990).

In rabbits administered radiolabelled arsenic (1 mg/kg subcutaneously as sodium arsenite), dimercaprol (0.2 mmol/kg intramuscularly) 1 hour later was shown to double the arsenic-74 concentration in the brain. In contrast, unithiol (0.2 mmol/kg intramuscularly) was found to decrease the arsenic-74 concentration to about one-fifth of that observed with dimercaprol administration (Hoover & Aposhian, 1983). Schäfer et al. (1991) demonstrated that arsenic depots after injection of arsenic trioxide into mice could be mobilised by oral administration of unithiol or succimer without increasing the brain deposition, however, oral administration of dimercaprol extensively increased the brain deposition or arsenic.

In mice given arsenic (5 mg subcutaneously as arsenic trioxide) immediately followed by unithiol (100 mg/kg intraperitoneally) arsenic excretion in the faeces exceeded that in the urine (Maehashi & Murata, 1986). In guinea pigs poisoned subcutaneously with arsenic trioxide (2.1 mg/kg) the combination of unithiol (0.1 mmol/kg both intraperitoneally and orally) and cholestyramine (0.2 g/kg orally) significantly enhanced the faecal elimination of arsenic suggesting that interruption of enterohepatic circulation of arsenic may be a valuable adjunct in the treatment of arsenic poisoning. Increased faecal excretion was not observed with intraperitoneal unithiol plus oral cholestyramine or oral plus intraperitoneal unithiol (Reichl et al., 1995).

Flora et al. (2005) compared the efficacy of succimer, unithiol and monoisoamyl-succimer in rats with chronic arsenic exposure (100 ppm sodium arsenite in drinking water for 10 weeks). Antidotes were given after arsenic exposure at a dose of 50 mg/kg for 5 days. Succimer was not effective at resolving arsenic-induced oxidative damage in cells or in reducing the arsenic burden. Unithiol was moderately effective against generation of reactive oxygen species due to intracellular access. However, monoisoamyl-succimer was the most effective antidote in reducing reactive oxygen species in the blood and brain. It was also marginally better at restoring the activity
of antioxidant enzymes.

An in vitro study of guinea-pig liver treated with arsenic trioxide demonstrated that administration of unithiol (and other antidotes) resulted in a shift to faecal elimination by increasing biliary excretion of arsenic. Unithiol was more effective than succimer or dimercaprol but was not as effective as 2,3-bis-(acetylthio)-propanesulphonamide (BAPSA) (Reichl et al., 1990).

8.1.3 Beryllium

Unithiol has been shown to enhance beryllium excretion and reduce beryllium-induced toxic effects in experimental animals.

Unithiol administration (0.7 mmol/kg intraperitoneally) appeared to increase the lethality of beryllium chloride in mice, but the result was not significant (Pethran et al., 1990).

In rats treated with beryllium (2.5 mg/kg intraperitoneally, as beryllium nitrate), immediate administration of unithiol (50 mg/kg intraperitoneally) or succimer (same dose) was shown to prevent most beryllium-induced biochemical alterations and reduce tissue beryllium concentrations. Unithiol was relatively more effective and resulted in significantly less marked lesions in the liver and kidneys (Mathur et al., 1994).

In another study beryllium nitrate was given to rats for 21 days (0.5 mg/kg, orally daily for 5 days/week) and unithiol or succimer (25 or 50 mg/kg, twice daily for 5 days) was administered 24 hours after the last dose of beryllium. Unithiol was effective at reducing beryllium in the liver, spleen and kidneys. The higher dose marginally elevated the faecal excretion of beryllium but also resulted in redistribution of beryllium into blood. Unithiol also reduced hepatic and renal lesions compared to succimer (Flora et al., 1995b).

In studies comparing antidotal therapy combined with an antioxidant (sodium selenite) supplementation, D-penicillamine with sodium selenite was found to be more efficacious at reducing beryllium toxicity (as measured by glycogen and protein concentrations in the liver, kidneys, lungs and uterus, with concentrations of liver enzymes and beryllium) than unithiol and sodium selenite (Johri et al., 2002; Johri et al., 2004).

8.1.4 Bismuth

Several studies comparing different antidotal agents have found unithiol to be an effective antidote in bismuth poisoning.

In a study of several antidotes comparing efficacy in bismuth poisoning, mice were given intraperitoneal bismuth citrate followed by an antidote 20 minutes later in a 10:1 molar ratio antidote:bismuth. All animals treated with unithiol survived and all in the control group died (Basinger et al., 1983).

In a study of several antidotes comparing efficacy in bismuth poisoning, rats were injected intraperitoneally with colloidal bismuth subcitrate (50 µmol/kg/day, for 14
days). The antidotes were given twice daily (250 µmol/kg/day) for 3 days. The
animals were killed on the fourth day and tissue samples analysed. Unithiol, succimer
and dimercaprol were most effective in lowering bismuth concentrations in most
organs, particularly the kidney and liver, resulting from higher elimination in urine by
unithiol and dimercaprol. Dimercaprol was the only antidote effective in lowering
bismuth concentrations in brain tissue. It was concluded that unithiol and succimer
were the antidotes of choice with dimercaprol reserved for very severe bismuth
poisoning because of its own toxicity (Slikkerveer et al., 1992).

Unithiol was shown to reduce the whole-body burden of bismuth in mice given an
intraperitoneal injection of bismuth acetate. The unithiol was given in drinking water
(100, 300 or 600 µg/mL) two days prior to and three days after the bismuth. The
renal concentration of bismuth was reduced by up to 90% and unithiol also
significantly reduced deposition of bismuth in the femur (Jones et al., 1996).

8.1.5 Cadmium

Antidotal therapy for cadmium is particularly problematic because the absorbed
metal rapidly becomes strongly bound to metallothionein, a low-molecular weight
metal-binding protein, whose synthesis is induced by cadmium. Several studies
have compared antidote efficacy in cadmium poisoning and concluded that, although
unithiol is effective, other metal-binding agents appear to be more efficacious (Eybl
et al., 1984; Eybl et al., 1985; Andersen & Nielsen, 1988; Srivastava et al., 1996).

Unithiol administration (0.7 mmol/kg intraperitoneally) increased the LD$_{50}$ of cadmium
chloride in mice from 9.1 mg/kg to 15.2 mg/kg (Pethran et al., 1990). Aposhian (1982)
also demonstrated that unithiol increases survival in mice injected with cadmium
chloride.

In a study comparing antidote efficacy, mice were given intraperitoneal cadmium
chloride at the previously determined LD$_{50}$ (0.0267 mmol/kg). This was followed by
the antidote at a dose of 1:2 or 1:5 (cadmium:antidote) molar ratios by the same route.
The animals were killed after 14 days. Succimer and unithiol were found to be most
effective at reducing lethality and the cadmium burden of the liver, kidneys and brain
tissue. The therapeutic index and therapeutic efficacy was highest for succimer
followed by unithiol (Srivastava et al., 1996).

In a similar study mice were given radiolabelled cadmium chloride (0.53 mmol/kg by
stomach tube) followed by the antidote (2.12 mmol/kg) 15 minutes later. The
animals were killed after 10 days. Unithiol provided some protection against lethality
(whereas succimer provided complete protection). Penicillamine, succimer and
unithiol were all able to reduce peristaltic toxicity of cadmium chloride and all
reduced whole-body retention of cadmium; succimer was most effective at reducing
body retention. Succimer, and particularly unithiol, decreased hepatic deposition of
cadmium and increased relative deposition in the kidneys and lungs. It was
concluded that succimer was the most effective antidote for cadmium poisoning
(Andersen & Nielsen, 1988).

Another study in mice compared antidote efficacy when given intravenously 10
seconds, 1 or 3 hours after intravenous cadmium chloride (3 µmol/kg) administration.
When given immediately after cadmium administration, all agents reduced the body burden of cadmium but efficacy declined when dosing occurred at 1 or 3 hours after administration. Unithiol was among the least effective of the antidotes investigated (Planas-Bohne & Lehman, 1983).

Unithiol (50 mg/kg intraperitoneally) administered to rats 24 hours after injection of radiolabelled cadmium (1 mg/kg intraperitoneally as cadmium chloride) did not have any effect on the excretion or tissue distribution of cadmium. By the time the antidote was given the cadmium was bound to metallothionein. Only dimercaprol was effective in mobilising cadmium from metallothionein into bile (Cherian, 1980).

Unithiol (3.61 mmol/kg) was as effective as succimer (same dose) in promoting survival in cadmium poisoned mice (1 mmol/kg cadmium chloride orally) when given immediately after administration of cadmium. However, unithiol administration resulted in a concentration of cadmium in the kidneys and liver that was approximately four times greater than those in succimer-treated animals (Basinger et al., 1988).

Unithiol did not affect faecal excretion of cadmium and the increase in urinary excretion was too small to affect body burden in rats given 0.4 mmol/kg of unithiol following dosing with radiolabelled cadmium (3 µmol/kg as cadmium chloride). The cadmium was given once; administration of the metal-binding agent started on the third day and was given daily, 5 times a week for 2 weeks (Rau et al., 1987). Administration of unithiol (0.1 mmol/kg) did not affect biliary excretion of cadmium in rats 3 days after intravenous exposure to cadmium (Zheng et al., 1990).

Unithiol had no effect on survival rate in cadmium-poisoned mice when administered intraperitoneally immediately after subcutaneous cadmium (20 mg/kg as cadmium chloride) at antidote to metal molar ratios of 1:1 or 2:1. At a ratio of 5:1 the survival rate was only 20%, whereas the survival rate with succimer was 100%. In another study where cadmium (0.5 mg/kg intravenously) was immediately followed by unithiol at a dose of 10:1, there was no increase in cadmium excretion or reduction in body burden. Unithiol did, however, decrease the cadmium concentration in the liver and gastrointestinal tract (Eybl et al., 1984).

In a study of antidotal efficacy in chronic cadmium poisoning in mice (2 mg of cadmium chloride intraperitoneally at 48 hours intervals for 5 doses) unithiol administration (225 mg/kg; 1.06 mmol/kg intraperitoneally) resulted in a significant increase in liver cadmium concentrations (39%). However, interpretation of this result is difficult since this group of mice were the only group to have a significant loss in body weight. Therefore the apparent increase in cadmium concentration could be due to changes in organ size rather than a reflection of the effect of unithiol on cadmium distribution. Similarly there was also a slight increase in kidney cadmium concentrations (Shinobu et al., 1983).

Unithiol had only a slight effect in reducing the cytotoxicity of cadmium in mammalian cell culture (Fischer, 1995). In another in vitro study using human platelets, unithiol was shown to protect against cadmium-induced stimulation of glutamate binding (Borges & Nogueira, 2008) but unithiol increased cadmium-induced inhibition of δ-aminolevulinate dehydratase (ALAD) in rat lung in vitro (Luchese et al., 2007).
8.1.6 Chromium

There is limited information on unithiol in chromium poisoning. Chromate-induced cytotoxicity (as measured by the chromate content of cells and inhibition of cell growth) was reduced in the presence of unithiol. This was only the case when cells were incubated with unithiol and chromate. If the unithiol was added before or after treatment with chromate it failed to restore chromate-induced cytotoxicity or reduce cellular chromate concentrations (Susa et al., 1994).

Lethality was reduced in mice injected with chromate (40 mg/kg intraperitoneally as potassium chromate) and then unithiol (500 mg/kg intraperitoneally) immediately afterwards. At half the chromate dose and 300 mg/kg of unithiol the liver and kidney content of chromium was reduced compared to controls. There was also increased renal excretion of chromium and suppression of chromate-induced increase in serum ornithine carbamyl transferase activity (Susa et al., 1994).

8.1.7 Cobalt

There is limited information on unithiol in cobalt poisoning. It has been shown to reduce the lethality of cobalt in some studies (Cherkes & Braver-Chernobulskaya, 1958; Eybl et al., 1985). In the latter study, although unithiol increased survival it also increased cobalt concentrations in the liver, gastrointestinal tract and carcass in mice receiving 1 mmol/kg of cobalt chloride. The unithiol was given in a dose of 5:1, antidote to metal ratio (Eybl et al., 1985).

8.1.8 Copper

Unithiol appears to be of benefit in copper-poisoned experimental animals.

Unithiol administration (0.7 mmol/kg intraperitoneally) increased the LD50 of copper chloride in mice from 59 mg/kg to 143 mg/kg (Pethran et al., 1990).

Mice receiving copper sulphate (10 mg/kg intraperitoneally, the approximate LD50) and then unithiol (132 mg/kg, 20 minutes later by the same route) were morphologically free of hepatic or renal evidence of toxicity, whereas control animals have extensive renal tubular necrosis (Mitchell et al., 1982).

In contrast unithiol has been shown to increase copper-induced haemolysis of human red blood cells in vitro. At a concentration of 0.3 mM unithiol increased the copper-induced haemolysis from 15% to approximately 25%. At 0.1 mM it was ineffective (Aaseth et al., 1984).

8.1.9 Gold

Unithiol has been shown to be of benefit in experimentally induced gold toxicity. It is able to reduce kidney gold concentrations and increase urinary excretion of gold.

In rats given 2 mg gold/kg intravenously (as Auro-Detoxin) and then oral unithiol (0.15-3 mmol/kg) 30 minutes later, it was demonstrated that unithiol reduced the gold
concentration in all organs except the liver and spleen. Similar effects were observed when unithiol was administered 24 hours after injection of gold. In contrast to the immediate treatment with unithiol delayed treatment with the lowest dose (0.15 mmol/kg) resulted in significantly decreased gold concentrations in the red blood cells, plasma, femur, muscle and skin. However, the concentration in the kidneys was significantly higher compared to controls (Gabard, 1980).

In another study rats were given 2 mg gold/kg intraperitoneally daily for 10 days then unithiol 0.75 mmol/kg daily from days 11 to 20. Unithiol administration decreased the gold concentration in the kidneys and in the skin, and increased it in the plasma. The concentrations in the other organs remained unchanged (Gabard, 1980).

In rats injected with gold sodium thiomalate (up to 0.198 mmol/kg intravenously), treatment with D-penicillamine, unithiol or succimer reduced renal toxicity, measured by urinary concentrations of protein, aspartate aminotransferase and glucose, and the blood urea nitrogen concentration. In addition all three antidotes increased urinary excretion of gold and significantly decreased liver and renal gold concentrations. Unithiol was the most effective antidote tested (Kojima et al., 1991). Characterisation of the gold in urine following treatment with gold sodium thiomalate and then unithiol has shown that it is present as a gold-unithiol complex. In the bile it was present as a gold-unithiol complex, high molecular weight compounds (probably proteins) and gold-L-cysteine (Kojima et al., 1992).

Takahashi et al. (1994) also demonstrated that administration of unithiol reduced renal toxicity (using the same parameters as above) in rats given an intraperitoneal dose (1.2 mmol/kg) immediately after intravenous injection of gold sodium thiomalate (0.026 mmol/kg). Compared to the other gold antidotes tested (bucillamine, captopril and tiopronin), only unithiol was able to significantly reduce the renal gold concentration at the lowest dose used (0.2 mmol/kg). None of the antidotes reduced the hepatic gold concentrations at doses of 0.2 or 0.4 mmol/kg.

Succimer and unithiol were the most effective antidotes at increasing survival in mice given gold sodium thiosulphate (200 mg/kg intraperitoneally, the approximate LD₉⁹). The antidotes were given by the same route 20 minutes after dosing at a ratio of 3:1, antidote to gold (Basinger et al., 1985).

8.1.10 Lead

Unithiol has been shown to increase lead excretion, reduce lead tissue concentrations (except in the brain) and to reduce lead-induced biochemical toxic effects, such as inhibition of δ-aminolevulinic acid dehydratase, in experimental animals.

In a study comparing dimercaprol and unithiol, rats received lead (2 mg/kg as lead acetate) intraperitoneally daily for 7 days, and then antidotal treatment (50 µmol/kg) daily for 3 days beginning 48 hours after the last lead dose. Bone and blood lead concentrations were not significantly different from controls. The concentration of lead in the kidneys was significantly reduced by both antidotes. In addition, both antidotes reduced δ-aminolevulinic acid excretion and appeared to reactivate δ-aminolevulinic acid dehydratase (Twarog & Cherian, 1983).
In another study rats received lead (2 mg/kg as lead acetate) intraperitoneally daily for 7 days and 6 days after the last dose unithiol was administered (25-200 µmol/kg). The highest dose of unithiol removed lead from kidneys, liver and bone, while the lower doses (25 and 50 µmol/kg) decreased only the kidney concentrations. Urinary excretion of lead was higher in animals given 100 or 200 µmol/kg of unithiol. Urinary excretion of δ-aminolevulinic acid was unchanged by unithiol administration in this study (Twarog & Cherian, 1984).

Administration of unithiol (0.5 mmol/kg subcutaneously daily for 4 days) was of benefit in rats poisoned with oral lead (10 mg/kg 6 days a week for 6 weeks). The effect of the antidotes was measured by changes in the concentrations of indicators of lead toxicity (blood δ-aminolevulinic acid dehydratase, zinc porphyrin, haemoglobin and haemocrit and urinary δ-aminolevulinic acid). Unithiol was shown to reduce lead-induced inhibition of δ-aminolevulinic acid dehydratase and increase blood zinc porphyrin and haemoglobin concentrations. Unithiol decreased lead-induced urinary excretion of δ-aminolevulinic acid. Unithiol also decreased blood, hepatic and renal lead concentrations, but did not mobilise lead from the brain (Sharma et al., 1987).

Another study in lead-poisoned rats (20 mg/kg intraperitoneally for 5 days) demonstrated that unithiol (25, 50 or 100 µmol/kg intraperitoneally daily 5 days a week for 7 weeks, starting 3 days after last lead dose) increased urinary excretion of lead (due to mobilisation of lead in bone), and reduced δ-aminolevulinic acid excretion but did not have a beneficial effect on lead-induced anaemia. In addition, the lethality of lead was unaffected by antidote administration (Hofmann & Segewitz, 1975). In the study by Llobet et al. (1990) unithiol administration at a dose of 2.90 mmol/kg given 10 minutes after intraperitoneal lead (0.58 mmol/kg of lead acetate trihydrate) reduced lethality in mice from 55% to 40%. Unithiol also caused a significant increase in urinary lead and a decrease in kidney lead concentrations.

In rats with chronic lead poisoning (lead acetate in drinking water, 50 mg/L for 86 days) administration of unithiol (0.27 mmol/kg intraperitoneally for up to 4 days) failed to alter lead concentrations in the brain (Aposhian et al., 1996). In a study on acute parenteral lead intoxication in mice antidotes (2 mmol/kg) were injected during 3 consecutive days after 7 daily injections of lead (50 mg/kg). Unithiol, sodium calcium edetate (EDTA, calcium disodium edetate, calcium disodium versenate, calcium EDTA) and D-penicillamine did not protect against lethality. Unithiol was, however, more efficient than succimer and several other antidotes including sodium calcium edetate in removing lead from the brain and kidneys (Xu & Jones, 1988).

Tandon et al. (1994) investigated the efficacy of combined metal-binding agents in lead-poisoned rats (lead acetate 0.1% in drinking water for 8 weeks). Animals were treated with calcium disodium ethylenediaminetetraacetic acid (EDTA sodium calcium edetate, succimer, unithiol, sodium calcium edetate and succimer or sodium calcium edetate and unithiol. All metal-binding agents were given in the same dose (0.3 mmol/4 mL/kg intraperitoneally) for 5 days, followed, after a 5 day break by another 5 day course. Efficacy was measured by metal concentrations in tissues and biochemical changes (blood δ-aminolevulinic acid dehydratase activity, zinc protoporphyrin, urinary δ-aminolevulinic acid and total urinary proteins). The administration of sodium calcium edetate or succimer resulted in more urinary lead excretion than unithiol. In addition, the combination of sodium calcium edetate and
succimer was more effective than sodium calcium edetate and unithiol. Both sodium calcium edetate and succimer were more effective than unithiol in reducing lead concentrations in blood, liver, kidney and femur. Only succimer reduced brain lead concentrations. All the metal-binding agents reversed lead-induced inhibition of δ-aminolevulinic acid dehydratase activity and increase in zinc protoporphyrin and urinary excretion of δ-aminolevulinic acid, but the effect was greater with combined therapy. Again the combination of sodium calcium edetate and succimer was more effective than sodium calcium edetate and unithiol.

A study in rats demonstrated that antidotal therapy in combination with zinc and copper supplementation was more effective at lowering blood lead concentrations than the antidote alone. However, supplementation with unithiol administration (0.3 mmol/kg intraperitoneally, daily for 5 days) did not result in an increase in urinary lead concentrations and unithiol was relatively less effective at promoting lead excretion than sodium calcium edetate and succimer. The lead was administered at a dose of 0.05 mmol/kg daily, 6 days/week for 6 weeks (Flora, 1991).

In mouse cortical cell cultures unithiol was shown to increase the toxicity of lead chloride (Rush et al., 2009). In another in vitro study using human platelets, unithiol was shown to protect against lead-induced stimulation of glutamate binding (Borges & Nogueira, 2008). Unithiol increased lead-induced inhibition of ALAD in human blood in vitro. In addition the inhibition of ALAD activity in the blood and liver of lead-exposed mice was also increased by unithiol treatment (Santos et al., 2006).

8.1.11 Mercury

8.1.11.1 Inorganic mercury

Unithiol has been shown to increase mercury excretion and decrease tissue concentrations in experimental animals. Most studies found that unithiol does not increase faecal excretion of mercury (Aaseth et al., 1982; Kachru & Tandon, 1986). However some studies have shown the opposite (Wannag A. & Aaseth J., 1980), but this may be an effect of decreased body burden of mercury with unithiol treatment (Gabard, 1976a). In addition, although some studies have found that unithiol mobilises mercury from the brain, others have found that unithiol is relatively ineffective in reducing brain mercury concentrations. The former observation may be due to contamination of brain tissue with blood which has a higher mercury concentration (Buchet & Lauwerys, 1989).

In rats with mercury toxicity (5 µmol/kg as mercuric chloride) unithiol (400 µmol/kg intramuscularly) was found to be the most effective antidote compared to sodium diethyldithiocarbamate (DDC) and pentetic acid (diethylenetriaminepentaacetic acid, DTPA) when given prior to exposure. Unithiol was shown to mobilise mercury in the urine and reduce concentrations in the liver and spleen. It did not increase faecal excretion (Kachru & Tandon, 1986). Treatment with unithiol (500 µmol/kg intravenously) 24 hours after mercury administration (2 µmol/kg intravenously as mercuric chloride) in mice reduced the mercury content of the kidneys to 60-70% of controls by 48 hours after administration of the antidote (Wannag & Aaseth, 1980).

Immediate treatment with unithiol (500 µmol/kg intravenously) after mercury
administration (5 µmol/kg intravenously as mercuric chloride) in rats prevented pathological changes in the kidneys and increased mercury excretion in the urine. When administration was delayed 24 hours, unithiol was relatively ineffective in reversing mercury-induced anuria. The kidney mercury concentration was significantly reduced, but pathological changes could not be prevented. Mercury concentrations in the blood, kidney and brain were reduced irrespective of whether the administration of unithiol was immediate or delayed. Immediate unithiol treatment did not change faecal mercury elimination whereas delayed administration resulted in increased faecal excretion (Wannag & Aaseth, 1980).

Administration of oral unithiol (30 µmol/200 g) was shown to normalise renal excretion of alkaline phosphatase in mercury-poisoned rats (0.75 mg/kg as intravenously mercuric chloride). The dose of unithiol was given at 6 or 24 hours after mercury and then once a day until the fifth day. Early administration of unithiol also abolished the effect of mercury on renal excretion of leucine aminopeptidase, but there was no effect on this enzyme if administration of unithiol was delayed until 24 hours after mercury exposure. Furthermore, early treatment with unithiol reduced mercury-induced lethality, whereas delayed treatment had no effect (Planas-Bohne, 1977).

In a study reported by Aaseth (1983), succimer or unithiol (1 mmol/kg daily for 4 days) given after a single intravenous dose of mercuric chloride (2 µmol/kg) to mice reduced the renal mercury concentration almost by a factor of three. Brain mercury concentrations were also reduced. Dimercaprol, in contrast, has long been known to increase mercury deposition in the brain after exposure to methyl mercury in mice (Berlin & Ullberg, 1963).

The efficacy of unithiol (220 mg/kg) and succimer (180 mg/kg) were compared in rats exposed to mercury (0.5 mg/kg as mercuric chloride intraperitoneally 5 times a week for 3 weeks). The antidotes were administered 7 days after the last mercury dose. Both antidotes were ineffective in removing mercury from the brain and unithiol was more effective in increasing urinary mercury excretion. This was also the case when the same dose of mercury was administered as phenyl mercury (Buchet & Lauwerys, 1989). In a study of various antidotes given in mercury-poisoned mice (as mercuric chloride 10 mg/kg), where the antidotes were given in doses of antidote:mercury molar ratios of 10, 15, 20 and 30:1, unithiol reduced lethality and was significantly more effective than succimer or dimercaprol. This was true for unithiol even at the smallest dose ratio of 10:1 (Jones et al., 1980).

Comparing succimer (100 µmol/kg orally) and unithiol (300 µmol/kg orally) in mercury-poisoned rats (0.5 mg as mercuric chloride) Planas-Bohne (1981) found that the rise in urinary mercury excreted in the succimer treated animals corresponded to the mercury content of the kidneys. In contrast, the urinary mercury concentration in the unithiol treated group was higher indicating removal of mercury from other organs. The dose of unithiol was three times that of succimer because only 30% of the unithiol was absorbed from the gut compared with 100% of the succimer. However, Cherian et al. (1988) reported that the increase in urinary excretion induced by unithiol (0.2-2.0 mmol/kg intraperitoneally) was almost equal to the amount of mercury lost from the kidneys in mercury-poisoned rats (0.1-2 mg/kg intraperitoneally or mercury vapour 0.5-2 mg/m³).
In rats with chronic mercury poisoning (0.5 mg mercury/kg, as mercuric chloride, intraperitoneally 5 days a week for 32 or 41 days) unithiol (0.27 mmol/kg intraperitoneally for up to 4 days) failed to alter mercury concentrations in the brain (Aposhian et al., 1996).

Both renal and biliary excretion of mercury were increased after administration of unithiol (12.5 mg intramuscularly) in mercury-poisoned rats (120 µg intravenously as \(^{203}\)mercuric chloride). The mercury content was decreased in all tissues, especially in the kidneys and the brain. Treatment with the diuretic spironolactone before administration of mercury further increased the biliary excretion of mercury observed with unithiol. However, the overall excretion of mercury was unchanged (Cikrt, 1978). In a similar study comparing unithiol (15 mg/kg intramuscularly) and unithiol combined with spironolactone and oral polythiol resin in mercury-poisoned rats (same dose as above) Cikrt & Lenger (1980) found that urinary excretion was higher with unithiol alone but the combination therapy resulted in increased faecal excretion. Both regimens significantly decreased the mercury content of all tissues.

Of 15 antidotes studied in mercury-poisoned mice (0.5 mg mercury intravenously as mercuric chloride) only unithiol (50 µmol/kg) was shown to have a favourable effect with increased urinary mercury excretion and reduced tissue concentrations (erythrocytes, plasma, liver, kidneys, brain, femur, muscle, spleen and intestine). Unithiol reduced the mercury concentration of the kidneys to approximately 40% of controls and the other organs to 50-80%. Faecal mercury excretion was decreased but this was due to a decreased body burden, and overall elimination was increased due to a large rise in the urinary mercury concentration (Gabard, 1976a). Similarly, oral unithiol (1 mmol/kg/day for 4 days) reduced the mercury concentration in the kidney to about 30% of controls in mercury-poisoned mice. Dosing with unithiol was started immediately after intravenous injection of mercury (2 µmol/kg as mercuric chloride). There was increased urinary excretion of mercury but faecal excretion was unchanged (Aaseth et al., 1982).

In a study in mercury-poisoned mice (5, 200, 300 or 400 µmol/kg of mercuric chloride orally) unithiol (100, 800, 1200 or 1600 µmol/kg orally) given 15 minutes later was most effective at reducing lethality. In addition oral administration was more effective than parenteral, probably because of reduction in gastrointestinal absorption of mercury. Unithiol also reduced mercury concentrations in the brain; intraperitoneal unithiol reduced mercury brain concentrations to about one third of controls whereas oral administration reduced concentrations to less than 15% of controls (Nielson & Andersen, 1991).

Simultaneous administration of sodium selenite and mercuric chloride decreased the efficacy of unithiol (300 µmol/kg orally) on mercury elimination in rats. The metal salts were given at a dose of 1.5 µmol/kg by intraperitoneal injection. When both metal salts were given together there was redistribution of mercury with reduced accumulation in the kidneys (decreased by more than 94%) and an increased concentration in the liver (increased about 6 times). Urinary excretion of mercury was also reduced compared to elimination in the absence of selenium (Jureša et al., 2005).

Kostial et al. (1984) investigated the influence of age on unithiol efficacy in rats (aged 2, 6 and 28 weeks old) with mercury toxicity (50 µg/kg intraperitoneally). Unithiol (50
mg/kg 3 times, 1 day after mercury administration and then at 24 hour intervals) decreased the body retention of mercury in all age groups, and was about twice as effective in adults compared to suckling rats. The reduced effectiveness was due to the reduced efficacy of unithiol in lowering kidney retention in young animals. This age difference was also confirmed in a later study (Kostial et al., 1991). In addition this study found that early treatment with oral unithiol in older rats given oral mercury increased mercury retention. However, this was in contrast to succimer, where early treatment while mercury was still in the gut decreased mercury retention.

An in vitro study on isolated perfused segments of rabbit proximal tubules exposed to inorganic mercury found that mercury was rapidly taken up by the tubular epithelial cells and resulted in cellular necrosis. The addition of unithiol provided complete protection against this effect. This appeared to be due to a negligible rate of net absorption of inorganic mercury ions from the lumen and low levels of ion accumulation. Unithiol-mercury complexes are not readily transported into proximal tubular cells and it is thought that unithiol reduces the renal mercury burden by extraction of mercury during the trans-epithelial transport of unithiol. The therapeutic efficacy of unithiol in mercury-induced renal damage may be linked to its transport at the basolateral membrane by the organic anionic transporter (OAT) system and to prevention of significant uptake of mercury by the proximal tubular cells due to the formation of unithiol-mercury complexes (Zalups et al., 1998). Another in vitro study confirmed that unithiol was effective at inhibiting mercury accumulation in renal proximal and distal tubular cells, and protecting against mercury-induced renal damage (Lash et al., 1998).

Unithiol, when incubated with mercuric chloride, partially restored cellular morphology, viability, intracellular adenosine triphosphate (ATP) concentrations and mitochondrial membrane potential in opossum kidney cells in vitro. Unithiol also had a protective effect on mitochondrial morphology and showed potent antioxidant activity (Carranza-Rosales et al., 2007). Similarly, unithiol was shown to reduce mercuric chloride toxicity in mouse cortical cell cultures (Rush et al., 2009). In another in vitro study using human platelets, unithiol was shown to protect against the inhibitory effect of mercury on glutamate binding (Borges & Nogueira, 2008).

8.1.11.2 Organic mercury

Oral unithiol administration (1 mmol/kg) to rats with methyl mercury poisoning (0.23 mg/kg intravenous as methyl mercury) reduced the biological half-life of the mercury body burden from 23.0 days to 4.3 days compared to controls. The mercury concentration was decreased in all tissues, particularly in the kidneys and the brain (Gabard, 1976b).

The effect of unithiol on motor impairment and cerebellar toxicity has been studied in mercury-exposed mice. Methylmercury was given in drinking water (40 mg/L) for 17 days with unithiol given on days 15 to 17 (150 mg/kg by intraperitoneal injection). The mice were tested for signs of toxicity 24 hours after the last dose of unithiol. The mercury-induced motor deficit was reduced in unithiol treated mice and unithiol also reduced mercury-induced lipid peroxidation in the cerebellum but did not prevent mercury-induced reduction of cerebellar glutathione peroxidase. Unithiol significantly reduced mercury deposition in the cerebellar cortex (Carvalho et al., 2007).
Unithiol is able to increase elimination of both organic and inorganic mercury from tissue, however with organic mercury the efficacy of unithiol is affected by the relative capacity of tissue for dealkylation of organic to inorganic mercury. In rats with chronic methyl mercury poisoning (10 ppm in drinking water for 9 weeks in a single dose study and 6 weeks in a repeated dose study) a single dose of unithiol (100 mg/kg intraperitoneally) was shown to reduce kidney inorganic and organic mercury concentrations by 38% and 59%, respectively. In addition, urinary inorganic and organic mercury concentrations increased by 7.2 and 28.3 fold, respectively, compared with pre-treatment concentrations. A single dose of unithiol was relatively ineffective at removing mercury from the brain and the mercury in this tissue was predominantly in the organic form due to slow dealkylation to inorganic mercury. In contrast, repeated doses of unithiol (100 mg/kg every 72 hours for 1, 2 or 3 doses) significantly decreased mercury concentrations in the brain, kidney and blood, but the decrease in the brain and blood was restricted to the organic mercury component. This was thought to reflect the slow dealkylation of methyl mercury in these tissues. This may be why unithiol is relatively ineffective at improving organic mercury-induced neurotoxicity (Pingree et al., 2001).

Unithiol no effect on methylmercury and increased the toxicity of ethylmercury in mouse cortical cell cultures (Rush et al., 2009).

8.1.12 Nickel

Unithiol has been shown to be efficacious in experimental nickel poisoning in animals, in terms of increased survival and reduced nickel-induced toxic effects.

Unithiol administered intraperitoneally at a 10:1 mole ratio of antidote to nickel, increased survival rate in mice poisoned with intraperitoneal nickel acetate (62 mg/kg). Antidotes were administrated 20 minutes after injection of nickel. Unithiol was less effective than D-penicillamine or sodium calcium edetate, although the small sample size prohibited any significant differentiation between them (Basinger et al., 1980).

Administration of unithiol (0.5 mmol/kg subcutaneously daily for 4 days) significantly enhanced the urinary excretion of nickel in rats poisoned with intraperitoneal nickel sulphate (4 mg/kg 6 days/week for 4 weeks). In unithiol treated animals there were significant reductions in nickel concentrations in renal and hepatic tissue and decreases in evidence of nickel-induced kidney and liver damage (as measured by plasma concentrations of ceruloplasmin and amino acids, blood glucose and glutathione, urinary amino acids, and renal, hepatic and cardiac concentrations of mitochondrial malic dehydrogenase, which is inhibited by nickel). Unithiol reduced the increase in plasma and urinary amino acids and blood glucose, but did not change the decreases in plasma ceruloplasmin and blood glutathione concentrations. There was no significant effect on mitochondrial malic dehydrogenase concentrations. Faecal nickel excretion was unchanged and unithiol was ineffective at mobilising nickel from the brain (Sharma et al., 1987).

Rats given nickel (1.5 mg/kg intraperitoneally as nickel sulphate daily, 6 days a week for 30 days) then unithiol (0.3 mmol/kg intraperitoneally daily for 5 days) had their
organs harvested 24 hour after the last injection. Unithiol reduced the nickel concentrations in the liver, blood, heart and kidney but not in the brain. Unithiol also reversed nickel-induced biochemical changes (decreased ceruloplasmin concentration and blood glucose; increased plasma and urine concentrations of amino acids) and increased faecal nickel excretion (Tandon et al., 1996).

8.1.13 Palladium

There is limited information on the effect of unithiol on palladium toxicity. It did not influence toxicity or reduce lethality in mice with acute palladium chloride poisoning (586 µmol/kg intraperitoneally). Unithiol was given subcutaneously at the same time as palladium at a dose of 2.93 mmol/kg (5 times the molar dose of metal) (Mráz et al., 1985).

8.1.14 Platinum

There is limited information on the effect of unithiol on platinum toxicity. A single injection of unithiol (1 mmol/kg) produced no significant change in renal platinum concentration in rats treated with cisplatin (4 or 6.5 mg/kg) 24 hours previously. After four daily treatments unithiol and succimer caused a significant increase in urinary excretion of platinum, but this was low, and represented only about 3% of the injected dose of platinum. It was concluded that none of the antidotes studied, unithiol, succimer or pentetic acid, were likely to be of benefit in the management of cisplatin-induced renal toxicity (Planas-Bohne et al., 1982).

8.1.15 Polonium

Several animal studies have shown that although unithiol can remove polonium-210 from most tissues it results in concentration of polonium in the kidneys, with the risk of renal damage. In addition, unithiol has been shown to cause renal damage when administered to polonium-poisoned animals (Poluboiarinova & Streltsova, 1964).

Rats were given approximately 0.3 µCi of polonium-210 intravenously followed 1.5 minutes later by intraperitoneal or oral administration an antidote (1 mmol/kg). The α-activity of tissue was determined 48 hours later. Administration of an antidote produced a marked decrease in polonium-210 retention in the blood, spleen and bone and, to a lesser extent, in the plasma. Unithiol but did not decrease polonium-210 retention in the kidneys and overall retention of polonium-210 in the blood, liver, spleen, skeleton and kidneys was increased by 40%. The effect of oral unithiol was approximately one third of the intraperitoneal dose, and following administration by this route the overall retention of polonium-210 was increased by approximately 50%. Retention of polonium-210 was particularly seen in the kidneys where it was transported but not excreted. In view of these findings it was concluded that although unithiol increased survival of rats given lethal doses of polonium-210, it was not a suitable antidote for polonium because it could potentiate the toxic effects of polonium on the kidneys (Volf, 1973).

In a study of rats given a lethal dose (40 µCi) of polonium-210 by intraperitoneal injection, administration of an antidote (0.2 mmol/kg) 1 minute, 90 minutes, 360 minutes and twice daily on days 2, 3, 4, 12, 22 and 32 increased the mean survival
time from 39 days to 106 days. Unithiol significantly decreased the polonium-210 content of all tissues studied except the kidneys. However, DMPA was found to be a more effective antidote and able to decrease polonium-210 in all tissues (Aposhian et al., 1987).

The study by Rencová et al. (1993) comparing a number of antidotes for polonium-210 also found that unithiol reduced retention in the bone, spleen and blood of rats but increased it in the kidneys. Indeed, the total body retention of polonium-210 could not be reduced to less than 85% of controls with any of the 9 antidotes used.

The same investigators (Volf et al., 1995) looked at the use of antidotes in rats with simulated wounds contaminated with polonium-210. After 2 weeks of unithiol treatment (intramuscularly at injection site at 1 hour and 5 days, and systemic treatment with intramuscular injection on days 1, 7, 9 and 12) polonium-210 at the wound site was reduced to 12% of controls. The retention in the liver, spleen, muscle and skeleton was reduced to 14-40%, but the blood content was unchanged and retention in the kidneys was increased to 340% of controls. Unithiol was effective at removing polonium-210 from the wound site when given either locally or systemically, but it was not effective at removing polonium-210 from the body as a whole. In a series of other experiments it was concluded that treatment with unithiol combined with another antidote (particularly sodium N,N’-di-(2-hydroxyethyl)-ethylenediamine-N’N’-biscarbodithioate; HOEtTTC) was the most effective method of removing polonium-210 from the body.

8.1.16 Selenium

There is limited information on the effect of unithiol on selenium toxicity. Unithiol administration (60 mg/kg intraperitoneally) had no effect on selenium-poisoned rats (2.24 mg of selenium/kg by subcutaneously). The concentration of selenium in urine and faeces was unchanged (Paul et al., 1989).

8.1.17 Silver

There is limited information on the effect of unithiol on silver toxicity. Unithiol administration (0.7 mmol/kg intraperitoneally) increased the LD50 of silver chloride in mice from 13.6 to 74 mg/kg (Pethran et al., 1990). In dogs given intravenous silver nitrate unithiol prevented the development of toxic pulmonary oedema and death (Romanov, 1967).

In an in vitro study of silver inhibition of Na,K-ATPase, which was probably due to deposition of the metal on sulphhydryl groups in the enzyme, it was found that the process was completely reversed by administration of unithiol (Hussain et al., 1994).

8.1.18 Strontium

There is limited information on the effect of unithiol on strontium toxicity. Unithiol did not affect survival rate in mice poisoned with strontium chloride (Domingo et al., 1990; Pethran et al., 1990).

8.1.19 Thallium
Unithiol is not of benefit in thallium poisoning in experimental animals.

In a study comparing the efficacy of Prussian blue (potassium ferric hexacyanoferrate II) and unithiol, rats were given an oral dose of 20 mg thallium (as thallium sulphate) and antidotal therapy was started 24 hours later. The rats were divided into 3 treatment groups: Prussian blue 50 mg/kg for 4 days, unithiol 5 mg/kg 6 times a day on day 1, 4 times on day 2 and 3 times on days 3 and 4. In the third group the animals were given both antidotes. Animals were killed on day 5 and the thallium content of organs determined. Prussian blue administration limited thallium distribution into tissues, whereas unithiol did not decrease thallium concentration in any organ, although it did decrease thallium concentrations in blood. The two drugs in combination decreased the thallium content in all organs but no more than Prussian blue alone. It was concluded that unithiol is not a useful antidote in thallium poisoning (Mulkey & Oehme, 2000).

Similarly, unithiol did not affect survival rate in mice given thallium sulphate (Pethran et al., 1990).

8.1.20 Tin

There is limited information on the effect of unithiol on tin toxicity. Unithiol and succimer have been investigated as antidotes in rats following a single intravenous dose dibutyltin dichloride (27 µmol/kg). The antidotes were given at two doses, 100 and 500 µmol/kg, orally and by intraperitoneal injection. Several parameters of organ toxicity were monitored from 6 hours to 8 weeks. Both drugs reduced dibutyltin dichloride-induced lesions of the bile duct, pancreas and liver. Unithiol was more effective than succimer in most measured parameters and the drugs were though to exert their protective effects on these organs by reducing biliary organotin excretion (Merkord et al., 2000).

In vitro studies with human erythrocytes incubated with tributyl tin have demonstrated that unithiol is unable to prevent the tributyl tin-mediated haemolysis of the cells (Gray et al., 1986; 1987).

8.1.21 Vanadium

There is limited information on the effect of unithiol on vanadium toxicity. However, it is unlikely to be useful since antidotes containing oxygen, rather than thiol groups such as unithiol, are more effective at binding vanadium.

Unithiol had no effect on lethality in mice poisoned with sodium vanadate (50 mg/kg intraperitoneally) or vanadyl sulphate (110 mg/kg intraperitoneally). Unithiol was given intraperitoneally 20 minutes after administration of vanadium, at a dose of 5:1 antidote to metal compound (Jones & Basinger, 1983).

Unithiol had no significant effect on the death rate, body weight reductions, or reduction in weights of legs and toes in chick eggs incubated with vanadium (Hamada, 1994).
A recent study, however, has shown that oxovanadium (VO$_{2}^{+}$) is capable of forming a [VO(DMPS)$_{2}$]$^{4-}$ complex with unithiol in aqueous solution (Williams & Baran, 2008). The significance of this *in vivo* remains to be elucidated.

### 8.1.22 Zinc

Unithiol can increase excretion of zinc and reduced lethality in zinc-poisoned animals, but more effective antidotes are available.

In a comparison of several antidotes against the effects of acute parenteral zinc intoxication in mice, unithiol efficiently reduced acute lethality. Succimer (10:1 antidote:zinc ratio) was given 20 minutes after a fatal dose of zinc (50 mg/kg) was administered. Survival was 73% with unithiol but other antidotes were equally or more effective (Basinger & Jones, 1981b).

In mice given zinc acetate (0.49 mmol/kg intraperitoneally) unithiol (2:1 or 5:1 molar ratios of antidote to metal) was the least effective of the six antidotes tested. Disodium calcium cyclohexanediaminetetraacetate (CDTA), sodium calcium edetate and pentetic acid and were the most effective (Llobet et al., 1988).

In a study comparing the efficacy of several antidotes mice were given intraperitoneal zinc acetate (66-330 mg/kg; LD$_{50}$ 108 mg/kg). Antidotal therapy was given 10 minutes later, also by intraperitoneal injection. Unithiol reduced the lethality in animals given 66-241 mg/kg of zinc acetate. In those given 330 mg/kg of zinc acetate lethality was 30% compared to 100% in control animals. Unithiol also increased renal excretion of zinc and reduced blood and heart tissue concentrations compared to controls. However, pentetic acid and CDTA were found to be more effective zinc antidotes in this study (Domingo et al., 1988).

### 8.2 Pharmacokinetics

There is information on unithiol pharmacokinetics in various species of experimental animals.

Following oral administration between 60% (dogs; Wiedemann et al., 1982) and 30% (rats; Gabard, 1978) of the dose is absorbed and plasma peak concentrations are reached after 30 to 45 minutes. Plasma protein binding was measured at 70% in dogs by equilibrium dialysis (Wiedemann et al., 1982). This is in agreement with the figure of 65-75%, determined in rats (Planas-Bohne & Lehmann, 1983).

After intravenous administration unithiol is mainly distributed in plasma and kidneys, only minor concentrations were measured in the brain and other organs. The apparent volume of distribution in dogs was calculated to be 0.160 mL/kg (Wiedemann et al., 1982). Most unithiol excreted in the bile of rats is in its altered form and recovery in bile was 40% of the administered dose (Zheng et al., 1990).

Although unithiol is mainly distributed to the extracellular compartment, studies have demonstrated uptake by cells. Planas-Bohne & Olinger (1981) studying the interaction of antidotes with methyl mercury bound to erythrocytes demonstrated that unithiol is lost from the extracellular fluid. Wiedemann et al. (1982) found that the
distribution volume of radiolabelled unithiol exceeded the extracellular volume in dogs. In vitro studies have demonstrated that unithiol is taken up by cells of the basolateral membrane of the kidney and can bind mercury within cells (see section 7).

Unithiol is rapidly eliminated from the body. The serum half life is approximately 20 to 60 minutes and plasma clearance is approximately 2.6 mL/min/kg. In dogs given radiolabelled unithiol 93% was eliminated within 3 days, with the bulk (98%) eliminated in the urine and the rest in the faeces (Wiedemann et al., 1982).

Gabard & Walser (1979) stated that unithiol is not involved in important metabolic pathways and a quantity is excreted unchanged; Maiorino et al. (1988) demonstrated the presence of several acyclic and cyclic oxidized metabolites in the urine of rabbits.

8.3 Toxicology

Unithiol is of low acute and chronic toxicity. Studies have determined the LD$_{50}$ for various species and examined the effect of acute or chronic unithiol administration on trace element concentrations.

In order of decreasing sensitivity to unithiol, animal species can be ranked as follows: cat, dog, guinea pig, rabbit, rat and mouse (Kli mova, 1958; Aposhian, 1983). The optical isomers of unithiol do not differ in their toxicity (Hsu et al., 1983).

8.3.1 Acute toxicity

Unithiol is of relatively low toxicity. By the parenteral route the acute LD$_{50}$ of unithiol for various species is about 1 to 2 g/kg (Planas-Bohne et al., 1980; Aposhian et al., 1981; Aposhian, 1982; Hruby and Donner, 1987; Pethran et al., 1990). After intraperitoneal injection of lethal doses rats are highly irritable for some minutes before they become apathetic followed by cessation of breathing and death within 12 hours. The LD50 for a single dose in rats was 5 mmol/kg (1.14 g/kg) and after dosing on 10 consecutive days was 30.8 mmol/kg (Planas-Bohne et al., 1980). No acute toxicity was observed in mice receiving oral unithiol (100, 300 or 600 µg/mL) for 5 days in drink water. These doses are equivalent to 18, 55 and 109 mg/kg/day or 0.1, 0.3 and 0.5 mmol/kg/day (Jones et al., 1996).

In rats treated with a single intraperitoneal dose of 1 mmol/kg of unithiol, urinary zinc and copper excretion was increased whereas the excretion of iron and manganese was unchanged (Gabard et al., 1979).

A single subcutaneous injection of unithiol (1.6 mmol/kg) in mice caused a significant increase in δ-aminolevulinic dehydratase activity in the blood and a decrease in the kidney, with no change in the liver or brain. Unithiol also significantly increased the zinc concentration of the kidneys but did not change liver or brain concentrations. There was also a significant increase in liver and kidney lipid peroxidation (Santos et al., 2005).

8.3.2 Chronic toxicity

Unithiol is of relatively low toxicity even in chronic administration. Hrdina et al. (1998)
studied the effects of repeated injection of unithiol on the heart of rabbits. The animals were given intravenous unithiol, 50 mg/kg once a week for 10 weeks. There was no change in iron or selenium concentrations. There was a slight decrease in myocardial concentrations of calcium, potassium and magnesium, but only the later was significantly different. These changes were not associated with any haematological, histological or physiological changes.

Mice receiving unithiol 300 µg/mL in drinking water for 3 months showed no signs of toxicity. Haematological and biochemical parameters were also unchanged (Jones et al., 1996).

Rats receiving 600 µmol/kg/day orally (126 mg/kg/day) on 5 days per week for 66 weeks did not show any adverse effects. Treatment for 36 weeks led to a reduction in copper-concentrations in the kidneys, liver and skin (Planas-Bohne et al., 1980). Beagle dogs treated for 6 months with doses up to 15 mg/kg/day intravenously or 45 mg/kg/day orally showed no significant changes in blood-concentrations of glucose, uric acid, creatinine, total protein, sodium, potassium, calcium, magnesium and iron, and activity of liver enzymes and cholinesterase in the serum. In addition, the red and white blood picture as well as gain in body weight remained unchanged. A dose-dependent decrease in the copper content was found in the serum, liver, kidney and spleen. The macroscopic and microscopic examination of several organs revealed no pathological changes. After treatment for 10 weeks at a dose of 2 x 75 mg/kg/day intravenously the following changes were noted: a depletion of copper in the serum and in various organs, an increase of the iron content of the liver and spleen, and a decrease in haemoglobin, haematocrit, red blood cells, alkaline phosphatase activity and zinc content in the blood (Szincicz et al., 1983).

8.3.3 Reproductive toxicity and teratogenicity

Unithiol does not appear to produce reproductive toxicity or teratogenicity.

No teratogenic effects were reported in the offspring of rats given 600 µmol/kg/day orally (126 mg/kg/day) on 5 days per week. Female rats were mated with untreated males after 14, 26 or 60 weeks of treatment with unithiol. Treatment was continued during pregnancy and nursing. The number of pregnant animals and the litter size was smaller in the treated group but the difference was not significant (Planas-Bohne et al., 1980).

No adverse effects were observed in mothers or offspring in mice given up to 630 mg/kg/day in two dosing regimens: from gestation day 14 until birth or from gestation day 14 until post-natal day 21. The no observed effect level (NOEL) of 630 mg/kg/day is much higher than that used in the treatment of human heavy metal poisoning (Domingo et al., 1990).

Mice given unithiol, up to 300 mg/kg, on days 6 to 15 of gestation showed no maternal or reproductive effects. Unithiol had a minor effect on maternal and fetal mineral metabolism which was variable and not dose related. These effects did not produce maternal or embryofetal toxicity (Bosque et al., 1990).

No teratogenic effects were reported in rabbits given unithiol (up to 100 mg/kg
intravenously daily) from days 6 to 18 of gestation (Anon, 1992/1993).

Unithiol has been shown to protect against the developmental toxicity of arsenic (Domingo et al., 1992) and mercury (Gomez et al., 1994) in experimental animals. Mice were given a single intraperitoneal injection of sodium arsenite on day 9 of gestation followed by immediate injection of dimercaprol or unithiol with further doses at 24, 48 and 72 hours. Dimercaprol did not protect against arsenic-induced developmental toxicity, whereas unithiol was protective at 150 and 300 mg/kg/day and was able to prevent embryotoxicity and fetotoxicity. The higher dose also prevented maternal arsenic toxicity (Domingo et al., 1992). Pregnant mice were given a single oral dose of 30 mg/kg of methyl mercury chloride on day 10 of gestation followed by dimercaprol (by subcutaneous injection) or unithiol (by gavage) at 24, 48 and 72 hours. Dimercaprol administration did not prevent maternal or developmental toxicity, whereas unithiol in doses up to 360 mg/kg/day significantly reduced maternal lethality. Treatment with the higher doses, 180 and 360 mg/kg/day, also protected against mercury-induced embryotoxicity and teratogenicity (Gomez et al., 1994).

8.3.4 Genotoxicity

Unithiol has been evaluated for mutagenicity in the Ames test with negative results (Aposhian et al., 1983; Ruprecht, 1997). Normal DNA synthesis was maintained with unithiol concentrations up to 8 µg/mL in an in vitro study using 3 murine tumour cell lines. Above 8 µg/mL unithiol inhibited DNA synthesis, and above 30 µg/mL inhibition exceeded 80% (Jones et al., 1996).

An in vitro study found that unithiol increased the incidence of nickel-induced DNA breaks in a human leukaemia cell line. There was also an increase in DNA breaks in bacterial plasmids (a simpler system). Succimer and dimercaprol also increased DNA breaks in plasmids in the presence of nickel, but the effect was strongest with succimer. These metal binding agents all generate hydrogen peroxide in solution but succimer is the most potent. Free radicals are thought to be involved in the DNA damage observed. For the most potent compound, succimer, the breakage of DNA was completely prevented by the presence of mannitol and partially reduced by antioxidants. This protective effect was not investigated for unithiol (Lynn et al., 1999).

9. Volunteer studies

There are three main studies of unithiol pharmacokinetics, all conducted by the same group, consequently some volunteers took part in more than one study. The characteristics of each study are as follows:

- The study by Maiorino et al. (1991) involved 10 male volunteers, aged 24-34 years, weighing 68-98 kg.
- The study by Hurlbut et al. (1994) involved 5 volunteers (4 male, 1 female), aged 24 to 32 years, weighing 49-93 kg.
- The study by Maiorino et al. (1996) involved 4 male volunteers, aged 23 to 27 years, weighing 86-91 kg.
9.1 Absorption

Unithiol is rapidly absorbed. In volunteers given 3 x 100 mg capsules, unithiol was detected in blood within 0.5 to 4 hours after ingestion. Maximal concentrations were reached within 3 to 4 hours (Maiorino et al., 1991).

In 4 male volunteers the oral bioavailability of unithiol was calculated to be 39%, with a range of 19-62% (Hurlbut et al., 1994).

9.2 Distribution

In volunteers given 3 x 100 mg capsules, metabolites (altered unithiol) were confined to the plasma portion of the blood suggesting that they were bound to plasma proteins (Maiorino et al., 1991). Plasma protein binding of unithiol was approximately 90% when measured by equilibrium dialysis in human plasma samples from 3 volunteers (Wiedemann et al., 1982). However in a further study by Maiorino et al. (1996), less than 1% of unithiol was present in an unaltered form in the plasma 5 hours after a single oral dose of 300 mg. The protein-bound unithiol and non-protein-bound unithiol disulphides were present as 62.5% and 36.6% of the total unithiol, respectively. The protein-bound unithiol was present as a unithiol-albumin complex (84%) and a higher molecular weight complex (16%).

In volunteers given unithiol 3 mg/kg intravenously over 5 minutes the volume of distribution varied from 2.67 to 15.4 L/kg (Hurlbut et al., 1994).

Although unithiol is mainly distributed to the extracellular compartment, studies have demonstrated uptake by cells. An in vitro study investigating the interaction of antidotes with methylmercury bound to erythrocytes demonstrated that unithiol is lost from the extracellular fluid (Planas-Bohne & Olinger, 1981) and uptake by human erythrocytes has been demonstrated in vitro (Wildenauer et al., 1982). Uptake of unithiol by the renal proximal cells is thought to be mediated by the organic anion transporter (Islinger et al., 2001; see section 7).

9.3 Elimination

Unithiol is rapidly metabolised and subject to renal elimination.

In volunteers given 3 x 100 mg unithiol capsules the elimination half-life in blood of unithiol and metabolites (altered unithiol) was 4.4 and 9.6 hours, respectively (Maiorino et al., 1991). Maiorino et al. (1996) determined the half-lives of unithiol and metabolites to be 1.8 and 20 hours, respectively. The long half-life of altered unithiol was thought to reflect the stability of the unithiol-albumin complex and since unithiol is released slowly, albumin may act as a reservoir for unithiol.

In volunteers given unithiol 3 mg/kg intravenously over 5 minutes blood concentrations declined rapidly with an apparent elimination half-life of 1.8 hours. By 96 hours 12% of the total unithiol found in the urine was excreted as the parent compound, representing 10% of the administered dose; 88% was present as disulphide metabolites (74% of the administered dose). The metabolites are eliminated more slowly than the parent compound, with an elimination half-life of 23 hours (range 19.8-
The apparent difference in blood and urine half-lives in the Maiorino et al. (1991) oral and Hurlbut et al. (1994) intravenous study may be due to different metabolites produced following administration by different routes. In addition the total unithiol concentration was determined at different time points (Hurlbut et al., 1994).

### 9.4 Metabolism

Unithiol is extensively metabolised and unchanged drug is present as only a small concentration in blood and urine. In volunteers given unithiol 3 mg/kg intravenously over 5 minutes only 12% of unchanged unithiol was detected in the blood after 15 minutes (Hurlbut et al., 1994). In volunteers given 3 x 100 mg unithiol capsules 3.7% was excreted as unchanged unithiol and 38.7% as metabolites by 15 hours. Of the total unithiol found in the urine by 15 hours, unchanged unithiol and metabolites represented 9% and 91%, respectively. The metabolites are thought to be disulphide compounds (Maiorino et al., 1991). In a later study (Maiorino et al., 1996) the unithiol disulphide metabolites were determined to be cyclic polymeric unithiol disulphides (97%), unithiol-cysteine mixed disulphide (2.5%) and acyclic unithiol disulphide (0.5%).

### 9.5 Effect of DMPS on the excretion of metals

Few volunteer studies on the effect of unithiol on metal excretion are available.

#### 9.5.1 Arsenic elimination

In addition to increasing urinary elimination of arsenic, unithiol has also been shown to alter the relative urinary concentrations of organoarsenic metabolites.

The arsenic-antidote complex was determined in the urine of Romanian subjects exposed to high concentrations of arsenic in drinking water (up to 16 µg/L). Samples were collected before and after oral administration of 300 mg of unithiol. Subjects had been asked to avoid seafood for three days prior to and during the collection period. The presence of a unithiol-monomethylarsenous acid (As³) complex was demonstrated in the urine samples of subjects given unithiol. Administration of unithiol resulted in a decrease in dimethylarsenic acid (As⁵) and an increase in monomethylarsonic acid (As³) concentrations. Monomethylarsenous acid (As³) is a substrate for the biomethylation of arsenic from monomethylarsonic acid (As³) to dimethylarsenic acid (As⁵); the formation of the unithiol-monomethylarsenic acid complex reduces the availability of monomethylarsenous acid (As³) for biomethylation and inhibits further methylation (Gong et al., 2002).

A similar change in urine concentrations of dimethylarsinic acid and monomethylarsonic acid was also found in the study by Aposhian et al. (1997) investigating arsenic excretion in two populations in Chile. In one town the drinking water contained 593 µg/L of arsenic, and in the other 21 µg/L (controls). Subjects were asked to exclude seafood from their diet for 3 days prior to the study and bottled water (arsenic <0.5 mg/L) was drunk throughout. Subjects were excluded if they had a history of previous antidotal therapy, hypersensitivity to similar metal-
binding agents or administration of other investigational drugs, serious renal or
psychiatric disease, abnormalities in blood biochemistry or urine analysis that could
interfere with evaluation, pregnancy, lactation or abuse of alcohol or recreational
drugs. There were 13 subjects in the high arsenic exposure group and 11 controls.
Urine samples were collected before and after oral administration of 300 mg unithiol.
In the 2 hour period after unithiol administration the urinary concentration of the
metabolites monomethylarsonic acid and dimethylarsinic acid represented 42% and
37-38%, respectively, with an inorganic arsenic concentration representing 20-22%
of the total urinary arsenic. The normal range of monomethylarsonic acid is 10-20%
and the percentage increase was almost the same for the two groups. The rise in
monomethylarsonic acid was accompanied by a decrease in dimethylarsinic acid.
The percentage of inorganic arsenic also increased with unithiol treatment.

9.5.2 Bismuth elimination

Two groups of 12 volunteers (age 26-65 years), who had been treated with colloidal
bismuth subcitrate for 28 days because of *Helicobacter pylori*-associated gastritis, took
part in a study of bismuth elimination with unithiol and succimer. Each subject
received a single oral dose of succimer or unithiol 30 mg/kg in a randomised single
blind study. The succimer or unithiol was given 7 to 14 days after the last dose of
bismuth. Both antidotes produced a 50-fold increase in urinary bismuth excretion
compared to control urine samples. The highest concentration was excreted within
the first 4 hours after dosing. No significant difference was observed in bismuth
elimination between succimer and unithiol and both were well tolerated (Slikkerveer et
al., 1998).

9.5.3 Cadmium elimination

Of the 6 metal-binding agents investigated in an *in vitro* study using human cell
cultures, unithiol, succimer and mercaptosuccinic acid were found to the most
effective at increasing cadmium movement from cells. Unithiol produced the most
rapid elimination from cells in the first two hours, but the other two agents mobilised
more cadmium than unithiol (Bakka et al., 1981).

9.5.4 Mercury elimination

Significant increases in urinary mercury elimination have been demonstrated with
unithiol administration.

The mercury elimination rate was determined in 5 healthy volunteers (4 male, 1
female, aged 24 to 32 years, 49-93 kg) given unithiol 3 mg/kg intravenously over 5
minutes. Unithiol increased mercury excretion by a factor of 24.2 in the 11 hours
after administration. No relationship was observed between the dose of unithiol and
the quantity of mercury excreted in the urine (Hurlbut et al., 1994). In the 4 male
subjects who had taken part in a previous oral study (Maiorino et al., 1991) the
quantity of mercury excreted in the 12 hours after intravenous administration was
less than that excreted in the same period after oral unithiol (Hurlbut et al., 1994).

Mercury elimination was examined after a unithiol challenge test in 12 male (66-96
kg), former chloralkali workers exposed to metallic mercury vapour for 2-18 years.
The investigation was undertaken 18-56 months after exposure has ceased. A single 300 mg dose of unithiol was given and this increased 24 urinary excretion of mercury by a factor of 7.6. A high proportion (62%) was excreted within the first 6 hours and this probably reflects mercury stored in the kidney (Sallsten et al., 1994).

The clinical efficacy of unithiol was investigated in 10 male volunteers (aged 19-45 years) with occupational mercury exposure (with a urine mercury concentration equal to or greater than 50 μg/g of creatinine). Each subject received unithiol 100 mg orally three times a day for 5 days. They had been asked to omit seafood from the diet for one month and to take no iron-containing vitamin preparations or medications for 2 weeks prior to the study. One subject developed a macular rash which resolved in two days. Otherwise, all the subjects remained well with no changes in renal or liver function, blood biochemistry or vital signs. In 9 of the 10 subjects mercury elimination was significantly enhanced during the first 24 hours after unithiol administration, and in all subjects the mean increase in mercury excretion was higher over the 5 day period compared to the baseline (Torres-Alanís et al., 1995).

Gonzalez-Ramirez et al. (1998) also studied the effect of unithiol on mercury elimination in volunteers with occupational exposure (5 males, 3 females, aged 21-57 years). The unithiol was given in 3 cycles: 3 days after an initial challenge test, unithiol was given for 8 days with 5 subsequent days with no treatment. This was followed by second cycle of 7 days of unithiol, a 5 day period of no treatment and then 6 days of unithiol. The unithiol was given orally 1 hour before breakfast, lunch and dinner in doses of 100 mg, 100 mg and 200 mg, respectively, on each treatment day. One subject developed a maculopapular rash and raised liver enzymes after the first course and did not receive further doses. Prior to treatment the mean total urinary mercury excreted in 24 hours was 504 μg (range 140-1692 μg) and during the first course of unithiol this rose to 1754 μg (range 657-2880 μg). The figure for the two subsequent courses became progressively lower (314 μg [range 152-658 μg] and 173 μg [range 74-443 μg]) but in both cases was higher than the period of no treatment which preceded it (106 μg [range 66-212 μg] and 48 μg [range 30-97 μg]). Unithiol was effective in lowering the body burden of mercury and increasing the urinary mercury concentration.

The elimination of mercury following unithiol administration was examined in 75 mercury-exposed volunteers from a gold mining area in the Philippines. Urine samples were collected before and 2 to 3 hours after unithiol administration (200 mg orally). In the first urine the mean concentration of inorganic mercury was 15.7 μg/g of creatinine and for organic mercury it was 2.2 μg/g of creatinine. In the samples after unithiol dosing the concentrations were 262 μg/g of creatinine and 14.5 μg/g of creatinine, respectively. Unithiol increased the inorganic urinary concentration by a factor of 16 and the organic mercury concentration by a factor of 5.1 (Drasch et al., 2007).

Mercury clearance during dialysis was investigated in an in vitro experiment using pooled plasma samples to which mercury and metal-binding agents had been added. Of the agents investigated acetylcysteine was the most effective in clearing mercury after 90 minutes of in vitro dialysis, reducing the mercury concentration in the perfusate by 73%, whereas unithiol removed almost 70% of mercury in the perfusate.
Unithiol was more effective than succimer but the results were not statistically different. In contrast the quantity of mercury removed from plasma without the presence of a metal-binding agent was very low at 5% (Ferguson & Cantilena, 1992).

9.5.5 Palladium elimination

There is limited information on palladium elimination with unithiol. In a study of 50 volunteers the elimination of palladium increased from 0.3 to 38 µg/g of creatinine and there was no difference between oral and intravenous administration of unithiol (Runow, 1996).

9.5.6 Trace element elimination

Unithiol has been shown to increase elimination of some trace elements in volunteer studies.

Trace element elimination was examined after a unithiol challenge test in 12 male (66-96 kg), former chloralkali workers exposed to metallic mercury vapour for 2-18 years. The investigation was undertaken 18-56 months after exposure has ceased. A single 300 mg dose of unithiol was given and this increased 24 hour urinary excretion of copper by a factor of 12 and zinc by 1.5 (Sallsten et al., 1994).

Eleven patients presenting with concerns over exposure to mercury in dental amalgam were given a unithiol challenge test, and the urinary elimination of trace elements examined. The patients (8 female, 3 male) had no known occupational exposure to mercury. The dose of unithiol was 3 mg/kg intravenously and urine samples were taken 1 hour before and 1 hour after. There was a significant increase in mercury excretion (3-107 fold) in all subjects. The elimination of chromium and manganese was unchanged and the urinary concentrations of cobalt, aluminium and molybdenum were too low for reliable measurement. The urine copper (2-119 fold), selenium (3-43.8 fold), zinc (1.6-44 fold) and magnesium (1.75-42.7 fold) concentrations were increased in most patients (Torres-Alanís et al., 2000).

Trace element blood concentrations were examined in 80 volunteers (51 females, 29 males) given 2 mg/kg unithiol intravenously. An increase in urinary copper and zinc concentrations were observed 30 and 120 minutes after injection. The selenium concentration was unaffected. There was also a decrease in blood concentrations of copper, zinc and selenium. However, this may have been due to a dilution effect since the concentrations returned to normal within 120 minutes of the injection and a similar effect was observed within iron concentrations (Høl et al., 2003).

10. Clinical studies – clinical trials

Few controlled clinical trials on unithiol are available, and most concern mercury.

10.1 Arsenic and unithiol clinical trials

Unithiol was investigated in a randomised placebo-controlled trial in the management of chronic arsenicosis due to contaminated drinking water (arsenic >50 µg/L) in
India. All the patients weighed 40-56 kg and had been drinking the water for more than 3 years. Subjects were excluded if they had ceased drinking arsenic-contaminated water for more than 3 months, had been treated with other antidotes, had a history of smoking, alcoholism, were taking hepatotoxic drugs or were serum positive for hepatitis B virus surface antigen. Pregnant or lactating women were also excluded.

A total of 21 patients were randomly assigned to 2 treatment groups: 11 patients (9 males, 2 females, mean age 30.63 years) received unithiol and 10 patients (5 males, 5 females, mean age 34.4 years) received the placebo. The unithiol dosage regimen was 100 mg 4 times a day for 1 week, repeated in the third, fifth and seventh week. Further ingestion of arsenic-contaminated drinking water was also stopped. Therapy with unithiol resulted in significant clinical improvement as evaluated by an objective clinical scoring system. Cessation of exposure and placebo also reduced clinical scores but the post-treatment scores were significantly lower for unithiol-treated subjects. Improvement in clinical scores for the placebo group was attributed to cessation of exposure, rest and provision of an adequate hospital diet. The most significant improvement was seen in the clinical score of weakness, pigmentation and lung disease. There were also significant increases in total urinary arsenic excretion with unithiol treatment, compared to no increase in the placebo group. Unithiol was well tolerated with no adverse effects reported (Guha Mazumder et al., 2001).

10.2 Copper (Wilson’s disease) and unithiol clinical trials

Wang et al. (2003) studied 28 patients with Wilson’s disease (18 males, 10 females aged 14-20 years). Patients were included on the basis of presence of extrapyramidal symptoms and signs, presence of characteristic corneal Kayser-Fleischer ring observed with a slit lamp, a serum ceruloplasmin <200 mg/L and copper oxidase concentration <0.21 units and urinary copper >100 μg (1.56 μmol)/24 hours. Group A received captopril, 1 mg/kg orally daily in 3 divided doses, Group B unithiol 20 mg/day intravenously and Group C both. Group D was the control group and did not receive either drug. Serum sulphydryl concentrations and 24 hour urinary copper concentrations were the markers of anticopper efficacy. Unithiol had a more potent anticopper effect than captopril and increased urinary copper concentrations and serum sulphydryl concentrations. Only 1 patient developed an adverse effect with transient elevation of alanine aminotransferase.

10.3 Lead and unithiol clinical trials

There are few clinical trials on the use of unithiol in lead poisoning.

One of the earliest reports of unithiol use in the treatment of lead poisoning was by Anatovskaya (1962). Sixty men with chronic lead toxicity were given 250 mg intramuscularly for 20 days. Blood concentrations of lead fell and urinary excretion increased. The clinical signs and symptoms improved subjectively and objectively. Haematological parameters and liver function improved in more patients in the unithiol-treatment group compared to controls given only supportive care. In addition patients treated with unithiol could be discharged from hospital 6 weeks earlier than controls.
A more recent study involved children attending a lead poisoning treatment clinic in Baltimore, USA, where lead paint was the main source of poisoning. The criteria for inclusion were a blood lead concentration of 400-600 µg/L, normal hepatic, renal and haematological function, no history of antidotal therapy within the previous 3 months, no concurrent disease and an age of 30 to 72 months. Six children (5 males, 1 female, aged 31 to 53 months) received a 5 day course of unithiol, 200 mg/m² daily. Another 6 children (1 male, 5 females, aged 38-69 months), received 400 mg/m² daily for 5 days. The drug was well tolerated in all cases. Administration of either dose reduced the blood lead concentration to approximately 78% of its pre-treatment concentration by 48 hours. After 96 hours the blood lead concentration was 76% and 68% of its pre-treatment concentration in the low and high dose group, respectively. Blood lead concentrations did not increase until 48 hours after cessation of therapy. Urinary excretion of both copper and zinc were increased, 2-30 fold and 1.2-9.1 fold, respectively with higher concentrations of both in the higher treatment group. There were no significant changes in plasma copper or zinc concentrations. The urinary concentration of lead increased 1.3-15 fold between the last pre-treatment day and the first treatment day (Chisolm & Thomas, 1985). This trial was later terminated following the occurrence of at least one case of Stevens-Johnson syndrome and succimer was used instead (Chisolm, 1990).

10.4 Mercury and unithiol clinical trials

There are a small number of clinical trials investigating the effect of unithiol on mercury toxicity. An early study undertaken in Iraq, with preliminary results reported by Bakir et al. (1976) was limited in scope due to various circumstances (Clarkson et al., 1981). A more recent study examined patients with chronic mercury exposure in the Philippines (Böse-O'Reilly et al., 2003). Another study in China examined the effects of antidotal treatment in acutely poisoned patients treated 5 months after exposure (Zhang, 1984). A Mexican study examined the effect of unithiol on mercury excretion in patients with high mercury concentrations due to use of mercury-containing facial cream (Garza-Ocañas et al., 1997).

The early study investigated antidotal therapy in patients with methyl mercury poisoning. The source was homemade bread made from wheat contaminated with a methyl mercury fungicide over the winter of 1971-1972. Antidotal agents where in limited supply and were not available until February 1972 after exposure had ceased. The conditions of the time did not allow for the implementation of a clinically controlled study but it was possible to obtain data on the effects of antidotes on blood mercury concentrations. D-penicillamine (12 patients), N-acetyl-DL-penicillamine (17), unithiol (10) and a thiolated resin (8) were used. There were 27 females and 20 males, aged from 18 months to 55 years. Ten other patients received a placebo and 6 received no specific treatment. The duration of treatment was variable but for unithiol was 4 to 15 days. All agents reduced blood mercury concentrations but unithiol was the most effective. However, the patients did not show any immediate clinical improvement, presumably because the duration of therapy was too short (Clarkson et al., 1981).

Unithiol was evaluated in the management of chronic mercury exposure, including exposure from mercury vapour, inorganic mercury and organic methyl mercury, in the gold mining area of Mount Diwata, in the Philippines. A total of 95 patients (no details...
given) were included in the study. There was no control group. Unithiol was given orally at a dose of 200 mg twice daily for 14 days for adults and 5 mg/kg/day for children. Patients were assessed by questionnaire, medical, including neurological, examination and neuropsychological testing before and after therapy. Blood, urine and hair samples were analysed for mercury concentrations before therapy and blood and urine after therapy. Two study populations were identified: those living near Mount Diwata and exposed to metallic and/or inorganic mercury (60 patients), and those living downstream in Monkayo who were exposed to methyl mercury (35 patients). Exposure to mercury continued during therapy with unithiol. The mercury concentrations in hair and blood did not differ between the two populations before unithiol therapy. The urine concentration was significantly higher in the Mount Diwata population (due to the differing pharmacokinetics of organic and inorganic mercury). There was therefore a higher renal excretion of mercury in the Mount Diwata population when treated with unithiol. However, the Monkayo population demonstrated a relative increase in renal excretion of mercury almost as high as the Mount Diwata population when given unithiol. Some patients (number not specified) did not respond to unithiol administration and showed no increase in mercury excretion. In the Monkayo group there was only a modest decrease in blood mercury concentrations, indicating the duration of treatment was too short to have a long-term effect on mercury stored in tissues. More than two-thirds of patients reported an improvement in subjective complaints after therapy and objective neurological parameters also showed significant improvement. Significant improvement was also demonstrated in two neuropsychological tests. The authors concluded that unithiol could increase mercury excretion but that a 14 day regimen was too short to have a permanent effect on mercury concentrations (Böse-O’Reilly et al., 2003). This study has a number of limitations including the absence of a control group, lack of details of patients (age, weight) and continued exposure to mercury during therapy.

Forty-one patients (aged 2 to 65 years) from 8 families were poisoned with mercury following ingestion of rice contaminated with an ethyl mercury seed dressing. One patient died soon after onset of symptoms and 8 were admitted in the initial acute phase of intoxication. The remaining 40 patients demonstrated a variety of clinical features 5 months after ingestion and 27 were treated with unithiol (250 mg daily by intramuscular injection) and/or succimer (500 mg twice daily by intravenous injection). The drugs were given for 3 days followed by a 4 day break and then another 3 day course, if required. Patients were given 1 to 8 courses until the urinary mercury concentration was normal. The 13 untreated patients showed little improvement in clinical features of toxicity but all those on therapy had some relief and 19 became asymptomatic. In 2 cases there was only slight improvement. In patients where the urinary concentration was measured before therapy, all but one had increased mercury excretion during antidotal administration. Side effects were mild and generally resolved within 30 minutes to 4 hours. Unithiol was found to be more effective, although no data distinguishing between the two drugs is given. In addition, the two antidotes were used interchangeably in some patients (Zhang, 1984).

Unithiol was also used in 12 females (aged 19-45 years) with mercury toxicity following use of a facial cream containing 5.9% mercurous chloride (calomel) for 2 to 10 years. Two patients were symptomatic (exanthe ma and tremor) and all had elevated urinary mercury concentrations. Subjects were given a 5 day course of
unithiol (200 mg/day) as outpatients. Only 8 subjects took the unithiol as prescribed and supplied 24 hours urine samples for analysis. In all cases there was a significant increase in urinary mercury concentrations after 24 hours of unithiol. One symptomatic patient has complete resolution of effects and the other had persistent tremor. Unithiol was well tolerated in all patients (Garza-Ocañas et al., 1997).

11. Case reports - clinical studies

In many clinical case reports of unithiol use in poisoning the authors do not determine a balance between the quantity of metal absorbed and excreted; this can be difficult where the dose ingested, injected or inhaled cannot be quantified. Clinical efficacy of unithiol is often only stated in terms of enhancing excretion and/or decreasing blood concentrations in the absence of severe adverse effects. In many cases, the authors are unable to distinguish between the effect of unithiol administration and the effect of supportive therapy (including removal from the source).

The efficacy of a metal-binding agent may be difficult to determine. After discontinuation of metal exposure (and absorption) a decrease in the blood concentration will occur without any therapy. Clinical efficacy should not be judged only by the amount of metal excretion or the decrease of blood concentrations. The reduction of the tissue content in the target organ and the restoration of pathological alterations also need to be considered. It is important to note that enhancement of the metal excretion by mobilisation may increase the metal burden of the target organ by redistribution, and conversely the body burden may be reduced without a striking decrease of the blood concentrations. However, in some case reports severe toxicity usually associated with a demonstrated high blood or urine concentration does not occur, and this may reasonably be assumed to be due to antidotal therapy. With these reservations in mind, it is clear that administration of unithiol can prevent development of toxicity and in symptomatic patients it can reduce recovery time and improve clinical signs and symptoms of toxicity.

Reference values for the metal and metalloids (Walker, 1998) are given as a guide at the start of each section to aid interpretation of the concentrations given in the case reports.

11.1 Use in antimony poisoning

Reference values for antimony (Walker, 1998):

<table>
<thead>
<tr>
<th>Group</th>
<th>Component</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>Serum/plasma</td>
<td>0.18 µg/L</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
<td>0.26 µg/L</td>
</tr>
<tr>
<td></td>
<td>Urine</td>
<td>0.05 µg/L</td>
</tr>
<tr>
<td>Adults (unexposed)</td>
<td>Urine</td>
<td>0.8 µg/L</td>
</tr>
</tbody>
</table>

There is limited information on the use of unithiol in antimony poisoning, but it appears to be of benefit in the management of poisoning with trivalent antimony compounds. There is no information on its use in the management of poisoning with the less toxic pentavalent antimony compounds.

A 2 year 11 month old child was treated with unithiol after ingestion of an unknown...
quantity of tartar emetic (antimony potassium tartrate). The clinical features, particularly massive fluid loss and dehydration, were consistent with antimony poisoning. She was given unithiol 65 mg intravenously then 3 x 100 mg daily for 10 days followed by 3 x 50 mg daily for another 10 days. She was also treated with exchange transfusion at 39 hours post-ingestion. The serum antimony concentration at 4.5 hours post-ingestion was 0.6 mg/L and the urine concentration at 7 hours 31 mg/L. Unithiol was considered effective in reducing the antimony concentration in the early stages of poisoning (Iffland & Bösche, 1987).

Unithiol has also been used with apparent success in other paediatric cases of antimony potassium tartrate poisoning (Kemper et al., 1989; Jekat & Kemper, 1990) and is recommended by others for the management of antimony poisoning (Chzhi-Tysan, 1959; Lauwers et al., 1990).

### 11.2 Use in arsenic poisoning

Reference values for arsenic (Walker, 1998):

<table>
<thead>
<tr>
<th>Type</th>
<th>Lower Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>&lt;0.13 µmol/L (&lt;10 µg/L)</td>
</tr>
<tr>
<td>Urine</td>
<td>&lt;0.13 µmol/24 hours (&lt;10 µg/24 hours) of inorganic arsenic</td>
</tr>
<tr>
<td>Urine 1</td>
<td>&lt;40 nmol/mmol creatinine (unexposed)</td>
</tr>
<tr>
<td>Urine 2</td>
<td>&lt;173 nmol/mmol creatinine (occupational exposure)</td>
</tr>
</tbody>
</table>

Unithiol has been used successfully in a number of cases of acute and chronic arsenic poisoning and is considered the antidote of choice for arsenic toxicity (Adam et al., 2003).

A 33-year-old female (62 kg) was treated with unithiol after accidental ingestion of arsenic paste (approximately 1.85 g of arsenic trioxide). She presented 100 hours after ingestion and was started on unithiol (250 mg intravenously every 6 hours for 48 hours, then 250 mg orally 3 times a day for 48 hours, followed by 250 mg every 12 hours for 23 days). Her condition improved after 2 days and she made a full recovery. The highest urinary arsenic concentrations occurred on hospital days 1-3 (Kruszewska et al., 1996).

Two brothers, aged 21 and 19 years, were treated with unithiol after ingestion of 4 g and 1 g, respectively, of a powder which was later identified as arsenic trioxide. Treatment with unithiol was started 32 and 48 hours after ingestion. In the older brother the blood arsenic concentration at 26 hours was 400 µg/L. He suffered a cardiac arrest just before unithiol was started but was successfully resuscitated. At 36 hours the blood arsenic concentration of the younger brother was 98 µg/L. Both men made a full recovery with no clinical or electrophysiological signs of arsenic neuropathy (Moore et al., 1994).

A 21-year-old male was treated with unithiol after intentional ingestion of 0.6 g of arsenic trioxide. He presented to hospital seven hours after ingestion and was dehydrated following diarrhoea, intestinal colic and vomiting. He was given a gastric lavage, rehydrated (on average 5.5 L of fluid/daily over 5 days) and given high dose unithiol. The parenteral regimen was 250 mg/hour on day 1, 125 mg/hour on day 2 and then 62.5 mg/hour on days 3-5. From days 6-12 he was given oral doses of 600-700 mg/day. The total dose given was 15.225 g. The serum arsenic concentration
on day 1 was 143 mg/L (urine 210,000 µg/L), on day 2, 29 mg/L (3800 µg/L), on day 3, 10 mg/L (1675 µg/L) and by day 8 was <1 mg/L (115 µg/L). He developed mild increases in transaminase concentrations but remained otherwise well (Horn et al., 2002). Heinrich-Ramm et al. (2003) examined the arsenic compounds excreted in this patient. In urine sampled on days 2-8 he excreted about 50 mg of arsenic of an estimated total ingested dose of 230 mg of arsenic. In the first urine sampled after unithiol therapy (11 hours post-ingestion) the arsenic concentration was 215 mg/L. This fell by a 1000-fold to 169 µg/L after 8 days of unithiol administration. As reported in other studies (see section 9.5.1), administration of unithiol resulted in a decrease in the urinary concentration of dimethylarsinic acid. In this patient the urinary concentration of dimethylarsinic acid did not exceed that observed in a reference population where it had accounted for 95% of the total arsenic excreted. In contrast, the urinary dimethylarsinic acid concentration in this patient accounted for <5% of the total arsenic excreted. This supports the theory that unithiol interferes with methylation of arsenic.

A 27-year-old female developed gastrointestinal effects, ECG changes and liver damage after ingestion of 9 g of arsenic trioxide. She was treated with intravenous fluids, activated charcoal and continous alkaline irrigation of the stomach over 36 hours. She was given succimer (15 mg/kg every 8 hours for 26 days) and intramuscular dimericarol (4 mg/kg every 4 hours) for 24 hours. A second course of dimericarol was administered on day 5 due to continued deterioration. She was also started on a regimen designed to enhance methylation of arsenic derivatives which are less toxic and more readily excreted. She was given hydroxocobalamin, methionine, folic acid, sodium bicarbonate, glutathione and intravenous unithiol (250 mg every 4 hours for 5 days). She began to improve within 48 hours with improved pulmonary function and ECG. Liver function tests began to resolve but were elevated for more than a month. She also received unithiol from days 15 to 18. Urinary arsenic concentrations fell rapidly in the first 10 days. At follow up one year later she had mild polyneuropathy. The role of succimer in this patient's recovery was not evaluated. Unithiol, with and without the methylating regimen, increased the proportion of methylated arsenic metabolites (monomethylarsonic acid and dimethylarsenic acid) in the urine (Vantroyen et al., 2004).

A 33-year-old female with chronic arsenic poisoning from an unknown source was treated with unithiol. She presented with a 1.5 year history of episodes of peripheral neuropathy, pancytopenia, ventricular tachycardia, gastrointestinal symptoms, skin rash and nail changes. Her blood arsenic concentration was 56 µg/L and the 24 hour urine concentration 130 µg/L. Analysis of well water demonstrated an arsenic concentration of 78 µg/L. Electromyography revealed moderate demyelinating neuropathy with axonal involvement. She was started on succimer 10 mg 3 times a day but serial urinary arsenic determination did not show any elimination. Her neuropathy continued to progress and she required ventilation. She was then started on unithiol at 250 mg/kg intravenously every 4 hours. During the first 24 hours of treatment the urinary arsenic concentration rose from 101 to 300 µg/L. There was also improvement in her neuropathy and she was continued on unithiol for 12 days. She was much improved, extubated and discharged in a wheelchair 10 days later. By 3 months she was walking on her own with some residual paraesthesiae and weakness in distal lower extremities. At follow up one year later she had only mild weakness and residual paraesthesiae controlled with amitriptyline.
Adam et al. (2003) reports 6 cases of arsenic poisoning, with retrospective comparison of the use of dimercaprol and unithiol. Three patients were treated with dimercaprol. Two of these patients with blood arsenic concentrations of 540 µg/L and 620 µg/L died within 34 hours and 6 days of exposure, respectively. One patient had a maximal blood arsenic concentration of 558 µg/L and developed paraplegia as a result of arsenic poisoning. The three patients treated with unithiol recovered fully. Two of these patients (including one with anuric renal failure) had very high blood arsenic concentrations of 2240 µg/L and 4469 µg/L. The third patient had a relatively mild course, after the early use of unithiol, despite a blood arsenic concentration of 245 µg/L. The authors concluded that unithiol is the treatment of choice for arsenic poisoning and that dimercaprol is obsolete.

11.3 Use in beryllium poisoning

No well documented case reports of unithiol use in beryllium poisoning could be found.

11.4 Use in bismuth poisoning

Reference values for bismuth (Walker, 1998):

- **Blood**
  - <0.5 nmol/L (<0.1 µg/L) basal
  - Up to 240 nmol/L (up to 50 µg/L) acceptable therapeutic
  - >480 nmol/L (>100 µg/L) risk of toxicity

- **Urine**
  - <0.5 nmol/L (<0.1 µg/L)

Unithiol has been used in both acute (Stevens et al., 1995; Bogle et al., 2000; Dargan et al., 2001; Dargan et al., 2003b; Ovaska et al., 2008) and chronic (Playford et al., 1990) bismuth poisoning, although clinical deterioration has been reported in one chronic case due to redistribution of tissue stores of bismuth (Teepker et al., 2002). Unithiol is considered an effective antidote for acute bismuth poisoning (Andersen, 1999).

Unithiol was started 24 hours after intentional ingestion of 2.88 g of bismuth subcitrate in a 13-year-old girl. She was given 30 mg/kg orally for 10 days and 10 mg/kg for 9 days. The serum bismuth concentration at 4 hours was 300 µg/L, 14 µg/L at 48 hours and 8 µg/L at 72 hours. At 10 days post-ingestion the serum bismuth concentration was 1.8 µg/L. She remained well throughout (Bogle et al., 2000).

In a similar case a 30-year-old male was started on unithiol after ingestion of 4.8 g of tripotassium dicitratobismuthate. He was admitted 2 hours post-ingestion with vomiting, but was otherwise well. The initial bismuth blood concentration was 424 µg/L and urine 10,000 µg/L. Oral unithiol was started on day 2 (200 mg four times daily for 10 days, then 200 mg twice daily for 10 days). He remained well and after antidotal therapy the blood concentration was 17 µg/L and urine 37 µg/L (Dargan et al., 2001).

A 21-year-old male developed bismuth toxicity after ingestion of 50 to 60 tablets of
tripotassium dicitratobismuthate. The blood bismuth concentration was 590 µg/L and he was initially given dimercaprol 150 mg intramuscularly. Four hours later he was started on haemodialysis. He was subsequently given unithiol 250 mg intravenously 4 hourly for 48 hours and then 250 mg 6 hourly for 48 hours, then 500 mg orally in two divided doses for 14 days (days 6 to 19 after ingestion). He received haemodialysis for the first 6 days and on days 8, 9 and 12. Each session lasted 4 hours and started 1 hour after unithiol administration. No significant clearance of bismuth occurred with dimercaprol. In contrast significant bismuth clearance was obtained with unithiol and despite improving renal function cessation of unithiol on day 20 resulted in a decrease in urinary bismuth clearance (Stevens et al., 1995).

Unithiol has been used in poisoning resulting from the use of bismuth iodoform paraffin paste used to pack a large wound of the sacrum following tumour excision. The patient began to develop neurological effects 5 days later and blood and urine bismuth concentrations were raised (340 µg/L and 2800 µg/L, respectively). The packing was removed and he was started on unithiol (intravenously 5 mg/kg four times daily for 5 days, 5 mg/kg three times daily for 5 days, and 5 mg/kg twice daily for 17 days, then orally 200 mg 3 times daily for 10 days, 200 mg twice daily for 14 days; 61 days in total). His neurological effects improved over the next month and the bismuth concentrations were normal after 55 days (Dargan et al., 2003b; Ovaska et al., 2008).

A 68-year-old male with renal impairment developed encephalopathy from ingestion of double the dose of tripotassium dicitratobismuthate (864 mg of bismuth daily) for 2 years. He was given unithiol 100 mg 3 times daily for 10 days. Renal clearance of bismuth increased 10-fold from 0.24 mL/minute to 2.4 mL/minute during this time. The whole blood bismuth concentration decreased from 880 µg/L to 46 µg/L over a 50 day period and he had marked improvement in cerebral function. There were no adverse effects (Playford et al., 1990).

In a 49-year-old female with encephalopathy from 5 years of chronic oral abuse of bismuth, unithiol had to be discontinued due to deterioration in her clinical condition. She was given 100 mg daily and there was a marked decrease in plasma bismuth concentrations with an increase in urinary bismuth concentrations. However, she deteriorated with cluster-like myoclonic jerks and stupor and the unithiol was stopped after 3 days. Her clinical condition improved over the next few weeks and lagged behind the plasma bismuth concentrations. They deceased from 550 µg/L to 30.4 µg/L by day 21 when she demonstrated marked improvement. The unithiol may have caused redistribution of bismuth from tissue stores and caused the clinical deterioration in this patient (Teepker et al., 2002).

11.5 Use in cadmium poisoning

Reference values for cadmium (Walker, 1998):

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>&lt;27 nmol/L (&lt;3 µg/L) non smokers</td>
</tr>
<tr>
<td></td>
<td>&lt;54 nmol/L (&lt;6 µg/L) smokers</td>
</tr>
<tr>
<td>Urine</td>
<td>44.5 nmol/L (5 g/L)</td>
</tr>
<tr>
<td></td>
<td>0.4-1.3 nmol/mmol creatinine (unexposed)</td>
</tr>
</tbody>
</table>
There is limited information on the use of unithiol in cadmium poisoning. In a woman with chronic occupational exposure to cadmium and signs and symptoms of toxicity, administration of unithiol increased the urinary concentration of cadmium from 1.8 to 4.2 μg/L (Daunderer, 1995).

11.6 Use in chromium poisoning

Reference values for chromium (Walker, 1998):

<table>
<thead>
<tr>
<th>Sample</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>&lt;10 nmol/L (&lt;0.5 μg/L)</td>
</tr>
<tr>
<td>Urine</td>
<td>&lt;5 nmol/L (&lt;0.25 μg/L)</td>
</tr>
</tbody>
</table>

There is limited information on the use of unithiol in chromium poisoning. An adult who fell in a pool of chromic acid was started on unithiol within an hour of exposure. He became anuric and chromium was detected in the dialysate. Urine excretion returned 2 days after exposure and the chromium concentration was 5859 μg/L. The maximum urinary chromium concentration, 13,614 μg/L, was obtained 12 hours after the start of unithiol therapy. The serum chromium concentration was 1,983 mg/L 24 hours after exposure. The patient recovered but no further details are given (Donner et al., 1986).

A 20-year-old male died after ingestion of 10-30 g of potassium dichromate. He was treated with haemodialysis (commenced at 2.5 hours) and continuous arterio-venous haemofiltration (at 16 hours). Unithiol (250 mg intravenously every 4 hours for 24 hours then 6 hourly) was started 13 hours after admission. The initial plasma concentration of chromium was 5.8 mg/L and urine 159 mg/L. He had a cardiac arrest and died 48 hours after admission (Pudill et al., 1989).

11.7 Use in cobalt poisoning

There is limited information on the use of unithiol in cobalt poisoning. Unithiol was used in 2 paediatric patients with ingestion of an unspecified cobalt compound from a chemistry set. The children were initially treated with penicillamine and then on the fifth day started on the less toxic unithiol (3 x 50 mg orally). There were slight increases in serum cobalt concentrations during unithiol therapy and it was stopped once the urine cobalt concentrations were normal. No further details are given (Müller et al., 1989).

11.8 Use in copper poisoning

There is limited information on the use of unithiol in acute copper poisoning. A 3-year-old child who ingested more than 3 g of copper sulphate received a gastric lavage within 30 minutes of ingestion and was commenced on unithiol therapy within an hour. The serum copper concentration did not reach a toxic concentration and urinary copper excretion was more than 10 times normal; no further details are given (Donner et al., 1986).

A 33-year-old female ingested an unknown quantity of copper sulphate and developed severe haemorrhagic gastroenteritis, dehydration, metabolic acidosis, renal failure, liver damage, intravascular haemolysis and methaemoglobinaemia. She was given unithiol
within 24 hours of ingestion until she developed anuria (more than 48 hours later). This patient survived with 10 days of intensive therapy and 5 weeks of hospitalisation. The serum copper concentration was normal on admission (5 hours post-ingestion) and as there were no measurements of copper excretion, the effectiveness of unithiol administration cannot be determined (Sinković et al., 2008).

11.8.1 Use in Wilson’s disease

Unithiol has been used with some success in patients with Wilson’s disease, usually those who fail to respond to penicillamine.

Walshe (1985) reported the use of unithiol (200 mg twice daily) in an adult patient with Wilson’s disease. He had initially been managed with penicillamine and trientine but had become intolerant to them. He developed proteinuria but remained well with unithiol. His copper excretion was maintained at 31.5-47.2 µmol (2000-3000 µg) daily. Two other patients were also tried on unithiol. One developed fever and a decreased leucocyte count which also occurred with a second test dose and further treatment was not given. The other patient took it for 10 days but then refused because of intense nausea. Other patients (number not specified) were given test doses and the resulting cupruresis was comparable with that obtained with penicillamine and trientine in most cases.

11.9 Use in gold poisoning

Unithiol has been used in iatrogenic gold poisoning and although the patient died from heart failure the unithiol was thought to be effective in removing gold from the body. No further details are given (Ashton et al., 1992a).

11.10 Use in lead poisoning

Reference values for lead (Walker, 1998):

<table>
<thead>
<tr>
<th></th>
<th>Blood</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Environmental exposure</td>
<td>&lt;0.5 µmol/L (&lt;10 µg/L)</td>
<td>&lt;100 nmol/24 hours (&lt;10 µg/24 hours)</td>
</tr>
</tbody>
</table>

Unithiol was first used in the management of chronic lead poisoning in Russia (Anatovskaya, 1962), and although unithiol has been used in subsequent cases of lead poisoning and has been shown to be of benefit in animal studies, succimer is usually the preferred antidote for lead poisoning, particularly in children (Angle, 1993) as it is the less toxic of the two antidotes (Andersen, 1999).

An adult with lead poisoning due to the use of a lead-containing ointment was treated with oral unithiol (400 mg then 200 mg 2 hourly). She had a blood lead concentration of 1150 µg/L with gastrointestinal effects and a paraesthesia. Within 36 hours the concentration has decreased to 570 µg/L and the maximum urinary lead concentration in 24 hours was 73000 µg/L. The blood concentration rose to 890 µg/L during an interruption of therapy due to lack of drug supply, but decreased rapidly once unithiol was recommenced. Therapy was continued over 2 months without adverse effects (Donner et al., 1987; Hruby & Donner, 1987).
A 24-year-old female developed lead poisoning after ingestion of instant lemon tea from a lead-glazed cup, over a period of 2.5 months. The reason for her illness was difficult to establish at first due to the unusual source, but once lead toxicity was confirmed she was treated with oral unithiol (5-10 mg/kg 3 times a day for 2 days, then 2.5 mg/kg twice daily) until the blood and urine lead concentrations were normal. Her initial whole blood and urine lead concentrations were 600 µg/L and 1700 µg/L, respectively. She recovered over a 4 month period (Autenrieth et al., 1998).

Unithiol treatment (parenteral and then two 5 day cycles) improved optic neuropathy caused by lead deposition in the eye. There was improvement in visual acuity, visual field and dark adaptation (Dambite, 1966).

11.11 Use in mercury poisoning

Unithiol is the antidote of choice in patients with mercury poisoning. It has been used successfully in the treatment of acute and chronic poisoning, involving metallic mercury, inorganic mercury salts and organic compounds. Andersen (1999) suggests that unithiol is the optimal antidote for inorganic mercury poisoning and that succimer is more effective in organic mercury intoxication.

In acute poisoning with mercuric salts the initial doses usually have to be given by the parenteral route because of damage to the gastrointestinal tract. Unithiol should be used in combination with haemofiltration in patients with mercury-induced renal failure.

Reference values for mercury (Walker, 1998):
- Blood <20 nmol/L (<4 µg/L)
- Urine <50 nmol/24 hours (<10 µg/24 hours)

11.11.1 Inorganic mercury compounds

Campbell et al. (1986) reported two patients with high mercury concentrations, due to occupational exposure, treated with unithiol. One patient aged 22 years was asymptomatic despite a urinary mercury concentration of 832 µg/24 hours. The other, aged 23 years, had clinical features of mercury toxicity (weight loss, muscle twitching, excessive salivation, night sweats). His urinary mercury concentration was 429 µg/24 hours. Both were given unithiol, 100 mg 3 times a day then 400 mg daily, for 2 months. The drug was well tolerated and during therapy the elimination half-life of mercury decreased from 33 days to 11 days. After 2 months the symptomatic patient had improved and the urinary mercury concentration was within acceptable limits.

Ashton & House (1989) describe two patients treated with unithiol after ingestion of inorganic mercury. The first patient, aged 19 years, ingested approximately 29 g of mercuric nitrate and presented to hospital within 1.5 hours. He was treated with dimercaprol initially and he developed acute renal tubular necrosis and hypotension. He was then given high dose intravenous unithiol, haemodialysis, haemofiltration and plasma exchange. The initial blood mercury concentration was very high but renal function returned at 10 days post-ingestion and he made a full recovery. Haemodialysis, haemofiltration and plasma exchange were ineffective as promoting mercury removal. The second patient, aged 42, ingested approximately 1 g of mercuric chloride. He was treated with high dose intravenous unithiol and then oral
administration. He recovered without developing renal impairment, despite an initial
mercury blood concentration of 600 µg/L.

Prompt administration of unithiol (at 8 hours post-ingestion) with intravenous fluid
therapy was thought to be responsible for the lack of renal impairment in a 53-year-old
man who had ingested approximately 50 g of mercuric iodide. He had vomited
repeatedly and this may also have decreased absorption, however, the blood and
urine mercury concentrations were high, at 1197 nmol/L and 159 nmol/L, respectively.
He was given unithiol intravenously 250 mg every 4 hours for 60 hours and then orally
twice daily for 18 days (Anderson et al., 1996).

A 19-year-old female vomited 30 minutes after ingestion of 3g of mercuric chloride and
was given a gastric lavage. She developed anuria one hour later and was started on
peritoneal dialysis and haemodialysis. She was given unithiol and dimercaprol and
urine excretion returned after 10 days with a polyuric phase at 20 days. Creatinine
clearance was normal by 100 days after ingestion (Nadig et al., 1985).

A 38-year-old male intentionally ingested 100 ml of mercuric chloride solution (of
unknown concentration) and developed vomiting, haematemesis and bloody diarrhoea
shortly afterwards. He was given a gastric lavage and once the history of ingestion
had been determined was stated on dimercaprol. However, he rapidly developed
oliguria and acute tubular necrosis. By 8 hours post-ingestion the urine output was
less than 10 mL/hour. The blood mercury concentration was 14,300 µg/L. The urine
mercury concentration before onset of anuria was 36,000 µg/L. He was started on
intravenous unithiol 10 hours after ingestion: 250 mg every 4 hours for 48 hours, then
250 mg every 6 hours for 48 hours and 250 mg 8 hourly. He required intravenous
fluids for hypovolaemic shock and haemodialysis for renal failure. The blood mercury
concentration remained high (at least 2 mg/L for the first 10 days) but kidney function
returned within 10 days and haemodialysis was no longer required. Administration of
unithiol was continued by the parenteral route because of ulceration of the
oesophagus and stomach. After about 4 weeks oral unithiol was given (300 mg 3
times a day), and unithiol was given for a total of 7 weeks until blood and urine
concentrations were considered to be non-toxic. The average mercury half-life is 40-
60 days and in this patient it was 2.5 days in the initial distribution phase and 8.1 days
in the terminal phase of metabolism and elimination. The patient made a full recovery
(Toet et al., 1994).

Haemodialysis is ineffective in enhancing mercury elimination (Toet et al., 1994; Pai
et al., 2000) even in patients treated with unithiol (Toet et al., 1994). However,
continuous venovenous haemofiltration was successful in enhancing elimination of
the mercury-unithiol complex in a patient with elevated blood mercury concentrations
(initially 5200 µg/L) following ingestion of an inorganic mercury salt (Pai et al., 2000).

Continuous venovenous haemofiltration in combination with unithiol was also
effective in the patient reported by Dargan et al. (2003a). A 40-year-old male
ingested approximately 1 g of mercuric sulphate and soon after presentation required
intubation and ventilation due to respiratory distress (his pharynx and epiglottis were
oedematous and haemorrhagic). He was started on intravenous unithiol (250 mg
every 4 hours for 4 days) 4.5 hours after ingestion. However he developed an
erythematous maculopapular rash with blistering on the lower legs and the dose of
unithiol was reduced to 250 mg every 8 hours. After another 6 days he was started on oral unithiol (200 mg/day for 9 days). Anuria developed by 12 hours post-ingestion and he was commenced in continuous venovenous haemofiltration 7 hours after ingestion. He was anuric for 11 days with oliguria for days 12 to 43. Continuous venovenous haemofiltration was continued for 14 days with 8 sessions of haemodialysis for renal support between days 16 and 37. He was discharged on day 50 asymptomatic with no neurological signs or symptoms. Continuous venovenous haemofiltration removed 12.7% of the ingested dose, mostly over the first 72 hours.

11.10.2 Organic mercury compounds

A 20-year-old male was given a gastric lavage and activated charcoal within 2 hours of ingesting haloperidol, benztrpine and 2-3 mouthfuls of a fungicide containing 0.69% methyl mercury and ethanol. The estimated dose of methyl mercury was 800 mg. He was started on oral D-penicillamine within 4 to 5 hours of ingestion. The whole blood mercury concentration 2 hours after ingestion was 1930 μg/L and at 24 hours was 1007 μg/L. Approximately 36 hours after ingestion he was started on acetylcysteine and haemodialysis. D-penicillamine was discontinued 3 days after ingestion and oral unithiol (200 mg every 6 hours) was started. He received unithiol for 14 days but due to mild anorexia and nausea elected not to continue taking it as an outpatient. The whole blood mercury concentration at this time was 355 μg/L and he remained well. Serum zinc and copper concentrations remained normal during unithiol therapy. Neurological examination was normal at 6 weeks and 1 year post-ingestion. Haemodialysis and D-penicillamine were relatively ineffective in clearing the mercury. The unithiol was also relatively ineffective but this may have been due to administration of a multivitamin and mineral preparation containing copper and zinc at the same time, which may have reduced efficacy (Lund et al., 1984).

In a 49-year-old female who ingested 125 g of fungicide containing 3.5% mercury in the form of methoxyethyl mercury treated with penicillamine and unithiol alternating every 2 weeks, unithiol reduced the protein binding of methoxyethyl mercury from 93% to 83%. Antidote therapy was continued for 12 weeks and she developed no renal or neurological effects (Köppel et al., 1982).

A 44-year-old man was treated with unithiol and succimer after ingestion of a solution of thiomersal. The ingested dose was 83 mg/kg although he vomited about 15 minutes later. He was given a gastric lavage just over 1 hour after ingestion and 300 mg of unithiol was instilled into the stomach via a nasogastric tube. This dose was repeated on days 2, 3, 9 and 10, and he was given 250 mg of intravenous unithiol on days 3, 8 and 17, with 750 mg on days 4, 5 and 11, and 1000 mg on days 12-16 and 23-29. He was also given oral succimer on days 17-23, 33-46 and 51-70. He received no antidotal therapy on days 6, 30-32 and 47-50. He developed renal failure on day 1 which persisted until day 40. He also developed gastritis, dermatitis, gingivitis, polyneuropathy and coma. He made a full recovery but the decline in mercury concentrations in the blood, urinary mercury excretion and renal mercury clearance were not influenced by antidotal therapy to a great extent. There was minimal or no increase in renal and blood clearance and no effect was detected after day 30 (Pfab et al., 1996).
11.11.3 Metallic mercury

In a patient with intrabronchial aspiration of metallic mercury the urine and plasma mercury concentrations remained high despite intermittent therapy with unithiol and penicillamine over a 14 month follow up period. However, the patient remained well apart from vomiting and faintness on admission and intermittent mild arthralgia thereafter (Batora et al., 2001). In a similar case, a 35-year-old male remained asymptomatic after rupture of a Miller-Abbot tube and subsequent aspiration. The 24 hour blood mercury concentration was 940 µg/L. He was treated with unithiol and the blood concentration decreased rapidly (Kummer & Michot, 1984).

There are a number of case reports of unithiol use in children with mercury toxicity (Bertram et al., 1989; Jekat & Kemper, 1990; Ruprecht, 1997). Unithiol was used in three children, aged 33 and 20 months and 6 years 10 months, with mercury toxicity from a broken thermometer. The thermometer had been broken on the carpet of the children’s room, which had under floor heating, about 8 months previously. Unithiol (50 mg 3 times daily) was given for up to 4 months and all the children recovered (von Mühlendahl, 1990).

Unithiol was used in the management of mercury poisoning in a 14-year-old girl with acrodynia. For 3 months her clinical features were diagnosed as a neurotic anxiety disorder but once the diagnosis of mercury toxicity was made she was treated with unithiol, 100 mg every other day and made a slow recovery. The source was metallic mercury spilt on a carpet that had been vacuumed up (Böckers et al., 1983).

11.11.4 Dermal mercury exposure

Unithiol was used in a 21-year-old diabetic male who developed mercury intoxication following use of a mercury-containing ointment for eczema for about 3 weeks. He developed classic signs of mercury poisoning with tiredness, sweating, mild fasciculation of extremities, ataxia, hand tremors, weight loss, proteinuria, anxiety and behavioural changes. The urinary mercury concentration was 0.252 mg/L and he was given oral unithiol for 12 days. The highest urine mercury concentration during therapy was 2.1 mg/L. He improved rapidly over a 2 week period, however, signs of neurological and renal damage, not typical of diabetes persisted (Pelclová et al., 2001).

Use of a mercury-containing cosmetic bleaching cream for 4 years caused nail dyschromia in a 56 year female. The nails were discoloured greenish-black and she had features of mercury toxicity with night sweats, insomnia and nervousness. Treatment with unithiol reduced the serum mercury concentration from 64 to15 µg/L; the urinary mercury concentration rose and peaked at 1660 µg/L on the 10th day. After the initial course of unithiol the serum mercury concentration increased and she was given a second course, lasting 3 weeks. The unithiol was well tolerated (Böckers et al., 1985).

11.11.5 Parenteral mercury exposure

Long-term unithiol administration has been used in the management of parenteral mercury poisoning. A 23-year-old male injected about 20 ml of metallic mercury
intravenously and mercury was visible on x-ray in the right ventricle with multiple emboli in the lung. Mercury was also seen in the abdomen and right forearm. Only 0.2 ml was removed from the heart by cardiac catheterisation and the blood mercury concentration rose to 294 μg/L. He was started on oral unithiol 300-800 mg a day and this continued for at least 4.5 years. The blood mercury and urine concentrations peaked at 1608 μg/L and 73,500 μg/L, respectively. He remained well except for intermittent chest pain. He developed no adverse effects to unithiol, and no reduction in plasma zinc, copper or selenium concentrations, although the urine copper concentrations were elevated (Ashton et al., 1992b). Batora et al. (2000) also used unithiol in a patient with intravenous mercury injection with elevated blood and urine concentrations (21.4 μg/L and 183.3 μg/L, respectively). They used only two courses of treatment over 17 days, and 6 weeks after therapy the blood concentration had fallen to 8.1 μg/L and the urine concentration increased to 397.6 μg/L. Mercury deposits were visible on both lung fields but by 1 year had almost completely disappeared. He remained well with only a temporary enzymuria (N-acetyl beta glucosaminidase) indicating subtle renal tubular damage.

A 35-year-old male presented with a history of gingivitis, weakness, pyrexia, anorexia and weight loss 6 weeks after intravenous injection of metallic mercury. Mercury was visible in the lungs, abdomen and injection site on X-ray and the urinary concentration was 500 μg/L. He was started on unithiol 2 days after admission on a 6 day course of 600 mg/day in 3 divided doses. After the first 24 hours of treatment the urinary mercury concentration rose to 7750 μg/L and he developed a moderate hypersensitivity-type skin reaction with resolved within 2 days. He was discharged one week after completion of unithiol therapy and had urine concentration 1100 μg/L with irritability and weakness. He did not return for a year when he presented with irritability, weakness, insomnia and tremor. The urinary mercury concentration was 2206 μg/L. Mercury was still visible on X-ray and he was given another course of unithiol. Over the next 4 years he was reviewed every 6 months and the urinary mercury concentration was 800-1000 μg/L. Two years after the original presentation he was given a third course of unithiol. At 5 years the concentration was 807 μg/L and a fourth course of unithiol produced a less dramatic increase in urinary elimination. Tremor and weakness persisted. Although unithiol increased elimination there appeared to be no change in the radiographic deposits mercury in the lungs and abdomen. It was not clear that the infrequent administration of unithiol was of any benefit to this patient (Torres-Alanís et al., 1997).

In another case of elemental mercury injection, a 27-year-old male, 65 kg, injected 1.5 mL (20 g) into his left cubital vein. Within 12 hours he developed pyrexia, tachycardia and dyspnoea and mercury was visible on chest X-ray. The serum mercury concentration was 172 μg/L on admission and peaked on day 6 at 274 μg/L. At 37 hours he was started on unithiol (200 mg orally every 8 hours) for 5 days, during which time he eliminated 8 mg of mercury. Three days later he was started on succimer (500 mg daily) for another 5 days. This resulted in the excretion of another 3 mg of mercury. Neither unithiol nor succimer were effective in enhancing elimination of mercury after intravenous injection (Eyer et al., 2006).

Unithiol was shown to be effective in enhancing mercury elimination and reducing renal irradiation in patients given radioactive chlormerodrin, an obsolete mercurial diuretic, for renal scintigraphy (Ogiński & Kloczkowski, 1973; Kloczkowski & Ogiński,
11.12 Use in nickel poisoning

There are no case reports of unithiol administration in nickel poisoning but it has been recommended (Daunderer, 1982).

11.13 Use in palladium poisoning

No well documented case reports of unithiol use in platinum poisoning could be found.

11.14 Use in platinum poisoning

No well documented case reports of unithiol use in platinum poisoning could be found.

11.15 Use in polonium poisoning

Experience with use of unithiol in polonium exposure is limited. Shantyr et al. (1969) reported 10 children who were contaminated with polonium-210 from a damaged polonium-beryllium neutron source. They had body burdens of 0.2-7.0 µCi, far above the maximal permissible burden. Some were treated with unithiol (number unknown) and all remained well with no changes in general health, blood or renal function over the 46 month period of monitoring. However, most of the children developed impairment of protein formation in the liver, manifested as an increase in albumin and a decrease in globulin. This was observed from 21 months and persisted through the remaining period of observation.

11.16 Use in selenium poisoning

No well documented case reports of unithiol use in selenium poisoning could be found.

11.17 Use in silver poisoning

There is limited information on the use of unithiol in silver poisoning. Unithiol was used in a patient with argyria after penicillamine had failed to increase the urinary excretion of silver. The patient was 60 years old and had developed argyria after 15 years use of silver nitrate to treat gingivitis due to ill-fitting dentures. Unithiol was given at a dose of 1-5 x 500 mg for 5 days then 2.5 g/day for another 5 days with a 5 day period in between. Even though the renal excretion of silver was increased by unithiol administration the total amount of excreted silver was low, only 1 µmol of silver in total. This was estimated to be approximately 1% or less of the total body burden of silver and it was concluded that unithiol was of no benefit in argyria (Aaseth et al., 1986).

In a 55-year-old patient with argyria, use of unithiol (3 x 100 mg/day) increased the urinary excretion of silver by approximately 100 fold. However, the total quantity of silver excreted was low. Administration of penicillamine did not affect silver excretion
11.18 Use in strontium poisoning

No well documented case reports of unithiol use in strontium poisoning could be found.

11.19 Use in tin poisoning

There is limited information on the use of unithiol in tin poisoning. Unithiol was used in dental assistant with tin exposure due to kneading of amalgam in the unprotected palm of the hand. The urinary concentration of tin was increased to 1094.4 µg/L with unithiol administration and clinical features (tiredness, dizziness and tremor) improved (Hruschka, 1990).

12. Summary of evaluation

12.1 Indications

Unithiol appears to be effective (in terms of accelerating metal excretion without causing severe adverse effects) in most cases of:

- acute and chronic intoxication by organic and inorganic mercury
- acute and chronic intoxication by bismuth
- chronic lead poisoning
- acute and chronic arsenic poisoning.

It has also been used with some success in cases of human poisoning with the following, but data are limited:

- trivalent antimony (there is no information on the less toxic pentavalent antimony compounds)
- chromium
- cobalt
- copper, including patients with Wilson's disease
- gold

Animal studies have demonstrated apparent benefit but experience of unithiol use in human poisoning is lacking for the following:

- beryllium
- cadmium
- nickel
- tin
- zinc

On the basis of animal or human case reports unithiol does not appear to be useful for the following:

- palladium
- platinum
- polonium
• silver (argyria)
• strontium
• thallium
• vanadium

See Table 5 (section 16.2) for a summary of the available information on unithiol use in metal and metalloid poisoning.

12.2 Advised routes and dose

Unithiol may be administered both orally and parenterally. In cases of acute heavy metal ingestion the parenteral route is strongly recommended, because given orally the drug may bind residues of the metal in the gut, promote absorption and decrease body burden.

High dose therapy should be avoided in patients with chronic poisoning without severe clinical symptoms because of the risk of sudden mobilisation of the metal from tissue stores with resultant clinical deterioration. This occurred, for example, in a patient with chronic bismuth toxicity, necessitating cessation of unithiol therapy (Teepker et al., 2002).

12.2.1 Oral administration

There is no standard regimen for unithiol administration; dosing and duration depends on clinical condition and blood and urine concentrations of the metal. High doses have been used and are well tolerated, but are not advised in chronically poisoned patients without severe clinical effects (see section 12.2). Unithiol should be taken on an empty stomach.

• Adults: The usual initial dose is 100-200 mg every 6-8 hours (3-4 times/day); this is then tapered over the following days or weeks.
• Children: The usual initial dose 50-100 mg every 6-8 hours (3-4 times/day); this is then tapered over the following days or weeks. Alternatively 5 mg/kg daily in 2 to 4 divided doses has been used (Willig et al., 1984; Chisholm and Thomas, 1985; Karpinski & Markoff, 1997; Böse-O’Reilly et al., 2003).

12.2.2 Parenteral administration

Unithiol may be administered parenterally by the intramuscular or slow intravenous injection over 5 minutes (1 mL/minute). The parental doses of unithiol for adults and children are given in Table 1. From day 4 frequency of dosing should be based on the patient’s clinical condition; parental unithiol may be continued or oral treatment may be started. Unithiol solution must be administered immediately after opening the vials, and any remaining after dosing must be discarded. Parenteral unithiol must not be mixed with other infusion solutions (as this may reduce antidotal efficacy).
Table 1: Parenteral unithiol dosage

<table>
<thead>
<tr>
<th>Day of treatment</th>
<th>Adults</th>
<th></th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose IM or slow IV</td>
<td>Total daily dose</td>
<td>Dose IM or slow IV</td>
</tr>
<tr>
<td>1</td>
<td>250 mg every 3-4 hours</td>
<td>1.5-2.0 g</td>
<td>5 mg/kg every 3-4 hours</td>
</tr>
<tr>
<td>2</td>
<td>250 mg every 4-6 hours</td>
<td>1.0-1.5 g</td>
<td>5 mg/kg every 4-6 hours</td>
</tr>
<tr>
<td>3</td>
<td>250 mg every 6-8 hours</td>
<td>0.75-1.0 g</td>
<td>5 mg/kg every 6-8 hours</td>
</tr>
<tr>
<td>4,5…</td>
<td>250 mg every 8-12 hours</td>
<td>0.50-0.75 g</td>
<td>5 mg/kg every 8-12 hours</td>
</tr>
</tbody>
</table>

12.3 Supportive therapy

Other supportive therapy, and gut decontamination, rehydration or cardiovascular support may be required. Haemofiltration in conjunction with unithiol administration is the renal replacement method of choice in patients with renal failure because it may enhance elimination of heavy metals (particularly mercury).

In cases of chronic poisoning identification and removal from source should also be undertaken.

12.4 Controversial issues

There are indications from animal studies that unithiol may be useful in the treatment of acute poisoning by beryllium, cadmium, nickel and tin and from a small number of human case reports for trivalent antimony, chromium, cobalt, copper and gold. However, there is a lack of good quality clinical data.

Diagnostic use of unithiol in cases of asymptomatic or suspected poisoning cannot be recommended. The metal-binding agent mobilises the metal resulting in redistribution which could increase the concentration at the target organ, despite an increased excretion.

It is still controversial, whether concurrent administration of more than one metal-binding agent is harmful or beneficial. If adequate doses of unithiol are given, are well tolerated and the duration of therapy long enough, then use of more than one metal-binding agent is not necessary.

12.5 Proposals for further studies

The mode of action of unithiol has not been fully elucidated and recent work has tended to focus on arsenic and mercury. Further study is required to determine the interaction of unithiol with individual metals and metalloids but also with the target organs. Modern tools, such as computer molecule modelling for complex formation, should be used to provide a better understanding of the biological processes involved.
There is also a clear need for more clinical trials on the role of unithiol in the treatment of poisoned patients, in particular to define the optimum dose, duration of therapy and route of administration of unithiol and compare it to other metal-binding agents such as succimer and sodium calcium edetate. There are large populations of individuals poisoned with metals and metalloids, particularly arsenic and mercury, from environmental sources. For the metals which are less commonly involved in poisoning and where clinical trials are unlikely to be practical unless a mass incident occurs, there is a need for well documented case reports with biochemical and chemical analyses used to determine the efficacy of the antidote used.

Evaluation of the risks and benefits of combined antidotal therapy is also an area that warrants further investigation.

The suggestion that unithiol is the optimal antidote for inorganic mercury poisoning and that succimer is more effective in organic mercury intoxication requires verification (Andersen, 1999).

12.6 Adverse effects

Unithiol is generally well tolerated and the incidence of adverse effects is low.

Administration of unithiol also increases elimination of some trace elements, particularly zinc and copper (Bertram, 1977; Mant, 1985; Aaseth et al., 1986; Sallsten et al., 1994; Torres-Alanís et al., 2000; Høl et al., 2003), but also selenium and magnesium (Torres-Alanís et al., 2000). This effect is only likely to be of clinical significance in patients on chronic unithiol therapy.

Skin reactions including rashes, pruritis and blistering have been reported (Dubinsky & Guida, 1979; Mant, 1985; Ashton et al., 1992a; Hla et al., 1992; Toet et al., 1994; Torres-Alanís et al., 1995; Torres-Alanís et al., 1997; Gonzalez-Ramirez et al., 1998; Böse-O'Reilly et al., 2003; Dargan et al., 2003a). Erythema multiforme with buccal ulceration (Ashton et al., 1992a) and depigmentation (Pagliuca et al., 1990) has been reported. Stevens-Johnson syndrome has been reported in a small number of cases (Chisholm, 1990; Chisholm, 1992; Van der Linde et al., 2008). Anaphylactic shock has not been reported (Ruprecht, 1997). In most cases allergic reactions have resolved within 3-5 days and generally no treatment is required. However, antihistamines and/or corticosteroids may be given if necessary.

Nausea may occur from oral administration (Lund et al., 1984; Walshe, 1985; Stevens et al., 1995; Gonzalez-Ramirez et al., 1998), and body fluids usually have a sulphur odour for 6-8 hours after unithiol administration. Mild elevation of liver enzymes (Chisolm & Thomas, 1985; Gonzalez-Ramirez et al., 1998; Wang et al., 2003), diuresis (Glukharen, 1965), fever and leucocytosis (Walshe, 1985) have been reported.

With the parenteral preparation cardiovascular reactions may occur, particularly if injected too rapidly. These effects are hypotension (Hurlbut et al., 1994), nausea (Stevens et al., 1995), dizziness and weakness (Dubinsky & Guida, 1979; Zhang, 1984). Necrosis and ulceration may occur at the injection site, but this is associated with high doses e.g. 100 mg/kg (Sanotsky et al., 1967).
12.7 Restrictions of use

Unithiol should not be administered in acute arsine poisoning (AsH₃), because it is ineffective and can increase arsine toxicity (Mizyukova & Petrunkin, 1974).

The administration of unithiol in cases of asymptomatic or suspected poisoning (a challenge or mobilisation test) cannot be recommended, because the metal-binding agent mobilises the metal from tissue stores resulting in redistribution and potentially increasing the concentration in the target organ, despite increasing excretion.

Renal impairment is not a restriction of use; haemofiltration is the renal replacement method of choice in patients with renal failure and in conjunction with unithiol administration may enhance elimination of heavy metals (particularly mercury).

13. Model information sheet

13.1 Uses

Unithiol is a derivative of dimercaprol (2,3-dimercapto-1-propanol, British Anti-Lewisite, BAL), and is replacing dimercaprol as one of the main antidotes used in the management of heavy metal poisoning. Unithiol has several advantages over dimercaprol including lower toxicity, increased solubility in water and lower lipid solubility. It is due to these properties that it is effective by oral administration.

Unithiol has been used in the management of acute and chronic poisoning with a number of different metals and metalloids, and is particularly useful for arsenic, bismuth and mercury. It has been used for other metals and metalloids. Unithiol can be given parenterally or orally depending on the clinical situation and severity of poisoning.

13.2 Dosage and route

Unithiol may be administered both orally and parenterally. In severe cases and/or acute poisoning parenteral administration is recommended. In cases of acute heavy metal ingestion the parenteral route is strongly recommended, because given orally the drugs may bind residues of the metal in the gut, promote the absorption and increase the body burden by this way.

High dose therapy should be avoided in patients with chronic poisoning without severe clinical symptoms because of the risk of sudden mobilisation of the metal from tissue stores with resultant clinical deterioration.

13.2.1 Oral administration

There is no standard regimen for unithiol administration; dosing and duration depends on clinical condition and blood and urine concentrations of the metal. High doses have been used and are well tolerated, but are not advised in chronically poisoned patients without severity clinical effects (see section 12.2). Unithiol should be taken on an empty stomach.
• **Adults**: The usual initial dose is 100-200 mg every 6-8 hours (3-4 times/day); this is then tapered over the following days or weeks.

• **Children**: The usual initial dose 50-100 mg every 6-8 hours (3-4 times/day); this is then tapered over the following days or weeks. Alternatively 5 mg/kg daily in 2 to 4 divided doses has been used.

### 13.2.2 Parenteral administration

Unithiol is given by IM or slow IV injection over 5 minutes (1 mL/minute). See table for dosing regimen. From day 4 frequency of dosing should be based on the patient’s clinical condition; parental unithiol may be continued or oral treatment may be started. Unithiol must not be mixed with other infusion solutions, as this may reduce its efficacy.

### Table: Parenteral unithiol dosage

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<tr>
<td>4,5…</td>
<td>250 mg every 8-12 hours</td>
<td>0.50-0.75 g</td>
</tr>
</tbody>
</table>

### 13.3 Precautions and contraindications

Unithiol should not be administered in acute arsine poisoning (AsH₃), because it is ineffective and can increase arsine toxicity.

The administration of unithiol in cases of asymptomatic or suspected poisoning (a challenge or mobilisation test) cannot be recommended, because the metal-binding agent mobilises the metal from tissue stores resulting in redistribution and potentially increasing the concentration in the target organ, despite increasing excretion.

The administration of more than one metal-binding agent at the same time cannot be recommended, as the risks and/or benefits of such therapy have not been evaluated.

The efficacy of a metal-binding agent may be difficult to determine. After discontinuation of metal exposure (and absorption) a decrease in the blood concentration will occur without any therapy. Clinical efficacy should not be judged only by the quantity of metal excretion or the decrease of blood concentrations. The reduction of the tissue content in the target organ and the restoration of pathological alterations also need to be considered. It is important to note that enhancement of the
metal excretion by mobilisation may increase the metal burden of the target organ by redistribution, and conversely the body burden may be reduced without a striking decrease of the blood concentrations.

During long-term therapy the blood concentrations and excretion of trace elements should be monitored carefully, because depletion of trace metals may play a role in the toxicity of metal-binding agent agents.

13.4 Pharmaceutical incompatibilities and drug interactions

Unithiol must not be mixed with other infusion solutions, as this may reduce antidotal efficacy.

Unithiol solution should be administered immediately after opening of the vials and all remainder must be discarded, because the compound is oxidised rapidly in contact with air.

Unithiol should not be given orally with mineral preparations or activated charcoal because unithiol may be inactivated. For the same reason the unithiol capsules should be taken at least one hour before a meal.

13.5 Side effects

Unithiol is generally well tolerated and the incidence of adverse effects is low.

Administration of unithiol also increases elimination of some trace elements, particularly zinc and copper, but also selenium and magnesium. This effect is only likely to be of clinical significance in patients on chronic unithiol therapy.

Skin reactions including rashes, pruritis and blistering have been reported. Erythema multiforme with buccal ulceration and depigmentation has been reported. Stevens-Johnson syndrome has been reported in a small number of cases. Anaphylactic shock has not been reported. In most cases allergic reactions have resolved within 3-5 days and generally no treatment is required. However, antihistamines and/or corticosteroids may be given if necessary.

Nausea may occur from oral administration, and body fluids usually have a sulphur odour for 6-8 hours after unithiol administration. Mild elevations of liver enzymes, diuresis, fever and leucocytosis have also been reported.

With the parenteral preparation cardiovascular reactions may occur, particularly if injected too rapidly. These effects are hypotension, nausea, dizziness and weakness.

Necrosis and ulceration may occur at the injection site, but this is associated with high doses.

13.6 Pregnancy and lactation

Teratogenic effects have not been demonstrated in animal studies, indeed studies have demonstrated that unithiol can protect against the developmental toxicity of
arsenic and mercury. Even though safety in human has not been established, pregnancy is not regarded as a contraindication. If unithiol is administered to pregnant women, the essential minerals should be monitored carefully, because metal-binding may cause a depletion of trace elements and it has been shown that zinc deficiency can cause teratogenic effects.

In general lactation should be avoided in metal poisoning.

13.7 Storage

The capsules should be stored in a dry place.

The shelf-life for the commercial available pharmaceutical preparations Dimaval® is claimed to be 5 years for the capsules 4 years for the ampoules. The expiry date is stated on each package.

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15. Author names, address
16. Additional information

16.1 Description of search strategy

Table 2: Results of EMBASE search, 5 April 2009.

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Table 3: Results of Pubmed search, using the EMBASE interface, 5 April 2009.

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<tr>
<td>3</td>
<td>dimercaptopropanol OR dimercaptopropane AND sulfonate [any field]</td>
<td>103</td>
</tr>
<tr>
<td>4</td>
<td>poisoning OR toxicity OR overdose [any field]</td>
<td>265512</td>
</tr>
<tr>
<td>5</td>
<td>1 and 4</td>
<td>208</td>
</tr>
<tr>
<td>6</td>
<td>2 and 4</td>
<td>158</td>
</tr>
<tr>
<td>7</td>
<td>3 and 4</td>
<td>62</td>
</tr>
<tr>
<td>8</td>
<td>5 and 6 and 7 remove duplicates</td>
<td>276</td>
</tr>
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</table>

Table 4: Results of Cochrane Library, 5 April 2009

<table>
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<tr>
<th>Number</th>
<th>Keywords</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Unithiol [MeSH term] in Central Register of Controlled Trials</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>Unithiol [MeSH term] in Cochrane reviews</td>
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</tr>
<tr>
<td>3</td>
<td>Unithiol [MeSH term] in other reviews</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Unithiol [MeSH term] in economic evaluations</td>
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</tbody>
</table>

16.2 Description of published evidence

Table 5: Summary of evidence of use of unithiol in metal and metalloid poisoning.
<table>
<thead>
<tr>
<th>Metal</th>
<th>Clinical trial data</th>
<th>Case reports</th>
<th>Animal studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimony</td>
<td>No data.</td>
<td>Used with apparent benefit in a small number of paediatric trivalent antimony compounds (Iffland &amp; Bösche, 1987; Kemper et al., 1989; Jekat &amp; Kemper, 1990). There is no information on its use in pentavalent antimony compounds.</td>
<td>Unithiol has been shown to increase survival (Basinger &amp; Jones, 1981a) and reduce the LD₅₀ (Chih-Chang, 1958) in antimony-poisoned experimental animals.</td>
</tr>
<tr>
<td>Arsenic</td>
<td>One randomized, single blinded, placebo-controlled study of 21 patients with chronic arsenicosis. Unithiol resulted in significant clinical improvement. Cessation of exposure and placebo also reduced clinical scores but these were significantly lower for unithiol-treated subjects. In the placebo group improvement was attributed to cessation of exposure and hospitalisation. There were significant increases in urinary arsenic excretion with unithiol treatment, compared to no increase in the placebo group. No adverse effects were reported (Guha Mazumder et al., 2001).</td>
<td>5 reports of acute arsenic poisoning involving 7 adult patients treated with unithiol as the only antidote (Moore et al., 1994; Kruszewska et al., 1996; Horn et al., 2002; Adam et al., 2003; Heinrich-Ramm et al. 2003). All patients showed increased urinary excretion and decreased plasma concentrations of arsenic. All patients recovered. 1 report where dimercaprol was used followed by succimer and unithiol together. Patient showed clinical improvement but contribution of unithiol difficult to determine (Vantroyen et al., 2004) 1 report of chronic arsenic poisoning. Administration of unithiol resulted in increased urinary excretion of arsenic and clinical improvement (Wax &amp; Thornton, 2000).</td>
<td>Unithiol increases survival (Tadlock &amp; Aposhian, 1980; Aposhian et al., 1982; Inns et al., 1990), increases the LD₅₀ (Aposhian et al., 1981), increases urinary (Maiorino &amp; Aposhian, 1985; Flora et al., 1995a) and faecal (Maehashi &amp; Murata, 1986; Reichl et al., 1995) elimination, reduces tissue concentrations (Kreppel et al., 1989; Kreppel et al., 1990; Schäfer et al., 1991) and reduces the severity of toxicity (Kreppel et al., 1989, Inns &amp; Rice, 1993; Flora et al., 1995a; Flora et al., 2005) in arsenic poisoned experimental animals.</td>
</tr>
<tr>
<td>Beryllium</td>
<td>No data.</td>
<td>No data.</td>
<td>Unithiol increases beryllium excretion and reduces beryllium-induced toxic effects in experimental animals (Mathur et al., 1994; Flora et al., 1995b; Johri et al., 2002; Johri et al., 2004).</td>
</tr>
<tr>
<td>Bismuth</td>
<td>No data.</td>
<td>3 cases of acute bismuth poisoning, involving a 13-year-old (Bogie et al., 2000) and 2 adults (Stevens et al., 1995; Dargan et al., 2001;</td>
<td>Unithiol increases survival (Basinger et al., 1983) and reduces tissue concentrations (Slikkerveer et al., 1992; Jones et al.,</td>
</tr>
<tr>
<td>Metal</td>
<td>Clinical trial data</td>
<td>Case reports</td>
<td>Animal studies</td>
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</tr>
<tr>
<td>Cadmium</td>
<td>No data.</td>
<td>1 case report. Unithiol in a patient with chronic occupational exposure increased urinary cadmium concentrations. No further information available (Daunderer, 1995).</td>
<td>Unithiol increases the LD$_{50}$ (Pethran et al., 1990), increases survival (Aposhian 1982; Andersen &amp; Nielsen, 1988; Basinger et al., 1988; Srivastava et al., 1996), reduces tissue concentrations (Planas-Bohne &amp; Lehman, 1983; Eybl et al., 1984; Srivastava et al., 1996) in cadmium poisoned experimental animals. However, in some studies there was no effect on survival (Eybl et al., 1984), excretion (Eybl et al., 1984, Rau et al., 1987; Zheng et al., 1990) or tissue distribution of cadmium (Cherian, 1980) and an increase in tissue concentrations was reported in some studies (Shinobu et al., 1983; Basinger et al., 1988). Although unithiol may be effective, other metal-binding agents appear to be more efficacious (Eybl et al., 1984; Eybl et al., 1985; Andersen &amp; Nielsen, 1988; Srivastava et al., 1996).</td>
</tr>
<tr>
<td>Chromium</td>
<td>No data.</td>
<td>2 case reports in adults; the effect of unithiol is unclear in both. 1 patient recovered (Donner et al., 1986); the other also received haemodialysis and haemofiltration but died 48 hours after admission (Pudill et al., 1989).</td>
<td>Apparent benefit demonstrated, but data are limited. Unithiol reduces chromate-induced cytotoxicity (in some circumstances) (Susa et al, 1994), reduces lethality and increases renal excretion of (Susa et al, 1994) in chromium-poisoned experimental animals.</td>
</tr>
<tr>
<td>Metal</td>
<td>Clinical trial data</td>
<td>Case reports</td>
<td>Animal studies</td>
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</tr>
<tr>
<td>Cobalt</td>
<td>No data.</td>
<td>2 paediatric cases of acute exposure. Unithiol was used after penicillamine and was associated with increased urinary cobalt concentrations (Müller et al., 1989).</td>
<td>Apparent benefit demonstrated, but data are limited. Unithiol has been shown to reduce the lethality of cobalt (Cherkes &amp; Braver-Chernobulskaia, 1958; Eybl et al., 1985) but to increase cobalt concentrations in some tissues (Eybl et al., 1985).</td>
</tr>
<tr>
<td>Copper</td>
<td>No data.</td>
<td>One paediatric case of acute ingestion; unithiol was associated with increased urinary copper excretion (Donner et al., 1986). In an adult case there was no measurement of copper excretion; the patient survived (Sinković et al., 2008).</td>
<td>Apparent benefit demonstrated, but data are limited. Unithiol increased the LD50 (Pethran et al., 1990) and reduced toxicity (Mitchell et al., 1982) in copper-poisoned experimental animals.</td>
</tr>
<tr>
<td>Gold</td>
<td>Wilson’s disease</td>
<td>In a randomised trial of 28 patients comparing unithiol and captopril, unithiol had a more potent anticopper effect. 1 patient on unithiol developed a transient, adverse effect (Wang et al., 2003).</td>
<td>Wilson’s disease In an unspecified number of patients copper excretion with unithiol was comparable to that of penicillamine. Unithiol was discontinued in 2 patients due to adverse effects (Walshe, 1985) Copper poisoning 1 case of iatrogenic poisoning where unithiol was thought to be effective in removing gold although no details are given (Ashton et al., 1992a). Unithiol increases survival (Basinger et al., 1985), reduces renal concentrations (Gabard, 1980; Kojima et al., 1991; Takahashi et al., 1994), increases urinary excretion (Kojima et al., 1991) and reduces renal toxicity (Kojima et al., 1991; Takahashi et al., 1994) in gold-poisoned in experimental animals</td>
</tr>
<tr>
<td>Lead</td>
<td>One controlled study of 60 males with chronic lead toxicity. Unithiol-treated patients had increased elimination and biochemical and clinical improvement, and were discharged 6 weeks earlier than controls (Anatovskaya, 1962). 12 children (aged 31 to 69 months) with chronic lead toxicity received one of two dose regimens of unithiol. All had reduced blood lead concentrations and</td>
<td>In 2 adult patients with chronic lead exposure unithiol decreased blood lead concentrations and increased urinary lead excretion (Donner et al., 1987; Hruby &amp; Donner, 1987; Autenrieth et al., 1998). Succimer is more commonly used in the management of lead poisoning.</td>
<td>Unithiol increases survival (Llobet et al., 1990), increases excretion (Hofmann &amp; Segewitz, 1975; Llobet et al., 1990), reduces tissue concentrations (Twarog &amp; Cherian, 1983; Twarog &amp; Cherian, 1984; Xu &amp; Jones, 1988; Llobet et al., 1990), except in the brain (Sharma et al., 1987; Aposhian et al., 1996) and reduces toxicity (Twarog &amp; Cherian, 1983; Sharma et al., 1987; Tandon et al., 1994) in lead-poisoned experimental animals.</td>
</tr>
<tr>
<td>Metal</td>
<td>Clinical trial data</td>
<td>Case reports</td>
<td>Animal studies</td>
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<tr>
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<td>increased urinary excretion (Chisolm &amp; Thomas, 1985).</td>
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<tr>
<td>Mercury</td>
<td>In patients with chronic exposure penicillamine (12 patients), N-acetyl-DL-penicillamine (17), unithiol (10) and a thiolated resin (8) were compared. The study was not clinically controlled. Although all agents reduced blood mercury concentrations and unithiol was the most effective there was no immediate clinical improvement, presumably because the duration of therapy was too short and therapy was started months after exposure (Clarkson et al., 1981). 27 patients were treated with unithiol and/or succimer. All had some relief (19 became asymptomatic). Most had increased mercury excretion. Unithiol was found to be more effective (data not provided and the two antidotes were used interchangeably in some patients) (Zhang, 1984). In a study of 95 patients with chronic exposure (vapour, inorganic mercury and methyl mercury) unithiol increased urinary mercury excretion in some but others (number not specified) showed no increase in mercury excretion. In more</td>
<td>Inorganic mercury 6 acute cases reported; 3 patients initially received dimercaprol (Nadig et al., 1985; Ashton &amp; House, 1989; Toet et al., 1994) and 4 developed renal failure (Nadig et al., 1985; Ashton &amp; House, 1989; Toet et al., 1994; Dargan et al., 2003a). Unithiol was shown to reduce the mercury elimination half-life in two cases (Toet et al., 1994; Dargan et al., 2003a). All patients recovered. In 2 chronic exposure cases unithiol decreased the elimination half-life of mercury (Campbell et al., 1986).</td>
<td>Unithiol increases excretion (Gabard, 1976a; Gabard, 1976b; Wannag &amp; Aaseth, 1980; Planas-Bohne, 1981; Aaseth et al., 1982; Buchet &amp; Lauwerys, 1989), decreases tissue concentrations (Gabard, 1976a; Gabard, 1976b Cikrt &amp; Lenger, 1980; Wannag &amp; Aaseth, 1980; Aaseth et al., 1982; Aaseth, 1983; Kachru &amp; Tandon, 1986) and reduces toxicity (Planas-Bohne, 1977; Jones et al., 1980; Nielson &amp; Andersen, 1991) in mercury-poisoned experimental animals.</td>
</tr>
<tr>
<td>Organic mercury 3 acute cases in adults. In 1 case unithiol was determined to be relatively ineffective possibly due to coadministration of a copper and zinc supplement (Lund et al., 1984). In another case where unithiol was alternated with penicillamine, the unithiol reduced mercury protein binding (Köppel et al., 1982). The 3rd patient was also treated with succimer; neither significantly increased mercury clearance (Pfab et al., 1996).</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Metallic mercury 2 cases of aspiration; both patients remained well but in 1 the mercury blood and urine concentrations remained high (Batora et al., 2001) and in the other the blood concentration decreased rapidly (Kummer &amp; Michot, 1984).</td>
<td></td>
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</tr>
<tr>
<td>Metal</td>
<td>Clinical trial data</td>
<td>Case reports</td>
<td>Animal studies</td>
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<tr>
<td></td>
<td>than two-thirds there was improvement in subjective complaints and objective neurological parameters. The 14 day regimen was too short to have a permanent effect on mercury concentrations (Böse-O’Reilly et al., 2003). Study limitations: absence of a control group, lack of details of patients (age, weight) and continued exposure to mercury during therapy. In 8 patients with chronic exposure from facial mercurous chloride cream there was a significant increase in urinary mercury concentrations after 24 hours of unithiol. One symptomatic patient recovered and the other had persistent tremor (Garza-Ocañas et al., 1997).</td>
<td>In 3 children (&lt;7 years) unithiol was associated with improved clinical signs and enhanced mercury excretion (von Mühlendahl, 1990). In a 14-year-old with acrodynia there was slow recovery with unithiol (Böckers et al., 1983).</td>
<td>In 8 patients with chronic exposure from facial mercurous chloride cream there was a significant increase in urinary mercury concentrations after 24 hours of unithiol. One symptomatic patient recovered and the other had persistent tremor (Garza-Ocañas et al., 1997).</td>
</tr>
<tr>
<td>Dermal mercury</td>
<td>In 2 cases of chronic exposure, unithiol increased urinary mercury concentrations (Böckers et al., 1985) Pelclová et al., 2001).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parenteral mercury</td>
<td>4 cases of mercury injection (Ashton et al., 1992b; Torres-Alanís et al., 1997; Batora et al., 2000; Eyer et al., 2006). Although unithiol increases urinary mercury concentrations, the effect may be small (Eyer et al., 2006) and there may be no change in radiographic deposits of mercury (Torres-Alanís et al., 1997) or clinical signs.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nickel</td>
<td>No data.</td>
<td>No data.</td>
<td>Unithiol increases survival (Basinger et al., 1980), increases excretion (Sharma et al., 1987) and reduces nickel-induced toxic effects (Sharma et al., 1987; Tandon et al., 1996).</td>
</tr>
<tr>
<td>Palladium</td>
<td>No data.</td>
<td>No data.</td>
<td>No benefit demonstrated, but data are limited. Unithiol did not influence toxicity or reduce lethality in palladium-poisoned animals (Mráz et al., 1985).</td>
</tr>
<tr>
<td>Platinum</td>
<td>No data.</td>
<td>No data.</td>
<td>No benefit demonstrated, but data are limited. A single dose of unithiol had no significant effect on renal platinum concentrations. After 4 treatments there was significant increase in urinary excretion of platinum, but this was low (Planas-Bohne et al., 1982).</td>
</tr>
<tr>
<td>Polonium</td>
<td>No data.</td>
<td>Children (number not specified).</td>
<td>Not recommended.</td>
</tr>
</tbody>
</table>

80
<table>
<thead>
<tr>
<th>Metal</th>
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<th>Case reports</th>
<th>Animal studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>known, but &lt;10) treated with unithiol after contamination with polonium-210 remained well over the 46 month period of monitoring with only impairment of protein formation in the liver (Shantyr et al., 1969).</td>
<td></td>
<td>Although unithiol can remove polonium-210 from most tissues (Aposhian et al., 1987) it results in concentration of polonium in the kidneys (Volf, 1973; Rencová et al., 1993; Volf et al., 1995).</td>
</tr>
<tr>
<td>Selenium</td>
<td>No data.</td>
<td>No data.</td>
<td>No benefit demonstrated, but data are limited. Unithiol had no effect in selenium-poisoned animals; the concentration of selenium in urine and faeces was unchanged (Paul et al., 1989).</td>
</tr>
<tr>
<td>Silver</td>
<td>No data.</td>
<td>In 2 cases of chronic silver toxicity unithiol increased urinary silver excretion but the quantity excreted was low (Aaseth et al., 1986; Kemper et al., 1989; Jekat and Kemper, 1990).</td>
<td>Unithiol increased the LD$_{50}$ of silver chloride in mice (Pethran et al., 1990), prevented the development of toxic pulmonary oedema and death in dogs (Romanov, 1967) and in vitro completely reversed silver inhibition of Na,K-ATPase (Hussain et al., 1994).</td>
</tr>
<tr>
<td>Strontium</td>
<td>No data.</td>
<td>No data.</td>
<td>No benefit demonstrated, but data are limited. Unithiol did not affect survival rate in strontium-poisoned experimental animals (Domingo et al., 1990; Pethran et al., 1990).</td>
</tr>
<tr>
<td>Thallium</td>
<td>No data.</td>
<td>No data.</td>
<td>Unithiol is ineffective in thallium-poisoned experimental animals (Pethran et al., 1990; Mulkey &amp; Oehme, 2000).</td>
</tr>
<tr>
<td>Tin</td>
<td>No data.</td>
<td>In 1 case unithiol increased urinary tin concentrations and clinical signs improved (Hruschka, 1990).</td>
<td>Apparent benefit demonstrated with reduced tin-induced lesions in rats (Merkord et al., 2000), but data are limited.</td>
</tr>
<tr>
<td>Vanadium</td>
<td>No data.</td>
<td>No data.</td>
<td>Unithiol had no effect on lethality in vanadium-poisoned mice (Jones &amp; Basinger, 1983) and no significant effect on the death rate, body weight reductions, or reduction in weights of legs and toes in chick eggs incubated with vanadium (Hamada, 1994). An in vitro study has shown that oxovanadium forms a complex with unithiol (Williams &amp; Baran, 2008).</td>
</tr>
</tbody>
</table>
Metal | Clinical trial data | Case reports | Animal studies
---|---|---|---
Zinc | No data. | No data. | Unithiol increases excretion (Domingo et al., 1988) and reduced lethality in zinc-poisoned experimental animals (Basinger & Jones, 1981b), but more effective antidotes are available (Basinger & Jones, 1981b; Domingo et al., 1988; Llobet et al., 1988).

Abbreviations

- **AAS**  Atomic Absorption Spectroscopy
- **ABCC2**  ATP-binding cassette, sub-family C
- **AES**  Atomic Emission Spectroscopy
- **ALAD**  δ-aminolevulinate dehydratase
- **BAL**  2,3-dimercaptopropanol; British Anti-Lewisite; dimercaprol (rINN)
- **BAPSA**  2,3-bis-(acetyltio)-propanesulphonamide
- **CAS**  Chemical Abstracts Service
- **CDTA**  cyclohexanediamintetraacetic acid
- **DDC**  sodium diethylidithiocarbamate
- **DMPA**  N-(2,3-dimercaptopropyl) phthalamic acid
- **DMSA**  Dimercaptosuccinic acid; succimer (rINN)
- **DTPA**  Diethylentriaminepentaacetic acid; pentetic acid (rINN)
- **EDTA**  Ethylenediaminetetraacetic acid; sodium calcium edetate (rINN)
- **g**  gram
- **HOEtTTC**  N,N’-di-(2-hydroxyethyl)-ethylenediamine-N’N’-biscarbodithioate
- **HPLC**  High Performance Liquid Chromatography
- **ICP**  Inductively Coupled Plasma
- **i.m.**  intramuscular
- **i.p.**  intraperitoneal
- **IPCS**  International Programme on Chemical Safety
- **IR**  infra-red
- **i.v.**  intravenous
- **k**  kilo (10^3)
- **L**  litre
- **LD**  Lethal Dose (subscript indicates percent mortality)
- **m**  milli (10^-3)
- **µ**  micro (10^-6)
- **µCi**  microCurie
- **min**  minute
- **MRP2**  multidrug resistance protein 2
- **NOEL**  no observed effect level
- **OAT1**  organic anion transporter 1
- **OAT3**  organic anion transporter 3
- **PAH**  p-aminohippurate
- **ppm**  parts per million (10^-6)
rINN  recognised international non-proprietary name