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**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

## 1 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 acids 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 (Hamel 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

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87 media such as gadolinium and radiopharmaceuticals such as indium-111 and technetium-99. These are  
 88 not discussed here.

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**2 Names and Chemical Formulae**

International non-proprietary name	pentetic acid
Synonyms	diethylenetriamine- <i>NNN'N'N'</i> -penta-acetic acid, <i>N,N</i> -bis[2-[bis(carboxymethyl)amino]ethyl]glycine, pentacarboxymethyl diethylenetriamine, acidum penteticum, acide pénétique, ácido pentético, diethylene triamine pentaacetic acid, DTPA
IUPAC name	[[[(Carboxymethyl)imino]bis(ethylenenitrilo)]-tetra-acetic acid
CAS No	67-43-6
Chemical formula	C <sub>14</sub> H <sub>23</sub> O <sub>10</sub>
Relative molecular mass	393.35

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International non-proprietary name	Calcium trisodium pentetate	Zinc trisodium pentetate
Synonyms	Ca-DTPA, [ <i>N,N</i> -bis[2-[bis(carboxymethyl)amino]ethyl]glycinato(5-)calciate(3-)] trisodium, sodium[[[carboxymethyl]imino]bis(ethylenenitrilo)]tetracetato]-calciate, [[[(carboxymethyl)imino]bis(ethylenenitrilo)] tetraacetic acid calcium complex trisodium salt, trisodium calcium diethylenetriamine pentaacetate, calcei trinatrici pentetas, calcium trisodium DTPA, pentetate calcium trisodium, pentétate de calcium trisodique, pentetato calcio y trisodi	Zn-DTPA, pentétate de zinc trisodique, pentetate zinc trisodium, pentetato zinc y trisodio, trisodium zinc diethylenetriamine pentaacetate, zinci trinatrici pentetas, zinc pentetate, zinc trisodium pentetate
<b>IUPAC name</b>		
CAS No	12111-24-9	65229-17-6 (zinc pentetate) 125833-02-5 (zinc trisodium pentetate)
Chemical formula	C <sub>14</sub> H <sub>18</sub> CaN <sub>3</sub> Na <sub>3</sub> O <sub>10</sub>	C <sub>14</sub> H <sub>18</sub> N <sub>3</sub> Na <sub>3</sub> O <sub>10</sub> Zn
Relative molecular mass	497.36	522.67

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Commercial Names: Ditripentat-Heyl (Heyl, Germany), Pentetate zinc trisodium injection and Pentetate calcium trisodium injection (Hameln, Germany)

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**Conversion factors**

	<b>Calcium trisodium pentetate</b>	<b>Zinc trisodium pentetate</b>
1 g	2.01 mmol	1.9 mmol
1 mg	2.01 µmol	1.9 µmol
1 mmol	497.4 mg	522.7 mg
1 µmol	497.4 µg	522.7 µg

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<sub>a</sub>: 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**

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146 Calcium trisodium pentetate can be made by mixing pentetic acid with sodium hydroxide and calcium  
147 chloride or calcium carbonate. Zinc trisodium pentetate can be made by mixing pentetic acid with  
148 sodium hydroxide and zinc oxide or zinc chloride.

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150 **4.2 Manufacturing Process**

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152 Not known.

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154 **4.3 Presentation and Formulation**

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

159

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

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165 **5 Analytical Methods**

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167 **5.1 Quality Control Procedures for the Antidote**

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169 Not known.

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171 **5.2 Methods for Identification of the Antidote**

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173 Not known.

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175 **5.3 Methods for Identification of the Antidote in Biological Samples**

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177 Not known.

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179 **5.4 Analysis of the Toxic Agent in Biological Samples**

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

184

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

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194 **6 Shelf-Life**

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196 The shelf-life for Ditripentat-Heyl is stated as 5 years for the ampoules. Ampoules of pentetate zinc

197 trisodium injection and pentetate calcium trisodium injection should be stored at 15 to 30 °C.  
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## **7 General Properties**

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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.

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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.

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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.

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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.

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

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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.

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## **8 Animal Studies**

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### **8.1 Pharmacodynamics**

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

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#### **8.1.1 Americium (Am)**

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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

248 al., 1979a).

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### 250 **Inhaled americium**

251 Lung lavage and chelation therapy were evaluated in beagles exposed to aerosols of americium-241  
252 oxide. Following exposure the lungs were lavaged on days 2, 7, 14, 28 and 42 (right lung) and 2, 10,  
253 21, 35 and 49 (left lung). Intravenous calcium trisodium pentetate (22  $\mu\text{mol/kg}$ ) was given on days 1 to  
254 4 and then twice weekly (18 doses in total) until the animals were sacrificed on day 64. The  
255 concentration of americium-241 in tissues was lower in treated dogs. Calcium trisodium pentetate  
256 prevented deposition in organs and removed americium-241 already deposited in the liver. It did not,  
257 however, remove americium deposited in bone. Americium was removed in all lung lavages but only  
258 the first 4 (two lavages of each lung) removed large quantities (Muggenburg & Mewhinney, 1981).

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### 260 **Parenteral americium**

261 Calcium and zinc trisodium pentetate were compared in beagle dogs exposed to americium-241. The  
262 dogs were given intravenous americium-241 and two weeks later were treated with subcutaneous  
263 injections of either calcium or zinc trisodium pentetate (6, 12 or 30  $\mu\text{mol/kg}$ ) either as a single dose or  
264 in divided doses. For a single daily injection there was not much difference between the salts in  
265 removing americium. Five daily doses of calcium trisodium pentetate had to be stopped within 3 days  
266 in two dogs as they developed severe toxicity from frequent administration of calcium trisodium  
267 pentetate (clinical details not stated). There appeared to be no significant difference between the salts  
268 but zinc trisodium pentetate seemed to be more effective in repeated doses. In the first 3 days dogs  
269 receiving calcium trisodium pentetate excreted 6.6% of the injected dose of americium compared to  
270 14.8% in those receiving zinc trisodium pentetate. Continued treatment with zinc trisodium pentetate  
271 removed all the americium-241 in the liver after 1 year of treatment and approximately 80% in the  
272 skeleton by 2 years (Lloyd et al., 1976). This study was repeated in order to reduce any physiological  
273 differences between the dogs given calcium or zinc trisodium pentetate. It also confirmed that for  
274 delayed treated there was no difference in calcium or zinc trisodium pentetate in removing americium-  
275 241 (Lloyd et al., 1977).

276

277 Beagle dogs intravenously injected with americium-241 were treated 2 weeks later with zinc trisodium  
278 pentetate. After 13 months of therapy the mobilisation of americium in two dogs receiving a single  
279 daily injection of 0.027 or 0.034 mmol/kg/day was similar to that in two dogs receiving a total of 0.035  
280 or 0.037 mmol/kg/day in five divided doses. Increasing the dose of zinc trisodium pentetate to 0.36 or  
281 5 mmol/kg/day only slightly increased the mobilisation of americium. Just before starting therapy the  
282 dogs averaged 43% americium in the liver and 46% in non-liver (mainly skeletal) tissue. After 2  
283 months of treatment retention in the liver was 2% of the pretreatment level, approximately 1% after 5  
284 months and was undetectable by 13 months. At 2 months the non-liver retention was 53% of the  
285 pretreatment level, 40% at 5 months and 27% at 13 months. In contrast, the half-life of americium in  
286 liver and non-liver tissue in control animals was 10 years (Lloyd et al., 1975).

287

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

292

293 Mice were treated with a single intraperitoneal injection of calcium or zinc trisodium pentetate (1  
294 mmol/kg) at various times after intravenous administration of americium-241. When given 24 hours  
295 after americium the pentetic acid salts were equally effective at removing americium from organs but  
296 zinc trisodium pentetate was slightly less effective at mobilising americium from the liver. When given  
297 on day 64 both salts had little mobilising effect on americium. It was clear that with early treatment, up  
298 to 5 hours after americium injection, the calcium salt is slightly more effective than zinc trisodium

299 pentetate but thereafter there was no difference in efficacy (Seidel, 1973).

300

301 The effect of calcium trisodium pentetate on the concentration of americium-241 in the skeleton, liver  
302 and kidneys was investigated in rats, and Syrian and Chinese hamsters. Americium-241 was given by  
303 intraperitoneal injection followed 24 hours later by intraperitoneal calcium trisodium pentetate (30 or  
304 1000  $\mu\text{mol/kg}$ ) and the animals were sacrificed 8 days later. A single injection of calcium trisodium  
305 pentetate mobilised americium in rats and Chinese hamster liver but was markedly less effective in the  
306 Syrian hamster. There was no relationship between the biological half-life of a radionuclide in an  
307 organ and the fraction of the radionuclide which is available for chelation (Seidel, 1978).

308

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

321

#### 322 **Parenteral americium, oral antidote**

323 The effectiveness of oral calcium and zinc trisodium pentetate was studied in rats after intravenous  
324 americium-241. Even a low dose of calcium or zinc trisodium pentetate (1 mM) in drinking water from  
325 20 minutes after injection for 18 days produced a significant reduction in the americium-241  
326 concentration in the liver and femur (Taylor & Volf, 1980).

327

#### 328 **Other studies**

329 The effectiveness of calcium trisodium pentetate in juvenile and adult baboons has been compared.  
330 The baboons, 4 to 5 years or 11 to 14 years, were given intravenous americium-241 followed by  
331 intravenous calcium trisodium pentetate (28.7  $\mu\text{mol/kg}$  three times a week for 4 weeks). In adult  
332 baboons the chelator was most effective when given soon after americium exposure (1 day or 1.5  
333 months), that is, when the americium was associated with soft tissues rather than bone. When given 1  
334 year after exposure an additional 8% of the body burden was removed, presumably from the skeleton.  
335 Comparing juveniles and adults treated 1.5 or 1.6 months after exposure for 10 to 12 treatments (3  
336 times a week), the cumulative net increase in urinary excretion of americium in juveniles was 2.5 times  
337 that of the adults. The overall decrease in the body burden of adult baboons was 15% compared to  
338 30% in the juveniles (Cohen et al., 1976).

339

340 The effect of zinc trisodium pentetate was examined in mice exposed to americium-241 during  
341 pregnancy. Female mice were given intraperitoneal americium-241 at various stages of gestation  
342 followed by subcutaneous zinc trisodium pentetate (300  $\mu\text{mol/kg}$ ) starting 10 minutes later. Mothers  
343 and young were sacrificed shortly afterwards. Treatment with zinc trisodium pentetate significantly  
344 reduced body burden of americium in both the mothers and the fetuses. There was no net increase in  
345 the transfer of americium to the unborn young. Exposure to americium-241 17 days before mating and  
346 treatment with 10 doses of zinc trisodium pentetate (completed 3 days before mating) also resulted in  
347 reduced fetal body burden. These data indicate that the hazard from americium to the unborn could be  
348 reduced by zinc trisodium pentetate treatment prior to or during pregnancy (Lloyd et al., 1985a).

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350 An *in vitro* study using a crystalline bone mineral surrogate, calcium hydroxyapatite, showed that zinc  
351 trisodium pentetate only removed 1.4% of the bound americium-241 (Guilmette et al., 2003).

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### 353 **8.1.1.1 Americium and plutonium**

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

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#### 358 **Parenteral americium and plutonium**

359 Mice were given an intraperitoneal injection of a mixture of americium-241, plutonium-237 and 239,  
360 and given calcium trisodium pentetate 3 days later. A dose of 500  $\mu\text{mol/kg}$  was given twice weekly for  
361 5 weeks; some subjects also received salicylic acid (2000  $\mu\text{mol/kg}$ ). Total body retention of plutonium  
362 and americium at the end of 34 days was significantly less in the mice treated with calcium trisodium  
363 pentetate compared to the controls. Salicylic acid did not enhance the effect of calcium trisodium  
364 pentetate (Jones et al., 1980).

365

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

374

375 Beagles were given intravenous calcium trisodium pentetate (3, 10, 30 or 300  $\mu\text{mol/kg}$ ) 30 minutes  
376 after intravenous plutonium-237 and 239 and americium-241 and were sacrificed 7 days later. The  
377 quantity of plutonium and americium retained was influenced strongly by the dose of calcium trisodium  
378 pentetate given. Plutonium retention was 77% in the dog given 3  $\mu\text{mol/kg}$  and 14% in the dog given  
379 300  $\mu\text{mol/kg}$ . For americium the corresponding figures were 40% and 9%. Similarly the liver  
380 retention was also reduced with higher doses of calcium trisodium pentetate; reduced from 18% to 2%  
381 with plutonium and 21% to 1% with americium (Lloyd et al., 1979b).

382

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

397

398 Rats were used in a study investigating the effect of delayed administration of pentetic acid salts after  
399 injection of plutonium-238 and americium-241. The animals were given calcium (first dose) or zinc  
400 trisodium pentetate (subsequent doses) at 30 minutes, 6 hours, days 1 to 3 or on days 1 to 3 after

401 subcutaneous or intramuscular plutonium-238 and americium-241. After subcutaneous plutonium-238  
402 and americium-241 the total body content of plutonium and americium were reduced to 15% and 25%,  
403 respectively, of those of controls. A single local injection was only marginally less effective than  
404 repeated dosing. Delayed administration reduced the efficacy of pentetic acid; when started at 6 hours  
405 or 1 day the total body count of plutonium was reduced to 50% and 60%, respectively, of controls.  
406 The corresponding figures for americium were 57% and 67%, respectively. After intramuscular  
407 plutonium-238 and americium-241 with pentetic acid started 30 minutes later the total body content of  
408 plutonium and americium were reduced by 32% and 22%, respectively, of controls. Delaying  
409 treatment again reduced efficacy. When started 6 hours or 1 day after exposure the total body count of  
410 plutonium was reduced to 66% and 74%, respectively, of controls. The corresponding figures for  
411 americium were 62% and 67%, respectively (Gray et al., 1994).

412

### **Simulated wound**

413 Another experiment studied the effect of calcium and then zinc trisodium pentetate on simulated  
414 wounds involving americium-241 and plutonium-238 nitrates in rats. After subcutaneous americium-  
415 241 and plutonium-238 nitrates local subcutaneous injection of calcium trisodium pentetate (30  
416  $\mu\text{mol/kg}$ ) at 30 minutes reduced the retention of plutonium-238 in the wound and other body tissues to  
417 38 and 20% of controls. The figures for americium-241 were 31 and 28% (Stradling et al., 1993b).

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### **Inhaled americium and plutonium**

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

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### **Inhaled americium and plutonium, oral antidote**

426 The efficacy of oral zinc trisodium pentetate was investigated in rats after inhalation of plutonium-238  
427 and americium-241. One hour or 4 days after inhalation of an aerosol of plutonium and americium zinc  
428 trisodium pentetate was given in drinking water at a dose of 95  $\mu\text{mol/kg/day}$  for 4, 7 or 14 days. The  
429 plutonium retention in the lungs, liver, carcass and total body when given from 1 hour for 14 days post-  
430 exposure was 11%, 22%, 38% and 18%, respectively, of those in control animals. There was still  
431 considerable reduction in plutonium retention even when the oral antidote was started 4 days after  
432 exposure; in the lungs and total body the retention was 26% and 34% of controls. The results were  
433 similar for americium. When given from 1 hour for 14 days post-exposure the americium content of  
434 the lungs and total body was 11% and 14%, respectively, of controls (Stradling et al., 1993a). In a  
435 second study in rats the continual administration of zinc trisodium pentetate in drinking water (95  
436  $\mu\text{mol/kg/day}$ ) started 1 hour after exposure reduced the plutonium-238 content of the lungs and total  
437 body to 2% and 8% of controls. The americium-241 content of the lungs and total body was reduced  
438 to 3% and 5% of controls. When started at 7 days after exposure the total body content of plutonium-  
439 238 and americium-241 were reduced to 17% and 20% of controls by 28 days. Increasing the oral dose  
440 to 950  $\mu\text{mol/kg/day}$  continually or to 3600  $\mu\text{mol/kg/day}$  every third day was no more effective than 95  
441  $\mu\text{mol/kg/day}$ . Similarly, additional intraperitoneal zinc trisodium pentetate (30  $\mu\text{mol/kg}$  twice weekly)  
442 did not increase the effectiveness of oral dosing (Gray et al., 1995).

443

444

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

451

452 **8.1.2 Antimony (Sb)**

453

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

457

458 In a study comparing survival rates of different antidotes in antimony poisoning, mice were given  
459 intraperitoneal antimony (III) potassium tartrate 120 mg/kg (LD<sub>50</sub> 54.6 mg/kg). The antidotes were  
460 given by the same route 1 hour later at a dose of 10:1 molar ratio of antidote to antimony (except  
461 for dimercaprol which was given at a 1:1 ratio). Succimer and unithiol were found to be the most  
462 effective antidotes; none of the five mice treated with calcium trisodium pentetate survived  
463 (Basinger & Jones, 1981a).

464

465 **8.1.3 Beryllium (Be)**

466

467 Pentetic acid is not a suitable chelating agent for beryllium. In rats calcium trisodium pentetate (0.3  
468 mmol/kg for 5 days after administration of beryllium 1 mg/kg parenterally 6 days/week for 3 weeks)  
469 was ineffective at reducing tissue concentrations of beryllium. It failed to normalise any biochemical  
470 parameters of beryllium toxicity and appeared to enhance the toxic effects of beryllium (Mathur et al.,  
471 1993).

472

473 In a similar study calcium trisodium pentetate (0.1 mmol/kg for 5 days after administration of beryllium  
474 1 mg/kg daily for 28 days by intraperitoneal injection) was the least effective chelator tested (as  
475 measured by biochemical alterations in liver and kidney function). It was moderately effective when  
476 used in combination with  $\alpha$ -tocopherol (Mathur et al., 2004).

477

478 **8.1.4 Bismuth (Bi)**

479 There is very little information on the efficacy of pentetic acid in chelating bismuth but it appears to be  
480 relatively ineffective. In a study of several antidotes comparing efficacy in bismuth poisoning, mice  
481 were given intraperitoneal bismuth citrate 125 mg/kg (LD<sub>50</sub> 71 mg/kg) followed by an antidote 20  
482 minutes later in a 10:1 molar ratio antidote:bismuth. Only 4 of the 10 animals treated with calcium  
483 trisodium pentetate survived compared to all the animals treated with succimer, unithiol, the  
484 calcium salt of ethylenediaminetetra(methylenephosphonic) acid (EDTPO) or N-acetyl-D,L-  
485 penicillamine (Basinger et al., 1983).

486

487 **8.1.5 Cadmium (Cd)**

488

489 Antidotal therapy for cadmium is particularly problematic because the absorbed metal rapidly  
490 becomes strongly bound to metallothionein, a low-molecular weight metal-binding protein whose  
491 synthesis is induced by cadmium. The efficacy of a large number of metal-binding agents,  
492 belonging to several chemical compound groups, has been investigated in cadmium toxicity  
493 (reviewed in Andersen, 1989a, 1989b), but in the majority of acute toxicity studies in experimental  
494 animals, both cadmium and antidote were injected at about the same time, reducing the relevance in  
495 relation to acute human intoxication.

496

497 Pentetic acid salts have been shown to be effective in cadmium poisoning by reducing body burden,  
498 increasing survival, reducing organ concentrations or reducing cadmium-induced organ damage  
499 (Cantilena & Klaassen, 1981; Planas-Bohne & Lehman, 1983; Eybl et al., 1984; Andersen et al.,  
500 1988; Basinger et al., 1988). Pentetic acid has also been shown to be effective in combination with  
501 dimercaprol (Cherian, 1980; Cherian, 1984; Cherian & Rodgers, 1982). Delayed administration of

502 pentetic acid has been shown to greatly reduce its efficacy in cadmium-poisoned experimental  
503 animals (Cantilena & Klaassen, 1982; Planas-Bohne & Lehman, 1983; Sarić et al., 2004) and in  
504 some cases it has been shown to be ineffective in these circumstances (Shinobu et al., 1983). Based  
505 on experimental data, Andersen (1989b) concluded that the optimal antidotal treatment for acute  
506 oral cadmium intoxication is oral administration of succimer and pentetic acid.

507

### 508 **Early treatment**

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

516

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

525

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

532

533 Oral pentetic acid (3.61 mmol/kg) was effective in promoting survival in cadmium-poisoned mice  
534 (1 mmol/kg cadmium chloride orally) when given immediately after administration of cadmium.  
535 Animals were killed at 8 days. Pentetic acid was not as effective as succimer in reducing cadmium  
536 concentrations in the liver and kidney (Basinger et al., 1988).

537

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

541

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

547

548 Oral treatment with zinc trisodium pentetate has been evaluated in cadmium poisoning. Rats, 6 days or  
549 6 weeks old, received cadmium in cow's milk or by stomach tube, respectively, followed by oral zinc  
550 trisodium pentetate (1.9 g/kg) over the first and second day (suckling rats) or immediately after and 24  
551 hours later (older rats). The animals were killed on day 6. In suckling rats the zinc trisodium pentetate  
552 decreased whole body retention by 7 times, and gut cadmium retention by 9 times; kidney and liver

553 retention was 2 and 3 times lower, respectively. In older animals the whole body retention of cadmium  
554 was decreased by 4 times and the gut and organ retention was decreased by 5 times. Oral zinc  
555 trisodium pentetate was therefore more effective at reducing gut retention in sucklings compared to  
556 older rats (but more cadmium was retained in the gut of suckling rats). Zinc trisodium pentetate was  
557 more effective at reducing organ retention in older rats (Kostial et al., 1987c).

558

### 559 **Early versus delayed treatment**

560 Another study in mice compared antidote efficacy when given intravenously 10 seconds, 1 or 3  
561 hours after intravenous cadmium chloride (3  $\mu\text{mol/kg}$ ) administration. When given immediately  
562 after cadmium administration, all agents reduced the body burden of cadmium but efficacy declined  
563 when dosing occurred at 1 or 3 hours after administration. Cadmium elimination was only  
564 increased on the first day. Calcium trisodium pentetate was the most effective antidote tested when  
565 given immediately after exposure, as measured by the reduced cadmium body burden. Repeated  
566 injections of 0.1 mmol/kg of calcium trisodium pentetate daily for 5 days/week for 4 weeks or the  
567 same dose in drinking water was no more effective than the first dose in increasing cadmium  
568 elimination (Planas-Bohne & Lehman, 1983).

569

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

584

585

### 586 **Delayed treatment**

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

597

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

602

603 Intraperitoneal calcium trisodium pentetate did not affect faecal excretion of cadmium and the

604 increase in urinary excretion was too small to affect body burden in rats given 0.4 mmol/kg  
605 following dosing with radiolabelled cadmium (3  $\mu$ mol/kg intravenously as cadmium chloride). The  
606 cadmium was given once; administration of the metal-binding agent started on the third day and  
607 was given daily, 5 times a week for 2 weeks (Rau et al., 1987).

608  
609 Mice were given intraperitoneal cadmium chloride (3 mg/kg) 6 days/week for 20 doses. On the 25th  
610 day some were treated with subcutaneous calcium trisodium pentetate every 2 days for 16 days (8  
611 doses in total) and were killed on the 41st day. A single dose of chelator was given at an antidote to  
612 cadmium ratio of 25:1. Calcium trisodium pentetate significantly decreased the cadmium  
613 concentration of the liver but not the kidneys, testes or brain. When calcium trisodium pentetate  
614 was given alone, without cadmium exposure, there was a significant increase in the zinc  
615 concentration of the kidneys, presumably related to increased zinc excretion (Eybl et al., 1998).

616  
617 Gale et al. (1983a) compared the efficacy of several metal-binding antidotes in mice given a  
618 sublethal intraperitoneal dose of radiolabelled cadmium (0.03 mg cadmium chloride). The antidote  
619 was given 4 weeks later. Calcium trisodium pentetate (873 mg/kg 3 times a week for 7 or 13 doses)  
620 was very effective at reducing the cadmium concentration in the kidney (reduced by 48%) but was  
621 ineffective in other organs and only reduced body burden by 6.7%. A more aggressive treatment  
622 regimen of 2000 mg/kg/day was terminated after 5 days because the animals had lost 20% of their  
623 body weight. Two days later the animals were moribund and were killed. The whole body  
624 radioactivity was found to have reduced by 11.4%. The mean reduction in cadmium burden in the  
625 kidney was 31.8% but only 5.3% in the liver.

626  
627 In another study by the same group mice were given intraperitoneal cadmium followed 14 days  
628 later by chelation therapy with zinc trisodium pentetate and/or diethyldithiocarbamate (both 2  
629 mmol/kg 3 times a week for 7 or 13 injections). Zinc trisodium pentetate caused statistically  
630 significant but relatively modest reductions in the renal, intestinal, testicular and myocardial  
631 cadmium burdens. It did not affect cadmium concentrations in the liver. Diethyldithiocarbamate  
632 was more effective than zinc trisodium pentetate alone but administration of both chelators caused a  
633 more marked depletion of the cadmium burden than either chelator alone. There was also a more  
634 rapid rate of both faecal and urinary excretion with administration of both agents (Gale et al.,  
635 1983b).

636  
637 **Other studies**  
638 An *in vitro* study demonstrated that pentetic acid suppressed metal accumulation in cells and  
639 reduced the cadmium-related growth inhibition in mammalian cell culture (Fischer, 1995).

640  
641 **8.1.6 Calcium (Ca)**  
642  
643 There is limited information on the effect of pentetic acid on calcium. Calcium trisodium pentetate is  
644 not expected to affect calcium elimination. Mice given pentetic acid immobilised on cellulose and  
645 incorporated into white wheat flour dough had reduced gastrointestinal uptake of strontium-85,  
646 calcium-47 and radium-226. The pentetic acid was given for 24 hours prior to ingestion of the isotopes  
647 and 48 hours after dosing (Bulman et al., 1983).

648  
649 **8.1.7 Californium (Cf)**  
650  
651 Pentetic acid is effective in removing californium from tissues (Graham et al., 1978).  
652  
653 Calcium trisodium pentetate (50 mg/kg by intraperitoneal injection) was very effective in removing  
654 californium-252 in a study in rats. The calcium trisodium pentetate was given immediately after

655 intratracheal administration of californium-252 and then every 3 days until the rats were sacrificed. On  
656 day 1 the whole body retention of californium was only 25% of the control group; this was less than 2%  
657 on day 32. In total 60% of intratracheally administered californium appeared in the urine on the first  
658 day after treatment. Retention in tissues was low or undetectable and in addition to preventing  
659 deposition in bone and tissue calcium trisodium pentetate resulted in more rapid clearance from the  
660 lungs. After 32 days the lungs of the treated animals contained only 5% of the amount retained by the  
661 controls (Graham et al, 1978).

662  
663 The effect of calcium trisodium pentetate on the concentration of californium-252 in the skeleton, liver  
664 and kidneys was investigated in rats, Syrian and Chinese hamsters. Californium-252 was given by  
665 intraperitoneal injection followed 24 hours later by intraperitoneal calcium trisodium pentetate (30 or  
666 1000  $\mu\text{mol/kg}$ ) and the animals were sacrificed 8 days later. A single injection of calcium trisodium  
667 pentetate mobilised californium-252 in rats and Chinese hamster liver but was markedly less effective  
668 in the Syrian hamster. In kidneys the efficacy of calcium trisodium pentetate increased in the order of  
669 rat, Syrian hamster and Chinese hamster. In another study calcium trisodium pentetate (30  $\mu\text{mol/kg}$ )  
670 was given on days 4, 11, 18 and then at 7 day intervals until day 81 and animals were sacrificed on day  
671 88. The efficacy was the same in the skeleton in all animals resulting in 50% of the control  
672 californium-252 concentration. In the liver and kidneys of Chinese hamsters over 90% of the  
673 californium-252 was mobilised but the efficacy was lower in the liver and kidneys in rats and Syrian  
674 hamsters. There was no relationship between the biological half-life of a radionuclide in an organ and  
675 the fraction of the radionuclide which is available for chelation (Seidel, 1978).

676

### 677 **8.1.8 Cerium (Ce)**

678

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

681

#### 682 **Parenteral cerium**

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

688

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

692

693 In mice given intraperitoneal cerium-144 followed 30 minutes later by one of several antidotes,  
694 intraperitoneal calcium trisodium pentetate (0.5 mmol) was the most effective at reducing whole  
695 body retention of cerium-144. Combination of calcium trisodium pentetate with another antidote  
696 (deferoxamine, D,L-penicillamine or sodium salicylate) did not enhance its therapeutic effect or  
697 change the deposition characteristics of kinetics of cerium (Gach alyi et al., 1986). Similarly a  
698 combination of deferoxamine and calcium trisodium pentetate was as effective in removing a mixture  
699 of niobium-95 and cerium-144 from tissues as each antidote when given separately (Gach alyi et al.,  
700 1989).

701

#### 702 **Simulated wound**

703 Calcium trisodium pentetate was used to evaluate removal of cerium-144 from wounds in rats.  
704 Simulated wounds were made with a scalpel and contaminated with cerium-144 and the excess fluid  
705 blotted off 1 minute later. All animals were given the chelating agent by intraperitoneal injection 1 hour

706 later (98, 28 or 7 mg/kg) and this was followed in two treatment groups at 2, 4 and 6 days or twice  
707 daily, respectively. Rats were sacrificed after 1 week. Calcium trisodium pentetate treatment increased  
708 excretion of cerium in all animals. The increase was high on the first day and thereafter was dose-  
709 dependent; the higher the dose, the greater the excretion. Frequent small doses of calcium trisodium  
710 pentetate were more effective than a single large dose (Takada & Fujita, 1979).

711

### **Oral cerium**

712 The use of oral zinc trisodium pentetate has been investigated after cerium-144 was added to cows'  
713 milk and fed to 6 day old rats. One group also received zinc trisodium pentetate (1.9 g/kg) in drops  
714 throughout days 1 and 2 and another group received zinc trisodium pentetate on days 2 and 3. The  
715 animals were killed 6 days after cerium administration. In control animals 94% of the cerium was in  
716 the gut at 6 days. Oral zinc trisodium pentetate significantly reduced cerium whole body retention in  
717 both treatment groups by 20 times. In the gut the retention was reduced by 25 times (Kostial et al,  
718 1987a).

719

720  
721 In contrast oral zinc trisodium pentetate increased retention of oral cerium-141 but reduced the  
722 retention of intraperitoneal cerium-141. With oral zinc trisodium pentetate the retention of oral cerium-  
723 141 was doubled in the whole body and gut, increased by factors of 5 in the carcass and liver, 10 in the  
724 femur and 50 in the kidneys. However, in this study the animals were killed at 24 hours and there was  
725 no measurement of excretion rate (Kargaćin & Kostial, 1985).

726

### **Inhaled cerium**

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

738

739  
740 A series of studies investigated the removal of inhaled cerium-144 in beagles. The dogs were  
741 exposed to an aerosol of cerium-144 for 10 minutes and then received once of several treatments  
742 and were sacrificed on day 28. In the first study dogs were given a bronchial lavage with saline or a  
743 solution containing 0.5 mM pentetic acid and 0.6 mM of calcium ion. Bronchial lavage was of the  
744 left lung only and was undertaken on days 0 and 5, or only on day 0 or day 5. It was estimated that  
745 each lavage treatment delivered a pentetic acid dose of 1.82 to 3.31 mg/kg. Lavage with pentetic  
746 acid solution on day 0 removed a significant quantity of cerium-144, whereas lavage on day 5  
747 removed a much smaller amount. Similarly, the urinary excretion of cerium increased in dogs  
748 treated with pentetic acid on day 0. At sacrifice the burden of cerium-144 in the lavaged left lung  
749 was less than in the untreated right lung. The 28 day cumulative radiation dose to the lungs, liver  
750 and skeleton of dogs lavaged with pentetic acid solution on the day of exposure was 49, 34, and  
751 36%, respectively, of those in the untreated group (Pfleger et al., 1972a). A second study  
752 investigated the efficacy of bilateral lung lavage with pentetic acid solution on the same treatment  
753 days as before. Although cerium-144 was recovered in the lavage fluid pentetic acid was more  
754 effective at removing cerium through increased renal excretion (Muggenburg et al., 1972).  
755 Intravenous pentetic acid was effective in removing cerium-144 after inhalation of an aerosol and was  
756 most effective when given soon after exposure. When pentetic acid was given 1 hour after exposure the

757 lung, liver and skeletal body burdens at 28 days were reduced to 40, 36 and 27% of the initial lung  
758 burden of the exposed untreated group. When the pentetic acid was delayed until 5 days after exposure  
759 there was a 50% decrease in the lung burden with very little effect on the liver and skeletal burdens.  
760 The urinary concentration of cerium-144 was 8 times the control when pentetic acid was given on day  
761 0 and only twice the control when given on day 5 (Pfleger et al., 1972b). The most effective  
762 treatment was bilateral bronchopulmonary lavage with pentetic acid on days 0 and 5. This  
763 produced the greatest reduction in the percentage initial lung burden in the lung, liver and skeleton  
764 compared to controls (Muggenburg et al., 1972).

765

#### 766 **Other studies**

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

783

784 In rats given intravenous cerium-144 at various stages of pregnancy and treated with an antidote 6  
785 hours later intraperitoneal calcium trisodium pentetate reduced the whole body retention of cerium-  
786 144 by 26 to 27%. Calcium trisodium pentetate decreased the deposition of cerium-144 in the  
787 fetuses and associated tissues and thereby reduced radiation exposure in the fetuses (Żylicz et al.,  
788 1975).

789

790 Pregnant rats received intravenous cerium-144 one day before they were expected to give birth and  
791 then on days 2, 9 and 16 after birth. This was followed 1 hour later by 50 mg of calcium trisodium  
792 pentetate by intravenous injection. Administration of calcium trisodium pentetate given before  
793 and/or after birth reduced the dose of cerium-144 received by the offspring (Bałtrukiewicz et al.,  
794 1976).

795

#### 796 **8.1.8.1 Cerium (Ce) and praseodymium (Pr)**

797

798 Praseodymium-144 is the daughter element of cerium-144 and exposure may involve both  
799 elements.

800 The effect of calcium trisodium pentetate on an inhaled mixture of cerium-144 and praseodymium-  
801 144 oxide has been studied in dogs. A 25% solution of calcium trisodium pentetate was given as an  
802 aerosol by inhalation over 1 hour and from the 10th day of the study intramuscular doses were  
803 given (42-55 mg/kg) as this route was found to be as effective as dosing by aerosol. Intramuscular  
804 pentetic acid was given 5 days a week for 3 weeks and then 3 times a week until the end of the  
805 study. The antidote was started at various times: immediately after inhalation of the radioactive  
806 mixture, 5, 27 or 90 days later, and then continued for the 128 days of the experiment. When given  
807 immediately after exposure the body burden was reduced by 90% within 30 days compared to only

808 a 30% reduction in untreated controls. Delayed treatment also increased elimination of cerium and  
809 praseodymium but the effect was small. The deposition of cerium and praseodymium in the  
810 skeleton was not significantly changed when administration of calcium trisodium pentetate was  
811 delayed (Tombropoulos et al., 1969).

812  
813 Similarly in rats exposed to an aerosol of cerium-144 (in equilibrium with praseodymium-144)  
814 treatment with an aerosol of pentetic acid (25% solution) reduced the radioactivity of the lungs by  
815 90% and liver retention was also reduced (to 4% of controls). Animals were treated immediately  
816 after cerium exposure then twice daily for 3 days and then once a day for the next 3 days, then  
817 every second day until the 15th day. In animals treated with the same pentetic acid regimen except  
818 that the first dose was given at 24 hours the retention of cerium was greater (77% in the lungs and  
819 89% in the liver) compared to controls (Tombropoulos & Bair, 1962).

820

### 821 **8.1.9 Cobalt (Co)**

822

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

825

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

829

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

837

838 In a study in mice where intraperitoneal cobalt chloride (0.6-1.8 mmol/kg) was immediately  
839 followed by an intraperitoneal dose of one of several chelators, sodium calcium edetate and calcium  
840 trisodium pentetate (3.1 mmol/kg) were the most effective antidotes tested. Calcium trisodium  
841 pentetate significantly increased urinary and decreased faecal cobalt concentrations. It also  
842 significantly decreased cobalt concentrations in the liver, brain, heart and blood (Llobet et al.,  
843 1986). In a similar study, intraperitoneal calcium trisodium pentetate (1.4, 2.36 or 3.5 mmol/kg)  
844 after intraperitoneal cobalt chloride (0.70 or 1.18 mmol/kg) was second only to sodium calcium  
845 edetate in increasing survival in mice (Llobet et al., 1985).

846

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

852

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

859 exposure in the fetuses (Żylicz et al., 1975).

860

#### 861 **8.1.10 Curium (Cm)**

862

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

864

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

870

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

877

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

895

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

906

#### 907 **8.1.11 Einsteinium (Es)**

908

909 There is limited information on the effect of pentetic acid following einsteinium exposure but it appears

910 to be effective (Parker et al., 1972; Smith, 1972).

911

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

917

#### 918 **8.1.12 Gallium (Ga)**

919

920 There is limited information on the effect of pentetic acid following gallium exposure but it appears to  
921 be ineffective. Calcium trisodium pentetate (at a quarter of its LD<sub>50</sub>) did not prevent death in mice  
922 when given immediately after intraperitoneal gallium nitrate (10.02 mmol/kg) (Domingo et al.,  
923 1987).

924

#### 925 **8.1.13 Lanthanum (La)**

926

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

934

#### 935 **8.1.14 Lead (Pb)**

936

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

940

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

944

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

952

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

958

959 In lead-poisoned rats both zinc trisodium pentetate and calcium trisodium pentetate increased  
960 urinary excretion of lead, and the calcium salt was more effective than the zinc salt; however,

961 neither salt increased survival rate (Hofman & Segewitz, 1975).

962

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

965

#### 966 **8.1.15 Manganese (Mn)**

967

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

970

971 Manganese poisoned rats (6 mg/kg by intraperitoneal injection daily for 25 days) were treated with one  
972 of several chelating agents (0.11 mmol/kg daily for 8 days) to evaluate efficacy at removing manganese  
973 from the brain and liver. Pentetic acid was particularly effective at removing manganese from the liver.

974 In an *in vitro* study using subcellular fractions from manganese poisoned rats (6 mg/kg by  
975 intraperitoneal injection daily for 40 days) pentetic acid was less effective removing only 18 to 50% of  
976 the manganese (Tandon & Singh, 1975).

977

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

982

#### 983 **8.1.16 Mercury (Hg)**

984

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

987

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

992

#### 993 **8.1.17 Neptunium (Np)**

994

995 There is no effective chelating agent for removal of neptunium (Ramounet et al., 1998; Stradling 1998).

996 The efficacy of pentetic acid is influenced by the valency of the neptunium compound. It appears to be  
997 more effective with neptunium in a valence state IV compared to V (Smith, 1972; Ramounet et al.,  
998 1998). Neptunium binds tightly to bone and pentetic acid tends to only affect soft tissue concentrations  
999 (Smith, 1972).

1000

1001 In rat studies pentetic acid-neptunium complexes (15 mg pentetic acid and 0.75 mg neptunium-237 V)  
1002 injected intramuscularly were not stable *in vivo*, and although there was an increase in urinary excretion  
1003 there was also an increase in organ retention of neptunium. It was concluded that pentetic acid is  
1004 unlikely to be effective in neptunium removal (Morin et al., 1973). When injected into rats neptunium-  
1005 239 V mixed with pentetic acid behaved the same as neptunium alone (Fritsch et al., 1987). These  
1006 studies used neptunium in valence state V and a study using intravenous neptunium-239 in valence  
1007 state IV showed that calcium trisodium pentetate had a high affinity for neptunium resulting in low  
1008 concentrations of retained neptunium (Fritsch et al., 1987).

1009

1010 Other studies confirm that pentetic acid is more effective with neptunium in the valence state IV  
1011 compared to V. Ramounet et al. (1998) examined the effect of localised pentetic acid treatment with

1012 the injection site close to that of neptunium administration. Intramuscular pentetic acid (30  $\mu\text{mol/kg}$ ) 2  
1013 or 20 minutes after intramuscular neptunium-239 IV significantly increased urinary excretion of  
1014 neptunium but was ineffective when given 1 hour after neptunium administration. The cumulative 3  
1015 day urinary excretion of neptunium in rats after pentetic acid given 20 minutes after dosing with  
1016 neptunium-237 IV was increased 233% compared to controls whereas the increase was only 42% for  
1017 neptunium-237 V. The neptunium concentration in liver, skeleton and at the injection site after pentetic  
1018 acid treatment were significantly decreased with neptunium-237 IV but the change in neptunium-237 V  
1019 was only significant in the liver. In contrast intravenous pentetic acid (30  $\mu\text{mol/kg}$ ) 30 minutes after  
1020 intravenous neptunium-239 IV, was ineffective in decreasing neptunium tissue concentrations (Paquet  
1021 et al., 1997).

1022  
1023 Subcutaneous calcium trisodium pentetate (50  $\mu\text{mol/kg}$ ) was the least effective chelator in rats given  
1024 intravenous neptunium-239. A higher dose (100  $\mu\text{mol/kg}$ ) was as effective as the other chelators tested  
1025 (including a combination of calcium trisodium pentetate and deferoxamine or LICAM (C)) and reduced  
1026 the body burden by approximately 50%. The combination of calcium trisodium pentetate and  
1027 deferoxamine was most effective at reducing the neptunium concentration in liver, kidney and muscle  
1028 (50 to 90%). Only this combination reduced neptunium concentrations in all soft tissues and bone.  
1029 LICAM (C) alone increased retention in muscles (up to 4 times) and kidney but this effect was reduced  
1030 when it was given in combination with calcium trisodium pentetate (Volf & Wirth, 1986).

#### 1031 **8.1.18 Nickel (Ni)**

1032  
1033  
1034 There is limited information on the effect of pentetic acid following nickel exposure. Intraperitoneal  
1035 calcium trisodium pentetate administered at a 10:1 mole ratio of antidote to nickel, increased the  
1036 survival rate in mice poisoned with intraperitoneal nickel acetate (62 mg/kg). Antidotes were  
1037 administered 20 minutes after injection of nickel. Of 14 antidotes tested calcium trisodium  
1038 pentetate was the third most effective agent, although the small sample size prohibited any  
1039 significant differentiation between them (Basinger et al., 1980).

#### 1040 **8.1.19 Niobium (Nb)**

1041  
1042  
1043 There is limited information on the effect of pentetic acid following niobium exposure. Calcium  
1044 trisodium pentetate (0.25 mmol/kg) was one of a number of decorporation agents investigated for  
1045 efficacy in mice administered 30 minutes after intraperitoneal injection of niobium-95. Calcium  
1046 trisodium pentetate was ineffective at removing niobium from tissues. The most effective compound  
1047 when given alone was deferoxamine, but the best result was obtained by a combination of  
1048 deferoxamine and calcium trisodium pentetate although using a mixture of decorporation agents did not  
1049 change the deposition characteristics of kinetics of niobium (Gachályi et al., 1987). In another study a  
1050 combination of deferoxamine and calcium trisodium pentetate was as effective in removing a mixture  
1051 of niobium-95 and cerium-144 from tissues as each antidote given separately (Gachályi et al., 1989).

#### 1052 **8.1.20 Platinum (Pt)**

1053  
1054  
1055 There is very little information on the effect of pentetic acid following platinum exposure. A single  
1056 intraperitoneal injection of calcium trisodium pentetate (1 mmol/kg) was totally ineffective in  
1057 reducing renal platinum concentration in rats treated with intravenous cisplatin (4 or 6.5 mg/kg)  
1058 24 hours previously (Planas-Bohne et al., 1982).

#### 1059 **8.1.21 Plutonium (Pu)**

1060  
1061  
1062 Pentetic acid salts are effective in removing plutonium from the body (Bhattacharyya & Peterson, 1979;

1063 Jones et al., 1980; Lloyd et al., 1979b; Stather et al., 1982; Lloyd et al., 1985b; Sullivan & Ruemmler,  
1064 1986; Szot et al., 1989; Volf, 1986) and the parenteral route is more effective than oral dosing (Sullivan  
1065 & Ruemmler, 1986). Pentetic acid removes little plutonium from bone but can prevent circulating  
1066 plutonium from deposition on bone surfaces. It is most effective when started soon after exposure  
1067 (Guilmette et al., 1979; Lloyd et al., 1979a).

1068  
1069 In animal studies both skeletal dose and bone sarcoma risk were reduced by pentetic acid chelation  
1070 (Jones et al., 1986) and pentetic acid is also effective in removing inhaled plutonium (Stather &  
1071 Rodwell, 1980; Stradling et al., 1986; Sérandour et al., 2007). However, calcium trisodium pentetate  
1072 failed to mobilise plutonium when it was administered as the tetrafluoride (McDonald et al., 1979) and  
1073 was ineffective in one study (Metivier et al., 1983) and effective in another (Stradling et al., 1986) when  
1074 the plutonium was administered as the tributyl phosphate complex.

1075  
1076 It has been shown that during the first 24 hours after calcium trisodium pentetate in plutonium-exposed  
1077 rats that 80-90% of the plutonium in the bile is in the form of the plutonium-pentetic acid complex  
1078 (Bhattacharyya & Peterson, 1979). Even though the bile is a minor excretion pathway for pentetic acid  
1079 it is the major pathway for excretion of hepatic plutonium (Bhattacharyya et al., 1978; Bhattacharyya &  
1080 Peterson, 1979).

### 1081 1082 **Parenteral plutonium**

1083  
1084 A study in beagles showed that early use of calcium trisodium pentetate is most effective in  
1085 decorporation of intravenous plutonium-239. Animals given intravenous calcium trisodium pentetate  
1086 (30 µmol/kg) at 1, 6, 30 or 150 minutes retained 31, 28, 34 and 44% of plutonium-239 respectively.  
1087 Those treated at 8 hours, 1 or 3 days retained 52, 50 and 70%, respectively. In addition, treatment at 1  
1088 or 6 minutes had a greater effect in reducing plutonium-239 in trabecular bone (where osteosarcomas  
1089 develop) compared to cortical bone (Lloyd et al., 1979a).

1090  
1091 The effect of twice weekly intravenous injections of calcium trisodium pentetate (0.036 or 0.18  
1092 mmol/kg at 6 hours or 0.18 mmol/kg at 6 or 89 days) after intravenous plutonium-239 was investigated  
1093 in beagles. The animals were sacrificed 12 weeks later. Treatment with calcium trisodium pentetate  
1094 starting at 6 hours after plutonium exposure was more effective than treatment starting on days 6 or 89.  
1095 This is because early dosing prevents deposition of plutonium in tissues. Removal from the liver was  
1096 similar for treatment at 6 hours or 6 days. With the kidney 98% of the plutonium was removed by  
1097 treatment at 6 hours, 88% by treatment at 6 days and only 32% when treatment was delayed until day  
1098 89. The high dose of calcium trisodium pentetate (0.18 mmol/kg) starting at 6 hours was more effective  
1099 than 0.036 mmol/kg, particularly in reducing bone retention of plutonium. It was twice as effective at  
1100 reducing the plutonium content of femurs. The high dose resulted in 61% of the plutonium initial dose  
1101 being excreted in the first day's urine compared to 40% with the low dose (Guilmette et al., 1979).

1102  
1103 Smith et al. (1961) studied the effect of calcium trisodium pentetate on the removal of plutonium from  
1104 miniature pigs. The pigs (40 to 60 kg) were given intravenous plutonium-239 followed 1 hour later by  
1105 intravenous calcium trisodium pentetate (9 g, so 150 to 225 mg/kg). The animals were sacrificed 6 or  
1106 7 days later. Calcium trisodium pentetate administration was associated with increased urinary  
1107 excretion of plutonium, particularly in the first 3 days. Approximately 90% of the dose was excreted.  
1108 The retention was reduced by a factor of 30 in the liver and by a factor of 10 in the skeleton. There was  
1109 little effect on retention in the kidneys. In another study pigs (62 to 75 kg) were given intravenous  
1110 calcium trisodium pentetate (1 g on day 1 and 2 g daily for 4 days) 2 months after intravenous  
1111 plutonium-239. This increased plutonium excretion by factors of approximately 40 to 100 in the urine  
1112 and 300 to 500 in the faeces.

1114 A study in mice showed that twice weekly injections of pentetic acid (0.5 mmol/kg) with salicylic acid  
1115 (2 mmol/kg) was more effective at removing plutonium-239 from tissues than pentetic acid alone.  
1116 Salicylic acid alone was ineffective. After 10 treatments with pentetic acid plutonium concentrations in  
1117 the skeleton were 15% of the injected dose but when both agents were used the mice were free of  
1118 plutonium (Schubert & Krogh Derr, 1978). In contrast, Humphreys & Stones (1980) found that  
1119 intraperitoneal calcium or zinc trisodium pentetate with salicylic acid was less effective than pentetic  
1120 acid salts alone in removing plutonium from tissues. The antidotes were given 3 days and 1 week after  
1121 intravenous injection of plutonium-239.

1122

### 1123 **Parenteral plutonium, oral antidote**

1124 The effectiveness of oral calcium and zinc trisodium pentetate was studied in rats after an intravenous  
1125 injection of plutonium-239. Zinc trisodium pentetate in drinking water (given from day 4 for 7 days) at  
1126 a dose exceeding the parenteral calcium trisodium pentetate dose by about 30 times was as effective as  
1127 the calcium trisodium pentetate in removing plutonium (Taylor & Volf, 1980).

1128

### 1129 **Inhaled plutonium**

1130 In beagle dogs exposed to an aerosol of plutonium tetrafluoride calcium trisodium pentetate was  
1131 ineffective in removing plutonium. Intraperitoneal calcium trisodium pentetate (0.5 g) was given 2  
1132 hours after exposure and continued for 12 injections over 58 days. There was no difference in the  
1133 plutonium burden in the lungs or the half-life of plutonium in the treated and untreated dogs. Urinary  
1134 excretion of plutonium was higher in the treated dogs but the increase was not significant (McDonald et  
1135 al., 1979).

1136

1137 Calcium trisodium pentetate was ineffective in rats that had been exposed to an aerosol of plutonium-  
1138 239 as the tributyl phosphate complex for 60 minutes. The chelator (30  $\mu$ mol/kg, 15 mg/kg) was given  
1139 by intramuscular injection 90 minutes before inhalation and/or 90 minutes after and 1, 2, 3, 6, 8 and 10  
1140 days after exposure. In one group of animals 1.25 mg of calcium trisodium pentetate was given by  
1141 inhalation 90 minutes after plutonium exposure followed by intravenous therapy. In the same study  
1142 intravenous calcium trisodium pentetate after intramuscular plutonium-239 as the tributyl phosphate  
1143 complex was also ineffective. The chelator was given by intravenous injection 30 minutes before  
1144 (group 1), by intramuscular injection 90 minutes after (group 2) and on days 1-3, 7, 10, 14, 17, 21, 24  
1145 and 28 (both groups) after plutonium exposure. Although calcium trisodium pentetate increased  
1146 urinary excretion of plutonium there was no significant decrease in plutonium retention in the skeleton.  
1147 Even dosing prior to plutonium exposure did not prevent plutonium translocation. Calcium trisodium  
1148 pentetate did not change the distribution of plutonium 30 days after plutonium exposure (Metivier et al.,  
1149 1983).

1150

1151 Pentetic acid salts were effective in another study involving inhalation of plutonium-238 as the tributyl  
1152 phosphate complex. Rats that had inhaled plutonium-238 were treated with intraperitoneal calcium and  
1153 then zinc trisodium pentetate (30  $\mu$ mol/kg) at 0.02, 0.25, 1, 2 and 3 days. Compared to controls only  
1154 6% of plutonium remained in the lungs, 9% in the liver and 8% in the carcass at 7 days (Stradling et al.,  
1155 1986).

1156

1157 Stather & Rodwell (1980) examined the effectiveness of calcium trisodium pentetate following  
1158 intravenous injection or inhalation of mixed oxides of plutonium and sodium in hamsters. After  
1159 inhalation the mice were given intraperitoneal calcium trisodium pentetate (14 mg/kg) at 3 hours and on  
1160 days 1, 2 and 4 and were sacrificed at 30 days. Treatment with calcium trisodium pentetate reduced the  
1161 plutonium content of the liver to 35% of controls. Calcium trisodium pentetate was more effective in  
1162 animals that had inhaled the plutonium compared to those that had received it by intravenous injection.

1163

1164

1165 **Inhaled plutonium, inhaled antidote**

1166 Stather et al. (1982) investigated the effectiveness of zinc trisodium pentetate following inhalation of  
1167 plutonium-238 oxide in hamsters. When the zinc trisodium pentetate was given by aerosol (2 µmol/kg  
1168 from day 7 at weekly intervals until day 147) the plutonium content of the lungs was reduced by about  
1169 25% with excretion mainly in the urine. After repeated inhalation of zinc trisodium pentetate the  
1170 amount of plutonium in extra-pulmonary tissues was similar to that at the beginning of decorporation  
1171 therapy suggesting that only a small proportion of plutonium entering the blood was deposited in  
1172 tissues. A second experiment studied the effect of inhalation and intraperitoneal zinc trisodium  
1173 pentetate (26 µmol/kg weekly from day 10 until day 143). With this regimen deposition in the carcass  
1174 (skeleton) was reduced by a factor of 2 but the relative amounts in the lungs compared with the amount  
1175 excreted in the urine and faeces was similar to that in the first experiment.

1176  
1177 Recent studies have examined the efficacy of a dry powder formulation of pentetic acid with improved  
1178 aerosolisation properties on the decorporation of plutonium-239. The pentetic acid was formulated on  
1179 to porous particles containing 75% pentetic acid with a mean diameter of 4.5 µm. With this  
1180 formulation 56% of the powder deposited in the lung and comprised 29% in the central airways and  
1181 27% in the alveolar region. This was tested in rats 6 days after inhalation of plutonium-239 oxide. The  
1182 rats were given 3.8 mg of powder (23 µmol/kg) by intratracheal administration using a dry powder  
1183 insufflator. The urinary excretion of plutonium remained high for 6 days after treatment with pentetic  
1184 acid and was increased by a factor of 4 for the first 4 days after treatment. Although this formulation of  
1185 pentetic acid increased excretion it did not enhance dissolution of plutonium-239 oxide particles in the  
1186 lungs (Gervelas et al., 2007).

1187  
1188 After inhalation of mixed isotopes of plutonium oxide the delayed intratracheal administration of a  
1189 dry powder of calcium trisodium pentetate (18 µmol/kg at 7 days) did not significantly reduce the  
1190 pulmonary plutonium retention but it did reduce translocation to the liver and skeleton. After  
1191 inhalation of plutonium nitrate early intratracheal administration (at 2 hours) of calcium trisodium  
1192 pentetate was more effective than intravenous injection (30 µmol/kg) at reducing pulmonary  
1193 retention and was as efficient in limiting extrapulmonary deposition. Delayed administration did  
1194 not reduce lung or extrapulmonary deposition (Sérandour et al., 2007).

1195  
1196 **Oral plutonium**  
1197 When rats were gavaged with plutonium-238, immediately followed by intravenous calcium trisodium  
1198 pentetate (0.25 mmol/kg) and killed a week later they retained slightly less plutonium than the controls  
1199 but excreted approximately 200 times more urinary plutonium-238. In this study systemic calcium  
1200 trisodium pentetate increased plutonium absorption 45-fold but reduced deposition in the skeleton and  
1201 liver (Sullivan et al., 1983).

1202  
1203 **Other studies**  
1204 The administration route was compared in adult and neonatal rats given oral or intraperitoneal  
1205 plutonium-238 followed 2 hours later by oral or intraperitoneal calcium trisodium pentetate (0.5  
1206 mmol/kg). Parenteral administration of calcium trisodium pentetate to adult rats was much more  
1207 effective than oral treatment, removing nearly 70% of plutonium. When oral plutonium was given to  
1208 adults followed by oral calcium trisodium pentetate plutonium absorption increased 20-fold and  
1209 retention was twice that of controls. When calcium trisodium pentetate was given by intraperitoneal  
1210 injection after oral plutonium absorption increased 5 fold but most was excreted in the urine. In adult  
1211 animals that received intravenous plutonium, treatment with oral calcium trisodium pentetate decreased  
1212 retention and increased urinary excretion by 10%. Retention after intraperitoneal calcium triodium  
1213 pentetate was a third of that in controls. Neonatal rats retain more plutonium in the gut and oral  
1214 calcium trisodium pentetate was more effective in removing ingested plutonium from the intestines,  
1215 liver and carcass than parenteral administration. Oral calcium trisodium pentetate also reduced deposits

1216 in the liver and skeleton after injection of plutonium but was not as effective as intraperitoneal calcium  
1217 trisodium pentetate (Sullivan & Ruemmler, 1986).

1218

1219 The effect of zinc trisodium pentetate was examined in mice exposed to plutonium-237 during  
1220 pregnancy. Female mice were given intraperitoneal injections of plutonium-237 at various stages of  
1221 gestation followed by subcutaneous zinc trisodium pentetate (300  $\mu\text{mol/kg}$ ) starting 10 minutes later.  
1222 Mothers and young were sacrificed shortly afterwards. Treatment with zinc trisodium pentetate  
1223 significantly reduced the body burden of plutonium-237 in both the mothers and the fetuses with no net  
1224 increase in the transfer of plutonium-237 to the unborn young (Lloyd et al., 1985a).

1225

1226 The effect of chelation therapy on the risk of cancer from plutonium-239 exposure has been evaluated  
1227 in mice. The animals were given intraperitoneal plutonium-239 at 10 weeks of age and then treatment  
1228 with subcutaneous zinc trisodium pentetate (37  $\mu\text{mol/kg}$ ) was started 3 days later for 2 weeks (daily  
1229 dosing), 2 months (daily for 2 weeks then 3 times weekly) or 1 year (daily dosing for 2 weeks, 3 times  
1230 weekly for 6 weeks then once weekly). The mice were followed for life and examined for bone  
1231 sarcoma. Both the skeletal dose and bone sarcoma risk were reduced by zinc trisodium pentetate  
1232 therapy. The incidence of bone sarcoma in mice given zinc trisodium pentetate was generally below  
1233 the dose-response curve for control mice (i.e. compared to controls, treated mice with higher skeletal  
1234 retention of plutonium had a lower incidence and delayed onset of bone sarcoma). It appeared that the  
1235 risk of cancer was reduced more than that corresponding to the decreased skeletal dose, suggesting that  
1236 zinc trisodium pentetate preferentially removes plutonium from the areas of bone commonly associated  
1237 with cancer such as the bone surface (Jones et al., 1986). A study in dogs also examined the risk of  
1238 cancer and the effect of chelation therapy. Control dogs died of osteocarcinoma between 1267 and  
1239 1594 days after intravenous injection of plutonium-239. Dogs given weekly subcutaneous injections of  
1240 calcium trisodium pentetate (30  $\mu\text{mol/kg}$ ) starting 2 hours after plutonium also died of osteocarcinoma  
1241 between 1462 and 1783 days. Dogs given daily subcutaneous injections of zinc trisodium pentetate (30  
1242  $\mu\text{mol/kg}$ ) starting 2 hours after plutonium had a mean survival time of 3520 days or 2.1 times that of the  
1243 dogs receiving calcium trisodium pentetate. Daily treatment with zinc trisodium pentetate reduced the  
1244 body burden of plutonium more efficiently than calcium trisodium pentetate and prevented deposition  
1245 of plutonium on bone surfaces (Bruenger et al., 1991).

1246

1247 Phan et al. (2004; 2006a; 2006b) have investigated the efficacy of pentetic acid encapsulated in  
1248 liposomes on plutonium decorporation. After intravenous plutonium-239 phytate, pentetic acid (6  
1249  $\mu\text{mol/kg}$ ) in liposomes was as effective as free pentetic acid (30  $\mu\text{mol/kg}$ ) in maintaining the plutonium  
1250 content of the femur below 4.3% of the injected dose after 16 days (Phan et al., 2004). In another  
1251 study rats were given various plutonium-238 phytate salt solutions by intravenous injection followed 1  
1252 hour later by a single injection of pentetic acid (3.2  $\mu\text{mol/kg}$ ) in stealth liposomes of 100 nm diameter.  
1253 This increased urinary plutonium excretion to over 90% of the injected dose and was able to reduce the  
1254 liver and skeleton burden even 30 days after a single dose. A dose of 0.3  $\mu\text{mol/kg}$  produced the same  
1255 reduction in skeletal burden as four injections of the free pentetic acid (30  $\mu\text{mol/kg}$ ) (Phan et al.,  
1256 2006b).

1257

1258 An *in vitro* study using a crystalline bone mineral surrogate, calcium hydroxyapatite, showed that zinc  
1259 trisodium pentetate only removed 0.086% of the bound plutonium-238 (Guilmette et al., 2003).

1260

1261 See also section 8.1.1.1 for studies of involving both plutonium and its daughter element americium.

1262

### 1263 **8.1.22 Polonium (Po)**

1264

1265 There is limited information on the use of pentetic acid in polonium exposure but it appears to be  
1266 ineffective.

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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 as that observed with some of the other antidotes (unithiol, D-penicillamine and 2-mercaptopyrionylglycine) (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 sacrificed 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

1318 strontium nitrate (3.78 mmol/kg) was the most effective agent at increasing urinary excretion of  
1319 strontium in mice. It did not increase faecal excretion. Calcium trisodium pentetate was also one of the  
1320 most effective agents at reducing tissue concentrations of strontium, particularly in the liver, kidney and  
1321 brain but not in bone (Ortega et al., 1989).

1322  
1323 In another study intraperitoneal calcium trisodium pentetate (615 mg/kg twice daily for 10 days) did not  
1324 cause significant increases in urinary or faecal excretion of strontium in mice when started 10 minutes  
1325 after subcutaneous strontium nitrate (95 mg/kg) administration. In tissues it only significantly  
1326 decreased the strontium concentration in kidney but not bone, liver or muscle (Colomina et al., 1991).

1327  
1328 Intraperitoneal calcium trisodium pentetate (2740 mg/kg twice daily for 5 days) resulted in significant  
1329 decreases in urinary and faecal excretion in mice when started 24 minutes after subcutaneous strontium  
1330 nitrate (95 mg/kg) administration. Calcium trisodium pentetate also significantly increased the blood  
1331 concentration of strontium but had no effect on the strontium concentration of other tissues (Llobet et  
1332 al., 1992).

1333  
1334 Mice given pentetic acid immobilised on cellulose and incorporated into white wheat flour dough had  
1335 reduced gastrointestinal uptake of strontium-85, calcium-47 and radium-226. The pentetic acid was  
1336 given for 24 hours prior to ingestion of the isotopes and 48 hours after dosing (Bulman et al., 1983).

### 1337 1338 **8.1.27 Thorium (Th)**

1339  
1340 Pentetic acid salts are partially effective in the removing thorium from the body (Stradling et al.,  
1341 1991). Decorporation of thorium remains a problem (Stradling et al., 1998) and a more effective  
1342 antidote agent is needed. Zinc trisodium pentetate is less effective than calcium trisodium pentetate  
1343 (Peter-Witt & Volf, 1985; Stradling et al., 1991), but when treatment is delayed they are equally  
1344 effective (Peter-Witt & Volf, 1985).

#### 1345 1346 **Inhaled thorium**

1347 Intraperitoneal calcium trisodium pentetate (30 µmol/kg) at 30 minutes, 6 hours, 0.25, 1, 2 and 3  
1348 days after inhalation of thorium-230 and 232 in rats did not appreciably enhance elimination of  
1349 thorium. It did decrease the thorium content of the liver and kidneys but these tissues only  
1350 contained a minor proportion of the thorium in the whole body. In animals given the same  
1351 treatment regimen and then calcium trisodium pentetate twice weekly from day 6 to 28 (so 12  
1352 injections) there was a further reduction in the retention of thorium in the body but it was still two  
1353 thirds that of controls. Another study investigated the effect of high doses of chelator. A single  
1354 dose of 300 or 1000 µmol/kg calcium or zinc trisodium pentetate or repeated dosing (300 µmol/kg  
1355 over three days) was no more effective at removing thorium than repeated treatment with 30  
1356 µmol/kg. A delay of only a day in administration markedly reduced the effectiveness of 1000  
1357 µmol/kg calcium trisodium pentetate. After intratracheal administration of thorium-234 the amount  
1358 in the lungs at 7 and 28 days after repeated dosing with 300 µmol/kg was still about one-half or  
1359 more of the controls (Stradling et al., 1991).

#### 1360 1361 **Parenteral thorium**

1362 Peter-Witt & Volf (1985) compared the efficacy of zinc and calcium trisodium pentetate in removing  
1363 thorium-234 in rats. The chelators were given by intraperitoneal or subcutaneous injection 1.5 minutes  
1364 after intravenous thorium. Calcium trisodium pentetate was more effective than zinc trisodium  
1365 pentetate over the whole dose range used (30 to 1000 µmol/kg). In the skeleton, for example, 1000  
1366 µmol/kg of zinc trisodium pentetate removed as much thorium as 30 µmol/kg of calcium trisodium  
1367 pentetate. Prompt administration of calcium trisodium pentetate reduced the thorium content of the  
1368 skeleton by 70% but when delayed by 6 hours or 4 days the thorium content was only reduced by 20%

1369 and 10%, respectively. The end effect of chelation depended on the time post-exposure it was initiated  
1370 and the number of doses. Early and repeated dosing was most effective.

1371

1372 Mice were given intraperitoneal thorium-234 followed by intramuscular calcium trisodium pentetate  
1373 (1.4 mmol/kg) for 3 consecutive days starting 3 minutes or 3 days later. The mice were killed at 4 or 8  
1374 days after thorium injection, respectively. With early treatment calcium trisodium pentetate  
1375 significantly reduced the tissue and body burden of thorium-234 and most was excreted within the first  
1376 24 hours. The whole body radioactivity was reduced by 72%, and the radioactivity of the bone and  
1377 liver was 50% and 8% of untreated controls. However, calcium trisodium pentetate did not reduce  
1378 thorium-induced lipid peroxidation in bone marrow (as measured by concentrations of  
1379 malondialdehyde). With delayed treatment calcium trisodium pentetate reduced thorium retention in  
1380 the body by 18%, liver by 23% and the femur by 28%. It did not prevent an increase in  
1381 malondialdehyde concentrations in bone but did reduce the concentrations in the liver (Chen et al.,  
1382 2005).

1383

1384 The effectiveness of calcium trisodium pentetate was evaluated in rats injected with monomeric (ionic)  
1385 and polymeric (colloidal) thorium-234. In the first study intraperitoneal calcium trisodium pentetate  
1386 (370 mg/kg) was given 2, 5, 6 and 7 days after intravenous thorium and the rats killed on the 8th day.  
1387 Most of the thorium was present in the skeleton with little in the soft tissues. Calcium trisodium  
1388 pentetate reduced the skeletal thorium retention to 43% of the injected dose. Urinary concentrations of  
1389 thorium were also increased with calcium trisodium pentetate, particularly after the first dose; thereafter  
1390 the effect diminished. In a second study rats were given intravenous polymeric thorium-234 followed  
1391 by calcium trisodium pentetate 330 mg/kg/day on days 3 to 6 and killed on day 7 or 660 mg/kg twice  
1392 daily on days 8 to 11 and were killed on day 16. Thorium in this form deposited mainly in the liver and  
1393 treatment with calcium trisodium pentetate at the lower dose had no effect on distribution and only  
1394 slightly increased urinary excretion. The higher dose of calcium trisodium pentetate reduced the liver  
1395 content of thorium from 53% to 40% of the injected dose and increased urinary excretion to 11%  
1396 compared to 0.4% in controls (Fried & Schubert, 1961).

1397

### 1398 **Simulated wound**

1399 The efficacy of calcium trisodium pentetate on the removal of thorium-234 from a simulated wound has  
1400 also been investigated. Rats were given an intramuscular injection of thorium-234 and 1 hour later  
1401 were treated with calcium trisodium pentetate as a single intramuscular injection around the site (local  
1402 treatment), five daily subcutaneous injections (systemic treatment) or one intramuscular injection  
1403 followed by 4 daily subcutaneous injections (combined treatment). The animals were killed at 7 days.  
1404 Combined local and systematic treatment with calcium trisodium pentetate was equally or more  
1405 effective than each of the treatments alone in reducing the retention of thorium-234 at the injection site  
1406 and in the organs. The thorium retention was about 60 to 70% less than controls with combined  
1407 treatment compared to 40% less with systemic treatment alone (Peter-Witt & Volf, 1984). In another  
1408 study rats were given intramuscular thorium-232 and 234 followed immediately by calcium  
1409 trisodium pentetate (0.1, 0.2, or 0.4 mmol/kg) injected around the wound site with or without citric  
1410 acid. Calcium trisodium pentetate was more effective when given with citric acid; by day 2 whole  
1411 body radioactivity decreased to 30.5% of the initial value and the wound site retained 23.6%. With  
1412 calcium trisodium pentetate or citric acid alone the whole body retention was 47% and 79%  
1413 respectively. Immediate treatment with calcium trisodium pentetate was more effective than  
1414 treatment with calcium trisodium pentetate and citric acid starting 24 hours after exposure (Rencová  
1415 et al., 2003).

1416

1417 In a study of antidotes in simulated wound contamination thorium-238 was given by subcutaneous  
1418 or intramuscular injection to rats. Subcutaneous calcium trisodium pentetate (30  $\mu$ mol/kg) was  
1419 given at 30 minutes close to the wound site followed by intraperitoneal zinc trisodium pentetate (30

1420  $\mu\text{mol/kg}$ ) at 6 and 24 hours. When calcium trisodium pentetate was given after 30 minutes the  
1421 thorium retention was only reduced to 79% of controls. The removal of thorium was mainly  
1422 through the local administration of chelating agents and repeated dosing by intraperitoneal injection  
1423 had a minimal effect. A delay in administration markedly decreased efficacy; when given at 6  
1424 hours and 1 day after thorium injection the thorium retention increased to 90 and 95% of controls,  
1425 respectively. The optimal treatment with calcium trisodium pentetate was subcutaneous injection  
1426 around the wound site at 30 minutes followed by intraperitoneal injection at 6 hours and on days 1,  
1427 2 and 3. This regime reduced the body content of thorium-238 to 80% of controls after  
1428 subcutaneous injection and 54% after intramuscular injection (Stradling et al., 1995).

### 1429 **8.1.28 Uranium (U)**

1430 There is no effective chelating agent for removal of uranium (Stradling, 1998). Several studies have  
1431 shown that pentetic acid is relatively ineffective in reducing the uranium body burden (Domingo et  
1432 al., 1989; Ortega et al., 1989; Domingo et al., 1990; Domingo et al., 1997; Ramounet-Le Gall et al.,  
1433 2003).

1434 In a study comparing 16 antidotes mice were given the antidote (at one quarter of the  $\text{LD}_{50}$   
1435 subcutaneously) 10 minutes after subcutaneous injection of uranyl dihydrate (2.15 to 464 mg/kg).  
1436 Although calcium trisodium pentetate effectively increased survival there was no increased urinary or  
1437 faecal excretion of uranium and it failed to reduce tissue concentrations. In bone there was a significant  
1438 increase in uranium concentrations (Ortega et al., 1989).

1439 Mice received 12 subcutaneous injections of uranyl acetate dehydrate (8 mg/kg) on alternate days  
1440 followed one day after the last dose by various chelators (at one quarter of their  $\text{LD}_{50}$ ) for 5 days.  
1441 Intraperitoneal calcium trisodium pentetate only decreased the uranium concentration in the liver; there  
1442 was no effect on the kidney concentration. In addition it did not increase faecal excretion of uranium  
1443 and significantly reduced uranium excretion in urine on days 3, 4 and 5 (Domingo et al., 1989).

1444 Intraperitoneal calcium trisodium pentetate had no beneficial effects on the parameters of uranium  
1445 toxicity in a study examining the effect of time of chelator administration. The antidotes were given 0,  
1446 0.25, 1, 4 and 24 hours after subcutaneous uranyl acetate dehydrate (10 mg/kg) (Domingo et al., 1990).

1447 Calcium trisodium pentetate was investigated for its effect on uranium nephrotoxicity in rats. The rats  
1448 were given subcutaneous uranyl acetate dihydrate (5 mg/kg) followed by intraperitoneal calcium  
1449 trisodium pentetate (250, 500 or 1000 mg/kg) at 0, 24, 48 and 72 hours. Calcium trisodium pentetate  
1450 showed a similar effect to Tiron in protecting against uranium nephrotoxicity although the increase in  
1451 creatinine clearance was more pronounced with calcium trisodium pentetate. In contrast calcium  
1452 trisodium pentetate was less effective at increasing uranium urinary excretion and reducing  
1453 accumulation in bone (Domingo et al., 1997).

1454 An *in vitro* study using a kidney proximal tubule cell line (LLC-PK<sub>1</sub>) demonstrated that pentetic acid  
1455 increased the cytotoxicity of uranium (Muller et al., 2006). An *in vivo* study in rats given calcium  
1456 trisodium pentetate (30  $\mu\text{mol/kg}$ ) at 2 minutes and zinc trisodium pentetate (30  $\mu\text{mol/kg}$ ) at 24 hours  
1457 after intraperitoneal injection of uranium (57, 147 or 639  $\mu\text{g/kg}$ ) found no additive effect on uranium  
1458 toxicity (Houpert et al., 2003).

### 1459 **8.1.29 Vanadium (V)**

1460 Although calcium trisodium pentetate can increase survival after low dose vanadium exposure, increase  
1461 excretion and reduce tissue concentrations in some organs it is not the most effective antidote for  
1462

1471 vanadium intoxication (Hansen et al., 1982; Jones & Basinger, 1983; Domingo et al., 1985; Domingo et  
1472 al., 1986; Domingo et al., 1990).

1473

1474 Intraperitoneal calcium trisodium pentetate (400 mg/kg) increased survival in mice when given 20  
1475 minutes after intraperitoneal administration of sodium orthovanadate or vanadyl sulphate (at doses  
1476 corresponding to their LD<sub>90-95</sub>) (Jones & Basinger, 1983). In another study intraperitoneal calcium  
1477 trisodium pentetate reduced mortality in mice when given immediately after intraperitoneal  
1478 administration of a low dose of sodium metavanadate (0.33 mmol/kg) but was ineffective after a high  
1479 dose (0.61 mmol/kg) (Domingo et al., 1985). Similarly, intraperitoneal calcium trisodium pentetate  
1480 (12.5 mmol/kg) only reduced mortality in mice after a low dose of sodium metavanadate (0.3  
1481 mmol/kg). Although calcium trisodium pentetate increased faecal concentrations of vanadium there  
1482 was no increase in urinary vanadium concentrations. It reduced the vanadium concentration in the  
1483 kidney and the heart but not the liver; calcium trisodium pentetate also protected against the  
1484 histopathological changes in the kidneys (Domingo et al., 1986).

1485

1486 In rats the vanadium content of the kidney was reduced by 7%, increased in the liver by 15% and  
1487 unchanged in the lungs with intraperitoneal calcium trisodium pentetate (30 µmol/kg) given 24 hours  
1488 after intraperitoneal administration of sodium metavanadate (5 µmol/kg). After 100 µmol/kg of  
1489 calcium trisodium pentetate the vanadium content was reduced by 9% in the kidney, 18% in the liver  
1490 and 25% in the lung, but calcium trisodium pentetate was not as effective as deferoxamine at the higher  
1491 dose. The vanadium concentration in the faeces was increased by the low dose of calcium trisodium  
1492 pentetate concentration and both urinary and faecal vanadium concentrations increased with the higher  
1493 dose of chelator. In addition calcium trisodium pentetate was more effective at removing tetravalent  
1494 vanadium than pentavalent vanadium from tissues (Hansen et al., 1982).

1495

1496 Intraperitoneal calcium trisodium pentetate (1553 mg/kg) increased survival in mice when given 10  
1497 minutes after intramuscular vanadyl sulphate (215-4640 mg/kg) but resulted in no significant increase  
1498 in urinary or faecal excretion of vanadium. It significantly decreased the vanadium concentration in the  
1499 liver (27%), spleen and heart but not the kidney (Domingo et al., 1990).

1500

1501 Pentetic acid decreased the death rate in chick eggs incubated with vanadyl sulphate but was  
1502 ineffective against sodium metavanadate. It had no significant effect on body weight reductions, or  
1503 reduction in weights of legs and toes in chick eggs incubated with vanadium (Hamada, 1994).

1504

1505 An *in vitro* study using human erythrocytes found that calcium trisodium pentetate was able to prevent  
1506 uptake of vanadium when added simultaneously to the cell medium. When added 2 hours after  
1507 vanadium, calcium trisodium pentetate caused a small reduction in the vanadium concentration and  
1508 prevented further increases in the vanadium concentrations in cells (Hansen et al., 1982).

1509

### 1510 **8.1.30 Ytterbium (Yb)**

1511

1512 There is limited information on the use of pentetic acid in ytterbium exposure although it appears to be  
1513 effective.

1514

1515 Rats were injected intravenously with either a colloidal form or a soluble citrate of ytterbium-169,  
1516 followed 24 hours later by intravenous calcium or zinc trisodium pentetate (14 mg/kg) as the free salt or  
1517 in liposomes. With zinc trisodium pentetate the highest rate of ytterbium-169 removal from tissues  
1518 occurred during the first two days with both the free or liposomal form. After this time the removal rate  
1519 of ytterbium was only slightly higher in animals given zinc trisodium pentetate compared to controls.  
1520 The liposomal encapsulated forms of the chelator were more effective than the free salts, particularly in  
1521 removing colloidal ytterbium-169. A second injection of liposomal zinc trisodium pentetate given 8

1522 days after the initial dose was not as effective in removing ytterbium as a second injection of the free  
1523 chelator. Calcium trisodium pentetate, as the free or liposomal preparation, was more effective than  
1524 zinc trisodium pentetate in removing colloidal ytterbium (Blank et al., 1984).

1525

1526 In comparing liposomal-bound and free zinc trisodium pentetate rats were treated with intravenous zinc  
1527 trisodium pentetate (14 mg/kg) 24 hours after intravenous ytterbium-169 citrate. Both forms of zinc  
1528 trisodium pentetate caused increased removal ytterbium from the body (3-4 times more than in  
1529 controls) but the liposomal-bound form was more effective. Both forms of zinc trisodium pentetate  
1530 were most effective within the first 48 hours (Blank et al., 1980).

1531

1532 Pregnant rats received ytterbium-169-pentetic acid complex by intravenous injection one day before  
1533 they were expected to give birth and then on days 2, 9 and 16 after birth. Between 2 and 20% of the  
1534 administered dose of ytterbium-169 passed in the milk to the newborn during lactation but this was  
1535 reduced to 0.2 to 0.9% when the ytterbium-169 was given as a pentetic acid complex. The quantity  
1536 of ytterbium-169 passed with the milk to the whole litter after each injection ranged from 1 to 10%  
1537 of the injected dose but this was reduced to 0.3 to 0.6% with the pentetic acid complex  
1538 (Bałtrukiewicz et al., 1976).

1539

### 1540 **8.1.31 Yttrium (Y)**

1541

1542 There is limited information on the use of pentetic acid in yttrium exposure although it appears to be  
1543 effective.

1544

1545 The efficacy of calcium trisodium pentetate was investigated in rats with puncture wounds  
1546 contaminated with yttrium-90. The yttrium-90 solution (2.55 MBq/kg) was injected intramuscularly in  
1547 the left femoral quadriceps to a depth of 5 mm. This was followed 15 minutes later by calcium  
1548 trisodium pentetate (34.7  $\mu$ mol/kg) given intravenously in the tail vein or by intramuscular infiltration  
1549 into the wound site. Intravenous calcium trisodium pentetate significantly reduced the radioactivity at  
1550 the wound site by up to 76% and in bone by up to 84% compared to controls. In contrast the  
1551 radioactivity in the kidneys increased over 24 hours and then fell to a similar level as the controls.  
1552 Intramuscular calcium trisodium pentetate reduced the radioactivity at the wound site by up to 35% and  
1553 in bone by up to 52%. There was no change in the radioactivity of liver or blood with either route of  
1554 dosing. Prompt, local treatment with calcium trisodium pentetate is more effective in reducing  
1555 radioactivity at the wound site than systemic treatment (Watanabe et al., 2005).

1556

### 1557 **8.1.32 Zinc (Zn)**

1558

1559 Pentetic acid is an effective antidote for acute zinc toxicity (Basinger & Jones, 1981b; Domingo et al.,  
1560 1988; Llobet et al., 1988; Llobet et al., 1989).

1561

1562 In mice given intraperitoneal zinc acetate (0.49 mmol/kg, the LD<sub>50</sub>) calcium trisodium pentetate (2:1  
1563 or 5:1 molar ratios of antidote to metal) was one of the most effective of the six antidotes tested, as  
1564 measured by percentage survival (Llobet et al., 1988).

1565

1566 In a comparison of several antidotes against the effects of acute intraperitoneal zinc intoxication in  
1567 mice, calcium trisodium pentetate efficiently reduced acute lethality. Intraperitoneal calcium  
1568 trisodium pentetate (10:1 antidote:zinc ratio) was given 20 minutes after a fatal dose of zinc (50  
1569 mg/kg) was administered. Survival was 86.7% with calcium trisodium pentetate but other antidotes  
1570 were equally or slightly more effective (Basinger & Jones, 1981b).

1571

1572 In a study comparing the efficacy of several antidotes mice were given intraperitoneal zinc acetate

1573 (66-330 mg/kg; LD<sub>50</sub> 108 mg/kg). Antidotal therapy was given 10 minutes later. Intraperitoneal  
1574 calcium trisodium pentetate (1569 mg/kg) was one of the most effective antidotes and prevented  
1575 death even at the highest dose of zinc (Domingo et al., 1988).  
1576

1577 After intravenous injection of zinc chloride (2.2 µmol/kg) in mice followed immediately by one of  
1578 several antidotes (at a zinc:chelator ratio of 1:10) calcium trisodium pentetate was the most  
1579 effective agent at reducing the body burden of zinc (Eybl et al., 1985).  
1580

1581 In mice calcium trisodium pentetate (4.2 mmol/kg) was given at 0.25, 0.5, 2, 12 or 24 hours after  
1582 intraperitoneal zinc acetate dihydrate (0.49 mmol/kg). Treatment with calcium trisodium pentetate  
1583 significantly increased the urinary excretion of zinc in all groups particularly when given 0.5 hours after  
1584 zinc administration. Faecal zinc excretion was significantly increased in all groups except when given  
1585 24 hours after the zinc. Calcium trisodium pentetate significantly decreased the zinc concentration in  
1586 liver and bone but not in spleen, heart or kidney (Llobet et al., 1989).  
1587

1588 In rats given intravenous zinc-65 at various stages of pregnancy and treated with an antidote 6  
1589 hours later zinc trisodium pentetate caused a 27 to 40% decrease in zinc-65 retention compared to  
1590 controls; calcium trisodium pentetate was less effective and resulted in a decrease of only 14 to  
1591 26%. In the fetuses, placentae and whole fetoplacental unit zinc trisodium pentetate was more  
1592 effective at reducing zinc-65 retention than calcium trisodium pentetate. Both compounds caused a  
1593 rise in the zinc concentration in the yolk sacs but overall treatment with an antidote reduced  
1594 radiation exposure in the fetuses (Żylicz et al., 1975).  
1595

## 1596 **8.2 Pharmacokinetics**

1597  
1598 In rats administered <sup>14</sup>C-labelled zinc trisodium pentetate by intraperitoneal injection about 75% was  
1599 excreted within the first 4 hours (Harmuth-Hoene et al., 1966). In rats administered <sup>14</sup>C-labelled  
1600 pentetic acid 95% of the radioactivity was excreted by the urine within 24 hours, 0.5% by the faeces  
1601 and 0.7-1.3% by expired carbon dioxide. It seems likely that metabolic decomposition takes place in  
1602 the kidneys (Havlicek et al., 1968).  
1603

1604 In another study, rats received intravenous <sup>14</sup>C-labelled pentetic acid and rapidly eliminated the carbon-  
1605 14 with 84% in the urine and 10% in the faeces during the first 24 hours. After direct administration of  
1606 <sup>14</sup>C-labelled pentetic acid solution into the lungs 75% was excreted in the urine and 25% in the faeces.  
1607 Tissue concentrations of carbon-14 were less than 1% of the administered dose at 24 hours (Crawley &  
1608 Haines, 1979).  
1609

1610 In rats only a very small proportion (0.12%) of calcium trisodium pentetate is excreted in bile by 24  
1611 hours after intravenous injection (Bhattacharyya & Peterson, 1979).  
1612

1613 The pharmacokinetics of pentetic acid can be modified by encapsulation in liposomes and recent  
1614 studies have demonstrated the potential of liposome-encapsulated pentetic acid in plutonium  
1615 decorporation (Phan et al., 2004; 2005; 2006a; 2006b). Liposome-encapsulated pentetic acid was able  
1616 to reach deposits of plutonium in the liver and bone. The pentetic acid penetrated the liver in larger  
1617 quantities than free pentetic acid and had a longer half-life, with the liver and the spleen acting as  
1618 reservoirs (Phan et al., 2004; Phan et al., 2005). Free pentetic acid was undetectable in plasma at 4  
1619 hours but encapsulated pentetic acid was still quantifiable at 24 and 48 hours after intravenous injection  
1620 (Phan et al., 2005).  
1621

## 1622 **8.3 Toxicology**

1623

### 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 (hydroxyethylethylenediaminetriacetic acid [HEDTA], ethylenediaminetetraacetic acid [EDTA], pentetic acid and cyclohexanediaminetetraacetic 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 impair 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<sub>50</sub> of pentetic acid is 587 mg/kg (1.49 mmol/kg) in rats (Srivastava et al., 1986) and for calcium trisodium pentetate the LD<sub>50</sub> 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<sub>50</sub> 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

1675 intramuscularly on days 3, 6, 9, 13, 16, 20, 23 and 26. There were no changes in liver or renal function  
1676 tests or biopsies (Fritsch et al., 1994).

1677

1678 In rats given calcium trisodium pentetate toxicity varied with the dose regimen. Lethality was  
1679 increased in rats given calcium trisodium pentetate in 5 intraperitoneal injections compared to those  
1680 given the same dose in 1 or 2 injections. For example, animals given 5 intraperitoneal injections 2  
1681 hours apart for 5 days had increased lethality compared to 2 injections 8 hours apart for 5 days.  
1682 Animals developed diarrhoea on the second day with congestion of mucous membranes and  
1683 conjunctiva and apathy. Death occurred from day 4 onwards. Post-mortem examination showed  
1684 congested intestines, haemorrhages of the intestines, lungs and sometimes the liver, with hyperaemic  
1685 kidneys. All rats receiving 5 injections of zinc trisodium pentetate daily for 5 days survived 30 days  
1686 without clinical signs (Planas-Bohne & Ebel, 1975).

1687

1688 In dogs subcutaneous calcium trisodium pentetate (22.5 to 24.6  $\mu\text{mol/kg}$  daily for 8 days) caused mild  
1689 anorexia, diarrhoea and occasional vomiting with rapid recovery after cessation of treatment. In  
1690 contrast, 5.8  $\mu\text{mol/kg}$  every 5 hours was fatal in all three dogs within 3 to 9 days. These animals  
1691 developed inappetance, diarrhoea, vomiting, melaena, abdominal tenderness, polydipsia, proteinuria  
1692 and haematuria. There was no liver damage. The most prominent gross findings on post-mortem  
1693 examination were haemorrhages in the gastrointestinal tract, particularly the duodenum and proximal  
1694 jejunum, and blood in the lumen. Subcutaneous zinc trisodium pentetate 9.2 to 9.7  $\mu\text{mol/kg}$  every 5  
1695 hours for 19 days caused only mild diarrhoea with subclinical melaena and haematuria (Taylor et al.,  
1696 1974).

1697

### 1698 **8.3.3 Chronic toxicity**

1699

1700 The relative safety of zinc trisodium pentetate is also confirmed by the investigation of Jones et al.  
1701 (1989). Long-term dosing with zinc trisodium pentetate (33  $\mu\text{mol/kg}$  daily or 415 to 3946 days) did not  
1702 result in significant depletion of chromium, copper, manganese or molybdenum in liver or bone in  
1703 beagles.

1704

### 1705 **8.3.4 Reproductive toxicology and teratogenicity**

1706

1707 In a toxicity study pregnant mice were given subcutaneous calcium trisodium pentetate (0.36 or 2.9  
1708 mmol/kg) daily until the offspring were 13 days old. There were no viable offspring from mice  
1709 receiving 2.9 mmol/kg calcium trisodium pentetate. There was only one fetus and this was dead at  
1710 birth but appeared grossly normal. With the lower dose fecundity, fetal development and growth rates  
1711 were normal but this may have been due to the presence of 58  $\mu\text{g}$  of zinc/g of diet (Fisher et al., 1975).

1712

1713 Increased fetal lethality and congenital malformations were observed in mice given calcium trisodium  
1714 pentetate. Mated female mice received five daily subcutaneous injections of 720 to 2,880  $\mu\text{mol/kg}$  of  
1715 calcium trisodium pentetate on days 2 to 6, 7 to 11 or 12 to 16 of gestation and were killed on day 18.  
1716 Fetal lethality was greater in the early and mid-gestation periods and the frequency of gross  
1717 malformations increased with increasing dose (Fisher et al., 1976).

1718

1719 These effects are caused by zinc deficiency and can be compared to the reproductive toxicity observed  
1720 with sodium edetate. Sodium edetate impairs reproduction and results in malformations but  
1721 simultaneous supplement with zinc prevents these effects (Swenerton & Hurley, 1971).

1722

1723 Zinc trisodium pentetate is safer than calcium trisodium pentetate in pregnancy. This salt did not cause  
1724 any malformations even at high doses in rats (Bömer, 1971) and mice (Fisher et al., 1975; Brummett &  
1725 Mays, 1977; Calder et al., 1979).

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### 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 *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  $\mu\text{g/mL}$  of the culture medium). Both the other two concentrations tested (0.135 and 1.351  $\mu\text{g/mL}$ ) 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  $\mu\text{g/mL}$  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  $\mu\text{g/mL}$ ) (Prosser, 1978).

In cultured human lymphocytes from 3 females, *in vitro* exposure to calcium trisodium pentetate (in concentrations as low as 10  $\mu\text{g/mL}$ ) 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  $\mu\text{g/mL}$ . 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  $\mu\text{g/mL}$ . Neither calcium nor zinc trisodium pentetate induced two-break aberrations in human lymphocytes. This study concluded that samples for cytogenetic 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

1777 inhaled americium-241 oxide or nitrite in hamsters (Stradling et al., 1984). Puchel was as effective as  
1778 calcium trisodium pentetate and the effect was not enhanced when both chelators were given together  
1779 for removal of thorium-234, plutonium-238 or 239 or americium-241 from the liver and bone of  
1780 hamsters and rats (Volf & Peter, 1984).

1781  
1782 Puchel was marginally more effective than zinc trisodium pentetate in removing plutonium-238  
1783 from the lungs in hamsters but produced adverse effects including inflammatory lung changes and  
1784 pnemonitis when given as an aerosol, and liver damage when given intraperitoneally (Stather et al.,  
1785 1982).

1786  
1787 *In vitro* studies using rat liver cytosol demonstrated that puchel does not remove cadmium from the  
1788 metallothionein complex (Planas-Bohne & Lehman, 1983; Rau et al., 1987). Although *in vitro*  
1789 studies have demonstrated that puchel can lower the body burden of cadmium by reducing the liver  
1790 (Rau et al., 1987) and kidney concentrations (Planas-Bohne & Lehman, 1983) its toxicity is too  
1791 great for it to be considered a chelator for use in humans (Rau et al., 1987). The LD<sub>50</sub> for puchel is  
1792 far lower than that of pentetic acid salts (Ellender et al., 1984).

1793  
1794 In summary, puchel is more toxic than pentetic acid salts and for removal of radionuclides puchel has  
1795 no advantage over the calcium and zinc salts of pentetic acid.

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## 1798 **9 Volunteer studies**

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### 1800 **9.1 Pharmacokinetics**

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#### 1802 **9.1.1 Intravenous injection**

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1804 Calcium trisodium pentetate is rapidly eliminated. By two hours after intravenous injection of 10 to 15  
1805 mg 30 to 40% was cleared, 50 to 70% by 4 hours and another 15 to 20% in the following 4 hours. By  
1806 24 hours 90 to 100% is eliminated (Stevens et al., 1962; Stather et al., 1983).

1807

1808 Elimination of intravenously administered pentetic acid salts is entirely via the urine; none is detected  
1809 in the faeces. Plasma levels of radioactivity after intravenous injection of radiolabelled calcium  
1810 trisodium pentetate averaged 10% of the dose at 1 hour and decreased rapidly thereafter. No  
1811 radioactivity was detected in plasma at 2 hours (Stevens et al., 1962).

1812

1813 After intravenous injection plasma retention of calcium trisodium pentetate could be expressed as three  
1814 components with half-lives of 1.4 minutes (60%), 14.3 minutes (20%) and 95 minutes (20%) (Stather et  
1815 al., 1983).

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#### 1817 **9.1.2 Oral**

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1819 Pentetic acid is very poorly absorbed from the gastrointestinal tract. After ingestion of radiolabelled  
1820 pentetic acid (3 or 50 mg) 95 to 100% was recovered in the faeces within 2 to 5 days and the rest was  
1821 excreted in urine. Radioactivity was not detected in the blood at any time (Stevens et al., 1962).

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#### 1823 **9.1.3 Inhalation**

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1825 When radiolabelled calcium trisodium pentetate was nebulised about 60% of the radioactivity was  
1826 retained by the equipment. Of 170 mg of calcium trisodium pentetate inhaled about 5% was exhaled,  
1827 2% was retained in the mouth, 24% excreted in the faeces and 69% in the urine (Stather et al., 1983).

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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  $\mu$ Ci 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

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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 yttrium-90 was studied in seven volunteers (aged 51 to 75 years). They were given intravenous injections of a tracer dose of yttrium-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 yttrium-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

1930 tests in a randomised, double-blind study of 54 patients with contact dermatitis to metals. Each of the  
1931 test metals was applied to two areas of skin that were untreated or pre-treated with calcium trisodium  
1932 pentetate and vehicle. Four control areas of skin were also treated with calcium trisodium pentetate and  
1933 vehicle or vehicle alone. The test substance was applied 10 minutes after application of the calcium  
1934 trisodium pentetate cream. Even in patients with positive patch tests the severity of the reaction was  
1935 reduced. This cream reduced allergic skin reactions to nickel, cobalt and copper but not to chromium  
1936 and palladium (Wöhrl et al., 2001).

## 11 Case reports

### 11.1 Americium

1943 Pentetic acid is useful in the treatment of americium exposure and has been used in several cases,  
1944 although it is relatively ineffective in removing americium from bone.

1946 **1976 Hanford americium incident:** A 64-year-old male was injured in an explosion involving nitric  
1947 acid, resin beads, metal, glass, plastic and other debris all contaminated with americium-241, resulting  
1948 in deposition in excess of 6 mCi mainly on the face and by inhalation. The victim suffered acid burns  
1949 and trauma from the explosion and had contaminated foreign body material embedded in the face, ears  
1950 and back (Breitenstein, 1983). An estimated 5-6 mCi was removed on the first day following on-site  
1951 decontamination and then intensive decontamination. For 2 months the victim received daily  
1952 decontamination baths where calcium trisodium pentetate was applied and washed off. The skin was  
1953 also scrubbed, and embedded material removed as it reached the skin surface (Jech et al., 1983).  
1954 Repeated intravenous dosing with pentetic acid salts over 3 years appeared to prevent systemic  
1955 retention of americium cleared from wound sites. Americium deposited in bone and liver prior to  
1956 pentetic acid treatment (started 2.5 hours post-exposure) was cleared quickly from the liver but  
1957 relatively slowly from bone (Thompson, 1983). Repeated samples were taken from this patient and in  
1958 examining 24 essential elements, zinc was the only trace metal excreted more rapidly than normal. For  
1959 each 1 g injection of calcium trisodium pentetate there was an 18 mg urinary loss of zinc (Kalkwarf et  
1960 al., 1983). Radiation doses to bone, lung and liver were below toxic concentrations and the only  
1961 manifestation of radiation effects were observed in the blood (Thompson, 1983). The peripheral  
1962 lymphocyte count declined from 1860 cells/mm<sup>3</sup> on the day of the accident to 530 mm<sup>-3</sup> one week later.  
1963 It remained depressed for several months (Breitenstein & Palmer, 1989). In lymphocyte cultures from  
1964 samples taken between 30 and 1857 days after the accident a high proportion of metaphases were  
1965 observed with two-break chromosome lesions and in all cultures the distribution of centric ring and  
1966 dicentric (or multicentric) chromosomes were significantly overdispersed relative to expected  
1967 dispersion (Littlefield et al., 1981). This patient died of complications of chronic coronary artery  
1968 disease 11 years after the accident. The total quantity of americium-241 excreted from the body was 41  
1969 MBq (1.1 mCi); of this almost half was excreted within the first 3 days of exposure. He was given a  
1970 total of 583 g of pentetic acid salts between 1976 and 1980 with no adverse effects reported and there  
1971 was no deposition of americium-241 in the bone and liver. Without this treatment it was estimated that  
1972 the deposition of 18.5 MBq (500 µCi) of americium-241 in the bone and liver would have produced  
1973 life-threatening doses of 0.07 Gy/day, 25 Gy/year to the bone and 1 Gy (100 rad)/day to the liver.  
1974 Pentetic acid also reduced the clearance half-time of the liver activity to approximately 20 days  
1975 compared to an expected 20 years for unchelated americium-241. All the americium in the liver was  
1976 cleared by day 400 although there was re-deposition after cessation of pentetic acid treatment. Pentetic  
1977 acid did not remove americium-241 from bone except for a small possible effect during the first week  
1978 (Breitenstein & Palmer, 1989).

1980 A 35-year-old, 70 kg, male was exposed to americium-241 by inhalation and received a body burden of

1981 1.8  $\mu$ Ci. The accident, which was thought to have occurred in 1965 or early 1966 was noticed when  
1982 alpha-activity was discovered in urine specimens in 1967 (Fasiska et al., 1971). He was given  
1983 intravenous calcium trisodium pentetate (1 g/week) from September 1967 and continued with only a  
1984 few interruptions through 1974. During chelation therapy the excretion rate of americium increased by  
1985 10 times compared to periods without chelation. There were no changes to liver or kidney function and  
1986 no adverse effects on haematology or cytogenetics (Rosen et al., 1980). Zinc analysis was performed  
1987 on urine samples from this patient during the last 3 months (September to November 1970) of a 5  
1988 month period of no chelation therapy and during a period of treatment (December 1970 to April 1971).  
1989 The mean urinary excretion of zinc during the rest period was  $0.65 \pm 0.13$  mg/day (range 0.2-0.9  
1990 mg/day) and during the treatment period it was  $3.15 \pm 0.70$  mg/day. The concentrations were highest in  
1991 the first 24 hours after the calcium trisodium pentetate infusion (Slobodien et al., 1973).

1992  
1993 In an industrial laboratory several workers were exposed to americium-241 by inhalation. The accident  
1994 was not recognised for several months and treatment with zinc or calcium trisodium pentetate was  
1995 started late. Four workers received chelation therapy of 1 g of pentetic acid salt in 250 ml of saline  
1996 intravenously for 4 to 11 treatments. There were no adverse effects reported. After the first dose of  
1997 pentetic acid there was increased excretion of americium by factors of 65 to 140 (urine) and 30 to 50  
1998 (faeces). Pentetic acid removed almost all americium-241 deposited in the liver. It was calculated that  
1999 dose reductions for the liver, bone surfaces, red bone marrow and lungs were 90, 28, 28 and 26%,  
2000 respectively, equivalent to an effective dose reduction of 40% (Roedler et al., 1989).

2001  
2002 Following a perforating wound in the forefinger involving americium-241 most of the activity of 244  
2003 nCi measured in the wound was removed by 3 surgical excisions. The increased radioactivity in urine  
2004 after pentetic acid injection (0.5 g intravenously on days 1 and 12 after the accident) indicated that  
2005 small amounts of americium were already absorbed into the body. It was calculated that 8 pCi was  
2006 excreted in the urine on day 1 (Ohlenschläger, 1971).

2007  
2008 A 57-year-old male and his 10-year-old son were accidentally and unknowingly exposed to americium-  
2009 241. The father, a laboratory researcher, had brought home a piece of material, later found to be  
2010 composed primarily of americium-241. This had occurred in late 1963 and was discovered in 1970.  
2011 The house was heavily contaminated and the family had to evacuate it until it had been decontaminated.  
2012 Other family members, the wife, an 18 year old daughter and a 20 year old son had elevated americium  
2013 body burdens (6.5 to 13 nCi) but the father and son were the most heavily contaminated (87 and 93 nCi,  
2014 respectively) (Whalen & Davies, 1972). The father and son received periods of calcium trisodium  
2015 pentetate treatment in 1970, 1973 and 1975. Prior to the treatment in 1975 the total body count of  
2016 americium-241 was  $69.6 \pm 2.7$  nCi in the father and  $20.1 \pm 1.6$  nCi in the son. Most was present in the  
2017 skeleton (75 to 85%) with smaller quantities in the liver and possibly the lungs. After an intravenous  
2018 infusion of calcium trisodium pentetate ( $23.3 \mu\text{mol/kg}$  and  $41.8 \mu\text{mol/kg}$ , respectively) once weekly for  
2019 4 weeks the body burden decreased to  $67.2 \pm 2.8$  nCi in the father and  $12.7 \pm 2.7$  nCi in the son. The  
2020 chelation therapy was more effective in the son (then aged 15 years) with a decreased in the body  
2021 burden of 37% compared to the father (62 years) with a decrease of only 2 to 4%. After each treatment  
2022 in the son the urinary excretion of zinc increased by 10 to 60-fold (Cohen et al., 1976).

### 2023 **11.1.1 Americium and curium**

2024  
2025  
2026 A worker accidentally inhaled over 1200 nCi of mixed oxides of curium-244 (75%) and americium-241  
2027 (25%). Nasal smears removed 212 nCi from the right nostril and 185 nCi from the left. The nasal  
2028 cavities were then irrigated and the skin decontaminated. Less than 3 hours after the accident the lungs  
2029 contained 456 nCi. At 2.5 hours after the incident he was given 4 ml of a 25% trisodium pentetate  
2030 solution by nebuliser. Over the first 7 days 1172 nCi was excreted in the faeces and all but 37 nCi was  
2031 eliminated from the chest. Pentetic acid was not given again until day 50 by which time 99.8% of the

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  $\mu$ Ci). 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 declined 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  $20 \pm 9$  nCi and the maximum permissible body burden is 4 nCi. The following day the body burden was  $9 \pm 8$  nCi and three days later it was less than  $5 \pm 5$  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

2083 increased excretion by several fold. Most inhaled californium is excreted in the faeces and Subject 1  
2084 excreted 13 nCi in the first 3 days compared to only 0.2 nCi in Subject 2 (Poda & Hall, 1975).

2085

### 2086 **11.3 Cerium**

2087

2088 Two workers were exposed to air-borne cerium-144/praseodymium-144. Clothing was contaminated  
2089 and nasal swabs confirmed exposure. Both men showered and were referred to the *in vivo* counting  
2090 facility. Subject 1 had a burden of  $\leq 0.25$   $\mu\text{Ci}$  of cerium-144 with 0.04  $\mu\text{Ci}$  in the lung. This was  
2091 estimated to be less than 1% of the maximum permissible body burden. No further action was taken.  
2092 Subject 2 had a burden of 12  $\mu\text{Ci}$  of cerium-144 with 2.1  $\mu\text{Ci}$  in the lung. It was estimated that he had  
2093 received as high as 10% of the maximum permissible body burden. He was started on intravenous  
2094 calcium trisodium pentetate and received 15 doses of 1 g over 116 days. Calcium trisodium pentetate  
2095 enhanced excretion of cerium and urine activity was undetectable after the last dose on day 116 (Glenn  
2096 et al., 1979).

2097

### 2098 **11.4 Curium**

2099

2100 A worker inhaled airborne curium-244 during removal of dry, solid waste from a decontamination  
2101 chamber. Filter paper smeared inside his nostrils removed 16.1 nCi from the left and 10.9 nCi from the  
2102 right. The nasal cavities were irrigated and the skin washed. At 2.5 hours after the incident he was  
2103 given 4 ml of a 25% trisodium pentetate by nebuliser. He was also given a laxative. Approximately  
2104 4.5 hours after exposure a reading of 14 nCi was taken from the worker's chest, this decreased rapidly  
2105 to 5 nCi within 4 days. Calculations showed that the pentetic acid did not significantly increase the  
2106 excretion of curium (Sanders, 1974).

2107

2108 See also case of curium-244 and americium-241 under americium (section 11.1.1).

2109

### 2110 **11.5 Iron**

2111

2112 Although pentetic acid has been used in the past as a chelator for both acute iron overdose  
2113 (Gokulanathan et al., 1963; Barr & Fraser, 1968) and iron overload (Fahey et al., 1961; Bannerman et  
2114 al., 1962; Smith, 1962; Müller-Eberhard et al., 1963; Smith, 1965; McDonald, 1966; Constantoulakis et  
2115 al., 1974; Strohmeyer, 1974) it has now been replaced by deferoxamine. It can be used in patients who  
2116 have deferoxamine toxicity (Wonke et al., 1989).

2117

2118 In iron overload zinc trisodium pentetate cannot be used as it is ineffective as an iron chelator (Pippard  
2119 et al., 1986). Therefore, pentetic acid must be given as the calcium salt, however, this has the  
2120 disadvantage of interfering with trace metal concentrations, particularly zinc, and zinc supplements  
2121 must be given. Zinc deficiency was reported in a child with thalassaemia who was allergic to  
2122 deferoxamine and was treated with subcutaneous pentetic acid. Low blood zinc concentrations were  
2123 managed successfully with zinc supplementation (Ridley, 1982).

2124

### 2125 **11.6 Lead**

2126

2127 Although pentetic acid is not the first line antidote for lead toxicity it has been used in the past. In 11  
2128 workers with lead exposure intramuscular calcium trisodium pentetate (0.5 or 1 g) rapidly increased  
2129 urinary excretion of lead, particularly within the first 12 hours after dosing. The drug was well  
2130 tolerated with local discomfort at the injection site in one patient and microhaematuria in another  
2131 (Brugsch et al., 1965).

2132

### 2133 **11.7 Manganese**

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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

2185 States Transuranium and Uranium Registries (USTUR) of Washington State University, USA, for post-  
2186 mortem analysis. The estimated exposure dose was calculated 6 years after the accident as 0.42  $\mu\text{Ci}$   
2187 (15.5 kBq), approximately ten times the maximum permissible body burden. At the time of autopsy  
2188 approximately 1% of the total plutonium-239 and 240 body burden remained in the lungs. Modelling  
2189 using the data obtained from the tissues showed that chelation therapy substantially reduced the burden  
2190 of plutonium in all organs except the lungs. The calculated reduction in plutonium concentration in  
2191 organs at the time of death was approximately 40% in the liver, 60% for all other soft tissues (muscle,  
2192 skin, glands, etc), 50% for the kidneys and 50% for the skeleton. Modelling showed that treatment with  
2193 calcium trisodium pentetate was as effective as calcium edetate even though it was delayed by more  
2194 than two years (James et al., 2007).

2195  
2196 An adult male inhaled and received an approximate body deposit of 0.4  $\mu\text{Ci}$  of plutonium-239.  
2197 Intravenous calcium trisodium pentetate (2 g in week 1, 1.6 g in weeks 2, and 11 to 12, 2 g in weeks 13  
2198 to 14, and 26, 27, 33, 46 and 50) initially increased the urinary excretion of plutonium by a factor of 55  
2199 but by week 50 it was only 19% of its original effectiveness. The calcium trisodium pentetate was  
2200 stopped for 43 weeks from weeks 51 to 92 and then 3 g was given in week 93. This increased urinary  
2201 excretion of plutonium to approximately the initial value (Norwood, 1962).

2202  
2203 A laboratory technician was involved in an accident with acidic plutonium (III) chloride, plutonium  
2204 (IV) chloride and plutonium nitrate. The solution contained 70% plutonium-239, 14% plutonium-240  
2205 and 16% americium-241. He was contaminated over almost his whole body with 10,000 to 50,000  
2206 dpm/67  $\text{cm}^2$ ; several areas on the face were greater than 500,000 dpm/67  $\text{cm}^2$ . These were small  
2207 second-degree burns containing almost 5  $\mu\text{g}$  of plutonium. His skin, except for the burns, was  
2208 decontaminated. At 2 weeks the scabs from the burns were removed and found to be heavily  
2209 contaminated with plutonium; the skin underneath was virtually free of plutonium. The first dose of  
2210 intravenous pentetic acid (1 g) was given within 1 hour of exposure and another dose at 5 hours.  
2211 Further doses were given on days 2 to 5, 13, 15 and 17. Pentetic acid was successful in promoting the  
2212 urinary excretion of plutonium (2,586 dpm/24 hours on day 0 and 105 dpm/24 hours on day 4) and by  
2213 55 days the urine concentration was almost the same as that observed before the accident (Lagerquist et  
2214 al., 1965).

2215  
2216 A worker was contaminated through a puncture wound from a sliver of metal contaminated with 2.3  $\mu\text{g}$   
2217 of plutonium (isotope not stated). The wound was determined to contain 1.8  $\mu\text{g}$  of plutonium, but this  
2218 may have been an underestimate depending on how deeply the plutonium had penetrated the wound.  
2219 Gross excision was not undertaken as this would have lead to permanent damage to the thumb. After  
2220 several attempts it was only on the fourth day that plutonium in the wound was localised and excised.  
2221 The excised tissues contained 0.73  $\mu\text{g}$  of plutonium, most located on the side of the finger where the  
2222 sliver of metal entered the thumb. Intravenous pentetic acid (1 g) was started within 1 hour and  
2223 repeated on days 1, 3, 4, 7, 9, 11, 14, 16 and 18. The overall effect of pentetic acid could not be  
2224 determined, possibly because the transfer of plutonium from the wound to the blood was low  
2225 (Lagerquist et al., 1965).

2226  
2227 A worker was contaminated with acidic plutonium nitrate (isotope not stated) and developed a second  
2228 degree burn on the shoulder. The burn was not decontaminated and healed without complications in  
2229 about 3 weeks. In the burn area there was  $0.3 \pm 0.1 \mu\text{Ci}$  of plutonium, mostly in the scab that formed  
2230 over the wound. Intravenous pentetic acid (1 g) was started within 1 hour and continued daily for 27  
2231 days. The worker developed a rash over this time which resolved once pentetic acid treatment ceased.  
2232 A total of 210,000 dpm was excreted in the first 60 days which represents 96.5% of the initial uptake of  
2233 plutonium. Pentetic acid was primarily responsible for elimination of this quantity of plutonium  
2234 (Lagerquist et al., 1967a).

2235

2236 An accident occurred when a bucket of burning plutonium chips (isotope not stated) was dropped into a  
2237 container of carbon tetrachloride. The explosion ruptured the front of the glovebox and plutonium  
2238 debris was spread over a wide area. The worker using the glove box sustained a severe injury to his left  
2239 hand, extensive contamination and probably inhalation exposure. The extent of contamination could  
2240 not be determined initially because it was greater than could be measured with the available equipment.  
2241 The victim was in mild shock on arrival at a medical facility and the left hand was wrapped in a plastic  
2242 bag to prevent further contamination. He was washed thoroughly and the washoff from the  
2243 decontamination contained approximately 1 mCi of plutonium. He was given intravenous pentetic acid  
2244 (1 g) within 1 hour of exposure and another dose 4 hours later. Examination of the injured hand  
2245 showed fractures of the thumb and second finger and contamination with approximately 30  $\mu$ Ci of  
2246 plutonium. The wounds were sutured and pentetic acid treatment given twice daily for the next 2 days  
2247 followed by dosing once daily for the 16 days. The skin was also decontaminated daily which resulted  
2248 in background radioactivity readings by day 10 except in the left hand which was not completely  
2249 decontaminated until a month after the injury. The amount of plutonium in the 24 hour urine sample  
2250 just prior to pentetic acid therapy was 10 times that of the blood. Each pentetic acid treatment was  
2251 followed by increased urinary excretion of plutonium. By the 12th day there was still a large quantity  
2252 of plutonium embedded in the thumb and it was amputated with the second finger. Approximately 133  
2253  $\mu$ Ci of plutonium was present in the amputated thumb and 1  $\mu$ Ci in the second finger leaving 4  $\mu$ Ci in  
2254 the hand. Amputation was followed by a decrease in the quantity of plutonium excreted. Pentetic acid  
2255 continued over the next 18 months at various doses and by various routes (intravenous, oral,  
2256 intramuscular). Three intravenous injections of 1 g/week were more effective in increasing excretion  
2257 than weekly 1 g treatments. Intramuscular injection around the thumb stump had little effect in  
2258 removing plutonium from the injury site. Oral pentetic acid (249 g) was given for 16 weeks. In the  
2259 first week four 1 g doses were given resulting in a 4 fold increase in excretion. This was followed by 5  
2260 g treatments on four days a week and then 5 g three times a week for 11 weeks. Over the 16 weeks  
2261 approximately  $7.4 \times 10^{-2}$   $\mu$ Ci was excreted. The victim had two more surgeries, at 11 and 18 months, to  
2262 remove the stump of the thumb to leave approximately 0.6  $\mu$ Ci of plutonium. Treatment with pentetic  
2263 acid resulted in elimination of approximately 8  $\mu$ Ci of plutonium via the urine (Lagerquist et al.,  
2264 1967b).

2266 A worker was contaminated with plutonium-239 after sustaining a puncture wound on the left hand just  
2267 distal to the first interphalangeal joint. The wound was decontaminated 30 minutes later with washing  
2268 and scrubbing of the area. A small wedge of tissue from around the wound was removed at  
2269 approximately 2.5 hours to further reduce the contamination. The plutonium in the excised tissue was  
2270 approximately 1  $\mu$ Ci and there was 91.3 nCi remaining in the wound. Tissue from a second surgical  
2271 excision contained approximately 0.1  $\mu$ Ci (98.9 nCi) and about 6.4 nCi remained in the wound. The  
2272 first dose of pentetic acid (1 g, route not stated) was given at 9 hours and repeated on days 3 to 6,  
2273 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  
2274 and 83 and finally another 2 g/day for 5 days starting on day 99. In total 28 g was given. Chelation  
2275 therapy increased urinary plutonium excretion and in the second and later courses excretion was  
2276 increased by a factor of 70. The first course of pentetic acid increased the faecal plutonium excretion  
2277 by a factor of 50 but was relatively ineffective thereafter (Swanberg & Henle, 1964).

2279 See also section 11.1.2 for cases involving both plutonium and its daughter element americium.

## 2281 **11.9 Protactinium**

2283 A chemical laboratory was contaminated with protactinium-231 but the accident was not recognised  
2284 until 2 weeks later. Traces of radioactivity were found in nose swabs of some workers and in two  
2285 subjects alpha activity was detected in their urine. Both were treated with pentetic acid (1 g daily for 4  
2286 days by intravenous infusion). Pentetic acid increased urinary excretion of protactinium by a factor of

2287 33 and 22 in these two workers. It was calculated that they had received no more than 10% of the  
2288 maximum permissible body burden (Giubileo, 1978).

2289

### 2290 **11.10 Uranium**

2291

2292 A deliberate ingestion of 15 g of non-radioactive uranium acetate in an adult male (103 kg) resulted in  
2293 rhabdomyolysis, liver dysfunction, myocarditis and acute renal failure. Plasma uranium concentrations  
2294 were high (3.24  $\mu\text{mol/L}$ ), but treatment with both calcium edetate and calcium trisodium pentetate was  
2295 ineffective in promoting uranium excretion in this patient with renal failure. The uranium plasma  
2296 concentration after 5 days of calcium edetate was 3.29  $\mu\text{mol/L}$  (Pavlakakis et al., 1996).

2297

2298

## 2299 **12 Summary of evaluation**

2300

2301 Pentetic acid salts have FDA approval for use in plutonium, curium and americium exposure by  
2302 inhalation, dermal and wound exposure. They may also be effective for enhancing elimination of other  
2303 transuranium elements such as berkelium or californium but data are limited. Pentetic acid salts are  
2304 effective for enhancing elimination of cerium and zinc. Administration of pentetic acid salts (orally or  
2305 parenterally) following ingestion of metals or radionuclides is not recommended as this is thought to  
2306 increase gastrointestinal absorption.

2307

2308 Pentetic acids salts may be useful for enhancing removal of cobalt, einsteinium, lanthanum, nickel,  
2309 promethium, scandium, strontium, ytterbium and yttrium but data are lacking. Cadmium chelation  
2310 remains a problem and pentetic acid salts have shown limited benefit in animal studies, particularly  
2311 in the more clinically relevant delayed administration studies.

2312

2313 Pentetic acid salts are not effective in removing antimony, beryllium, bismuth, gallium, lead, mercury,  
2314 neptunium, niobium, platinum, polonium, thorium and uranium; they are not useful for radioactive  
2315 iodine (Hameln Pharmaceuticals, 2004). The effectiveness of pentetic acid salts for radium or calcium  
2316 has not been determined. Although pentetic acid salts have been shown to increase elimination of  
2317 manganese in both animals studies and a human case report it did not prevent manganese-induced  
2318 Parkinson's disease in a human case (Holzgraefe et al., 1986).

2319

2320 Pentetic acid salts can mobilise iron and vanadium but more effective chelating agents are available.

2321

2322 Many animal studies have shown that the effectiveness of pentetic acid salts is similar to that of  
2323 ethylenediaminetetraacetic acid salts, and pentetic acid salts have been used in cases of heavy metal  
2324 poisoning that do not respond to this or other chelators. No controlled studies have, however, been  
2325 performed and a favourable effect is not always demonstrated in case reports or in experimental studies.

2326

2327 Pentetic acid salts are generally well tolerated and repeated dosing may be needed for years after  
2328 exposure to a radioactive element. There were no adverse effects reported in a worker exposed to  
2329 americium given 583 g of pentetic acid salts over a 5 year period (Breitenstein & Palmer, 1989). In  
2330 another case were no adverse effects reported after 322 g over 337 weeks with the longest period of  
2331 uninterrupted treatment of 1 g/week for 134 weeks (Rosen et al., 1980).

2332

2333 Calcium trisodium pentetate is more effective in early treatment but it also chelates trace elements.  
2334 Consequently, calcium trisodium pentetate is usually used for the first few doses followed by zinc  
2335 trisodium pentetate for long-term treatment. Monitoring of trace elements with supplementation, if  
2336 necessary, is recommended in patients receiving long-term calcium trisodium pentetate therapy.

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2338 Pentetic acid salts are usually given parentally but can be given by inhalation following pulmonary  
2339 contamination or used for dermal decontamination. Oral dosing is used less commonly as  
2340 bioavailability is low.

2341

2342 **12.1 Indications**

2343

2344 Pentetic acid salts should be used in cases of inhalation, dermal or wound exposure to americium,  
2345 californium, cerium, curium and plutonium. Administration of pentetic acid salts (orally or  
2346 parenterally) following ingestion of metals or radionuclides is not recommended as this is thought to  
2347 increase gastrointestinal absorption (see section 12.4).

2348

2349 Pentetic acid salts can also be considered for other transuranics and radioactive metals or metals where  
2350 data are limited or unavailable or where other chelators are available or ineffective. This includes  
2351 cobalt, einsteinium, iron, lanthanum, nickel, promethium, scandium, strontium, ytterbium, yttrium and  
2352 zinc.

2353

2354 **12.2 Advised routes and dose**

2355

2356 The dosing regimen of pentetic acid salts should be individually tailored depending on the route of  
2357 exposure and the severity of intoxication. Specialist advice should be sought for patients with radiation  
2358 exposure.

2359

2360 Treatment may need to be continued for weeks, months or even years. Dosing is usually with the  
2361 calcium salt for the first day or so and then with the less toxic zinc salt (Gerber & Thomas, 1992). In  
2362 the medical case reports of 646 individuals who received calcium or zinc trisodium pentetate collated  
2363 by the Radiation Emergency Assistance Center/Training Site (REAC/TS) 72% of individuals treated  
2364 with calcium trisodium pentetate received only 1 or 2 doses and the rest 3 or more. Of those given zinc  
2365 trisodium pentetate 50% received 1 or 2 doses and the rest 3 or more. One subject received 338 doses  
2366 of calcium trisodium pentetate (1 g) over 6.5 years and another received 574 doses of zinc trisodium  
2367 pentetate (1 g) over 3.5 years (FDA, 2004).

2368

2369 Calcium and zinc trisodium pentetate can be given in 5% dextrose, lactated Ringer's or 0.9% saline  
2370 (Hameln Pharmaceuticals, 2004).

2371

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2374

2375 **12.2.1 Adults**

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2377 **12.2.1.1 Intravenous**

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2379 30 µmol/kg (approximately 15 mg/kg) calcium trisodium pentetate (so 1 g for a 70 kg adult) by slow  
2380 intravenous injection (in 5 ml over 3 to 4 minutes) or by intravenous infusion (in 100 to 250 ml of 0.9%  
2381 saline, lactated Ringer's or 5% dextrose over 30 minutes).

2382

2383 For a severe contamination the first dose given immediately after the accident may be doubled.  
2384 Treatment should then continue with zinc trisodium pentetate. The dose should not exceed 1 g/day for  
2385 prolonged treatment and the dose can be reduced during prolonged treatment (as the quantity of  
2386 material to be chelated is reduced) (Gerber & Thomas, 1992; Hameln Pharmaceuticals, 2004).

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2388 **12.2.1.2 Oral administration**

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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-Eberhard 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

2440 colloid or insoluble in the gastrointestinal tract (and therefore less absorbable), nasal and/or lung lavage  
2441 and decontamination of skin and wounds (Gerber & Thomas, 1992).

2442  
2443 Surgical debridement of contaminated wounds may be considered. Wound probes are available that  
2444 detect radionuclide emissions (Breitenstein, 2003).

2445  
2446 Once an estimate of dose of radioactivity incorporated can be calculated the need for chelation therapy  
2447 can be assessed (Breitenstein, 2003).

2448

## 2449 **12.4 Controversial issues**

2450

### 2451 **12.4.1 Pentetic acid after ingestion of metals or radionuclides**

2452

2453 Administration of pentetic acid salts, by any route, following ingestion of metals or radionuclides is  
2454 not recommended as this is thought to increase gastrointestinal absorption.

2455

2456 Various animal studies have demonstrated increased absorption after administration of pentetic acid  
2457 salts following ingestion of metals or radionuclides. For example, oral administration of zinc  
2458 trisodium pentetate increased retention of oral cerium-141; the cerium-141 concentration was  
2459 doubled in the whole body and gut, increased by factors of 5 in the carcass and liver, 10 in the  
2460 femur and 50 in the kidneys. However, the animals were killed at 24 hours and there was no  
2461 measurement of excretion rate (Kargaćin & Kostial, 1985). Intravenous calcium trisodium  
2462 pentetate after oral plutonium in rats resulted in increased plutonium absorption but the absorbed  
2463 material was rapidly excreted and there was reduced deposition in the skeleton and liver (Sullivan  
2464 et al., 1983).

2465

2466 In contrast in rats given oral cerium-144 oral zinc trisodium pentetate was very effective in  
2467 reducing whole body burden and gut retention, even when given a day after cerium administration  
2468 (Kostial et al., 1987a). Oral treatment with zinc trisodium pentetate has also been shown to be  
2469 effective in reducing organ retention after oral cadmium exposure in rats (Kostial et al., 1987c) and  
2470 in mice oral pentetic acid was effective in promoting survival when given immediately after oral  
2471 cadmium (Basinger et al., 1988).

2472

2473 There is no information on the use of pentetic acid following oral exposure to radionuclides in humans.  
2474 In one case of metal ingestion where calcium trisodium pentetate was used an adult male drank  
2475 potassium permanganate solution over 4 weeks. Although intravenous calcium trisodium pentetate  
2476 decreased the serum concentration and increased urinary excretion of manganese, it did not prevent the  
2477 development of progressive Parkinson's disease which started 9 months after exposure. The effect of  
2478 calcium trisodium pentetate on absorption of manganese cannot be determined in this case (Holzgraefe  
2479 et al., 1986).

2480

2481 Oral dosing after exposure via other routes such as inhalation or wound contamination has been  
2482 used occasionally. Although oral bioavailability is low this route has been shown to be effective in  
2483 some studies. Oral calcium and zinc trisodium were effective in reducing the americium-241  
2484 concentrations in the liver and femur after intravenous americium in rats (Taylor & Volf, 1980). Zinc  
2485 trisodium pentetate in drinking water was effective in reducing plutonium and americium retention in  
2486 the lungs and total body in rats after inhalation of plutonium-238 and americium-241 (Stradling et al.,  
2487 1993a; Gray et al., 1995).

2488

### 2489 **12.4.2 Oral pentetic acid after inhalation or wound contamination by metals or radionuclides**

2490

2491 There is very limited information on the effectiveness of oral pentetic acid salts in humans following  
2492 radionuclide exposure. In many cases pentetic acid was also given parentally and it is not possible to  
2493 determine the effect of oral pentetic acid alone. Oral pentetic acid may be a more practical or  
2494 convenient route of administration for long-term therapy.

2495

2496 The effectiveness of oral pentetic acid was evaluated in a worker with extensive contamination and  
2497 probably inhalation exposure following an explosion involving plutonium. Oral pentetic acid was  
2498 given for 16 weeks starting at least 9 months after the accident. In the first week four 1 g oral doses  
2499 resulted in a 4 fold increase in plutonium excretion. This was followed by 5 g treatments on 4 days a  
2500 week and then 5 g three times a week for 11 weeks. Over the 16 weeks approximately  $7.4 \times 10^{-2}$   $\mu\text{Ci}$   
2501 was excreted which was about 10 times the amount expected without treatment (Lagerquist et al.,  
2502 1967b).

2503

### 2504 **12.4.3 Different formulations of pentetic acid and its salts**

2505

2506 Various efforts have been made to increase the efficacy of pentetic acid. Puchel, the lipophilic  
2507 derivative of pentetic acid, is generally no more effective than pentetic acid and is more toxic.  
2508 Consequently it is no longer used. More recent work has focused on the use of pentetic acid in  
2509 liposomes (Phan et al., 2004; 2005; 2006a; 2006b) and improving the properties of aerosolised pentetic  
2510 acid (Gervelas et al., 2007).

2511

2512 In rats the pharmacokinetics of pentetic acid are modified by encapsulation in liposomes and can reach  
2513 deposits of plutonium in the liver and bone. The pentetic acid in liposomes penetrated the liver in  
2514 larger quantities than free pentetic acid and had a longer half-life, with the liver and the spleen acting as  
2515 reservoirs (Phan et al., 2004; Phan et al., 2005). Free pentetic acid is undetectable in plasma at 4 hours  
2516 but encapsulated pentetic acid was still quantifiable at 24 and 48 hours after intravenous injection (Phan  
2517 et al., 2005). After intravenous plutonium-239 pentetic acid in liposomes was as effective as free  
2518 pentetic acid in maintaining the plutonium content of the femur below 4.3% of the injected dose after  
2519 16 days (Phan et al., 2004). Pentetic acid in liposomes increased urinary plutonium excretion to over  
2520 90% of the injected dose in rats. This formulation also reduced the liver and skeleton burden even 30  
2521 days after a single dose. A dose of 0.3  $\mu\text{mol/kg}$  in liposomes produced the same reduction in skeletal  
2522 burden as four injections of the free pentetic acid (30  $\mu\text{mol/kg}$ ) (Phan et al., 2006b).

2523

2524 Gervelas et al. (2007) studied pentetic acid formulated on to porous particles. This was tested in rats 6  
2525 days after inhalation of plutonium-239 oxide. It was given by intratracheal administration using a dry  
2526 powder insufflator and was found to increase the urinary excretion of plutonium by a factor of 4 for the  
2527 first 4 days after treatment. In addition the excretion of plutonium remained high for 6 days. Although  
2528 this formulation of pentetic acid increased excretion it did not enhance dissolution of plutonium-239  
2529 oxide particles in the lungs.

2530

### 2531 **12.5 Proposals for further studies**

2532

2533 The potential risks and benefits of the use of pentetic acid after oral exposure to metals and  
2534 radionuclides warrants further investigation since this is an issue that influences the point at which  
2535 antidote or decorporation treatment is initiated.

2536

2537 In addition the efficacy of oral pentetic acid also requires evaluation. Although most cases of  
2538 exposure involve inhalation or wound contamination for which nebulised or injection of pentetic acid  
2539 salts is suitable, the long duration of treatment required in some cases makes parenteral administration  
2540 inconvenient and it can be uncomfortable. This can influence patient compliance.

2541

2542 More studies on the efficacy and benefits of the different formulations of pentetic acid are needed.  
2543

## 2544 **12.6 Adverse effects** 2545

2546 Pentetic acid salts are generally well tolerated. The medical case reports of 646 individuals who  
2547 received calcium or zinc trisodium pentetate is held by the Radiation Emergency Assistance  
2548 Center/Training Site (REAC/TS), part of the Oak Ridge Universities (ORAU), Tennessee, USA (FDA,  
2549 2004). Of these 646 subjects adverse event information was collected for 310 individuals. Of these  
2550 only 19 (6.1%) reported adverse events which included nausea, diarrhoea, headache, light-headedness,  
2551 chest pain, allergic reactions, dermatitis, metallic taste and injection site reactions (Hameln  
2552 Pharmaceuticals, 2004).  
2553

2554 Microhaematuria was reported in one patient given a second dose of intramuscular calcium trisodium  
2555 pentetate (0.5 g) for lead poisoning (Brugsch et al., 1965). In a review of 23 workers given intravenous  
2556 calcium trisodium pentetate (518 injections in total) after radiation accidents over a 34 year period there  
2557 was no change in renal function (Grappin et al., 2007). Decreased activity of  $\delta$ -aminolevulinic  
2558 dehydratase (ALAD), a zinc-containing enzyme, was observed in a 15-year-old patient treated with  
2559 calcium trisodium pentetate (Cohen et al., 1976).  
2560

2561 No skin reactions were reported with a 10% calcium trisodium pentetate cream used in patients with  
2562 contact allergic dermatitis to metals (Wöhrl et al., 2001).  
2563

2564 Cough and/or wheezing have been reported in two individuals given nebulised calcium trisodium  
2565 pentetate; one of these subjects had a history of asthma (Hameln Pharmaceuticals, 2004).  
2566

2567 Calcium trisodium pentetate also chelates trace elements and these should be monitored in patients  
2568 receiving repeated or long-term dosing with calcium trisodium pentetate. Supplements should be given  
2569 as required.  
2570

## 2571 **12.7 Restrictions for use** 2572

2573 Administration of pentetic acid salts (orally or parenterally) following ingestion of metals or  
2574 radionuclides is not recommended as this is thought to increase gastrointestinal absorption (see  
2575 section 12.4).  
2576

2577 Calcium trisodium pentetate must not be administered during pregnancy because of reproductive  
2578 toxicity as a result of zinc and manganese chelation (Mays et al., 1976). The use of zinc trisodium  
2579 pentetate should be considered as an alternative. Calcium trisodium pentetate is also contraindicated in  
2580 patients with hypercalcaemia.  
2581

2582 Dose reduction is not required in patients with renal impairment but haemodialysis may be required to  
2583 eliminate the chelate. High efficiency high reflux dialysis is recommended (Hameln Pharmaceuticals,  
2584 2004).  
2585

2586 Calcium trisodium pentetate should be used with caution in patients with haemochromatosis. Three  
2587 patients with severe haemochromatosis died after receiving intramuscular calcium trisodium pentetate  
2588 in doses up to 4 g/day. One patient became comatose and died after a total dose of 14 g and two others  
2589 died after 2 weeks of daily treatment (FDA, 2004). These cases are very similar and could be the same  
2590 as those reported by Fairbanks et al. (1963). Pentetic acid (1 g daily for 14 days) was given to three  
2591 patients with haemochromatosis. All three were mentally obtunded during the period of treatment,  
2592 although one had been disorientated and drowsy prior to dosing and one was borderline schizophrenic.

2593 Two patients who were seriously ill at the time of treatment became comatose and died. No cause of  
2594 their neurological deterioration was determined at post-mortem examination. The third patient survived  
2595 but she developed drowsiness, dysathria and lesions on the lingual and buccal mucosa. Another patient  
2596 with less severe haemochromatosis received intravenous calcium trisodium pentetate 30 g over 12 days  
2597 and developed no adverse effects (Kemble, 1964). Similarly 4 other patients with haemochromatosis  
2598 received varying doses of calcium trisodium pentetate (12 g in 3 days, 9 g in 17 days) without adverse  
2599 effects (Fahey et al., 1961). A causal relationship between calcium trisodium pentetate administration  
2600 and the fatal outcome in these patients has not been established and caution is recommended.

2601

## 2602 **13 Model information Sheet**

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### 2604 **13.1 Uses**

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2606 Pentetic acid salts should be used in cases of inhalation, dermal or wound exposure to americium,  
2607 californium, cerium, curium and plutonium.

2608

2609 It can also be considered for other transuranics and radioactive metals or metals where data are limited  
2610 or unavailable or where other chelators are unavailable or ineffective. This includes cobalt,  
2611 einsteinium, iron, lanthanum, nickel, promethium, scandium, strontium, ytterbium, yttrium and zinc.

2612

### 2613 **13.2 Dosage and Route**

2614

2615 The dosing regimen of pentetic acid salts should be individually tailored depending on the route of  
2616 exposure and the severity of intoxication. Specialist advice should be sought for patients with radiation  
2617 exposure.

2618

2619 Treatment may need to be continued for weeks, months or even years. Dosing is usually with the  
2620 calcium salt for the first day or so and then with the less toxic zinc salt.

2621

#### 2622 **13.2.1 Adults**

2623

##### 2624 **13.2.1.1 Intravenous**

2625

2626 30 µmol/kg (approximately 14 mg/kg) calcium trisodium pentetate (so 1 g for a 70 kg adult) by slow  
2627 intravenous injection (in 5 ml over 3 to 4 minutes) or by intravenous infusion (in 100 to 250 ml of 0.9%  
2628 saline, lactated Ringer's or 5% dextrose over 30 minutes).

2629

2630 For a severe contamination the first dose given immediately after the accident may be doubled.  
2631 Treatment should then continue with zinc trisodium pentetate. The dose should not exceed 1 g/day for  
2632 prolonged treatment and the dose can be reduced during prolonged treatment (as the quantity of  
2633 material to be chelated is reduced).

2634

##### 2635 **13.2.1.2 Oral administration**

2636

2637 1 g of zinc trisodium pentetate/day in micronised capsules can be considered for long-term therapy. A  
2638 higher dose (up to 5 g/day) can be used in short-term therapy.

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##### 2640 **13.2.1.3 Nebuliser administration**

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2642 Pentetic acid salts may also be given by nebuliser following accidental inhalation of radioactive  
2643 material.

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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.

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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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October 2008

3562 **16 Additional information**

3563

3564 None.

3565 **Abbreviations**

3566		
3567	AAS	Atomic Absorption Spectroscopy
3568	AES	Atomic Emission Spectroscopy
3569	ALAD	$\delta$ -aminolevulinic dehydratase
3570	Am	americium
3571		
3572	Bq	Becquerel, the SI unit of radioactivity
3573		
3574	CAS	Chemical Abstracts Service
3575	Cd	cadmium
3576	Ce	cerium
3577	Cf	californium
3578	Ci	Curie (1 Ci = 37 GBq; 37 GB = 37. 10 <sup>9</sup> Bq)
3579	Cm	curium
3580	Cr	chromium
3581	Cu	copper
3582		
3583	dpm	disintegrations per minute
3584	DTPA	diethylenetriaminepentaacetic acid
3585		
3586	EDTA	ethylenediaminetetraacetic acid
3587	EDTPO	ethylenediaminetetra(methylenephosphonic) acid
3588		
3589	FDA	Food and Drug Administration (United States)
3590	Gy	Gray, unit of the absorbed dose
3591		1 Gy = 100 rad
3592		
3593	HEDTA	hydroxyethylethylenediaminetriacetic acid
3594	Hg	mercury
3595		
3596	ICP	Inductively Coupled Plasma
3597	IPCS	International Programme on Chemical Safety
3598		
3599	LD	Lethal Dose
3600	LICAM(C)	N <sup>1</sup> , N <sup>5</sup> , N <sup>10</sup> , N <sup>14</sup> -tetrakis(2,3-dihydroxy-4-carboxybenzoyl)-tetraazatetradecane,
3601		tetrasodium salt
3602		
3603	m	milli (10 <sup>-3</sup> )
3604	$\mu$	micro (10 <sup>-6</sup> )
3605	Mn	manganese
3606		
3607	Nb	niobium
3608	Ni	nickel
3609	Np	neptunium
3610		
3611	Pb	lead
3612	Pm	promethium
3613	Po	polonium
3614	Pu	plutonium
3615		

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3616	Rad	radiation absorbed dose, unit absorbed dose
3617	RDD	Radiation Dispersal Device
3618	REAC/TS	Radiation Emergency Assistance Center/Training Site
3619		
3620	Sb	antimony
3621	Sc	scandium
3622	Sr	strontium
3623		
3624	Th	thorium
3625		
3626	U	uranium
3627	USTUR	United States Transuranium and Uranium Registries
3628		
3629	Y	yttrium
3630	Yb	ytterbium
3631	Zn	zinc
3632		