IPCS EVALUATION OF ANTIDOTES FOR POISONING BY METALS AND METALLOIDS

**Pentetic acid**
(diethylenetriaminepentaacetic acid, DTPA; calcium trisodium pentetate, Ca-DTPA; zinc trisodium pentetate, Zn-DTPA)

Initial draft by F.W. Jekat, F.H. Kemper & M.-L. Weischer, 1995
Updated by N Bates, Guy's & St Thomas' Poisons Unit, London, UK, October 2008
Introduction

Pentetic acid (diethylenetriaminepentaacetic acid, DTPA) was first synthesized in 1954 (Durbin et al., 1998). It is a polyaminopolycarboxylic acid chelator, like ethylenediamine tetraacetic acid (EDTA) and its salts (e.g. sodium calcium edetate).

Pentetic acid is used as the calcium or zinc trisodium salt which acts by exchanging calcium or zinc ions for a metal with a higher binding capacity. The salts have been used in Europe and the USA (Ménétrier et al., 2005) as chelating agents for heavy metals and as decorporation agents for radionuclides. They are used most commonly to enhance elimination of radioactive metals following radiological accidents and are now approved by the United States Food and Drug Administration (FDA) as pharmacological countermeasures to potential radiological release or nuclear detonation including exposure from a Radiation Dispersal Device (RDD), more commonly termed a dirty bomb.

Pentetic acid salts have FDA approval for use in plutonium, curium and americium exposure by inhalation, dermal and wound exposure. They may also be effective for enhancing elimination of other transuranium elements such as berkelium or californium but data are limited. Pentetic acid salts are effective for enhancing elimination of cerium and zinc.

Pentetic acid salts may be useful for enhancing removal of cobalt, einsteinium, lanthanum, nickel, promethium, scandium, strontium, ytterbium and yttrium but data are lacking and most of the data is from animal studies. Furthermore, the pattern and natural history of toxicity with most of these metals in humans is not well described and so the role of chelation with pentetic acid salts is difficult to determine. Cadmium chelation remains a problem and pentetic acid salts have shown limited benefit in animal studies, particularly in the more clinically relevant delayed administration studies.

Pentetic acid salts are not effective in removing antimony, beryllium, bismuth, gallium, lead, mercury, neptunium, niobium, platinum, polonium, thorium and uranium. Pentetic acid is not useful for radioactive iodine (Hameln Pharmaceuticals, 2004). The effectiveness of pentetic acid salts for radium or calcium has not been determined. Although pentetic acid salts have been shown to increase elimination of manganese in both animals studies and a human case report it did not prevent manganese-induced Parkinson’s disease in a human case (Holzgraefe et al., 1986).

Pentetic acid salts can mobilise iron and vanadium but more effective chelating agents are available.

In many studies early dosing with calcium trisodium pentetate is more effective than zinc trisodium pentetate but there is no difference in efficacy between the salts when given later. For most metals pentetic acid is relatively ineffective in mobilising metal from bone and is most effective when given soon after exposure when the metal is still in the circulation or soft tissues. Administration of pentetic acid salts (orally or parenterally) following ingestion of metals or radionuclides is not recommended as this is thought to increase gastrointestinal absorption.

Puchel, the lipophilic derivative of pentetic acid, although effective in removing some metals, is more toxic than calcium and zinc pentetate and it is not used in humans.

Pentetic acid, both as the calcium or zinc trisodium salt, is well tolerated but both salts also chelate essential trace elements and so these should be monitored in patients receiving repeated or long-term dosing with these agents.

In addition to its use as an antidote, pentetic acid is commonly used in medicine as a carrier for contrast
media such as gadolinium and radiopharmaceuticals such as indium-111 and technetium-99. These are not discussed here.

2 Names and Chemical Formulae

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<thead>
<tr>
<th>International non-proprietary name</th>
<th>pentetic acid</th>
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<tr>
<td>Synonyms</td>
<td>diethylenetriamine-(N\NN'N'')-penta-acetic acid, (N,N)-bis[2-[bis(carboxymethyl)amino]ethyl]glycine, pentacarboxymethyl diethylenetriamine, acidum penteticum, acide penétique, ácido pentético, diethylene triamine pentaacetic acid, DTPA</td>
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<table>
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<th>Calcium trisodium pentetate</th>
<th>Zinc trisodium pentetate</th>
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<td>Synonyms</td>
<td>Ca-DTPA, ([N,N–\text{bis}[2-[\text{bis(carboxymethyl)}\text{amino}]\text{ethyl}]\text{glycinato}(5-\text{calciate}(3-))] trisodium, sodium[[[\text{carboxymethyl})\text{imino}]\text{bis(ethylenenitrilo)]}tetraceto]-calcinate, ([[\text{carboxymethyl})\text{imino}]\text{bis(ethylenenitrilo)]} tetraacetic acid calcium complex trisodium salt, trisodium calcium diethylenetriamine pentacetate,, calcii trinatrii pentetas, calcium trisodium DTPA, pentetate calcium trisodium, pentétate de calcium trisodique, pentetato calcio y trisodi</td>
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Commercial Names: Ditripentat-Heyl (Heyl, Germany), Pentetate zinc trisodium injection and Pentetate calcium trisodium injection (Hameln, Germany)
### Conversion factors

<table>
<thead>
<tr>
<th></th>
<th>Calcium trisodium pentetate</th>
<th>Zinc trisodium pentetate</th>
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<tr>
<td>1 g</td>
<td>2.01 mmol</td>
<td>1.9 mmol</td>
</tr>
<tr>
<td>1 mg</td>
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</tr>
<tr>
<td>1 µmol</td>
<td>497.4 µg</td>
<td>522.7 µg</td>
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Analytical grade pentetic acid is available from several manufacturers.

### 3 Physico-chemical Properties

- **Physical condition:** crystalline
- **Colour:** not known
- **Melting point:** 219-220 °C
- **Boiling point:** not known
- **Solubility:** Readily soluble in water and alkalis; not readily soluble in ethanol or apolar solvents
- **Optical properties:** not known
- **Acidity:** not known
- **$pK_a$:** not known
- **Stability in light:** No specific advice with respect to storage is necessary
- **Thermal stability:** stable
- **Refractive index and Specific gravity:** not applicable
- **Loss of weight on drying:** not known
- **Excipients and pharmaceutical aids:** not known
- **Pharmaceutical incompatibilities:** None known

### 4 Pharmaceutical Formulation and Synthesis

#### 4.1 Routes of Synthesis
Calcium trisodium pentetate can be made by mixing pentetic acid with sodium hydroxide and calcium chloride or calcium carbonate. Zinc trisodium pentetate can be made by mixing pentetic acid with sodium hydroxide and zinc oxide or zinc chloride.

4.2 Manufacturing Process

Not known.

4.3 Presentation and Formulation

Pentetate zinc trisodium injection and pentetate calcium trisodium injection are available from Hameln Pharmaceuticals GmbH, Germany. Each salt is available as a 5 mL ampoule containing 200 mg in boxes of 5 ampoules. These products are available for inhalation or injection.

Ditripentat-Heyl is available from Heyl Chemisch-pharmazeutische Fabrik GmbH & Co., Germany. Each 5 mL ampoule contains 1 g of calcium trisodium pentetate and it is available in boxes of 5 ampoules of intravenous injection or infusion.

5 Analytical Methods

5.1 Quality Control Procedures for the Antidote

Not known.

5.2 Methods for Identification of the Antidote

Not known.

5.3 Methods for Identification of the Antidote in Biological Samples

Not known.

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).

Specialist advice is essential for dose assessment following a radiation accident as this assists in determining appropriate management and the expected clinical course. Radioactivity measurements of the wound (if applicable), skin or chest (following inhalation), nasal swabs, urine and faeces are also used to assess dose. In many cases the victim is not wearing a dosimeter (and this only measures external exposure not the internal dose). In addition the standard models for calculating intake from routine occupational exposures may not be applicable and individual-specific models may have to be developed and applied for internal dose calculations (Toohey, 2003).

6 Shelf-Life

The shelf-life for Ditripentat-Heyl is stated as 5 years for the ampoules. Ampoules of pentetate zinc...
trisodium injection and pentetate calcium trisodium injection should be stored at 15 to 30°C.

7 General Properties

Pentetic acid (diethylenetriaminepentaacetic acid, DTPA) is a polycarboxylic acid chelator, like ethylenediaminetetraacetic acid (EDTA). Compounds of this type have been used for many years as industrial and analytical reagents because they chelate many metals.

Pentetic acid is used as the calcium or zinc trisodium salt which act by exchanging calcium or zinc ions for a metal with a higher binding capacity. The salts have been used in Europe and the USA (Ménétrier et al., 2005) as chelating agents for heavy metals and as decorporation agents for radionuclides.

Treatment with calcium or zinc trisodium pentetate should be started as soon after exposure as possible as the efficacy decreases if treatment is delayed, that is when the bulk of the metal ions are no longer in the circulation. Generally treatment is started with calcium trisodium pentetate as this is more efficacious and then zinc trisodium pentetate is used after the first day or so as it is less toxic than the calcium salt. If calcium trisodium pentetate is not available treatment should not be delayed and the zinc salt should be given.

Pentetic acid salts are usually given by intravenous injection or infusion. Solutions can also be used for dermal and ocular decontamination, and it can be given by nebuliser following inhalation exposure. Pentetic acid salts have poor oral bioavailability and administration by this route is rarely used. If oral dosing is used higher doses may be needed for effect.

Pentetic acid salts have short biological half-lives compared to heavy metals and radionuclides and treatment may be required for several years.

Pentetic acid salts are generally well tolerated but because of their ability, particularly observed with calcium trisodium pentetate, to increase elimination of trace elements monitoring is essential and supplementation may be required.

8 Animal Studies

8.1 Pharmacodynamics

Extensive investigations in animals have shown that pentetic acid salts are effective in removing several heavy metals and radionuclides from the body.

8.1.1 Americium (Am)

Pentetic acid is very effective in removing americium from the body (Lloyd et al., 1979a; Jones et al., 1980; Lloyd et al., 1985b; Volf, 1986; Volf & Peter, 1986), and it also seems to be the optimal antidote (Stradling et al., 1984; Stradling et al., 1986) for removing inhaled americium. With early use (i.e. within the first 24 hours after exposure) the calcium salt was found to be slightly more effective than the zinc salt (Seidel, 1973; Seidel, 1975), but thereafter there was no difference in efficacy (Seidel, 1973; Seidel, 1975; Lloyd et al., 1976; Lloyd et al., 1977). The loss of effect from delayed initiation of treatment cannot be compensated for by increasing the total cumulative dose of pentetic acid salts (Seidel, 1975). The earlier the chelating agent is given the greater the removal of americium (Lloyd et
Inhaled americium

Lung lavage and chelation therapy were evaluated in beagles exposed to aerosols of americium-241 oxide. Following exposure the lungs were lavaged on days 2, 7, 14, 28 and 42 (right lung) and 2, 10, 21, 35 and 49 (left lung). Intravenous calcium trisodium pentetate (22 µmol/kg) was given on days 1 to 4 and then twice weekly (18 doses in total) until the animals were sacrificed on day 64. The concentration of americium-241 in tissues was lower in treated dogs. Calcium trisodium pentetate prevented deposition in organs and removed americium-241 already deposited in the liver. It did not, however, remove americium deposited in bone. Americium was removed in all lung lavages but only the first 4 (two lavages of each lung) removed large quantities (Muggenburg & Mewhinney, 1981).

Parenteral americium

Calcium and zinc trisodium pentetate were compared in beagle dogs exposed to americium-241. The dogs were given intravenous americium-241 and two weeks later were treated with subcutaneous injections of either calcium or zinc trisodium pentetate (6, 12 or 30 µmol/kg) either as a single dose or in divided doses. For a single daily injection there was not much difference between the salts in removing americium. Five daily doses of calcium trisodium pentetate had to be stopped within 3 days in two dogs as they developed severe toxicity from frequent administration of calcium trisodium pentetate (clinical details not stated). There appeared to be no significant difference between the salts but zinc trisodium pentetate seemed to be more effective in repeated doses. In the first 3 days dogs receiving calcium trisodium pentetate excreted 6.6% of the injected dose of americium compared to 14.8% in those receiving zinc trisodium pentetate. Continued treatment with zinc trisodium pentetate removed all the americium-241 in the liver after 1 year of treatment and approximately 80% in the skeleton by 2 years (Lloyd et al., 1976). This study was repeated in order to reduce any physiological differences between the dogs given calcium or zinc trisodium pentetate. It also confirmed that for delayed treated there was no difference in calcium or zinc trisodium pentetate in removing americium-241 (Lloyd et al., 1977).

Beagle dogs intravenously injected with americium-241 were treated 2 weeks later with zinc trisodium pentetate. After 13 months of therapy the mobilisation of americium in two dogs receiving a single daily injection of 0.027 or 0.034 mmol/kg/day was similar to that in two dogs receiving a total of 0.035 or 0.037 mmol/kg/day in five divided doses. Increasing the dose of zinc trisodium pentetate to 0.36 or 5 mmol/kg/day only slightly increased the mobilisation of americium. Just before starting therapy the dogs averaged 43% americium in the liver and 46% in non-liver (mainly skeletal) tissue. After 2 months of treatment retention in the liver was 2% of the pretreatment level, approximately 1% after 5 months and was undetectable by 13 months. At 2 months the non-liver retention was 53% of the pretreatment level, 40% at 5 months and 27% at 13 months. In contrast, the half-life of americium in liver and non-liver tissue in control animals was 10 years (Lloyd et al., 1975).

A study in beagles showed that early use of calcium trisodium pentetate is most effective in decorporation of americium-241. Animals given calcium trisodium pentetate (30 µmol/kg) at 1, 6, 30 or 150 minutes retained 3, 10, 29 and 45% of americium-241 respectively. Those treated at 8 hours, 1 or 3 days retained 58, 73 and 72%, respectively (Lloyd et al., 1979a).

Mice were treated with a single intraperitoneal injection of calcium or zinc trisodium pentetate (1 mmol/kg) at various times after intravenous administration of americium-241. When given 24 hours after americium the pentetic acid salts were equally effective at removing americium from organs but zinc trisodium pentetate was slightly less effective at mobilising americium from the liver. When given on day 64 both salts had little mobilising effect on americium. It was clear that with early treatment, up to 5 hours after americium injection, the calcium salt is slightly more effective than zinc trisodium...
pentetate but thereafter there was no difference in efficacy (Seidel, 1973).

The effect of calcium trisodium pentetate on the concentration of americium-241 in the skeleton, liver and kidneys was investigated in rats, and Syrian and Chinese hamsters. Americium-241 was given by intraperitoneal injection followed 24 hours later by intraperitoneal calcium trisodium pentetate (30 or 1000 µmol/kg) and the animals were sacrificed 8 days later. A single injection of calcium trisodium pentetate mobilised americium in rats and Chinese hamster liver but was markedly less effective in the Syrian hamster. There was no relationship between the biological half-life of a radionuclide in an organ and the fraction of the radionuclide which is available for chelation (Seidel, 1978).

The effect of calcium trisodium pentetate on americium-241 elimination in adult baboons has been studied. The baboons were given intravenous americium-241 followed by intravenous calcium trisodium pentetate (28.7 µmol/kg) twice weekly for 9 or 11 doses. The chelating agent was started 1.5 or 13 months after americium exposure. In the baboon treated 13 months after exposure the daily urinary radioactivity was increased by factors as large as 70 above pre-treatment concentrations. By comparing with the control it was calculated that 88% of americium-241 excreted (7.8% of the body burden) of the total was removed as a result of chelation therapy. Faecal excretion was unchanged. When treated 1.5 months after exposure urinary excretion was enhanced by factors of 17 to 56 for the first 24 hours. A total of 21.3% of the body burden was excreted in 20 days during which 9 treatments had been given. It was calculated that approximately 74% of the americium removed by chelation was in the urine and 26% in the faeces. Americium in the liver was much easier to remove with calcium trisodium pentetate than americium in bone (Cohen et al., 1974).

Parenteral americium, oral antidote

The effectiveness of oral calcium and zinc trisodium pentetate was studied in rats after intravenous americium-241. Even a low dose of calcium or zinc trisodium pentetate (1 mM) in drinking water from 20 minutes after injection for 18 days produced a significant reduction in the americium-241 concentration in the liver and femur (Taylor & Volf, 1980).

Other studies

The effectiveness of calcium trisodium pentetate in juvenile and adult baboons has been compared. The baboons, 4 to 5 years or 11 to 14 years, were given intravenous americium-241 followed by intravenous calcium trisodium pentetate (28.7 µmol/kg three times a week for 4 weeks). In adult baboons the chelator was most effective when given soon after americium exposure (1 day or 1.5 months), that is, when the americium was associated with soft tissues rather than bone. When given 1 year after exposure an additional 8% of the body burden was removed, presumably from the skeleton. Comparing juveniles and adults treated 1.5 or 1.6 months after exposure for 10 to 12 treatments (3 times a week), the cumulative net increase in urinary excretion of americium in juveniles was 2.5 times that of the adults. The overall decrease in the body burden of adult baboons was 15% compared to 30% in the juveniles (Cohen et al., 1976).

The effect of zinc trisodium pentetate was examined in mice exposed to americium-241 during pregnancy. Female mice were given intraperitoneal americium-241 at various stages of gestation followed by subcutaneous zinc trisodium pentetate (300 µmol/kg) starting 10 minutes later. Mothers and young were sacrificed shortly afterwards. Treatment with zinc trisodium pentetate significantly reduced body burden of americium in both the mothers and the fetuses. There was no net increase in the transfer of americium to the unborn young. Exposure to americium-241 17 days before mating and treatment with 10 doses of zinc trisodium pentetate (completed 3 days before mating) also resulted in reduced fetal body burden. These data indicate that the hazard from americium to the unborn could be reduced by zinc trisodium pentetate treatment prior to or during pregnancy (Lloyd et al., 1985a).
An in vitro study using a crystalline bone mineral surrogate, calcium hydroxyapatite, showed that zinc trisodium pentetate only removed 1.4% of the bound americium-241 (Guilmette et al., 2003).

8.1.1.1 Americium and plutonium

Pentetic acid salts are very effective at removing americium and plutonium from tissues. Americium is the daughter element of plutonium and exposure may involve both elements.

Parenteral americium and plutonium

Mice were given an intraperitoneal injection of a mixture of americium-241, plutonium-237 and 239, and given calcium trisodium pentetate 3 days later. A dose of 500 µmol/kg was given twice weekly for 5 weeks; some subjects also received salicylic acid (2000 µmol/kg). Total body retention of plutonium and americium at the end of 34 days was significantly less in the mice treated with calcium trisodium pentetate compared to the controls. Salicylic acid did not enhance the effect of calcium trisodium pentetate (Jones et al., 1980).

The effect of delayed treatment with zinc trisodium pentetate or LICAM(C) was studied in beagle dogs exposed to plutonium-239 and americium-241. Daily subcutaneous injections of zinc trisodium pentetate (30 µmol/kg) were given two weeks after intravenous plutonium-239 and americium-241. Zinc trisodium pentetate was more effective at decreasing the total body plutonium content and the total body americium content than LICAM(C). Zinc trisodium pentetate was far more effective in removing plutonium and americium from liver tissue and americium from non-liver tissue than LICAM(C). Americium-241 was undetectable in liver tissue by 16 weeks of treatment with zinc trisodium pentetate (Mays et al., 1986).

Beagles were given intravenous calcium trisodium pentetate (3, 10, 30 or 300 µmol/kg) 30 minutes after intravenous plutonium-237 and 239 and americium-241 and were sacrificed 7 days later. The quantity of plutonium and americium retained was influenced strongly by the dose of calcium trisodium pentetate given. Plutonium retention was 77% in the dog given 3 µmol/kg and 14% in the dog given 300 µmol/kg. For americium the corresponding figures were 40% and 9%. Similarly the liver retention was also reduced with higher doses of calcium trisodium pentetate; reduced from 18% to 2% with plutonium and 21% to 1% with americium (Lloyd et al., 1979b).

The influence of age on efficacy of chelation was investigated in beagles aged 3 months (juveniles), 1.9 years (young adults) and 10 years (mature adults). Two weeks after an intravenous injection of a mixture of americium-241 and plutonium-239 subcutaneous zinc trisodium pentetate (30 µmol/kg/day) was started and given for the 154 days of the experiment. Zinc trisodium pentetate caused a marked increase in excretion of both americium and plutonium in urine and faeces. The chelation therapy was most effective in juveniles and less effective in mature adults. For example, retention of americium in the liver decreased from a pretreatment level of approximately 50% in the adults to about 10% in mature adults and less than 1% in the young adults at about 140 days of treatment. In contrast, liver retention in juveniles decreased from a pretreatment level of about 16% to undetectable by 28 days of treatment. For plutonium, retention in the liver decreased from adult pretreatment levels of about 30% to almost 10% in the mature adults and 6% in the young adults at 140 days of treatment. In juvenile livers retention of plutonium fell from 15% to undetectable by 56 days of treatment. Zinc trisodium pentetate was also more effective in younger subjects in mobilising americium and plutonium from other tissue (e.g. the skeleton) (Lloyd et al., 1985b).

Rats were used in a study investigating the effect of delayed administration of pentetic acid salts after injection of plutonium-238 and americium-241. The animals were given calcium (first dose) or zinc trisodium pentetate (subsequent doses) at 30 minutes, 6 hours, days 1 to 3 or on days 1 to 3 after
subcutaneous or intramuscular plutonium-238 and americium-241. After subcutaneous plutonium-238 and americium-241 the total body content of plutonium and americium were reduced to 15% and 25%, respectively, of those of controls. A single local injection was only marginally less effective than repeated dosing. Delayed administration reduced the efficacy of pentetic acid; when started at 6 hours or 1 day the total body count of plutonium was reduced to 50% and 60%, respectively, of controls. The corresponding figures for americium were 57% and 67%, respectively. After intramuscular plutonium-238 and americium-241 with pentetic acid started 30 minutes later the total body content of plutonium and americium were reduced by 32% and 22%, respectively, of controls. Delaying treatment again reduced efficacy. When started 6 hours or 1 day after exposure the total body count of plutonium was reduced to 66% and 74%, respectively, of controls. The corresponding figures for americium were 62% and 67%, respectively (Gray et al., 1994).

Simulated wound

Another experiment studied the effect of calcium and then zinc trisodium pentetate on simulated wounds involving americium-241 and plutonium-238 nitrates in rats. After subcutaneous americium-241 and plutonium-238 nitrates local subcutaneous injection of calcium trisodium pentetate (30 \( \mu \)mol/kg) at 30 minutes reduced the retention of plutonium-238 in the wound and other body tissues to 38 and 20% of controls. The figures for americium-241 were 31 and 28% (Stradling et al., 1993b).

Inhaled americium and plutonium

In rats that had inhaled a mixture of nitrates of americium-241 and plutonium-238 treatment with intraperitoneal calcium and then zinc trisodium pentetate (30 \( \mu \)mol/kg) at 0.02, 0.25, 1, 2 and 3 days reduced the plutonium and americium concentrations to 10% and 5%, respectively, of controls at 7 days (Stradling et al., 1986).

Inhaled americium and plutonium, oral antidote

The efficacy of oral zinc trisodium pentetate was investigated in rats after inhalation of plutonium-238 and americium-241. One hour or 4 days after inhalation of an aerosol of plutonium and americium zinc trisodium pentetate was given in drinking water at a dose of 95 \( \mu \)mol/kg/day for 4, 7 or 14 days. The plutonium retention in the lungs, liver, carcass and total body when given from 1 hour for 14 days post-exposure was 11%, 22%, 38% and 18%, respectively, of those in control animals. There was still considerable reduction in plutonium retention even when the oral antidote was started 4 days after exposure; in the lungs and total body the retention was 26% and 34% of controls. The results were similar for americium. When given from 1 hour for 14 days post-exposure the americium content of the lungs and total body was 11% and 14%, respectively, of controls (Stradling et al., 1993a). In a second study in rats the continual administration of zinc trisodium pentetate in drinking water (95 \( \mu \)mol/kg/day) started 1 hour after exposure reduced the plutonium-238 content of the lungs and total body to 2% and 8% of controls. The americium-241 content of the lungs and total body was reduced to 3% and 5% of controls. When started at 7 days after exposure the total body content of plutonium-238 and americium-241 were reduced to 17% and 20% of controls by 28 days. Increasing the oral dose to 950 \( \mu \)mol/kg/day continually or to 3600 \( \mu \)mol/kg/day every third day was no more effective than 95 \( \mu \)mol/kg/day. Similarly, additional intraperitoneal zinc trisodium pentetate (30 \( \mu \)mol/kg twice weekly) did not increase the effectiveness of oral dosing (Gray et al., 1995).

Another experiment compared the efficacy of prolonged oral and intraperitoneal injection of zinc trisodium pentetate started 4 or 28 days after exposure. Animals were killed at 4, 28, 52 and 76 days. Over the same period of treatment oral dosing with zinc trisodium pentetate was as effective as repeated injection. The most reduction of plutonium-238 or americium-241 in animals treated by either method was due to removal from the lungs and was more effective when started at 4 days compared to 28 days (Stradling et al., 1993a).
8.1.2 Antimony (Sb)

There is very little information on the efficacy of pentetic acid in chelating antimony but one study demonstrated that it was ineffective for trivalent antimony intoxication. More effective antidotes are available.

In a study comparing survival rates of different antidotes in antimony poisoning, mice were given intraperitoneal antimony (III) potassium tartrate 120 mg/kg (LD₅₀ 54.6 mg/kg). The antidotes were given by the same route 1 hour later at a dose of 10:1 molar 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 effective antidotes; none of the five mice treated with calcium trisodium pentetate survived (Basinger & Jones, 1981a).

8.1.3 Beryllium (Be)

Pentetic acid is not a suitable chelating agent for beryllium. In rats calcium trisodium pentetate (0.3 mmol/kg for 5 days after administration of beryllium 1 mg/kg parenterally 6 days/week for 3 weeks) was ineffective at reducing tissue concentrations of beryllium. It failed to normalise any biochemical parameters of beryllium toxicity and appeared to enhance the toxic effects of beryllium (Mathur et al., 1993).

In a similar study calcium trisodium pentetate (0.1 mmol/kg for 5 days after administration of beryllium 1 mg/kg daily for 28 days by intraperitoneal injection) was the least effective chelator tested (as measured by biochemical alterations in liver and kidney function). It was moderately effective when used in combination with α-tocopherol (Mathur et al., 2004).

8.1.4 Bismuth (Bi)

There is very little information on the efficacy of pentetic acid in chelating bismuth but it appears to be relatively ineffective. In a study of several antidotes comparing efficacy in bismuth poisoning, mice were given intraperitoneal bismuth citrate 125 mg/kg (LD₅₀ 71 mg/kg) followed by an antidote 20 minutes later in a 10:1 molar ratio antidote:bismuth. Only 4 of the 10 animals treated with calcium trisodium pentetate survived compared to all the animals treated with succimer, unithiol, the calcium salt of ethylenediaminetetra(methylene phosphonic) acid (EDTPO) or N-acetyl-D,L-penicillamine (Basinger et al., 1983).

8.1.5 Cadmium (Cd)

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. The efficacy of a large number of metal-binding agents, belonging to several chemical compound groups, has been investigated in cadmium toxicity (reviewed in Andersen, 1989a, 1989b), but in the majority of acute toxicity studies in experimental animals, both cadmium and antidote were injected at about the same time, reducing the relevance in relation to acute human intoxication.

Pentetic acid salts have been shown to be effective in cadmium poisoning by reducing body burden, increasing survival, reducing organ concentrations or reducing cadmium-induced organ damage (Cantilena & Klaassen, 1981; Planas-Bohne & Lehman, 1983; Eybl et al., 1984; Andersen et al., 1988; Basinger et al., 1988). Pentetic acid has also been shown to be effective in combination with dimercaprol (Cherian, 1980; Cherian, 1984; Cherian & Rodgers, 1982). Delayed administration of
pentetic acid has been shown to greatly reduce its efficacy in cadmium-poisoned experimental animals (Cantilena & Klaassen, 1982; Planas-Bohne & Lehman, 1983; Sarić et al., 2004) and in some cases it has been shown to be ineffective in these circumstances (Shinobu et al., 1983). Based on experimental data, Andersen (1989b) concluded that the optimal antidotal treatment for acute oral cadmium intoxication is oral administration of succimer and pentetic acid.

**Early treatment**

Cantilena & Klaassen (1981) found that intraperitoneal calcium trisodium pentetate (0.9 g/kg) was the most effective antidote at increasing survival in mice when given immediately after intravenous cadmium (4-10 mg of cadmium/kg). Intraperitoneal calcium trisodium pentetate increased urinary excretion of cadmium by 60% with a significant decrease in faecal excretion. Calcium trisodium pentetate was also the most effective agent tested in reducing organ cadmium concentrations. It resulted in significant decreases in the cadmium concentration in the blood, pancreas, liver, kidney, spleen, gut, testes, bone and muscle.

The effect of zinc trisodium pentetate and calcium trisodium pentetate were compared in cadmium-poisoned mice when administered intraperitoneally immediately after subcutaneous cadmium (20 mg/kg as cadmium chloride). They were effective at increasing survival, and the calcium salt was more effective than the zinc salt. In another study where cadmium (0.5 mg/kg intravenously) was immediately followed by an antidote at a dose of 10:1 molar ratio of antidote to cadmium, there were significant decreases in cadmium concentrations in the liver, kidneys and gastrointestinal tract and a reduction in body burden with both zinc and calcium trisodium pentetate. Cadmium-induced lipid peroxidation was also prevented with all the antidotes tested (Eybl et al., 1984).

Pentetic acid increased survival in mice when given orally mixed with cadmium compared to animals given cadmium alone. Pentetic acid did not prevent renal or hepatic cadmium-induced damage but reduced gastrointestinal damage and completely prevented testicular changes. Although pentetic acid increased the relative renal deposition the absolute amount in the kidneys was reduced due to lower intestinal absorption and the total quantity in the kidneys was less than in the control animals (Andersen et al., 1988).

Oral pentetic acid (3.61 mmol/kg) was effective in promoting survival in cadmium-poisoned mice (1 mmol/kg cadmium chloride orally) when given immediately after administration of cadmium. Animals were killed at 8 days. Pentetic acid was not as effective as succimer in reducing cadmium concentrations in the liver and kidney (Basinger et al., 1988).

After intravenous cadmium chloride (2.2 µmol/kg) in mice followed immediately by one of several antidotes (at a cadmium:chelator ratio of 1:10) calcium trisodium pentetate was the most effective agent at reducing the body burden of cadmium (Eybl et al., 1985).

Intraperitoneal calcium trisodium pentetate (632.5 mg/kg) given to rats 1 minute, 1, 2 or 4 hours after intravenous cadmium chloride (3.5 mg/kg) reduced the serum enzyme concentrations which are characteristic of hepatic damage following cadmium exposure. The histopathological changes in the liver were also reduced and although calcium trisodium pentetate reduced kidney cadmium concentrations, the liver concentrations were higher than in the controls (Basinger et al., 1987).

Oral treatment with zinc trisodium pentetate has been evaluated in cadmium poisoning. Rats, 6 days or 6 weeks old, received cadmium in cow’s milk or by stomach tube, respectively, followed by oral zinc trisodium pentetate (1.9 g/kg) over the first and second day (suckling rats) or immediately after and 24 hours later (older rats). The animals were killed on day 6. In suckling rats the zinc trisodium pentetate decreased whole body retention by 7 times, and gut cadmium retention by 9 times; kidney and liver
retention was 2 and 3 times lower, respectively. In older animals the whole body retention of cadmium was decreased by 4 times and the gut and organ retention was decreased by 5 times. Oral zinc trisodium pentetate was therefore more effective at reducing gut retention in sucklings compared to older rats (but more cadmium was retained in the gut of suckling rats). Zinc trisodium pentetate was more effective at reducing organ retention in older rats (Kostial et al., 1987c).

Early versus delayed treatment

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. Cadmium elimination was only increased on the first day. Calcium trisodium pentetate was the most effective antidote tested when given immediately after exposure, as measured by the reduced cadmium body burden. Repeated injections of 0.1 mmol/kg of calcium trisodium pentetate daily for 5 days/week for 4 weeks or the same dose in drinking water was no more effective than the first dose in increasing cadmium elimination (Planas-Bohne & Lehman, 1983).

Another study by Cantilena & Klaassen (1982) demonstrated the importance of time on the efficacy of antidotes in cadmium toxicity. Intraperitoneal calcium trisodium pentetate (0.9 g/kg) was administered 0, 2, 13, 36 or 72 hours after administration of intravenous cadmium (1 mg/kg) in mice and the animals were killed on day 5. For all antidotes, administration immediately after cadmium resulted in 50-75% of the dose being eliminated in the urine compared with 0.1% in controls, and although later doses also increased elimination the effect was less than that observed with immediate administration. Calcium trisodium pentetate increased urinary excretion of cadmium over the 5 day period when given immediately after the metal and only on day 1 when given at 2 or 12 hours. When given at 36 hours urinary excretion was only increased on day 2 and when given at 72 hours urinary excretion was increased on days 4 and 5. The magnitude of the increased cadmium elimination declined with increasing time between administration of the metal and the antidote. The cadmium concentration in tissues only decreased when the antidote was given immediately after the metal. Even a delay of 2 hours resulted in no significant decrease in organ cadmium concentrations. Calcium trisodium pentetate was the most effective antidote tested.

Delayed treatment

Even a delay in administration of 30 minutes can significantly reduce the efficacy of calcium trisodium pentetate in cadmium-poisoned rats. When given immediately, 30 or 60 minutes after oral cadmium administration intraperitoneal calcium trisodium pentetate (1 mmol/kg) reduced the cadmium concentration in the liver by 53%, 39% and 9%, respectively. The corresponding values for the kidney were 14%, 23% and 11%. So although the urinary concentration of cadmium was very high in the first 24 hours after dosing (30 minutes after cadmium) it was not reflected in lower renal retention. The organ concentrations of iron, copper and zinc were also examined in this study; only zinc was significantly higher in the kidney and lower in the liver after calcium trisodium pentetate (Sarić et al., 2004). Cherian & Rodgers (1982) also found that although intraperitoneal pentetic acid increased urinary cadmium concentrations there was no reduction in tissue retention.

In a study of antidotal efficacy in chronic cadmium poisoning in mice (2 mg of cadmium chloride intraperitoneally at 48 hour intervals for 5 doses) calcium trisodium pentetate (225 mg/kg intraperitoneally every third day for 10 doses) starting one week later had no significant effect on liver or kidney cadmium concentrations (Shinobu et al., 1983).

Intraperitoneal calcium trisodium pentetate 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 following dosing with radiolabelled cadmium (3 µmol/kg intravenously 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).

Mice were given intraperitoneal cadmium chloride (3 mg/kg) 6 days/week for 20 doses. On the 25th day some were treated with subcutaneous calcium trisodium pentetate every 2 days for 16 days (8 doses in total) and were killed on the 41st day. A single dose of chelator was given at an antidote to cadmium ratio of 25:1. Calcium trisodium pentetate significantly decreased the cadmium concentration of the liver but not the kidneys, testes or brain. When calcium trisodium pentetate was given alone, without cadmium exposure, there was a significant increase in the zinc concentration of the kidneys, presumably related to increased zinc excretion (Eybl et al., 1998).

Gale et al. (1983a) compared the efficacy of several metal-binding antidotes in mice given a sublethal intraperitoneal dose of radiolabelled cadmium (0.03 mg cadmium chloride). The antidote was given 4 weeks later. Calcium trisodium pentetate (873 mg/kg 3 times a week for 7 or 13 doses) was very effective at reducing the cadmium concentration in the kidney (reduced by 48%) but was ineffective in other organs and only reduced body burden by 6.7%. A more aggressive treatment regimen of 2000 mg/kg/day was terminated after 5 days because the animals had lost 20% of their body weight. Two days later the animals were moribund and were killed. The whole body radioactivity was found to have reduced by 11.4%. The mean reduction in cadmium burden in the kidney was 31.8% but only 5.3% in the liver.

In another study by the same group mice were given intraperitoneal cadmium followed 14 days later by chelation therapy with zinc trisodium pentetate and/or diethyldithiocarbamate (both 2 mmol/kg 3 times a week for 7 or 13 injections). Zinc trisodium pentetate caused statistically significant but relatively modest reductions in the renal, intestinal, testicular and myocardial cadmium burdens. It did not affect cadmium concentrations in the liver. Diethyldithiocarbamate was more effective than zinc trisodium pentetate alone but administration of both chelators caused a more marked depletion of the cadmium burden than either chelator alone. There was also a more rapid rate of both faecal and urinary excretion with administration of both agents (Gale et al., 1983b).

Other studies
An in vitro study demonstrated that pentetic acid suppressed metal accumulation in cells and reduced the cadmium-related growth inhibition in mammalian cell culture (Fischer, 1995).

8.1.6 Calcium (Ca)

There is limited information on the effect of pentetic acid on calcium. Calcium trisodium pentetate is not expected to affect calcium elimination. Mice given pentetic acid immobilised on cellulose and incorporated into white wheat flour dough had reduced gastrointestinal uptake of strontium-85, calcium-47 and radium-226. The pentetic acid was given for 24 hours prior to ingestion of the isotopes and 48 hours after dosing (Bulman et al., 1983).

8.1.7 Californium (Cf)

Pentetic acid is effective in removing californium from tissues (Graham et al., 1978).

Calcium trisodium pentetate (50 mg/kg by intraperitoneal injection) was very effective in removing californium-252 in a study in rats. The calcium trisodium pentetate was given immediately after
intratracheal administration of californium-252 and then every 3 days until the rats were sacrificed. On day 1 the whole body retention of californium was only 25% of the control group; this was less than 2% on day 32. In total 60% of intratracheally administered californium appeared in the urine on the first day after treatment. Retention in tissues was low or undetectable and in addition to preventing deposition in bone and tissue calcium trisodium pentetate resulted in more rapid clearance from the lungs. After 32 days the lungs of the treated animals contained only 5% of the amount retained by the controls (Graham et al, 1978).

The effect of calcium trisodium pentetate on the concentration of californium-252 in the skeleton, liver and kidneys was investigated in rats, Syrian and Chinese hamsters. Californium-252 was given by intraperitoneal injection followed 24 hours later by intraperitoneal calcium trisodium pentetate (30 or 1000 µmol/kg) and the animals were sacrificed 8 days later. A single injection of calcium trisodium pentetate mobilised californium-252 in rats and Chinese hamster liver but was markedly less effective in the Syrian hamster. In kidneys the efficacy of calcium trisodium pentetate increased in the order of rat, Syrian hamster and Chinese hamster. In another study calcium trisodium pentetate (30 µmol/kg) was given on days 4, 11, 18 and then at 7 day intervals until day 81 and animals were sacrificed on day 88. The efficacy was the same in the skeleton in all animals resulting in 50% of the control californium-252 concentration. In the liver and kidneys of Chinese hamsters over 90% of the californium-252 was mobilised but the efficacy was lower in the liver and kidneys in rats and Syrian hamsters. There was no relationship between the biological half-life of a radionuclide in an organ and the fraction of the radionuclide which is available for chelation (Seidel, 1978).

8.1.8 Cerium (Ce)

Pentetic acid has long been recognised as a useful chelating agent for cerium (Catsch & Lê, 1957), as it reduces both organ and whole body retention.

Parenteral cerium

Rats given intravenous cerium-144 were treated with intraperitoneal calcium trisodium pentetate (1.5 mmol/kg) 1 hour later. The urinary and faecal excretion of cerium was greatest on the first day and declined thereafter; the increase in faecal elimination was smaller that that of urinary excretion. At 15 days the concentrations of cerium were decreased by treatment with calcium trisodium pentetate in all organs except the spleen (Takada, 1972).

Intravenous zinc trisodium pentetate (1.25 mmol/kg) given 4 days after intravenous cerium-144 injection caused decreased cerium concentrations in liver and bone and increased urinary and faecal concentrations (Guhl, 1979).

In mice given intraperitoneal cerium-144 followed 30 minutes later by one of several antidotes, intraperitoneal calcium trisodium pentetate (0.5 mmol) was the most effective at reducing whole body retention of cerium-144. Combination of calcium trisodium pentetate with another antidote (deferoxamine, D,L-penicillamine or sodium salicylate) did not enhance its therapeutic effect or change the deposition characteristics of kinetics of cerium (Gachályi et al., 1986). Similarly a combination of deferoxamine and calcium trisodium pentetate was as effective in removing a mixture of niobium-95 and cerium-144 from tissues as each antidote when given separately (Gachályi et al., 1989).

Simulated wound

Calcium trisodium pentetate was used to evaluate removal of cerium-144 from wounds in rats. Simulated wounds were made with a scalpel and contaminated with cerium-144 and the excess fluid blotted off 1 minute later. All animals were given the chelating agent by intraperitoneal injection 1 hour
later (98, 28 or 7 mg/kg) and this was followed in two treatment groups at 2, 4 and 6 days or twice daily, respectively. Rats were sacrificed after 1 week. Calcium trisodium pentetate treatment increased excretion of cerium in all animals. The increase was high on the first day and thereafter was dose-dependent; the higher the dose, the greater the excretion. Frequent small doses of calcium trisodium pentetate were more effective than a single large dose (Takada & Fujita, 1979).

Oral cerium

The use of oral zinc trisodium pentetate has been investigated after cerium-144 was added to cows’ milk and fed to 6 day old rats. One group also received zinc trisodium pentetate (1.9 g/kg) in drops throughout days 1 and 2 and another group received zinc trisodium pentetate on days 2 and 3. The animals were killed 6 days after cerium administration. In control animals 94% of the cerium was in the gut at 6 days. Oral zinc trisodium pentetate significantly reduced cerium whole body retention in both treatment groups by 20 times. In the gut the retention was reduced by 25 times (Kostial et al, 1987a).

In contrast oral zinc trisodium pentetate increased retention of oral cerium-141 but reduced the retention of intraperitoneal cerium-141. With oral zinc trisodium pentetate the retention of oral cerium-141 was doubled in the whole body and gut, increased by factors of 5 in the carcass and liver, 10 in the femur and 50 in the kidneys. However, in this study the animals were killed at 24 hours and there was no measurement of excretion rate (Kargačin & Kostial, 1985).

Inhaled cerium

The use of calcium trisodium pentetate has been investigated for inhaled cerium-144 in dogs. After inhalation of cerium-144 on fused clay particles by aerosol dogs received repeated bronchial lavage with or without intravenous calcium trisodium pentetate (50 mg). Dogs treated with calcium trisodium pentetate excreted 1.8% of the initial lung burden during the first 70 days compared to 0.2% in dogs given only lavage. Lung lavage removed cerium in every case even though the treatment period spanned 2 to 56 days. Two of 8 dogs in the chelation and lavage group and 3 of 4 dogs in the lavage only group died from radiation pneumonitis and pulmonary fibrosis. Death occurred at 170 and 296 days in the first group and 210 to 228 days in the second group. The percentage tissue distribution of these 5 dogs was similar regardless of whether it had received chelation therapy. The chelating agent was ineffective in this study because the cerium-144 was present on insoluble clay particles (Muggenburg et al., 1975).

A series of studies investigated the removal of inhaled cerium-144 in beagles. The dogs were exposed to an aerosol of cerium-144 for 10 minutes and then received once of several treatments and were sacrificed on day 28. In the first study dogs were given a bronchial lavage with saline or a solution containing 0.5 mM pentetic acid and 0.6 mM of calcium ion. Bronchial lavage was of the left lung only and was undertaken on days 0 and 5, or only on day 0 or day 5. It was estimated that each lavage treatment delivered a pentetic acid dose of 1.82 to 3.31 mg/kg. Lavage with pentetic acid solution on day 0 removed a significant quantity of cerium-144, whereas lavage on day 5 removed a much smaller amount. Similarly, the urinary excretion of cerium increased in dogs treated with pentetic acid on day 0. At sacrifice the burden of cerium-144 in the lavaged left lung was less than in the untreated right lung. The 28 day cumulative radiation dose to the lungs, liver and skeleton of dogs lavaged with pentetic acid solution on the day of exposure was 49, 34, and 36%, respectively, of those in the untreated group (Pfleger et al., 1972a). A second study investigated the efficacy of bilateral lung lavage with pentetic acid solution on the same treatment days as before. Although cerium-144 was recovered in the lavage fluid pentetic acid was more effective at removing cerium through increased renal excretion (Muggenburg et al., 1972). Intravenous pentetic acid was effective in removing cerium-144 after inhalation of an aerosol and was most effective when given soon after exposure. When pentetic acid was given 1 hour after exposure the
lungs, liver and skeletal body burdens at 28 days were reduced to 40, 36 and 27% of the initial lung burden of the exposed untreated group. When the pentetic acid was delayed until 5 days after exposure there was a 50% decrease in the lung burden with very little effect on the liver and skeletal burdens. The urinary concentration of cerium-144 was 8 times the control when pentetic acid was given on day 0 and only twice the control when given on day 5 (Pfleger et al., 1972b). The most effective treatment was bilateral bronchopulmonary lavage with pentetic acid on days 0 and 5. This produced the greatest reduction in the percentage initial lung burden in the lung, liver and skeleton compared to controls (Muggenburg et al., 1972).

Other studies

The influence of age on the efficacy of chelation therapy has been investigated in rats with cerium-141 exposure. Intraperitoneal calcium trisodium pentetate (380 µmol/kg) was given to 2 and 6 week old rats 24 and 48 hours after intraperitoneal injection of cerium-141. The animals were killed 6 days after cerium administration. Calcium trisodium pentetate reduced the whole body retention of cerium in both groups but was 1.2 times more effective in older animals. Chelation also reduced cerium retention in organs with little difference in the age groups (Kargačin et al., 1986). In a similar study 2 and 6 to 8 week old rats were treated with intraperitoneal calcium trisodium pentetate (380 µmol/kg) 24 and 48 or 72 and 96 hours after intraperitoneal cerium-141. The animals were killed 6 days after cerium administration. Calcium trisodium pentetate reduced the whole body retention of cerium in both groups but was more effective in older animals. Efficacy also decreased with the time delay between exposure and treatment. The influence of age on the efficacy of chelation treatment was different for various organs and tissues, e.g., for liver and gut, therapy was more effective in older animals and for the bone it was more effective in younger animals but equally effective in both groups for the kidneys (Kargačin & Kostial, 1986). In a related study where intraperitoneal calcium trisodium pentetate (380 µmol/kg) was given immediately, 24 and 48 hours after cerium-141 administration the treatment was twice as effective in older (6 weeks old) than younger (2 weeks old) rats (Kargačin et al., 1983).

In rats given intravenous cerium-144 at various stages of pregnancy and treated with an antidote 6 hours later intraperitoneal calcium trisodium pentetate reduced the whole body retention of cerium-144 by 26 to 27%. Calcium trisodium pentetate decreased the deposition of cerium-144 in the fetuses and associated tissues and thereby reduced radiation exposure in the fetuses (Żylicz et al., 1975).

Pregnant rats received intravenous cerium-144 one day before they were expected to give birth and then on days 2, 9 and 16 after birth. This was followed 1 hour later by 50 mg of calcium trisodium pentetate by intravenous injection. Administration of calcium trisodium pentetate given before and/or after birth reduced the dose of cerium-144 received by the offspring (Baltrukiewicz et al., 1976).

8.1.8.1 Cerium (Ce) and praseodymium (Pr)

Praseodymium-144 is the daughter element of cerium-144 and exposure may involve both elements. The effect of calcium trisodium pentetate on an inhaled mixture of cerium-144 and praseodymium-144 oxide has been studied in dogs. A 25% solution of calcium trisodium pentetate was given as an aerosol by inhalation over 1 hour and from the 10th day of the study intramuscular doses were given (42-55 mg/kg) as this route was found to be as effective as dosing by aerosol. Intramuscular pentetic acid was given 5 days a week for 3 weeks and then 3 times a week until the end of the study. The antidote was started at various times: immediately after inhalation of the radioactive mixture, 5, 27 or 90 days later, and then continued for the 128 days of the experiment. When given immediately after exposure the body burden was reduced by 90% within 30 days compared to only
a 30% reduction in untreated controls. Delayed treatment also increased elimination of cerium and praseodymium but the effect was small. The deposition of cerium and praseodymium in the skeleton was not significantly changed when administration of calcium trisodium pentetate was delayed (Tombropoulos et al., 1969).

Similarly in rats exposed to an aerosol of cerium-144 (in equilibrium with praseodymium-144) treatment with an aerosol of pentetic acid (25% solution) reduced the radioactivity of the lungs by 90% and liver retention was also reduced (to 4% of controls). Animals were treated immediately after cerium exposure then twice daily for 3 days and then once a day for the next 3 days, then every second day until the 15th day. In animals treated with the same pentetic acid regimen except that the first dose was given at 24 hours the retention of cerium was greater (77% in the lungs and 89% in the liver) compared to controls (Tombropoulos & Bair, 1962).

8.1.9 Cobalt (Co)

Pentetic acid can increase overall survival in experimental animals but the effect on cobalt tissue concentrations appears to be variable.

In an early study in rats (170 to 210 g) intravenous cobalt chloride was immediately followed by pentetic acid (200 µmol/rat) and the animals killed 48 hours later. Intraperitoneal pentetic acid reduced cobalt concentrations in the liver, muscle and bone but not in the kidney (Lê, 1964).

Rats were given intraperitoneal cobalt chloride (0.06 mmol/kg/day 3 days/week for 4 weeks) and 24 hours after the last injection given intraperitoneal calcium trisodium pentetate daily for 5 days. Calcium trisodium pentetate significantly increased the urinary concentration of cobalt during the first and fifth day of treatment but not on the days in between. Faecal excretion of cobalt was significantly increased on days 1, 3 and 4 only. At 6 days after the last cobalt injection there was no decrease in cobalt concentrations in the kidney, brain or plasma and pentetic acid actually increased the concentration in the heart (Llobet & Domingo, 1988).

In a study in mice where intraperitoneal cobalt chloride (0.6-1.8 mmol/kg) was immediately followed by an intraperitoneal dose of one of several chelators, sodium calcium edetate and calcium trisodium pentetate (3.1 mmol/kg) were the most effective antidotes tested. Calcium trisodium pentetate significantly increased urinary and decreased faecal cobalt concentrations. It also significantly decreased cobalt concentrations in the liver, brain, heart and blood (Llobet et al., 1986). In a similar study, intraperitoneal calcium trisodium pentetate (1.4, 2.36 or 3.5 mmol/kg) after intraperitoneal cobalt chloride (0.70 or 1.18 mmol/kg) was second only to sodium calcium edetate in increasing survival in mice (Llobet et al., 1985).

After intravenous injection of cobalt chloride (2.2 µmol/kg) in mice followed immediately by one of several antidotes (at a cobalt:chelator ratio of 1:10) calcium trisodium pentetate was the most effective agent at reducing the body burden of cobalt. In another study no mice survived after subcutaneous cobalt chloride (1 mmol/kg) but those given calcium trisodium pentetate at a chelator: cobalt ratio of 5:1 all survived (Eybl et al., 1985).

In rats given intravenous cobalt-60 at various stages of pregnancy and treated with an antidote 6 hours later neither calcium trisodium pentetate nor cobalt trisodium pentetate reduced the whole body retention of cobalt-60. Both compounds significantly decreased the deposition of cobalt-60 in the fetuses and chorioallantoic placentae but there was no effect on retention in the whole fetoplacental unit. Both compounds caused a rise in the cobalt-60 concentration in the yolk sacs, particularly in the later stages of pregnancy but overall treatment with an antidote reduced radiation
exposure in the fetuses (Żylicz et al., 1975).

### 8.1.10 Curium (Cm)

Pentetic acid is effective at chelating curium, particularly when given by continuous infusion.

The comparative effectiveness of the calcium and zinc salts of pentetic acid in removing curium-242 from tissues has been studied in the rat. When given early (1.5 minutes or 1.5 hours after 1.5 µCi/kg intravenous curium) intraperitoneal calcium trisodium pentetate was more effective than zinc trisodium pentetate. In contrast when given late (24 hours after curium dosing) there was no difference in the effectiveness of the two compounds (Takada & Volf, 1977).

Curium is rapidly transported from the lungs after pulmonary exposure (this is not the case with plutonium, for example) and is present as particles believed to be the hydroxide. Pentetic acid salts are thought to act, not by chelating the particles, but by blocking their binding to serum proteins. This leaves the particles free to be excreted in the urine with little deposition in liver or bone. This effect was observed in rats by maintaining blood concentrations of pentetic acid salts at greater than 0.002 mg/L (Stradling et al., 1979).

Two dose regimens of pentetic acid were evaluated in rats following a single inhalation exposure to a mixture of curium-244 (92%) and curium-243 (8%) lasting 13 minutes. The rats were treated with calcium (105 or 700 µmol/kg) or zinc (105 µmol/kg) trisodium pentetate by intraperitoneal injection on days 1, 4, 8 and 11 or zinc trisodium pentetate by subcutaneous infusion (30 or 200 µmol/kg) starting on day 1. All animals were sacrificed at 14 days. All treated animals showed decreased concentrations of curium in lung, liver and bone compared to controls. The zinc salt was as effective as the calcium salt at 105 µmol/kg but the higher dose of calcium trisodium pentetate was better than either at the lower dose at decreasing liver and lung concentrations of curium but not the concentration in bone. A dose effect was not observed when zinc trisodium pentetate was given by continuous infusion. The curium concentration in bone in animals given a continuous infusion was about half that in those treated with intraperitoneal injections. Also the liver burden in those on continuous infusion was about one third of that on low dose injections. The urinary concentration of curium was twice that in animals treated with pentetic acid compared to controls. The curium concentration in bone after 14 days in animals receiving the pentetic acid injections was the same as that of untreated controls killed 1 day after exposure, suggesting that pentetic acid can remove curium from bone. How this applies to humans is unclear because the rate of bone turnover in rodents is much higher than that of humans (Guilmette & Muggenburg, 1985).

A study in dogs compared the effect of pentetic acid by daily injection and continuous infusion following inhaled aerosols of curium-244. All the dogs (except controls) received calcium trisodium pentetate (30 µmol/kg intravenously at 1 hour) followed by zinc trisodium pentetate injection (30 µmol/kg intravenously on days 1 to 4 and then twice weekly) or by infusion (30 or 120 µmol/kg intravenously beginning 1 day later). Each treatment regimen was continued for 64 days. All three pentetic acid regimens were effective at reducing the radiation dose. With zinc trisodium pentetate injection a total of 89% of the initial pulmonary burden was removed, compared to 94% with the low dose infusion and 97% with the high dose infusion. After 64 days most of the retained curium was in the lungs, liver and bone. Infused zinc trisodium pentetate prevented translocation of more than 99.5% of curium to the liver and 97 to 99% to bone and kidney (Guilmette & Muggenburg, 1992).

### 8.1.11 Einsteinium (Es)

There is limited information on the effect of pentetic acid following einsteinium exposure but it appears
to be effective (Parker et al., 1972; Smith, 1972).

Mice were given an intramuscular injection of einsteinium-253 and treated with intraperitoneal pentetic acid (1.5 mg). The first dose was given at 2 hours then daily for 5 days and after a 2 day rest period given daily until the 14th day. Pentetic acid increased urinary excretion of einsteinium, moderately decreased skeletal concentration (to 60% of controls) and rapidly decreased the liver concentration, which was negligible by 14 days (Parker et al., 1972).

8.1.12 Gallium (Ga)

There is limited information on the effect of pentetic acid following gallium exposure but it appears to be ineffective. Calcium trisodium pentetate (at a quarter of its LD$_{50}$) did not prevent death in mice when given immediately after intraperitoneal gallium nitrate (10.02 mmol/kg) (Domingo et al., 1987).

8.1.13 Lanthanum (La)

There is limited information on the effect of pentetic acid following lanthanum exposure. The effect of a 25% aerosol of calcium trisodium pentetate was studied in macaques given an aerosol of lanthanum-140. The maximum deposition of lanthanum in the lung was 500 µg and the estimated quantity of calcium trisodium pentetate administered was 12 mg. When lanthanum and calcium trisodium pentetate were given together the quantity of lanthanum cleared from the lung did not exceed 90%. When the calcium trisodium pentetate was given 1 hour later clearance was reduced to 65% (Ducousso et al., 1971).

8.1.14 Lead (Pb)

Although some studies have shown that pentetic acid can reduce lead concentrations in some tissues, others have demonstrated no antidotal effect and it is not the drug of choice for lead poisoning as more effective antidotes are available.

Intravenous calcium trisodium pentetate (1.1 mmol/kg given over 6 hours) 17 days after intravenous lead administration (7 mg/kg) was effective at reducing the bone concentration of lead in rats (Hammond, 1971).

In the study by Llobet et al. (1990) mice given intraperitoneal calcium trisodium pentetate at a dose of 1.16 or 2.90 mmol/kg given 10 minutes after intraperitoneal lead (0.58 mmol/kg of lead acetate trihydrate) had a lethality of 100 and 90%, respectively. Calcium trisodium pentetate (3.13 mmol/kg) significantly increased urinary and faecal lead excretion when given 15 minutes after lead dosing (37.8 mmol/kg of lead acetate trihydrate). In tissues calcium trisodium pentetate significantly reduced the lead concentration in the kidney but not in the brain, liver, spleen, blood or bone.

Jones et al. (1994) investigated the effect of various metal-binding agents in lead poisoned mice (10 intraperitoneal injections of lead 5 mg/kg, as lead acetate, over 12 days). Antidotes were started 3 days after the last lead dose and given by intraperitoneal injection at a dose of 1 mmol/kg/day for 4 doses with or without another 4 doses 3 days later. Zinc trisodium pentetate acid reduced brain and kidney lead concentrations when given for 8 days but did not reduce bone concentrations.

In lead-poisoned rats both zinc trisodium pentetate and calcium trisodium pentetate increased urinary excretion of lead, and the calcium salt was more effective than the zinc salt; however,
neither salt increased survival rate (Hofman & Segewitz, 1975).

In mammalian cell cultures, pentetic acid increased lead uptake but did not exacerbate lead toxicity (Fischer et al., 1998).

8.1.15 Manganese (Mn)

Pentetic acid can increase removal of manganese but its efficacy is variable and it appears to be most effective at high doses.

Manganese poisoned rats (6 mg/kg by intraperitoneal injection daily for 25 days) were treated with one of several chelating agents (0.11 mmol/kg daily for 8 days) to evaluate efficacy at removing manganese from the brain and liver. Pentetic acid was particularly effective at removing manganese from the liver. In an in vitro study using subcellular fractions from manganese poisoned rats (6 mg/kg by intraperitoneal injection daily for 40 days) pentetic acid was less effective removing only 18 to 50% of the manganese (Tandon & Singh, 1975).

In a study of the efficacy of various chelating agents in manganese poisoned mice (0.23, 0.46 or 0.92 mmol/kg of manganese) intraperitoneal pentetic acid was only effective at high doses (0.92 mmol/kg). The chelating agents in this study were given 10 minutes after intraperitoneal manganese administration (Tandon & Khandelwal, 1982).

8.1.16 Mercury (Hg)

Pentetic acid is not the drug of choice in mercury poisoning (Kachru & Tandon, 1986), as more effective metal binding agents are available.

In rats with mercury toxicity (5 µmol/kg as mercuric chloride by intraperitoneal injection) intramuscular calcium trisodium pentetate (400 µmol/kg) was ineffective when given prior to exposure. It did not increase urinary or faecal mercury concentrations or reduce tissue concentrations (Kachru & Tandon, 1986).

8.1.17 Neptunium (Np)

There is no effective chelating agent for removal of neptunium (Ramounet et al., 1998; Stradling, 1998). The efficacy of pentetic acid is influenced by the valency of the neptunium compound. It appears to be more effective with neptunium in a valence state IV compared to V (Smith, 1972; Ramounet et al., 1998). Neptunium binds tightly to bone and pentetic acid tends to only affect soft tissue concentrations (Smith, 1972).

In rat studies pentetic acid-neptunium complexes (15 mg pentetic acid and 0.75 mg neptunium-237 V) injected intramuscularly were not stable in vivo, and although there was an increase in urinary excretion there was also an increase in organ retention of neptunium. It was concluded that pentetic acid is unlikely to be effective in neptunium removal (Morin et al., 1973). When injected into rats neptunium-239 V mixed with pentetic acid behaved the same as neptunium alone (Fritsch et al., 1987). These studies used neptunium in valence state V and a study using intravenous neptunium-239 in valence state IV showed that calcium trisodium pentetate had a high affinity for neptunium resulting in low concentrations of retained neptunium (Fritsch et al., 1987).

Other studies confirm that pentetic acid is more effective with neptunium in the valence state IV compared to V. Ramounet et al. (1998) examined the effect of localised pentetic acid treatment with
the injection site close to that of neptunium administration. Intramuscular pentetic acid (30 µmol/kg) 2 or 20 minutes after intramuscular neptunium-239 IV significantly increased urinary excretion of neptunium but was ineffective when given 1 hour after neptunium administration. The cumulative 3 day urinary excretion of neptunium in rats after pentetic acid given 20 minutes after dosing with neptunium-237 IV was increased 233% compared to controls whereas the increase was only 42% for neptunium-237 V. The neptunium concentration in liver, skeleton and at the injection site after pentetic acid treatment were significantly decreased with neptunium-237 IV but the change in neptunium-237 V was only significant in the liver. In contrast intravenous pentetic acid (30 µmol/kg) 30 minutes after intravenous neptunium-239 IV, was ineffective in decreasing neptunium tissue concentrations (Paquet et al., 1997).

Subcutaneous calcium trisodium pentetate (50 µmol/kg) was the least effective chelator in rats given intravenous neptunium-239. A higher dose (100 µmol/kg) was as effective as the other chelators tested (including a combination of calcium trisodium pentetate and deferoxamine or LICAM (C)) and reduced the body burden by approximately 50%. The combination of calcium trisodium pentetate and deferoxamine was most effective at reducing the neptunium concentration in liver, kidney and muscle (50 to 90%). Only this combination reduced neptunium concentrations in all soft tissues and bone. LICAM (C) alone increased retention in muscles (up to 4 times) and kidney but this effect was reduced when it was given in combination with calcium trisodium pentetate (Volf & Wirth, 1986).

8.1.18 Nickel (Ni)

There is limited information on the effect of pentetic acid following nickel exposure. Intraperitoneal calcium trisodium pentetate administered at a 10:1 mole ratio of antidote to nickel, increased the survival rate in mice poisoned with intraperitoneal nickel acetate (62 mg/kg). Antidotes were administered 20 minutes after injection of nickel. Of 14 antidotes tested calcium trisodium pentetate was the third most effective agent, although the small sample size prohibited any significant differentiation between them (Basinger et al., 1980).

8.1.19 Niobium (Nb)

There is limited information on the effect of pentetic acid following niobium exposure. Calcium trisodium pentetate (0.25 mmol/kg) was one of a number of decorporation agents investigated for efficacy in mice administered 30 minutes after intraperitoneal injection of niobium-95. Calcium trisodium pentetate was ineffective at removing niobium from tissues. The most effective compound when given alone was deferoxamine, but the best result was obtained by a combination of deferoxamine and calcium trisodium pentetate although using a mixture of decorporation agents did not change the deposition characteristics of kinetics of niobium (Gachályi et al., 1987). In another study a combination of deferoxamine and calcium trisodium pentetate was as effective in removing a mixture of niobium-95 and cerium-144 from tissues as each antidote given separately (Gachályi et al., 1989).

8.1.20 Platinum (Pt)

There is very little information on the effect of pentetic acid following platinum exposure. A single intraperitoneal injection of calcium trisodium pentetate (1 mmol/kg) was totally ineffective in reducing renal platinum concentration in rats treated with intravenous cisplatin (4 or 6.5 mg/kg) 24 hours previously (Planas-Bohne et al., 1982).

8.1.21 Plutonium (Pu)

Pentetic acid salts are effective in removing plutonium from the body (Bhattacharyya & Peterson, 1979;
Jones et al., 1980; Lloyd et al., 1979b; Stather et al., 1982; Lloyd et al., 1985b; Sullivan & Ruemmler, 1986; Szot et al., 1989; Volf, 1986) and the parenteral route is more effective than oral dosing (Sullivan & Ruemmler, 1986). Pentetic acid removes little plutonium from bone but can prevent circulating plutonium from deposition on bone surfaces. It is most effective when started soon after exposure (Guilmette et al., 1979; Lloyd et al., 1979a).

In animal studies both skeletal dose and bone sarcoma risk were reduced by pentetic acid chelation (Jones et al., 1986) and pentetic acid is also effective in removing inhaled plutonium (Stather & Rodwell, 1980; Stradling et al., 1986; Sérandour et al., 2007). However, calcium trisodium pentetate failed to mobilise plutonium when it was administered as the tetrafluoride (McDonald et al., 1979) and was ineffective in one study (Metivier et al., 1983) and effective in another (Stradling et al., 1986) when the plutonium was administered as the tributyl phosphate complex.

It has been shown that during the first 24 hours after calcium trisodium pentetate in plutonium-exposed rats that 80-90% of the plutonium in the bile is in the form of the plutonium-pentetic acid complex (Bhattacharyya & Peterson, 1979). Even though the bile is a minor excretion pathway for pentetic acid it is the major pathway for excretion of hepatic plutonium (Bhattacharyya et al., 1978; Bhattacharyya & Peterson, 1979).

Parenteral plutonium

A study in beagles showed that early use of calcium trisodium pentetate is most effective in decorporation of intravenous plutonium-239. Animals given intravenous calcium trisodium pentetate (30 µmol/kg) at 1, 6, 30 or 150 minutes retained 31, 28, 34 and 44% of plutonium-239 respectively. Those treated at 8 hours, 1 or 3 days retained 52, 50 and 70%, respectively. In addition, treatment at 1 or 6 minutes had a greater effect in reducing plutonium-239 in trabecular bone (where osteosarcomas develop) compared to cortical bone (Lloyd et al., 1979a).

The effect of twice weekly intravenous injections of calcium trisodium pentetate (0.036 or 0.18 mmol/kg at 6 hours or 0.18 mmol/kg at 6 or 89 days) after intravenous plutonium-239 was investigated in beagles. The animals were sacrificed 12 weeks later. Treatment with calcium trisodium pentetate starting at 6 hours after plutonium exposure was more effective than treatment starting on days 6 or 89. This is because early dosing prevents deposition of plutonium in tissues. Removal from the liver was similar for treatment at 6 hours or 6 days. With the kidney 98% of the plutonium was removed by treatment at 6 hours, 88% by treatment at 6 days and only 32% when treatment was delayed until day 89. The high dose of calcium trisodium pentetate (0.18 mmol/kg) starting at 6 hours was more effective than 0.036 mmol/kg, particularly in reducing bone retention of plutonium. It was twice as effective at reducing the plutonium content of femurs. The high dose resulted in 61% of the plutonium initial dose being excreted in the first day’s urine compared to 40% with the low dose (Guilmette et al., 1979).

Smith et al. (1961) studied the effect of calcium trisodium pentetate on the removal of plutonium from miniature pigs. The pigs (40 to 60 kg) were given intravenous plutonium-239 followed 1 hour later by intravenous calcium trisodium pentetate (9 g, so 150 to 225 mg/kg). The animals were sacrificed 6 or 7 days later. Calcium trisodium pentetate administration was associated with increased urinary excretion of plutonium, particularly in the first 3 days. Approximately 90% of the dose was excreted. The retention was reduced by a factor of 30 in the liver and by a factor of 10 in the skeleton. There was little effect on retention in the kidneys. In another study pigs (62 to 75 kg) were given intravenous calcium trisodium pentetate (1 g on day 1 and 2 g daily for 4 days) 2 months after intravenous plutonium-239. This increased plutonium excretion by factors of approximately 40 to 100 in the urine and 300 to 500 in the faeces.
A study in mice showed that twice weekly injections of pentetic acid (0.5 mmol/kg) with salicylic acid (2 mmol/kg) was more effective at removing plutonium-239 from tissues than pentetic acid alone. Salicylic acid alone was ineffective. After 10 treatments with pentetic acid plutonium concentrations in the skeleton were 15% of the injected dose but when both agents were used the mice were free of plutonium (Schubert & Krogh Derr, 1978). In contrast, Humphreys & Stones (1980) found that intraperitoneal calcium or zinc trisodium pentetate with salicylic acid was less effective than pentetic acid salts alone in removing plutonium from tissues. The antidotes were given 3 days and 1 week after intravenous injection of plutonium-239.

**Parenteral plutonium, oral antidote**

The effectiveness of oral calcium and zinc trisodium pentetate was studied in rats after an intravenous injection of plutonium-239. Zinc trisodium pentetate in drinking water (given from day 4 for 7 days) at a dose exceeding the parenteral calcium trisodium pentetate dose by about 30 times was as effective as the calcium trisodium pentetate in removing plutonium (Taylor & Volf, 1980).

**Inhaled plutonium**

In beagle dogs exposed to an aerosol of plutonium tetrafluoride calcium trisodium pentetate was ineffective in removing plutonium. Intraperitoneal calcium trisodium pentetate (0.5 g) was given 2 hours after exposure and continued for 12 injections over 58 days. There was no difference in the plutonium burden in the lungs or the half-life of plutonium in the treated and untreated dogs. Urinary excretion of plutonium was higher in the treated dogs but the increase was not significant (McDonald et al., 1979).

Calcium trisodium pentetate was ineffective in rats that had been exposed to an aerosol of plutonium-239 as the tributyl phosphate complex for 60 minutes. The chelator (30 µmol/kg, 15 mg/kg) was given by intramuscular injection 90 minutes before inhalation and/or 90 minutes after and 1, 2, 3, 6, 8 and 10 days after exposure. In one group of animals 1.25 mg of calcium trisodium pentetate was given by inhalation 90 minutes after plutonium exposure followed by intravenous therapy. In the same study intravenous calcium trisodium pentetate after intramuscular plutonium-239 as the tributyl phosphate complex was also ineffective. The chelator was given by intravenous injection 30 minutes before (group 1), by intramuscular injection 90 minutes after (group 2) and on days 1-3, 7, 10, 14, 17, 21, 24 and 28 (both groups) after plutonium exposure. Although calcium trisodium pentetate increased urinary excretion of plutonium there was no significant decrease in plutonium retention in the skeleton. Even dosing prior to plutonium exposure did not prevent plutonium translocation. Calcium trisodium pentetate did not change the distribution of plutonium 30 days after plutonium exposure (Metivier et al., 1983).

Pentetic acid salts were effective in another study involving inhalation of plutonium-238 as the tributyl phosphate complex. Rats that had inhaled plutonium-238 were treated with intraperitoneal calcium and then zinc trisodium pentetate (30 µmol/kg) at 0.02, 0.25, 1, 2 and 3 days. Compared to controls only 6% of plutonium remained in the lungs, 9% in the liver and 8% in the carcass at 7 days (Stradling et al., 1986).

Stather & Rodwell (1980) examined the effectiveness of calcium trisodium pentetate following intravenous injection or inhalation of mixed oxides of plutonium and sodium in hamsters. After inhalation the mice were given intraperitoneal calcium trisodium pentetate (14 mg/kg) at 3 hours and on days 1, 2 and 4 and were sacrificed at 30 days. Treatment with calcium trisodium pentetate reduced the plutonium content of the liver to 35% of controls. Calcium trisodium pentetate was more effective in animals that had inhaled the plutonium compared to those that had received it by intravenous injection.
Inhaled plutonium, inhaled antidote

Stather et al. (1982) investigated the effectiveness of zinc trisodium pentetate following inhalation of plutonium-238 oxide in hamsters. When the zinc trisodium pentetate was given by aerosol (2 µmol/kg from day 7 at weekly intervals until day 147) the plutonium content of the lungs was reduced by about 25% with excretion mainly in the urine. After repeated inhalation of zinc trisodium pentetate the amount of plutonium in extra-pulmonary tissues was similar to that at the beginning of decorporation therapy suggesting that only a small proportion of plutonium entering the blood was deposited in tissues. A second experiment studied the effect of inhalation and intraperitoneal zinc trisodium pentetate (26 µmol/kg weekly from day 10 until day 143). With this regimen deposition in the carcass (skeleton) was reduced by a factor of 2 but the relative amounts in the lungs compared with the amount excreted in the urine and faeces was similar to that in the first experiment.

Recent studies have examined the efficacy of a dry powder formulation of pentetic acid with improved aerosolisation properties on the decorporation of plutonium-239. The pentetic acid was formulated on to porous particles containing 75% pentetic acid with a mean diameter of 4.5 µm. With this formulation 56% of the powder deposited in the lung and comprised 29% in the central airways and 27% in the alveolar region. This was tested in rats 6 days after inhalation of plutonium-239 oxide. The rats were given 3.8 mg of powder (23 µmol/kg) by intratracheal administration using a dry powder insufflator. The urinary excretion of plutonium remained high for 6 days after treatment with pentetic acid and was increased by a factor of 4 for the first 4 days after treatment. Although this formulation of pentetic acid increased excretion it did not enhance dissolution of plutonium-239 oxide particles in the lungs (Gervelas et al., 2007).

After inhalation of mixed isotopes of plutonium oxide the delayed intratracheal administration of a dry powder of calcium trisodium pentetate (18 µmol/kg at 7 days) did not significantly reduce the pulmonary plutonium retention but it did reduce translocation to the liver and skeleton. After inhalation of plutonium nitrate early intratracheal administration (at 2 hours) of calcium trisodium pentetate was more effective than intravenous injection (30 µmol/kg) at reducing pulmonary retention and was as efficient in limiting extrapulmonary deposition. Delayed administration did not reduce lung or extrapulmonary deposition (Sérandour et al., 2007).

Oral plutonium

When rats were gavaged with plutonium-238, immediately followed by intravenous calcium trisodium pentetate (0.25 mmol/kg) and killed a week later they retained slightly less plutonium than the controls but excreted approximately 200 times more urinary plutonium-238. In this study systemic calcium trisodium pentetate increased plutonium absorption 45-fold but reduced deposition in the skeleton and liver (Sullivan et al., 1983).

Other studies

The administration route was compared in adult and neonatal rats given oral or intraperitoneal plutonium-238 followed 2 hours later by oral or intraperitoneal calcium trisodium pentetate (0.5 mmol/kg). Parenteral administration of calcium trisodium pentetate to adult rats was much more effective than oral treatment, removing nearly 70% of plutonium. When oral plutonium was given to adults followed by oral calcium trisodium pentetate plutonium absorption increased 20-fold and retention was twice that of controls. When calcium trisodium pentetate was given by intraperitoneal injection after oral plutonium absorption increased 5 fold but most was excreted in the urine. In adult animals that received intravenous plutonium, treatment with oral calcium trisodium pentetate decreased retention and increased urinary excretion by 10%. Retention after intraperitoneal calcium triodium pentetate was a third of that in controls. Neonatal rats retain more plutonium in the gut and oral calcium trisodium pentetate was more effective in removing ingested plutonium from the intestines, liver and carcass than parenteral administration. Oral calcium trisodium pentetate also reduced deposits
in the liver and skeleton after injection of plutonium but was not as effective as intraperitoneal calcium trisodium pentetate (Sullivan & Ruemmler, 1986).

The effect of zinc trisodium pentetate was examined in mice exposed to plutonium-237 during pregnancy. Female mice were given intraperitoneal injections of plutonium-237 at various stages of gestation followed by subcutaneous zinc trisodium pentetate (300 µmol/kg) starting 10 minutes later. Mothers and young were sacrificed shortly afterwards. Treatment with zinc trisodium pentetate significantly reduced the body burden of plutonium-237 in both the mothers and the fetuses with no net increase in the transfer of plutonium-237 to the unborn young (Lloyd et al., 1985a).

The effect of chelation therapy on the risk of cancer from plutonium-239 exposure has been evaluated in mice. The animals were given intraperitoneal plutonium-239 at 10 weeks of age and then treatment with subcutaneous zinc trisodium pentetate (37 µmol/kg) was started 3 days later for 2 weeks (daily dosing), 2 months (daily for 2 weeks then 3 times weekly) or 1 year (daily dosing for 2 weeks, 3 times weekly for 6 weeks then once weekly). The mice were followed for life and examined for bone sarcoma. Both the skeletal dose and bone sarcoma risk were reduced by zinc trisodium pentetate therapy. The incidence of bone sarcoma in mice given zinc trisodium pentetate was generally below the dose-response curve for control mice (i.e. compared to controls, treated mice with higher skeletal retention of plutonium had a lower incidence and delayed onset of bone sarcoma). It appeared that the risk of cancer was reduced more than that corresponding to the decreased skeletal dose, suggesting that zinc trisodium pentetate preferentially removes plutonium from the areas of bone commonly associated with cancer such as the bone surface (Jones et al., 1986). A study in dogs also examined the risk of cancer and the effect of chelation therapy. Control dogs died of osteocarcinoma between 1267 and 1594 days after intravenous injection of plutonium-239. Dogs given weekly subcutaneous injections of calcium trisodium pentetate (30 µmol/kg) starting 2 hours after plutonium also died of osteocarcinoma between 1462 and 1783 days. Dogs given daily subcutaneous injections of zinc trisodium pentetate (30 µmol/kg) starting 2 hours after plutonium had a mean survival time of 3520 days or 2.1 times that of the dogs receiving calcium trisodium pentetate. Daily treatment with zinc trisodium pentetate reduced the body burden of plutonium more efficiently than calcium trisodium pentetate and prevented deposition of plutonium on bone surfaces (Bruenger et al., 1991).

Phan et al. (2004; 2006a; 2006b) have investigated the efficacy of pentetic acid encapsulated in liposomes on plutonium decolorization. After intravenous plutonium-239 phytate, pentetic acid (6 µmol/kg) in liposomes was as effective as free pentetic acid (30 µmol/kg) in maintaining the plutonium content of the femur below 4.3% of the injected dose after 16 days (Phan et al., 2004). In another study rats were given various plutonium-238 phytate salt solutions by intravenous injection followed 1 hour later by a single injection of pentetic acid (3.2 µmol/kg) in stealth liposomes of 100 nm diameter. This increased urinary plutonium excretion to over 90% of the injected dose and was able to reduce the liver and skeleton burden even 30 days after a single dose. A dose of 0.3 µmol/kg produced the same reduction in skeletal burden as four injections of the free pentetic acid (30 µmol/kg) (Phan et al., 2006b).

An in vitro study using a crystalline bone mineral surrogate, calcium hydroxyapatite, showed that zinc trisodium pentetate only removed 0.086% of the bound plutonium-238 (Guilmette et al., 2003).

See also section 8.1.1.1 for studies of involving both plutonium and its daughter element americium.

8.1.22 Polonium (Po)

There is limited information on the use of pentetic acid in polonium exposure but it appears to be ineffective.
Rats were given intravenous polonium-210 followed 1.5 minutes later by intraperitoneal administration of one of a number of antidotes (1 mmol/kg). Calcium trisodium pentetate was the least effective antidote and did not reduce organ concentrations of polonium. Although there was a slight increase in the concentration of polonium in the kidneys it was not as large at that observed with some of the other antidotes (unithiol, D-penicillamine and 2-mercaptopropionylglycine) (Volf, 1973).

8.1.23 Promethium (Pm)

There is limited information on the effectiveness of pentetic acid in promethium exposure but it appears to be effective. Rats given intravenous promethium-143 were treated with intraperitoneal pentetic acid (0.3 mmol in 1 mL of 10% calcium gluconate-calcium glucoheptanate solution) 1 hour or 48 hours later. Early treatment with pentetic acid reduced skeletal deposition to approximately 50% at a chelator:metal ratio of 100:1. When treatment was delayed by 48 hours promethium was principally mobilised from the liver although there was also significant removal from the skeleton. It was less effective at reducing kidney retention and delayed treatment was less effective than early treatment (Smith, 1970).

Miniature pigs were treated with 3 g intravenous calcium trisodium pentetate at 1 hour then 1 g at 24 and 48 hours and finally 1 g weekly injections at 70 days after intravenous promethium-147 and 148 (prompt treatment group). Other pigs were treated with 1 g once a week for 11 weeks commencing 28 (delayed) or 78 days (long delayed treatment group) after promethium injection. Animals were slaughtered at around 100 days after promethium administration, except for the long delayed treatment group who were sacrificed at 155 days. Prompt treatment removed more than 70% of the promethium within 48 hours and there was still enhanced removal until approximately 10 days after calcium trisodium pentetate administration. This early treatment probably removed promethium from the liver. Later treatment in this group (from 70 days) also resulted in increased removal presumably from the skeleton. The calculated half-life in untreated animals was more than 2000 days compared to 300 days in treated animals. At 100 days the quantity of promethium retained in the body was 88% in untreated animals and 12% and 38% in those treated within 1 day or at 28 days, respectively. When treatment was delayed until 78 days the retention was 44% at 155 days (Smith & Amster, 1970).

8.1.24 Praseodymium (Pr)

There is limited information on the use of pentetic acid in praseodymium exposure. Praseodymium-144 is a daughter element of cerium-144, see section 8.1.8.1.

8.1.25 Radium (Ra)

There is very limited information on the use of pentetic acid in radium exposure. Mice given pentetic acid immobilised on cellulose and incorporated into white wheat flour dough had reduced gastrointestinal uptake of strontium-85, calcium-47 and radium-226. The pentetic acid was given for 24 hours prior to ingestion of the isotopes and 48 hours after dosing (Bulman et al., 1983).

8.1.26 Strontium (Sr)

Pentetic acid is expected to be effective in increasing the elimination rate of strontium-85 (Norwood, 1960).

Intraperitoneal calcium trisodium pentetate (3.1 mmol/kg) given 10 minutes after intraperitoneal
strontium nitrate (3.78 mmol/kg) was the most effective agent at increasing urinary excretion of strontium in mice. It did not increase faecal excretion. Calcium trisodium pentetate was also one of the most effective agents at reducing tissue concentrations of strontium, particularly in the liver, kidney and brain but not in bone (Ortega et al., 1989).

In another study intraperitoneal calcium trisodium pentetate (615 mg/kg twice daily for 10 days) did not cause significant increases in urinary or faecal excretion of strontium in mice when started 10 minutes after subcutaneous strontium nitrate (95 mg/kg) administration. In tissues it only significantly decreased the strontium concentration in kidney but not bone, liver or muscle (Colomina et al., 1991).

Intraperitoneal calcium trisodium pentetate (2740 mg/kg twice daily for 5 days) resulted in significant decreases in urinary and faecal excretion in mice when started 24 minutes after subcutaneous strontium nitrate (95 mg/kg) administration. Calcium trisodium pentetate also significantly increased the blood concentration of strontium but had no effect on the strontium concentration of other tissues (Llobet et al., 1992).

Mice given pentetic acid immobilised on cellulose and incorporated into white wheat flour dough had reduced gastrointestinal uptake of strontium-85, calcium-47 and radium-226. The pentetic acid was given for 24 hours prior to ingestion of the isotopes and 48 hours after dosing (Bulman et al., 1983).

8.1.27 Thorium (Th)

Pentetic acid salts are partially effective in the removing thorium from the body (Stradling et al., 1991). Decorporation of thorium remains a problem (Stradling et al., 1998) and a more effective antidote agent is needed. Zinc trisodium pentetate is less effective than calcium trisodium pentetate (Peter-Witt & Volf, 1985; Stradling et al., 1991), but when treatment is delayed they are equally effective (Peter-Witt & Volf, 1985).

Inhaled thorium

Intraperitoneal calcium trisodium pentetate (30 µmol/kg) at 30 minutes, 6 hours, 0.25, 1, 2 and 3 days after inhalation of thorium-230 and 232 in rats did not appreciably enhance elimination of thorium. It did decrease the thorium content of the liver and kidneys but these tissues only contained a minor proportion of the thorium in the whole body. In animals given the same treatment regimen and then calcium trisodium pentetate twice weekly from day 6 to 28 (so 12 injections) there was a further reduction in the retention of thorium in the body but it was still two thirds that of controls. Another study investigated the effect of high doses of chelator. A single dose of 300 or 1000 µmol/kg calcium or zinc trisodium pentetate or repeated dosing (300 µmol/kg over three days) was no more effective at removing thorium than repeated treatment with 30 µmol/kg. A delay of only a day in administration markedly reduced the effectiveness of 1000 µmol/kg calcium trisodium pentetate. After intratracheal administration of thorium-234 the amount in the lungs at 7 and 28 days after repeated dosing with 300 µmol/kg was still about one-half or more of the controls (Stradling et al., 1991).

Parenteral thorium

Peter-Witt & Volf (1985) compared the efficacy of zinc and calcium trisodium pentetate in removing thorium-234 in rats. The chelators were given by intraperitoneal or subcutaneous injection 1.5 minutes after intravenous thorium. Calcium trisodium pentetate was more effective than zinc trisodium pentetate over the whole dose range used (30 to 1000 µmol/kg). In the skeleton, for example, 1000 µmol/kg of zinc trisodium pentetate removed as much thorium as 30 µmol/kg of calcium trisodium pentetate. Prompt administration of calcium trisodium pentetate reduced the thorium content of the skeleton by 70% but when delayed by 6 hours or 4 days the thorium content was only reduced by 20%
and 10%, respectively. The end effect of chelation depended on the time post-exposure it was initiated and the number of doses. Early and repeated dosing was most effective.

Mice were given intraperitoneal thorium-234 followed by intramuscular calcium trisodium pentetate (1.4 mmol/kg) for 3 consecutive days starting 3 minutes or 3 days later. The mice were killed at 4 or 8 days after thorium injection, respectively. With early treatment calcium trisodium pentetate significantly reduced the tissue and body burden of thorium-234 and most was excreted within the first 24 hours. The whole body radioactivity was reduced by 72%, and the radioactivity of the bone and liver was 50% and 8% of untreated controls. However, calcium trisodium pentetate did not reduce thorium-induced lipid peroxidation in bone marrow (as measured by concentrations of malondialdehyde). With delayed treatment calcium trisodium pentetate reduced thorium retention in the body by 18%, liver by 23% and the femur by 28%. It did not prevent an increase in malondialdehyde concentrations in bone but did reduce the concentrations in the liver (Chen et al., 2005).

The effectiveness of calcium trisodium pentetate was evaluated in rats injected with monomeric (ionic) and polymeric (colloidal) thorium-234. In the first study intraperitoneal calcium trisodium pentetate (370 mg/kg) was given 2, 5, 6 and 7 days after intravenous thorium and the rats killed on the 8th day. Most of the thorium was present in the skeleton with little in the soft tissues. Calcium trisodium pentetate reduced the skeletal thorium retention to 43% of the injected dose. Urinary concentrations of thorium were also increased with calcium trisodium pentetate, particularly after the first dose; thereafter the effect diminished. In a second study rats were given intravenous polymeric thorium-234 followed by calcium trisodium pentetate 330 mg/kg/day on days 3 to 6 and killed on day 7 or 660 mg/kg twice daily on days 8 to 11 and were killed on day 16. Thorium in this form deposited mainly in the liver and treatment with calcium trisodium pentetate at the lower dose had no effect on distribution and only slightly increased urinary excretion. The higher dose of calcium trisodium pentetate reduced the liver content of thorium from 53% to 40% of the injected dose and increased urinary excretion to 11% compared to 0.4% in controls (Fried & Schubert, 1961).

Simulated wound

The efficacy of calcium trisodium pentetate on the removal of thorium-234 from a simulated wound has also been investigated. Rats were given an intramuscular injection of thorium-234 and 1 hour later were treated with calcium trisodium pentetate as a single intramuscular injection around the site (local treatment), five daily subcutaneous injections (systemic treatment) or one intramuscular injection followed by 4 daily subcutaneous injections (combined treatment). The animals were killed at 7 days. Combined local and systematic treatment with calcium trisodium pentetate was equally or more effective than each of the treatments alone in reducing the retention of thorium-234 at the injection site and in the organs. The thorium retention was about 60 to 70% less than controls with combined treatment compared to 40% less with systemic treatment alone (Peter-Witt & Volf, 1984). In another study rats were given intramuscular thorium-232 and 234 followed immediately by calcium trisodium pentetate (0.1, 0.2, or 0.4 mmol/kg) injected around the wound site with or without citric acid. Calcium trisodium pentetate was more effective when given with citric acid; by day 2 whole body radioactivity decreased to 30.5% of the initial value and the wound site retained 23.6%. With calcium trisodium pentetate or citric acid alone the whole body retention was 47% and 79% respectively. Immediate treatment with calcium trisodium pentetate was more effective than treatment with calcium trisodium pentetate and citric acid starting 24 hours after exposure (Rencová et al., 2003).

In a study of antidotes in simulated wound contamination thorium-238 was given by subcutaneous or intramuscular injection to rats. Subcutaneous calcium trisodium pentetate (30 µmol/kg) was given at 30 minutes close to the wound site followed by intraperitoneal zinc trisodium pentetate (30
µmol/kg) at 6 and 24 hours. When calcium trisodium pentetate was given after 30 minutes the thorium retention was only reduced to 79% of controls. The removal of thorium was mainly through the local administration of chelating agents and repeated dosing by intraperitoneal injection had a minimal effect. A delay in administration markedly decreased efficacy; when given at 6 hours and 1 day after thorium injection the thorium retention increased to 90 and 95% of controls, respectively. The optimal treatment with calcium trisodium pentetate was subcutaneous injection around the wound site at 30 minutes followed by intraperitoneal injection at 6 hours and on days 1, 2 and 3. This regime reduced the body content of thorium-238 to 80% of controls after subcutaneous injection and 54% after intramuscular injection (Stradling et al., 1995).

8.1.28 Uranium (U)

There is no effective chelating agent for removal of uranium (Stradling, 1998). Several studies have shown that pentetic acid is relatively ineffective in reducing the uranium body burden (Domingo et al., 1989; Ortega et al., 1989; Domingo et al., 1990; Domingo et al., 1997; Ramounet-Le Gall et al., 2003).

In a study comparing 16 antidotes mice were given the antidote (at one quarter of the LD$_{50}$ subcutaneously) 10 minutes after subcutaneous injection of uranyl dihydrate (2.15 to 464 mg/kg). Although calcium trisodium pentetate effectively increased survival there was no increased urinary or faecal excretion of uranium and it failed to reduce tissue concentrations. In bone there was a significant increase in uranium concentrations (Ortega et al., 1989).

Mice received 12 subcutaneous injections of uranyl acetate dehydrate (8 mg/kg) on alternate days followed one day after the last dose by various chelators (at one quarter of their LD$_{50}$) for 5 days. Intraperitoneal calcium trisodium pentetate only decreased the uranium concentration in the liver; there was no effect on the kidney concentration. In addition it did not increase faecal excretion of uranium and significantly reduced uranium excretion in urine on days 3, 4 and 5 (Domingo et al., 1989).

Intraperitoneal calcium trisodium pentetate had no beneficial effects on the parameters of uranium toxicity in a study examining the effect of time of chelator administration. The antidotes were given 0, 0.25, 1, 4 and 24 hours after subcutaneous uranyl acetate dehydrate (10 mg/kg) (Domingo et al., 1990).

Calcium trisodium pentetate was investigated for its effect on uranium nephrotoxicity in rats. The rats were given subcutaneous uranyl acetate dihydrate (5 mg/kg) followed by intraperitoneal calcium trisodium pentetate (250, 500 or 1000 mg/kg) at 0, 24, 48 and 72 hours. Calcium trisodium pentetate showed a similar effect to Tiron in protecting against uranium nephrotoxicity although the increase in creatinine clearance was more pronounced with calcium trisodium pentetate. In contrast calcium trisodium pentetate was less effective at increasing uranium urinary excretion and reducing accumulation in bone (Domingo et al., 1997).

An in vitro study using a kidney proximal tubule cell line (LLC-PK$_i$) demonstrated that pentetic acid increased the cytotoxicity of uranium (Muller et al., 2006). An in vivo study in rats given calcium trisodium pentetate (30 µmol/kg) at 2 minutes and zinc trisodium pentetate (30 µmol/kg) at 24 hours after intraperitoneal injection of uranium (57, 147 or 639 µg/kg) found no additive effect on uranium toxicity (Houpert et al., 2003).

8.1.29 Vanadium (V)

Although calcium trisodium pentetate can increase survival after low dose vanadium exposure, increase excretion and reduce tissue concentrations in some organs it is not the most effective antidote for
vanadium intoxication (Hansen et al., 1982; Jones & Basinger, 1983; Domingo et al., 1985; Domingo et al., 1986; Domingo et al., 1990).

Intraperitoneal calcium trisodium pentetate (400 mg/kg) increased survival in mice when given 20 minutes after intraperitoneal administration of sodium orthovanadate or vanadyl sulphate (at doses corresponding to their LD_{90-95}) (Jones & Basinger, 1983). In another study intraperitoneal calcium trisodium pentetate reduced mortality in mice when given immediately after intraperitoneal administration of a low dose of sodium metavanadate (0.33 mmol/kg) but was ineffective after a high dose (0.61 mmol/kg) (Domingo et al., 1985). Similarly, intraperitoneal calcium trisodium pentetate (12.5 mmol/kg) only reduced mortality in mice after a low dose of sodium metavanadate (0.3 mmol/kg). Although calcium trisodium pentetate increased faecal concentrations of vanadium there was no increase in urinary vanadium concentrations. It reduced the vanadium concentration in the kidney and the heart but not the liver; calcium trisodium pentetate also protected against the histopathological changes in the kidneys (Domingo et al., 1986).

In rats the vanadium content of the kidney was reduced by 7%, increased in the liver by 15% and unchanged in the lungs with intraperitoneal calcium trisodium pentetate (30 µmol/kg) given 24 hours after intraperitoneal administration of sodium metavanadate (5 µmol/kg). After 100 µmol/kg of calcium trisodium pentetate the vanadium content was reduced by 9% in the kidney, 18% in the liver and 25% in the lung, but calcium trisodium pentetate was not as effective as deferoxamine at the higher dose. The vanadium concentration in the faeces was increased by the low dose of calcium trisodium pentetate concentration and both urinary and faecal vanadium concentrations increased with the higher dose of chelator. In addition calcium trisodium pentetate was more effective at removing tetravalent vanadium than pentavalent vanadium from tissues (Hansen et al., 1982).

Intraperitoneal calcium trisodium pentetate (1553 mg/kg) increased survival in mice when given 10 minutes after intramuscular vanadyl sulphate (215-4640 mg/kg) but resulted in no significant increase in urinary or faecal excretion of vanadium. It significantly decreased the vanadium concentration in the liver (27%), spleen and heart but not the kidney (Domingo et al., 1990).

Pentetic acid decreased the death rate in chick eggs incubated with vanadyl sulphate but was ineffective against sodium metavanadate. It had no significant effect on body weight reductions, or reduction in weights of legs and toes in chick eggs incubated with vanadium (Hamada, 1994).

An in vitro study using human erythrocytes found that calcium trisodium pentetate was able to prevent uptake of vanadium when added simultaneously to the cell medium. When added 2 hours after vanadium, calcium trisodium pentetate caused a small reduction in the vanadium concentration and prevented further increases in the vanadium concentrations in cells (Hansen et al., 1982).

8.1.30 Ytterbium (Yb)

There is limited information on the use of pentetic acid in ytterbium exposure although it appears to be effective.

Rats were injected intravenously with either a colloidal form or a soluble citrate of ytterbium-169, followed 24 hours later by intravenous calcium or zinc trisodium pentetate (14 mg/kg) as the free salt or in liposomes. With zinc trisodium pentetate the highest rate of ytterbium-169 removal from tissues occurred during the first two days with both the free or liposomal form. After this time the removal rate of ytterbium was only slightly higher in animals given zinc trisodium pentetate compared to controls. The liposomal encapsulated forms of the chelator were more effective than the free salts, particularly in removing colloidal ytterbium-169. A second injection of liposomal zinc trisodium pentetate given 8
days after the initial dose was not as effective in removing ytterbium as a second injection of the free
chelator. Calcium trisodium pentetate, as the free or liposomal preparation, was more effective than
zinc trisodium pentetate in removing colloidal ytterbium (Blank et al., 1984).

In comparing liposomal-bound and free zinc trisodium pentetate rats were treated with intravenous zinc
trisodium pentetate (14 mg/kg) 24 hours after intravenous ytterbium-169 citrate. Both forms of zinc
trisodium pentetate caused increased removal ytterbium from the body (3-4 times more than in
controls) but the liposomal-bound form was more effective. Both forms of zinc trisodium pentetate
were most effective within the first 48 hours (Blank et al., 1980).

Pregnant rats received ytterbium-169-pentetic acid complex by intravenous injection one day before
they were expected to give birth and then on days 2, 9 and 16 after birth. Between 2 and 20% of the
administered dose of ytterbium-169 passed in the milk to the newborn during lactation but this was
reduced to 0.2 to 0.9% when the ytterbium-169 was given as a pentetic acid complex. The quantity
of ytterbium-169 passed with the milk to the whole litter after each injection ranged from 1 to 10%
of the injected dose but this was reduced to 0.3 to 0.6% with the pentetic acid complex
(Baltrukiewicz et al., 1976).

8.1.31 Yttrium (Y)

There is limited information on the use of pentetic acid in yttrium exposure although it appears to be
effective.

The efficacy of calcium trisodium pentetate was investigated in rats with puncture wounds
contaminated with yttrium-90. The yttrium-90 solution (2.55 MBq/kg) was injected intramuscularly in
the left femoral quadriiceps to a depth of 5 mm. This was followed 15 minutes later by calcium
trisodium pentetate (34.7 µmol/kg) given intravenously in the tail vein or by intramuscular infiltration
into the wound site. Intravenous calcium trisodium pentetate significantly reduced the radioactivity at
the wound site by up to 76% and in bone by up to 84% compared to controls. In contrast the
radioactivity in the kidneys increased over 24 hours and then fell to a similar level as the controls.
Intramuscular calcium trisodium pentetate reduced the radioactivity at the wound site by up to 35% and
in bone by up to 52%. There was no change in the radioactivity of liver or blood with either route of
dosing. Prompt, local treatment with calcium trisodium pentetate is more effective in reducing
radioactivity at the wound site than systemic treatment (Watanabe et al., 2005).

8.1.32 Zinc (Zn)

Pentetic acid is an effective antidote for acute zinc toxicity (Basinger & Jones, 1981b; Domingo et al.,
1988; Llobet et al., 1988; Llobet et al., 1989).

In mice given intraperitoneal zinc acetate (0.49 mmol/kg, the LD$_{50}$) calcium trisodium pentetate (2:1
or 5:1 molar ratios of antidote to metal) was one of the most effective of the six antidotes tested, as
measured by percentage survival (Llobet et al., 1988).

In a comparison of several antidotes against the effects of acute intraperitoneal zinc intoxication in
mice, calcium trisodium pentetate efficiently reduced acute lethality. Intraperitoneal calcium
trisodium pentetate (10:1 antidote:zinc ratio) was given 20 minutes after a fatal dose of zinc (50
mg/kg) was administered. Survival was 86.7% with calcium trisodium pentetate but other antidotes
were equally or slightly more effective (Basinger & Jones, 1981b).

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. Intraperitoneal calcium trisodium pentetate (1569 mg/kg) was one of the most effective antidotes and prevented death even at the highest dose of zinc (Domingo et al., 1988).

After intravenous injection of zinc chloride (2.2 µmol/kg) in mice followed immediately by one of several antidotes (at a zinc:chelator ratio of 1:10) calcium trisodium pentetate was the most effective agent at reducing the body burden of zinc (Eybl et al., 1985).

In mice calcium trisodium pentetate (4.2 mmol/kg) was given at 0.25, 0.5, 2, 12 or 24 hours after intraperitoneal zinc acetate dihydrate (0.49 mmol/kg). Treatment with calcium trisodium pentetate significantly increased the urinary excretion of zinc in all groups particularly when given 0.5 hours after zinc administration. Faecal zinc excretion was significantly increased in all groups except when given 24 hours after the zinc. Calcium trisodium pentetate significantly decreased the zinc concentration in liver and bone but not in spleen, heart or kidney (Llobet et al., 1989).

In rats given intravenous zinc-65 at various stages of pregnancy and treated with an antidote 6 hours later zinc trisodium pentetate caused a 27 to 40% decrease in zinc-65 retention compared to controls; calcium trisodium pentetate was less effective and resulted in a decrease of only 14 to 26%. In the fetuses, placenta and whole fetoplacental unit zinc trisodium pentetate was more effective at reducing zinc-65 retention than calcium trisodium pentetate. Both compounds caused a rise in the zinc concentration in the yolk sacs but overall treatment with an antidote reduced radiation exposure in the fetuses (Żylicz et al., 1975).

### 8.2 Pharmacokinetics

In rats administered $^{14}$C-labelled zinc trisodium pentetate by intraperitoneal injection about 75% was excreted within the first 4 hours (Harmuth-Hoene et al., 1966). In rats administered $^{14}$C-labelled pentetic acid 95% of the radioactivity was excreted by the urine within 24 hours, 0.5% by the faeces and 0.7-1.3% by expired carbon dioxide. It seems likely that metabolic decomposition takes place in the kidneys (Havlicek et al., 1968).

In another study, rats received intravenous $^{14}$C-labelled pentetic acid and rapidly eliminated the carbon-14 with 84% in the urine and 10% in the faeces during the first 24 hours. After direct administration of $^{14}$C-labelled pentetic acid solution into the lungs 75% was excreted in the urine and 25% in the faeces. Tissue concentrations of carbon-14 were less than 1% of the administered dose at 24 hours (Crawley & Haines, 1979).

In rats only a very small proportion (0.12%) of calcium trisodium pentetate is excreted in bile by 24 hours after intravenous injection (Bhattacharyya & Peterson, 1979).

The pharmacokinetics of pentetic acid can be modified by encapsulation in liposomes and recent studies have demonstrated the potential of liposome-encapsulated pentetic acid in plutonium decorporation (Phan et al., 2004; 2005; 2006a; 2006b). Liposome-encapsulated pentetic acid was able to reach deposits of plutonium in the liver and bone. The pentetic acid penetrated the liver in larger quantities than free pentetic acid and had a longer half-life, with the liver and the spleen acting as reservoirs (Phan et al., 2004; Phan et al., 2005). Free pentetic acid was undetectable in plasma at 4 hours but encapsulated pentetic acid was still quantifiable at 24 and 48 hours after intravenous injection (Phan et al., 2005).

### 8.3 Toxicology
8.3.1 Acute toxicity

Of the two common salts of pentetic acid, the calcium trisodium pentetate is more toxic than zinc trisodium pentetate. In a study on the toxicity of the calcium and zinc salts of various chelating agents (hydroxyethylendiaminetriacetic acid [HEDTA], ethylenediaminetetraacetic acid [EDTA], pentetic acid and cycloandiaminetetraacetic acid) calcium trisodium pentetate was the most toxic and zinc trisodium pentetate the least toxic of the compounds tested (Eybl et al., 1974). In general the zinc salt of pentetic acid is at least as efficient as calcium trisodium pentetate, but zinc trisodium pentetate appears to be much safer (Lloyd et al., 1976; Lloyd et al., 1977).

A study in mice has showed that zinc trisodium pentetate is 2.5 times less toxic than calcium trisodium pentetate. However if the same quantity is given in divided doses zinc trisodium pentetate is 30 times less toxic than the calcium salt (Catsch & von Wedelstaedt, 1965).

Calcium trisodium pentetate has been shown to impaire the incorporation of iron-59 into erythrocytes and to affect bone marrow synthesis (Ebel, 1975; Planas-Bohne & Ebel, 1975).

Calcium trisodium pentetate depletes both zinc and manganese concentrations in tissues. There is no correlation between the effect on the zinc concentration and the dose. A single intraperitoneal dose of calcium trisodium pentetate (2 mmol/kg) increased the daily excretion of zinc from 1.48 to 199 µg/rat. The same dose given in 5 injections over the day increased the daily zinc excretion to 279 µg/rat (Planas-Bohne & Ebel, 1975). The effect on the manganese concentration is dose-dependent (Planas-Bohne & Olinger, 1976).

The LD$_{50}$ of pentetic acid is 587 mg/kg (1.49 mmol/kg) in rats (Srivastava et al., 1986) and for calcium trisodium pentetate the LD$_{50}$ has been determined as 6.7 mmol/kg (Llobet et al., 1988), 3.6 g/kg (6.94 mmol/kg) (Cantilena & Klaassen, 1981), 12.5 mmol/kg (Domingo et al., 1985; Llobet et al., 1985; Llobet et al., 1985) and 9.53 g/kg (19.2 mmol/kg) (Morgan, 1973) in mice.

In toxicity studies of puchel (the lipophilic derivative of pentetic acid) intraperitoneal doses of 1000 or 2000 mg/kg in mice resulted in prostration, cyanosis, tremor and rapid diaphragmatic activity within 10 minutes followed by death within 1 hour. Death occurred within 4 hours following 600 or 800 mg/kg. Animals given 300 mg/kg recovered within 24 hours. No adverse effects were observed at 30 or 100 mg/kg. In animals that died there was tubular degeneration of the renal cortex and liver haemorrhage at post-mortem examination. The LD$_{50}$ for puchel was determined as 530 ± 44 mg/kg in mice (Ellender et al., 1984).

8.3.2 Subchronic toxicity

Intraperitoneal calcium trisodium pentetate at doses up to 1000 mg/kg (once or daily for 5 days or weekly for 1 month) had no effect on hepatic function in mice, as measured by the clearance of sulphobromophthalein and the concentration of alanine aminotransferase (Morgan & Smith, 1974a). Transient histological changes were noted in the liver of mice after calcium trisodium pentetate in acute (1, 2.5 or 5 g/kg by intraperitoneal injection) and subacute (10, 100 or 250 mg/kg intravenously once daily, 5 days/week for 30 treatment days) toxicity studies. Transient changes were also observed in the kidney after acute doses but no effects were observed in the intestine with any dose (Morgan & Smith, 1974b). There was no evidence of toxicity in rats exposed to drinking water containing up to 30 mmol zinc trisodium pentetate for 21 days. There were no significant differences in intestinal DNA synthesis or iron utilisation compared to controls (Taylor & Volf, 1980).

In toxicity studies in baboons pentetic acid (30 µmol/kg) was given intravenously on day 0 and
intramuscularly on days 3, 6, 9, 13, 16, 20, 23 and 26. There were no changes in liver or renal function tests or biopsies (Fritsch et al., 1994).

In rats given calcium trisodium pentetate toxicity varied with the dose regimen. Lethality was increased in rats given calcium trisodium pentetate in 5 intraperitoneal injections compared to those given the same dose in 1 or 2 injections. For example, animals given 5 intraperitoneal injections 2 hours apart for 5 days had increased lethality compared to 2 injections 8 hours apart for 5 days. Animals developed diarrhoea on the second day with congestion of mucous membranes and conjunctiva and apathy. Death occurred from day 4 onwards. Post-mortem examination showed congested intestines, haemorrhages of the intestines, lungs and sometimes the liver, with hyperaemic kidneys. All rats receiving 5 injections of zinc trisodium pentetate daily for 5 days survived 30 days without clinical signs (Planas-Bohne & Ebel, 1975).

In dogs subcutaneous calcium trisodium pentetate (22.5 to 24.6 µmol/kg daily for 8 days) caused mild anorexia, diarrhoea and occasional vomiting with rapid recovery after cessation of treatment. In contrast, 5.8 µmol/kg every 5 hours was fatal in all three dogs within 3 to 9 days. These animals developed inappetence, diarrhoea, vomiting, melaena, abdominal tenderness, polydipsia, proteinuria and haematuria. There was no liver damage. The most prominent gross findings on post-mortem examination were haemorrhages in the gastrointestinal tract, particularly the duodenum and proximal jejunum, and blood in the lumen. Subcutaneous zinc trisodium pentetate 9.2 to 9.7 µmol/kg every 5 hours for 19 days caused only mild diarrhoea with subclinical melaena and haematuria (Taylor et al., 1974).

8.3.3 Chronic toxicity

The relative safety of zinc trisodium pentetate is also confirmed by the investigation of Jones et al. (1989). Long-term dosing with zinc trisodium pentetate (33 µmol/kg daily or 415 to 3946 days) did not result in significant depletion of chromium, copper, manganese or molybdenum in liver or bone in beagles.

8.3.4 Reproductive toxicology and teratogenicity

In a toxicity study pregnant mice were given subcutaneous calcium trisodium pentetate (0.36 or 2.9 mmol/kg) daily until the offspring were 13 days old. There were no viable offspring from mice receiving 2.9 mmol/kg calcium trisodium pentetate. There was only one fetus and this was dead at birth but appeared grossly normal. With the lower dose fecundity, fetal development and growth rates were normal but this may have been due to the presence of 58 µg of zinc/g of diet (Fisher et al., 1975).

Increased fetal lethality and congenital malformations were observed in mice given calcium trisodium pentetate. Mated female mice received five daily subcutaneous injections of 720 to 2,880 µmol/kg of calcium trisodium pentetate on days 2 to 6, 7 to 11 or 12 to 16 of gestation and were killed on day 18. Fetal lethality was greater in the early and mid-gestation periods and the frequency of gross malformations increased with increasing dose (Fisher et al., 1976).

These effects are caused by zinc deficiency and can be compared to the reproductive toxicity observed with sodium edetate. Sodium edetate impairs reproduction and results in malformations but simultaneous supplement with zinc prevents these effects (Swenerton & Hurley, 1971).

Zinc trisodium pentetate is safer than calcium trisodium pentetate in pregnancy. This salt did not cause any malformations even at high doses in rats (Bömer, 1971) and mice (Fisher et al., 1975; Brummett & Mays, 1977; Calder et al., 1979).
8.3.5 Genotoxicity

Calcium trisodium pentetate has been shown to inhibit DNA synthesis in intestinal crypt cells (Weber et al., 1970; Bohne, 1972), kidney and intestinal mucosa (Taylor & Jones, 1972), regenerating liver (Gabard, 1974), and erythro- and myelopoetic cells (Ebel, 1975) of treated rats and in vitro cultures of Chinese hamster cells (Lücke-Huhle, 1976). This inhibition is due to interference with the zinc and manganese required for DNA synthesis. Supplementation with zinc or manganese partially reversed the inhibition and co-administration of both elements resulted in normal synthesis in liver cells (Gabard, 1974). Zinc trisodium pentetate does not affect DNA synthesis in kidney, intestinal mucosa (Taylor & Jones, 1972) or regenerating liver (Gabard, 1974) of treated rats or in vitro cultures of Chinese hamster cells (Lücke-Huhle, 1976).

In cultured Chinese hamster cells calcium trisodium pentetate did not affect the chromosome aberration rate up to a concentration of $10^{-2}$ mol/L (Miltenburger & Bauer, 1972).

In cultured human lymphocytes calcium trisodium pentetate inhibited metaphase at the highest concentration (13.51 µg/mL of the culture medium). Both the other two concentrations tested (0.135 and 1.351 µg/mL) increased the number of sister chromatid exchanges but the increase was only significant for the higher concentration, which corresponded approximately to the blood concentration after a single intravenous administration. Similarly, the highest concentration (27 µg/mL of the culture medium) of puchel also inhibited metaphase. A small increase in sister chromatid exchanges was observed at the two other concentrations of puchel tested (0.27 and 2.70 µg/mL) (Prosser, 1978).

In cultured human lymphocytes from 3 females, in vitro exposure to calcium trisodium pentetate (in concentrations as low as 10 µg/mL) resulted in an 80% reduction in mitotic indices; there was no reduction seen in lymphocyte cultures from 2 males. There was complete suppression of mitoses in all samples with exposure to calcium trisodium pentetate 40 µg/mL. With zinc trisodium pentetate there was minor suppression in mitotic indices in lymphocytes from women and none in men at exposure to 40 or 80 µg/mL. Neither calcium nor zinc trisodium pentetate induced two-break aberrations in human lymphocytes. This study concluded that samples for cytogenic studies in patients treated with pentetic acid should be taken only when the chelator has cleared from the blood, so just prior to dosing (Littlefield et al., 1984).

8.4 Puchel

Lipophilic compounds have a greater ability to cross membranes and enter cells. For this reason a more lipophilic derivative of pentetic acid, named puchel, was developed and expected to be more effective in removing radionuclides from tissues and organs. It was usually given as its pentasodium salt.

Studies in hamsters revealed that inhaled puchel was more effective than calcium trisodium pentetate at increasing clearance of plutonium-238 given by intrapulmonary injection. Intraperitoneal puchel was also more effective in reducing liver retention after intravenous injection of plutonium-238, although much higher doses were required to remove plutonium from the liver than were used in the inhalation experiment (Stradling et al., 1981). When puchel was compared to calcium trisodium pentetate in removing thorium-234 in rats the combination of both chelators was as effective as calcium trisodium pentetate alone. In addition, when puchel was given alone 4 days after thorium injection or daily for 5 days starting 1.5 minutes after thorium it significantly increased the thorium content of the liver and spleen (Peter & Volf, 1981).

Puchel did not prove to be significantly more effective than zinc trisodium pentetate in removing
inhaled americium-241 oxide or nitrite in hamsters (Stradling et al., 1984). Puchel was as effective as calcium trisodium pentetate and the effect was not enhanced when both chelators were given together for removal of thorium-234, plutonium-238 or 239 or americium-241 from the liver and bone of hamsters and rats (Volf & Peter, 1984).

Puchel was marginally more effective than zinc trisodium pentetate in removing plutonium-238 from the lungs in hamsters but produced adverse effects including inflammatory lung changes and pneumonitis when given as an aerosol, and liver damage when given intraperitoneally (Stather et al., 1982).

In vitro studies using rat liver cytosol demonstrated that puchel does not remove cadmium from the metallothionein complex (Planas-Bohne & Lehman, 1983; Rau et al., 1987). Although in vitro studies have demonstrated that puchel can lower the body burden of cadmium by reducing the liver (Rau et al., 1987) and kidney concentrations (Planas-Bohne & Lehman, 1983) its toxicity is too great for it to be considered a chelator for use in humans (Rau et al., 1987). The LD₅₀ for puchel is far lower than that of pentetic acid salts (Ellender et al., 1984).

In summary, puchel is more toxic than pentetic acid salts and for removal of radionuclides puchel has no advantage over the calcium and zinc salts of pentetic acid.

9 Volunteer studies

9.1 Pharmacokinetics

9.1.1 Intravenous injection

Calcium trisodium pentetate is rapidly eliminated. By two hours after intravenous injection of 10 to 15 mg 30 to 40% was cleared, 50 to70% by 4 hours and another 15 to 20% in the following 4 hours. By 24 hours 90 to 100% is eliminated (Stevens et al., 1962; Stather et al., 1983).

Elimination of intravenously administered pentetic acid salts is entirely via the urine; none is detected in the faeces. Plasma levels of radioactivity after intravenous injection of radiolabelled calcium trisodium pentetate averaged 10% of the dose at 1 hour and decreased rapidly thereafter. No radioactivity was detected in plasma at 2 hours (Stevens et al., 1962).

After intravenous injection plasma retention of calcium trisodium pentetate could be expressed as three components with half-lives of 1.4 minutes (60%), 14.3 minutes (20%) and 95 minutes (20%) (Stather et al., 1983).

9.1.2 Oral

Pentetic acid is very poorly absorbed from the gastrointestinal tract. After ingestion of radiolabelled pentetic acid (3 or 50 mg) 95 to 100% was recovered in the faeces within 2 to 5 days and the rest was excreted in urine. Radioactivity was not detected in the blood at any time (Stevens et al., 1962).

9.1.3 Inhalation

When radiolabelled calcium trisodium pentetate was nebulised about 60% of the radioactivity was retained by the equipment. Of 170 mg of calcium trisodium pentetate inhaled about 5% was exhaled, 2% was retained in the mouth, 24% excreted in the faeces and 69% in the urine (Stather et al., 1983).
Calcium trisodium pentetate clearance from the lungs is relatively slow, with a half-life of 75 minutes. The length of time that a therapeutically useful amount of calcium trisodium pentetate is retained in the body after inhalation is approximately double that obtained after intravenous injection (Stather et al., 1983).

9.2 Effect of pentetic acid on the pharmacokinetics of metals

9.2.1 Iron

An experimental study carried out in 17 haematologically normal volunteers investigated the effect of several substances on the gastrointestinal absorption of iron. The subjects were given 2 µCi of iron-59 with 5 mg of iron (as ferrous sulphate), 50 mg ascorbic acid and the test compound orally. The test compounds were given in doses of 0:1, 1:1, 10:1 and 50:1 as molar ratios of compound to iron. Pentetic acid had no significant effect on iron absorption when given in a ratio of 1:1, but at ratios of 10:1 or 50:1 iron absorption was reduced (Davis & Deller, 1967).

9.2.2 Lanthanum

A chelate of lanthanum-140 (1.5 mg) and pentetic acid (5 mg) was administered intravenously to four volunteers. By 24 hours the average urinary excretion of lanthanum (as a percentage of the injected dose) was 64.4%, with a range of 60.4 to 71.8% (Kroll et al., 1957).

The elimination of lanthanum-140 was studied in two volunteers (aged 52 and 73 years). They were given intravenous lanthanum-140 chloride followed 24 hours later by calcium trisodium pentetate. This was given as an intravenous infusion (586 mg or 2340 mg) daily for 2 or 4 days. The administration of calcium trisodium pentetate increased lanthanum-190 urinary excretion by 9 to 10 fold (Rosoff et al., 1961).

9.2.3 Promethium

Palmer et al. (1970) investigated the impact of intravenous calcium trisodium pentetate on the toxicokinetics of promethium-143 in 6 volunteers. The chelator removed 90%, 20% and 5% of the promethium-143 from the body, mostly in urine, when administered 30 minutes, 24 hours and 80 days, respectively, after intravenous promethium-143. Faecal excretion of promethium was also enhanced by calcium trisodium pentetate but remained fairly constant up to 24 hours after dosing with promethium-143. No faecal samples were available for the volunteers who received calcium trisodium pentetate 80 days after promethium-143 administration.

9.2.4 Scandium

Calcium trisodium pentetate was more effective than calcium edetate in removing scandium-46 from the body. Chelators were started 24 hours after injection of scandium-46 and given on three consecutive days. The total urinary excretion of scandium-46 over the three days of chelation therapy varied from 27 to 42% with calcium trisodium pentetate and 8 to 16% for calcium edetate. When the chelator was given over 3 days starting on the sixth day after scandium-46 administration the total urinary excretion over the three days of chelation therapy was 8 to 15% with calcium trisodium pentetate and 5.5 to 7.4% for calcium edetate. Enhanced excretion also occurred for several days after discontinuation of calcium trisodium pentetate administration (Spencer & Rosoff, 1965).

9.2.5 Strontium
In an adult female a mixture of 10 g calcium alginate, 3 g ferri(II)hexacyanoferrate, 130 mg potassium iodide and 5 g zinc trisodium pentetate given immediately after orally administered strontium-85 reduced the strontium absorption by 18-fold (Kostial et al., 1987b).

9.2.6 Yttrium

After a chelate of yttrium-90 (1 mg) and pentetic acid (5 mg) was administered intravenously to six volunteers almost all of the yttrium was excreted in urine within 8 hours of injection (Kroll et al., 1957). The elimination of ytterium-90 was studied in seven volunteers (aged 51 to 75 years). They were given intravenous injections of a tracer dose of ytterium-90 as a weak chelate (ytterbium-90 nitrilotriacetate) daily for 5 days, followed 24 hours after the third dose by calcium trisodium pentetate. The volunteers were given 117, 586 or 2340 mg of calcium trisodium pentetate by infusion daily for 4 days. Chelation therapy markedly increased urinary excretion of ytterium-90. The average cumulative urinary excretion of ytterbium-90 in controls was 3.8% of the administered dose. This was increased 10 fold by treatment with calcium trisodium pentetate. An increase in the dose of chelator did not increase excretion of ytterbium and four consecutive doses of 586 mg were as effective as four infusions of 2340 mg (Rosoff et al., 1961).

9.2.7 Zinc

In a study of the fate of zinc chelates in humans, twelve volunteers aged 32 to 70 years were given a tracer dose of zinc-65 trisodium pentetate by intravenous injection. The zinc-65 plasma concentration decreased rapidly within the first hour. After 4 hours it was approximately half of the 1 hour value (0.6% of the dose/L) and was very low at 8 hours (0.3%). The uptake of zinc-65 into red blood cells increased slowly over 8 hours. At 1 hour the zinc-65 concentration in red blood cells was one third that of plasma and at 8 hours was 3 times higher than the plasma concentration. This suggests that zinc-65 trisodium pentetate can enter cells or may be adsorbed on to the cell surface (Rosoff et al., 1971). The effect of calcium trisodium pentetate on zinc excretion was studied in five volunteers aged 56 to 73 years. A single tracer dose of zinc-65 was given intravenously followed by calcium trisodium pentetate (2 g by intravenous infusion over 2 hours on 3 successive days). The chelating agent was given 7 to 114 days after administration of zinc-65. Calcium trisodium pentetate was effective in removing zinc-65. Prior to dosing the urinary excretion of zinc was low, usually less than 1%. When calcium trisodium pentetate was given on day 7 the urinary excretion of zinc-65 increased from 0.3% to 8.9%. On the following day the urinary excretion was still elevated (twice as high as on the day before chelation) but not as high as the previous day. Calcium trisodium pentetate also increased zinc excretion when given 114 days after administration of zinc-65 (Spencer & Rosoff, 1966).

10 Clinical studies

10.1 Studies on the removal of metals, metalloids or radionuclides

There are no controlled clinical studies on the use of pentetic acid in human poisoning involving metals, metalloids or radionuclides.

10.2 Other clinical studies

A 10% cream of calcium trisodium pentetate has been shown to reduce the number of positive patch
tests in a randomised, double-blind study of 54 patients with contact dermatitis to metals. Each of the test metals was applied to two areas of skin that were untreated or pre-treated with calcium trisodium pentetate and vehicle. Four control areas of skin were also treated with calcium trisodium pentetate and vehicle or vehicle alone. The test substance was applied 10 minutes after application of the calcium trisodium pentetate cream. Even in patients with positive patch tests the severity of the reaction was reduced. This cream reduced allergic skin reactions to nickel, cobalt and copper but not to chromium and palladium (Wöhrl et al., 2001).

11 Case reports

11.1 Americium

Pentetic acid is useful in the treatment of americium exposure and has been used in several cases, although it is relatively ineffective in removing americium from bone.

1976 Hanford americium incident: A 64-year-old male was injured in an explosion involving nitric acid, resin beads, metal, glass, plastic and other debris all contaminated with americium-241, resulting in deposition in excess of 6 mCi mainly on the face and by inhalation. The victim suffered acid burns and trauma from the explosion and had contaminated foreign body material embedded in the face, ears and back (Breitenstein, 1983). An estimated 5-6 mCi was removed on the first day following on-site decontamination and then intensive decontamination. For 2 months the victim received daily decontamination baths where calcium trisodium pentetate was applied and washed off. The skin was also scrubbed, and embedded material removed as it reached the skin surface (Jech et al., 1983). Repeated intravenous dosing with pentetic acid salts over 3 years appeared to prevent systemic retention of americium cleared from wound sites. Americium deposited in bone and liver prior to pentetic acid treatment (started 2.5 hours post-exposure) was cleared quickly from the liver but relatively slowly from bone (Thompson, 1983). Repeated samples were taken from this patient and in examining 24 essential elements, zinc was the only trace metal excreted more rapidly than normal. For each 1 g injection of calcium trisodium pentetate there was an 18 mg urinary loss of zinc (Kalkwarf et al., 1983). Radiation doses to bone, lung and liver were below toxic concentrations and the only manifestation of radiation effects were observed in the blood (Thompson, 1983). The peripheral lymphocyte count declined from 1860 cells/mm$^3$ on the day of the accident to 530 mm$^3$ one week later. It remained depressed for several months (Breitenstein & Palmer, 1989). In lymphocyte cultures from samples taken between 30 and 1857 days after the accident a high proportion of metaphases were observed with two-break chromosome lesions and in all cultures the distribution of centric ring and dicentric (or multicentric) chromosomes were significantly overdispersed relative to expected dispersion (Littlefield et al., 1981). This patient died of complications of chronic coronary artery disease 11 years after the accident. The total quantity of americium-241 excreted from the body was 41 MBq (1.1 mCi); of this almost half was excreted within the first 3 days of exposure. He was given a total of 583 g of pentetic acid salts between 1976 and 1980 with no adverse effects reported and there was no deposition of americium-241 in the bone and liver. Without this treatment it was estimated that the deposition of 18.5 MBq (500 µCi) of americium-241 in the bone and liver would have produced life-threatening doses of 0.07 Gy/day, 25 Gy/year to the bone and 1 Gy (100 rad)/day to the liver. Pentetic acid also reduced the clearance half-time of the liver activity to approximately 20 days compared to an expected 20 years for unchelated americium-241. All the americium in the liver was cleared by day 400 although there was re-deposition after cessation of pentetic acid treatment. Pentetic acid did not remove americium-241 from bone except for a small possible effect during the first week (Breitenstein & Palmer, 1989).

A 35-year-old, 70 kg, male was exposed to americium-241 by inhalation and received a body burden of
1.8 µCi. The accident, which was thought to have occurred in 1965 or early 1966 was noticed when alpha-activity was discovered in urine specimens in 1967 (Fasiska et al., 1971). He was given intravenous calcium trisodium pentetate (1 g/week) from September 1967 and continued with only a few interruptions through 1974. During chelation therapy the excretion rate of americium increased by 10 times compared to periods without chelation. There were no changes to liver or kidney function and no adverse effects on haematology or cytogenetics (Rosen et al., 1980). Zinc analysis was performed on urine samples from this patient during the last 3 months (September to November 1970) of a 5 month period of no chelation therapy and during a period of treatment (December 1970 to April 1971). The mean urinary excretion of zinc during the rest period was 0.65 ± 0.13 mg/day (range 0.2-0.9 mg/day) and during the treatment period it was 3.15 ± 0.70 mg/day. The concentrations were highest in the first 24 hours after the calcium trisodium pentetate infusion (Slobodien et al., 1973).

In an industrial laboratory several workers were exposed to americium-241 by inhalation. The accident was not recognised for several months and treatment with zinc or calcium trisodium pentetate was started late. Four workers received chelation therapy of 1 g of pentetic acid salt in 250 ml of saline intravenously for 4 to 11 treatments. There were no adverse effects reported. After the first dose of pentetic acid there was increased excretion of americium by factors of 65 to 140 (urine) and 30 to 50 (faeces). Pentetic acid removed almost all americium-241 deposited in the liver. It was calculated that dose reductions for the liver, bone surfaces, red bone marrow and lungs were 90, 28, 28 and 26%, respectively, equivalent to an effective dose reduction of 40% (Roedler et al., 1989).

Following a perforating wound in the forefinger involving americium-241 most of the activity of 244 nCi measured in the wound was removed by 3 surgical excisions. The increased radioactivity in urine after pentetic acid injection (0.5 g intravenously on days 1 and 12 after the accident) indicated that small amounts of americium were already absorbed into the body. It was calculated that 8 pCi was excreted in the urine on day 1 (Ohlenschläger, 1971).

A 57-year-old male and his 10-year-old son were accidentally and unknowingly exposed to americium-241. The father, a laboratory researcher, had brought home a piece of material, later found to be composed primarily of americium-241. This had occurred in late 1963 and was discovered in 1970. The house was heavily contaminated and the family had to evacuate it until it had been decontaminated. Other family members, the wife, an 18 year old daughter and a 20 year old son had elevated americium body burdens (6.5 to 13 nCi) but the father and son were the most heavily contaminated (87 and 93 nCi, respectively) (Whalen & Davies, 1972). The father and son received periods of calcium trisodium pentetate treatment in 1970, 1973 and 1975. Prior to the treatment in 1975 the total body count of americium-241 was 69.6 ± 2.7 nCi in the father and 20.1 ± 1.6 nCi in the son. Most was present in the skeleton (75 to 85%) with smaller quantities in the liver and possibly the lungs. After an intravenous infusion of calcium trisodium pentetate (23.3 µmol/kg and 41.8 µmol/kg, respectively) once weekly for 4 weeks the body burden decreased to 67.2 ± 2.8 nCi in the father and 12.7 ± 2.7 nCi in the son. The chelation therapy was more effective in the son (then aged 15 years) with a decreased in the body burden of 37% compared to the father (62 years) with a decrease of only 2 to 4%. After each treatment in the son the urinary excretion of zinc increased by 10 to 60-fold (Cohen et al., 1976).

### 11.1.1 Americium and curium

A worker accidentally inhaled over 1200 nCi of mixed oxides of curium-244 (75%) and americium-241 (25%). Nasal smears removed 212 nCi from the right nostril and 185 nCi from the left. The nasal cavities were then irrigated and the skin decontaminated. Less than 3 hours after the accident the lungs contained 456 nCi. At 2.5 hours after the incident he was given 4 ml of a 25% trisodium pentetate solution by nebuliser. Over the first 7 days 1172 nCi was excreted in the faeces and all but 37 nCi was eliminated from the chest. Pentetic acid was not given again until day 50 by which time 99.8% of the

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soluble curium and 62.3% of the soluble americium had been excreted. The elimination of
radioactivity while receiving pentetic acid (from days 50 to 118, route and dose not stated) was 1.85
nCi (61% curium, 39% americium). It was calculated that with pentetic acid therapy only 0.31 nCi of
americium and very little curium would have been excreted. The ratio of americium to curium in blood
and faecal samples was 1:3, which is the same as the inhaled mixture (Sanders, 1974).

11.1.2 Americium and plutonium

Americium is a daughter element of plutonium and exposures often involve both elements.

A 45-year-old male suffered a puncture wound on the left thumb while cleaning a storage container that
was contaminated with americium and plutonium. He had been wearing protective clothing and was
unaware of the wound until he left the work area. A radiation survey of the wound confirmed
contamination. He underwent surface decontamination with the area repeatedly washed and monitored.
A blood sample at this time confirmed that contamination has entered the systemic circulation. The
decision was made to begin chelation therapy about 30 minutes after discovery of the wound and 20
minutes later ‘chelation ointment’ (no details given) was applied to the wound; several applications
were made and the wound bandaged. He was also given 1 g of calcium trisodium pentetate via
inhalation. Seven days later specialist advice was sought and a 5 day course of zinc trisodium
pentetate was started. The following day the thumbnail was removed, the surrounding tissue excised
and the wound closed with sutures. Measurement of the excised tissue demonstrated that about half the
activity remained in the wound. The retention of americium at the wound site showed a two-
exponential function with half-lives of 10 and 4600 days. Plutonium was measured in the urine for 58
days after the accident. Both the initial inhalation of chelating agent and the 5 days of therapy starting
on day 7 had increased the urinary concentration of plutonium. Modelling estimates of the deposition
at the wound site were 400 Bq of plutonium-238, 2240 Bq of plutonium-239/240 and 1060 Bq of
americium-241. It was estimated that about 70% of the initial wound activity was removed by surgical
procedures and less than 1% by chelation therapy (Bailey et al., 2003).

After a plutonium fire in a fabrication plant approximately 400 workers were evaluated and 25 were
found to exceed the maximum permissible lung burden of plutonium (0.016 µCi). Eight of these
individuals were treated with intravenous calcium trisodium pentetate; 3 workers were given five daily
1 g injections and 5 workers were treated for 4 days. Compared to untreated subjects those given
calcium trisodium pentetate had a peak in urinary excretion of plutonium and americium which rapidly
decayed and then a rise to concentrations similar to those on day 2 followed by a steady decline.
Untreated subjects had no peak in excretion. Calcium trisodium pentetate was stopped after 4 or 5 days
because the increases in excretion were small and short-lived (Hammond et al., 1968).

11.2 Californium

Two workers accidentally inhaled californium-252 in a laboratory and the exposure was detected on
leaving the work area when the protective clothing was found to be contaminated. Subject 1 was
contaminated on the arm and nasal swabs were positive. Skin decontamination and nasal lavage was
undertaken and then sodium bicarbonate and calcium lactate were given orally to reduce gastric acidity.
No skin contamination was detected in Subject 2. Although only Subject 1 was contaminated and had
confirmed inhalation of californium both men were treated. They were each given a laxative and 1 g of
calcium trisodium pentetate by aerosol. They were given two more doses of calcium trisodium
pentetate by inhalation on the 4th and 18th day. Subject 1 had an initial body burden of 20 ± 9 nCi and
the maximum permissible body burden is 4 nCi. The following day the body burden was 9 ± 8 nCi
and three days later it was less than 5 ± 5 nCi. There was rapid renal clearance of the californium on
the first day; the effect of the calcium trisodium pentetate was unclear but treatment on day 1 may have
increased excretion by several fold. Most inhaled californium is excreted in the faeces and Subject 1 excreted 13 nCi in the first 3 days compared to only 0.2 nCi in Subject 2 (Poda & Hall, 1975).

### 11.3 Cerium

Two workers were exposed to air-borne cerium-144/praseodymium-144. Clothing was contaminated and nasal swabs confirmed exposure. Both men showered and were referred to the in vivo counting facility. Subject 1 had a burden of $\leq 0.25 \, \mu$Ci of cerium-144 with 0.04 $\mu$Ci in the lung. This was estimated to be less than 1% of the maximum permissible body burden. No further action was taken. Subject 2 had a burden of 12 $\mu$Ci of cerium-144 with 2.1 $\mu$Ci in the lung. It was estimated that he had received as high as 10% of the maximum permissible body burden. He was started on intravenous calcium trisodium pentetate and received 15 doses of 1 g over 116 days. Calcium trisodium pentetate enhanced excretion of cerium and urine activity was undetectable after the last dose on day 116 (Glenn et al., 1979).

### 11.4 Curium

A worker inhaled airborne curium-244 during removal of dry, solid waste from a decontamination chamber. Filter paper smeared inside his nostrils removed 16.1 nCi from the left and 10.9 nCi from the right. The nasal cavities were irrigated and the skin washed. At 2.5 hours after the incident he was given 4 ml of a 25% trisodium pentetate by nebuliser. He was also given a laxative. Approximately 4.5 hours after exposure a reading of 14 nCi was taken from the worker’s chest, this decreased rapidly to 5 nCi within 4 days. Calculations showed that the pentetic acid did not significantly increase the excretion of curium (Sanders, 1974).

See also case of curium-244 and americium-241 under americium (section 11.1.1).

### 11.5 Iron

Although pentetic acid has been used in the past as a chelator for both acute iron overdose (Gokulanathan et al., 1963; Barr & Fraser, 1968) and iron overload (Fahey et al., 1961; Bannerman et al., 1962; Smith, 1962; Müller-Eberhard et al., 1963; Smith, 1965; McDonald, 1966; Constantoulakis et al., 1974; Strohmeyer, 1974) it has now been replaced by deferoxamine. It can be used in patients who have deferoxamine toxicity (Wonke et al., 1989).

In iron overload zinc trisodium pentetate cannot be used as it is ineffective as an iron chelator (Pippard et al., 1986). Therefore, pentetic acid must be given as the calcium salt, however, this has the disadvantage of interfering with trace metal concentrations, particularly zinc, and zinc supplements must be given. Zinc deficiency was reported in a child with thalassaemia who was allergic to deferoxamine and was treated with subcutaneous pentetic acid. Low blood zinc concentrations were managed successfully with zinc supplementation (Ridley, 1982).

### 11.6 Lead

Although pentetic acid is not the first line antidote for lead toxicity it has been used in the past. In 11 workers with lead exposure intramuscular calcium trisodium pentetate (0.5 or 1 g) rapidly increased urinary excretion of lead, particularly within the first 12 hours after dosing. The drug was well tolerated with local discomfort at the injection site in one patient and microhaematuria in another (Brugsch et al., 1965).

### 11.7 Manganese
A 66-year-old male accidentally drank 125 ml of an 8% potassium permanganate (10 g) solution over 4 weeks following a dispensing error (he should have been given potassium iodate). He was treated with intravenous calcium trisodium pentetate and developed zinc deficiency 2 weeks later, which resolved with supplementation. He was given 6 courses of treatment over 9 months and although calcium trisodium pentetate decreased the serum concentration and increased urinary excretion of manganese, it did not prevent the development of progressive Parkinson’s disease which started 9 months after exposure (Holzgraefe et al., 1986).

11.8 Plutonium

A worker accidentally spilt a solution of plutonium-239 nitrate on his skin. He immediately washed the area but did not seek medical attention until the following day. By this time the area was burnt, swollen, blistered and painful. The area was positive for alpha activity and 1 g of pentetic acid was given intravenously. A 340 ml sample of urine was heavily contaminated with plutonium (120 Bq).

The wound was irrigated with pentetic acid solution and bandaged. The victim was then started on a course of pentetic acid: 0.5 g twice daily on days 2 to 4, 0.5 g once daily for days 6 to 20, 0.25 g once daily for days 21 to 33 with no treatment on days 5, 14 and 24. The contaminated skin was cleaned and dressed regularly. The necrotic skin was removed on days 6 and 7 and gave readings of 66.6 and 37 kBq, respectively. The epithelium was renewed by the end of the 4th week. The radioactivity of the wound decreased from days 5 to 7. The bandages used on the burn also had high plutonium contamination with 39.7 kBq on day 1 and 42.6 on day 2. The urinary excretion of plutonium rose by 6 times after the first dose of pentetic acid. The calculated exposure was 23 kBq and 22 kBq was eliminated in excreta, therefore pentetic acid removed 95.6% of incorporated plutonium. The effectiveness of late pentetic acid was probably because the maximum penetration of plutonium only occurred on the third day by which time pentetic acid was available in the circulation (Khokhryakov et al., 2003).

Schofield & Lynn (1973) examined the effectiveness of pentetic acid in six cases of plutonium contamination. There were four inhalation cases. In 3 subjects the plutonium was thought to have been plutonium oxide or plutonium oxide/uranium oxide mixture. In subject 4 the source was an aerosol of plutonium nitrate. Subjects 1 to 3 were given 0.25 g of IV pentetic acid on day 0 and subject 4 was given 1 g on days 4 and 29 and 0.25 g on day 50. Pentetic acid was ineffective in subjects 1, 2 and 3. In subject 4 pentetic acid increased excretion by 10 to 15%. Two other subjects had wound contamination; in one case (subject 5) a sliver of plutonium metal penetrated his left index finger and the other subject received a deep puncture wound to the end of one of his fingers (subject 6). In both cases the wounds were excised and pentetic acid administered (1 g on days 0 and 1 and then 0.25 g on days 4 to 14 in subject 5; 0.25 g on day 0 and then 0.10 g on days 1 to 3 in subject 6). In subject 5 pentetic acid removed 5190 pCi of plutonium during the first 40 days and 29% of incorporated plutonium was excreted. Pentetic acid failed to significantly enhance plutonium excretion in subject 6.

A 41-year-old male worker was contaminated with an acidic aerosol mist of plutonium and was alerted to the release by a monitor in an adjacent room. From 12 hours he was treated with intravenous calcium edetate (1 g/week on alternate weeks) and this continued intermittently for 6 months. Calcium edetate increased the plutonium concentration in the urine by 8-fold and this was maintained for 6 months. There was no effect on faecal excretion. Oral calcium edetate had no effect on urinary plutonium excretion. Intravenous calcium trisodium pentetate was given intermittently between 865 and 1642 days after the incident and this increased urinary excretion of plutonium on the days of injection by 50-fold. Although the effect on faecal excretion was variable there was a trend towards the higher end of the range. The victim died about 38 years after the exposure aged 79 from extensive carcinomatosis secondary to adenocarcinoma of the prostate gland. He donated his body to the United
States Transuranium and Uranium Registries (USTUR) of Washington State University, USA, for post-mortem analysis. The estimated exposure dose was calculated 6 years after the accident as 0.42 µCi (15.5 kBq), approximately ten times the maximum permissible body burden. At the time of autopsy approximately 1% of the total plutonium-239 and 240 body burden remained in the lungs. Modelling using the data obtained from the tissues showed that chelation therapy substantially reduced the burden of plutonium in all organs except the lungs. The calculated reduction in plutonium concentration in organs at the time of death was approximately 40% in the liver, 60% for all other soft tissues (muscle, skin, glands, etc), 50% for the kidneys and 50% for the skeleton. Modelling showed that treatment with calcium trisodium pentetate was as effective as calcium edetate even though it was delayed by more than two years (James et al., 2007).

An adult male inhaled and received an approximate body deposit of 0.4 µCi of plutonium-239. Intravenous calcium trisodium pentetate (2 g in week 1, 1.6 g in weeks 2, and 11 to 12, 2 g in weeks 13 to 14, and 26, 27, 33, 46 and 50) initially increased the urinary excretion of plutonium by a factor of 55 but by week 50 it was only 19% of its original effectiveness. The calcium trisodium pentetate was stopped for 43 weeks from weeks 51 to 92 and then 3 g was given in week 93. This increased urinary excretion of plutonium to approximately the initial value (Norwood, 1962).

A laboratory technician was involved in an accident with acidic plutonium (III) chloride, plutonium (IV) chloride and plutonium nitrate. The solution contained 70% plutonium-239, 14% plutonium-240 and 16% americium-241. He was contaminated over almost his whole body with 10,000 to 50,000 dpm/67 cm²; several areas on the face were greater than 500,000 dpm/67 cm². These were small second-degree burns containing almost 5 µg of plutonium. His skin, except for the burns, was decontaminated. At 2 weeks the scabs from the burns were removed and found to be heavily contaminated with plutonium; the skin underneath was virtually free of plutonium. The first dose of intravenous pentetic acid (1 g) was given within 1 hour of exposure and another dose at 5 hours. Further doses were given on days 2 to 5, 13, 15 and 17. Pentetic acid was successful in promoting the urinary excretion of plutonium (2,586 dpm/24 hours on day 0 and 105 dpm/24 hours on day 4) and by 55 days the urine concentration was almost the same as that observed before the accident (Lagerquist et al., 1965).

A worker was contaminated through a puncture wound from a sliver of metal contaminated with 2.3 µg of plutonium (isotope not stated). The wound was determined to contain 1.8 µg of plutonium, but this may have been an underestimate depending on how deeply the plutonium had penetrated the wound. Gross excision was not undertaken as this would have lead to permanent damage to the thumb. After several attempts it was only on the fourth day that plutonium in the wound was localised and excised. The excised tissues contained 0.73 µg of plutonium, most located on the side of the finger where the sliver of metal entered the thumb. Intravenous pentetic acid (1 g) was started within 1 hour and repeated on days 1, 3, 4, 7, 9, 11, 14, 16 and 18. The overall effect of pentetic acid could not be determined, possibly because the transfer of plutonium from the wound to the blood was low (Lagerquist et al., 1965).

A worker was contaminated with acidic plutonium nitrate (isotope not stated) and developed a second degree burn on the shoulder. The burn was not decontaminated and healed without complications in about 3 weeks. In the burn area there was 0.3 ± 0.1 µCi of plutonium, mostly in the scab that formed over the wound. Intravenous pentetic acid (1 g) was started within 1 hour and continued daily for 27 days. The worker developed a rash over this time which resolved once pentetic acid treatment ceased. A total of 210,000 dpm was excreted in the first 60 days which represents 96.5% of the initial uptake of plutonium. Pentetic acid was primarily responsible for elimination of this quantity of plutonium (Lagerquist et al., 1967a).
An accident occurred when a bucket of burning plutonium chips (isotope not stated) was dropped into a container of carbon tetrachloride. The explosion ruptured the front of the glovebox and plutonium debris was spread over a wide area. The worker using the glovebox sustained a severe injury to his left hand, extensive contamination and probably inhalation exposure. The extent of contamination could not be determined initially because it was greater than could be measured with the available equipment. The victim was in mild shock on arrival at a medical facility and the left hand was wrapped in a plastic bag to prevent further contamination. He was washed thoroughly and the washoff from the decontamination contained approximately 1 mCi of plutonium. He was given intravenous pentetic acid (1 g) within 1 hour of exposure and another dose 4 hours later. Examination of the injured hand showed fractures of the thumb and second finger and contamination with approximately 30 µCi of plutonium. The wounds were sutured and pentetic acid treatment given twice daily for the next 2 days followed by dosing once daily for the 16 days. The skin was also decontaminated daily which resulted in background radioactivity readings by day 10 except in the left hand which was not completely decontaminated until a month after the injury. The amount of plutonium in the 24 hour urine sample just prior to pentetic acid therapy was 10 times that of the blood. Each pentetic acid treatment was followed by increased urinary excretion of plutonium. By the 12th day there was still a large quantity of plutonium embedded in the thumb and it was amputated with the second finger. Approximately 133 µCi of plutonium was present in the amputated thumb and 1 µCi in the second finger leaving 4 µCi in the hand. Amputation was followed by a decrease in the quantity of plutonium excreted. Pentetic acid continued over the next 18 months at various doses and by various routes (intravenous, oral, intramuscular). Three intravenous injections of 1 g/week were more effective in increasing excretion than weekly 1 g treatments. Intramuscular injection around the thumb stump had little effect in removing plutonium from the injury site. Oral pentetic acid (249 g) was given for 16 weeks. In the first week four 1 g doses were given resulting in a 4 fold increase in excretion. This was followed by 5 g treatments on four days a week and then 5 g three times a week for 11 weeks. Over the 16 weeks approximately $7.4 \times 10^2$ µCi was excreted. The victim had two more surgeries, at 11 and 18 months, to remove the stump of the thumb to leave approximately 0.6 µCi of plutonium. Treatment with pentetic acid resulted in elimination of approximately 8 µCi of plutonium via the urine (Lagerquist et al., 1967b).

A worker was contaminated with plutonium-239 after sustaining a puncture wound on the left hand just distal to the first interphalangeal joint. The wound was decontaminated 30 minutes later with washing and scrubbing of the area. A small wedge of tissue from around the wound was removed at approximately 2.5 hours to further reduce the contamination. The plutonium in the excised tissue was approximately 1 µCi and there was 91.3 nCi remaining in the wound. Tissue from a second surgical excision contained approximately 0.1 µCi (98.9 nCi) and about 6.4 nCi remained in the wound. The first dose of pentetic acid (1 g, route not stated) was given at 9 hours and repeated on days 3 to 6, followed by 3 g on day 50 and 1 g daily on days 51 to 54. A third course (2 g) was given on days 79, 81 and 83 and finally another 2 g/day for 5 days starting on day 99. In total 28 g was given. Chelation therapy increased urinary plutonium excretion and in the second and later courses excretion was increased by a factor of 70. The first course of pentetic acid increased the faecal plutonium excretion by a factor of 50 but was relatively ineffective thereafter (Swanberg & Henle, 1964).

See also section 11.1.2 for cases involving both plutonium and its daughter element americium.

### 11.9 Protactinium

A chemical laboratory was contaminated with protactinium-231 but the accident was not recognised until 2 weeks later. Traces of radioactivity were found in nose swabs of some workers and in two subjects alpha activity was detected in their urine. Both were treated with pentetic acid (1 g daily for 4 days by intravenous infusion). Pentetic acid increased urinary excretion of protactinium by a factor of
33 and 22 in these two workers. It was calculated that they had received no more than 10% of the maximum permissible body burden (Giubileo, 1978).

11.10 Uranium

A deliberate ingestion of 15 g of non-radioactive uranium acetate in an adult male (103 kg) resulted in rhabdomyolysis, liver dysfunction, myocarditis and acute renal failure. Plasma uranium concentrations were high (3.24 µmol/L), but treatment with both calcium edetate and calcium trisodium pentetate was ineffective in promoting uranium excretion in this patient with renal failure. The uranium plasma concentration after 5 days of calcium edetate was 3.29 µmol/L (Pavlakis et al., 1996).

12 Summary of evaluation

Pentetic acid salts have FDA approval for use in plutonium, curium and americium exposure by inhalation, dermal and wound exposure. They may also be effective for enhancing elimination of other transuranium elements such as berkelium or californium but data are limited. Pentetic acid salts are effective for enhancing elimination of cerium and zinc. Administration of pentetic acid salts (orally or parenterally) following ingestion of metals or radionuclides is not recommended as this is thought to increase gastrointestinal absorption.

Pentetic acid salts may be useful for enhancing removal of cobalt, einsteinium, lanthanum, nickel, promethium, scandium, strontium, ytterbium and yttrium but data are lacking. Cadmium chelation remains a problem and pentetic acid salts have shown limited benefit in animal studies, particularly in the more clinically relevant delayed administration studies.

Pentetic acid salts are not effective in removing antimony, beryllium, bismuth, gallium, lead, mercury, neptunium, niobium, platinium, polonium, thorium and uranium; they are not useful for radioactive iodine (Hameln Pharmaceuticals, 2004). The effectiveness of pentetic acid salts for radium or calcium has not been determined. Although pentetic acid salts have been shown to increase elimination of manganese in both animals studies and a human case report it did not prevent manganese-induced Parkinson’s disease in a human case (Holzgraefe et al., 1986).

Pentetic acid salts can mobilise iron and vanadium but more effective chelating agents are available.

Many animal studies have shown that the effectiveness of pentetic acid salts is similar to that of ethylenediaminetetraacetic acid salts, and pentetic acid salts have been used in cases of heavy metal poisoning that do not respond to this or other chelators. No controlled studies have, however, been performed and a favourable effect is not always demonstrated in case reports or in experimental studies.

Pentetic acid salts are generally well tolerated and repeated dosing may be needed for years after exposure to a radioactive element. There were no adverse effects reported in a worker exposed to americium given 583 g of pentetic acid salts over a 5 year period (Breitenstein & Palmer, 1989). In another case were no adverse effects reported after 322 g over 337 weeks with the longest period of uninterrupted treatment of 1g/week for 134 weeks (Rosen et al., 1980).

Calcium trisodium pentetate is more effective in early treatment but it also chelates trace elements. Consequently, calcium trisodium pentetate is usually used for the first few doses followed by zinc trisodium pentetate for long-term treatment. Monitoring of trace elements with supplementation, if necessary, is recommended in patients receiving long-term calcium trisodium pentetate therapy.
Pentetic acid salts are usually given parentally but can be given by inhalation following pulmonary contamination or used for dermal decontamination. Oral dosing is used less commonly as bioavailability is low.

12.1 Indications

Pentetic acid salts should be used in cases of inhalation, dermal or wound exposure to americium, californium, cerium, curium and plutonium. Administration of pentetic acid salts (orally or parenterally) following ingestion of metals or radionuclides is not recommended as this is thought to increase gastrointestinal absorption (see section 12.4).

Pentetic acid salts can also be considered for other transuranics and radioactive metals or metals where data are limited or unavailable or where other chelators are available or ineffective. This includes cobalt, einsteinium, iron, lanthanum, nickel, promethium, scandium, strontium, ytterbium, yttrium and zinc.

12.2 Advised routes and dose

The dosing regimen of pentetic acid salts should be individually tailored depending on the route of exposure and the severity of intoxication. Specialist advice should be sought for patients with radiation exposure.

Treatment may need to be continued for weeks, months or even years. Dosing is usually with the calcium salt for the first day or so and then with the less toxic zinc salt (Gerber & Thomas, 1992). In the medical case reports of 646 individuals who received calcium or zinc trisodium pentetate collated by the Radiation Emergency Assistance Center/Training Site (REAC/TS) 72% of individuals treated with calcium trisodium pentetate received only 1 or 2 doses and the rest 3 or more. Of those given zinc trisodium pentetate 50% received 1 or 2 doses and the rest 3 or more. One subject received 338 doses of calcium trisodium pentetate (1 g) over 6.5 years and another received 574 doses of zinc trisodium pentetate (1 g) over 3.5 years (FDA, 2004).

Calcium and zinc trisodium pentetate can be given in 5% dextrose, lactated Ringer’s or 0.9% saline (Hameln Pharmaceuticals, 2004).

12.2.1 Adults

12.2.1.1 Intravenous

30 µmol/kg (approximately 15 mg/kg) calcium trisodium pentetate (so 1 g for a 70 kg adult) by slow intravenous injection (in 5 ml over 3 to 4 minutes) or by intravenous infusion (in 100 to 250 ml of 0.9% saline, lactated Ringer’s or 5% dextrose over 30 minutes).

For a severe contamination the first dose given immediately after the accident may be doubled. Treatment should then continue with zinc trisodium pentetate. The dose should not exceed 1 g/day for prolonged treatment and the dose can be reduced during prolonged treatment (as the quantity of material to be chelated is reduced) (Gerber & Thomas, 1992; Hameln Pharmaceuticals, 2004).

12.2.1.2 Oral administration
1 g of zinc trisodium pentetate/day in micronised capsules can be considered for long-term therapy. A higher dose (up to 5 g/day) can be used in short-term therapy (Gerber & Thomas, 1992).

### 12.2.1.3 Nebuliser administration

Pentetic acid salts may also be given by nebuliser following accidental inhalation of radioactive material (Ménétrier et al., 2005; Jin, 2008).

A 30 minute inhalation of calcium trisodium pentetate made from 4 ml of a solution (1 g) or from micronised powder can be given and repeated over the following days (Gerber & Thomas, 1992).

### 12.2.1.4 Cutaneous administration

Healthy skin can be washed with a 2% slightly acidic (pH 4-5) solution of calcium trisodium pentetate. Wounds can be irrigated with a 20% concentrated, sterile solution of calcium trisodium pentetate and mucosal surfaces irrigated with a 2% solution (Gerber & Thomas, 1992).

### 12.2.1.5 Local infiltration

Calcium trisodium pentetate can be infiltrated into wounds (Ménétrier et al., 2005) but because intramuscular injection is painful a local anaesthetic, such as procaine, should be added to the solution (Gerber & Thomas, 1992).

### 12.2.2 Children

Based on the dose of 1 g in a 70 kg adult children should be given 14 mg/kg by intravenous injection of either salt to a maximum of 1 g.

In the past doses of 20-25 mg/kg (Muller-Eberhardt et al., 1963) and 40 mg/kg in 2 divided doses (Gokulanathan et al., 1963) of calcium trisodium pentetate by intramuscular injection have been used in the treatment of iron overload. Intramuscular injection is painful and not recommended.

The safety and efficacy of the pentetic acid salts by inhalation or oral dosing has not been evaluated in paediatric patients.

### 12.3 Supportive Therapy

Specialist advice should be sought for the management of radiation accidents. This may require a multidisciplinary approach with radiation protection and dosimetry professionals, and medical and nursing staff trained and experienced in managing victims of radiation exposure (Breitenstein, 2003).

Initially, burns and trauma injuries should take priority over radiation exposure in most cases. Contaminated clothing should be removed and decontamination of the skin undertaken. Washing with soap or detergents is the most common method of decontamination (Breitenstein, 2003). Care should be taken not to abrade the skin.

Thereafter it is essential to prevent further incorporation of any radioactive material including administration of laxatives to enhance gastrointestinal transit, antacids for radionuclides that become...
colloid or insoluble in the gastrointestinal tract (and therefore less absorbable), nasal and/or lung lavage
and decontamination of skin and wounds (Gerber & Thomas, 1992).

Surgical debridement of contaminated wounds may be considered. Wound probes are available that
detect radionuclide emissions (Breitenstein, 2003).

Once an estimate of dose of radioactivity incorporated can be calculated the need for chelation therapy
can be assessed (Breitenstein, 2003).

12.4 Controversial issues

12.4.1 Pentetic acid after ingestion of metals or radionuclides

Administration of pentetic acid salts, by any route, following ingestion of metals or radionuclides is
not recommended as this is thought to increase gastrointestinal absorption.

Various animal studies have demonstrated increased absorption after administration of pentetic acid
salts following ingestion of metals or radionuclides. For example, oral administration of zinc
trisodium pentetate increased retention of oral cerium-141; the cerium-141 concentration was
doubled in the whole body and gut, increased by factors of 5 in the carcass and liver, 10 in the
femur and 50 in the kidneys. However, the animals were killed at 24 hours and there was no
measurement of excretion rate (Kargačić & Kostial, 1985). Intravenous calcium trisodium
pentetate after oral plutonium in rats resulted in increased plutonium absorption but the absorbed
material was rapidly excreted and there was reduced deposition in the skeleton and liver (Sullivan
et al., 1983).

In contrast in rats given oral cerium-144 oral zinc trisodium pentetate was very effective in
reducing whole body burden and gut retention, even when given a day after cerium administration
(Kostial et al., 1987a). Oral treatment with zinc trisodium pentetate has also been shown to be
effective in reducing organ retention after oral cadmium exposure in rats (Kostial et al., 1987c) and
in mice oral pentetic acid was effective in promoting survival when given immediately after oral
cadmium (Basinger et al., 1988).

There is no information on the use of pentetic acid following oral exposure to radionuclides in humans.
In one case of metal ingestion where calcium trisodium pentetate was used an adult male drank
potassium permanganate solution over 4 weeks. Although intravenous calcium trisodium pentetate
decreased the serum concentration and increased urinary excretion of manganese, it did not prevent the
development of progressive Parkinson’s disease which started 9 months after exposure. The effect of
calcium trisodium pentetate on absorption of manganese cannot be determined in this case (Holzgraefe
et al., 1986).

Oral dosing after exposure via other routes such as inhalation or wound contamination has been
used occasionally. Although oral bioavailability is low this route has been shown to be effective in
some studies. Oral calcium and zinc trisodium were effective in reducing the americium-241
concentrations in the liver and femur after intravenous americium in rats (Taylor & Volf, 1980). Zinc
trisodium pentetate in drinking water was effective in reducing plutonium and americium retention in
the lungs and total body in rats after inhalation of plutonium-238 and americium-241 (Stradling et al.,
1993a; Gray et al., 1995).

12.4.2 Oral pentetic acid after inhalation or wound contamination by metals or radionuclides
There is very limited information on the effectiveness of oral pentetic acid salts in humans following radionuclide exposure. In many cases pentetic acid was also given parentally and it is not possible to determine the effect of oral pentetic acid alone. Oral pentetic acid may be a more practical or convenient route of administration for long-term therapy.

The effectiveness of oral pentetic acid was evaluated in a worker with extensive contamination and probably inhalation exposure following an explosion involving plutonium. Oral pentetic acid was given for 16 weeks starting at least 9 months after the accident. In the first week four 1 g oral doses resulted in a 4 fold increase in plutonium excretion. This was followed by 5 g treatments on 4 days a week and then 5 g three times a week for 11 weeks. Over the 16 weeks approximately $7.4 \times 10^{-2} \mu\text{Ci}$ was excreted which was about 10 times the amount expected without treatment (Lagerquist et al., 1967b).

### 12.4.3 Different formulations of pentetic acid and its salts

Various efforts have been made to increase the efficacy of pentetic acid. Puchel, the lipophilic derivative of pentetic acid, is generally no more effective than pentetic acid and is more toxic. Consequently it is no longer used. More recent work has focused on the use of pentetic acid in liposomes (Phan et al., 2004; 2005; 2006a; 2006b) and improving the properties of aerosolised pentetic acid (Gervelas et al., 2007).

In rats the pharmacokinetics of pentetic acid are modified by encapsulation in liposomes and can reach deposits of plutonium in the liver and bone. The pentetic acid in liposomes penetrated the liver in larger quantities than free pentetic acid and had a longer half-life, with the liver and the spleen acting as reservoirs (Phan et al., 2004; Phan et al., 2005). Free pentetic acid is undetectable in plasma at 4 hours but encapsulated pentetic acid was still quantifiable at 24 and 48 hours after intravenous injection (Phan et al., 2005). After intravenous plutonium-239 pentetic acid in liposomes was as effective as free pentetic acid in maintaining the plutonium content of the femur below 4.3% of the injected dose after 16 days (Phan et al., 2004). Pentetic acid in liposomes increased urinary plutonium excretion to over 90% of the injected dose in rats. This formulation also reduced the liver and skeleton burden even 30 days after a single dose. A dose of 0.3 µmol/kg in liposomes produced the same reduction in skeletal burden as four injections of the free pentetic acid (30 µmol/kg) (Phan et al., 2006b).

Gervelas et al. (2007) studied pentetic acid formulated on to porous particles. This was tested in rats 6 days after inhalation of plutonium-239 oxide. It was given by intratrachael administration using a dry powder insufflator and was found to increase the urinary excretion of plutonium by a factor of 4 for the first 4 days after treatment. In addition the excretion of plutonium remained high for 6 days. Although this formulation of pentetic acid increased excretion it did not enhance dissolution of plutonium-239 oxide particles in the lungs.

### 12.5 Proposals for further studies

The potential risks and benefits of the use of pentetic acid after oral exposure to metals and radionuclides warrants further investigation since this is an issue that influences the point at which antidote or decorporation treatment is initiated.

In addition the efficacy of oral pentetic acid also requires evaluation. Although most cases of exposure involve inhalation or wound contamination for which nebulised or injection of pentetic acid salts is suitable, the long duration of treatment required in some cases makes parenteral administration inconvenient and it can be uncomfortable. This can influence patient compliance.
More studies on the efficacy and benefits of the different formulations of pentetic acid are needed.

### 12.6 Adverse effects

Pentetic acid salts are generally well tolerated. The medical case reports of 646 individuals who received calcium or zinc trisodium pentetate is held by the Radiation Emergency Assistance Center/Training Site (REAC/TS), part of the Oak Ridge Universities (ORAU), Tennessee, USA (FDA, 2004). Of these 646 subjects adverse event information was collected for 310 individuals. Of these only 19 (6.1%) reported adverse events which included nausea, diarrhoea, headache, light-headedness, chest pain, allergic reactions, dermatitis, metallic taste and injection site reactions (Hameln Pharmaceuticals, 2004).

Microhaematuria was reported in one patient given a second dose of intramuscular calcium trisodium pentetate (0.5 g) for lead poisoning (Brugsch et al., 1965). In a review of 23 workers given intravenous calcium trisodium pentetate (518 injections in total) after radiation accidents over a 34 year period there was no change in renal function (Grappin et al., 2007). Decreased activity of \( \delta \)-aminolevulinic dehydratase (ALAD), a zinc-containing enzyme, was observed in a 15-year-old patient treated with calcium trisodium pentetate (Cohen et al., 1976).

Cough and/or wheezing have been reported in two individuals given nebulised calcium trisodium pentetate; one of these subjects had a history of asthma (Hameln Pharmaceuticals, 2004).

Calcium trisodium pentetate also chelates trace elements and these should be monitored in patients receiving repeated or long-term dosing with calcium trisodium pentetate. Supplements should be given as required.

### 12.7 Restrictions for use

Administration of pentetic acid salts (orally or parenterally) following ingestion of metals or radionuclides is not recommended as this is thought to increase gastrointestinal absorption (see section 12.4).

Calcium trisodium pentetate must not be administered during pregnancy because of reproductive toxicity as a result of zinc and manganese chelation (Mays et al., 1976). The use of zinc trisodium pentetate should be considered as an alternative. Calcium trisodium pentetate is also contraindicated in patients with hypercalcaemia.

Dose reduction is not required in patients with renal impairment but haemodialysis may be required to eliminate the chelate. High efficiency high reflux dialysis is recommended (Hameln Pharmaceuticals, 2004).

Calcium trisodium pentetate should be used with caution in patients with haemochromatosis. Three patients with severe haemochromatosis died after receiving intramuscular calcium trisodium pentetate in doses up to 4 g/day. One patient became comatose and died after a total dose of 14 g and two others died after 2 weeks of daily treatment (FDA, 2004). Theses cases are very similar and could be the same as those reported by Fairbanks et al. (1963). Pentetic acid (1 g daily for 14 days) was given to three patients with haemochromatosis. All three were mentally obtunded during the period of treatment, although one had been disorientated and drowsy prior to dosing and one was borderline schizophrenic.
Two patients who were seriously ill at the time of treatment became comatose and died. No cause of their neurological deterioration was determined at post-mortem examination. The third patient survived but she developed drowsiness, dysarthria and lesions on the lingual and buccal mucosa. Another patient with less severe haemochromatosis received intravenous calcium trisodium pentetate 30 g over 12 days and developed no adverse effects (Kemble, 1964). Similarly 4 other patients with haemochromatosis received varying doses of calcium trisodium pentetate (12 g in 3 days, 9 g in 17 days) without adverse effects (Fahey et al., 1961). A causal relationship between calcium trisodium pentetate administration and the fatal outcome in these patients has not been established and caution is recommended.

13 Model information Sheet

13.1 Uses

Pentetic acid salts should be used in cases of inhalation, dermal or wound exposure to americium, californium, curium, curium and plutonium.

It can also be considered for other transuranics and radioactive metals or metals where data are limited or unavailable or where other chelators are unavailable or ineffective. This includes cobalt, einsteinium, iron, lanthanum, nickel, promethium, scandium, strontium, ytterbium, yttrium and zinc.

13.2 Dosage and Route

The dosing regimen of pentetic acid salts should be individually tailored depending on the route of exposure and the severity of intoxication. Specialist advice should be sought for patients with radiation exposure.

Treatment may need to be continued for weeks, months or even years. Dosing is usually with the calcium salt for the first day or so and then with the less toxic zinc salt.

13.2.1 Adults

13.2.1.1 Intravenous

30 µmol/kg (approximately 14 mg/kg) calcium trisodium pentetate (so 1 g for a 70 kg adult) by slow intravenous injection (in 5 ml over 3 to 4 minutes) or by intravenous infusion (in 100 to 250 ml of 0.9% saline, lactated Ringer’s or 5% dextrose over 30 minutes).

For a severe contamination the first dose given immediately after the accident may be doubled. Treatment should then continue with zinc trisodium pentetate. The dose should not exceed 1 g/day for prolonged treatment and the dose can be reduced during prolonged treatment (as the quantity of material to be chelated is reduced).

13.2.1.2 Oral administration

1 g of zinc trisodium pentetate/day in micronised capsules can be considered for long-term therapy. A higher dose (up to 5 g/day) can be used in short-term therapy.

13.2.1.3 Nebuliser administration

Pentetic acid salts may also be given by nebuliser following accidental inhalation of radioactive material.
A 30 minute inhalation of calcium trisodium pentetate made from 4 ml of a solution (1 g) or from micronised power can be given and repeated over the following days.

13.2.1.4 Cutaneous administration

Healthy skin can be washed with a 2% slightly acidic (pH 4-5) solution of calcium trisodium pentetate. Wounds can be irrigated with a 20% concentrated, sterile solution of calcium trisodium pentetate and mucosal surfaces irrigated with a 2% solution.

13.2.1.5 Local infiltration

Calcium trisodium pentetate can be infiltrated into wounds, but because intramuscular injection is painful a local anaesthetic, such as procaine, should be added to the solution.

13.2.2 Children

Based on the dose of 1 g in a 70 kg adult children should be given 14 mg/kg by intravenous injection of either salt to a maximum of 1 g.

In the past doses of 20-25 mg/kg and 40 mg/kg in 2 divided doses of calcium trisodium pentetate by intramuscular injection have been used in the treatment of iron overload. Intramuscular injection is painful and not recommended.

The safety and efficacy of the pentetic acid salts by inhalation or oral dosing has not been evaluated in paediatric patients.

13.3 Precautions and Contraindications

Administration of pentetic acid salts (orally or parenterally) following ingestion of metals or radionuclides is not recommended as this is thought to increase gastrointestinal absorption.

Calcium trisodium pentetate is contraindicated in patients with hypercalcaemia.

Dose reduction is not required in patients with renal impairment but haemodialysis may be required to eliminate the chelate. High efficiency high reflux dialysis is recommended.

Calcium trisodium pentetate should be used with caution in patients with haemochromatosis.

13.4 Pharmaceutical incompatibilities and drug interactions

None known.

13.5 Adverse effects

Pentetic acid salts are generally well tolerated. Adverse effects reported include nausea, diarrhoea, headache, light-headedness, chest pain, allergic reactions, dermatitis, microhaematuria, metallic taste and injection site reactions.

Cough and/or wheezing may occur after nebulised calcium trisodium pentetate; patients with pre-existing asthma may be more at risk.
Calcium trisodium pentetate also chelates trace elements and these should be monitored in patients receiving repeated or long-term dosing with calcium trisodium pentetate. Supplements should be given as required.

13.6 Use in pregnancy and lactation

Calcium trisodium pentetate must not be administered during pregnancy because of reproductive toxicity as a result of zinc and manganese chelation; the use of zinc trisodium pentetate should be considered.

It is not known whether calcium and zinc trisodium pentetate are excreted in breast milk but women with radiation exposure should not breastfeed.

13.7 Storage

The shelf-life of the commercially available pharmaceutical preparation ditripentat-Heyl is stated as 5 years. Pharmaceutical products containing calcium or zinc trisodium pentetate should be stored at 15 to 30 °C.

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16 Additional information

None.
### Abbreviations

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<tr>
<th>Abbreviation</th>
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<tr>
<td>AAS</td>
<td>Atomic Absorption Spectroscopy</td>
</tr>
<tr>
<td>AES</td>
<td>Atomic Emission Spectroscopy</td>
</tr>
<tr>
<td>ALAD</td>
<td>δ-aminolevulinic dehydratase</td>
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<td>Am</td>
<td>Americium</td>
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<tr>
<td>Bq</td>
<td>Becquerel, the SI unit of radioactivity</td>
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<td>CAS</td>
<td>Chemical Abstracts Service</td>
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<td>Cd</td>
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<tr>
<td>Ci</td>
<td>Curie (1 Ci = 37 GBq; 37 GB = 37.10^9 Bq)</td>
</tr>
<tr>
<td>Cm</td>
<td>Curium</td>
</tr>
<tr>
<td>Cr</td>
<td>Chromium</td>
</tr>
<tr>
<td>Cu</td>
<td>Copper</td>
</tr>
<tr>
<td>dpm</td>
<td>Disintegrations per minute</td>
</tr>
<tr>
<td>DTPA</td>
<td>Diethylenetriaminepentaacetic acid</td>
</tr>
<tr>
<td>EDTA</td>
<td>Ethylenediaminetetraacetic acid</td>
</tr>
<tr>
<td>EDTPO</td>
<td>Ethylenediaminetetra(methyleneephosphonic) acid</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration (United States)</td>
</tr>
<tr>
<td>Gy</td>
<td>Gray, unit of the absorbed dose</td>
</tr>
<tr>
<td></td>
<td>1 Gy = 100 rad</td>
</tr>
<tr>
<td>HEDTA</td>
<td>Hydroxyethylethylenediaminetriacetic acid</td>
</tr>
<tr>
<td>Hg</td>
<td>Mercury</td>
</tr>
<tr>
<td>ICP</td>
<td>Inductively Coupled Plasma</td>
</tr>
<tr>
<td>IPCS</td>
<td>International Programme on Chemical Safety</td>
</tr>
<tr>
<td>LD</td>
<td>Lethal Dose</td>
</tr>
<tr>
<td>LICAM(C)</td>
<td>N₁⁴, N₅⁴, N₁⁰⁴-tetrakis(2,3-dihydroxy-4-carboxybenzoyl)-tetraazatetradecane, tetrasodium salt</td>
</tr>
<tr>
<td>m</td>
<td>Milli (10⁻³)</td>
</tr>
<tr>
<td>µ</td>
<td>Micro (10⁻⁶)</td>
</tr>
<tr>
<td>Mn</td>
<td>Manganese</td>
</tr>
<tr>
<td>Nb</td>
<td>Niobium</td>
</tr>
<tr>
<td>Ni</td>
<td>Nickel</td>
</tr>
<tr>
<td>Np</td>
<td>Neptunium</td>
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<tr>
<td>Pb</td>
<td>Lead</td>
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<tr>
<td>Pm</td>
<td>Promethium</td>
</tr>
<tr>
<td>Po</td>
<td>Polonium</td>
</tr>
<tr>
<td>Pu</td>
<td>Plutonium</td>
</tr>
<tr>
<td></td>
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<tr>
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</tr>
<tr>
<td>3616</td>
<td>Rad</td>
</tr>
<tr>
<td>3617</td>
<td>RDD</td>
</tr>
<tr>
<td>3618</td>
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</tr>
<tr>
<td>3620</td>
<td>Sb</td>
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<tr>
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<tr>
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<tr>
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<td>Zn</td>
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