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7 **IPCS EVALUATION OF ANTIDOTES**  
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9 **IN POISONING BY METALS AND METALLOIDS**  
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16  
17 **Succimer**  
18 **(2,3-Dimercaptosuccinic acid, DMSA)**  
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36 Units corrected Feb 07, updated March 2009  
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40	<b>1. INTRODUCTION</b>	<b>5</b>
41	<b>2. NAME AND CHEMICAL FORMULA</b>	<b>5</b>
42	<b>3. PHYSICO-CHEMICAL PROPERTIES</b>	<b>6</b>
43	<b>4. PHARMACEUTICAL FORMULATION AND SYNTHESIS</b>	<b>7</b>
44	4.1 Routes of synthesis	7
45	4.2 Presentation and formulation	7
46	<b>5. ANALYTICAL METHODS</b>	<b>7</b>
47	5.1 Quality control procedures for the antidote	7
48	5.2 Methods for identification of the antidote	8
49	5.3. Methods for analysis of the antidote in biological samples	8
50	5.4 Analysis of the toxic agent in biological samples	8
51	<b>6. SHELF-LIFE</b>	<b>8</b>
52	<b>7. GENERAL PROPERTIES</b>	<b>8</b>
53	<b>8. ANIMAL STUDIES</b>	<b>9</b>
54	<b>8.1 Pharmacodynamics</b>	<b>10</b>
55	8.1.1 Aluminium	10
56	8.1.2 Antimony	10
57	8.1.3 Arsenic	10
58	8.1.4 Beryllium	13
59	8.1.5 Bismuth	14
60	8.1.6 Cadmium	14
61	8.1.7 Chromium	17
62	8.1.8 Cobalt	18
63	8.1.9 Copper	18
64	8.1.10 Gold	19
65	8.1.11 Lead	19
66	8.1.11.1 Effect of succimer on gastrointestinal lead absorption	23
67	8.1.11.2 Effect of succimer on brain lead concentrations	24
68	8.1.11.3 Effect of succimer on lead-induced neurotoxicity	24
69	8.1.12 Manganese	25
70	8.1.13 Mercury	25
71	8.1.14 Nickel	29
72	8.1.15 Palladium	29
73	8.1.16 Platinum	30
74	8.1.17 Polonium	30
75	8.1.18 Promethium	31
76	8.1.19 Selenium	31

77	8.1.20	Silver	31
78	8.1.21	Strontium	32
79	8.1.22	Thallium	32
80	8.1.23	Tin	32
81	8.1.24	Vanadium	33
82	8.1.25	Zinc	33
83	<b>8.2</b>	<b>Pharmacokinetics</b>	<b>34</b>
84	<b>8.3</b>	<b>Toxicology</b>	<b>35</b>
85	8.3.1	Acute toxicity	35
86	8.3.1.2	Subacute toxicity (28 days)	35
87	8.3.2	Chronic toxicity (180 days)	35
88	8.3.3	Reproductive toxicity and teratogenicity	35
89	8.3.4	Genotoxicity	36
90	<b>9.</b>	<b>VOLUNTEER STUDIES</b>	<b>37</b>
91	<b>9.1</b>	<b>Absorption</b>	<b>37</b>
92	<b>9.2</b>	<b>Distribution</b>	<b>37</b>
93	9.3	Elimination	38
94	9.4	Metabolism	38
95	<b>9.5</b>	<b>Effect of succimer on the excretion of metals</b>	<b>38</b>
96	9.5.1	Bismuth elimination	38
97	9.5.2	Cadmium elimination	38
98	9.5.3	Lead elimination	39
99	9.5.4	Mercury elimination	39
100	9.5.5	Trace element elimination	40
101	<b>10.</b>	<b>CLINICAL STUDIES – CLINICAL TRIALS</b>	<b>41</b>
102	<b>10.1</b>	<b>Arsenic and succimer clinical trials</b>	<b>41</b>
103	<b>10.2</b>	<b>Copper and succimer clinical trials</b>	<b>41</b>
104	<b>10.3</b>	<b>Lead and succimer clinical trials</b>	<b>42</b>
105	10.3.1	Study by the Treatment of Lead-Exposed Children (TLC) Study Group	45
106	<b>10.4</b>	<b>Mercury and succimer clinical trials</b>	<b>46</b>
107	<b>11</b>	<b>CASE REPORTS – CLINICAL STUDIES</b>	<b>47</b>
108	<b>11.1</b>	<b>Aluminium</b>	<b>47</b>
109	<b>11.2</b>	<b>Antimony</b>	<b>47</b>
110	<b>11.3</b>	<b>Arsenic</b>	<b>48</b>
111	<b>11.4</b>	<b>Beryllium</b>	<b>51</b>
112	<b>11.5</b>	<b>Bismuth</b>	<b>52</b>
113	<b>11.6</b>	<b>Cadmium</b>	<b>52</b>
114	<b>11.7</b>	<b>Cobalt</b>	<b>52</b>
115	<b>11.8</b>	<b>Copper</b>	<b>52</b>

116	11.8.1 Use in Wilson's disease	52
117	<b>11.9 Gold</b>	<b>52</b>
118	<b>11.10 Lead</b>	<b>53</b>
119	11.10.1 Acute lead poisoning in children	53
120	11.10.2 Chronic lead poisoning in children	54
121	11.10.3 Chronic lead poisoning in adults	54
122	11.10.4 Chronic lead poisoning in pregnancy	56
123	<b>11.11 Manganese</b>	<b>57</b>
124	<b>11.12 Mercury</b>	<b>57</b>
125	<b>11.13 Thallium</b>	<b>61</b>
126	<b>11.14 Tin</b>	<b>61</b>
127	<b>12. SUMMARY OF EVALUATION</b>	<b>61</b>
128	12.1 Indications	61
129	12.2 Advised routes and dose	62
130	12.3 Other consequential or supportive therapy	62
131	12.4 Controversial issues and areas of insufficient information	63
132	12.5 Proposals for further studies	63
133	12.6 Adverse effects	64
134	12.7 Restrictions for use	65
135	<b>13. MODEL INFORMATION SHEET</b>	<b>66</b>
136	13.1 Use	66
137	13.2 Dosage and route	67
138	13.3 Precautions/contraindications	68
139	13.4 Pharmaceutical incompatibilities and drug interactions	68
140	13.5 Adverse effects	68
141	13.6 Use in pregnancy and lactation	68
142	13.7 Storage	69
143	<b>14. REFERENCES</b>	<b>69</b>
144	<b>ABBREVIATIONS</b>	<b>90</b>

145 **1. INTRODUCTION**

146  
147 Succimer (meso-2,3-dimercaptosuccinic acid, DMSA) was originally used to increase  
148 antimony uptake during treatment for schistosomiasis, in the form of antimony a,a'-  
149 dimercapto potassium succinate (Friedman et al., 1954); it was Liang et al. (1957a)  
150 who first demonstrated its effectiveness as a metal-binding agent. From the mid-  
151 1950s succimer was studied and used in China (Liang et al., 1957a; Wang et al.,  
152 1965; Li & Ding, 1989; Ding & Liang, 1991) and Russia (Petrunkin, 1956; 1959) for the  
153 treatment of metal poisoning.

154  
155 Friedheim (1963) published an improved synthetic method in the early 1960s but the  
156 wider use of succimer as a therapeutic metal-binding agent did not occur until  
157 Friedheim & Corvi (1975) demonstrated the efficiency of succimer in mercury  
158 poisoning in mice and guinea pigs.

159  
160 Both succimer and unithiol (2,3-dimercapto-1-propanesulphonic acid, DMPS) are  
161 derivatives of dimercaprol (2,3-dimercapto-1-propanol, British Anti-Lewisite, BAL), and  
162 they are replacing dimercaprol as the main antidote used in the management of heavy  
163 metal poisoning (Aposhian et al., 1995; Andersen, 1999). These derivatives have  
164 several advantages over dimercaprol including lower toxicity, increased solubility in  
165 water and lower lipid solubility. It is due to these properties that they are effective by  
166 oral administration. Also, succimer decreases the brain deposition of lead (Cory-  
167 Slechta, 1988) and methyl mercury (Aaseth & Friedheim, 1978). Succimer is less  
168 toxic than unithiol and where these two drugs appear to have similar efficacy as an  
169 antidote for a particular metal, succimer is generally preferred.

170  
171 Succimer has been demonstrated to be an efficient antidote for many heavy metals  
172 and metalloids, including antimony, inorganic and organic arsenic, lead, and inorganic  
173 and organic mercury, and to possess some antidotal efficiency for others, such as  
174 cobalt, organic tin and platinum. Its antidotal spectrum is still under investigation.  
175 Also, clinical investigations of its efficiency in human metal intoxications are  
176 accumulating, and the efficacy of succimer has been reported in the treatment of  
177 human intoxications with lead, mercury and arsenic. Due to the high stability of the  
178 succimer complexes with technetium, they are also used as scintigraphic agents, e. g.  
179 in various renal disorders.

180  
181 Succimer is well tolerated and adverse effects are relatively rare. The most common  
182 adverse effects are mild gastrointestinal discomfort, skin reactions, and transient,  
183 clinically insignificant elevated liver enzymes. Symptoms are usually mild, self-limiting  
184 and do not require cessation of therapy.

185  
186 Experimental and clinical uses of metal-binding agents with special emphasis on  
187 succimer have previously been reviewed by Aposhian (1983), Aposhian & Aposhian  
188 (1990), Ding & Liang (1991), Aposhian et al. (1992); Aposhian et al. (1995) and  
189 Andersen (2004).

190

191

192 **2. NAME AND CHEMICAL FORMULA**

193  
194 Succimer is structurally analogous to dimercaprol. It has an asymmetric carbon atom  
195 and can occur in the D-, L- or meso-form. The meso-form is easier to prepare, more

196 readily available and used in most animal and clinical studies; it is the form available in  
197 pharmaceutical preparations.

198  
199 International non-proprietary name: Succimer

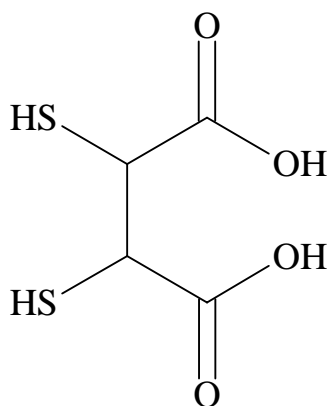
200  
201 Synonyms: DMSA, DMS, dimercaptosuccinic acid, 2,3-dimercaptobutanedioic acid,  
202 DIM-SA, meso-2,3-dithiosuccinic acid, Rol-7977

203  
204 IUPAC name: 2,3-bis-sulfanylbutanedioic acid

205  
206 CAS number: 304-55-2

207  
208 Molecular formula:  $C_4H_6O_4S_2$

209  
210



211  
212

213 Relative molecular mass: 182.22

214  
215 Conversion table: 1 g = 5.5 mmol  
216 1 mmol = 182.2 mg  
217 g/L = 5.5 mmol/L  
218 mmol/L = 0.182 g/L

219

220 Manufacturer: Succimer is available in the the west as Chemet® from Sanofi-Aventis,  
221 174, av. de France 75013, Paris, France and distributed by Ovation Pharmaceuticals,  
222 Inc., Deerfield, Illinois, USA. It is also available from pharmaceutical manufacturers in  
223 Asia (e.g. YoungCom Company Ltd, Shenzhen, China).

224

225

### 226 3. PHYSICO-CHEMICAL PROPERTIES

227

228

229 Physical condition: White crystalline powder with characteristic mecaptan  
230 odour and taste

231

232 Melting point: 196-198°C (meso-form)  
233 124-125°C (DL-form)

234

235 Boiling point: Not applicable

236		
237	Solubility:	Meso-succimer is sparingly soluble; it can be titrated with
238		alkali to pH around 5.5 or mixed in sodium bicarbonate
239		5.5% to dissolve it (Aposhian, 1983).
240		DL-succimer is readily soluble in water.
241		
242	Optical properties:	Not applicable as the racemate is used.
243		
244	Acidity:	Meso-succimer is a weak acid.
245		
246	pK <sub>a</sub> :	pK <sub>1</sub> 2.71, pK <sub>2</sub> 3.48, pK <sub>3</sub> 8.89, pK <sub>4</sub> 10.79 (for α,α'-
247		dimercaptosuccinic acid; Lenz & Martell, 1965).
248		
249	Stability in light:	No special conditions with respect to storage are
250		necessary. Succimer should be stored a room temperature
251		(15-30 °C).
252		
253	Thermal stability:	Stable (e.g., aqueous solution may be sterilised and the
254		substance may also be heated for drying)
255		
256	Refractive index and	
257	specific gravity:	Not applicable
258		
259		
260		

## 261 **4. PHARMACEUTICAL FORMULATION AND SYNTHESIS**

### 263 **4.1 Routes of synthesis**

264 Synthetic procedures have been published by Owen & Sultanbawa (1949) and  
 265 Friedheim et al. (1954). Based on the same principles, Friedheim (1963) published an  
 266 improved synthetic method.  
 267

### 270 **4.2 Presentation and formulation**

271 Dry preparations of succimer are highly stable at room temperature. It is available in  
 272 gelatin capsules 100 mg per capsule under the trade name Chemet® (McNeil, 1994).  
 273 Succimer has been given intravenously following sterile filtration by a hospital  
 274 pharmacy (Hantson et al., 2003).  
 275

## 279 **5. ANALYTICAL METHODS**

### 281 **5.1 Quality control procedures for the antidote**

282 The purity of succimer has been confirmed by nuclear magnetic resonance  
 283 spectroscopy and by elemental analysis (Graziano et al., 1978a).  
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## 5.2 Methods for identification of the antidote

Succimer is identified by converting it into the fluorescent bimane derivative as described below.

## 5.3. Methods for analysis of the antidote in biological samples

General methods for quantitation of thiol compounds are unspecific and of limited value for *in vivo* determination of specific compounds. Succimer and its metabolites may be quantitatively measured in tissue fluids and urine after derivatisation of the thiol groups by monobromobimane (Maiorino et al., 1986; 1987). After ion interaction high performance liquid chromatography (HPLC), the highly stable bimane derivatives can be detected by their strong fluorescence. Alternatively, succimer may be determined by gas chromatography after electrothermal reduction and extraction with ethyl acetate (Knudsen & McGown, 1988).

## 5.4 Analysis of the toxic agent in biological samples

Metals and metalloids can be analysed by sensitive standard methods, such as atomic absorption spectroscopy (AAS) or inductively coupled plasma-atomic emission spectroscopy (ICP-AES).

## 6. SHELF-LIFE

According to Aposhian (1983), solutions of succimer are remarkably stable for a dimercapto compound, especially at an acidic pH. The capsules should be stored at room temperature (15-30°C). No special shelf-life is given but an expiry date is usually given on the package. For preparations where no expiry date is given, the shelf-life should be at least 5 years.

## 7. GENERAL PROPERTIES

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

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

Succimer has similar metal-binding properties as dimercaprol, but the metal complexes are much more hydrophilic and thus have a much lower toxicity than the corresponding complexes with dimercaprol. One disadvantage with the lipophilic metal-binding agents, including dimercaprol, is that they generally enhance the deposition of toxic metals in organs that do not normally receive appreciable amounts of the metal e.g. the brain and the fetus. This kind of redistribution has not

336 been reported with succimer. Further, succimer itself is among the least toxic of the  
337 metal-binding agents. It may therefore be given for an extensive time period, while  
338 treatment with dimercaprol and sodium calcium edetate (EDTA, calcium disodium  
339 edetate, calcium disodium versenate, calcium EDTA) is limited to about one week per  
340 treatment session. As opposed to dimercaprol and sodium calcium edetate, succimer  
341 may be given orally as it is readily absorbed in the gastrointestinal tract, and is rapidly  
342 eliminated.

343  
344 It should be noted that succimer is not a true chelating agent; a chelator is a molecule  
345 which binds a metal or metalloid ion by at least two functional groups to form a stable  
346 ring complex known as a chelate. For mercury, it has been shown that succimer (and  
347 unithiol) do not form a true chelate and as such both could be considered suboptimal  
348 as metal antidotes (George et al., 2004). However, there are currently no other  
349 substances readily available with the advantages of these two drugs (high water  
350 solubility with relatively low toxicity).

351  
352 The mechanism of action of succimer has not been fully elucidated. Due to the  
353 softness of the two vicinal thiol-groups, succimer is especially suited as an antidote for  
354 soft or intermediate metal ions, while it may be less efficient with hard metal ions. A  
355 study of the lead, cadmium and mercury complexes formed with succimer using  
356 potentiometric and infrared methods indicated that the complex formed depends on  
357 the metal ion. In the cases of lead and cadmium, one oxygen and one sulphur act as  
358 donors, whereas with mercury, two sulphur atoms act as donors (Rivera et al., 1989).  
359 The compounds formed with various arsenic species have been studied only to a  
360 limited degree. Most likely, covalent bonding is involved. Thus, the two organic  
361 arsenic compounds phenyldichloroarsine and trans-2-chlorovinylarsine oxide form five-  
362 membered rings with succimer (O'Connor et al., 1989). Recently, multidrug resistance  
363 protein 2 (MRP2 or ATP-binding cassette, sub-family C [ABCC2]) has been showed to  
364 be involved in the renal proximal tubular elimination of succimer complexes of  
365 methylmercury (Zalups & Bridges, 2009).

366  
367 It is often assumed, that clinical effectiveness of a metal-binding agent is linked to the  
368 stability constant *in vitro* where the greater the stability constant of a metal-binding  
369 agent, the greater the mobilisation of that ion following administration of the metal-  
370 binding agent. In a comparative study, Matsuda (1968) found stabilities in decreasing  
371 order for complexes formed with the disodium salt of succimer to be cadmium > lead >  
372 iron > mercury > zinc > nickel. However, Jones et al. (1980) found no correlation  
373 between the stability constant and survival in mercury-poisoned mice treated with  
374 several different metal-binding agents (succimer was used in this study but no stability  
375 constant was given). In addition, stability values may differ between studies owing to  
376 different experimental conditions. They are, therefore, not directly comparable, and  
377 although these stability constants are valid estimates of the relative efficiency of the  
378 agent for binding a series of related metal ions they are not valid *in vivo*.  
379 Consequently, data on stability constants are not given in this monograph, but may be  
380 found elsewhere (Agren & Schwarzenbach, 1955; Lenz & Martell, 1965; Egorova,  
381 1972).

382  
383  
384  
385

## 8. ANIMAL STUDIES

## 386 **8.1 Pharmacodynamics**

387

### 388 **8.1.1 Aluminium**

389

390 Animal studies on the efficacy of succimer in aluminium toxicity have failed to  
391 demonstrate its effectiveness.

392

393 In a comparative study of the effect of metal-binding agents for acute aluminium  
394 intoxication, mice were given aluminium nitrate (3-7 mmol/kg by intraperitoneal  
395 injection). Metal-binding agents were given by the same route immediately after. A  
396 dose of succimer corresponding to 33% of the LD<sub>50</sub> did not influence lethality (an LD<sub>50</sub>  
397 of 13.6 mmol/L was used). Although succimer reduced the aluminium concentration in  
398 the kidney, spleen and liver, it did not increase the urinary and faecal excretion of  
399 aluminium (Domingo et al., 1986).

400

401 In another study, however, no protection from succimer was observed in mice  
402 poisoned by aluminium chloride (Ting et al., 1965).

403

### 404 **8.1.2 Antimony**

405

406 In animal experiments with various antimony compounds, succimer was consistently  
407 more efficient than dimercaprol in reducing lethality (reviewed by Ding & Liang, 1991).

408

409 An early Chinese study demonstrated that succimer is the most efficient antidote in  
410 experimental antimony intoxication. Administration of succimer raised the LD<sub>50</sub> of  
411 tartar emetic (antimony potassium tartrate) from 31 mg/kg to 491 mg/kg (Liang et al.,  
412 1957a). Another early study demonstrated that succimer eliminated antimony-induced  
413 inhibition of neuronal activity in rabbits (Hsu & Chang, 1957).

414

415 Administration of succimer to mice given antimony-125 resulted in a 6-fold increase in  
416 urinary excretion of the radioactive metal (Liang et al., 1980). Succimer (500 mg/kg  
417 intravenously), decreased antimony concentrations in all tissues after intravenous  
418 administration of tartar emetic (8 mg/kg) in rabbits (Liang et al., 1957b). Succimer  
419 also corrected antimony-induced T wave inversion and reduced lethality after a lethal  
420 dose of tartar emetic in dogs (Liang et al., 1964).

421

422 In a study comparing survival rates of different antidotes in antimony poisoning, mice  
423 were given intraperitoneal antimony potassium tartrate 120 mg/kg (LD<sub>50</sub> 54.6 mg/kg).  
424 The antidotes were given by the same route 1 hour later at a dose of 10:1 mole ratio  
425 of antidote to antimony (except for dimercaprol which was given at a 1:1 ratio).  
426 Succimer and unithiol were found to be the most efficacious antidotes for antimony  
427 potassium tartrate poisoning, with succimer the superior of the two (Basinger & Jones,  
428 1981b).

429

430 The effectiveness of succimer has also been demonstrated against other antimony  
431 compounds such as antimonyl ammonium gluconate (Chu et al., 1958) and antimonyl  
432 ammonia triacetic acid (Wu et al., 1962).

433

### 434 **8.1.3 Arsenic**

435

436 Several research groups have demonstrated that unithiol and succimer are more

437 efficient than dimercaprol and D-penicillamine in experimental animals including mice,  
438 rats and rabbits with arsenic toxicity (Ding and Liang 1991, Aposhian and Aposhian  
439 1990, Aposhian et al 1981, 1984, Graziano et al. 1978a, Kreppel et al. 1989, 1990).  
440 Also, unithiol and succimer were superior to dimercaprol in the treatment of systemic  
441 arsenic toxicity following percutaneously lewisite exposure (Inns & Rice, 1993).

442  
443 Mückter et al. (1997) argue that succimer and unithiol have advantages over  
444 dimercaprol in the treatment of arsenic poisoning since they are more effective in  
445 preventing arsenic from crossing epithelial boundaries and entering cells and they  
446 enhance the excretion of arsenic more rapidly and completely. In addition, succimer  
447 and unithiol are less toxic than dimercaprol. However, dimercaprol appears to be  
448 more effective in restoring cellular function to tissues which are poorly penetrated by  
449 unithiol or succimer. Dimercaprol also has the disadvantage of increasing arsenic  
450 concentrations in the brain; this is not the case with succimer or unithiol.

451  
452 Succimer is an effective antidote after acute administration of arsenic compounds to  
453 mice (Ting et al. 1965; Tadlock & Aposhian, 1980; Aposhian et al. 1981) and rats  
454 (Okonishnikova, 1965; Graziano et al., 1978b). In these studies, the LD<sub>50</sub> of sodium  
455 arsenite was increased considerably, and the excretion of arsenite was enhanced by  
456 administration of succimer. Schäfer et al. (1991) demonstrated that after injection of  
457 arsenic trioxide into mice arsenic depots could be mobilised by oral administration of  
458 succimer or unithiol without increasing the brain deposition, however, oral  
459 administration of dimercaprol extensively increased the brain deposition of arsenic. In  
460 mice poisoned with sodium arsenite (0.129 mmol/kg subcutaneously) succimer (0.8  
461 mmol/kg intraperitoneally) given 90 minutes later was found to increase the LD<sub>50</sub> by  
462 4.4 fold (Aposhian et al., 1981).

463  
464 Kreppel et al. (1989) compared the effectiveness of D-penicillamine, dimercaprol,  
465 unithiol and succimer as antidotes in acute arsenic intoxication using different  
466 controlled experimental settings. In one study mice received arsenic trioxide (9-14  
467 mg/kg subcutaneously). Treatment with succimer after 30 minutes afforded almost  
468 complete protection against the lethal effects of arsenic, whereas D-penicillamine was  
469 ineffective. In a second study, mice and guinea pigs were injected subcutaneously  
470 with 8.4 mg/kg arsenic trioxide (containing a tracer dose of arsenic-74). An antidote  
471 (0.7 mmol/kg intraperitoneally) was given 30 minutes later. As determined 4 and 12  
472 hours after the arsenic injection, D-penicillamine was unable to reduce the arsenic-74  
473 content in any of the organs investigated (blood, liver, kidneys, lungs, heart, brain,  
474 testes, spleen, skeletal muscle, and skin). In contrast, dimercaprol, unithiol and  
475 succimer markedly reduced the tissue content of arsenic-74 compared to controls.  
476 Finally, the ability of the antidotes to reverse the biochemical effects of arsenic was  
477 investigated *in vitro* using suspensions of isolated renal tubule cells. The marked  
478 inhibition of gluconeogenesis induced by 30 µmol/L arsenic trioxide was almost  
479 completely reversed upon addition of 90 µmol of either dimercaprol, unithiol or  
480 succimer. In this experimental model too, D-penicillamine was ineffective.

481  
482 In mice given arsenic trioxide, intraperitoneal administration of succimer (0.7 mmol/kg)  
483 0.5 minutes later was more effective than the same dose of unithiol. When the  
484 antidote was given 30 minutes after the arsenic, succimer and unithiol showed  
485 reduced but similar efficacy. The efficacy of the antidotes for reducing arsenic organ  
486 concentrations was investigated in mice and guinea pigs. Animals received 8.4  
487 mg/kg (0.043 mmol/kg) of radiolabelled arsenic trioxide subcutaneously and an

488 antidote (0.7 mmol/kg intraperitoneally) 30 minutes later. Both unithiol and succimer  
489 and the two in combination were more effective than dimercaprol in reducing organ  
490 concentrations of arsenic. In addition, dimercaprol increased arsenic concentrations  
491 in the brain, whereas succimer and unithiol did not. Succimer increased the arsenic  
492 content of bile but unithiol and the two in combination did not (Kreppel et al., 1990).

493  
494 In rabbits poisoned with dermal lewisite, dimercaprol, succimer and unithiol were all  
495 shown to reduce the incidence and severity of liver changes. There was no difference  
496 between the three agents at the dose of 40  $\mu$ mol/kg. Compared to dimercaprol,  
497 succimer and unithiol may have prolonged survival time and the relatively low toxicity  
498 of succimer and unithiol allowed high doses (160  $\mu$ mol/kg) to be given (Inns & Rice,  
499 1993). In a study of intravenous lewisite poisoning in rabbits there was no difference  
500 between the level of protection provided by the three antidotes (Inns et al., 1990).

501  
502 Aposhian et al. (1982) demonstrated the effectiveness of succimer in rabbits exposed  
503 to subcutaneous lewisite. Succimer increased survival when given orally or  
504 subcutaneously. Similarly, in mice injected with sodium arsenite (0.14 mmol/kg  
505 subcutaneously), intraperitoneal succimer (0.25 mmol/kg) was a potent antidote, even  
506 when given 2 hours later (Tadlock & Aposhian, 1980).

507  
508 Maiorino & Aposhian (1985) investigated the urinary metabolites of sodium arsenite in  
509 rabbits given sodium arsenite (1 mg subcutaneously) and succimer or other water-  
510 soluble dimercaptans (0.2 mmol/kg intramuscularly) 1 hour later. The urinary  
511 excretion of total arsenic between 0 and 24 hours was elevated after antidote  
512 administration. However, urinary excretion of total arsenic between 24 and 48 hours  
513 was significantly lower than controls. The relative amounts of inorganic arsenic,  
514 methylarsonate, and dimethylarsinate found in urine from 0 to 24 hours of rabbits  
515 given only sodium arsenite were similar to those reported for human subjects given  
516 arsenite orally, indicating that the rabbit biotransforms arsenite similarly to man.  
517 Succimer increased arsenite and arsenate excretion, decreased dimethylarsinate  
518 excretion but did not increase methylarsonate excretion. Slightly different effects on  
519 arsenite metabolism occurred when N-(2,3-dimercaptopropyl)phthalamidic acid  
520 (DMPA) or unithiol were given. These results suggest that succimer and related  
521 dimercaptans, in addition to increasing the excretion of inorganic arsenic, also  
522 influence the ratio between the various toxic and detoxified arsenic species. Of the  
523 three antidotes used, unithiol was the most effective at removing arsenic from the  
524 body.

525  
526 Succimer or unithiol (both at 50 mg/kg) also significantly increased renal arsenic  
527 excretion in rats with chronic arsenic poisoning (sodium arsenate 1 mg/kg orally 6  
528 days a week of 3 weeks). Both also restored arsenic-induced inhibition of  $\delta$ -  
529 aminolevulinic acid dehydratase activity and hepatic glutathione concentrations.  
530 Although both antidotes reduced arsenic-induced histopathological lesions, succimer  
531 was more effective (Flora et al., 1995a). Another study on chronic arsenic exposure  
532 compared succimer and dimercaprol. Rats were fed a diet containing 1000 ppm of  
533 arsenic for 17 days followed by intraperitoneal succimer or dimercaprol (30 mg/kg/day)  
534 for 4 days. There were significant differences in the arsenic organ concentrations in  
535 animals treated with succimer or dimercaprol, but they were significantly less than  
536 controls. On a molar basis succimer was more effective than dimercaprol. Urinary  
537 excretion on day 1 and faecal excretion on day 2 was significantly higher with  
538 succimer than dimercaprol (Graziano et al., 1978b).

539  
540 In mice given arsenic (5 mg subcutaneously as arsenic trioxide) immediately followed  
541 by succimer (100 mg/kg intraperitoneally) 80.6% and 81.3% of the arsenic dose was  
542 excreted in the urine within 24 and 48 hours, respectively, but these figures were not  
543 significantly different from the controls. However, there was a significant difference in  
544 urinary excretion in the first 12 hours: 76.3% compared to 37.8% in controls. There  
545 was no significant change in faecal excretion of arsenic (Maehashi & Murata, 1986).

546  
547 Flora et al. (2005) compared the efficiency of succimer, unithiol and monoisoamyl-  
548 succimer in rats with chronic arsenic exposure (100 ppm sodium arsenite in drinking  
549 water for 10 weeks). Antidotes were given after arsenic exposure at a dose of 50  
550 mg/kg for 5 days. Succimer was not effective at resolving arsenic-induced oxidative  
551 damage to cells or in reducing the arsenic burden. Unithiol was moderately effective  
552 against the generation of reactive oxygen species due to intracellular access.  
553 However, monoisoamyl-succimer was the most effective antidote in reducing reactive  
554 oxygen species in the blood and brain. It was also marginally better at restoring the  
555 activity of antioxidant enzymes.

556  
557 An *in vitro* study of guinea-pig liver treated with arsenic trioxide demonstrated that  
558 administration of succimer (and other antidotes) resulted in a shift to faecal elimination  
559 by increasing biliary excretion of arsenic. 2,3-bis-(acetylthio)-propanesulphonamide  
560 (BAPSA) was the most effective followed by unithiol, succimer and then dimercaprol  
561 (Reichl et al., 1990).

562  
563 Quantitative comparisons of dimercaprol, D-penicillamine, unithiol and succimer as  
564 antidotes for acute arsenic intoxication in mice (Aposhian et al., 1981; Kreppel et al.,  
565 1989) demonstrate that D-penicillamine is virtually without antidotal effect, and that  
566 dimercaprol is 20-40 times less efficient than unithiol and succimer. Unithiol and  
567 succimer have similar efficiency but succimer is considered the less toxic of the two.

#### 568 569 **8.1.4 Beryllium**

570  
571 Succimer has been shown to enhance beryllium excretion and reduce beryllium-  
572 induced toxic effects in experimental animals but unithiol appears to more effective.

573  
574 In rats treated with beryllium (2.5 mg/kg intraperitoneally, as beryllium nitrate),  
575 immediate administration of succimer (50 mg/kg intraperitoneally) or unithiol (same  
576 dose) was shown to prevent most beryllium-induced biochemical alterations and  
577 reduce tissue beryllium concentrations. Unithiol was relatively more effective and  
578 resulted in significantly less marked lesions in the liver and kidneys than succimer  
579 (Mathur et al., 1994).

580  
581 In another study beryllium nitrate was given to rats for 21 days (0.5 mg/kg, orally daily  
582 for 5 days/week) and succimer or unithiol (25 or 50 mg/kg, twice daily for 5 days) was  
583 administered 24 hours after the last dose of beryllium. Both drugs cause mobilisation  
584 of beryllium into the faeces but the rate of removal was greater with unithiol. Unithiol  
585 was also effective at reducing beryllium in the liver, spleen and kidneys. Also hepatic  
586 and renal histopathological lesions were less marked with unithiol compared to those  
587 in animals treated with succimer (Flora et al., 1995b).

588

589 In contrast succimer administration (0.7 mmol/kg intraperitoneally) decreased the LD<sub>50</sub>  
590 of beryllium chloride in mice from 277 mg/kg to 247 mg/kg, but the effect was not  
591 significant (Pethran et al., 1990).

592

### 593 **8.1.5 Bismuth**

594

595 In experimental animals both succimer and unithiol have been shown to be effective  
596 antidotes and mobilisers of tissue bismuth.

597

598 In a study comparing antidote efficacy in bismuth poisoning, mice were given  
599 intraperitoneal bismuth citrate followed by an antidote 20 minutes later in a 10:1 molar  
600 ratio antidote:bismuth. All animals treated with succimer survived and all in the control  
601 group died. Further, succimer extensively reduced the deposition of bismuth in liver  
602 and kidneys (Basinger et al., 1983).

603

604 In another study rats were injected intraperitoneally with colloidal bismuth subcitrate  
605 (50 µmol/kg/day, for 14 days). The antidotes were given twice daily (250 µmol/kg/day)  
606 for 3 days. The animals were killed on the fourth day and tissue samples analysed.  
607 Unithiol, succimer and dimercaprol were most effective in lowering bismuth  
608 concentrations in most organs, particularly the kidney and liver, resulting from higher  
609 elimination in urine by unithiol and dimercaprol. Dimercaprol was the only antidote  
610 effective in lowering bismuth concentrations in brain tissue. It was concluded that  
611 unithiol and succimer were the antidotes of choice, with dimercaprol, because of its  
612 own toxicity, reserved for very severe bismuth poisoning (Slikkerveer et al., 1992).

613

614 Succimer was shown to reduce the whole-body burden of bismuth in mice given an  
615 intraperitoneal injection of bismuth acetate. The succimer was given in drinking water  
616 (100, 300 or 600 µg/mL) two days prior to and three days after the bismuth. Unithiol  
617 was more effective than succimer at preventing accumulation of bismuth in the femur  
618 and the kidney in mice (Jones et al., 1996).

619

### 620 **8.1.6 Cadmium**

621

622 Antidotal therapy for cadmium is particularly problematic because the absorbed metal  
623 rapidly becomes strongly bound to metallothionein, a low-molecular weight metal-  
624 binding protein whose synthesis is induced by cadmium. The efficacy of a large  
625 number of metal-binding agents, belonging to several chemical compound groups, has  
626 been investigated in cadmium toxicity (reviewed in Andersen, 1989a, 1989b), but in  
627 the majority of acute toxicity studies in experimental animals, both cadmium and  
628 antidote were injected at about the same time, reducing the relevance in relation to  
629 acute human intoxication. These studies have concluded that, although succimer has  
630 some effect, particularly in acute cadmium exposure (Cantilena & Klaassen, 1981;  
631 Eybl et al., 1984; Basinger et al., 1988; Andersen & Nielsen, 1988; Andersen, 1989a;  
632 Srivastava et al., 1996), other metal-binding agents appear to be more efficacious  
633 (Jones et al., 1978; Basinger et al., 1981b; Andersen 1989b). Also results have been  
634 conflicting, for example succimer has been shown to reduce (Bakka & Aaseth, 1979;  
635 Mason, 1981), increase (Eybl et al., 1984) and not affect (Bakka & Aaseth, 1979;  
636 Cantilena & Klaassen, 1981; Shinobu et al., 1983) kidney concentrations of cadmium.  
637 However, this is probably an effect of differences in doses used and times of  
638 administration. Delayed administration of succimer has been shown to greatly reduce  
639 its efficacy in cadmium-poisoned experimental animals (Cantilena & Klaassen, 1982a;

640 Planas-Bohne & Lehman, 1983) and in some cases it has been shown to be  
641 ineffective in these circumstances (Gale et al., 1983; Shinobu et al., 1983; Rau et al.,  
642 1987).

643  
644 Subcutaneous injection of succimer reduced cadmium sulphate lethality in mice and  
645 raised the LD<sub>50</sub> from 6 to 13 mg/kg (Ting et al., 1965). Similarly, succimer  
646 administration (0.7 mmol/kg intraperitoneally) increased the LD<sub>50</sub> of cadmium chloride  
647 in mice from 9.1 mg/kg to 41.2 mg/kg (Pethran et al., 1990). Cantilena & Klaassen  
648 (1981) also found that succimer (0.74 g/kg intraperitoneally) increased survival in mice  
649 when given immediately after intravenous injection of cadmium (4-10 mg of  
650 cadmium/kg). There were significant increases in urinary excretion of cadmium and  
651 reduction in faecal excretion. Succimer also resulted in significant decreases in the  
652 cadmium concentration in the liver and brain, although there was no significant  
653 change in the kidneys. Another study by Cantilena & Klaassen (1982a) demonstrated  
654 the importance of time on the efficacy of antidotes in cadmium toxicity. Succimer  
655 (0.74 g/kg intraperitoneally) was administered 0, 2, 13, 36 or 72 hours after  
656 administration of intravenous cadmium (1 mg/kg). For all antidotes, administration  
657 immediately after cadmium resulted in 50-70% of the dose eliminated in the urine  
658 compared with 0.1% in controls. Although, later doses also increased elimination the  
659 effect was less than that observed with immediate administration. Succimer caused a  
660 30% decrease in the renal cadmium concentration when given immediately after the  
661 metal but there was no effect when given later. This lack of effect with delayed  
662 antidote administration was also seen with cadmium concentrations in the liver.

663  
664 In a study comparing antidote efficacy, mice were given intraperitoneal cadmium  
665 chloride at the previously determined LD<sub>50</sub> (0.0267 mmol/kg). This was immediately  
666 followed by the antidote at a dose of 1:2 or 1:5 (cadmium:antidote) molar ratios by the  
667 same route. The animals were killed after 14 days. Succimer and unithiol were found  
668 to be most effective at reducing lethality and the cadmium burden of the liver, kidneys  
669 and brain tissue. The therapeutic index and therapeutic efficacy was highest for  
670 succimer followed by unithiol (Srivastava et al., 1996).

671  
672 Succimer had no significant effect on survival rate in cadmium-poisoned mice when  
673 administered intraperitoneally immediately after subcutaneous cadmium (20 mg/kg as  
674 cadmium chloride) at antidote to metal molar ratios of 1:1. At an antidote to metal  
675 molar ratio of 2:1 there was a significant increase in survival and at a ratio of 5:1 the  
676 survival rate was 100%, compared to the survival rate with unithiol of only 20%. In  
677 another study where cadmium (0.5 mg/kg intravenously) was immediately followed by  
678 succimer at a dose of 10:1, there were significant decreases in cadmium  
679 concentrations in the liver and gastrointestinal tract and a reduction in body burden.  
680 However, the cadmium concentration was increased in the kidneys with succimer.  
681 Cadmium-induced lipid peroxidation was also prevented with succimer administration  
682 (Eybl et al., 1984).

683  
684 Succimer (3.61 mmol/kg) was as effective as unithiol (same dose) in promoting  
685 survival in cadmium poisoned mice (1 mmol/kg cadmium chloride orally) when given  
686 immediately after administration of cadmium. Succimer was the most effective  
687 antidote in terms of survival and reduced cadmium concentrations in the liver and  
688 kidney. Animals killed after 2 days showed no evidence of liver or stomach necrosis  
689 or evidence of kidney damage (Basinger et al., 1988).

690

691 Another study in mice compared antidote efficacy when given intravenously 10  
692 seconds, 1 or 3 hours after intravenous cadmium chloride (3  $\mu\text{mol/kg}$ ) administration.  
693 When given immediately after cadmium administration, all agents reduced the body  
694 burden of cadmium but efficacy declined when dosing occurred at 1 or 3 hours after  
695 administration. Succimer was more effective than unithiol (Planas-Bohne & Lehman,  
696 1983).

697  
698 Succimer did not affect faecal excretion of cadmium and the increase in urinary  
699 excretion was too small to affect body burden in rats given 0.4 mmol/kg of succimer  
700 following dosing with radiolabelled cadmium (3  $\mu\text{mol/kg}$  as cadmium chloride). The  
701 cadmium was given once; administration of the metal-binding agent started on the  
702 third day and was given daily, 5 times a week for 2 weeks (Rau et al., 1987).  
703 Administration of succimer (0.1 mmol/kg) 3 days after intravenous exposure to  
704 cadmium did not affect biliary excretion of the metal in rats (Zheng et al., 1990).

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

714  
715 In a study of antidotal efficacy in chronic cadmium poisoning in mice (2 mg of  
716 cadmium chloride intraperitoneally at 48 hours intervals for 5 doses) succimer  
717 administration (195 mg/kg intraperitoneally) one week later resulted in no significant  
718 changes in liver or kidney cadmium concentrations (Shinobu et al., 1983).

719  
720 The cadmium concentration in rats treated with succimer was studied by Mason  
721 (1981). Rats were given 3 doses (in some experiments 5 doses) of cadmium (1 mg/kg  
722 subcutaneously) at 48 hour intervals. Starting 7 days after the last dose the animals  
723 were given succimer (50 mg/kg intraperitoneally) daily 5 days a week for 17 days.  
724 Liver concentrations of cadmium were lower in succimer-treated animals but the  
725 kidney concentration was unchanged.

726  
727 Gale et al. (1983) compared the efficacy of several metal-binding antidotes in mice  
728 given a sublethal intraperitoneal dose of cadmium (0.03 mg cadmium chloride). The  
729 antidote was given 4 weeks later. Succimer (404 mg/kg 3 times a week for 7 or 13  
730 doses) was ineffective; it did not reduce the cadmium concentration in any organ or  
731 the total body retention of cadmium, and urinary and faecal excretion were  
732 unchanged.

733  
734 Succimer provided complete protection against lethality in mice given radiolabelled  
735 cadmium chloride (0.53 mmol/kg by stomach tube) followed by the antidote (2.12  
736 mmol/kg) 15 minutes later. The animals were killed after 10 days. Penicillamine,  
737 succimer and unithiol were all able to reduce peristaltic toxicity of cadmium chloride  
738 and all reduced whole-body retention of cadmium; succimer was most effective at  
739 reducing body retention. Succimer, and particularly unithiol, decreased hepatic  
740 deposition of cadmium and increased relative deposition in the kidneys and lungs. It  
741 was concluded that succimer was the most effective antidote for cadmium poisoning

742 (Andersen & Nielsen, 1988). However, succimer had only a minor effect on organ  
743 distribution of cadmium; it slightly enhanced the relative deposition of cadmium in  
744 lungs, kidneys and carcass and slightly reduced the relative hepatic deposition of  
745 cadmium (Andersen & Nielsen, 1988; Andersen 1989a). Also parenteral  
746 administration of antidotes reduced the toxicity of oral cadmium (Andersen 1989a).  
747

748 The combined data from the reviews by Andersen (1989a; 1989b) indicate that after  
749 oral administration of highly toxic doses of cadmium, oral administration of succimer  
750 efficiently reduced toxicity and intestinal cadmium uptake, while intraperitoneal  
751 administered succimer had only a marginal antidotal effect. Based on experimental  
752 data, the optimal antidotal treatment of acute oral cadmium intoxication is oral  
753 administration of succimer or parenteral treatment with pentetic acid  
754 (diethylenetriaminepentaacetic acid, DTPA). Combined administration of oral  
755 succimer (2, 4 or 6 mmol/kg) and intraperitoneal triethylenetetraaminehexaacetic acid  
756 (TTHA; 250, 500 or 750  $\mu$ mol/kg) 15 minutes after an oral dose of cadmium chloride  
757 (0.5, 1 or 1.5 mmol/kg) at greater than the LD<sub>99</sub> reduced the whole-body retention of  
758 cadmium in mice but did not change the relative tissue distribution (Andersen, 1989a).  
759 This result is unique, as it is the only published demonstration, that two antidotes may  
760 act synergistically when applied after administration of cadmium by a route relevant for  
761 human exposure.  
762

763 In a study comparing meso-succimer and racemic-succimer in rats, both antidotes  
764 caused a moderate reduction in whole-body retention of cadmium with racemic-  
765 succimer slightly more efficient than meso-succimer. Rats were given an  
766 intraperitoneal injection of radiolabelled cadmium chloride (0.03 mg) followed by  
767 succimer (1 mM/kg) 1 hour and 24 hours later. Whole-body counting was conducted  
768 on days 1, 2, 3 and 6. At the end of the experiment both agents caused a decrease in  
769 cadmium whole-body retention with a decrease of 83% in controls and 74% and 64%  
770 in groups treated with meso-succimer and racemic-succimer, respectively. The  
771 reduction was the same with body agents for cadmium retention in the liver (57% in  
772 controls and 47% in both groups of succimer-treated animals). Only racemic-succimer  
773 produced a significant reduction in retention of cadmium in the kidney (Blanuša et al.,  
774 2000).  
775

776 An *in vitro* study on mouse fibroblasts found that succimer was ineffective at reducing  
777 cadmium-induced cell injury (as measured by lysosomal incorporation of neutral red)  
778 (Borenfreund & Puerner, 1986). In another study succimer had only a slight effect in  
779 reducing the cytotoxicity of cadmium in mammalian cell culture (Fischer, 1995).  
780 Incubation of cadmium-saturated metallothionein with succimer resulted in release of  
781 cadmium, although DMPA was more effective (Zheng et al., 1990). Succimer  
782 increased cadmium-induced inhibition of  $\delta$ -aminolevulinatase (ALAD) in rat  
783 lung *in vitro* (Luchese et al., 2007).  
784

### 785 **8.1.7 Chromium**

786  
787 There is limited information on succimer in chromium poisoning. Lethality was  
788 reduced in mice injected with chromate (40 mg/kg intraperitoneally as potassium  
789 chromate) and then succimer (500 mg/kg intraperitoneally) immediately afterwards. At  
790 half the chromate dose and 300 mg/kg of succimer the liver and kidney content of  
791 chromium was reduced compared to controls. There was also increased renal

792 excretion of chromium and suppression of chromate-induced increase in serum  
793 ornithine carbamyl transferase activity (Susa et al, 1994).

794  
795 Chromate-induced cytotoxicity (as measured by the chromate content of cells and  
796 inhibition of cell growth) was reduced in the presence of succimer. This was only the  
797 case when cells were incubated with succimer and chromate. If the succimer was  
798 added before or after treatment with chromate it failed to restore chromate-induced  
799 cytotoxicity or reduce cellular chromate concentrations (Susa et al, 1994).

800

### 801 **8.1.8 Cobalt**

802

803 Succimer is effective in cobalt poisoning but more efficacious antidotes are available.

804

805 Intravenous or intraperitoneal administration of succimer soon after intraperitoneal  
806 administration of cobalt chloride to mice reduced lethality as well as the concentrations  
807 of cobalt in various organs (Eybl et al., 1985a; Llobet et al., 1985, 1986). However, in  
808 these studies sodium calcium edetate and pentetic acid were more efficient antidotes  
809 than succimer.

810

811 Intravenous administration of succimer (1 g/kg) to mice 10 minutes after administration  
812 of cobalt chloride (200 mg/kg intraperitoneally) reduced lethality from 19/20 to 4/20  
813 (Ting et al., 1965). Another study also demonstrated reduced lethality in mice where  
814 peritoneal succimer was given immediately after intraperitoneal injection of cobalt  
815 chloride. Although the faecal and urinary excretion of cobalt was reported not to be  
816 affected by succimer, the cobalt content of major organs was found to be reduced by  
817 the succimer treatment. The optimal antidote in this study, however, was sodium  
818 calcium edetate (Llobet et al., 1986).

819

820 In another study, the same group (Llobet et al., 1985) used a similar experimental  
821 design. The ED<sub>50</sub> for succimer was found to be 1.5 mmol/kg for preventing lethality  
822 after 1.18 mmol cobalt chloride. Sodium calcium edetate and pentetic acid were  
823 more efficient than succimer. In a similar study, succimer increased the total body  
824 burden and did not change the deposition of cobalt in major organs; pentetic acid was  
825 the most efficient antidote (Eybl et al., 1985a).

826

### 827 **8.1.9 Copper**

828

829 Succimer appears to be of benefit in copper-poisoned experimental animals, but  
830 unithiol is more effective.

831

832 Intravenous succimer (1 g/kg) reduced the lethality of intraperitoneal copper chloride  
833 (20 mg/kg) from 86% to 5% in mice (Ting et al., 1965). Similarly, succimer  
834 administration (0.7 mmol/kg intraperitoneally) increased the LD<sub>50</sub> of copper chloride in  
835 mice from 59 mg/kg to 126 mg/kg (Pethran et al., 1990).

836

837 In normal mice the mean 24 hours urinary excretion of copper after succimer (1  
838 mmol/kg twice daily for 4 days) was 17.9 µg compared to 32.8 µg after unithiol  
839 (Aposhian et al., 1989). Oral administration of succimer increases the urinary copper  
840 excretion in rats injected with copper (Yan et al., 1993). Also in a study in copper-  
841 poisoned mice by Jones et al. (1981), although succimer was highly efficient in  
842 reducing lethality, unithiol was more effective.

843  
844 Further, these antidotes agents reduced copper-induced haemolysis of human red  
845 blood cells *in vitro* (Aaseth et al., 1984). At a concentration of 0.3 mM succimer  
846 reduced the copper-induced haemolysis from 15% to 2.0-2.5%. At 0.1 mM it was less  
847 effective and reduced haemolysis to 8%. Similarly, incubation of human red blood  
848 cells with copper sulphate and succimer reduced copper-induced haemolysis from  
849 15% to 2% (Yang et al., 1987). In contrast, an *in vitro* study on mouse fibroblasts  
850 found that succimer was ineffective at reducing copper-induced cell injury (as  
851 measured by lysosomal incorporation of neutral red) (Borenfreund & Puerner, 1986).

#### 852 853 **8.1.10 Gold**

854  
855 Experimental animal studies have demonstrated that succimer is an effective antidote  
856 for acute gold intoxication, and efficiently reduced the toxicity of intraperitoneal sodium  
857 bis(thiosulfato)gold(I) (Basinger et al., 1985) and the nephrotoxicity of injected gold  
858 sodium thiomalate (Kojima et al., 1991). Several studies (Aaseth et al., 1980; Mason,  
859 1983; Basinger et al., 1985, Kojima et al., 1991) have shown that succimer significantly  
860 enhances the excretion of gold after injection of gold compounds in rats or mice.

861  
862 Succimer and unithiol were the most effective antidotes at increasing survival in mice  
863 given gold sodium thiosulphate (200 mg/kg intraperitoneally, the approximate LD99).  
864 The antidotes were given by the same route 20 minutes after dosing at a ratio of 3:1,  
865 antidote to gold. Survival was 18/20 in the succimer-treated mice and 16/20 in those  
866 given unithiol (Basinger et al., 1985).

867  
868 In rats injected with gold sodium thiomalate (up to 0.198 mmol/kg intravenously),  
869 treatment with D-penicillamine, unithiol or succimer reduced renal toxicity, as measured  
870 by urinary concentrations of protein, aspartate aminotransferase and glucose, and the  
871 blood urea nitrogen concentration. In addition all three antidotes increased urinary  
872 excretion of gold and significantly decreased liver and renal gold concentrations.  
873 Unithiol was the most effective antidote tested and succimer the least effective of the  
874 three (Kojima et al., 1991). Characterisation of the gold in urine following treatment with  
875 gold sodium thiomalate and then succimer has shown that it is present as a gold-  
876 succimer complex. In the bile it was present as a gold-succimer complex, high  
877 molecular weight compounds (probably proteins) and gold-L-cysteine (Kojima et al.,  
878 1992).

879  
880 Seven daily administrations to mice of succimer (1 mmol/kg) after a single intramuscular  
881 injection of aurothiomalate (35 µmol/kg) significantly enhanced the excretion of gold  
882 compared to control animals given only the gold injection (Aaseth et al., 1980). In this  
883 study, D-penicillamine was more efficient than succimer in mobilising gold. A two week  
884 treatment period with succimer (50 mg/kg/day) after a single subcutaneous injection of  
885 gold (5 mg/kg as sodium aurothiolate) to rats reduced the renal gold concentration by  
886 50% compared to non-treated rats (Mason, 1983).

#### 887 888 **8.1.11 Lead**

889  
890 Succimer has been shown to increase lead excretion, reduce lead tissue  
891 concentrations (including the brain in some studies) and to reduce lead-induced toxic  
892 biochemical effects, such as inhibition of  $\delta$ -aminolevulinic acid dehydratase, in  
893 experimental animals. Reports specifically investigating the effects of succimer on

894 gastrointestinal lead absorption, brain lead concentrations and lead-induced  
895 neurotoxicity are discussed in separate sections (see 8.1.11.1, 8.1.11.2 and 8.1.11.3,  
896 respectively).

897  
898 Succimer was more efficient than D-penicillamine in reducing tissue concentrations  
899 and enhancing the urinary excretion of lead in mice and rats. Orally or parenterally  
900 administered succimer efficiently reduced lead tissue concentrations and enhanced  
901 the urinary excretion of lead in experimental animals treated with lead acetate, thus  
902 succimer reduced the brain, bone, spleen, liver and kidney concentrations of lead in  
903 mice (Friedheim et al., 1976) and rats (Graziano et al., 1978a). Succimer efficiently  
904 reduced tissue and bone lead and enhanced urinary lead excretion in rabbits given  
905 lead acetate. In this study, succimer corrected lead-induced disturbances in porphyrin  
906 metabolism (Okonishnikova et al., 1976).

907  
908 Injected succimer and injected cyclohexanediaminetetraacetic acid (CDTA) were the  
909 most efficient of 16 antidotes tested against acute parenteral lead intoxication in mice.  
910 The antidotes (2 mmol/kg) were injected during 3 consecutive days after 7 daily  
911 injections of lead (50 mg/kg). In this study, injected unithiol, sodium calcium edetate  
912 and D-penicillamine did not protect against lethality. Unithiol was, however, more  
913 efficient than succimer and several other antidotes including sodium calcium edetate  
914 in removing lead from the brain and kidneys. In a limited experiment sodium calcium  
915 edetate and D-penicillamine were only marginally efficient after oral administration,  
916 while oral administration of succimer significantly reduced liver, kidney, brain and bone  
917 lead concentrations (Xu & Jones, 1988).

918  
919 In the study by Llobet et al. (1990) succimer administration at a dose of 2.90 mmol/kg  
920 given 10 minutes after intraperitoneal lead (0.58 mmol/kg of lead acetate trihydrate)  
921 reduced lethality in mice from 55% to 40%. Succimer also caused a significant  
922 increase in urinary lead but had no significant effects on organ concentrations of lead.

923  
924 Tandon et al. (1994) investigated the efficacy of combined metal-binding agents in  
925 lead-poisoned rats (lead acetate 0.1% in drinking water for 8 weeks). Animals were  
926 treated with sodium calcium edetate, succimer, unithiol, sodium calcium edetate and  
927 succimer or sodium calcium edetate and unithiol. All metal-binding agents were given  
928 in the same dose (0.3 mmol/4 mL/kg intraperitoneally) for 5 days, followed after a 5  
929 day break by another 5 day course. Efficacy was measured by metal concentrations  
930 in tissues and biochemical changes (blood  $\delta$ -aminolevulinic acid dehydratase activity,  
931 zinc protoporphyrin, urinary  $\delta$ -aminolevulinic acid and total urinary proteins). The  
932 administration of sodium calcium edetate or succimer resulted in more urinary lead  
933 excretion than unithiol. In addition, the combination of sodium calcium edetate and  
934 succimer was more effective than sodium calcium edetate and unithiol. Both sodium  
935 calcium edetate and succimer were more effective than unithiol in reducing lead  
936 concentrations in blood, liver, kidney and femur. Only succimer reduced brain lead  
937 concentrations. All the metal-binding agents reversed lead-induced inhibition of  $\delta$ -  
938 aminolevulinic acid dehydratase activity and increases in zinc protoporphyrin and  
939 urinary excretion of  $\delta$ -aminolevulinic acid, but the effect was greater with combined  
940 therapy. Again the combination of sodium calcium edetate and succimer was more  
941 effective than sodium calcium edetate and unithiol.

942  
943 In acute parenteral lead intoxication in rats (40 mg/kg by intraperitoneal injection daily

944 for 5 days), injected sodium calcium edetate (25 mmol/kg intraperitoneally daily for 5  
945 days) or orally administered succimer (12.5 mmol/kg orally twice daily for 5 days) were  
946 equally efficient in increasing the erythrocyte  $\delta$ -aminolevulinic acid dehydratase  
947 activity and decreasing the urinary excretion of  $\delta$ -aminolevulinic acid towards normal  
948 concentrations. When administered together, these antidotes were even more  
949 effective. In the same study, oral succimer was more effective than injected sodium  
950 calcium edetate in lowering blood, liver, kidney and brain concentrations of lead,  
951 whereas sodium calcium edetate slightly increased the lead concentration in brain  
952 tissue. There was no difference in the urinary lead excretion between the two agents.  
953 Again, combined antidote treatment was more effective in enhancing urinary lead  
954 excretion and reducing organ lead concentrations, except in the brain (Flora et al.,  
955 1995c). In another dose-response experiment with the same dosing regimen, similar  
956 results were obtained. The most important result in that study was an extensive and  
957 consistent reduction in brain and bone lead concentrations in animals treated with  
958 various combinations of both antidotes, or with one at a comparatively high dosage  
959 (Tandon et al., 1998).

960  
961 Jones et al. (1994) investigated the effect of various metal-binding agents in lead  
962 poisoned mice (10 intraperitoneal injections of lead 5 mg/kg, as lead acetate, over 12  
963 days). Antidotes were started 3 days after the last lead dose and given by  
964 intraperitoneal injection at a dose of 1 mmol/kg/day for 4 doses with or without another  
965 4 doses 3 days later. In a second experiment mice were given lead at twice the dose  
966 of the first experiment over an additional 2 week period. Mice were then treated with  
967 succimer or sodium calcium edetate 1 mmol/kg/day over a 12 day period. Sodium  
968 calcium edetate, pentetic acid and succimer all consistently reduced brain and kidney  
969 lead concentrations. Bone lead was mobilised by some treatments with sodium  
970 calcium edetate or succimer, but less effectively than soft organ lead. The authors  
971 summarised available data on effects of succimer and sodium calcium edetate on  
972 brain lead concentrations and concluded that succimer treatment reduces brain lead  
973 concentrations under all conditions hitherto examined.

974  
975 Pappas et al. (1995) studied the effect of oral succimer administration on urinary  
976 excretion of  $\delta$ -aminolevulinic acid and lead, blood zinc protoporphyrin concentrations,  
977 and tissue concentrations of lead in rats exposed to lead in drinking water for 35 days,  
978 both during and after cessation of lead exposure. Even in rats still exposed to lead,  
979 succimer reversed the haematological effects of lead, increased urinary lead excretion  
980 and decreased blood, brain, kidney, liver and bone lead concentrations.

981  
982 In a controlled study of rats exposed to lead acetate (0.01 or 0.5% in drinking water for  
983 6 months), succimer (three 5 day courses of 0.5% over 6 months) was not able to  
984 reverse the experimentally-induced lead nephropathy. A slight improvement in renal  
985 function, but not in the pathological alterations, was most likely mediated by the  
986 haemodynamic effect of succimer (Khalil-Manesh et al., 1992).

987  
988 Yu et al. (2008) studied the effect of succimer on fetal development in lead-exposed  
989 mice. After exposure to lead acetate (0.1% in drinking water) for 4 weeks, female  
990 mice were mated and 4 days later given succimer (50 mg/kg) or succimer (50 mg/kg),  
991 calcium carbonate (400 mg/kg) and ascorbic acid (100 mg/kg). The treatments were  
992 given in water, by gavage, every other day until parturition. Succimer, although it  
993 decreased the blood lead concentrations in the mothers, increased lead

994 concentrations in the liver and bone of the fetuses and delayed early physical and  
995 neural development of offspring (as measured by pinna unfolding, incisor eruption,  
996 eye opening and righting reflex and cliff avoidance, respectively). Use of calcium and  
997 ascorbic acid reduced the transfer of lead to the fetus.  
998

999 Growth in weight, length or head circumference in monkeys exposed to lead (in oral  
1000 fluids) from birth to 1 or 2 years of age did not vary significantly as a function of the  
1001 blood lead concentration. Succimer therapy (30 mg/kg/day for 5 days then 20 mg/kg  
1002 for 14 days at 53 and 65 weeks of age) did not significantly affect weight, length or  
1003 head circumference. Target blood lead concentrations were 350-450 µg/L (1.69-1.93  
1004 µmol/L) and antidote therapy and cessation of exposure reduced lead concentrations  
1005 significantly faster than cessation of exposure alone, but this effect was lost after  
1006 succimer therapy ceased. This study demonstrated that blood lead concentrations  
1007 associated with reduced size in human children is not associated with a similar effect  
1008 in monkeys over the first 2 years of life (Lasky et al., 2001).  
1009

1010 Smith et al. (2000) investigated succimer-induced excretion of essential elements in  
1011 rhesus monkeys chronically exposed to lead from birth to 1 year of age. Lead had  
1012 been given daily in oral fluids to achieve a blood lead concentration of 350-450 µg/L.  
1013 Lead administration was stopped when succimer treatment was started at 1 year.  
1014 Succimer was given in the standard regimen: 10 mg/kg 3 times a day for 5 days then  
1015 twice daily for 14 days. Blood lead concentrations fell dramatically in the succimer-  
1016 treated and control animals, although in the former it declined significantly more.  
1017 Succimer rapidly and significantly increased urinary lead concentrations and  
1018 collectively the total urinary excretion of lead increased by more than 4-fold in the  
1019 succimer-treated group. Succimer also increased the urinary excretion of essential  
1020 elements (calcium, iron, manganese, nickel, zinc, cobalt, copper and magnesium) but  
1021 only when the cumulative total excretion over the first 5 days was considered. None  
1022 of the increases were significant when the elements were considered individually,  
1023 although zinc was only marginally non-significant. Succimer, therefore, has a small  
1024 but measurable effect on essential element excretion.  
1025

1026 A study in rats demonstrated that antidotal therapy in combination with zinc and  
1027 copper supplementation was more effective at lowering blood lead concentrations  
1028 than the antidote alone. In addition, supplementation with succimer administration  
1029 (0.3 mmol/kg intraperitoneally, daily for 5 days) restored δ-aminolevulinic acid  
1030 dehydratase concentrations and reduced blood zinc protoporphyrin concentrations.  
1031 However, the lead concentration in the brain was increased with supplementation and  
1032 succimer treatment, but the rise was not significant. The lead was administered at a  
1033 dose of 0.05 mmol/kg daily, 6 days/week for 6 weeks (Flora, 1991).  
1034

1035 In mouse cortical cell cultures succimer had no effect on the toxicity of lead chloride  
1036 (Rush et al., 2009) and it increased lead-induced inhibition of ALAD in human blood *in*  
1037 *vitro*. In addition the inhibition of ALAD activity in the blood, kidney and liver of lead-  
1038 exposed mice was increased by succimer treatment (Santos et al., 2006).  
1039

1040 In most available animal studies, antidotal therapy was initiated soon after short-term  
1041 parenteral lead administration. After prolonged exposure of rats to lead in drinking  
1042 water, which is a more realistic exposure regimen in relation to occupational or  
1043 environmental lead poisoning, repeated injections of succimer resulted in extensive  
1044 reductions in lead concentrations in the blood, brain, liver and kidney, however, bone

1045 lead concentrations were not affected. Four months after cessation of succimer  
1046 treatment, blood and soft tissue lead concentrations had increased due to  
1047 redistribution of bone lead (Cory-Slechta, 1988) indicating extensive redistribution of  
1048 bone lead and necessity of several courses of treatments with succimer in chronic  
1049 lead intoxication. This is in agreement with the clinical evidence (see the section on  
1050 human studies).

1051  
1052 Based on the extensive database reviewed above, succimer seems to be the most  
1053 efficacious antidote both in reducing lethality, preventing intestinal uptake, enhancing  
1054 excretion and decreasing brain lead concentrations (Friedheim et al., 1976;  
1055 Okoshnikova et al., 1976; Graziano et al., 1978a; Cory-Slechta, 1988; Xu & Jones,  
1056 1988; Jones et al., 1994; Flora et al., 1995c; Aposhian et al., 1995; Tandon et al.,  
1057 1998). Either oral succimer alone or the combination of oral succimer and parenteral  
1058 sodium calcium edetate may be the most efficient antidote treatment presently  
1059 available.

1060

#### 1061 **8.1.11.1 Effect of succimer on gastrointestinal lead absorption**

1062

1063 An important question in the management of lead intoxication is the possible  
1064 enhancing or inhibiting effect of antidotes on intestinal lead absorption.

1065

1066 In a study to investigate this concern rats were given a single oral dosage of  
1067 radiolabelled lead-203 (25 mg/kg), followed by whole-body counting and counting of  
1068 total urine collected in metabolism cages and treated with one of several antidotes.  
1069 Parenteral administration of 0.11 mmol/kg of sodium calcium edetate, succimer, D-  
1070 penicillamine or dimercaprol immediately after administration of lead increased the  
1071 intestinal lead uptake (estimated as the whole-body retention plus the urinary lead  
1072 output at 144 hours after dosing). However, the net retention of lead (estimated as the  
1073 whole-body retention) was not affected by antidote therapy, except for a slight  
1074 increase in dimercaprol-treated animals. Also, oral administration of the antidotes  
1075 immediately after the oral lead dosage did not increase the intestinal lead absorption.  
1076 The whole-body retention, however, was extensively reduced in groups given sodium  
1077 calcium edetate or succimer orally, but not in groups given dimercaprol or D-  
1078 penicillamine orally. The oral administration of succimer following oral dosing with  
1079 lead markedly reduced the passage of lead from the gut into the body, indicating that  
1080 the succimer-lead complex is poorly absorbed (Kapoor et al., 1989). Graziano et al.  
1081 (1978a) found that dietary succimer protected against the metabolic toxicity of dietary  
1082 lead. Mice had raised erythrocyte protoporphyrin after being fed a diet containing 600  
1083 ppm lead; this effect did not occur when succimer was added to the diet.

1084

1085 Succimer was found to decrease gastrointestinal absorption of lead in monkeys.  
1086 Rhesus monkeys were exposed to lead in oral fluids daily from birth to 1 year of age to  
1087 achieve a blood concentration of 350 to 400 µg/L. Animals were given an intravenous  
1088 (5 µg) and oral (72.6 µg) dose of lead-204 immediately before succimer treatment to  
1089 evaluate gastrointestinal absorption and whole-body retention. Oral succimer was  
1090 given in the standard 19 day regimen starting at 53 and 65 weeks of age. Succimer  
1091 significantly reduced the gastrointestinal absorption of lead compared to controls. It  
1092 also increased the urinary excretion of endogenous lead by 4-fold and decreased  
1093 faecal excretion of endogenous lead by 33%. Although succimer reduced whole-  
1094 body retention of endogenous lead, the majority of the lead tracer (77%) was retained  
1095 when assessed after 5 days of treatment (Cremin et al., 2001).

1096  
1097 **8.1.11.2 Effect of succimer on brain lead concentrations**  
1098  
1099 Smith et al. (1998) studied the relationship between brain and blood lead  
1100 concentrations during oral succimer treatment of rats exposed to lead in the drinking  
1101 water for 30 or 40 days from birth. Seven days of treatment reduced lead  
1102 concentrations in the blood much more than in the brain. Continued treatment for a  
1103 total of 21 days did not reduce the blood concentration further, but did decrease the  
1104 brain lead concentration compared to control animals. This study indicates, that the  
1105 blood lead concentration, the hitherto most widely used parameter to measure the  
1106 success of antidote treatment, does not predict an important outcome of the treatment,  
1107 that is, a reduced brain concentration of lead. This observation was confirmed in a  
1108 primate study on the effect of succimer on brain lead concentrations. Rhesus  
1109 monkeys were chronically administered lead for 5 weeks in oral fluids to obtain a  
1110 blood lead concentration of 350-400 µg/L. Succimer was given orally in food in the  
1111 standard regimen: 10 mg/kg 3 times daily for 5 days then twice daily for 14 days. One  
1112 day before succimer a biopsy of the prefrontal cortex was taken to determine initial  
1113 brain lead concentrations. Blood lead concentrations were not measurably different  
1114 in the succimer-treated and control group; blood lead concentrations were only  
1115 significantly different from the control group on day 5 of succimer treatment.  
1116 Cessation of lead exposure resulted in a significant reduction of blood lead  
1117 concentrations in both groups. This decline in blood lead was rapid over the first 5  
1118 days of succimer treatment without further decline over the next 14 days. There was  
1119 no significant difference in lead concentrations in the brain in either the succimer-  
1120 treated animals or the controls, although there was a reduction in concentration due to  
1121 cessation to exposure (Cremin et al., 1999).

1122  
1123 A more recent study in rats confirmed that the reduction in blood lead concentrations  
1124 with succimer treatment overestimates the reduction in brain lead concentrations.  
1125 Rats were exposed to lead from birth until 40 days of age followed by one or two  
1126 courses of oral succimer (50 mg/kg/day for 7 days followed by 25 mg/kg/day for 2  
1127 weeks). One course of succimer significantly reduced blood and brain lead  
1128 concentrations compared to controls and two courses were even more effective.  
1129 However, succimer-induced reductions in brain lead concentrations lagged behind  
1130 blood lead reductions and were generally smaller in magnitude. This is due to  
1131 differences in the toxicokinetics of lead in the brain and blood and because brain lead  
1132 is less accessible to succimer. In addition, a rebound in the lead concentration was  
1133 detected in blood but not in the brain. When the effect of the second regimen was  
1134 studied it was found that there was a greater benefit in terms of reduced brain  
1135 concentrations compared to blood. This finding suggests that repeated dosing  
1136 regimens could continue to reduce brain lead concentrations even after the blood  
1137 concentration appears to have stabilised (Stangle et al., 2004).

1138  
1139 **8.1.11.3 Effect of succimer on lead-induced neurotoxicity**  
1140

1141 In a behavioural study using a forced swim model in mice, treatment with succimer  
1142 during 6 weeks concomitant with lead exposure in the drinking water (0.5%) was  
1143 associated with an exacerbation of lead-induced behavioural anomalies (Stewart et  
1144 al., 1995). A previous study had shown similar effects with sodium calcium edetate  
1145 treatment of lead intoxication (Cory-Slechta & Weiss, 1989), but the enhancement of  
1146 lead neurotoxicity could be explained by a transiently increased brain deposition of

1147 lead induced by sodium calcium edetate (Cory-Slechta et al., 1987). Both results, but  
1148 especially that with succimer, are disturbing. In the few studies and case reports on  
1149 lead-exposed children or occupationally-exposed adults, succimer therapy reversed  
1150 lead-induced behavioural anomalies and neuromotor impairment in some studies  
1151 (Haust et al., 1989; Grandjean et al., 1991; Bhattacharya et al., 1998; Berg et al.,  
1152 2000), but was without a definitive effect in others (Rogan et al., 2001; Dietrich et al.,  
1153 2004). Also, in a further experimental study of lead-induced hyperactivity in mice,  
1154 succimer from 6 weeks after cessation of lead exposure alleviated lead-induced  
1155 behavioural anomalies and reduced blood lead concentrations in both sexes, but more  
1156 effectively in male than in females (Stewart et al., 1996). Succimer has also been  
1157 shown to improve cognitive function in monkeys with chronic lead exposure (Laughlin  
1158 et al., 1999). In a study of lead-induced behavioural hyperactivity during habituation,  
1159 treatment with succimer after cessation of lead exposure reduced lead neurotoxicity in  
1160 rats (Gong & Evans, 1997).

1161  
1162 The effects of succimer on cognitive function in rats with and without lead exposure  
1163 has been compared. Rats were exposed to lead from 24 hours after birth (initially via  
1164 milk as lead was added to the mothers' drinking water and then directly via drinking  
1165 water). On day 30 the pups were weaned and lead exposure ceased. Succimer was  
1166 given twice daily via oral lavage from day 31 (50 mg/kg/day for 1 week then 25  
1167 mg/kg/day for 2 weeks). Succimer significantly improved learning, attention and  
1168 arousal regulation in lead-exposed rats. In contrast, in rats without lead exposure  
1169 succimer produced lasting cognitive and affective dysfunction similar in severity to that  
1170 observed in rats with the highest lead exposure. The authors discourage the use of  
1171 succimer in children without elevated tissue concentrations of lead or other heavy  
1172 metals (Beaudin et al., 2007; Stangle et al., 2007).

1173

#### 1174 **8.1.12 Manganese**

1175

1176 Experimental studies on the antidotal and mobilising effects of metal-binding agents in  
1177 manganese intoxication are scarce. The polyaminopolycarboxylic acids (e.g. pentetic  
1178 acid, sodium calcium edetate) appear to be the most efficient and succimer seems to  
1179 be without mobilising effect on parenterally administered manganese in experimental  
1180 animals.

1181

1182 In mice given manganese chloride (92 mmol/kg intraperitoneally) survival was 3-5%.  
1183 Administration of succimer, at the same dose, only increased survival to 17% (Tandon  
1184 & Khandelwal, 1982a). Similarly, succimer (two 40 mg/kg intraperitoneal injections,  
1185 then another at 12 and 25 days) was ineffective in manganese-poisoned rabbits.  
1186 Urinary and faecal excretion of manganese did not increase with succimer  
1187 (Khandelwal et al., 1980).

1188

1189 A number of metal-binding agents were compared in manganese-exposed rats. The  
1190 animals were given 0.10 mmol/kg of manganese-54 by intraperitoneal injection and  
1191 then the antidote (0.5 mmol/kg, exact timing not given). Another dose of the antidote  
1192 was given 24 hours later. Succimer did not significantly decrease concentrations of  
1193 manganese in any tissue (Tandon & Khandelwal, 1982b).

1194

#### 1195 **8.1.13 Mercury**

1196

1197 The antidotal efficiency of succimer in acute inorganic mercury intoxication and  
1198 mobilising effect on systemic mercury is well established in experimental animals.  
1199 The studies reviewed below almost solely used parenteral administration of mercury  
1200 compounds and antidotes. As this does not reflect the clinical situation in most cases,  
1201 evaluation of optimal antidotes for treatment of human mercury intoxication is difficult  
1202 based on such studies.

1203  
1204 Thus, succimer efficiently reduced the concentrations of mercury in various organs of  
1205 mice and guinea pigs injected with mercuric chloride (Friedheim & Corvi, 1975).  
1206 Magos (1976) reported that all 15 rats (3 groups of 5) given three injections of  
1207 succimer (10, 20 or 40 mg/kg per injection) at 30 minutes, 4 and 24 hours after a  
1208 single injection of mercury (2.4 mg/kg as mercuric chloride) survived as compared to a  
1209 survival of 2 of 5 given the same dose of mercury alone. Succimer treatment resulted  
1210 in a dose-related enhancement of urinary mercury excretion and reduction of whole-  
1211 body mercury retention. Also when injected 8 days after mercury administration or  
1212 when given in the drinking water, succimer efficiently enhanced the urinary excretion  
1213 of inorganic mercury in this study. Succimer was also effective at reducing mercury  
1214 body burden in mice injected with methyl mercury.

1215  
1216 In a comparison of five antidotes (succimer, unithiol, D-penicillamine, N-acetyl-D-  
1217 penicillamine [NAPA], dimercaprol) in acute inorganic mercury intoxication, both  
1218 mercuric chloride (10 mg/kg, which is >LD<sub>98</sub>) and the antidotes (given 20 minutes after  
1219 mercury at different doses between 10 and 30 times molar excess) were injected  
1220 intraperitoneally into mice. Based on prevention of mercury-induced lethality,  
1221 dimercaprol was consistently the least efficient antidote, while the four other antidotes  
1222 were all efficient. A relative ranking is difficult, as the efficiency depended on the  
1223 molar ratio between mercury and antidote (Jones et al., 1980). In another study by  
1224 the same group, mercury (10 mg/kg of mercuric chloride) was administered  
1225 intraperitoneally to mice followed 20 minutes later by an antidote by the same route at  
1226 a 10 times molar excess. Twenty-nine antidotes were tested. Succimer and  
1227 dimercaprol had a similar efficiency (40% survival), while NAPA, D-penicillamine and  
1228 unithiol were more efficient in reducing lethality (60% survival) (Basinger et al.,  
1229 1981a).

1230  
1231 In several studies in mice or rats injected with inorganic mercury salts, succimer or  
1232 unithiol effectively increased mercury elimination estimated from reduced body  
1233 burden, kidney concentrations or increased urinary excretion of mercury. Unithiol was  
1234 slightly more efficient than succimer (Planas-Bohne, 1981b; Aaseth, 1983; Eybl et al.,  
1235 1985b; Buchet & Lauwerys 1989). However, repeated injections of either antidote  
1236 eventually mobilised similar amounts of renal mercury (Buchet & Lauwerys, 1989).  
1237 The effectiveness of parenterally administered dimercaprol (15, 30 or 60 mg/kg) and  
1238 succimer (50, 100 or 200 mg/kg) in protecting against mercury-induced nephrotoxicity  
1239 was compared in rats. Mercuric chloride (0.68 mg/kg) was followed by the antidote at  
1240 0, 24, 48 and 72 hours. Dimercaprol at the highest dose exacerbated mercury-  
1241 induced proteinuria, while succimer afforded dose-related increases in urinary mercury  
1242 elimination and significantly decreased renal mercury deposition (de la Torre et al.,  
1243 1998).

1244  
1245 Oral succimer (1 mmol/kg/day for 4 days) reduced the mercury concentration in the  
1246 kidney to about 30% of controls in mercury-poisoned mice. Dosing with succimer was  
1247 started immediately after intravenous injection of mercury (2 µmol/kg as mercuric

1248 chloride). There was increased urinary excretion of mercury but faecal excretion was  
1249 unchanged (Aaseth et al., 1982). In a histopathological study, mercuric chloride (30  
1250  $\mu\text{mol/kg}$  intraperitoneally) given to mice caused degeneration and necrosis of proximal  
1251 tubular cells. When succimer was given immediately after the mercuric chloride, no or  
1252 negligible pathological changes were seen. In the same study, succimer reduced the  
1253 kidney deposition of a single intravenous dose of mercuric chloride, when administered  
1254 immediately or 24 hours later (Aaseth et al., 1982).

1255  
1256 The efficacy of succimer (180 mg/kg) and unithiol (220 mg/kg) were compared in rats  
1257 chronically exposed to mercury (0.5 mg/kg as mercuric chloride intraperitoneally 5  
1258 times a week for 3 weeks). The antidotes were administered 7 days after the last  
1259 mercury dose. Both antidotes were ineffective in removing mercury from the brain and  
1260 succimer was less effective in increasing urinary mercury excretion. This was also the  
1261 case when the same dose of mercury was administered as phenyl mercury (Buchet &  
1262 Lauwerys, 1989). In a study of various antidotes given in mercury-poisoned mice (10  
1263 mg/kg as mercuric chloride), where the antidotes were given in doses of  
1264 antidote:mercury molar ratios of 10, 15, 20 and 30:1, the survival ratio was 38%, 60%,  
1265 70% and 70%, respectively. However, unithiol was significantly more effective, even at  
1266 the smallest dose ratio of 10:1 (Jones et al., 1980).

1267  
1268 Comparing succimer (100  $\mu\text{mol/kg}$  orally) and unithiol (300  $\mu\text{mol/kg}$  orally) in mercury-  
1269 poisoned rats (0.5 mg as mercuric chloride) Planas-Bohne (1981a) found that the rise  
1270 in urinary mercury excreted in the succimer-treated animals corresponded to the  
1271 mercury content of the kidneys. In contrast, the urinary mercury concentration in the  
1272 unithiol-treated group was higher, indicating removal of mercury from other organs.  
1273 The dose of unithiol was three times that of succimer because only 30% of the unithiol  
1274 is absorbed from the gut compared with 100% of the succimer.

1275  
1276 Injection of a single dose of succimer immediately after injection of mercuric chloride  
1277 into mice reduced the total body burden of mercury. The deposition of mercury in the  
1278 kidneys was particularly reduced; the renal mercury content in animals given 20 times  
1279 the molar excess of succimer was less than half that in the untreated control group. In  
1280 this study, only unithiol was slightly more efficient than succimer in reducing the total  
1281 body burden and the renal deposition of mercury (Eybl et al., 1985b).

1282  
1283 In a study reported by Aaseth (1983), succimer or unithiol (1 mmol/kg daily for 4 days)  
1284 given after a single intravenous dose of mercuric chloride (2  $\mu\text{mol/kg}$ ) to mice reduced  
1285 the renal mercury concentration almost by a factor of three. Brain mercury  
1286 concentrations were also reduced. Dimercaprol, in contrast, has long been known to  
1287 increase mercury deposition in the brain after exposure of methyl mercury exposure in  
1288 mice (Berlin & Ullberg, 1963).

1289  
1290 These studies almost solely used parenteral administration of mercury and antidote.  
1291 Two studies are, however, of special interest in relation to acute human mercury  
1292 intoxication due to employment of relevant exposure routes. Buchet & Lauwerys  
1293 (1989) reported that succimer could mobilise mercury accumulated in the kidney and  
1294 to a lesser extent in the liver and could enhance the urinary mercury excretion in rats  
1295 pre-treated by inhalation with different concentrations of mercury vapours. Succimer,  
1296 however, was inefficient in removing mercury accumulated in the brain after exposure  
1297 to mercury vapours.

1298

1299 Nielsen & Andersen (1991) administered radiolabelled mercuric chloride (5, 200, 300  
1300 or 400  $\mu\text{mol/kg}$ ) to mice by oral intubation and observed dose-related lethality and  
1301 depression of gastrointestinal motility. Antidotes were administered, either by the  
1302 peritoneal or oral route, 15 minutes later at 4 times molar excess. Succimer and  
1303 unithiol were superior to dimercaprol and NAPA, both in reducing lethality and  
1304 alleviating the intestinal stasis induced by mercuric chloride. Further, succimer and  
1305 unithiol efficiently reduced the whole-body retention of the oral dose and prevented  
1306 mercury deposition in the brain. Oral administration of succimer or unithiol was more  
1307 efficient than parenteral administration in reducing whole-body retention and organ  
1308 deposition of mercury. Based on the endpoints used in the study, unithiol was a more  
1309 efficient antidote than succimer (Nielsen & Andersen, 1991).

1310  
1311 Concerning organic mercury compounds, succimer is an efficient antidote for  
1312 mobilising methyl mercury and for protecting against toxicity. Extensive daily  
1313 intraperitoneal doses of succimer (2 x 100 mg/kg to mice and 250-1000 mg/kg to  
1314 guinea pigs) were more efficient than similar doses of D-penicillamine in reducing  
1315 brain, liver and kidney concentrations of methyl mercuric bromide (Friedheim & Corvi,  
1316 1975). In a similar study in rats, intraperitoneal administration of much lower doses of  
1317 succimer (3 x 40 mg/kg during 48 hours) after a single subtoxic oral dose of 3.36  
1318 mg/kg Hg as methyl mercuric chloride) increased the urinary mercury excretion more  
1319 than 10 times (Magos, 1976). In the same study, treatment with succimer in the  
1320 drinking water reduced the whole-body, brain, liver and kidney concentrations of  
1321 injected methyl mercury in mice by 50-70%.

1322  
1323 Eight days of oral succimer (75 mg/kg/day) in mice injected with methyl mercuric  
1324 chloride reduced the brain concentration of mercury by about 75%. Succimer was  
1325 more efficient than monomercaptosuccinic acid or NAPA in reducing brain mercury  
1326 concentrations (Aaseth & Friedheim, 1978).

1327  
1328 The progressive development of body weight loss, granule cell necrosis in the  
1329 cerebellum, flailing reflex and crossing of hind legs in rats after mercury (8 mg/kg as  
1330 day as methyl mercury chloride, orally for 8 days), could be reduced or prevented in  
1331 animals treated with succimer (75 mg daily in drinking water for 3 days), starting 1-5  
1332 days after the last dose of mercury. Succimer treatment reduced the body burden and  
1333 brain content of mercury by about 60% (Magos et al., 1978).

1334  
1335 Simultaneous administration of sodium selenite and mercuric chloride decreased the  
1336 efficacy of succimer (500  $\mu\text{mol/kg}$  orally) on mercury elimination in rats. The metal  
1337 salts were given at a dose of 1.5  $\mu\text{mol/kg}$  by intraperitoneal injection. When both metal  
1338 salts were given together the mercury concentration in the liver decreased with no  
1339 change in the kidneys. Urinary excretion of mercury was also reduced compared to  
1340 elimination in the absence of selenium (Jureša et al., 2005).

1341  
1342 Kostial et al. (1991) investigated the influence of age and timing of administration on  
1343 succimer efficacy in rats (aged 1-2 and 6-8 weeks old) with mercury exposure. The  
1344 antidote was given early (0 and 24 hours after mercury) or late (24 and 48 or 48 and  
1345 72 hours) after mercury. Parental antidote had a much lower efficacy on parental  
1346 metal exposure in younger animals. This is due to differences in gastrointesintal  
1347 absorption and different organ distribution, particularly immaturity of the kidney. In  
1348 contrast, oral antidotal therapy (early and late) was more effective in young animals  
1349 after oral metal exposure. In addition this study found that early treatment with

1350 succimer while mercury was still in the gut decreased mercury retention. However,  
1351 this was in contrast to unithiol, where early treatment with oral unithiol in older rats  
1352 given oral mercury increased mercury retention.

1353  
1354 In mouse cortical cell cultures succimer was shown to reduce mercuric chloride toxicity  
1355 but it had no effect on methylmercury and increased the toxicity of ethylmercury (Rush et  
1356 al., 2009).

#### 1357 1358 **8.1.14 Nickel**

1359  
1360 Succimer has been shown to be effective in experimental nickel poisoning in animals  
1361 by reducing tissue damage and nickel concentrations.

1362  
1363 Succimer (1 g/kg subcutaneously) reduced the lethality of nickel chloride (200 mg/kg  
1364 intraperitoneally) in mice from 100% to 5%. The LD<sub>50</sub> was raised from 49 mg/kg to 282  
1365 mg/kg in the succimer-treated group (Ting et al., 1965).

1366  
1367 Xie et al. (1994; 1995; 1996) investigated various antidotal agents as potential  
1368 antidotes for acute nickel intoxication in mice. Nickel (5 mg as nickel sulphate/kg  
1369 intraperitoneally) was followed by the antidote (400 µmol/kg) 30 minutes or 24 hours  
1370 later. These studies demonstrated that intraperitoneal injection of succimer  
1371 consistently afforded protection against the acute toxicity of nickel chloride as  
1372 evidenced by reduced pulmonary (Xie et al., 1996) or testicular (Xie et al., 1995)  
1373 effects, renal or hepatic lipid peroxidation, increased urinary and faecal nickel excretion  
1374 and decreased nickel concentrations in various organs. In addition, succimer was  
1375 effective in removing nickel from the body without redistribution to the brain (Xie et al.,  
1376 1994).

1377  
1378 Rats given nickel (1.5 mg/kg intraperitoneally as nickel sulphate daily, 6 days a week  
1379 for 30 days) then succimer (0.3 mmol/kg intraperitoneally daily for 5 days) had their  
1380 organs harvested 24 hour after the last injection. Succimer reduced the nickel  
1381 concentrations in the liver, blood, heart and kidney but not in the brain. Succimer also  
1382 reversed nickel-induced biochemical changes (decreased ceruloplasmin concentration  
1383 and blood glucose; increased plasma and urine concentrations of amino acids) and  
1384 increased faecal nickel excretion (Tandon et al., 1996).

1385  
1386 Succimer administered intraperitoneally at a 10:1 mole ratio of antidote to nickel,  
1387 increased the survival rate in mice poisoned with intraperitoneal nickel acetate (62  
1388 mg/kg). Antidotes were administered 20 minutes after injection of nickel. Succimer  
1389 was less effective than unithiol, D-penicillamine, disodium calcium edetate,  
1390 triethylenetetramine or calcium pentetic acid, although the small sample size prohibited  
1391 any significant differentiation between them (Basinger et al., 1980).

#### 1392 1393 **8.1.15 Palladium**

1394  
1395 There is limited information on the effect of succimer on palladium toxicity. It did not  
1396 influence toxicity or reduce lethality in mice with acute palladium chloride poisoning  
1397 (586 µmol/kg intraperitoneally). Succimer was given subcutaneously at the same time  
1398 as palladium at a dose of 2.93 mmol/kg (5 times the molar dose of metal) (Mráz et al.,  
1399 1985).

1400

1401 **8.1.16 Platinum**

1402  
1403 There is limited information on the effect of succimer on platinum toxicity. Succimer  
1404 seems a possible antidote for enhancement of platinum excretion. The reduction of  
1405 renal platinum concentrations were, however, modest, and the studies too short in  
1406 duration to determine whether succimer could enforce a more rapid renal recovery.

1407  
1408 In acute toxicity studies, subcutaneous succimer (1 g/kg) in mice reduced lethality after  
1409 platinum chloride administration (50 mg/kg intraperitoneally) from 65% to 20% (Ting et  
1410 al., 1965).

1411  
1412 A single injection of succimer (1 mmol/kg) produced no significant change in renal  
1413 platinum concentration in rats treated with cisplatin (4 or 6.5 mg/kg) 24 hours  
1414 previously. After four daily treatments unithiol and succimer caused a significant  
1415 increase in urinary excretion of platinum, but this was low, and represented only about  
1416 3% of the injected dose of platinum. It was concluded that none of the antidotes  
1417 studied, unithiol, succimer or pentetic acid, were likely to be of benefit in the  
1418 management of cisplatin-induced renal toxicity (Planas-Bohne et al., 1982).

1419  
1420 In rats, administration of intravenous *cis*-dichlorodiammineplatinum(II) (9 mg/kg and  
1421 again on day 8) followed by intraperitoneal administration of succimer (30 mg/kg 3  
1422 hours later and 15 mg/kg daily for 4 days) reduced platinum concentrations in the  
1423 kidneys but not the liver. After 6 mg/kg of *cis*-dichlorodiammineplatinum(II) succimer  
1424 at doses of 100 or 200 mg/kg (as a single dose on day 1 and in two divided doses on  
1425 days 2 to 8) reduced the renal concentration to approximately half of controls.  
1426 However, even though the platinum mobilising effect of succimer was comparable to  
1427 that of the more efficient dithiocarbamate derivatives, succimer was unable to prevent  
1428 platinum-induced renal damage. Increased urinary N-acetyl- $\beta$ D-glucosaminidase and  
1429 creatinine excretion were reported and the renal damage was verified histologically  
1430 (Graziano et al., 1981).

1431  
1432 Jones & Basinger (1989) found that dithiocarbamates were more effective than  
1433 succimer in reducing platinum concentrations in the liver and kidneys of rats. Platinum  
1434 concentrations in these organs of succimer-treated rats were not significantly different  
1435 from controls.

1436  
1437 A study in rats given intravenous *cis*-dichlorodiammineplatinum followed immediately  
1438 by succimer (2 mmol/kg) demonstrated that succimer significantly reduced lipid  
1439 peroxidation, which is believed to be responsible for the platinum-induced renal  
1440 damage. There was no effect on lipid peroxidation in the liver. Succimer also  
1441 reversed the decline in antioxidant enzymes (catalase, glutathione, superoxide  
1442 dismutase) observed with platinum. The urinary concentration of platinum was not  
1443 determined in this study (Mishima et al., 1999).

1444  
1445 **8.1.17 Polonium**

1446  
1447 Several animal studies have shown that although succimer can remove polonium-210  
1448 from some tissues it results in significant concentration in the kidneys and has no  
1449 significant effect on total body retention.

1450

1451 In a study of rats given a lethal dose (40  $\mu$ Ci) of polonium-210 by intraperitoneal  
1452 injection, administration of an antidote (0.2 mmol/kg) 1 minute, 90 minutes, 360  
1453 minutes and twice daily on days 2, 3, 4, 12, 22 and 32 increased the mean survival  
1454 time from 39 days to 106 days. Further studies demonstrated that administration of  
1455 succimer could be delayed up to 1 hour but not as long as 3 hours to obtain significant  
1456 improvement in survival. Although succimer significantly decreased the polonium-210  
1457 content of organs it was significantly less effective than the other antidotes studied and  
1458 the concentration in the kidneys was increased. Even after 21 or 40 days of treatment  
1459 with succimer the concentration of polonium in the kidneys was greater than that of the  
1460 controls. DMPA was found to be a more effective decorporating agent for polonium  
1461 (Aposhian et al., 1987).

1462  
1463 The study by Rencová et al. (1993) comparing a number of antidotes for polonium-210  
1464 also found that succimer reduced retention in the liver and spleen of rats but increased  
1465 it in the kidneys. Indeed, the total body retention of polonium-210 could not be  
1466 reduced to less than 85% of controls with any of the 9 antidotes used. Repeated  
1467 injections of succimer over 2 weeks did not affect overall body retention of polonium,  
1468 although there was less accumulation in the kidneys.

1469  
1470 Rencová et al. (2000) compared the efficacy of succimer and its derivatives in  
1471 mobilisation and detoxification in rats exposed to polonium-210 (11 kBq by intravenous  
1472 injection). The antidote (0.4 mmol/kg subcutaneously) was given immediately after  
1473 exposure 1 hour later and repeated once daily for 5 days. Administration of succimer  
1474 caused a significant decrease in polonium-210 excretion via the faeces and an  
1475 decrease polonium concentration in the liver, blood, spleen, skeleton and muscles.  
1476 There was an increase in polonium excretion in the urine but a higher concentration in  
1477 the kidneys. The effectiveness of the antidotes declined with a delay in administration.  
1478 In this study mono-*N*-(*i*-butyl)-*meso*-2,3-dimercaptosuccinic acid (Mi-BDMA) was found  
1479 to be the best mobilising agent for polonium-210.

1480  
1481 The same investigators (Volf et al., 1995) looked at the use of antidotes in rats with  
1482 simulated wounds contaminated with polonium-210. Comparing repeated  
1483 administration of unithiol and succimer, unithiol was found to be more effective as it  
1484 mobilised about 9 times more polonium from the injection site than in untreated  
1485 controls. Succimer mobilised less polonium and this was deposited in the kidneys.

#### 1486 1487 **8.1.18 Promethium**

1488  
1489 There is limited information on the effect of succimer on promethium toxicity.  
1490 Administration of succimer to mice given promethium-147 resulted in a 12-fold  
1491 increase urinary excretion of the radioactive metal (Liang et al., 1980).

#### 1492 1493 **8.1.19 Selenium**

1494  
1495 There is limited information on the effect of succimer on selenium toxicity. Succimer  
1496 administration (50.9 mg/kg intraperitoneally) had no effect on selenium-poisoned rats  
1497 (2.24 mg of selenium/kg by subcutaneously). The concentration of selenium in faeces  
1498 was unchanged (Paul et al., 1989).

#### 1499 1500 **8.1.20 Silver**

1501

1502 There is limited information on the effect of succimer on silver toxicity. In mice  
1503 experimentally poisoned with silver nitrate (20 mg/kg intraperitoneally), 11/20 were  
1504 killed in the control group versus 1/20 given succimer (1 g/kg intravenously). Succimer  
1505 (1 mg/kg subcutaneously) significantly increased the LD<sub>50</sub> of silver nitrate in mice from  
1506 24 mg/kg to 208 mg/kg (Ting et al., 1965). In another study succimer administration  
1507 (0.7 mmol/kg intraperitoneally) increased the LD<sub>50</sub> of silver chloride in mice from 13.6  
1508 mg/kg to 76.5 mg/kg (Pethran et al., 1990).

1509

#### 1510 **8.1.21 Strontium**

1511

1512 There is limited information on the effect of succimer on strontium toxicity.  
1513 Administration of succimer to mice given strontium-90 resulted in a 2-fold increase  
1514 urinary excretion of the radioactive metal (Liang et al., 1980).

1515

1516 Succimer administration (0.7 mmol/kg intraperitoneally) did not change the LD<sub>50</sub> of  
1517 strontium chloride in mice. The LD<sub>50</sub> was 3000 mg/kg in controls and 2980 mg/kg in  
1518 succimer-treated animals (Pethran et al., 1990).

1519

#### 1520 **8.1.22 Thallium**

1521

1522 There is limited information on the effect of succimer on thallium toxicity.  
1523 Administration of succimer to mice given thallium-204 resulted in an 11-fold increase  
1524 urinary excretion of the radioactive metal (Liang et al., 1980).

1525

1526 Succimer administration (0.7 mmol/kg intraperitoneally) worsened thallium toxicity and  
1527 decreased the LD<sub>50</sub> of thallium chloride in mice. The LD<sub>50</sub> was 49 mg/kg in controls  
1528 and 32.2 mg/kg in succimer-treated animals (Pethran et al., 1990).

1529

1530 The efficacy of succimer and Prussian blue were compared in thallium-poisoned rats.  
1531 Thallium sulphate (30 mg/kg) was given by gavage and the antidote was given 24  
1532 hours later at a dose of 15 mg/kg (succimer) or 50 mg/kg (Prussian blue) twice daily for  
1533 5 days. Survival in controls was 21% compared to 45% in the succimer-treated group  
1534 and 70% in the Prussian blue-treated group. In addition, succimer failed to reduce  
1535 thallium concentrations in the brain. Prussian blue was a more effective antidote than  
1536 succimer in thallium toxicosis (Rusyniak et al., 2003).

1537

#### 1538 **8.1.23 Tin**

1539

1540 There is limited information on the effect of succimer on organic tin toxicity, although it  
1541 does appear to be effective.

1542

1543 Although succimer was not able to reduce acute lethality in mice due to dibutyltin  
1544 dichloride, it reduced the toxic effects on thymus and bile ducts more efficiently than  
1545 dimercaprol (Merkord & Hennighausen, 1984). A later study demonstrated that the  
1546 bile duct toxicity of dialkyltin compounds (20 mg/kg orally) with chain lengths of 4-6  
1547 carbon atoms could be reduced by treatment with succimer (18.2 mg/kg  
1548 intraperitoneally 10 minutes later), in both rats and mice (Hennighausen et al., 1988).

1549

1550 Succimer and unithiol have been investigated as antidotes in rats following a single  
1551 intravenous dose of dibutyltin dichloride (27 µmol/kg). The antidotes were given at two  
1552 doses, 100 and 500 µmol/kg, orally and by intraperitoneal injection. Several

1553 parameters of organ toxicity were monitored from 6 hours to 8 weeks. Both drugs  
1554 reduced dibutyltin dichloride-induced lesions of the bile duct, pancreas and liver.  
1555 Succimer was less effective than unithiol in most measured parameters and the drugs  
1556 were though to exert their protective effects on these organs by reducing biliary  
1557 organotin excretion (Merkord et al., 2000).

1558  
1559 *In vitro* studies with human erythrocytes incubated with tributyl tin have demonstrated  
1560 that succimer provided protection against tributyl tin-mediated haemolysis of the cells.  
1561 It was more effective than unithiol but less effective than dimercaprol (Gray et al.,  
1562 1986; 1987).

#### 1563 1564 **8.1.24 Vanadium**

1565  
1566 There is limited information on the effect of succimer on vanadium toxicity. It has not  
1567 been shown to be effective and is unlikely to be useful since antidotes containing  
1568 oxygen, rather than thiol groups such as succimer, are more effective at binding  
1569 vanadium.

1570  
1571 Succimer (1.65 or 3.30 mmol/kg) administered by intraperitoneal injection immediately  
1572 after intraperitoneal administration of sodium metavanadate (0.33 mmol/kg) to mice  
1573 was ineffective as an antidote. Rather, succimer seemed to potentiate the acute  
1574 toxicity of vanadium; lethality was 50% at the lower dose of succimer and 70% in  
1575 animals given the higher dose (Domingo et al., 1985).

1576  
1577 Succimer had no effect on lethality in mice poisoned with vanadyl sulphate (110 mg/kg  
1578 intraperitoneally). It appeared to be a more effective antidote for sodium vanadate (50  
1579 mg/kg intraperitoneally) but was considered a poor vanadium antidote overall.  
1580 Succimer was given intraperitoneally 20 minutes after administration of vanadium, at a  
1581 dose of 5:1 antidote to metal compound (Jones & Basinger, 1983).

#### 1582 1583 **8.1.25 Zinc**

1584  
1585 Succimer can increase excretion of zinc and reduce lethality in zinc-poisoned animals,  
1586 but more effective antidotes are available.

1587  
1588 Lethality was 85% in mice given intraperitoneal zinc chloride (50 mg/kg) and this was  
1589 reduced to 10% when treated with succimer (1 g/kg subcutaneously). Similarly, all  
1590 animals died when given intraperitoneal zinc nitrate (300 mg/kg) and intravenous  
1591 succimer (1 g/kg) reduced lethality to 45%. Mice given intraperitoneal zinc-65 excreted  
1592 0.5% of the radioactivity in 2 hours. Animals treated with succimer (1 g/kg  
1593 subcutaneously) excreted 30.8% over the same period (Ting et al., 1965).

1594  
1595 In a comparison of several antidotes against the effects of acute parenteral zinc  
1596 intoxication in mice, succimer efficiently reduced acute lethality. Succimer (10:1  
1597 antidote:zinc ratio) was given 20 minutes after a fatal dose of zinc (50 mg/kg) was  
1598 administered. Survival was 86.7% with succimer but other antidotes were equally or  
1599 slightly more effective (Basinger & Jones, 1981a). Eybl et al. (1985a) found that  
1600 succimer administered to zinc-exposed mice at a metal to antidote ratio of 1 :10 did not  
1601 influence the zinc body burden and had minimal effect on tissue concentrations of zinc.

1602

1603 In mice given zinc acetate (0.49 mmol/kg intraperitoneally), succimer (2:1 or 5:1 molar  
1604 ratio of antidote to metal), although effective, had a low efficacy. Disodium calcium  
1605 cyclohexanediaminetetraacetate (CDTA), sodium calcium edetate and pentetic acid  
1606 and were the most effective (Llobet et al., 1988).

1607  
1608 In a study comparing the efficacy of several antidotes mice were given intraperitoneal  
1609 zinc acetate (66-330 mg/kg; LD<sub>50</sub> 108 mg/kg). Antidotal therapy was given 10 minutes  
1610 later, also by intraperitoneal injection. Succimer afforded no protection at higher doses  
1611 of zinc (153, 241 and 330 mg/kg) where lethality was 70%, 90% and 100%. At the  
1612 lowest dose of zinc (66 mg/kg) lethality was 60% in controls and 20% in the succimer-  
1613 treated group. However, succimer did increase renal excretion of zinc and reduced  
1614 blood, kidney and heart tissue concentrations compared to controls. However,  
1615 pentetic acid and CDTA were found to be more effective zinc antidotes in this study  
1616 (Domingo et al., 1988).

### 1617 1618 **8.1.26 Radiopeptides**

1619  
1620 Succimer has been evaluated for its effect on radiopeptide renal retention as a means  
1621 of reducing the radiation dose to the kidney in patients receiving radiopeptide therapy  
1622 for cancer. Rats were given intravenous lutetium-177-DOTA-tyr(3)-octreotate (<sup>177</sup>Lu-  
1623 DOTATATE) followed 30 minutes later by succimer (0.15 mg/g by intraperitoneal  
1624 injection). This reduced renal retention of the radiopeptide by 15.6% at 72 hours  
1625 without significantly affecting uptake in other organs. In contrast, a preliminary study  
1626 demonstrated that administration of succimer 1 hour prior to administration of the  
1627 radiopeptide increased the renal uptake by 43% at 24 hours (Moorin et al., 2007).

## 1628 1629 **8.2 Pharmacokinetics**

1630  
1631 The distribution of orally administered radiolabelled succimer in the rats was studied by  
1632 Okonishnikova & Nirenburg (1974). Succimer is rapidly taken up by the gastric  
1633 mucosa after administration. The highest serum concentration was found 30 minutes  
1634 after oral administration, and 95% of the radioactivity was eliminated from the body by  
1635 24 hours. Neither, unaltered or altered succimer were detected in the bile of rats  
1636 (Zheng et al., 1990).

1637  
1638 Succimer is highly hydrophilic due to its two carboxylic groups, and is probably unable  
1639 to act intracellularly. Accordingly, studies by Liang et al. (1986) indicate that succimer  
1640 is distributed mainly in extracellular fluid. The hydrophilicity reduces the intestinal  
1641 absorption of succimer. It is, however, absorbed more efficiently than sodium calcium  
1642 edetate and pentetic acid.

1643  
1644 Planas-Bohne & Olinger (1981) studying the interaction of antidotes with methyl mercury  
1645 bound to erythrocytes *in vitro* demonstrated that succimer was the most effective  
1646 antidote testing at releasing methyl mercury from cells.

1647  
1648 A whole-body autoradiographic study of the distribution of intravenously administered  
1649 radiolabelled succimer in mice demonstrated deposition in a number of tissues, mainly  
1650 blood, lungs, kidneys, skin and gastrointestinal content. Most of the radioactivity was  
1651 excreted within 24 hours (Liang et al., 1982).

1652  
1653 After oral administration of uniformly radiolabelled succimer to monkeys, 18% of the

1654 radioactivity was excreted in urine, 65% in faeces and 2% was exhaled as carbon  
1655 dioxide. After intravenous administration, urine was by far the most important  
1656 excretion route (McGown et al., 1984).

1657

### 1658 **8.3 Toxicology**

1659

1660 Succimer is of low toxicity during acute, subacute or chronic exposure of various  
1661 species.

1662

#### 1663 **8.3.1 Acute toxicity**

1664

1665 The acute oral LD<sub>50</sub> of succimer in mice and rats is 3 g/kg or higher (Stohler & Frey,  
1666 1964; Aposhian et al., 1981; McNeil, 1994), while the parenteral LD<sub>50</sub> is 2 g/kg or  
1667 higher (Friedheim & Corvi, 1975; Graziano et al., 1978b; Cantilena & Klaassen, 1981;  
1668 Aposhian et al., 1984; Basinger et al., 1985; Kreppel et al., 1990; Srivastava et al.,  
1669 1996).

1670

1671 Succimer (0.74 g/kg intraperitoneally, approximately a quarter of the LD<sub>50</sub>), daily for 3  
1672 days or twice daily for 7 days, produced no histopathological lesions in mice.  
1673 Succimer did not affect urinary concentrations of calcium, magnesium, iron,  
1674 manganese or zinc but significantly increased urinary elimination of copper (Graziano  
1675 et al., 1978b; Cantilena & Klaassen, 1982b).

1676

1677 A single subcutaneous injection of succimer (1.6 mmol/kg) in mice caused a significant  
1678 increase in liver and kidney lipid peroxidation. There was no change in δ-  
1679 aminolevulinic dehydratase activity in the blood, kidney, liver or brain and it did not  
1680 change zinc concentrations in the kidneys, liver or brain (Santos et al., 2005).

1681

1682 In dogs, intravenous succimer at 12 mg/kg led to a slight transient decrease in femoral  
1683 blood pressure with strong reflex tachycardia and an increase in blood flow (Klimmek  
1684 et al., 1993).

1685

#### 1686 **8.3.1.2 Subacute toxicity (28 days)**

1687

1688 Succimer 300 mg/kg/day (route?) reduced to 150 mg/kg/day after 8 days and higher  
1689 oral doses to Beagle dogs resulted in death due to renal failure (5/8). Ulcerative  
1690 lesions in the upper gastrointestinal tract (4/8), slight pancreatic islet cell atrophy (2/8)  
1691 and slight acute hepatitis (1/8) were observed as well. Succimer at a dose of 100  
1692 mg/kg/day induced occasional diarrhoea and very slight histopathological changes in  
1693 various organs in some of the animals. reference?

1694

#### 1695 **8.3.2 Chronic toxicity (180 days)**

1696

1697 Histological investigation after 3 and 6 months of intraperitoneal succimer (100 or 200  
1698 mg/kg/day 5 days/week) in rats did not reveal pathological changes. Also, serum  
1699 chemistry and blood parameters were no different compared to controls (Graziano et  
1700 al., 1978b).

1701

#### 1702 **8.3.3 Reproductive toxicity and teratogenicity**

1703

1704 Succimer has been shown to produce embryo- and fetotoxicity usually at doses

1705 associated with maternal toxicity. Reproductive toxicity may be due to its effects on  
1706 mineral metabolism (Paternain et al., 1990; Taubeneck et al., 1992). However,  
1707 succimer can also protect against the developmental toxicity of mercury and possibly  
1708 other metals.

1709  
1710 Pregnant mice were given succimer (410, 820 or 1640 mg/kg/day subcutaneously) on  
1711 days 6-15 of gestation. Haematological and biochemical analyses were unchanged,  
1712 but in the group given the largest dose there were significant increases in the number  
1713 of resorptions, incidence of stunting and the number of live fetuses per litter. Maternal  
1714 toxicity was also observed at this dose. There was also significant reduction in fetal  
1715 body weight and length in the two highest treatment groups. Succimer is embryotoxic  
1716 at a dose of 1640 mg/kg/day and fetotoxic at 820 mg/kg/day. It is also teratogenic at  
1717 these two doses. At a dose of 410 mg/kg/day succimer was mildly fetotoxic but not  
1718 teratogenic (Domingo et al., 1988).

1719  
1720 In another study pregnant mice were given succimer (400 or 800 mg/kg orally or by  
1721 subcutaneous injection) on days 6-15 of gestation. Succimer administration did not  
1722 result in maternal toxicity. There was no effect on fetal or placental weight but some  
1723 fetuses in the succimer-treated group had skeletal abnormalities. Succimer did not  
1724 affect zinc, iron, calcium or magnesium concentrations, but copper concentrations in  
1725 fetal liver showed a dose-dependent decrease (Taubeneck et al., 1992).

1726  
1727 In two studies on the teratogenic effects of succimer rats were given 100, 300 or 1000  
1728 mg/kg on days 6-15 of gestation. Maternal toxicity was evidenced by decreased  
1729 weight gain and was observed at all doses. There were no changes in haematological  
1730 or blood analyses. Fetotoxicity, in terms of increased resorptions, increased post-  
1731 implantation loss, and reduced fetal body weight, was observed at all doses. Succimer  
1732 was not teratogenic in this study and the no-observed-effect level for maternal and  
1733 fetal toxicity was less than 100 mg/kg/day (Domingo et al., 1990). Another part of this  
1734 study also looked at the effect of succimer on mineral metabolism. There was no  
1735 effect on fetal or maternal magnesium concentrations but fetal and maternal hepatic  
1736 copper concentrations were reduced. Succimer decreased zinc and calcium  
1737 concentrations in the fetal liver (Paternain et al., 1990).

1738  
1739 Succimer has been shown to protect against the developmental toxicity of mercury in  
1740 experimental animals. Subcutaneous succimer (80, 160 and 320 mg/kg) was given  
1741 immediately after oral administration of a teratogenic dose of methyl mercury (25  
1742 mg/kg) to mice on day 10 of gestation, and 24, 48 and 72 hours thereafter. Succimer  
1743 at 160 and 320 mg/kg significantly decreased the embryo-lethality of methyl mercury  
1744 and 320 mg/kg reduced the incidence of skeletal anomalies and cleft palate (Sanchez  
1745 et al., 1993).

#### 1746 1747 **8.3.4 Genotoxicity**

1748  
1749 Succimer appeared non-mutagenic when tested with 5 different mutant strains of  
1750 *Salmonella typhimurium* in the plate incorporation version of the Ames  
1751 Salmonella/Mammalian-Microsome mutagenicity test and in the CHO/HGPRT  
1752 (Chinese Hamster Ovary Hypoxanthine-Guanine Phosphoribosyl Transferase)  
1753 mammalian cell forward mutation assay (reference? Is it McNeil, 1994?)

1754  
1755 Normal DNA synthesis was maintained with succimer concentrations up to 1 µg/mL in

1756 an *in vitro* study using 3 murine tumour cell lines. Above 1 µg/mL succimer inhibited  
1757 DNA synthesis (Jones et al., 1996).

1758  
1759 An *in vitro* study found that succimer increased the incidence of nickel-induced DNA  
1760 breaks in a human leukaemia cell line. The effect was studied further with bacterial  
1761 plasmids (a simpler system) and the combination of nickel and succimer caused an  
1762 increase in DNA breaks but not when each was given alone. Although unithiol and  
1763 dimercaprol also increased DNA breaks in plasmids in the presence of nickel, the  
1764 effect was strongest with succimer. These metal-binding agents all generate hydrogen  
1765 peroxide in solution but succimer is the most potent. Free radicals are thought to be  
1766 involved in the DNA damage observed. The breakage of DNA was completely  
1767 prevented by the presence of mannitol and partially reduced by antioxidants. The  
1768 increase in plasmid DNA breakage was also demonstrated with iron and succimer in  
1769 combination (Lynn et al., 1999).

1770  
1771

## 1772 **9. VOLUNTEER STUDIES**

1773  
1774 There are several studies of succimer pharmacokinetics, many conducted by the same  
1775 group, consequently some volunteers took part in more than one study. The  
1776 characteristics of each study are as follows:

- 1777
- 1778 • A preliminary study by McNeil (1994) involved 11 male volunteers, but no details  
1779 about them are given.
  - 1780 • The study by Aposhian et al. (1989) involved 6 male volunteers, aged 22-31 years;  
1781 their body weights are not given.
  - 1782 • The study by Maiorino et al. (1989) involved 2 male volunteers, aged 22 and 25  
1783 years, weighing 86 and 79 kg, respectively.
  - 1784 • The study by Maiorino et al. (1990) involved 5 male volunteers, aged 22-35 years,  
1785 weighing 60-85 kg.
  - 1786 • The study by Dart et al. (1994) involved 5 male volunteers, aged 24-39 years,  
1787 weighing 60-84 kg.

1788

### 1789 **9.1 Absorption**

1790  
1791 Succimer is taken up to some degree in the intestinal tract. One study in volunteers  
1792 found rapid but incomplete gastrointestinal absorption of radiolabelled succimer (16, 32  
1793 or 48 mg/kg) with peak serum concentrations occurring 1-2 hours post-ingestion  
1794 (McNeil, 1994). In another study the peak concentration occurred 2-4 hours after  
1795 ingestion in adults and children with lead poisoning and healthy adults (Dart et al.,  
1796 1994).

1797

### 1798 **9.2 Distribution**

1799  
1800 A small volume of distribution indicating extracellular compartmentalisation and a  
1801 biphasic elimination curve, indicating a two-compartment distribution were  
1802 demonstrated in a volunteer study after oral administration of radiolabelled succimer  
1803 (McNeil, 1994).

1804

1805 After an oral dose of succimer (10 mg/kg), 92-95% of the succimer in the plasma is

1806 covalently bound to proteins, mainly to albumin. It is confined to the plasma and does  
1807 not enter red blood cells (Maiorino et al., 1990).

1808

### 1809 **9.3 Elimination**

1810

1811 Up to 40% of an oral dose of succimer is excreted in urine within 16 hours (Dart et al.,  
1812 1994). The peak elimination of altered succimer after oral administration in a volunteer  
1813 study was 2-4 hours after ingestion (Aposhian et al., 1989).

1814

1815 The apparent elimination half life was about 48 hours in a volunteer study after oral  
1816 administration of radiolabelled succimer (McNeil, 1994).

1817

1818 The primary route of excretion of succimer is urinary with plasma and whole blood half-  
1819 lives and urinary elimination half-life of less than 4 hours in humans (Maiorino et al.,  
1820 1990; Dart et al., 1994).

1821

### 1822 **9.4 Metabolism**

1823

1824 Succimer is extensively metabolised. In a volunteer study only 2.5% of oral succimer  
1825 (10 mg/kg) was excreted as unaltered succimer and 18% as metabolites in the urine  
1826 by 14 hours. The altered succimer made up 88% of the total succimer excreted in the  
1827 urine (Aposhian et al., 1989).

1828

1829 In a related study the major urinary metabolite of succimer in humans was identified as  
1830 a mixed disulphide with 2 molecules of L-cysteine. Minor metabolites found were a  
1831 mixed disulphide with one cysteine residue and a cyclic disulphide of succimer. More  
1832 than 90% of urinary succimer is excreted as the succimer-cysteine mixed disulphide  
1833 (Maiorino et al., 1989).

1834

### 1835 **9.5 Effect of succimer on the excretion of metals**

1836

1837 Few volunteer studies on the effect of succimer on metal excretion are available.

1838

#### 1839 **9.5.1 Bismuth elimination**

1840

1841 Two groups of 12 volunteers (age 26-65 years), who had been treated with colloidal  
1842 bismuth subcitrate for 28 days because of *Helicobacter pylori*-associated gastritis, took  
1843 part in a study of bismuth elimination with unithiol and succimer. Each subject  
1844 received a single oral dose of succimer or unithiol (30 mg/kg) in a randomised single  
1845 blind study. The succimer or unithiol was given 7 to 14 days after the last dose of  
1846 bismuth. Both antidotes produced a 50-fold increase in urinary bismuth excretion  
1847 compared to control urine samples. The highest concentration was excreted within the  
1848 first 4 hours after dosing. No significant difference was observed in bismuth  
1849 elimination between succimer and unithiol and both were well tolerated (Slikkerveer et  
1850 al., 1998).

1851

#### 1852 **9.5.2 Cadmium elimination**

1853

1854 Of the 6 metal-binding agents investigated in an *in vitro* study using human cell  
1855 cultures, unithiol, succimer and mercaptosuccinic acid were found to be the most effective  
1856 at increasing cadmium movement from cells. Although, unithiol produced the most

1857 rapid elimination from cells in the first two hours, the other two agents mobilised more  
1858 cadmium (Bakka et al., 1981).

1859  
1860 Succimer enhanced cadmium elimination from human red blood cells *in vitro*.  
1861 Cadmium (10 ppm as chloride) was added to human blood, incubated for 1 hour and  
1862 then dialysed against various antidotes. Although all enhanced elimination, sodium  
1863 calcium edetate and glutathione were the most effective (Sheabar & Yannai, 1989).

### 1864 1865 **9.5.3 Lead elimination**

1866  
1867 Oral administration of succimer (10 mg/kg) to volunteers resulted in a small but  
1868 significant increase in urinary excretion of lead which peaked at 4 hours after ingestion.  
1869 The cumulative urinary excretion of lead by 6 hours after administration of succimer  
1870 exceeded the urinary excretion in the 8 hours prior to administration (Aposhian et al.,  
1871 1989).

1872  
1873 Oral administration of succimer (10 or 30 mg/kg) to adults immediately after ingestion  
1874 of 200 µg of the stable isotope lead-204 decreased the faecal and increased the  
1875 urinary output of lead. Also, the fraction of the dose recovered after the experimental  
1876 period was decreased in the succimer-treated group. These results suggest that  
1877 succimer increased intestinal lead absorption and mediated redistribution into tissues.  
1878 However, the study was small with only 12 subjects (4 in each group and 4 controls)  
1879 and the differences were not statistically significant (Smith et al., 1994).

1880  
1881 The elimination of lead with succimer or sodium calcium edetate was compared in 34  
1882 male lead workers. The workers had a mean age of 39.6 years and had blood lead  
1883 concentrations of 290-770 mg/L. A single oral dose of succimer (10 mg/kg) was given  
1884 to 34 subjects and 17 of these also received sodium calcium edetate (1 g  
1885 intravenously) either 2 weeks before or after the succimer. Urinary lead concentrations  
1886 peaked at 2 hours after succimer and 4 hours after sodium calcium edetate. Lead  
1887 excretion was less with succimer and plateaued at 6-8 hours. Excretion of lead was  
1888 higher with succimer in those subjects who had previously received sodium calcium  
1889 edetate (Lee et al., 1995).

### 1890 1891 **9.5.4 Mercury elimination**

1892  
1893 Roels et al. (1991) studied three groups of male workers to investigate mercury  
1894 excretion after succimer: Group A (23-49 years, n = 16) was the unexposed control  
1895 group, Group B (27-41 years, n = 11) had been removed from exposure for at least 2  
1896 years and Group C (21-58 years, n = 16) were currently still exposed to mercury  
1897 vapour at an average air concentration of 110 µg/m<sup>3</sup>. The mean blood and urinary  
1898 mercury concentrations in the three groups were as follows: Group A 1.6 µg/L and 2.1  
1899 µg/g of creatinine, Group B 2.8 µg/L and 6.9 µg/g of creatinine and Group C 25.6 µg/L  
1900 and 119 µg/g of creatinine, respectively. The subjects were given a single oral 2 g  
1901 dose of succimer and the average increase in 24 hour urinary mercury excretion varied  
1902 between 20 µg Hg in the group removed from exposure and 600 µg in the group with  
1903 present high exposure, compared to 4 µg in the unexposed control group. Most (50-  
1904 70%) of the mercury excreted following succimer administration appeared within the  
1905 first 8 hours. The ratio between average 24 hour urinary mercury excretion after and  
1906 before oral succimer administration varied between 4 and 2.5 µg, with the higher  
1907 values in groups with the highest and most recent exposure to mercury vapour. The

1908 correlations between pre- and post-succimer urinary mercury excretion were  
1909 statistically significant in all groups, most strongly in the control and in the group  
1910 removed from exposure, suggesting that succimer-induced excretion represents renal  
1911 mercury deposits in individuals without recent exposure (Roels et al., 1991).

1912  
1913 A study in former chloralkali workers investigated the usefulness of a succimer to  
1914 measure the mercury body burden as part of a larger study of the health effects of  
1915 mercury. The exposed group (n=119) underwent physical, neurological and  
1916 neurobehavioural examination. They completed a detailed questionnaire and  
1917 information was gathered about their work history including an estimation of the  
1918 mercury air concentration to which they had been exposed. The control group (n=101)  
1919 were unexposed workers matched for age, race and gender. No details of the  
1920 subjects, such as age range, weight, sex ratio, are provided. Baseline 24 hour urine  
1921 samples were collected and 2 weeks later the subjects were given 2 doses of succimer  
1922 10 mg/kg 8 hours apart. Another 24 hour urine sample was collected from 24 hours  
1923 after the first succimer dose. For the exposed workers the mean duration of exposure  
1924 was 7 years and the mean time since the last exposure was 6.1 years. The average  
1925 urine mercury concentration before succimer was 4.3 µg/24 hours and 7.8 µg/24 hours  
1926 after. There was no association between past mercury exposure and urinary excretion  
1927 before and after succimer administration. This was true for occupational exposure and  
1928 exposure to dental amalgam as indicated by the number of mercury amalgam  
1929 surfaces. However, the failure of the challenge with succimer to reflect past mercury  
1930 exposure may have been due to the long time period (several years) since the last  
1931 exposure. It was concluded that the succimer challenge test was not a useful  
1932 biomarker of past mercury exposure (Frumkin et al., 2001).

1933  
1934 Mercury clearance during dialysis was investigated in an *in vitro* experiment using  
1935 pooled plasma samples to which mercury and metal-binding agents had been added.  
1936 Of the agents investigated acetylcysteine was the most effective in clearing mercury  
1937 after 90 minutes of *in vitro* dialysis, reducing the mercury concentration in the perfusate  
1938 by 73%, whereas succimer removed over 60% of mercury in the perfusate. Unithiol  
1939 was more effective than succimer but the results were not statistically different. In  
1940 contrast the quantity of mercury removed from plasma without the presence of a metal-  
1941 binding agent was very low at 5% (Ferguson & Cantilena, 1992).

#### 1942 1943 **9.5.5 Trace element elimination**

1944  
1945 Succimer has been shown to increase elimination of some trace elements in volunteer  
1946 studies.

1947  
1948 Oral administration of succimer (10 mg/kg) to volunteers resulted in small but  
1949 significant increases in urinary excretion of zinc and copper which peaked at 4 hours  
1950 after ingestion. There was no change in the elimination of 27 other metals and  
1951 elements (Aposhian et al., 1989).

1952  
1953 In a study of 21 children with high blood lead concentrations, succimer up to doses of  
1954 1050 mg/m<sup>2</sup>/day (comparable to 30 mg/kg/day) did not enhance urinary excretion of  
1955 zinc, copper, calcium or iron (Graziano et al., 1988). In several other studies, 30  
1956 mg/kg/day of succimer has been shown to slightly enhance urinary excretion of zinc  
1957 (Graziano et al., 1985; Fournier et al., 1988; Haust et al., 1989; Grandjean et al., 1990)  
1958 and copper (Friedhiem et al., 1978; Graziano et al., 1985; Haust et al., 1989).

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## **10. CLINICAL STUDIES – CLINICAL TRIALS**

There are few clinical trials on the efficacy of succimer in poisoning with metals and metalloids. The exception is lead poisoning, particularly in children, which has been the subject of a number of clinical trials. There are a few small trials in mercury-poisoned patients and one good quality trial in subjects with chronic arsenicosis.

### **10.1 Arsenic and succimer clinical trials**

Succimer was evaluated as an antidote for chronic arsenic poisoning due to natural contamination of drinking water in West Bengal, India. Twenty-one patients were randomised into 2 groups: 11 patients (10 males, 1 female, mean age 25.5 years) received succimer 1400 mg/day in 4 divided doses for 7 days followed by 1050 mg/day in 3 divided doses for 2 weeks. This regimen was repeated after a drug-free period of 3 weeks. The second group (10 males, mean age 32.2 years) received placebo capsules in the same dosing regimen. The patients did not know which they received. Patients were included if they had a history of drinking water with an arsenic concentration of 50 µg/L or more (0.05 mg/L) for 2 years or more with clinical signs and symptoms of chronic arsenicosis. Clinical features were evaluated using an objective score system before and after treatment. All patients were hospitalised during treatment. Patients were excluded if they had stopped drinking the water for more than 5 months, smoked, drank alcohol, took hepatotoxic drugs, and were hepatitis B positive, pregnant or less than 18 years old. Skin was biopsied before and after treatment; hair and nail samples were also taken. Urine samples were obtained 2 days before and at 48 and 72 hours after starting treatment.

Succimer did not result in any significant clinical improvement. Excretion of arsenic before treatment, at 48 and 72 hours was comparable in the succimer and placebo subjects. There was no change in liver function tests or the arsenic concentration in hair and nails. There was no difference in the arsenic-related skin effects with succimer or the placebo. Succimer was well tolerated in all patients. It was concluded that succimer was ineffective in the treatment of chronic arsenicosis in humans (Guha Mazumder et al., 1998).

### **10.2 Copper and succimer clinical trials**

Ren et al. (1998) investigated the efficacy of succimer in patients with Wilson's disease. There were 120 patients divided into 2 groups of 60: Group A received succimer (20-30 mg/kg twice daily) and Group B received penicillamine (20-30 mg/kg 4 times daily). Group A comprised 34 males and 26 females with a mean age 20 years and a mean duration of illness of 2.5 years. Forty subjects received succimer for 6 months to 2 years, and 20 subjects for more than 2 years. Group B comprised 31 males, 29 females with a mean age of 18 years, and a mean duration of illness of 3 years. Thirty-eight subjects received penicillamine for 6 months to 2 years and 22 received it for more than 2 years. The severity of illness was graded according to the modified Goldstein method. All patients had received therapy with unithiol or sodium calcium edetate before starting long-term therapy with succimer or penicillamine. All patients also received 560 mg of zinc gluconate daily and were advised to take a copper-poor diet. For the succimer-treated group improvement was observed in 80%

2010 of subjects taking it for 6 months to 2 years and 85% in those taking it for more than 2  
2011 years. The figures for the penicillamine treated group were 58% and 59%,  
2012 respectively. Urinary copper concentrations were significantly different in both groups.  
2013 In the succimer-treatment group 9 patients (15%) suffered gingival suffusion, epistaxis,  
2014 rash and mild abdominal distension. All patients responded to supportive care and  
2015 none had to stop treatment because of severe adverse effects. The incidence of  
2016 adverse effects was lower in the succimer-treated group.

2017

### 2018 **10.3 Lead and succimer clinical trials**

2019

2020 There are a number of clinical trials on the effects of succimer therapy in lead-  
2021 poisoned patients which have demonstrated that it is effective at reducing blood lead  
2022 concentrations. Many of the studies have involved children, and of particular note is  
2023 the large study by the Treatment of Lead-Exposed Children (TLC) Study Group in the  
2024 USA (see section 10.3.1).

2025

2026 Friedheim et al. (1978) studied the efficacy of oral succimer (8.4 - 12.7 mg/kg/day  
2027 increasing to 28.1 - 42.2 mg/kg/day by the 5th day, n=5) and intravenous sodium  
2028 calcium edetate (12.2 - 16.5 mg/kg/day for 5 days, n=4) in lead-smelter workers, aged  
2029 27 to 50 years. Succimer appeared to lower blood lead significantly more than  
2030 sodium calcium edetate while the opposite effect was noted on the urinary excretion of  
2031 lead. The blood lead concentration decreased significantly from an average of 970  
2032 µg/L to 600 µg/L on day 2 and 430 µg/L on day 5 in patients treated with succimer.  
2033 Some patients complained of gastrointestinal upset but otherwise succimer was well  
2034 tolerated. Succimer produced a slight increase in the urinary copper concentration but  
2035 did not affect the concentrations of zinc, calcium, magnesium or iron. This early study  
2036 clearly established the safety and effectiveness of succimer in lowering blood lead  
2037 concentrations in poisoned patients. No cognitive tests were performed and the dose  
2038 of sodium calcium edetate was probably too low to allow for a direct comparison of  
2039 efficacy between the two antidotes used.

2040

2041 Nine adults with lead toxicity were treated with 30 mg/kg/day succimer for 5 days,  
2042 except for 2 subjects started on lower doses, one because of a history of atopy, the  
2043 other was treated for 15 days due a high initial blood lead concentration. The blood  
2044 lead concentrations were reduced by 35-81% compared to initial values and the  
2045 urinary lead excretion was on average increased by one order of magnitude. Three  
2046 weeks after treatment, clinical indices of lead poisoning had stabilised or improved in  
2047 all patients. Succimer was well tolerated and, of the trace elements, only zinc plasma  
2048 concentrations were significantly reduced (Fournier et al., 1988).

2049

2050 Graziano et al. (1985) studied the effect of succimer on the blood lead concentration  
2051 and urinary lead excretion in 18 men, aged 24 to 58 years, with occupational exposure.  
2052 A blood lead concentration of 600 to 990 µg/L was required for inclusion in the study,  
2053 although equipment failure and reliance on an external laboratory meant that 2  
2054 subjects were included who had blood lead concentrations of 440 and 450 µg/L.  
2055 Analysis of data from these subjects did not affect the findings and were not excluded.  
2056 Subjects were excluded from the study if they had known sensitivity to antidotes,  
2057 history or the presence of serious cardiovascular, renal, liver, endocrine, metabolic or  
2058 gastrointestinal disease, an electrocardiogram (ECG) abnormality, history of chronic  
2059 alcohol or drug abuse, use of any study drug within the previous month, use of any  
2060 drugs (except sodium calcium edetate) with well-defined organ toxicity within the

2061 previous 6 months or inability to give informed consent because of diminished mental  
2062 capacity. Each subject was admitted to hospital for 7 days and randomly assigned to  
2063 receive succimer in doses of 10, 20 or 30 mg/kg/day in 3 divided doses for 5 days.  
2064 Each subject was followed-up at 1 and 2 weeks after discharge. The mean initial  
2065 blood concentration did not differ between the 3 groups. A dose-related maximum  
2066 reduction in blood lead was seen by day 5 when the blood lead concentrations were  
2067 reduced by 35.5%, 58.3% and 72.5% after 10, 20 and 30 mg/kg/day, respectively.  
2068 Urinary lead excretion was also increased. All patients showed increased  $\delta$ -  
2069 aminolevulinic acid dehydratase activity and decreased urinary coproporphyrin  
2070 excretion. Further, subjective symptoms of lead intoxication were alleviated in some  
2071 patients. Succimer had no effect on iron or magnesium excretion and resulted in only  
2072 mild increases in copper and zinc excretion. Blood lead concentrations rebounded  
2073 after cessation of therapy indicating mobilisation of lead from bone.

2074  
2075 Graziano et al. (1988) studied 21 children, aged 2-7 years, with blood lead  
2076 concentrations of 310-490  $\mu\text{g/L}$ . The children were divided into groups receiving either  
2077 sodium calcium edetate (1000  $\text{mg/m}^2/\text{day}$  intravenously in 2 divided doses for 5 days)  
2078 or succimer (350, 700 or 1050  $\text{mg/m}^2/\text{day}$  orally in 3 divided doses for 5 days,  
2079 corresponding to the doses of 10, 20 or 30 mg/kg/day used adults). The succimer was  
2080 administered in food or drink. Subjects were excluded if they had a known  
2081 hypersensitivity to the antidotes, had a history of serious cardiovascular, renal, hepatic,  
2082 endocrine, metabolic or gastrointestinal disease, clinical features of lead toxicity, an  
2083 abnormal ECG, use of any investigational drug within the previous month or use of any  
2084 drug with well defined organ toxicity within the previous 6 months. Four children were  
2085 treated twice, each receiving succimer or sodium calcium edetate at different times.  
2086 The study demonstrated a positive correlation between dose and lead mobilising effect  
2087 for succimer, the highest dose being more efficient than sodium calcium edetate.  
2088 There were rebound increases in blood lead concentrations after cessation of therapy  
2089 and the rebound was largest after the lowest dose of succimer. Erythrocyte  $\delta$ -  
2090 aminolevulinic acid dehydratase activity rose in all four treatment groups but the  
2091 highest dose of succimer was significantly more effective. Succimer did not increase  
2092 urinary excretion of zinc, calcium, iron or copper; it was well tolerated with no serious  
2093 adverse effects reported.

2094  
2095 Chisolm (1990) also observed rebound increases in the blood lead concentration  
2096 within 2.5 weeks after cessation of therapy in 4 children with lead intoxication treated  
2097 with succimer. Succimer was given as 5 courses each lasting 10 days (1050  
2098  $\text{mg/m}^2/\text{day}$  for 5 days followed by 350  $\text{mg/m}^2/\text{day}$  for 5 days).

2099  
2100 Graziano et al. (1992) examined the efficacy and safety of succimer in lead-intoxicated  
2101 children. Twenty-three children aged 1-10 years with blood lead concentrations of  
2102 550-690  $\mu\text{g/L}$  (2.41 - 3.33  $\mu\text{mol/L}$ ) were included in the study. Nineteen children were  
2103 given succimer (1050  $\text{mg/m}^2/\text{day}$ ) for 5 days and 4 received intravenous sodium  
2104 calcium edetate (1000  $\text{mg/m}^2/\text{day}$  in two divided doses) for 5 days. On discharge the  
2105 succimer-treated children were either given no further antidote or received succimer  
2106 350 or 750  $\text{mg/m}^2/\text{day}$  on days 7 to 20. The sodium calcium edetate-treated children  
2107 received no further antidote. The children were only discharged once their home  
2108 environment had been cleared of lead hazards. Exclusion criteria were the same as  
2109 those for Graziano et al. (1988) outlined above. The mean blood lead concentration in  
2110 the succimer group decreased by 61% compared to 45% in the sodium calcium  
2111 edetate-treated children. Urinary lead excretion was comparable in both groups.

2112 Succimer was more effective in restoring metabolic activity to the haem pathway. After  
2113 14 days the mean blood lead concentrations for the no antidote, low succimer and high  
2114 succimer groups were 73%, 66% and 50% of the pre-treatment values, respectively.  
2115

2116 Besunder et al. (1995) undertook a retrospective review of paediatric lead toxicity  
2117 cases to investigate the efficacy of succimer. Children were included if they had a  
2118 blood lead concentration of 1.21 to 2.36  $\mu\text{mol/L}$  (250-490  $\mu\text{g/L}$ ) and were excluded if  
2119 they had received antidotal therapy in the previous 28 days, received another antidote  
2120 with succimer, there was evidence of non-compliance or the drug was given as part of  
2121 a pharmaceutical drug sponsored study. There was no control group. Homes were  
2122 inspected and efforts made to reduce exposure before antidotal therapy was started.  
2123 Radiographic and laboratory studies were also undertaken before commencement of  
2124 succimer therapy. A total of 46 children were identified but 18 were excluded. Of the  
2125 remaining 28, 15 were male and 13 female, the mean age was 44 months with a mean  
2126 blood lead concentration of 370  $\mu\text{g/L}$  and mean zinc protoporphyrin of 710  $\mu\text{g/L}$ . The  
2127 children received the standard 19 day regiment of succimer and the blood lead  
2128 concentration fell during the first 5 days but stayed constant over the remaining 14  
2129 days. It rose again over the 2 weeks following cessation of therapy and then  
2130 decreased again slightly over the next 2 months. In contrast the zinc protoporphyrin  
2131 decreased over the first 5 weeks before stabilising. The difference in pre-treatment  
2132 concentrations of zinc protoporphyrin achieved significance on day 14 but was greatest  
2133 at mean day 34. The blood lead concentration fell by 43% in this study and after  
2134 treatment remained at 26 to 31% lower than pre-treatment concentrations; 80% of  
2135 patients had a 20% or greater reduction in blood lead concentrations. The decrease in  
2136 zinc protoporphyrin was attributed to a reduction in biochemical lead toxicity and not a  
2137 change in iron status. No significant adverse effects were observed except for  
2138 neutropenia in one patient.  
2139

2140 Farrar et al. (1999) compared the efficiency of two dosing regimens of succimer in  
2141 children with lead poisoning. Children aged 1 to 12 years with a blood lead  
2142 concentration between 250 to 690  $\mu\text{g/L}$  were eligible. Each child was randomly  
2143 assigned to a treatment group. Exclusion criteria were any suspicion of poor  
2144 compliance, clinical symptoms of lead encephalopathy, previous adverse effects to  
2145 succimer, antidotal therapy within the previous month, and abnormalities in creatinine  
2146 or liver enzymes. Standard therapy was 1050  $\text{mg/m}^2/\text{day}$  in 3 divided doses for 5 days  
2147 followed by 700  $\text{mg/m}^2/\text{day}$  in 2 divided doses for 14 days. The alternate therapy was  
2148 2 courses, separated by 7 days, of 1050  $\text{mg/m}^2/\text{day}$  in 3 divided doses for 5 days.  
2149 There were 7 children on the standard regimen (5 female, 2 male, mean age 25  
2150 months) and 4 on the alternate regimen (3 female, 1 male, mean age 31 months). The  
2151 blood concentration in the standard group decreased from 330 to 270  $\mu\text{g/L}$  and in the  
2152 alternate group from 330 to 230  $\mu\text{g/L}$ ; there was no significant difference between the  
2153 groups. No clinical adverse effects were observed in any child and two short high  
2154 dose periods were as safe and effective as the standard regimen.  
2155

2156 O'Connor & Rich (1999) evaluated the effectiveness of succimer in children with blood  
2157 lead concentrations of 300-450  $\mu\text{g/L}$  (1.45-2.17  $\mu\text{mol/L}$ ). There were 19 children in the  
2158 succimer group (mean age 39.8 months, 13 females and 6 males, mean blood lead  
2159 concentration 349  $\mu\text{g/L}$ ) and 20 in the control group (mean age 40.8 months, 7 females  
2160 and 13 males, mean blood lead concentration 330  $\mu\text{g/L}$ ). Children with a previous  
2161 lead concentration above 450  $\mu\text{g/L}$  treated with antidotal therapy were excluded.  
2162 Families were instructed on reducing lead in the domestic environment and follow up

2163 inspections were also undertaken to ensure remedial action had been performed. In  
2164 the treatment group children less than 15 kg received 100 mg 3 times daily for 5 days  
2165 and then 100 mg twice daily for 14 days. Children over 15 kg received 200 mg 3 times  
2166 daily for 5 days and then 200 mg twice daily for 14 days. The blood lead  
2167 concentrations in the succimer-treated and the placebo groups were not statistically  
2168 different at 1 month or 6 months. This apparent lack of effect of succimer may have  
2169 been due to a number of reasons including poor patient compliance, continued  
2170 exposure during the duration of the study and small sample size.

### 2171 2172 **10.3.1 Study by the Treatment of Lead-Exposed Children (TLC) Study Group**

2173  
2174 Several studies were undertaken by the Treatment of Lead-Exposed Children (TLC)  
2175 Study Group in the USA involving 780 children aged 12 to 33 months with blood lead  
2176 concentrations of 220-440 µg/L (0.96-2.12 µmol/L). Enrolment was conducted  
2177 between 1994 and 1997 and children were randomly assigned to the succimer or  
2178 placebo group and compliance was determined by medication diaries and pill counting.  
2179 All children received multivitamin and mineral supplementation. All homes were  
2180 inspected and either cleaned or the families moved to lead-safe housing. There were  
2181 6 dose regimens based on body surface area and up to three 26 day courses were  
2182 given; 89% of children had finished treatment by 6 months and all by 13 months. The  
2183 children were followed for 3 years. Succimer capsules were too large for the children  
2184 to swallow and they were opened and the contents sprinkled onto food or juice (TLC  
2185 Trial Group, 2000; Rogan et al., 2001; Dietrich et al., 2004; Peterson et al., 2004; Chen  
2186 et al., 2005).

2187  
2188 The first study by this group examined the safety and efficacy of succimer. All children  
2189 had a decrease in blood lead concentrations. In the placebo group the change was  
2190 gradual and in the succimer-treated group there was an abrupt drop. The blood lead  
2191 concentration in the treatment group was 45 µg/L lower than the placebo group after 6  
2192 months in the programme. There were more rashes on the scalp in the succimer-  
2193 treated group (3.5% versus 1.3%) but there was no statistically significant excess of  
2194 any adverse event in the succimer-treated group. This was also the case with blood  
2195 counts and liver function tests (TLC Trial Group, 2000).

2196  
2197 Rogan et al. (2001) examined the effect of succimer on the neurophysiological function  
2198 in these children. By 36 months the intelligence quotient (IQ) of the succimer-treated  
2199 children was 1 point lower than that of the placebo group, and the behaviour of the  
2200 former was rated as slightly worse by a parent. The succimer-treated children did  
2201 have slightly better scores on the development neuropsychological assessment but the  
2202 differences were not statistically significant. Overall, succimer did not improve scores  
2203 of cognition, behaviour or neurophysiological function. A reanalysis of the data from  
2204 the trial by Liu et al. (2002) showed no benefit of a reduction in the blood lead  
2205 concentration on cognitive test scores over the first 6 months. By 36 months the  
2206 children in the placebo group who had the greatest decrease in blood lead  
2207 concentrations showed the greatest increase in cognitive scores. This effect was not  
2208 observed in the children treated with succimer suggesting that lead-induced cognitive  
2209 defects are irreversible.

2210  
2211 Dietrich et al. (2004) looked at the influence of succimer on neurodevelopment  
2212 measured at 7 years of age (by which time 647 children remained in the study). The  
2213 children were subjected to a series of standard neuropsychological tests to evaluate

2214 cognitive, behavioural, psychological and school performance. This study found that  
2215 succimer treatment was not associated with neurodevelopment benefits in terms of  
2216 cognitive, behaviour or neuromotor end-points.  
2217

2218 In another study, Peterson et al. (2004) found that succimer did not have a beneficial  
2219 effect on the growth of lead-poisoned children and may, in fact, have a detrimental  
2220 effect. The height difference in the succimer-treated children compared to controls  
2221 was -0.27 cm at 34 months.  
2222

2223 The overall conclusion of the studies by the TLC Group was that although succimer  
2224 lowers blood lead concentrations it cannot be recommended for the treatment of  
2225 children with blood lead concentrations of 220-440 µg/L (0.96-2.12 µmol/L).  
2226

#### 2227 **10.4 Mercury and succimer clinical trials**

2228

2229 Forty-one patients (aged 2 to 65 years) from 8 families were poisoned with mercury  
2230 following ingestion of rice contaminated with an ethyl mercury seed dressing. One  
2231 patient died soon after onset of symptoms and 8 were admitted in the initial acute  
2232 phase of intoxication. The remaining 40 patients demonstrated a variety of clinical  
2233 features 5 months after ingestion and 27 were treated with unithiol (250 mg daily by  
2234 intramuscular injection) and/or succimer (500 mg twice daily by intravenous injection).  
2235 The drugs were given for 3 days followed by a 4 day break and then another 3 day  
2236 course, if required. Patients were given 1 to 8 courses until the urinary mercury  
2237 concentration was normal. The 13 untreated patients showed little improvement in  
2238 clinical features of toxicity but all those on therapy had some relief and 19 became  
2239 asymptomatic. In 2 cases there was only slight improvement. In patients where the  
2240 urinary concentration was measured before therapy, all but one had increased mercury  
2241 excretion during antidotal administration. Side effects were mild and generally  
2242 resolved within 30 minutes to 4 hours. Unithiol was found to be more effective,  
2243 although no data distinguishing between the two drugs is given. In addition, the two  
2244 antidotes were used interchangeably in some patients (Zhang, 1984).  
2245

2246 A group of 53 men were exposed to elemental mercury vapour during repair work on  
2247 mercury tubes in a chloralkali factory. Workers were exposed when welding  
2248 equipment volatilised mercury remaining in the pipes. They continued to work while  
2249 the mercury condensed and began to rain down on them collecting in their clothes and  
2250 shoes and on body surfaces. Few wore protective equipment and masks were only  
2251 worn for a limited time. They were not decontaminated. Subsequently several  
2252 workers became ill. After several days, mercury poisoning was diagnosed based on  
2253 elevated urinary mercury concentrations. A total of 26 men were hospitalised from day  
2254 19 up to day 36 after the exposure. They were followed up 2 weeks later and owing to  
2255 continued symptoms were treated with succimer (30 mg/kg every 8 hours) or NAPA  
2256 (250 mg every 6 hours) for approximately 2 weeks between days 29 and 46. Twelve  
2257 subjects who still had high mercury concentrations were hospitalised (between days 73  
2258 and 116) for a 4 day study on the efficacy of succimer and NAPA. Data were  
2259 incomplete for one patient so he was excluded from the analysis. Antidotes did not  
2260 produce a steady increase in mercury excretion but rather peaks and troughs related  
2261 to dosing. Both drugs increased mercury elimination; succimer produced a 3-fold  
2262 increase and NAPA a 2-fold increase in mercury excretion (Bluhm et al., 1992).  
2263  
2264

2265 **11 CASE REPORTS – CLINICAL STUDIES**

2266  
2267 Except in the case of lead intoxication, few clinical studies of the efficiency of succimer  
2268 in metal intoxications have been published. In the following section, the case report  
2269 literature on succimer is critically reviewed.

2270  
2271 In many clinical case reports of succimer use in poisoning the authors do not  
2272 determine a balance between the quantity of metal absorbed and excreted; this can be  
2273 difficult where the dose ingested, injected or inhaled cannot be quantified. Clinical  
2274 efficacy of succimer is often only stated in terms of enhancing excretion and/or  
2275 decreasing blood concentrations in the absence of severe adverse effects. In many  
2276 cases, the authors are unable to distinguish between the effect of succimer  
2277 administration and the effect of supportive therapy (including removal from the source).

2278  
2279 The efficacy of a metal-binding agent may be difficult to determine. After  
2280 discontinuation of metal exposure (and absorption) a decrease in the blood  
2281 concentration will occur without any therapy. Clinical efficacy should not be judged  
2282 only by the amount of metal excretion or the decrease of blood concentrations. The  
2283 reduction of the tissue content in the target organ and the restoration of pathological  
2284 alterations also need to be considered. It is important to note that enhancement of the  
2285 metal excretion by mobilisation may increase the metal burden of the target organ by  
2286 redistribution, and conversely the body burden may be reduced without a striking  
2287 decrease of the blood concentrations. However, in some case reports severe toxicity  
2288 usually associated with a demonstrated high blood or urine concentration does not  
2289 occur, and this may reasonably be assumed to be due to antidotal therapy. With  
2290 these reservations in mind, it is clear that administration of succimer can prevent  
2291 development of toxicity and in symptomatic patients it can reduce recovery time and  
2292 improve clinical signs and symptoms of toxicity.

2293  
2294 Reference values for the metal and metalloids (Walker, 1998) are given as a guide at  
2295 the start of each section to aid interpretation of the concentrations given in the case  
2296 reports.

2297  
2298 **11.1 Aluminium**

2299  
2300 Animal studies on the efficacy of succimer in aluminium poisoning have given mixed  
2301 results and clinical experience is completely absent.

2302  
2303 **11.2 Antimony**

2304  
2305 The efficacy of succimer in antimony poisoning has not been fully evaluated, however,  
2306 it could be considered since it has been shown to be effective in animal studies.

2307  
2308 Human antimony intoxication is very rare. The first clinical report on the use of  
2309 succimer in China concerned the treatment of two patients with cardiac dysfunction  
2310 and toxic hepatitis following a very high dose of intravenous potassium antimony  
2311 tartrate given in mistake by hospital staff for glucose. In both cases, intravenous  
2312 administration of succimer was associated with a successful recovery (Zhang & Ye,  
2313 1962).

2314  
2315 A 32 year old male with acquired immunodeficiency syndrome (AIDS) and visceral

2316 leishmaniasis was accidentally given an overdose of sodium stibogluconate (a  
2317 pentavalent antimony compound). He was given 6.5 g intravenously instead of 0.65 g.  
2318 He remained well for the first 48 hours and then developed raised pancreatic enzyme  
2319 activities without clinical evidence of pancreatitis. At 72 hours succimer was started  
2320 (10 mg/kg parenterally every 8 hours for 48 hours). The patient recovered but the  
2321 succimer did not appear to change the pharmacokinetics of antimony in this case  
2322 (Reymond & Desmeules, 1998).

2323

### 2324 **11.3 Arsenic**

2325

2326 Reference values for arsenic (Walker, 1998):

2327	Blood	<0.13 $\mu\text{mol/L}$ (<10 $\mu\text{g/L}$ )
2328	Urine	<0.13 $\mu\text{mol/24 hours}$ (<10 $\mu\text{g/24 hours}$ ) of inorganic arsenic
2329	Urine	<40 nmol/mmol creatinine (unexposed)
2330		<173 nmol/mmol creatinine (occupational exposure)

2331

2332 Succimer has been used successfully in a number of cases of acute organic and  
2333 inorganic arsenic poisoning but unithiol is considered the antidote of choice for arsenic  
2334 toxicity (Adam et al., 2003). Succimer is not useful in chronic arsenicosis (see section  
2335 10.1 and Fournier et al., 1988; Kew et al., 1993; Wax & Thornton, 2000).

2336

2337 The case reports reviewed below describe several survivals, apparently without  
2338 sequelae, despite ingestion of large doses of organic or inorganic arsenic compounds,  
2339 several times the lethal dose. Due to the delay and low intensity of the antidotal  
2340 treatment in some of the cases, survival is likely to be due to supportive treatment.  
2341 Accordingly, and due to the wide variation in antidote treatments, the recommendation  
2342 for clinical treatment of human arsenic intoxication still rests on animal experiments,  
2343 which clearly indicate that succimer and unithiol should now substitute dimercaprol and  
2344 D-penicillamine in the treatment of arsenic intoxication.

2345

2346 In an early report a 46 year old man with chronic alcoholism ingested 2 g of arsenic  
2347 trioxide. Half an hour later he started to vomit and after 8 hours he had diarrhoea. He  
2348 was brought to hospital, underwent gastric lavage and was given charcoal. No specific  
2349 antidote was given and the patient was transferred to another hospital for further  
2350 treatment. Upon arrival he had arterial occlusion in the right leg and anticoagulation  
2351 therapy was started. As this condition prevented intramuscular injections with  
2352 dimercaprol, succimer was given (300 mg orally every 6 hours for 3 days) starting 21  
2353 hours after ingestion. The patient eliminated 27.03 mg of arsenic in his urine during  
2354 the 3 days of therapy. After cessation of succimer therapy, the urinary arsenic  
2355 elimination decreased extensively. The patient developed a polyneuropathy 3 weeks  
2356 later (Lenz et al., 1981). It was not clear whether this was due to the late institution of  
2357 succimer therapy, the short duration time or was a result of his alcoholism. This case  
2358 report indicates that succimer may be useful in acute arsenic intoxication, however, it  
2359 should be given for a longer than the 3 days used here.

2360

2361 A 20 year old male drug user drank a herbicide solution containing about 80 g of  
2362 monosodium methanearsenate to commit suicide. After extensive vomiting, he was  
2363 admitted to intensive care in a state of shock with early liver and renal involvement. He  
2364 was treated with succimer, 30 mg/kg/day for 4 periods of 5 days over 30 days. Over  
2365 this period the serum arsenic concentration declined from more than 2871  $\mu\text{g/L}$  down  
2366 to 6  $\mu\text{g/L}$ , and the urinary arsenic from almost 80 mg/L to 21  $\mu\text{g/L}$ . While kidney

2367 function normalised, elevated transaminases indicated liver damage, most likely due to  
2368 a subsequently diagnosed chronic hepatitis. Succimer was well tolerated (Shum et al.,  
2369 1995).

2370  
2371 Acute arsenic poisoning due to food contamination with arsenic trioxide occurred in  
2372 117 individuals. They had gastrointestinal symptoms typical of acute arsenic  
2373 intoxication and were all treated with oral or parenteral succimer for 6 weeks. The  
2374 incidence of neuritis, liver and cardiac toxicity was 7.7%, 32.54% and 35.9%,  
2375 respectively. The average urinary arsenic concentration was 3.9 mg/L and all patients  
2376 recovered (Dong et al., 1993).

2377  
2378 A patient who had accidentally ingested a mouthful of Fowler's solution (1% potassium  
2379 arsenite) was treated with succimer. The mean daily urinary excretion of arsenic was  
2380 32  $\mu\text{mol/day}$  during succimer treatment (30 mg/kg/day for 5 days) and plasma  
2381 concentrations of arsenic fell from 0.24 to 0.10  $\mu\text{mol/L}$ . Clinical effects resolved over a  
2382 few days (Fournier et al., 1988).

2383  
2384 A 30 year old male ingested approximately 25 g of arsenic trioxide and made himself  
2385 vomit soon after. He was treated with activated charcoal, whole bowel irrigation with  
2386 polyethylene glycol-electrolyte and intravenous fluids. Neither dimercaprol or succimer  
2387 were immediately available so he was started on intravenous acetylcysteine,  
2388 penicillamine, calcium disodium edetate and sodium bicarbonate to alkalinise the  
2389 urine. Succimer (800 mg 3 times daily) was started 24 hours after admission. He  
2390 remained in hospital for another 24 hours and was discharged on succimer, 800 mg 3  
2391 times daily for 5 days and then 800 mg twice daily for 14 days. The blood arsenic  
2392 concentration was over 600 nmol/L on the first day and fell rapidly within the first 3  
2393 days. He was well at follow up 2 weeks later when the urinary arsenic concentration  
2394 was almost within the normal range (Isbister et al., 2004).

2395  
2396 A 28 year old male presented to hospital 3 hours after ingestion of approximately 10 g  
2397 of arsenic trioxide. He had gastrointestinal effects and was started on intravenous  
2398 fluids and whole bowel irrigation with polyethylene glycol-electrolyte solution.  
2399 Succimer was unavailable so he was started on calcium disodium edetate. Succimer  
2400 (500 mg 3 times daily) was started 11 hours post-ingestion and he was given sodium  
2401 bicarbonate to alkalinise the urine. The blood arsenic concentration was  
2402 approximately 3750 nmol/L on the first day and fell rapidly within the first 2 days. He  
2403 was discharged to the ward on day 4 and continued on succimer until day 34 when his  
2404 urinary arsenic concentration was almost within the normal range. He had no  
2405 evidence of sequelae (Isbister et al., 2004).

2406  
2407 A 27 year old female developed gastrointestinal effects, ECG changes and liver  
2408 damage after ingestion of 9 g of arsenic trioxide. She was treated with intravenous  
2409 fluids, activated charcoal and continuous alkaline irrigation of the stomach over 36  
2410 hours. She was given succimer (15 mg/kg every 8 hours for 26 days) and  
2411 intramuscular dimercaprol (4 mg/kg every 4 hours) for 24 hours. A second course of  
2412 dimercaprol was administered on day 5 due to continued deterioration. She was also  
2413 started on a regimen designed to enhance methylation of arsenic derivatives which are  
2414 less toxic and more readily excreted. She was given hydroxocobalamin, methionine,  
2415 folinic acid, sodium bicarbonate, glutathione and intravenous unithiol (250 mg every 4  
2416 hours for 5 days). She began to improve within 48 hours with improved pulmonary  
2417 function and ECG. Liver function tests began to resolve but were elevated for more

2418 than a month. She also received unithiol from days 15 to 18. Urinary arsenic  
2419 concentrations fell rapidly in the first 10 days. At follow up one year later she had mild  
2420 polyneuropathy. The role of succimer in this patient's recovery was not evaluated.  
2421 Unithiol, with and without the methylating regimen, increased the proportion of  
2422 methylated arsenic metabolites (monomethylarsonic acid and dimethylarsenic acid) in  
2423 the urine (Vantroyen et al., 2004).

2424  
2425 A 26 year old male developed arsenic poisoning after his wife gave him arsenic  
2426 trioxide, probably 10 g over two weeks. He developed hepatitis, pancreatitis,  
2427 neurological disorders, respiratory distress, renal failure and cardiovascular  
2428 disturbances. Diagnosis of arsenic toxicity was not available initially and antidotal  
2429 therapy was started on day 4 of hospitalisation. He was given intramuscular  
2430 dimercaprol (4 mg/kg every 4 hours for the first day and then every 12 hours on the  
2431 second day). Unithiol was not available and succimer was only available as an oral  
2432 preparation. This was not suitable due to the presence of ileus. An intravenous  
2433 preparation of succimer was made and started on the same day as dimercaprol. He  
2434 was given succimer from day 4 to 14 intravenously (20 mg/kg/day for 5 days and then  
2435 10 mg/kg/day for 6 days) and via peritoneal dialysis (20 mg/L of dialysate, with 12 L  
2436 exchanged daily for 5 days, then 10 mg/L for 6 days). He also received haemodialysis  
2437 and haemofiltration. It was calculated that over an 11 day period 14.5 mg of arsenic  
2438 was eliminated in the urine, 26.7 mg by haemodialysis, 17.8 mg by peritoneal dialysis  
2439 and 7.8 mg by continuous venovenous haemofiltration. These quantities are negligible  
2440 compared to the estimated amount ingested. He died on day 26 from multiple organ  
2441 failure, complicated by subarachnoid haemorrhage and a generalised infection with  
2442 *Aspergillus fumigatus*. Intravenous and intraperitoneal succimer was well tolerated  
2443 with no change in haemodynamic parameters (Hantson et al., 2003).

2444  
2445 A 39 year old female was evaluated for diarrhoea, nausea, vomiting, dermatological  
2446 changes, pancytopenia, renal failure, progressive weakness and polyneuropathy. She  
2447 progressed to quadriplegia and ventilator dependence and was diagnosed with arsenic  
2448 poisoning. The serum arsenic concentration was 290 µg/kg and the urine 2000 µg/L.  
2449 She was given succimer (10 mg/kg 3 times daily) for 33 days over a 45 day period.  
2450 The serum arsenic concentration decreased to less than 10 µg/kg after 20 days and  
2451 the urine concentration was 20 µg/L on day 40. Succimer administration had no  
2452 demonstrable effect on arsenic clearance. She was in intensive care for 44 days and  
2453 hospitalised for a total of 4 months. She spent another 8 months in a rehabilitation  
2454 centre and 5 years later still had peripheral neuropathy. No source of the arsenic was  
2455 determined but criminal intent was suspected. Hair analysis suggested that exposure  
2456 occurred over a period of at least 2 months (Stenehjem et al., 2007).

2457  
2458 Succimer was used in a patient with lead and arsenic poisoning after use of a Korean  
2459 herbal medicine. She presented with malaise, weakness, arthralgia, and periorbital and  
2460 ankle oedema. She was anaemic and jaundiced with abdominal tenderness. The  
2461 urinary and blood arsenic concentrations were 400 µg/L and 20 µg/L, respectively. For  
2462 lead the figures were 1460 µg/L and 700 µg/L respectively. The medicine she had  
2463 been taking contained 26.4 mg/g lead and 9.65 mg/g arsenic. She had been taking  
2464 approximately 140 mg of lead and 50 mg of arsenic daily for a month. She was given  
2465 succimer (270 mg 3 times daily in two 7 day courses). She recovered clinically after  
2466 the first course and the blood lead concentration fell to the upper limit of normal and  
2467 the arsenic to within the normal range after the second course. There were no  
2468 adverse effects reported (Mitchell-Heggs et al., 1990).

2469  
2470 Succimer has also been used in paediatric arsenic poisoning. A 22 month old child  
2471 ingested an ant killer containing about 0.65 g of sodium arsenate (0.047 mg/kg). She  
2472 was pale and lethargic when hospitalised, with gastrointestinal symptoms and initially  
2473 treated with gastric lavage, intravenous fluids and intramuscular dimercaprol (3 mg/kg  
2474 at 9 hours post-ingestion). By 12 hours she had a decreased urine output and periods  
2475 of tachycardia but was otherwise well. Although succimer was recommended she was  
2476 treated with D-penicillamine (17.24 mg/kg every 6 hours for 9 doses) and was  
2477 discharged on day 6. She was readmitted 3 days later (9 days post-ingestion)  
2478 because of a high urinary arsenic concentration (650 µg/L from day 5). She had a rash  
2479 that may have been due to the D-penicillamine and was started on succimer (10 mg/kg  
2480 every 8 hours). After 4 days of succimer the urinary arsenic concentration was 96  
2481 µg/L. The relative efficacy of succimer is difficult to evaluate in this case because  
2482 more than one antidote was used and few samples were taken during succimer  
2483 therapy (Cullen et al., 1995).

2484  
2485 Succimer does not appear to be useful in the treatment of chronic arsenicosis. A 35  
2486 year old male developed arsenic toxicity after use of an Indian ethnic remedy. He had  
2487 Mees' lines on the finger nails and evidence of peripheral sensorimotor neuropathy.  
2488 The urinary arsenic concentration was 63 µg/L. He was treated with unithiol (100 mg 3  
2489 times daily) for 3 weeks and later succimer (400 mg 3 times daily) for 2 weeks but had  
2490 no subjective improvement in muscle strength (Kew et al., 1993).

2491  
2492 In another patient with chronic exposure to arsenic, plasma and urine concentrations  
2493 were not high; however, the concentration of arsenic in the hair was very high at 272  
2494 µg/g and he had clinical features consistent with arsenic toxicity. Succimer therapy (30  
2495 mg/kg/day for 5 days) failed to decrease plasma concentrations (0.15 µmol/L) and  
2496 renal excretion only increased 1.5 fold. Clinical recovery occurred over several months  
2497 (Fournier et al., 1988).

2498  
2499 A 33 year old female with chronic arsenic poisoning from an unknown source  
2500 presented with a 1.5 year history of episodes of peripheral neuropathy, pancytopenia,  
2501 ventricular tachycardia, gastrointestinal symptoms, skin rash and nail changes. Her  
2502 blood arsenic concentration was 56 µg/L and the 24 hour urine concentration 130 µg/L.  
2503 Analysis of well water demonstrated an arsenic concentration of 78 µg/L.  
2504 Electromyography revealed moderate demyelinating neuropathy with axonal  
2505 involvement. She was started on succimer 10 mg 3 times a day but serial urinary  
2506 arsenic determination failed to show any elimination. Her neuropathy continued to  
2507 progress and she required ventilation. She was then started on unithiol at 250 mg/kg  
2508 intravenously every 4 hours. During the first 24 hours of treatment the urinary arsenic  
2509 concentration rose from 101 to 300 µg/L. There was also improvement in her  
2510 neuropathy and she was continued on unithiol for 12 days. She was much improved,  
2511 extubated and discharged in a wheelchair 10 days later. By 3 months she was walking  
2512 on her own with some residual paraesthesiae and weakness in distal lower extremities.  
2513 At follow up one year later she had only mild weakness and residual paraesthesiae  
2514 controlled with amitriptyline (Wax & Thornton, 2000).

#### 2515 2516 **11.4 Beryllium**

2517  
2518 Data on antidotal treatment of beryllium intoxication in humans are not available, but  
2519 animal studies suggest that unithiol is more effective.

2520

## 2521 **11.5 Bismuth**

2522

2523 Only a few cases of antidotal treatment of humans exposed to bismuth are reported,  
2524 and unithiol in particular seems to be effective. Succimer does not appear to have  
2525 been used in a case of bismuth toxicity and its role in human bismuth intoxication is  
2526 unclear. However, in cases where no other antidote is available, the similarity in  
2527 general antidotal spectrum of these two compounds would warrant the institution of  
2528 succimer treatment, particularly in light of the efficacy of succimer demonstrated in  
2529 experimental bismuth poisoning and elimination studies in humans.

2530

## 2531 **11.6 Cadmium**

2532

2533 No well documented case reports of succimer use in acute cadmium poisoning could  
2534 be found. In animal experiments, several compounds (sodium calcium edetate,  
2535 pentetic acid, succimer and unithiol) were all efficient antidotes following a highly toxic  
2536 oral cadmium dose (Andersen, 1989a; 1989b). Presently however, there is no antidote  
2537 available for mobilisation of aged body burdens of cadmium. Development of metal-  
2538 binding agents able to mobilise hepatic and renal cadmium burdens has been  
2539 attempted for many years, and several efficacious experimental compounds are  
2540 available, yet, due to their toxicity, there is still a long way to go before humans can be  
2541 successfully treated for cadmium toxicity (Andersen, 2004).

2542

## 2543 **11.7 Cobalt**

2544

2545 The available experimental data indicate that injected aminopolycarboxylic acids (e.g.  
2546 sodium calcium edetate, pentetic acid) are the optimal antidotes for injected cobalt,  
2547 while injected succimer has some efficiency. It is difficult to advance a metal-binding  
2548 agent for acute human cobalt intoxication as long as animal experiments with a more  
2549 relevant exposure route than injection of cobalt salts are not available.

2550

## 2551 **11.8 Copper**

2552

2553 No well documented case reports of succimer use in acute copper poisoning could be  
2554 found.

2555

### 2556 **11.8.1 Use in Wilson's disease**

2557

2558 Succimer seems to have a role in human chronic copper intoxication as seen in  
2559 Wilson's disease. In China, hundreds of patients with Wilson's disease have been  
2560 treated with succimer since the late 1960s (Ding & Liang, 1991). A dose of succimer  
2561 of 1 mg/kg given twice daily, was associated with clinical improvement in 80% of  
2562 patients. The double dose given orally for 4 weeks increased cupruresis 4-fold. Even  
2563 in late stages of the disease succimer treatment was clearly associated with  
2564 improvement of clinical features and laboratory parameters (Yang et al., 1987).

2565

## 2566 **11.9 Gold**

2567

2568 Succimer has not been used in human cases of severe gold intoxication. Careful  
2569 monitoring of gold therapy on an individual patient basis has greatly reduced the  
2570 incidence of side effects. Animal studies suggest that succimer is an efficient

2571 mobilising agent for gold but clinical cases data are lacking.

2572

## 2573 **11.10 Lead**

2574

2575 Reference values for lead (Walker, 1998):

2576       Blood           <0.5 µmol/L (0.05 µmol/dL; <100 µg/L; <10 µg/dL) environmental  
2577                           exposure

2578       Urine            <100 nmol/24 hours (<10 µg/24 hours) normal adults

2579

2580 Succimer has been used in a number of acute and chronic adult and paediatric lead  
2581 poisoning cases, and in 1991 succimer was licensed in the USA for the treatment of  
2582 children with blood lead concentrations greater than 45 µg/dL (2.15 µmol/L) (US  
2583 Department of Health and Human Services, 1991).

2584

2585 A widely used sodium calcium edetate provocation test for diagnostic estimation of the  
2586 lead body burden must be considered obsolete and dangerous for the patient, in  
2587 agreement with a recommendation by the US Committee on Drugs (1995). Also, the  
2588 scientific basis and the validity of the results of the test have been seriously challenged  
2589 (Graziano, 1993). The combined animal experimental data and the human data  
2590 indicate that succimer preferentially mobilises soft tissue lead and recently deposited  
2591 bone lead depots, whereas aged bone lead deposits are inaccessible to succimer. In  
2592 contrast sodium calcium edetate is capable of mobilising aged bone lead deposits with  
2593 the risk of ensuing increased brain deposition; however, sodium calcium edetate is  
2594 less efficient than succimer in mobilising soft tissue lead.

2595

2596 A major problem in antidotal treatment of chronic lead intoxication is the rebound of  
2597 blood lead upon cessation of therapy, which occurs after all the antidotes. This  
2598 rebound, which is conceivably predominantly due to mobilisation of bone lead, may  
2599 necessitate repeated dosing schedules.

2600

2601 The studies of Liebelt et al. (1994) and Besunder et al. (1995) confirm the efficacy of  
2602 succimer in paediatric lead intoxication. Comparison of the intervention studies  
2603 presently available of childhood low level lead exposure cohorts, treated or untreated,  
2604 indicate that lead abatement alone may reduce blood lead and biochemical indices of  
2605 lead toxicity; the fall however, is larger in groups also treated with sodium calcium  
2606 edetate, dimercaprol + sodium calcium edetate, D-penicillamine, succimer, or sodium  
2607 calcium edetate + succimer, and among these antidotes, succimer must be considered  
2608 the most safe and efficient (Graziano et al., 1992; Glotzer, 1993; Liebelt et al., 1994;  
2609 Besunder et al., 1995; Helzner, 1996; Besunder et al., 1997).

2610

### 2611 **11.10.1 Acute lead poisoning in children**

2612

2613 A 5.5-year-old child vomited and complained of abdominal pain after ingesting small  
2614 lead pellets from an ankle weight. An X-ray revealed thousands of small radiopaque  
2615 pellets in the gastrointestinal tract. Haematological studies were normal and she was  
2616 well. She received whole bowel irrigation with polyethylene glycol-electrolyte solution  
2617 and within 24 hours passed 11 stools containing metallic pellets and other foreign  
2618 bodies (e.g. beads). Pellets were still seen on X-ray and were too numerous to count.  
2619 She was unable to tolerate the whole bowel irrigation and was started in a high fibre  
2620 diet. A 13 hour blood lead concentration was 57 µg/dL (2.7 µmol/L) and she was  
2621 started on succimer. On the first day of succimer therapy she excreted 2273 µg of

2622 lead in the urine over 24 hours and 834 µg on the second day. She had a mildly raised  
2623 alanine aminotransferase probably due to the succimer but otherwise remained well.  
2624 The peak blood lead concentration was 79 µg/dL (3.8 µmol/L) at approximately 36  
2625 hours after ingestion. On discharge she had only 13 pellets remaining in the gut and at  
2626 45 days none were visible. She had mild developmental and language delays and  
2627 lead was found in paint in the home with evidence of chewing on one surface. Her two  
2628 brothers had blood lead concentrations of less than 10 µg/dL. Six months after  
2629 ingestion the blood lead concentration was 25 µg/dL (1.2 µmol/L) (McKinney, 2000).

2630  
2631 A 21 month old child presented to hospital 12 hours after ingestion of lead pellets. She  
2632 was well on examination and abdominal X-ray revealed two pellets in the duodenal  
2633 bulb. A previous routine blood lead concentration had been 12 µg/dL (0.58 µmol/L)  
2634 and on admission this was 47 µg/dL (2.2 µmol/L). She was admitted and given whole  
2635 bowel irrigation with polyethylene glycol-electrolyte solution. A repeat X-ray at 24  
2636 hours after admission showed the pellets to be in the caecal region and she was  
2637 started on succimer 1050 mg/m<sup>2</sup>/day in 3 divided doses. The blood lead concentration  
2638 24 hours later was 48 µg/dL (2.35 µmol/L) and an X-ray revealed that the pellets had  
2639 not moved. At 72 hours after ingestion one pellet was removed by endoscopy; the  
2640 other could not be visualised and she was given another course of whole bowel  
2641 irrigation. The second pellet was finally removed by colonoscopy 24 hours later. The  
2642 blood lead concentration at this time was 25 µg/dL (1.2 µmol/L). She remained well  
2643 and completed the 19 day course of succimer. At 10 days after discharge the blood  
2644 lead concentration was 16 µg/dL (0.77 µmol/L). In this case, despite the presence of  
2645 lead in the gut, succimer therapy did not appear to increase lead absorption (Clifton et  
2646 al., 2002).

### 2647 2648 **11.10.2 Chronic lead poisoning in children**

2649  
2650 A 13 month old child presented with a one month history of vomiting and lethargy and  
2651 soon after arrival had a convulsion. She was anaemic with a blood lead concentration  
2652 of 244 µg/dL (11.7 µmol/L). She had a history of pica of paint (16% lead on  
2653 subsequent analysis) and an X-ray revealed multiple flakes of paint throughout the  
2654 gastrointestinal tract. She was intubated and ventilated and started on intravenous  
2655 sodium calcium edetate 40 mg/kg/day for 10 days. She was also given whole bowel  
2656 irrigation with polyethylene glycol-electrolyte solution 500 mL/hour for 36 hours.  
2657 Thereafter the X-ray was clear and she was started on oral succimer (10 mg/kg 3  
2658 times a day for 5 days and 10 mg/kg twice daily for 14 days). Her urinary lead  
2659 concentration on both antidotes was 166000 µg/g of creatinine. She was extubated on  
2660 day 2 and transferred to the ward on day 5. She had tremor and hyperreflexia but by  
2661 discharge on day 24 she was walking and had a blood lead concentration of 41 µg/dL  
2662 (1.97 µmol/L). Over the next 16 months she was given 6 further courses of succimer  
2663 and had a current blood concentration of 30 µg/dL (1.44 µmol/L), with normal physical  
2664 and neurological development (Dargan et al., 2001).

### 2665 2666 **11.10.3 Chronic lead poisoning in adults**

2667  
2668 Chronic poisoning due to ingestion of lead-contaminated flour was diagnosed by the  
2669 sodium calcium edetate provocation test followed by oral succimer challenge, resulting  
2670 in an 11-fold increase in urinary lead excretion. The original blood lead concentration  
2671 was 90 µg/dL (4.3 µmol/L) and the victim, a 33 year old male, was treated with a 5 day  
2672 course of succimer. This corrected clinical lead poisoning symptoms, increased

2673 urinary lead excretion and decreased blood lead to 21 µg/dL (1 µmol/L). Seven weeks  
2674 after treatment the blood lead concentration has risen to 33 µg/dL (1.58 µmol/L) but  
2675 clinical signs of lead intoxication did not reappear during several months of follow-up.  
2676 This case suggests that oral succimer may offer a safer diagnostic provocation test in  
2677 lead poisoning than the traditional sodium calcium edetate test (Bentur et al., 1987).

2678  
2679 Haust et al. (1989) treated a 37 year old male with severe occupational lead  
2680 intoxication over several years with extensive oral doses of succimer and iron  
2681 supplementation, which increased the serum-ferritin to normal values without any toxic  
2682 effect. Before succimer therapy, he had been treated with dimercaprol and sodium  
2683 calcium edetate and then sodium calcium edetate alone. During 3 years a total of  
2684 64.5 g of sodium calcium edetate had not improved the patient's clinical condition. He  
2685 suffered from anorexia, colic, insomnia and various neuropsychiatric symptoms. At  
2686 the time this case was reported, a total of 189 g of succimer given during 6 courses in  
2687 141 days of treatment over two years had mobilised about 375 mg lead. The urinary  
2688 lead excretion was increased about 7 times, and the blood lead was reduced to about  
2689 1/5th of the pretreatment values during the treatment courses, but gradually  
2690 rebounded to the pretreatment concentrations after each treatment. Also, subjective  
2691 and clinical signs of lead intoxication were alleviated, but gradually reappeared as the  
2692 blood lead increased after the treatment courses. As the lead body burden of this  
2693 patient was still immensely high, he will probably require repeated antidotal therapy for  
2694 life.

2695  
2696 A similar, but less severe case was reported by Grandjean et al (1991). The blood  
2697 lead concentration was initially reduced by a factor of about 10 by succimer but  
2698 gradually increased after cessation of therapy. As the patient developed  
2699 hypersensitivity to succimer, treatment was discontinued after 3 courses. However,  
2700 the treatment apparently had a long-lasting effect both on blood lead concentrations  
2701 and on the patient's mental capacity.

2702  
2703 A 52 year old male was admitted with nausea, abdominal pain and difficulty  
2704 concentrating. The blood lead concentration was 3.4 µmol/L (0.7 mg/L) and an  
2705 abdominal X-ray revealed a large quantity of radiopaque pellets in the colon. He was  
2706 given succimer in 3 courses of 7 days and each was associated with a decrease in  
2707 blood lead concentrations. However, the concentration remained high and an X-ray  
2708 showed that the lead shot had not moved. A total of 895 lead pellets (total weight 120  
2709 g) were removed by laparotomy. He was given 2 further courses of succimer and his  
2710 clinical condition gradually improved as the blood lead concentration decreased to  
2711 within the normal range (Berg et al., 2000).

2712  
2713 Meggs et al. (1994) reported three patients with lead toxicity from retained gunshot  
2714 pellets. All the subjects were male aged 35 to 47 years old and the time between  
2715 injury and diagnosis of lead toxicity was 8 months to 9 years. All were treated with  
2716 succimer prior to surgical removal of lead pellets and fragments. The succimer was  
2717 well tolerated in all cases and associated with improved clinical status and reduced  
2718 blood lead concentrations. The third patient in this group was reported in more detail  
2719 by Aly et al. (1993). He had received an accidental shotgun injury resulting in wounds  
2720 to the left chest wall and an open pneumothorax. He was treated supportively and  
2721 discharged with a haemoglobin concentration of 9 g/dL and pellets still in the inner and  
2722 outer chest wall. He was readmitted 7 weeks later with abdominal pain, weakness,  
2723 weight loss and a haemoglobin concentration of 7.2 g/dL. Examinations were

2724 unrevealing and the cause of his anaemia was not determined. He returned 2 weeks  
2725 later for removal of pellets which were causing discomfort in his back. Then 4 months  
2726 after the accident he was admitted with recurrent abdominal pain, fatigue and  
2727 continued weight loss. His haemoglobin was 9.6 g/dL and the blood lead  
2728 concentration was 300 µg/dL. He was treated with succimer (10 mg/kg 3 times daily  
2729 for 5 days and then 10 mg/kg twice daily for 14 days). Clinical features of lead toxicity  
2730 began to improve by day 3 of therapy. By the end of the course the haemoglobin had  
2731 risen from 8 to 12 g/dL and erythrocyte pyrimidine 5'-nucleotidase activity had also  
2732 increased from a low of approximately 15% of expected. The residual pellets were  
2733 then removed surgically and he was given a second course of succimer. Thereafter  
2734 the blood lead concentration decreased from 95 µg/dL (4.56 µmol/L) to 15 µg/dL (0.72  
2735 µmol/L).

2736  
2737 Succimer was also used in a 39 year old male with lead toxicity from retained gun shot  
2738 fragments. He presented with recurrent abdominal pain, constipation, weakness,  
2739 irritability and headache. He was pale with a greyish discolouration on the gingival  
2740 tooth border, consistent with a lead-line. The gun shot wound had occurred 15 years  
2741 earlier and fragments were seen on X-rays of the face, chest and abdomen. His blood  
2742 lead concentration was 201.9 µg/dL (9.69 µmol/L) with anaemia and basophilic  
2743 stippling. He was treated with succimer (10 mg/kg 3 times a day for 5 days then twice  
2744 a day for 14 days) and the blood lead concentration decreased to 64 mg/L with clinical  
2745 improvement. He returned 3 months later with a recurrence of clinical effects and a  
2746 blood lead concentration of 159 µg/dL (2.8 µmol/L). He received another course of  
2747 succimer after which most symptoms resolved, except weakness and irritability. The  
2748 blood lead concentration was 29 µg/dL (1.39 µmol/L) and two bullet fragments were  
2749 removed from his face but he declined further surgery (Akhtar et al., 2003).

2750

#### 2751 **11.10.4 Chronic lead poisoning in pregnancy**

2752

2753 A 38 year old woman was diagnosed with chronic lead poisoning at 25 weeks  
2754 gestation. She had anaemia and abdominal pain. After a further delay of 4 weeks for  
2755 obstetric and toxicological consultation she was treated with succimer (10 mg/kg every  
2756 8 hours for 5 days, then 10 mg/kg every 12 hours for 13 days). She also received  
2757 iron and calcium supplementation and was only completed 18 days of the succimer  
2758 course due to recurrent nausea and vomiting. The blood lead concentration prior to  
2759 treatment was 44 µg/dL (2.12 µmol/L) and after the succimer was virtually unchanged  
2760 at 43.9 µg/dL (2.1 µmol/L). The source of the lead was not identified, but other  
2761 members of the family did not have toxic concentrations. At parturition the blood lead  
2762 concentration was 57.6 µg/L (2.76 µmol/L) and she gave birth to a baby girl who  
2763 appeared normal (weight 3.04 kg). However, the lead concentration in the cord blood  
2764 was 126 µg/dL (6.08 µmol/L) and at 4 days old the baby was given intravenous  
2765 dimercaprol and sodium calcium edetate. She also had jaundice and elevated  
2766 transaminases. The blood concentration prior to antidotal therapy was 74.7 µg/dL  
2767 (3.59 µmol/L) and 7 hours later was 46.7 µg/dL (2.25 µmol/L). After 3 days  
2768 dimercaprol and sodium calcium edetate edetate were stopped and after 24 hours the  
2769 baby was started on succimer (350 mg/m<sup>2</sup> every 8 hours for 5 days then 350 mg/m<sup>2</sup>  
2770 every 12 hours for 14 days). At the end of succimer therapy the blood lead  
2771 concentration was 35.2 µg/dL (1.70 µmol/L). At 6 weeks old her blood lead  
2772 concentration was 30.7 µg/dL (1.48 µmol/L) and then 38.9 µg/dL (1.88 µmol/L) at 77  
2773 days. She was given another 19 day course of succimer and at age 5 months and 6.5  
2774 months the concentrations were 21.5 µg/dL (1.04 µmol/L) and 30.5 µg/dL (1.47

2775  $\mu\text{mol/L}$ ), respectively. She appeared normal with appropriate behaviour throughout  
2776 (Horowitz & Mirkin, 2001).

2777  
2778 In another case of congenital lead poisoning oral succimer did not increase urinary  
2779 lead excretion. The 24 year old mother had been diagnosed with lead toxicity at 30  
2780 weeks gestation after presenting with abdominal pain, anaemia and confusion. Her  
2781 blood lead concentration was  $5.2 \mu\text{mol/L}$  ( $107.6 \mu\text{g/dL}$ ). She was treated with  
2782 intramuscular dimercaprol and intravenous sodium calcium edetate. She had  
2783 antepartum haemorrhage 36 hours later and after induction of labour gave birth to a  
2784 baby girl. The child was flaccid and arreflexic with bilateral diaphragmatic palsy. She  
2785 was intubated and ventilated. The mother's lead concentration 12 hours before birth  
2786 was  $2.3 \mu\text{mol/L}$  ( $47.6 \mu\text{g/dL}$ ) and the concentration in the cord blood was  $7.6 \mu\text{mol/L}$   
2787 ( $157.3 \mu\text{g/dL}$ ). The concentration of erythrocyte porphyrins was raised in the baby and  
2788 she had increased bone density on X-ray. Within 24 hours of birth the baby was  
2789 started on intramuscular dimercaprol and intravenous sodium calcium edetate. The  
2790 blood lead concentration initially rose to  $11 \mu\text{mol/L}$  ( $227.7 \mu\text{g/dL}$ ) within 48 hours and  
2791 then decreased rapidly. On day 7 intravenous calcium disodium edetate was stopped  
2792 and she was started on oral succimer ( $30 \text{ mg/kg/day}$ ). However during 3 weeks of  
2793 succimer therapy the urinary lead concentration fell and the blood concentration  
2794 remained relatively constant. Succimer was stopped on day 31 and sodium calcium  
2795 edetate was recommenced 48 hour later. This was followed by an increase in urinary  
2796 lead concentrations. By day 42 facial, bulbar, proximal-limb and diaphragmatic muscle  
2797 activity had improved sufficiently to allow extubation. By day 53 the blood lead  
2798 concentration had fallen to a satisfactory concentration and she was again started on  
2799 oral succimer. However as this was followed by an increase in blood lead and a fall in  
2800 the urinary lead concentration she was given another two courses of sodium calcium  
2801 edetate. At 5.5 months after birth the baby's blood lead concentration was  $1.8 \mu\text{mol/L}$   
2802 ( $37.3 \mu\text{g/dL}$ ) and she was again given oral succimer, this time  $60 \text{ mg/kg/day}$  (double  
2803 the normal dose). This resulted in a decrease in blood lead and a rise in urinary lead  
2804 concentration. At 6.5 months she was found to have sensorineural deafness. She  
2805 was discharged home on succimer aged 7.5 months and with a blood lead  
2806 concentration of  $0.95 \mu\text{mol/L}$  ( $19.7 \mu\text{g/dL}$ ). The source of the lead was a herbal  
2807 remedy taken by the mother periodically over a 9 year period (Tait et al., 2002).

### 2808 2809 **11.11 Manganese**

2810  
2811 In animals studies the polyaminopolycarboxylic acids (e.g. pentetic acid, sodium  
2812 calcium edetate) appear to be the most efficient antidotes for manganese poisoning.

2813  
2814 There was no significant improvement in clinical condition or reduction in blood  
2815 manganese concentrations in 2 workers treated with a 21 day course of succimer ( $25$   
2816  $\text{mg/kg/day}$  for 7 days followed by  $15 \text{ mg/kg/day}$  for 14 days) (Angle, 1995).

### 2817 2818 **11.12 Mercury**

2819  
2820 Reference values for mercury (Walker, 1998):

2821	Blood	$<20 \text{ nmol/L}$ ( $<4 \mu\text{g/L}$ )
2822	Urine	$<50 \text{ nmol/24 hours}$ ( $<10 \mu\text{g/24 hours}$ )

2823  
2824 Unithiol is the antidote of choice in patients with mercury poisoning, although succimer  
2825 has been used in some cases with varying success. Andersen (1999) suggests that

2826 unithiol is the optimal antidote for inorganic mercury poisoning and that succimer is  
2827 more effective in organic mercury intoxication.

2828  
2829 The combined data indicate that succimer and unithiol are efficient antidotes in  
2830 experimental acute inorganic and organic mercury intoxication in animals. While  
2831 monoalkylesters of succimer, in particular the isoamyl ester, are more efficient  
2832 mobilisers of body stores of mercury than succimer and unithiol, human use of this  
2833 type of compound must await development of less toxic derivatives and extensive  
2834 safety testing. Also an increasing body of evidence indicate that succimer and unithiol  
2835 can be used safely in human poisonings by various mercury compounds, as indicated  
2836 by the case and cohort studies reviewed below. Due to the possibility of succimer or  
2837 unithiol therapy for extended time periods via the oral route with a low rate of adverse  
2838 side effects, these compounds are superior to dimercaprol, D-penicillamine and  
2839 NAPA.

2840  
2841 Two jewellers (aged 35 and 50 years) inhaled mercury vapours for about 30 minutes  
2842 while melting a block of gold with an unknown mercury content. They were admitted  
2843 to hospital 16 hours later, short of breath with fatigue, nausea and pain at various  
2844 sites. Renal function was normal. Both were given intramuscular dimercaprol for 5  
2845 days, followed by oral succimer (30 mg/kg) for 5 days. Both blood and urine mercury  
2846 concentrations fell rapidly from initial high values (293.5 and 93.3 µg/L). The data  
2847 suggest that the urinary mercury elimination was increased after the change from  
2848 dimercaprol to succimer therapy, while the blood mercury concentration was  
2849 unchanged (Houeto et al., 1994).

2850  
2851 A family of 9 children, aged 3 months to 13.5 years, were exposed to metallic mercury  
2852 after they had been playing with it in their home for several days. None of the children  
2853 had any clinical features of mercury toxicity but all had elevated urine mercury  
2854 concentrations, ranging from 61 to 1,213 µg/g creatinine, with a mean of 214.3 µg/g  
2855 creatinine. All the children were treated with succimer (30 mg/kg/day for 5 days) and  
2856 during this period the mean of all urine mercury concentration measurements  
2857 increased by 268%. The children were discharged on succimer 20 mg/kg/day for 2  
2858 weeks. By 6 weeks after discharge the urine mercury concentration in the children  
2859 varied from 71 to 239 µg/g creatinine, with a mean of 102.1 µg/g creatinine. They  
2860 received another 2 weeks of antidote therapy. At day 261 after the start of succimer  
2861 treatment the mean urine mercury concentration was 27.4 µg/g creatinine but 2 of the  
2862 children (both aged 1.5 years) still had concentrations greater than 50 µg/g creatinine.  
2863 Although the family had been relocated they had taken a mercury-contaminated couch  
2864 with them and this may have been a source of continued exposure. This was  
2865 removed and these 2 children were given another course of succimer. By 12 months  
2866 after the start of succimer the urine mercury concentrations in the 2 children were 11  
2867 and 9 µg/g creatinine. The children's mother had mercury concentrations less than 50  
2868 µg/g creatinine and was not treated (Forman et al., 2000).

2869  
2870 There are a number of other cases where succimer has been used in paediatric  
2871 mercury poisoning with apparent success (Schwartz et al., 1992; Baudouin et al.,  
2872 1997; Solis et al., 2000; Velez et al., 2002; Michaeli-Yossef et al., 2007).

2873  
2874 A 31 year old male presented to hospital after intentional ingestion of approximately  
2875 40 g of mercuric oxide. A radiopaque mass was visible in the stomach on X-ray. He  
2876 was treated with intravenous fluids, activated charcoal and whole bowel irrigation with

2877 polyethylene glycol-electrolyte solution. He was started on intramuscular dimercaprol  
2878 (4 mg/kg then 3 mg/kg every 6 hours) 6 hours post-exposure. The blood and urine  
2879 concentrations were 1300 µg/L and 2,220 µg/L/24 hours, respectively. On the fifth  
2880 day dimercaprol was stopped and he was started on succimer (10 mg/kg every 8  
2881 hours for 10 days). He was discharged on the seventh day and by day 18 the blood  
2882 and urine concentrations were 150 µg/L and 308 µg/L/24 hours, respectively. The  
2883 only clinical effects reported were vomiting, epigastric and abdominal discomfort.  
2884 Dimercaprol had been used initially because the patient was receiving whole bowel  
2885 irrigation (until the X-rays demonstrated the gastrointestinal tract was clear of  
2886 radiopaque material) and administration of oral succimer was impractical. Although he  
2887 received extensive gut decontamination and early antidotal therapy it is not clear that  
2888 these had any impact on clinical outcome in this case (Ly et al., 2002).

2889  
2890 A 64 year old woman with emphysema, hypertension, osteoporosis and peripheral  
2891 disease was admitted for intestinal obstruction due to Crohn's disease. A Cantor tube  
2892 was used to relieve the obstruction but this ruptured during surgery and at least 10 ml  
2893 of metallic mercury was released into the intestine. Seventeen days later she  
2894 underwent a laproscopically-assisted ileocolic resection for persistent ileus and  
2895 worsening of Crohn's disease. During the resection mercury was observed to spill into  
2896 the peritoneum but no effort was made to recovery it. The mercury became more  
2897 widely spread in the weeks following the operation, but she was discharged 6 weeks  
2898 later without knowledge of the accident. Six weeks later she began to complain of  
2899 fatigue, insomnia, alopecia, dizziness and headaches. She was readmitted 2 years  
2900 later with abdominal problems and X-rays revealed opacities in the abdomen. Her  
2901 serum mercury concentration was 485 µg/L and she was informed of the accident for  
2902 the first time. She was given two course of succimer but this appeared to have no  
2903 effect on her mercury concentrations or clinical features. Her mercury concentrations  
2904 were monitored over the next few years and were consistently above 100 µg/L in  
2905 blood and 300 µg/L in urine. Her health continued to decline although the role of  
2906 mercury on top of her pre-existing diseases is difficult to define. She was diagnosed  
2907 with lung cancer and died 8.5 years after the mercury accident (Haas et al., 2003).

2908  
2909 Three workers (aged 28, 33 and 40 years) presented to an occupational health nurse  
2910 after they recognised mercury exposure by the colour change of gold jewellery two of  
2911 them were wearing. Blood mercury concentrations were 289 to 353 µg/L and two of  
2912 the men had experienced an acute afebrile illness and rash; one had fatigue. Only  
2913 one worker elected to receive antidotal therapy and had succimer 500 mg 3 times a  
2914 day for 5 days, followed by 500 mg twice daily for 14 days. Blood mercury  
2915 concentrations did not differ between this worker and the two who received no  
2916 antidote, although concentrations fell dramatically in all three. Two subjects were  
2917 asymptomatic by 2 months and the third (who received succimer) had fatigue and  
2918 difficulty sleeping. By 6 months he complained of occasional headaches only. The  
2919 benefit of succimer in this case is unclear (Hodgman & Benitez, 1998).

2920  
2921 Of the 3 patients described by Fournier et al. (1988) 2 had been exposed to mercury  
2922 vapour and one to a mercury-containing skin ointment. All had clinical features of  
2923 mercury toxicity but had blood concentrations below the detection limit (0.05 µmol/L).  
2924 Succimer (30 mg/kg/day for 5 days) increased the urinary mercury excretion 1.5, 2.8  
2925 and 8.4-fold, respectively, while blood mercury concentrations remained below the  
2926 detection limit. Clinical features improved in all patients.

2927

2928 An 81 year old female developed amyotrophic lateral sclerosis (ALS) that may have  
2929 been due to chronic inhalation of the vapour of mercury used during pressure therapy  
2930 of lymphoedema (given twice a year from 1987 to January 2004). She had dysphonia,  
2931 dysarthria, muscular atrophy of both hands, the right scapular girdle and the lower limbs  
2932 and to a lesser extent in the tongue. The mercury blood concentration was 13.4 µg/L  
2933 and 2 µg/L in the spinal fluid. She was excreting large quantities of mercury (7282  
2934 µg/g of creatinine) and was started on succimer (30 µg/kg/day for 4 weeks) in July  
2935 2004. The mercury excretion reduced to 2.9 µg/g of creatinine with no change in  
2936 blood or spinal fluid concentrations. The disease progressed slowly and she died in  
2937 February 2005 (Praline et al., 2007). Costa et al. (2008) commenting on this case  
2938 report advise caution in the use of metal-binding agents in the treatment of ALS at  
2939 they may worsen the patient's clinical condition.

2940  
2941 A 40 year old male was treated with succimer after intentional injection of  
2942 approximately 3 mL of metallic mercury into the dorsal vein of his left hand. He had  
2943 also ingested the same quantity. Within 24 hours he developed chest discomfort and  
2944 dyspnoea. Mercury was visible on chest X-ray and the ECG was consistent with  
2945 pulmonary embolism. At 36 hours post-exposure the blood and urine mercury  
2946 concentrations were 208 µg/L and 216 µg/L, respectively. Renal function had  
2947 declined and he was started on succimer (10 mg/kg 3 times a day for 5 days then 10  
2948 mg/kg twice daily for 14 days) at 36 hours. By 72 hours his renal and pulmonary  
2949 status were improving. He completed the succimer and was discharged 21 days post-  
2950 exposure; his only complaint was mild exertional dyspnoea. Mercury was still visible  
2951 on chest X-ray. The blood and urine mercury concentrations at this time were 248  
2952 µg/L and 397 µg/L, respectively. Although he improved significantly after  
2953 administration of succimer it is unclear whether there was any causal relationship  
2954 between the antidote and clinical improvement in this case (McFee & Caraccio, 2001).

2955  
2956 In another case of elemental mercury injection, a 27 year old male, 65 kg, injected 1.5  
2957 mL (20 g) into his left cubital vein. Within 12 hours he developed pyrexia, tachycardia  
2958 and dyspnoea and mercury was visible on chest X-ray. The serum mercury  
2959 concentration was 172 µg/L on admission and peaked on day 6 at 274 µg/L. At 37  
2960 hours he was started on unithiol (200 mg orally every 8 hours) for 5 days, during which  
2961 time he eliminated 8 mg of mercury. Three days later he was started on succimer  
2962 (500 mg daily) for another 5 days. This resulted in the excretion of another 3 mg of  
2963 mercury. Neither unithiol nor succimer were effective in enhancing elimination of  
2964 mercury after intravenous injection (Eyer et al., 2006).

2965  
2966 A 44 year old male was treated with unithiol and succimer after ingestion of a solution  
2967 of thiomersal. The ingested dose was 83 mg/kg although he vomited about 15  
2968 minutes later. He was given a gastric lavage just over 1 hour after ingestion and 300  
2969 mg of unithiol was instilled into the stomach via a nasogastric tube. This dose was  
2970 repeated on days 2, 3, 9 and 10, and he was given 250 mg of intravenous unithiol on  
2971 days 3, 8 and 17, with 750 mg on days 4, 5 and 11, and 1000 mg on days 12-16 and  
2972 23-29. He was also given oral succimer on days 17-23, 33-46 and 51-70. He  
2973 received no antidotal therapy on days 6, 30-32 and 47-50. He developed renal failure  
2974 on day 1 which persisted until day 40. He also developed gastritis, dermatitis,  
2975 gingivitis, polyneuropathy and coma. He made a full recovery but the decline in  
2976 mercury concentrations in the blood, urinary mercury excretion and renal mercury  
2977 clearance were not influenced by antidotal therapy to a great extent. There was  
2978 minimal or no increase in renal and blood clearance and no effect was detected after

2979 day 30 (Pfab et al., 1996).

2980

### 2981 **11.13 Thallium**

2982

2983 There is limited information on the use of succimer in thallium toxicosis as Prussian  
2984 blue is commonly used.

2985

2986 Succimer has been used in China to treat a case of thallium poisoning and was  
2987 reported to improve the patient's clinical condition and gradually reduce the urinary  
2988 thallium concentration (Li et al., 1988).

2989

### 2990 **11.14 Tin**

2991

2992 Two women were poisoned by drinking red wine which had been intentionally  
2993 contaminated with trimethyltin for homicidal intent. One woman died after one week  
2994 with multiorgan failure despite intravenous succimer therapy. The other gradually  
2995 recovered over several months from severe neuropsychiatric symptoms. She was  
2996 treated for several weeks with oral succimer, apparently improving her clinical  
2997 condition (Kreyberg et al., 1992; Jacobsen, 1999).

2998

2999

## 3000 **12. SUMMARY OF EVALUATION**

3001

3002 Succimer appears to be a safe and efficient metal-binding agent. It is more efficient  
3003 and less toxic than many other antidotes used in the treatment of poisoning with heavy  
3004 metals.

3005

### 3006 **12.1 Indications**

3007

3008 Succimer appears to be effective (in terms of significant reduction of lethality in animal  
3009 studies and clinical use associated with a favourable outcome or proven enhanced  
3010 elimination of the heavy metal) in most cases of:

3011

- 3012 • acute arsenic intoxication
- 3013 • copper intoxication (Wilson's disease)
- 3014 • acute and chronic lead intoxication
- 3015 • acute and chronic organic and inorganic mercury intoxication

3016

3017 Based on an overall evaluation of animal data and case reports, succimer may possess  
3018 some antidotal efficacy in poisonings with

3018

- 3019 • antimony
- 3020 • cobalt
- 3021 • zinc

3021

3022 It has also been used with some apparent success in cases of human poisoning with  
3023 the following, but data are limited:

3024

- 3025 • thallium
- tin

3025

3026  
3027 Animal studies have demonstrated apparent benefit but experience of succimer use in  
3028 human poisoning is lacking for the following:  
3029 • acute cadmium intoxication  
3030 • beryllium  
3031 • bismuth  
3032 • chromium  
3033 • gold  
3034 • nickel  
3035 • promethium  
3036 • silver

3037  
3038 On the basis of animal or human case reports succimer does not appear to be useful  
3039 for the following:  
3040 • aluminium  
3041 • chronic arsenic intoxication  
3042 • manganese  
3043 • palladium  
3044 • platinum  
3045 • polonium  
3046 • selenium  
3047 • silver  
3048 • strontium  
3049 • vanadium

## 3050 3051 **12.2 Advised routes and dose**

3052  
3053 The recommended dosage regimen for adults is 10 mg/kg 3 times daily for 5 days,  
3054 followed by 10 mg/kg/ twice daily for 14 days.

3055  
3056 Children should be treated in the same way with initial dose 10 mg/kg 3 times daily (or  
3057 1050 mg/m<sup>2</sup>/day in 3 divided doses) for 5 days followed by 10 mg/kg/ twice daily (or  
3058 350 mg/m<sup>2</sup>/day in 2 divided doses) for 14 days. Succimer has been used in children  
3059 as young as 7 (Tait et al., 2002) and 8 days (Horowitz & Mirkin, 2001).

3060  
3061 The dosage regimen reported for adults with Wilson's disease in China has been 1 g  
3062 by intravenous injection twice daily or 4 g/day orally (Ding & Liang, 1991).

3063  
3064 Intravenous succimer has been used in a patient where administration of oral  
3065 capsules was impractical due to the presence of ileus. The dose given was 20  
3066 mg/kg/day for 5 days and then 10 mg/kg/day for 6 days. This was well tolerated with  
3067 no change in haemodynamic parameters (Hantson et al., 2003).

## 3068 3069 **12.3 Other consequential or supportive therapy**

3070  
3071 Standard supportive therapy should be given to all patients with heavy metal  
3072 poisoning.

3073  
3074 Identification and removal from the source is also important, particularly with lead  
3075 poisoning which is often found in the domestic environment and is a significant hazard

3076 to children.

3077  
3078 Chronic lead intoxication often leads to iron deficiency and there is a need for iron  
3079 supplementation along with antidotal therapy. This is hazardous during sodium  
3080 calcium edetate therapy but has been shown to be safe and efficient during succimer  
3081 treatment (Haust et al., 1989; Graziano et al., 1992).

#### 3082 3083 **12.4 Controversial issues and areas of insufficient information**

3084  
3085 Until more unambiguous human data are available, caution is needed to assure  
3086 removal from metal exposure before succimer therapy is instituted.

3087  
3088 Even though the present knowledge of effects of antidotal therapy on lead-induced  
3089 neurotoxicity is based mainly on subjective evaluations of small groups or single  
3090 cases, there is no doubt that metal-binding agents effectively alleviate the  
3091 neurotoxicity of lead in severe poisoning. The question is whether there are any  
3092 beneficial effects of antidote treatment on lead-induced neuropsychological  
3093 dysfunction in low-level lead intoxication of children.

3094  
3095 There are still too little research data available outside Asia to routinely recommend  
3096 succimer in the treatment of Wilson's disease.

3097  
3098 The proposed efficiency of succimer in non-metallic intoxications (Ding & Liang, 1991),  
3099 as based on clinical improvement associated with its use and limited animal data, in  
3100 poisonings with nereis toxins, methyl aziridine, snake venom and mushroom  
3101 poisoning, should be considered controversial, and its clinical use in these poisonings  
3102 is not recommended.

#### 3103 3104 **12.5 Proposals for further studies**

3105  
3106 Further studies of succimer in patients with Wilson's disease seem warranted.

3107  
3108 Evaluation of succimer as an antidote in mercury exposure is lacking. This requires  
3109 further study and in particular its role in organic, rather than inorganic or metallic,  
3110 mercury poisoning (Andersen, 1999).

3111  
3112 The concern over antidote treatment and increased gastrointestinal absorption of  
3113 metal needs to be resolved. After oral administration of cadmium or mercury to mice,  
3114 oral administration of some antidotes, including succimer and unithiol, reduced  
3115 intestinal metal uptake (Andersen et al., 1988a; Andersen, 1989a; Nielsen &  
3116 Andersen, 1991). Similarly whole-body retention and gastrointestinal absorption were  
3117 reduced in lead-exposed rats treated with succimer (Kapoor et al., 1989) and oral  
3118 succimer was found to decrease gastrointestinal absorption of lead in monkeys  
3119 (Cremin et al., 2001). In contrast, a small study in volunteers suggested that succimer  
3120 increased intestinal lead absorption and mediated redistribution into tissues (Smith et  
3121 al., 1994). This is an important issue that warrants further investigation since it  
3122 influences the point at which antidotal treatment should be initiated.

3123  
3124 Further investigation is needed on the recent findings that succimer-induced  
3125 reductions in the blood lead concentration does not reliably reflect reductions in the  
3126 lead concentration of brain tissue (Smith et al., 1998; Stangle et al., 2004), and it has

3127 been suggested that the brain lead concentration could be reduced further with  
3128 continued succimer treatment after the blood lead concentration has apparently  
3129 stabilised (Stangle et al., 2004).

3130  
3131 Studies with intravenous formulations of succimer would also be useful as this route is  
3132 more practicable in patients with serious central nervous depression or severe  
3133 gastrointestinal effects that prevent oral administration.

3134  
3135 A number of esters of succimer, particularly mono and dimethyl esters, have been  
3136 synthesised and are being investigated in efforts to improve the effectiveness of  
3137 antidotal treatment in some metal poisonings, for example cadmium (Kalia & Flora,  
3138 2005).

## 3139 **12.6 Adverse effects**

3140  
3141 The safety of succimer has been demonstrated during more than 30 years of clinical  
3142 use in China, both in heavy metal poisonings and in long-term use in hundreds of  
3143 patients with Wilson's disease (Yang et al., 1987; Ding & Liang, 1991).

3144  
3145 Doses up to 30 mg/kg for several days (Graziano et al., 1985; Fournier et al., 1988)  
3146 and up to 80 mg/kg for one day have been well tolerated in adults (Arnold, 1981).

3147  
3148 Doses of succimer up to 1050 mg/m<sup>2</sup>/day (equivalent to 30 mg/kg to adults), were well  
3149 tolerated in children with lead exposure (Graziano et al., 1988; Chisolm 1990). In one  
3150 case a patient received a total of 189 g succimer over 2 years; the maximum succimer  
3151 dosage was 30 mg/kg/day. The drug was well tolerated without the development of  
3152 severe adverse subjective or clinical symptoms related to succimer treatment. Only  
3153 marginal effects on serum and urine chemistry were noted, except for markers related  
3154 to lead intoxication and iron deficiency that were corrected with combined iron and  
3155 succimer therapy (Haust et al., 1989).

3156  
3157 Adverse reactions during succimer therapy include mild neutropenia (Zhang, 1984;  
3158 McNeil, 1994; Besunder et al., 1995), light to moderate drowsiness, mild  
3159 gastrointestinal discomfort, skin reactions, decreased haemoglobin and transient,  
3160 clinically insignificant elevated liver enzymes (Graziano et al., 1985; Vincent et al.,  
3161 1986; Marcus et al., 1991; Grandjean et al., 1991; Bluhm et al., 1992; Chisolm, 1992;  
3162 McNeil, 1994; McKinney, 2000). Facial swelling (Bluhm et al., 1992), hyperthermia  
3163 (Marcus et al., 1991), dizziness and weakness (Zhang, 1984) have also been  
3164 reported. Symptoms are usually mild, self-limiting and do not require cessation of  
3165 therapy.

3166  
3167 Hypersensitivity has been reported in an adult following initiation of a third course of  
3168 succimer for lead toxicity. Three days after the start of the course he developed  
3169 vesicular eruptions on the oral mucosa, glans penis and perianal region. These  
3170 effects rapidly resolved when the succimer was stopped 6 days later. Four months  
3171 later, a challenge was performed with increasing doses of succimer. A similar reaction  
3172 occurred after a dose of 4 mg/kg/day and was aggravated during a dose increase to  
3173 30 mg/kg/day. The adverse reaction was alleviated when the dose was reduced to 10  
3174 mg/kg/day and was well tolerated for 10 days. However, during a fifth succimer  
3175 treatment period using the low dose of 10 mg/kg/day, more pronounced mucous and  
3176 skin eruptions developed and further succimer treatment was declined (Grandjean et  
3177

3178 al., 1991).

3179  
3180 Haemolytic anaemia has been reported in a patient with glucose-6-phosphate  
3181 dehydrogenase deficiency treated with succimer for occupational lead intoxication.  
3182 The dose of succimer was 800 mg (10 mg/kg) 3 times a day for 5 days then 800 mg  
3183 twice daily. After cessation of treatment on day 8 haematological values normalised  
3184 (Gerr et al., 1994). Succimer has been used in several children with glucose-6-  
3185 phosphate dehydrogenase deficiency without adverse incident (Chisolm, 1992;  
3186 Graziano et al., 1992).

3187  
3188 There were no changes in mildly abnormal liver function tests in 15 children with lead  
3189 poisoning treated with succimer (Kuntzelmanm & Angle, 1992). Similarly, pre-existing  
3190 neonatal jaundice resolved during succimer treatment in a child with elevated blood  
3191 lead concentrations (Horowitz & Mirkin, 2001).

3192  
3193 Several investigations in experimental animals and humans have documented, that  
3194 succimer treatment has only a marginal affect on essential trace element  
3195 homeostasis. Several studies have shown that the urinary excretion of copper, zinc,  
3196 calcium, magnesium and iron are not adversely enhanced with succimer  
3197 administration (Friedheim et al. 1978; Graziano et al., 1985; Fournier et al., 1988;  
3198 Smith et al., 2000).

3199  
3200 Few cases of succimer overdose have been reported but it appears to be associated  
3201 with a benign clinical course. A 3 year old girl ingested 2.4 g of succimer (185 mg/kg)  
3202 and extensive clinical evaluation failed to indicate signs of intoxication (Sigg et al.,  
3203 1997; Sigg et al., 1998). An adult receiving succimer for arsenic poisoning (500 mg 3  
3204 times a day for 4 days, then twice daily for 7 days) took an intentional overdose of 43  
3205 to 87 mg/kg of succimer with 1.2 g of fexofenadine. He remained well except for a  
3206 sensation of jitteriness and palmar keratosis. All blood parameters measured were  
3207 normal (Buchwald, 2001).

3208  
3209 The use of succimer in children without elevated tissue concentrations of lead or other  
3210 heavy metals is strongly discouraged. In rats without lead exposure succimer  
3211 produces lasting cognitive and affective dysfunction (Beaudin et al., 2007; Stangle et  
3212 al., 2007)

## 3213 3214 **12.7 Restrictions for use**

3215  
3216 In patients with previous or ongoing allergic reactions, especially mucosal and skin  
3217 eruptions, signs of recrudescence or exacerbation should be carefully monitored  
3218 during therapy with succimer.

3219  
3220 The administration of succimer in cases of asymptomatic or suspected poisoning (a  
3221 challenge or mobilisation test) cannot be recommended, because the metal-binding  
3222 agent mobilises the metal from tissue stores resulting in redistribution and potentially  
3223 increasing the concentration in the target organ, despite increasing excretion.

3224  
3225 Renal impairment is not a restriction of use; haemofiltration is the renal replacement  
3226 method of choice in patients with renal failure and in conjunction with succimer  
3227 administration may enhance elimination of heavy metals.

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### 13. MODEL INFORMATION SHEET

#### 13.1 Use

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

Succimer has been used in the management of acute and chronic poisoning with a number of different metals and metalloids, and is particularly useful for lead. It has been used for other metals and metalloids and the availability of information on succimer use is summarised in the table.

#### Summary of the different types of data available on the use of succimer for metal poisoning.

Metal	Clinical trial data	Case reports	Animal studies
Aluminium	No data	No data	No benefit demonstrated
Antimony	No data	Used with apparent benefit in one report, no effect in another	Benefit demonstrated
Arsenic	No benefit demonstrated in chronic arsenicosis, no data on acute poisoning	Benefit demonstrated in acute intoxication only	Benefit demonstrated
Beryllium	No data	No data	Benefit demonstrated, but unithiol appears to be more effective
Bismuth	No data	No data	Benefit demonstrated
Cadmium	No data	No data	Benefit demonstrated, efficacy declines with time
Chromium	No data	No data	Bpparent benefit demonstrated, but data are limited
Cobalt	No data	No data	Benefit demonstrated, but more efficacious antidotes are available
Copper	Benefit demonstrated in patients with Wilson's disease	No data	Benefit demonstrated, but unithiol appears to be more effective
Gold	No data	No data	Benefit demonstrated
Lead	Benefit demonstrated	Recommended as the antidote of choice	Benefit demonstrated

<b>Metal</b>	<b>Clinical trial data</b>	<b>Case reports</b>	<b>Animal studies</b>
Manganese	No data	No benefit demonstrated, but data are limited	No benefit demonstrated
Mercury	Benefit demonstrated	Benefit demonstrated, although unithiol is more commonly used; succimer has been suggested as preferable for organic mercury	Benefit demonstrated
Nickel	No data	No data	Benefit demonstrated
Palladium	No data	No data	No benefit demonstrated, but data are limited
Platinum	No data	No data	Apparent benefit demonstrated but data are limited and conflicting
Polonium	No data	No data	Results in redistribution to the kidneys but does not enhance elimination
Promethium	No data	No data	Apparent benefit demonstrated, but data are very limited
Selenium	No data	No data	No benefit demonstrated, but data are very limited
Silver	No data	No data	Apparent benefit demonstrated, but data are limited
Strontium	No data	No data	No benefit demonstrated, but data are limited
Thallium	No data	Apparent benefit in one case, but Prussian blue is more commonly used	No benefit demonstrated
Tin	No data	Apparent benefit in one case, but data are limited	Apparent benefit demonstrated, but data are limited
Vanadium	No data	No data	No benefit demonstrated and unlikely to be of use; more efficacious antidotes are available
Zinc	No data	No data	Benefit demonstrated but more efficacious antidotes are available

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### **13.2 Dosage and route**

The recommended dosage regimen for adults is 10 mg/kg 3 times daily for 5 days, followed by 10 mg/kg/ twice daily for 14 days.

3254 Children should be treated in the same way with initial dose 10 mg/kg 3 times daily (or  
3255 1050 mg/m<sup>2</sup>/day in 3 divided doses) for 5 days followed by 10 mg/kg/ twice daily (or  
3256 350 mg/m<sup>2</sup>/day in 2 divided doses) for 14 days. Succimer has been used in neonates.

3257  
3258 If the oral route is impractical succimer has been given intravenously in the same  
3259 doses as above, divided in three daily doses, following adequate sterile filtration.

3260  
3261 In severe chronic lead intoxication, rapid rebound in the blood lead concentration  
3262 occurs upon cessation of antidote therapy, and multiple courses must be given, guided  
3263 by monitoring blood lead concentrations and blood chemistry.

### 3264 3265 **13.3 Precautions/contraindications**

3266  
3267 Succimer is of low toxicity, but adequate urine output should be ensured and  
3268 maintained during treatment. It may be beneficial to give extra oral fluids as succimer  
3269 may be mildly irritating to the gastric mucosa. Succimer has an unpleasant smell and  
3270 taste.

3271  
3272 Hypersensitivity is rare but if it occurs succimer should be withdrawn and another  
3273 antidote considered.

### 3274 3275 **13.4 Pharmaceutical incompatibilities and drug interactions**

3276  
3277 Succimer should not be given orally with mineral preparations or activated charcoal  
3278 because it may be inactivated.

### 3279 3280 **13.5 Adverse effects**

3281  
3282 The clinical data available indicate that succimer is well tolerated. Daily doses up to  
3283 30 mg/kg/day (adults and children) for up to one week followed by 10-20 mg/kg/day for  
3284 two weeks were not associated with significant adverse effects. Even longer treatment  
3285 does not seem to be associated with significant affection on the essential trace  
3286 element homeostasis. Patients should, however, be monitored carefully with regard to  
3287 mucous membrane reactions.

3288  
3289 Adverse effects include light to moderate drowsiness, mild abdominal disturbances,  
3290 skin reactions, neutropenia, decreased haemoglobin and transient mild elevation of  
3291 liver enzymes have been reported. Symptoms are usually mild, self-limiting and do not  
3292 require cessation of therapy.

3293  
3294 Slight enhancement of urinary excretion of copper and zinc has been reported at the  
3295 highest recommended doses. There is one case reported with apparent  
3296 hypersensitivity manifested as mucocutaneous vesicular flare. Haemolytic anaemia  
3297 may occur in patients with glucose-6-phosphate dehydrogenase deficiency.

### 3298 3299 **13.6 Use in pregnancy and lactation**

3300  
3301 Teratogenic effects have been demonstrated in animals given high doses resulting in  
3302 maternal toxicity, but succimer has been shown to protect against the developmental  
3303 toxicity of mercury. Even though safety in human has not been established,  
3304 pregnancy is not regarded as a contraindication: succimer has been used in pregnant

3305 women with lead toxicity without apparent adverse effects. If succimer is  
3306 administered to pregnant women, the essential minerals should be monitored  
3307 carefully, because metal-binding may cause a depletion of trace elements and it has  
3308 been shown that zinc deficiency can cause teratogenic effects.

3309  
3310 Breast feeding should, in general, be avoided during heavy metal poisoning.

3311  
3312 **13.7 Storage**

3313  
3314 Succimer gelatin capsules should be stored at room temperature (15-30°C).

3315  
3316  
3317 **14. References**

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4344	<b>Abbreviations</b>	
4345		
4346	AAS	atomic absorption spectroscopy
4347	ABCC2	ATP-binding cassette, sub-family C
4348	AIDS	acquired immunodeficiency syndrome
4349	ALAD	$\delta$ -aminolevulinatase
4350	ALS	amyotrophic lateral sclerosis
4351	BAL	2,3-dimercaptopropanol; British Anti-Lewisite; dimercaprol (rINN)
4352	BAPSA	2,3-bis-(acetylthio)-propanesulphonamide
4353	CAS	Chemical Abstracts Service
4354	CDTA	cyclohexanediarninetetraacetic acid
4355	CHO/HGPRT	Chinese Hamster Ovary/Hypoxanthine-Guanine Phosphoribosyl
4356		Transferase
4357	DMPA	<i>N</i> -(2,3-dimercaptopropyl)phthalamidic acid,
4358	DMPS	Dimercaptopropanesulphonic acid; unithiol (rINN)
4359	DMSA	Dimercaptosuccinic acid; succimer (rINN)
4360	DTPA	Diethylenetriaminepentaacetic acid; pentetic acid (rINN)
4361	ECG	electrocardiogram
4362	ED50	median effective dose
4363	EDTA	Ethylenediaminetetraacetic acid; sodium calcium edetate (rINN)
4364	g	gram
4365	HPLC	high performance liquid chromatography
4366	ICP-AES	inductively coupled plasma-atomic emission spectroscopy
4367	IPCS	International Programme on Chemical Safety
4368	IQ	intelligence quotient
4369	k	kilo ( $10^3$ )
4370	kBq	kiloBecquerel
4371	LD	Lethal Dose (subscript indicates percent mortality)
4372	$\mu$	micro ( $10^{-6}$ )
4373	$\mu$ Ci	microCurie
4374	m	milli ( $10^{-3}$ )
4375	Mi-BDMA	mono- <i>N</i> -( <i>i</i> -butyl)- <i>meso</i> -2,3-dimercaptosuccinic acid
4376	MRP2	multidrug resistance protein 2
4377	NAPA	<i>N</i> -acetyl-D-penicillamine
4378	ppm	parts per million ( $10^{-6}$ )
4379	rINN	recognised international non-proprietary name
4380	TLC	Treatment of Lead Exposed Children
4381	TTHA	Triethylenetetraaminehexaacetic acid
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