

Review of Succimer for treatment of lead poisoning

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Date 10th March 2010

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1. Summary

Succimer is an analogue of dimercaprol (2,3-dimercapto-1-propanol, British Anti-Lewisite, BAL), and has replaced dimercaprol as one of the main antidotes used in the management of poisoning by lead and other heavy metals. The advantages of succimer are that it is effective by oral administration because it is soluble in water, it is well-tolerated, has relatively low toxicity and can be given at the same time as iron supplements to treat iron deficiency anaemia. It does not cause significant increase in urinary excretion of essential minerals unlike the other widely-used lead chelating agent, sodium calcium EDTA.

Lead poisoning is a major public health concern around the world but many of the countries where the risks are greatest have only limited access to chelating agents. This application presents evidence to support addition of succimer to the WHO Essential Medicines List primarily for treatment of lead poisoning in children, for which it is most commonly used.

Guidelines on the treatment of lead poisoning in children produced by the USA, UK, and France, recommend chelation to produce immediate reduction in blood lead concentrations and increase in rate of elimination, and to improve symptoms. Succimer is recommended mainly for asymptomatic children with moderate lead poisoning (45-69 mcg/l), who can be protected from further exposure. For severe poisoning it is recommended that other antidotes are given parenterally, thus necessitating hospital admission.

There is evidence that succimer is associated with short-term clinical improvement in lead-poisoned children, but there is little evidence that asymptomatic children gain any long-term clinical benefit or improved long-term outcomes from reductions in blood lead concentrations.

There are no guidelines applicable to countries which have limited access to the full range of chelating agents, limited facilities for hospital inpatient treatment, or limited capability for routine monitoring of blood lead concentrations. In such circumstances it might be considered appropriate to extend the indications for succimer to include children with severe poisoning. In communities where it is difficult to protect children from continuing exposure to lead, there may be risks associated with giving succimer to asymptomatic children with high or moderately raised blood lead concentrations, and so the risks of using succimer may need to be weighed against the risks of withholding it.

Treatment with succimer is likely to cost less than treatment with other lead-chelating agents because it can be given without admitting the patient to hospital. It is difficult to calculate cost-effectiveness because there is no clear-cut clinical outcome that can be measured. There is no good evidence that succimer reverses or prevents long-term cognitive impairment due to lead poisoning, and therefore no evidence that it has any impact on the costs to society of lead poisoning.

In the long-term it is probably more cost-effective to prevent exposure than to treat poisoning. While it is important to improve the availability of succimer and facilities for treatment of lead poisoning, this should not detract from efforts to remove lead from the environment.

Although there is no evidence that succimer is cost-effective or associated with long-term benefits in individuals with lead poisoning, there is evidence that it produces short-term clinical improvement, and the cost of treatment is likely to be less than treatment with a parenteral chelator.

Succimer may also be useful for treatment of arsenic and mercury poisoning, but although these are significant public health problems in some communities, they are not as widespread as lead poisoning, and are outside the scope of this application.

2. Name of the focal point in WHO submitting or supporting the application

J Tempowski, HSE/PHE/EPE

3. Name of the organization(s) consulted and/or supporting the application

European Association of Poisons Centres and Clinical Toxicologists
American Academy of Clinical Toxicology

4. International Nonproprietary Name (INN, generic name) of the medicine

The International non-proprietary name of the medicine is succimer.

Commonly used synonyms include: DMSA, and 2,3-dimercaptosuccinic acid.

5. Formulation proposed for inclusion

Succimer is a white crystalline powder. It is available in gelatin capsules, each containing beads coated with 100 mg succimer.

The capsules should be stored at room temperature (15-25°C) avoiding excessive heat (Lundbeck, 2009).

6. International availability -

Succimer is available

as Succicaptal, from Serb Laboratories, 53, rue de Villeirs de L'ilse Adam, 75020 Paris, France. www.serb-lab.com;

and as Chemet® from Lundbeck Inc., Deerfield, Illinois 60015, USA www.lundbeckInc.com.

It is also available from pharmaceutical manufacturers in Asia (e.g. YoungCom Company Ltd, Shenzhen, China www.cnyoungcom.com).

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

This application presents evidence for an individual medicine: succimer. Listing is requested for succimer as an example of a therapeutic group of chelating agents used for lead poisoning and structurally related to dimercaprol. The other medicine in the group is, unithiol, (DMPS; 2,3-dimercaptopropane sulfonate).

8. Public health relevance

8.1 Epidemiological information on burden of disease due to lead poisoning

Lead is a common environmental contaminant that affects the neurological, haematological, gastrointestinal and renal systems. Primary routes of absorption are ingestion or inhalation; cutaneous absorption of inorganic lead is low. Absorption of lead from the gut is estimated to be 5-15% in adults but 30-50% in children. Absorption from the lung is about 40%.

Acutely absorbed lead is distributed first to the blood where 98% of the lead becomes bound in the red blood cells, the remainder is available for redistribution to the soft tissues such as

the liver, kidneys, lung, brain, muscles and heart. Lead rapidly crosses the blood-brain barrier and physiologically significant concentrations of lead are deposited in the brain even with acute elevations in blood lead concentration. The half-life of lead in blood of around 20-30 days. Lead that is not excreted moves into bones and teeth where it accumulates. The half-life of lead in the skeleton ranges from years to decades. About 73% of the total body burden of lead in children is in the bones and teeth, compared with 90% in adults.

Although bone stores are inert, lead can leave the bone and re-enter blood and soft tissue organs. The concentration of lead in blood is derived from lead absorbed during the current exposure and lead redistributed from other tissues where it had been stored after a previous exposure. Lead is excreted very slowly so continuing exposure to small doses can eventually lead to a substantial body burden.

Lead exposure is associated with adverse effects at any age, but young children are particularly susceptible. Lead exposure affects cognitive, motor, behavioural and physical development, and is associated with juvenile delinquency, criminal behaviour and other antisocial behaviours (Nevin, 2007). Not only do children absorb a higher proportion of ingested lead and distribute more of it to soft tissues rather than to bone, the immature blood-brain barrier allows a greater penetration of lead into the central nervous system, and developing body systems are more susceptible to injury at the cellular level. Children are more likely than adults to have iron deficiency which enhances lead absorption, changes its kinetics and works synergistically to increase the vulnerability of children to developmental delays (Woolf et al., 2007).

Lead in the environment is a major global risk factor. A review of over 700 studies published between 1995 and 2001 estimated that 120 million people had blood lead concentrations of 5-10 mcg/dl, and about the same number had concentrations above 10 mcg/dl (Prüss-Üstün et al., 2003).

Regional blood lead concentrations vary widely from country to country but are greatest in developing regions. The 2001 survey found that 97% of children with raised blood lead concentrations lived in developing regions (Prüss-Üstün et al., 2003). However, many countries in these regions lack good data on the extent of the problem because they have limited capability to detect environmental contamination or screen children for lead poisoning.

It is estimated that mild mental retardation and cardiovascular outcomes resulting from exposure to lead amount to almost 1% of the total global burden of disease, with the highest burden in developing regions. The outcomes attributable to lead amount to about 12.9 million disability-adjusted life years or DALYs, (the DALY is a summary measure of population health which combines morbidity and mortality) placing lead in 16th position in the global list of leading risk factors for health, but in some regions it is more important (Fewtrell et al., 2004).

Mortality from lead encephalopathy in children is high if chelating agents are not available. For example, in the USA mortality was about 65% in the 1940s, but by the 1960s had declined to less than 5% among similar cases treated with chelators (Woolf et al., 2007).

Many factors contribute to the greater impact of lead exposures in the developing world, including the climate, prevalence of children living near to and working on industrial sites, lack of awareness of toxicity of lead, limited occupational safety and hygiene, limited access to chelating agents (Falk, 2003) and prevalence of iron deficiency anaemia which increases susceptibility to the toxic effects of lead (Ide & Parker, 2005) (see Table 1 from Falk, 2003).

Table 1 Developing World – risk factors for lead toxicity . From Falk, 2003.

Exposure	Multiple sources: differ from those in the United States Industrial sites located in or near residential areas Hot climates: more intense exposure to outdoor environments Child labour Inadequate environmental monitoring capacity and data Inadequate tracking of lead use and consumption
Health	Poor nutrition enhances lead toxicity Limited knowledge of toxic chemicals among caregivers Laboratory monitoring capacity inadequate; lack of equipment and training Absence or incomplete disease surveillance Drug treatment (chelating agents often unavailable)
Prevention	Lack of protective or safety equipment or technology Poor industrial engineering controls Limited safety and hygiene programmes Absent or in appropriate regulations Uneven implementation of standards and regulations Rare or infrequent inspections or enforcement Slow or incomplete adoption of new measures

Leaded petrol is the most important source of lead exposure in the general population in countries where it is still being used (Prüss-Üstün et al., 2003), exposure occurring either directly through air and dusts, or indirectly through food.

In developing countries where leaded fuel is no longer used there are many other sources of lead that are capable of leading to widespread and severe childhood lead poisoning. Lead is a valuable commodity and in many developing countries informal, backyard smelting and unsafe lead recycling, including car battery repair and recycling and recycling of other lead-contaminated waste, has become a widespread activity, exposing large populations to the short and long-term effects of lead, though the global magnitude of the problem is not documented (Haefliger et al., 2009). Lead mining and industrial lead smelting are important sources of lead exposure; other sources include lead-glazed ceramics, cottage industries using lead, flour from mills using lead-containing grinding machinery, cosmetics and other consumer products (Fewtrell et al., 2003, Falk, 2003, Meyer et al., 2008). Ethnic medicines containing lead either by design (particularly Ayurvedic medicines) or as a result of contamination, may contribute significantly to lead intake of local populations in both developing countries and Western countries (Karalliedde, 2009).

There is little epidemiological data on numbers of children occupationally exposed to lead or suffering short term and long-term effects as a result (Ide & Parker, 2005). Mass lead poisonings with serious health consequences continue to be reported (Haefliger et al., 2009)

8.2 Assessment of current use

8.2.1 Treatment of children with lead poisoning

The indication for using succimer to treat lead poisoning is based primarily on the patient's blood lead concentration and clinical condition. The possibility of continuing exposure also needs to be taken into consideration.

Succimer was approved by US Food and Drug Administration (FDA) in 1991 for treatment of lead poisoning in children with blood concentrations above 45 mcg/dL who are protected from continuing exposure to lead (Anon, 1991).

Two guidelines for the treatment of lead poisoning have been published by American Association of Pediatrics, the first by the Committee on Drugs (1995), and the second by the

Committee on Environmental Health (2005). Guidelines have also been published by the UK National Poisons Information Service (TOXBASE 2009) and the Ministère de la Santé et des Solidarité (2006). All these guidelines recommend treatment with succimer for children who have blood lead concentrations between 45 mcg/dL and 69 mcg/dL, who are protected from continuing exposure to lead and have no signs of encephalopathy (**Appendix Table 1**).

Encephalopathic patients may have symptoms of nausea, vomiting and lead colic all of which would delay and reduce absorption of an oral chelating agent. There is evidence that succimer may be less effective in reducing blood lead levels at high blood lead concentrations (see Section 10.2.2).

For children with blood concentrations higher than 69 mcg/dL or signs of encephalopathy, the Committee on Drugs (1995), the French Ministère de la Santé et des Solidarité (2006), and POISINDEX (2009), recommend dimercaprol combined with sodium calcium EDTA, while the UK National Poisons Information Service (TOXBASE, 2009) and the Committee on Environmental Health (2005) recommend sodium calcium EDTA alone. An expert review in one of the standard clinical toxicology textbooks recommends dimercaprol combined with sodium calcium EDTA (Henretig, 2006). We found no reports of use of succimer as the only agent for treating children with blood levels of this order (see Sections 10.3 and 10.4).

The use of succimer in children with blood concentrations below 69 mcg/dL and symptoms of lead poisoning not suggestive of encephalopathy is not specifically contraindicated by the Committee on Drugs, (1995), the UK National Poisons Information Service (TOXBASE 2009) and the Ministère de la Santé et des Solidarité (2006), but the Committee on Environmental Health (2005) recommends parenteral treatment for any symptomatic child, warning that premonitory symptoms, such as headache and somnolence, may progress rapidly to reduced consciousness with lethargy or stupor, and convulsions.

Although none of the guidelines recommend routine chelation for children with blood concentrations below 45 mcg/dL they allow for its use when blood lead concentrations persist in the range between 25-45 mcg/dL despite repeated efforts to remove lead from the environment.

Of the other agents which have been used to treat lead poisoning, Unithiol (2,3-dimercapto-1-propanesulphonic acid, DMPS) is not recommended by US guidelines or licensed in the US, having been abandoned after a patient developed Stevens-Johnson syndrome during a study of its use in treating lead poisoning in children (Chisolm, 1992; Anderson & Bates). D-penicillamine is considered to be a third-line drug for lead poisoning in the US (Committee on drugs, 1995; Committee on Environmental Health, 2005) but is listed as an alternative to succimer by the UK National Poisons Information Service (TOXBASE, 2009).

Table 2 in the Appendix compares the attributes, advantages and limitations of the agents most commonly used for treating lead poisoning.

We found no guidelines designed for use in countries with limited access to the full range of chelating agents, limited facilities for hospital inpatient treatment, limited capability for measuring blood lead concentrations, or limited ability to protect children from continuing exposure.

A report from Peru in (Zavaleta, 2001) identified problems which may limit the possibilities for identification and treatment of lead poisoning in the developing world:

- scarce clinical expertise and limited clinical experience in the treatment of children with high blood lead concentrations,
- a limited number of laboratories able to measure blood lead concentrations hampering physicians' ability to diagnose lead intoxication,

- lack of chelating agents,
- lead sources not identified or uncontrolled because reporting of lead intoxication cases was not mandatory,
- environmental investigations not conducted among communities where cases had been diagnosed,
- national health systems not sufficiently effective for it to be practical to apply CDC guidelines.

Of all chelating agents, succimer is most convenient for use in rural areas of developing countries because it is can be given orally, does not necessitate hospital admission and has a good adverse effect profile. For example, succimer was used in the context of prevention programmes in Peru (Zavaleta, 2001) in the Andes (Counter et al., 2003) for children with moderate to severe chronic and acute lead intoxication including some with blood lead concentrations above 70 mcg/dL, and in Senegal when urgent therapy was needed to reduce high blood lead concentrations (Joanna Tempowski, personal communication). Succimer reduced blood lead concentrations in many of these children (See sect 10. 6)., but evidence of long term benefits for individuals has not been reported, and the extent to which treated children were subsequently protected after treatment from continuing exposure to lead was unclear.

Those who have addressed the issue of lead poisoning in developing countries recommend that the decision to treat with chelating agents should be made on a case by case basis and limited to children at risk of encephalopathy and death (Zavaleta 2001) or with "severely elevated blood lead concentrations" (Counter et al., 2007). Their arguments against more routine use are

- chelating agents have a limited value in reducing the incidence or severity of the sequelae of lead poisoning (see Sect 10)
- there is no evidence that chelation can prevent adverse developmental and intellectual outcomes in children who continue to be exposed to very high environmental lead concentrations (Meyer et al., 2008)
- there is a risk that chronically poisoned children who receive chelation therapy then return to a high-lead environment soon afterwards while their blood lead concentrations are still high, could be at risk of acute lead toxicity
- continuing chelation could result in depletion of essential metals such as zinc and iron.

Zaveleta (2001) also expressed concern that focusing attention on improving availability of chelating agents and medical facilities might detract from efforts to protect the population from environmental lead hazards.

There are several environmental, social and demographic developmental risk factors that increase vulnerability of children to lead poisoning (Binns et al., 2007). Many of these factors are likely to have a greater impact in developing countries and may provide justification for giving succimer to children with lower blood lead concentrations than specified in the existing guidelines.

A final factor that must be taken into account in the risk-benefit analysis is the possibility of adverse effects from succimer if it is given without first establishing that a child has raised blood lead concentrations. Recent animal studies have shown that succimer produced cognitive and affective dysfunction comparable to that associated with high blood lead concentrations when it was given in the absence of lead exposure (Beaudin et al., 2007, Stangle et al., 2007).

8.2.2 Other indications

Although succimer is not approved by the FDA for management of lead poisoning in adults, (United States Department of Health and Human Services 1991), POISINDEX (2009) recommends considering its use in adults with acute or chronic lead poisoning in the absence of encephalopathy or protracted vomiting; the UK National Poisons Information Service (2009) recommends its use for symptomatic adults with no features of encephalopathy; and Henretig (2006), recommends succimer in adults with mild symptoms or blood lead concentrations between 70-100 mcg/dL. There is some evidence that pharmacokinetics and distribution of DMSA is different in poisoned children compared with poisoned adults (Dart et al., 1994).

Based on animal studies and clinical use associated with a favourable outcome or proven enhanced elimination, succimer appears to be useful for management of acute arsenic poisoning and for both acute and chronic poisoning with organic and inorganic mercury. Animal data and limited human case reports indicate that succimer may be an effective antidote for poisonings with antimony, bismuth, copper, thallium, alkyl tin, and zinc. (Anderson & Bates). These are less common than lead poisoning and are not such a widespread public health problem.

9. Treatment details

Diagnosis of lead poisoning depends on blood lead concentrations, and physical examination focussing on neurological function. X-rays and haematological evaluation can support diagnosis but are not routine investigations.

9.1 Dosage regimen

The most commonly recommended dosage regimen for children is an initial dose 10 mg/kg or 350 mg/m² orally, every 8 hours for 5 days, followed by 10 mg/kg or 350 mg/m² orally every 12 hours for 14 days. (Committee on Drugs, 1995 ; Ministère de la Santé et des Solidarité, 2006; Henretig, 2006; datasheet from Lundbeck Inc, 2009 ; Anderson & Bates). The same dosage regimen is used for adults i.e. 10 mg/kg orally every 8 hours for 5 days, followed by 10 mg/kg orally every 12 hours for 14 days. (Anderson & Bates; POISINDEX, 2009; TOXBASE, 2009).

The UK National Poisons Information Service (TOXBASE, 2009) recommends giving the same initial dose 30 mg/kg/day for 5 days, then assessing the individual's urine lead excretion and blood lead concentration, and only continuing treatment with 30 mg/kg/day beyond 5 days if the blood lead concentration is still high. This approach depends on regular clinical review and ready access to a laboratory able to undertake frequent analyses (Bradberry & Vale, 2009).

It is important to monitor blood lead concentrations during therapy and at least once a week after therapy until they are stable. In severe chronic lead intoxication the initial fall in blood lead achieved by antidote therapy may be followed by a rapid rise, as lead stored in brain, kidney and bone is mobilised. A rebound in blood lead concentration may occur within days or weeks following a course of succimer treatment. Additional courses may be indicated depending on the magnitude of the post-treatment lead concentration and the patient's clinical status but a treatment-free period is recommended between courses to allow time for the redistribution.

Guidelines differ in the duration of treatment free period recommended. The Committee on Drugs (1995) recommends a minimum of 2 days; TOXBASE (2009) recommends 2 days before a second course of treatment and 5-7 days before a third course; Bradberry & Vale (2009) recommend at least 1 week; while the Datasheet from Lundbeck Inc (2009) and POISINDEX, (2009) recommend a minimum of 2 weeks between courses unless blood lead

concentrations indicate the need for more prompt treatment;

When the oral route is impractical, succimer can be given intravenously, following adequate sterile filtration, in the same doses as above, divided in three daily doses. It was well tolerated with no change in haemodynamic parameters when a regime of 20 mg/kg/day intravenously for 5 days and then 10 mg/kg/day for 6 days was given to a patient who could not be given oral capsules due to the presence of ileus (Hantson et al., 2003 quoted by Anderson & Bates).

9.2 Monitoring

Liver function should be monitored before starting succimer and weekly during therapy because mild and transient elevations in serum transaminases have been reported. (POISINDEX, 2009)

The datasheet from Lundbeck Inc (2009) recommends obtaining a complete blood count with white blood cell differential and direct platelet counts before treatment, and monitoring weekly during treatment because mild to moderate neutropenia has been observed in some patients receiving succimer. Therapy should be withheld or discontinued if the absolute neutrophil count (ANC) is below 1200/ μ L and the patient followed closely to document recovery of the ANC to about 1500/ μ L or to the patient's baseline neutrophil count.

In patients with iron deficiency, iron supplements should be given during chelation. One of the advantages of succimer compared with dimercaprol is the possibility of being able to give iron at the same time. (**Appendix, Table 2**)

10. Summary of comparative effectiveness in a variety of clinical settings:

10.1 Identification of clinical evidence

We used the IPCS reviews of succimer (Anderson & Bates) and lead (Bates & Dargan) to identify relevant papers. We also undertook searches for papers published in or after 1995 about succimer being used to treat lead poisoning in children, and about prevalence and management of lead poisoning in developing countries. We searched EMBASE and MEDLINE for succimer or DMSA alone and combined with "lead poisoning" (as a MESH term) in humans and searched Google Scholar using terms "exposure to lead" "DMSA OR succimer "developing countries".

The available evidence includes case reports and controlled and uncontrolled studies of the short-term and long-term efficacy and safety of succimer in acute and chronic lead poisoning. Uncontrolled studies and case reports are of limited use for evaluating efficacy because it is usually impossible to distinguish how much the improvement in an individual's condition and decrease in lead concentrations was due to succimer and how much was due to cessation of exposure or supportive therapy. Also, in uncontrolled studies in young children treated with chelating agents it is impossible to determine whether long-term changes in blood lead concentrations or health outcomes reflect the decrease in blood lead concentrations that occur without intervention after 2 years of age rather than the effects of chelation (Rischitelli et al., 2006).

Few case reports include a calculation of the balance between the quantity of metal absorbed and excreted because of the difficulty in quantifying the dose absorbed (Anderson & Bates). It may also be difficult to quantify the amount of lead excreted when this involves collecting urine from young children (Graziano et al., 1988) or uncooperative patients (Bradberry et al., 2009).

10.2 Clinical evidence of efficacy

The effectiveness of succimer in lead poisoning has been evaluated by measuring physiological and biochemical changes which would be expected to improve clinical outcome. Such changes are more objective measures than improvement in symptoms, which may be difficult to assess in chronic lead poisoning.

blood lead concentration: Blood lead concentration is the accepted indicator of toxicity, and reduction in blood lead is the most commonly used measure of efficacy in treatment of lead poisoning. Blood lead concentration reflects current and past exposure to lead but does not necessarily reflect redistribution of lead in the body or the amount removed from the body (Bradberry & Vale, 2009).

urinary excretion of lead; approximately 70% of total lead clearance occurs through urine, so increase in urinary excretion is the best measure of the amount of lead removed from the body, and considered to be essential to the assessment of efficacy of chelating agents (Bradberry & Vale, 2009).

erythrocyte δ -aminolevulinic acid dehydratase (ALA-D) activity: ALA-D is an enzyme involved in haem synthesis. At low to moderate concentrations of lead in whole blood, >99% of the lead is associated with the erythrocyte and the main binding site is ALA-D. Lead inhibits ALA-D activity, so erythrocyte ALA-D activity is inversely correlated with blood lead and is a very sensitive marker of lead exposure at blood concentrations of 30 mcg/dL and above (Anderson & Bates).

erythrocyte zinc protoporphyrin concentration (ZPP): lead disrupts the enzyme catalyzing the insertion of iron into haem, such that zinc is inserted instead of iron, resulting in raised zinc protoporphyrin concentrations. There is a good correlation between erythrocyte protoporphyrin or zinc protoporphyrin and lead at blood lead concentrations above 25 mcg/dL. ZPP is also elevated by iron deficiency anaemia. (Anderson & Bates). Red blood cell function responds more slowly to changes in total body lead than blood lead concentration so an elevated ZPP in a child without iron deficiency indicates a longer duration of exposure to lead.

The following summary is concerned mainly with studies and case reports of childhood exposure. Clinical studies are summarised in **Appendix Table 3**

10.2.1 Human volunteer studies of effect of succimer on raised lead concentrations

Human volunteer studies provided evidence that succimer rapidly and significantly increased urinary excretion of lead, even in individuals with very low exposure to lead, in both controls and lead-exposed individuals (Hoet et al., 2006). Clinical trials, summarised by Anderson & Bates, established that 5 days treatment with succimer in adults with elevated blood lead concentrations lowered blood lead concentrations and increased urinary lead excretion. Succimer was well tolerated, and had no effect on excretion of essential elements apart from zinc.

A small study of the pharmacokinetics and distribution of succimer in 11 individuals (5 healthy adults, 3 adults with lead poisoning and 3 children with lead poisoning) suggested that these characteristics may be different in children with lead poisoning, compared with adults with lead poisoning or healthy adult volunteers (Dart et al., 1994).

10.2.2 Optimum dose and duration of treatment in children

The first study to demonstrate the efficacy of succimer in reducing blood lead concentration and increasing excretion of lead in children and to establish the dose, was a randomized study of 21 children, aged 2-5 years, with blood lead concentrations 31-49 mcg/dL due to chronic exposure (Graziano et al., 1988). Succimer 1050 mg/m²/day for 5 days reduced blood lead concentration and increased urinary lead output during the first 5 days and produced greater

changes than those produced by 350 mg/m²/day (10 mcg/dL) or 700 mg/m²/day (20 mcg/dL). At the end of 5 days treatment, blood lead concentrations began to rise again.

In a subsequent study, four children with blood lead concentrations between 42-70 mcg/dL were given a dose of 1050 mg/m²/day for 3 days, followed by 350 mg/m²/day for 5 days. This was also too low to prevent a rebound, which, in three of the children with baseline blood concentrations > 50 mcg/dL, occurred even before treatment finished (Chisolm, 1990).

The regimen recommended by the Committee on Drugs (1995), POISINDEX (2009) and the datasheet (Lundbeck, 2009) is based on a study by Graziano et al. (1992) in children with blood lead concentrations between 50-69 mcg/dL. Three regimens were compared: 1050 mg/m²/d for 5 days followed by 700 mg/m²/day for 14 days (n=6); 1050 mg/m²/d followed by 350 mg/m²/day for 14 days (n=6); and 1050 mg/m²/d for 5 days with no more succimer (n=7). The decrease in mean blood lead concentration after 5 days was 61% across all groups, and the rebound by day 13 occurred in all groups, but was smallest in the group treated with 700 mg/m²/day. By day 34 the mean blood lead concentration in the group given 700 mg/m²/d was 76.7% of the pretreatment value, which was similar to the other groups.

An alternative regime, repeating the 5 day course of 30 mg/kg/day after a 7 day break, produced a lowering of blood lead concentration comparable to the standard therapy, but used approximately 30% less drug, in a small randomized unblinded trial, involving 11 children with blood lead concentrations ranging 27-31 mcg/dL (Farrar et al., 1999). Safety was also comparable to the standard therapy.

Bradberry & Vale (2009) demonstrated that in adults with blood lead concentrations over ≥50 mcg/dL, repeated 5 day courses of succimer were as effective in reducing blood lead and increasing urinary excretion as the 19 day regime, as long as a 7 day treatment-free period was included to allow redistribution of lead from bone. Extending treatment beyond 5 days was also beneficial in achieving an increased rate of urinary excretion beyond 5 days and a continued fall in blood lead concentrations (Bradberry & Vale, 2009).

10.2.3 Effectiveness in reducing blood lead concentrations

Succimer achieves a 20-30% mean reduction in blood lead concentration after rebound (Graziano et al., 1992, Besunder et al., 1995, Liebelt et al., 1994, Farrar et al., 1999, O'Connor & Rich 1999).

Effectiveness for blood lead concentrations ranging from 25 – 60 mcg/dL was demonstrated in a retrospective uncontrolled cohort study (Liebelt et al., 1994), which compared treatment with succimer 30 mg/kg/d for 5 days then 20 mg/kg/d for 14 days in children with blood lead concentrations between 45- 60 mcg/dL (n=7) and in children with concentrations of 25-45 mcg/dL (n=23). The overall net reduction in blood lead concentration (31% and 26% respectively) was not significantly different, nor was there any significant difference between the groups at any stage from the start of treatment up to day 67 and 60 respectively.

However, a study of 17 adult patients with blood lead levels ≥ 50 mcg/dL, (Vale & Bradberry, 2009) found a correlation between baseline blood lead concentration and the extent of decline during 30 five-day courses of succimer 30 mg/kg/day, patients with higher blood lead concentrations experiencing a relatively smaller fall over 5 days chelation.

Some studies have noted a difference in individual response to succimer. In an uncontrolled retrospective case series, (Besunder et al., 1995), 28 children with blood lead concentrations ranging from 25-49 mcg/dL were given succimer 30 mg/kg/d for 5 days, then 20 mg/kg for 14 days. By 18 days post treatment the mean blood lead concentration had decreased by 43%, ± 20.8% and by 80 days post-treatment mean blood lead was 31% ± 21.9% lower than pre-treatment. In 80% of the children the reduction in blood lead concentration after rebound was

20% or more, but in the remaining 20% of children the reduction in blood lead concentration was less than 20%, and they were judged to be non-responders. The variable that distinguished responders from non-responders was not identified.

In a randomized, double blind, placebo-controlled trial involving children with baseline blood lead concentrations between 30-45 mcg/dL, (O'Connor & Rich, 1999), succimer treatment did not result in a decrease in blood lead concentrations, but because the sample size was small it was uncertain whether this was due to a failure to respond to succimer, non-compliance with treatment or continued exposure to lead in the environment.

Chisolm (2000) noted a wide range of response to succimer in patients who were considered to show excellent or good compliance. This study monitored blood lead concentrations for 6 weeks in 59 children with pretreatment blood lead concentrations ranging between 25-70 mcg/dL, who received succimer 1050 mg/m²/d for 5 days, then 700 mg/m²/d for 21-23 days.

Bradberry & Vale (2009) found evidence in the literature and as a result of their own research in adults, of an individual variation in response to succimer.

10.2.4 Increased urinary excretion of lead.

24 hour urine specimens were collected for 6 days in two studies described in section 10.2.2. Children with blood lead concentrations 31-49 mcg/dL given 5 days treatment with succimer at doses of 1050 mg/m²/day, 350 mg/m²/day or 700 mg/m²/day, (Graziano et al., 1988), and children with blood lead concentrations between 50-69 mcg/dL given either 1050 mg/m²/d for 5 days followed by 700 mg/m²/day for 14 days (n=6); 1050 mg/m²/d followed by 350 mg/m²/day for 14 days (n=6); or 1050 mg/m²/d for 5 days with no more succimer (n=7) (Graziano, 1992). Urine lead excretion rose in the first 24 hours, then declined gradually throughout the course of treatment.

(Chisolm, 2000) studied urine excretion in 59 children with pretreatment blood lead concentrations ranging between 25-70 mcg/dL. They received succimer 1050 mg/m²/d for 5 days, then 700 mg/m²/d for 21-23 days. The amount of lead excreted from the urine during the first 8 hours exceeded the estimated amount that would be removed from the blood pool and there was no constant ratio between the amount of lead estimated to be removed from the blood pool at 8 hours, 24 hours and 5 days, and the actual amount found in the urine. This was interpreted as indicating that lead had been removed directly from stores in the kidney. Measurements of urine lead/creatinine ratios in 6 children during the second phase of treatment, from day 7 to day 23, showed that diuresis of lead continued and was substantially higher than pre- and post-treatment, even though the blood lead concentration changed very little. Urinary lead generally peaked during the second or third hour after administration of the drug, increasing dramatically by six to ten fold.

10.2.5 Changes in indicators of lead toxicity

Succimer is effective in restoring erythrocyte ALA-D activity and decreasing ZPP concentrations.

The doses of succimer shown to be most effective in reducing blood lead concentrations in children with baseline blood lead concentrations between 31-69 mcg/L were also most effective in restoring erythrocyte ALA-D activity. Succimer 1050 mg/m²/d for 5 days followed by 700 mg/m²/d for 14 days was more effective than succimer given for only 5 days or given for 14 days at a lower dose of 350 mg/m²/day, and more effective than sodium calcium EDTA (Graziano et al., 1988; Graziano et al., 1992).

Changes in erythrocyte ALA-D activity were shown to mirror changes in blood lead concentrations when succimer 1050 mg/m²/day for 5 days followed by 700 mg/m²/day for 21-

23 days, was given to children with pretreatment blood lead concentrations ranging between 25-70 mcg/dL. (Chisolm, 2000).

Succimer decreased whole blood zinc protoporphyrin concentrations in children with blood lead concentrations ranging from 25-49 mcg/dL given succimer 30 mg/kg/d for 5 days, then 20 mg/kg for 14 days. There was a 12% decrease in zinc protoporphyrin concentrations at 18 days post-treatment and a 32% decrease by 80 days post-treatment (Besunder et al., 1995).

The small double-blind placebo-controlled trial described in 10.2.2., in which succimer treatment failed to produce a decrease in blood concentrations, also found there was no significant difference in zinc erythrocyte protoporphyrin concentrations between succimer-treated children and placebo-treated children at any time after -treatment (O'Connor and Rich, 1999).

10.2.6 Comparison of succimer with sodium calcium EDTA and dimercaprol

Succimer 1050 mg/m²/day and 700 mg/m²/day for 5 days produced a greater reduction in blood lead concentration than sodium calcium EDTA 1000mg/m²/day for 5 days, in children with blood lead levels 31-49 mcg/dL (Graziano et al., 1988), but produced a smaller increase in urinary lead output. This was interpreted as being due to more rapid mobilization of lead from bone by sodium calcium EDTA into the blood, soft tissues and urine, with the potential to increase the concentration of lead in the brain.

A second study compared succimer with sodium calcium EDTA for treatment of children with blood lead concentrations 50-69 mcg/dL (n=19) (Graziano et al., 1992). Treatment for 5 days with succimer 1050 mg/m²/day produced a 61% decrease in blood lead concentration compared with a 45% reduction in 4 children who received sodium calcium EDTA for 5 days. In children with blood lead concentrations 70-mcg/dL or more, succimer (n=3) produced a similar reduction in blood lead compared to sodium calcium EDTA plus dimercaprol (n=2) and the rebound increase at end of treatment was similar in both groups. Urinary excretion during the 1st day was virtually identical in children treated with succimer compared with those treated with sodium calcium EDTA, then from day 1 to day 5 urinary excretion declined steadily but the decline was less rapid in the EDTA group. Compared with the slower decline in blood lead concentration and slower restoration of erythrocyte ALA-D activity the sustained lead diuresis indicated that sodium calcium EDTA mobilized larger amounts of lead from bone than succimer did. It was noted that this might not be desirable since substantial quantities of lead rapidly mobilized from the skeleton could be redistributed to the brain and other soft tissues.

Besunder et al., (1997) compared treatment of children with succimer and sodium calcium EDTA (n=22) and treatment with sodium calcium EDTA and dimercaprol (n=23). Both treatments resulted in blood lead concentrations that were significantly lower than pre-treatment values (succimer + EDTA v succimer + dimercaprol resulted in 38.5% and 34.4% reduction respectively) but there was no difference between the treatment groups in percentage reduction from pretreatment values. In both groups the reduction in blood lead concentration was greater than from succimer alone. The combination of chelating agents was thought to be more effective in reducing blood, brain, liver and kidney content of lead than succimer because dimercaprol and succimer remove lead mostly from soft tissues and blood whereas sodium calcium EDTA removes lead primarily from bone and plasma.

Besunder et al., (1997) therefore concluded that succimer could be substituted for dimercaprol to treat children with blood lead concentrations of 70 mcg/dL or less, which would be less traumatic for the child than parenteral dimercaprol and less likely to produce adverse reactions.

10.2.7 Long-term effectiveness

10.2.7.1 Long-term effect on blood lead concentrations

Uncontrolled studies showed that treatment with succimer produced changes in blood lead concentrations during and immediately after treatment, but without controls it was impossible to estimate the extent to which these changes were also affected by efforts to remove lead from the domestic environment (Rischitelli et al., 2006).

Two randomized, double blind, placebo-controlled trials found that initial differences in blood lead concentrations between placebo-treated and succimer-treated children disappeared after several months (O'Connor & Rich, 1999, Rogan et al., 2001). In the first trial, children with blood lead concentrations between 30-45 mcg/dL were given either succimer (n=20) or placebo (n=19). Children weighing less than 15 kg were given succimer 300 mg for 5 days, then 200 mg for 14 days, and children over 15 kg were given 600 mg for 5 days then 400 mg for 14 days. There was no significant difference in mean blood lead concentrations between the treated group and the placebo group at the end of treatment or after 6 months (O'Connor & Rich, 1999), but the small sample size may have influenced the results.

The second, a multi-center randomized placebo-controlled double-blind clinical trial in the USA, the Treatment of Lead-exposed children (TLC) study, included 780 children aged 12 -33 months old (mean 2 years, standard deviation 0.5 year) with blood lead concentrations of 20-44 µg/dL. The treated group was given 1050 mg/m²/day for 7 days then 700 mg/m²/day for 19 days. To prevent continued exposure to lead, children moved to lead-safe housing, or had their homes cleaned. There was a difference in blood lead concentrations between placebo and treated groups at about 9-10 months but one year after treatment the difference was said to have largely disappeared (Rogan et al., 2001).

10.2.7.2 Long-term effect on cognitive and behavioural development:

Evidence from studies in children is limited. The TLC study found no improvement in cognition, behaviour, or neuropsychological function in children given succimer compared with the placebo group at 36 months (Rogan et al., 2001), or 60 months (Deitrich et al., 2004). The association between blood lead concentration and IQ score at 5 and 7 years of age was examined by Chen et al., (2005) and found to be similar in succimer and placebo groups.

In view of the limited evidence from studies in children, and the severity of the impact of childhood lead exposure on cognitive and behavioural development it is important to note results of animal studies in this area.

Studies on rats showed that doses of succimer sufficient to reduce brain lead concentrations could lessen lead-induced impairments in learning ability, attention, and regulation of arousal and/or emotion (Stangle et al., 2007; Beaudin et al., 2007). It was suggested that the TLC study might not have given enough succimer to remove substantial amounts of lead from the brain, and also that the cognitive tasks tested by the TLC study were less likely to be improved by succimer than the tasks tested by the rodent study (Stangle et al., 2007; Beaudin et al., 2007).

However, studies of rhesus monkeys exposed to lead from day 8 of life to either 1 or 2 years of age at levels to produce blood lead concentrations between 35-40 mcg/dL did not find clear evidence of whether or not succimer was beneficial in lowering tactile defensiveness behaviour, a sensory disorder that has been linked to hyperactivity, distractibility, and academic learning problems in children (Moore et al., 2008). Primate studies are more likely to be relevant to humans than rodent studies, and there is evidence of differences between rodents and primates in the effect of succimer on brain lead levels (Cremin, et al., 1999).

The effect of succimer chelation on cognitive impairment is therefore still unclear.

10.2.7.3 Long-term effect on locomotion and gait:

In a subsample of 161 children in the TLC trial, children treated with succimer performed better than the placebo group in locomotion and gait tests carried out when they had reached at least the age of 60 months, but it was uncertain how long these effects would persist (Bhattacharya, 2007).

10.2.7.4 Long term effect on growth:

Another study from the TLC trial found that the height difference in the succimer-treated children compared to controls was -0.27 cm at 34 months, showing that succimer had no beneficial effect on the growth and may even have had a detrimental effect (Peterson et al., 2004).

10.2.8 Adverse effects of succimer

10.2.8.1 Cognitive impairment in absence of lead exposure

Succimer given to rats not previously exposed to lead produced lasting cognitive and affective dysfunction similar to that produced by a high intake of lead (Beaudin et al., 2007; Stangle et al., 2007). These results suggest there might be a risk in giving succimer to children who do not have elevated tissue concentrations of lead, though the authors caution that the treatment regime given to the rodents may have been more “aggressive” than the clinical regimen.

10.2.7.2 Enhanced gastrointestinal absorption of lead

There has been concern that succimer might enhance gastrointestinal absorption of lead. If this were the case, children treated with succimer could be at risk of increased gastrointestinal uptake if they continuing to be exposed to lead.

The suggestion that gastrointestinal absorption of lead might be enhanced by succimer, was based on a study in non-lead exposed adults given a single tracer dose of stable lead isotope followed by either oral succimer or placebo (Smith et al., 1994). However this was not supported by a more recent study using a juvenile non-human primate model of moderate childhood lead intoxication, which found that oral succimer significantly reduced the gastrointestinal absorption of lead (Cremin et al., 2001).

Gastrointestinal lead absorption was increased by parenteral succimer in rodents (Kapoor et al., 1989), but rodent studies may not extrapolate directly to humans (Cremin, 1999).

10.3 Case reports of use after chronic exposure (Table 4)

There are five reports of succimer being used to treat children with symptoms of chronic lead poisoning. Four children with blood lead concentrations ranging from 173-550 mcg/dL had a history of pica, and three of them had radio-opaque material still in the gastrointestinal tract, (Gordon et al., 1998; Dargan et al., 2001; Chin & Charlton, 2004; Smith et al., 2007;). The fifth child had a blood lead concentration of 61 mcg/dL due to being administered a contaminated ethnic remedy for the first 7 months of life (Wolf et al., 2008).

All were initially treated with parenteral chelation, following the guidelines from the Committee on Drugs (1995), with gastrointestinal decontamination to remove lead from the gastrointestinal tract in some cases. Succimer was given at different stages of treatment: in three cases it was given after a period of parenteral chelation (Dargan et al., 2001; Smith et al., 2007; Wolf et al., 2008) in one case it was initiated on the same day as parenteral chelation (Chin & Charlton, 2004), and in the other case it was started as soon as whole bowel irrigation was completed, after 3 days of a 5 day course of parenteral chelation (Gordon et al., 1998).

The contribution of succimer to the initial decrease in blood lead concentrations could not be determined. In the four cases where follow up was continued for 6 months or more, repeated courses of succimer were effective in reducing lead concentrations when they rebounded and eventually stabilized below 40 mcg/dL. In two cases where there was follow-up to 16 months and 2 years respectively, treatment had apparently successfully prevented long-term developmental effects from chronic lead toxicity.

Succimer has been used to treat newborn children following chronic intrauterine exposure (Tait et al., 2002, Horowitz & Mirkin, 2001) (**Table 5**). Newborn children of women with lead poisoning have blood lead concentrations closely reflecting those of the mother. Succimer was ineffective in increasing urinary lead excretion in a pre-term infant (24 weeks) possibly due to immature enzyme systems (Tait et al., 2002), but was effective in a pre-term infant born at 35 weeks (Powell et al., 2006).

10.4 Case reports of use after acute exposure (Table 6)

Ingested lead objects are dissolved by stomach acids. The dissolved lead passes into the duodenum where it is absorbed into the blood stream.

Early after ingestion of a lead object, when a child is asymptomatic with raised blood lead concentration, the lead is mostly in the blood where it can be easily chelated and removed. McKinney (2006) demonstrated a rapid increase in lead absorption between the first and second days after ingestion and noted that the clinical significance of blood lead concentrations after acute ingestion is problematic because they may be obtained before complete absorption and distribution to soft tissues.

The first aim of treatment is therefore to speed progress of the object through the gastrointestinal tract, for example, by using a prokinetic agent to encourage passage through the stomach; then whole body irrigation to speed passage beyond the stomach. The object may need to be removed surgically if it is not passed out of the body within a given time.

We found 7 reports of children treated with succimer after acute exposure to lead, all of whom survived. Three children with concentrations > 100 mcg/dL were given parenteral treatment before being given succimer (Esernio-Jenssen et al., 1996; Deitrich et al., 2000; VanArsdale et al., 2004). Two of these children had ingested lead objects several weeks before admission (Esernio-Jenssen et al., 1996; VanArsdale et al., 2004). Endoscopy undertaken to remove the objects was unsuccessful in one case so intestinal lavage was undertaken (Esernio-Jenssen et al., 1996). There was no increase in blood lead above the baseline. At least one more course of succimer was required to reduce blood concentrations below 40 mcg/dL.

Succimer was the only chelating agent used in four children with baseline blood concentrations between 47-57 mcg/dL following ingestion of lead objects were given one course of succimer after whole bowel irrigation, endoscopy or colonoscopy (Mowad et al., 1998; Clifton et al., 2002; McKinney, 2006; St Clair & Benjamin, 2008). There was no increase in lead absorption from the gastrointestinal tract.

In all these children succimer limited the rebound in blood lead concentrations. Long term developmental problems that could have been due to a previous chronic exposure to lead were reported in two children.

Succimer is not recommended for treatment of children with encephalopathy, and we found no reports of its being used in this way.

10.5 Use in communities in developing countries

There are few published reports of succimer being used “in the field” in developing countries.

A small study was carried out in the Ecuadorian Andes among children living and working in Pb-glazing cottage industry, as part of a larger programme addressing the problems of chronic moderate to severe lead intoxication in the community (Counter et al., 2003). After nearly a year of a lead education/prevention programme 35 children with pre-treatment blood concentrations ranging from 17.5-83 mcg/dL, mean 43.4 mcg/dL, were given succimer: 2000 mg/kg for 10 days in children weighing equal to or less than 25 kg, and 400 mg /day for 10 days in or children weighing more than 25 kg. The dose regimen was designed to conserve medication while maintaining effective chelation. Blood concentrations were significantly reduced mean 34.3 mcg/dL (range 10.5-67.1 mcg/dL) 3 weeks after treatment, but most remained above 10 mcg/dL., probably because the children continued to be exposed and possibly because the dose of succimer was too low (Bradberry & Vale, 2009). No health-related side effects were associated with use of succimer.

The use of succimer in Lima, Peru, to treat three children with high lead concentrations (96.9, 87.2 and 219.9 mcg/dL respectively), was described in a USAID project report (Zavaleta, 2001). Short-term reductions in lead concentrations were recorded but this was not a medical report so there was no assessment of long-term effects of treatment.

Succimer and sodium calcium EDTA were used in a mass poisoning incident in Senegal, West Africa, in 2008 (Tempowski, personal communication). From the 50 children initially investigated, 41 children were selected for urgent chelation therapy to reduce their blood lead concentrations. 23 children received three rounds of chelation therapy, 17 received two rounds and one child received one round. When 39 of the 41 treated children were re-examined all showed significant improvement in their clinical and neurological status. Lead blood concentrations after treatment, available for 23 children, had decreased significantly, they were still significantly elevated in 17 children (74%) indicating the need for further cycles of chelation therapy (WHO, 2009).

11. Summary of comparative evidence on safety:

11.1 Overview

The manufacturer’s data sheet (Lundbeck, 2009) estimates that open US and foreign studies have given succimer to approximately 250 patients with lead poisoning, of which 191 were children. This does not include subjects in controlled studies. The total patient exposure is unknown, but is likely to be substantial as succimer has been in use in China since 1977 (Ding & Liang, 1991) and was approved for use in the US in 1991.

The data sheet summarises adverse events reported with the administration of succimer for treatment of lead and other heavy metal intoxication. Causal relationships to succimer have not been definitely established (Lundbeck, 2009).

No significant adverse effects were associated with daily doses of succimer up to 30 mg/kg/day (adults and children) for up to one week followed by 10-20 mg/kg/day for two weeks. Even longer treatment does not seem to be associated with significant effects on essential trace element homeostasis.

Adverse effects associated with succimer treatment in children, in order of reported frequency, include gastrointestinal disturbances, transient mild elevation of liver enzymes, respiratory symptoms, skin reactions, light to moderate drowsiness and other mild CNS effects, and mild neutropenia. Symptoms are usually mild, self-limiting and most do not require cessation of therapy. Two cases of muco-cutaneous hypersensitivity have been described (see Section

11.6).

Succimer is well tolerated in clinical studies (Graziano et al., 1988; Graziano et al., 1992, Besunder et al., 1995; O'Connor & Rich, 1999; Farrar et al., 1999; Chisolm, 2000; TLC Trial Group, 2000). The TLC trial, in which 396 children were treated with succimer, 119 of them receiving two courses and 77 of them receiving three courses, found little evidence of toxicity from succimer (TLC Trial Group, 2000). There was no significant excess of any symptoms or laboratory abnormality in either the treated or placebo group, except that a history of trauma or evidence of trauma on physical examination was more frequent in children given succimer than in those given placebo. There was no explanation for this and it might have been due to chance.

Adverse effects reported in clinical trials are summarised in Table 7.

11.2 Dosage

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

Doses of succimer up to 1050 mg/m²/day (equivalent to 30 mg/kg to adults), were well tolerated in children with lead exposure (Graziano et al., 1988; Chisolm 1990). In one case a patient received a total of 189 g succimer over 2 years; the maximum succimer dosage was 30 mg/kg/day. The drug was well tolerated without the development of severe adverse subjective or clinical symptoms related to succimer treatment. Only marginal effects on serum and urine chemistry were noted, except for markers related to lead intoxication and iron deficiency that were corrected with combined iron and succimer therapy (Haust et al., 1989).

11.3 Gastro-intestinal effects

Gastro-intestinal effects such as nausea, vomiting, diarrhoea, appetite loss, have been reported in 12% of cases reported to the manufacturer. In a study of 21 children, Graziano et al. (1988) reported vomiting in 3 children, 2 of whom also received penicillin. In a study of 23 children, treatment had to be discontinued prematurely in one patient because of vomiting and diarrhoea (Liebelt et al., 1994). Vomiting was reported for 4 out of 22 children given succimer, including one child who had more than one episode of emesis (Besunder et al., 1997).

Side effects reported in the 396 children in the TLC trial included diarrhoea (47%), vomiting (25.2%), abdominal pain (15.2%) and nausea (7.8%) (TLC Trial Group, 2000).

11.4 Hepatic effects

Transient mild elevations of serum transaminases have been observed in 6-10% of patients during succimer therapy (Lundbeck, 2009).

Mild elevation in hepatic alanine aminotransferase (ALT) was recorded in 17 patients out of 30 treated with succimer (Liebelt et al., 1994). The mean pretreatment ALT was 22 +/- 4mU/ml (ref range 0-22 mU/ml); during or post treatment the peak ALT was 26 +/- 3mU/ml (p=0.001).

Chisolm (2000) reported raised alkaline phosphatase in 2 children out of a series of 59. In a study of 23 children slightly raised aspartate aminotransferase and ALT were reported in one child but these were not clinically significant and were rapidly reversible (Graziano et al., 1992)

In the TLC trial, in 396 treated children, abnormal laboratory values were confirmed for two children (0.5%) with alkaline phosphatase 5 times the local upper limit of normal; for one child (0.3%) with aspartate aminotransferase twice the local upper limit of normal and for one

child (0.3%) with alanine aminotransferase twice the upper limit of normal (TLC Trial Group, 2000).

Several other studies tested liver function but found no abnormalities (Graziano et al., 1988, Chisolm, 1990; Kuntzelmanm & Angle, 1992, Farrar et al., 1999; O'Connor & Rich, 1999).

Pre-existing neonatal jaundice resolved during succimer treatment in a child with elevated blood lead concentrations (Horowitz & Mirkin, 2001).

11.5 Respiratory effects

Graziano et al. (1992) reported head cold and rhinorrhea in 6 patients, head cold in one patient, nasal congestion in 2 patients, and conjunctivitis in 1 patient. All resolved within one week and may not have been related to succimer.

11.6 Dermatological effects

Rashes including papular rash, herpetic rash, mucocutaneous eruptions and pruritis have been reported in about 4% of patients (Lundbeck Inc, 2009).

The TLC trial reported scalp rashes in 3.2 % of children and rashes elsewhere on the body reported in 34.3%. However, these also occurred in the placebo group and there was no significant difference in occurrence between the two groups (TLC Trial Group, 2000).

In an earlier study (Graziano et al., 1992) one patient had a fine papular rash on her chest but a similar heat rash had previously been reported for this patient before she received succimer.

A healthy adult volunteer given 30 mg/kg succimer (Captomer-250 from Thorne Research Inc, Dover, Idaho, USA), orally, experienced burning sensation of the lips approximately 6 minutes after the dose, followed by nausea and vomiting, tingling of the extremities and an urticarial-type rash. No more succimer was given and he made a full recovery when treated with antihistamines and ondansetron (Archbold et al., 2003)

An allergic mucocutaneous reaction was reported on repeated administration of succimer in an adult patient. He developed a severe vesicular reaction during a third course of treatment, followed by development of hypersensitivity during a fifth course of treatment in spite of the use of lower doses. Three days after the start of the third course the patient developed vesicular eruptions on the oral mucosa, glans penis and perianal region. These effects rapidly resolved when the succimer was stopped 6 days later. Four months later, a challenge was performed with increasing doses of succimer. A similar reaction occurred after a dose of 4 mg/kg/day and was aggravated during a dose increase to 30 mg/kg/day. The adverse reaction was alleviated when the dose was reduced to 10 mg/kg/day and was well tolerated for 10 days. However, during a fifth succimer treatment period using the low dose of 10 mg/kg/day, more pronounced mucous and skin eruptions developed and further succimer treatment was declined (Grandjean et al., 1991).

Bradberry et al. (2009) reported a major mucocutaneous reaction in an adult with no history of atopy or allergy. After the second dose the patient complained of pruritus affecting the neck. This developed into an erythematous rash over the neck and forearms associated with a mild fever. No more succimer was given. About 24 hours after the second dose the patient developed oropharyngeal ulcers that settled over 4 days with conservative treatment. The patient had received five previous course of DMSA without developing a skin reaction.

11.7 CNS effects

Drowsiness, dizziness, sensorimotor neuropathy, sleepiness and paraesthesia have been reported in about 6% of patients (Lundbeck Inc, 2009).

The TLC trial reported irritability in 28.8% of treated children, and change in sleep behaviour in 22.7% (TLC Trial Group, 2000).

11.8 Haematological effects

Neutropenia in one patient in a series of 28 children (Besunder et al., 95), and the TLC trial reported neutropenia in 3 children treated with succimer (0.8%), but this was not significantly different from the frequency of neutropenia in the control group (TLC Trial Group, 2000).

Haemolytic anaemia was reported in an adult with glucose-6-phosphate dehydrogenase deficiency who had occupational lead intoxication and was treated with succimer 2.4g (10 mg/kg) daily for 5 days then 1.6 g daily for 8 days. After cessation of treatment haematological values normalised (Gerr et al., 1994). However, succimer was used in 5 children with glucose-6-phosphate dehydrogenase deficiency without adverse incident (Manufacturer's data, Chisolm, 2000; Graziano et al., 1992) and one child with sickle cell disease (Chisolm, 2000).

An adult treated with succimer experienced severe hyperthermia which was initially associated with hypotension and apparent severe fluid loss, and on rechallenge with hypertension and diaphoresis (Marcus et al., 1991).

Anderson & Bates quote reports of adverse events associated with use of succimer to treat other heavy metals. Facial swelling was associated with succimer used to treat occupational exposure to elemental mercury vapour (Bluhm et al., 1992).

A fall in haemoglobin was reported in 12 of 41 children (29%) who were treated with a total of 65 courses of succimer (Okose, 1991), but details such as the individual values, the magnitude of the fall and details of exposure and treatment were not reported. In a study of 18 adults with elevated blood lead concentrations, haemoglobin level fell from 12.2 to 11.9 gm/dL in one man who received succimer 30 mg/kg for 5 days, but this was not reported to be clinically significant (Graziano et al., 1985). However a study comparing 22 children treated with succimer and sodium calcium EDTA with 23 children treated with sodium calcium EDTA and dimercaprol found haemoglobin concentration fell by day 5 of therapy in both treatment groups and there was no difference between them (Besunder et al., 1997).

11.9 Trace element homeostasis

Investigations in experimental animals and humans have found succimer treatment to have only a marginal affect on essential trace element homeostasis. Several studies have shown that the urinary excretion of copper, zinc, calcium, magnesium and iron are not adversely enhanced with succimer administration in the recommended doses (Friedheim et al., 1978; Graziano et al., 1985; Fournier et al., 1988; Smith et al., 2000). Even larger doses (up to 80mg/kg/day in adults) and a longer duration of treatment (up to 2 years at a maximum of 30mg/kg/day) have not been associated with problems other than a correctable tendency to iron deficiency during treatment over two years (Haust et al., 1989).

11.10 Overdose

Few cases of succimer overdose have been reported but it appears to be associated with a benign clinical course. A 3 year old girl ingested 2.4 g of succimer (185 mg/kg) and extensive clinical evaluation failed to indicate signs of intoxication (Sigg et al., 1997; Sigg et al., 1998).

An adult receiving succimer for arsenic poisoning (500 mg 3 times a day for 4 days then 500 mg twice daily for 7 days) took an intentional overdose of 4-8 g, (43 to 87 mg/kg) of succimer with 1.2 g of the non-sedating antihistamine, fexofenadine. He remained well except for a sensation of jitteriness and palmar keratosis which resolved within 4 weeks. All blood parameters measured were normal (Buchwald, 2001).

11.11 Identification of variation in safety due to health systems and patient factors

On the basis of this review of adverse effects, succimer should be used with caution in certain patients.

Patients with previous or ongoing allergic reactions, especially mucosal and skin eruptions, signs of recrudescence or exacerbation should be carefully monitored during therapy with succimer.

In patients with an absolute neutrophil count below 1200/mcL, succimer, should be withheld or discontinued. Re-exposure should be avoided unless the benefit of therapy clearly outweighs the potential risk of another episode of neutropenia and then only with careful patient monitoring (manufacturer's data).

Patients with liver disease should be monitored closely if treated with succimer.

It has recently been suggested that succimer may be hazardous if given in the absence of lead (Beaudin et al., 2007, Stangle et al., 2007).

11.12 Safety of succimer compared with other commonly used chelating agents

There is more safety data available for succimer than for the other oral agents in this class and this has influenced its selection as an example of the therapeutic group. Compared with other antidotes for lead poisoning, succimer has a better adverse effect profile and causes less urinary loss of minerals (see Appendix Table 2).

Dimercaprol is associated with a high incidence of adverse effects: nausea, vomiting, hypertension, prolongation of partial thromboplastin time, fever, rashes, pain at injection site, kidney dysfunction and zinc depletion. Dimercaprol is contraindicated in children with nut allergy because it is dissolved in peanut oil and in children with glucose-6-phosphatase deficiency.

Calcium sodium edetate causes local reactions at injection sites, fever, calcium abnormalities, nephrotoxicity that is dose and infusion rate-related, and excretion of essential minerals.

D-penicillamine causes skin rash or zinc/iron depletion (common), kidney or marrow dysfunction (uncommon), and anaphylaxis. Its safety for treating lead poisoning has not been established (Committee on Environmental Health, 2005).

12 Summary of available data on comparative cost and cost-effectiveness

12.1 Cost of succimer

Succimer is not listed in International drug price indicator guide or in other sources of international drug prices (MSF.org, and UNICEF.org) recommended by WHO.

In 2008, in the UK, the cost of 100 x 100 mg capsules of succimer was around £1,500. A 15 kg child would need 43 x 100 mg capsules, so the cost of a single course of treatment for would be around £650 at 2008 prices.

In 2003 it was estimated the cost of using succimer in Zambia to treat children exposed to lead contaminated soil would be 195\$ per child per year (World Bank, 2003), but it was not clear how this figure was calculated.

Besides the cost of the chelating agent, the overall cost of medical treatment of lead poisoning in a child would include

- cost of testing for blood lead
- cost of routine investigations: haematology and biochemistry, possibly radiography
- direct medical costs of treatment and follow-up
- cost of removing lead from the child's home, or removing the child to a safer environment to protect from continuing exposure to lead

In the USA, in the late 1990's, Kemper et al., (1998) calculated that oral chelation, including drug therapy, follow-up visits and laboratory monitoring, cost \$253. In 2002, Brown estimated that oral chelation cost £2,046, while Stefanak et al., (2005) calculated that in Ohio, screening and treating children with blood lead concentrations 20-45 mcg/dL, cost \$969.

12.2 Comparison of cost of succimer with costs of other chelators.

The associated costs of preparation and storage are likely to be less for succimer than for a parenteral agent.

The overall cost of treatment with succimer is likely to be less than costs of treatment with parenteral chelating agents which include in-patient stay in hospital and probably higher costs of monitoring for and treating adverse effects and side effects. Kemper et al., (1998) calculated that that the cost of intravenous chelation, including costs of drug therapy, follow-up visits and laboratory monitoring \$1843, which was considerably more than the \$253 cost of oral chelation.

The table below uses available data on prices to compare approximate costs.

Agent	Cost	Dose	Cost for a 15 kg child
Dimercaprol (net price in British National Formulary, 2009)	£42.73 per 2 ml amp 50 mg/ml)	2.5-3 mg/kg every 4 hours for 2 days, 2-4 times on 3 rd day then 1-2 times daily for 10 days	45 mg dose = 1 amp x 36 = £1,538
Dimercaprol (International Drug Price Indicator, 2007)	\$75.20 per 2 ml amp	2.5-3 mg/kg every 4 hours for 2 days, 2-4 times on 3 rd day then 1-2 times daily for 10 days	36 amp = \$2,707
Succimer (UK cost price, 2008)	£1487.67 for 100 (100 mg capsules) = approx £15 each Or £79 for 20 x (300 mg caps) = approx £4 each	May need to repeat	43 x 100mg = £650
Sodium Calcium EDTA (net price in British National Formulary, 2009)	£7.29 / 5 ml amp (200 mg/ml = 1000mg per amp)	40 mg/kg twice daily for up to 5 days; may need up to 3 courses separated by at least 7 days	Dose = 600 mg = 1 amp; x 10 = £72

12.3 Cost-effectiveness

Assessments have been made of the global burden of disease due to lead poisoning (Prüss-Üstün et al., 2003; Fewtrell et al., 2003), the social costs of childhood lead exposure in the US (Stefanak et al., 2005; Meunnig, 2009) the cost-effectiveness of strategies to reduce environmental contamination in the US (Nevin et al., 2008) and the comparative cost-effectiveness of strategies for screening for lead poisoning in the US (Kemper, et al., 1998).

We could not find a published assessment of the cost-effectiveness of treating childhood lead poisoning with succimer. It is difficult to make such an assessment in the absence of a clear-cut clinical outcome that could be costed. Cost per life saved is an inappropriate measure of effectiveness for succimer because it is not used to treat life-threatening acute poisoning. Using reduction of disability as a measure of effectiveness is also problematic because there is very limited evidence that succimer has an impact on long-term disability due to the effect of lead on cognitive and behavioural development.

The effective use of succimer depends on access to adequate facilities for monitoring lead in blood and urine, and healthcare staff able to diagnose and treat lead poisoning, so estimates of the cost of making succimer available in developing countries may need to include the costs of providing laboratory facilities and training healthcare staff.

Perhaps the most contentious question is whether it could ever be cost-effective to treat individuals who cannot be protected from continuing exposure to lead.

It is probably more cost-effective to prevent exposure than to treat poisoning, so while it is important to improve availability of chelating agents and facilities for treatment of lead poisoning, this should not detract from efforts to reduce environmental contamination. It is technologically possible to reduce lead emissions, clean contaminated sites and replace hazardous products and unsafe working practices with safer alternatives, and feasible to devise strategies to identify, control, monitor, and eliminate environmental lead exposures and hazards. Although the cost of implementing and enforcing such strategies may seem prohibitive, the long-term costs of lead poisoning include costs of caring for and educating mentally retarded children; the lower wages and earning power, productivity losses when affected children reach adulthood (Brown, 2002), and the costs of increased juvenile delinquency and other criminal behaviours (Stefanak et al., 2005; Nevin et al., 2008).

From the point of view of a child with lead poisoning and its family, chelation is the only available treatment and the cost is small compared with the benefits of even short-term improvement.

Although there is no evidence that succimer is cost-effective or associated with long-term benefits in individuals with lead poisoning, there is evidence that it produces short-term clinical improvement, and the cost of treatment is likely to be less than treatment with a parenteral chelator.

13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

Succimer was approved by FDA in 1991 for paediatric use.(FDA medical bulletin).

14. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia)

Succimer is included in the Chinese Pharmacopoeia (Sweetman, 2007; Ding & Liang, 1991).

15. Proposed (new/adapted) text for the WHO Model Formulary

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Abbreviations used in the tables

ALA-D = erythrocyte δ -aminolevulinic acid
dehydratase;
BAL = dimercaprol;
DMSA = succimer;
EDTA = sodium calcium edetate

Pb = lead

WBI = whole bowel irrigation
ZnP = zinc protoporphyrin)

Table 1 Comparison of Guidelines on treatment of lead poisoning in children

Guideline	25-45 mcg/dL	45-70 mcg/dL and asymptomatic	45-70 mcg/dL symptoms not suggestive of encephalopathy	>70 mcg/dL with or without symptoms	Encephalopathy
Committee on Environmental Health, 2005	Chelation not indicated	DMSA or sodium calcium EDTA if the patient is allergic to succimer,	EDTA	Parenteral therapy with EDTA	Parenteral therapy with sodium calcium EDTA
Committee on Drugs, 1995	Chelation therapy not to be used routinely, but some patients may benefit from oral chelation to enhance excretion, if blood concentrations persist in this range despite repeated environmental intervention	DMSA or sodium calcium EDTA.	Succimer or EDTA	The most efficacious parenteral agent available. Dimercaprol i.m. and sodium calcium EDTA i.v. as a single dose or a continuous infusion, 4 h after starting dimercaprol. Continue for minimum 72 h. Then either <ul style="list-style-type: none"> continue parenteral therapy with sodium calcium EDTA and dimercaprol for 5 days or <ul style="list-style-type: none"> continue sodium calcium EDTA alone for 5 days. Treatment can be repeated depending on blood lead concentrations and symptoms. A minimum 2 days without treatment should elapse before starting another course	As for children with blood lead >70 mcg/dL. Continue chelation with dimercaprol and sodium calcium EDTA until patient is clinically stable before changing therapy.
TOXBASE, 2009	DMSA indicated only if blood lead concentrations are persistently raised. Give for 5 days initially, then reassess. If needed give a lower dose for 14 days or give penicillamine.	DMSA for 5 days initially, then reassess. If needed give a lower dose for 14 days		Sodium calcium EDTA	Sodium calcium EDTA
Ministère de la Santé et des Solidarité, 2006	Chelation not indicated	DMSA		For blood lead >100 mg/dL give dimercaprol and sodium calcium EDTA For blood lead 70-100 mg/dL give sodium calcium EDTA and DMSA	Dimercaprol and sodium calcium EDTA
Centres for Disease Control, 2002	Chelation not indicated	Chelation therapy		Hospitalization and chelation therapy	Hospitalization and chelation therapy

Guideline	25-45 mcg/dL	45-70 mcg/dL and asymptomatic	45-70 mcg/dL symptoms not suggestive of encephalopathy	>70 mcg/dL with or without symptoms	Encephalopathy
POISINDEX, 2009	Chelation not indicated	DMSA Use DMPS only if medically necessary. Not recommended for concomitant use with Sodium calcium EDTA with or without BAL. Should not be used if exposure to lead continues.	DMSA. If vomiting necessitates parenteral therapy give Sodium calcium EDTA with BAL	dimercaprol with sodium calcium EDTA .	Dimercaprol with sodium calcium EDTA

Table 2 Comparison of succimer with other antidotes

	Succimer	Sodium calcium edetate	Dimercaprol	D-penicillamine	Unithiol (DMPS)
Usual route of administration	Orally. Has been given intravenously to adults.	Intravenously. Has been given intramuscularly. but only rarely	Intramuscularly only	Orally only	Orally intramuscularly or intravenously.
Dose	30 mg/kg/d in 3 divided doses for 5 days then 20 mg/kg/d in 2 divided doses for 14 d.	1000 mg/m ² body surface area/d	75 mg/m ² body surface area every 4 hours	10-15 mg/kg/d	Oral: 50-100 mg every 6-8 h or 5 mg/kg in 2-4 doses Parenteral: 5 mg/kg every 3-4 h (day 1), every 4-6 h (day 2), every 7-8 h (day 3), every 8-12 h (day 4) and thereafter based on clinical condition
Contraindications	Hepatic insufficiency or ongoing exposure to lead		Nut allergy (drug is dissolved in peanut oil) or glucose-6-phosphate dehydrogenase deficiency	Renal insufficiency or ongoing exposure to lead	
Side effects and ADRs	Common side effects in up to 10% of cases: transient rash, elevated liver enzymes, skin rash (both uncommon), abdominal distress, and neutropenia.	Local reaction at injection sites, pain at injection site if given i.m.; fever, calcium abnormalities, renal dysfunction that is dose and infusion-rate-related,	High incidence of adverse effects: nausea, vomiting, hypertension, prolongation of partial thromboplastin time, fever, rashes, pain at injection site; renal dysfunction, zinc depletion, haemolysis in glucose-6-phosphate dehydrogenase deficiency	Common: skin rash or zinc/iron depletion Uncommon: renal dysfunction, eosinophilia, leucopenia, thrombocytopenia, neutropenia, anaphylaxis	Gastrointestinal discomfort, skin reactions, mild neutropenia, elevated liver enzymes, hypotension after rapid i.v. infusion; some patients develop hypersensitivity. One report of Steven's Johnson syndrome
Mode of action	Water soluble analogue of dimercaprol	Increases urinary excretion of lead through formation of non-ionizing salts. Removes lead from extracellular compartment only; does not enter cells.	Promotes renal excretion through formation of stable non toxic soluble lead chelates		Water soluble analogue of dimercaprol

	Succimer	Sodium calcium edetate	Dimercaprol	D-penicillamine	Unithiol (DMPS)
When to use it	<p>1st line treatment if</p> <ul style="list-style-type: none"> • blood lead 45-69mcg/dL • exposure has been controlled • no symptoms of encephalopathy 	<p>2nd line treatment when blood lead = 45 - 70 mcg/dL if the patient cannot take DMSA, (e.g. protracted vomiting or allergy to succimer)</p> <p>When blood lead >70 mcg/dL with or without symptoms, either alone (TOXBASE, 2009) or following pre-treatment with dimercaprol (POISINDEX, 2009, Ministère de la Santé et des Solidarité, 2006)</p>	<p>When blood lead = > 70 mcg/dL with or without symptoms pre-treatment for Sodium calcium EDTA</p> <p>For patients with encephalopathy as pre-treatment for sodium calcium EDTA</p>	<p>When blood lead is consistently = 25-45 mcg/dL, as an alternative to DMSA (TOXBASE, 2009)</p> <p>3rd line agent for use only when there are unacceptable adverse reactions to both DMSA and sodium calcium EDTA and it is important to continue chelation (Committee on Drugs, 1995)</p> <p>Close monitoring of renal function and peripheral blood counts during therapy is recommended</p>	
Advantages	<p>Can be given orally</p> <p>Less toxic than Sodium calcium EDTA</p> <p>Iron can be given at same time</p> <p>No significant effect on excretion of essential minerals: iron, calcium, magnesium. Zinc excretion is increased but less than with Sodium calcium EDTA</p>	<p>The most efficient chelating agent</p>	<p>When given as pre-treatment for sodium calcium EDTA, avoids precipitation of lead encephalopathy and causes a more rapid decline in blood lead when used with Sodium calcium EDTA</p>		<p>Can be given orally</p>
Limitations	<p>Expensive.</p> <p>Commonly used products have an unpleasant taste and smell that may limit compliance</p>	<p>Binds essential minerals, (zinc copper, manganese), which are then excreted in urine.</p> <p>Forms nephrotoxic complex with lead</p> <p>May cause lead to be redistributed from bone stores to brain tissue causing encephalopathy.</p>	<p>Unstable, difficult to store, May not result in appreciable differences in post chelation blood lead concentrations, rate of change in blood lead levels may be irrelevant.</p> <p>High toxicity</p> <p>Iron cannot be given at the same time because it forms a chelate that is a potent emetic.</p>	<p>Cannot be given with milk, milk products or iron supplements (may reduce blood penicillamine concentrations).</p> <p>Limited effectiveness: 18% reduction in blood lead concentration after rebound;</p> <p>Adverse reactions are common.</p> <p>Not approved by FDA for this indication. Safety and efficacy not established for treating lead poisoning.</p>	<p>Appears to be more toxic than DMSA but data is limited</p> <p>Not approved by FDA but registered in Germany.</p>

Table 3 Clinical studies of succimer (DMSA) treatment of lead poisoning in children

Reference	Study design	Subjects	Intervention	Duration of FU	Baseline Blood lead level (BLL)	Blood Lead levels (BLL) during and after treatment	Other effects of DMSA	Summary
Graziano et al., 1988	Randomized study	Age 2-7 years N = 21	Grp 1 DMSA 350 mg/m ² /day for 5 days (n=5) Grp 2 DMSA 700 g/m ² /day for 5 days (n=5) Grp 3 DMSA 1050 g/m ² /day for 5 days (n=5) Grp 4 EDTA 1000 mg/m ² /day iv for 5 days (n=6)	20 d	31-49 mcg/dL	DMSA 1050 mg/m ² /day, was significantly more effective in lowering blood lead levels than either lower doses of DMSA or EDTA	ALA-D activity rose in all 4 groups during therapy. 1050 g/m ² /d was significantly more effective in rejuvenating ALA-D activity than either lower doses of DMSA or EDTA. Urinary Pb excretion was higher in the EDTA group than each of the DMSA groups DMSA 1050 mg/m ² /day produced significantly higher urinary Pb excretion than 350 mg/m ² /d or 700 mg/m ² /d (p<0.0001) EDTA significantly increased urinary excretions of zinc, copper, iron and calcium whereas DMSA did not.	There was a positive correlation between dose and lead mobilizing effect by DMSA. The highest DMSA dose was more efficient than EDTA.
Chisolm, 1990	Case series	Age not stated; N = 4	DMSA 1050 mg/m ² /day for 5 d then 350 mg/ m ² /day for 5 days. 1 child given a 2 nd course		Pt 1 42 mcg/dL Pt 2 52 mcg/dL Pt 3 60 mcg/dL Pt 4 70 mcg/dL	In patients 1,2 and 3, BLL increased during second 5 d of treatment In patient 4, BLL rebounded to 52 mcg/dL within 10 d of start of treatment.		

Reference	Study design	Subjects	Intervention	Duration of FU	Baseline Blood lead level (BLL)	Blood Lead levels (BLL) during and after treatment	Other effects of DMSA	Summary
Leibelt et al., 1994	Retrospective cohort study	Age 5-161 mo (mean 34 m) N=30	DMSA 30 mg/kg/d for 5 d, then 20 mg/kg/d for 14 d. Patients in both groups required multiple course of treatment (2-6 courses) Environmental lead abatement	At least 6 mo	20-60 mcg/dL Grp 1: (n=23) <45 mcg/dL (mean 31 ± 2 mcg/dL) Grp 2 (n=7) >45 mcg/dL (mean 51 ± 2 mcg/dL)	BLL during treatment Grp 1 19 ± 1.2 mcg/dL mean - 60% Grp 2 30 ± 2 mcg/dL, 2 mean 58% Rebound Grp 1 mean rebound 70% of pre-treatment value by mean day 41 (20 d post-treatment); plateau at 74% by day 67 Grp 2 mean rebound 69% of pre-treatment value by mean day 37. (18 d post-treatment) Plateau at 69% by day 60. Overall net reduction Grp 1 26% Grp 2 31% Differences between the groups were not significant at any stage.	Pre-treatment ZnP Grp 1: 61±16 mcg/dL Grp 2 146 ±47 mcg/dL Not significant. Peak ZnP Grp 1 111 ±24 mcg/dL Grp 2 257 ±133 mcg/dL Not significant. Adverse effects Vomiting and diarrhoea (n=1) Mildly raised ALT 26 ± 3mU/mL, significantly higher than pre-treatment levels	Prior chelation therapy did not affect the percentage reduction in BLL or rebound. There was no significant difference between the two groups in the average number of courses of treatment, needed to achieve adequate BLL reduction.
Besunder et al., 1995	Retrospective case series. No control	Age 12 - 147 mo; 46 treated, 18 excluded n = 28	DMSA 30 mg/kg/d for 5 d, then 20 mg/kg/d for 14 d. Home inspection and abatement of lead and family counselling	80 d	26-49 mcg/dL (8 d before treatment)	Mean BLL post-treatment: 18d: -43 % (± 20.8%); 80 d: -31% (± 20.2%) Approx 80% of patients had a 20% or more change in BLL during follow-up (95% CI, 61, 92%).	ZnP post-treatment: 18d, -12% (± 21.7%); 80 d, -32% (± 21.9%). No significant adverse effects except neutropenia in one patient	Decrease in ZnP indicated a reduction in biochemical toxicity of lead.

Reference	Study design	Subjects	Intervention	Duration of FU	Baseline Blood lead level (BLL)	Blood Lead levels (BLL) during and after treatment	Other effects of DMSA	Summary
Besunder et al., 1997	Retrospective case review	Age 10-77 mo N=45	Grp 1 (n=23): BAL 300-500 mg/m ² /d for 3 d and EDTA 1000 – 1500 mg/m ² /d for 5 d, Grp 2 (n=22) EDTA 1000 – 1500 mg/m ² /d for 5 d, then either DMSA 30 mg/kg/d for 5 d (n=11). or DMSA 30 mg/kg/d for 5 d then DMSA 20 mg/kg/d for 14 d (n=11). The first dose of BAL or DMSA was given at least 4h before starting EDTA infusion.	33 d	BAL + EDTA 58 ± 14 DMSA+ EDTA 50 ± 10	BAL +EDTA: Post-treatment: 17±10; (-71.2% ± -19.8%) At follow-up -38.5% ± 16.7% DMSA + EDTA: Post-treatment: 10±4 (-79.9% ± 8.7%) At follow-up: -34.4 ± 22.2%) Within each group differences between pre-treatment, post-treatment and follow-up levels were significantly different, but the differences between the groups after 5 days treatment and at follow-up were not significantly different There was no significant difference between children receiving 5 days DMSA compared with those receiving 19 days DMSA.	Mean pre-treatment ZnP BAL + EDTA: 169 ±108 mcg/dL DMSA+ EDTA: 116 ±99 (p=0.03)	The blood lead concentrations were significantly lower than pre-treatment values in both groups but the percentage reduction from pre-treatment did not differ between the groups.
Chisolm, 2000	Open label case series	Age 12-65 mo N=59	DMSA 1050 mg/m ² /d for 5 d, then 700 mg/m ² /d for 21-23 d Relocation to lead-safe housing	21 d	25-70 mcg/dL	Mean BLL post-treatment: <35% of pre-treatment value. Nearly all the decrease occurred during day 1-5 of therapy; From day 7 to day 23 there was no substantial decrease. 2-3 wks post-treatment rebounded to 58% of pre-treatment value	During 5 days post-treatment urine lead increased 6-10 fold. In 6 children 6 hourly lead/creatinine ratios at weekly intervals from day 7 to day 23 showed continuing diuresis of lead There was no increase in excretion of Zn or Cu. ALA-D activity mirrored the change in BLL.	There was no constant ratio between amount of lead estimated to be removed from the blood pool and amount found in the urine.

Reference	Study design	Subjects	Intervention	Duration of FU	Baseline Blood lead level (BLL)	Blood Lead levels (BLL) during and after treatment	Other effects of DMSA	Summary
Graziano et al., 1992		Age 1-10 years (n=23)	<p>Study 1 Grp 1 (N=4): EDTA 1000/mg/m²/d for 5 d Grp2 (n=7): DMSA 1050 mg/m²/d for 5 d Grp 3 (n=6) DMSA 1050 mg/m²/d for 5 d, then 350 mg/m²/d for 14 d Grp 4 (n=6) DMSA 1050 mg/m²/d for 5 d then 700 mg/m²/d for 14 d.</p> <p>Study 2 Grp 1 (n=2) EDTA 1000 mg/m²/d for 5 d and BAL 300 mg/m²/d for 3 d Grp 2 Grp 2 DMSA 1050 mg/m²/d for 5 d</p> <p>Lead hazard removal from homes</p>		<p>Study 1 55-69 mcg/dL</p> <p>Study 2 70-77 mcg/dL</p>	<p>Mean BLL</p> <p>Study 1 After 5 d, Grp 1 mean BLL = 29.8 mcg/dL (-45%) Grp 2, 3 and 4, mean BLL = 20.5 (-61%) (p<0.0007 for difference between groups)</p> <p>8 d post-treatment (day 13) mean BLL as percentage of pre-treatment value Grp 1 89% Grp 2 73 % Grp 3 66% Grp 4 50% No significant difference between groups.</p> <p>Ater 34d, Grp 4 mean BLL = 76.7% post-treatment value.</p> <p>Study 2 Comparable decline in BLL for both groups, but lowest point occurred more quickly in Grp 1</p>	<p>After 1 day, mean urinary excretion in groups 2, 3 & 4 = 430 mcg lead/d.</p> <p>Mean total lead eliminated during days 1-5 = 1.29 mg lead.</p> <p>ALA-D activity in Study 1 Grp 1 fell rapidly by day 13. Grp 2 and 3 activity fell by day 13 and remained low Grp 4 activity remained relatively high</p> <p>Increase in urinary zinc in groups treated with EDTA = 6.6 fold compared with groups treated with DMSA = 1.6 fold</p> <p>Urinary calcium excretion increased by nearly two-fold in all groups.</p>	DMSA was more effective than EDTA at restoring metabolic activity to the haem pathway.
O'Connor & Rich, 1999	Randomized, double blind, placebo controlled trial	Age 2.5-5y N=39. Treatment group N=19 Control grp N=20	<p>Children <15kg: DMSA 100 mg t.i.d. for 5 d, then 100 mg b.i.d. for 14 d</p> <p>Children>15 kg: DMSA 200 mg t.i.d. for 5 d then 200 mg b.i.d. for 14 d</p> <p>Domestic cleaning and repair undertaken in 58% of homes in treated group and 60% of homes in placebo group (difference not significant).</p>	6 mo	<p>30-45 mcg/dL</p> <p>DMSA group: mean = 34.9 ± 4.7 mcg/dL;</p> <p>Placebo group mean = 33 ± 6.2 mcg/dL</p>	<p>At 1 mo DMSA group (N=14) mean BLL = 27.4 ± 7.5 mcg/d (approx 20-25% decrease)</p> <p>Placebo group (N=15) mean BLL = 33.2 ± 10.3 mcg/dL</p> <p>At 6 mo DMSA group (N=17) mean BLL = 28.8 ± 6.4 mcg/d Placebo group (N=20) mean BLL = 25.1 ± 6.8 mcg/dL</p> <p>There was no significant difference in reduction of BLL between groups at 1 month or 6 months.</p>	<p>There was no statistical difference in mean corpuscular volume and haemoglobin concentration at study entry between placebo and treatment groups</p> <p>There was no difference in mean ZnP between the groups at any time during the study.</p> <p>Mean initial ZnP: DMSA group = 71.6 ± 37.2 g/dL Placebo group = 59.8 ± 31.6 g/dL</p> <p>Mean ZnP at 1 mo: DMSA group = 69.6 ± 27.8 g/dL Placebo group = 66.9 ± 30.9 g/dL</p> <p>Mean ZnP at 6 mo: DMSA group = 48.8 ± 28.4 g/dL Placebo group = 39.7 ± 18.0 g/dL</p>	

Reference	Study design	Subjects	Intervention	Duration of FU	Baseline Blood lead level (BLL)	Blood Lead levels (BLL) during and after treatment	Other effects of DMSA	Summary
Farrar et al., 1999	Randomized, but not blinded. No placebo	14 enrolled, 3 excluded n=11. Grp 1, mean age = 25 mo ± 6 Grp 2 mean age = 31 mo ± 11	Grp 1 (n=7) DMSA 1050 mg/m ² /day for 5 d then 700 mg/m ² /day for 14 d Grp 2. (n=4) DMSA 1050 mg/m ² /day for 5 d, repeated after a 7 d break	6 w	27– 41 mcg/dL Grp 1 mean = 33 ± 4 mcg/dL Grp 2 mean = 33 ± 6 mcg/dL	4-6 w post-treatment Grp 1 mean BLL = 27 ± 6 (81% ± 8% of pre-treatment value). (p=0.0005) Grp 2 mean BLL = 23 ± 4 mcg/dL (69% ± 14 % of pre-treatment value). (p=0.045) No significant difference between treatments (p=0.1)	.	Post-treatment BLL was measured after rebound would have occurred. Both dosing regimes resulted in a similar reduction.
TLC Trial Group, 2000	Randomized, placebo-controlled, double blind multi-centre trial	Age 12-33 mo N = 780 (1854 evaluated)	Grp 1 (n=396) 1050 mg/m ² /d for 7 d then 700 mg/m ² /d for 19 d, repeated up to 3 times. Placebo group (n=384) Homes cleaned or children moved to lead safe houses	12 mo	20-44 mcg/dL	BLL decreased gradually in placebo- treated children, and abruptly in DMSA-treated children followed by a rebound. At 7 wk after start of treatment BLL in DMSA group = 72% of baseline, and in the placebo group BLL = 88% of baseline. During 6 mo after start of treatment, the mean BLL was 4.5 mcg/dL lower in the DMSA group than in the placebo group (95% confidence intervals 3.7-5.3 mcg/dL). During the 12 mo after start of treatment, mean BLL was 2.7 mcg/dL lower in the DMSA group than in the placebo group (95% CI 1.9-3.5 mcg/dL lower.	Not measured	More rashes on the scalp in treated group but no statistically significant excess of any adverse event in the DMSA treated group, for blood counts and liver function tests.
Rogan et al., 2001	Randomized, placebo-controlled, double blind multi-centre trial	As above	As above	36 mo	As above		Intelligence quotient of DMSA-treated children was 1 point lower than placebo-treated children, and behaviour rated as slightly worse by a parent. Treated children had slightly better scores on developmental neuropsychological assessment but differences were not statistically significant.	DMSA did not improve cognition, behaviour or neuropsychological function.

Reference	Study design	Subjects	Intervention	Duration of FU	Baseline Blood lead level (BLL)	Blood Lead levels (BLL) during and after treatment	Other effects of DMSA	Summary
Dietrich et al., 2004	Randomized, placebo-controlled, double blind multi-centre trial	As above	As above	60 mo until about 7 y old	As above		At 7 years of age DMSA was not associated with cognitive, behavioural or neuromotor improvements in children with blood lead levels between 20 and 44 mcg/dL. Scores for attention and executive functions were worse for DMSA-treated children.	DMSA did not improve cognition, behaviour or neuropsychological function.
Peterson et al., 2004	Randomized, placebo-controlled, double blind multi-centre trial	As above	As above	34 mo	As above		Difference in mean change in height between children on DMSA compared with children on placebo From baseline to 9 mo, was -0.27 cm [95% CI -0.42 to -0.11],. During 34 mo of follow-up was -0.43 cm [95% CI, -0.77 to-0.09) Similar differences in weight gain were not statistically significant.	DMSA has no beneficial effect on growth and may possibly have a detrimental effect.
Battachrya et al., 2007	Randomized, placebo-controlled, double blind multi-centre trial	Sub-group from TLC study: N= 161 Age at least 5 years	Subgroups of children, at least 5 years old, who had completed DMSA or placebo therapy. Placebo group N= 81 DMSA group n=80.		As above		Some improvement in postural balance implying beneficial effects of DMSA therapy to the proprioceptive system. DMSA did not improving vestibular functionality The DMSA-treated group performed better in locomotion and gait tests than the placebo group.	

Table 4 Case reports of chronic lead intoxication in children treated with succimer

Reference	Age	Source	Baseline blood lead mcg/dL	Signs & symptoms	Treatment	blood Pb after treatment	Outcome
Smith et al., 2007	3 y	Pica; opaque material in gastrointestinal tract and appendix	644	Vomiting, abdominal pain, constipation, weakness, ataxia; raised free erythrocyte protoporphyrin	Parenteral BAL and EDTA for 5 d. Day 6: appendectomy. Day 6 1 st course DMSA followed by second course after 3 mo	15 mcg/dL	No evidence of developmental delay at 2 y
Dargan et al., 2001	13 mo	Pica; paint chips visible on radiograph throughout gastrointestinal tract	244	Vomiting, lethargy, convulsion, anaemia	WBI for 3d. EDTA i.v. for 10 d Followed by DMSA 7 courses over 16 mo .	30 mcg/dL at 16 mo	Normal physical and neurological development at 16 mo
Woolf et al., 2008	1y	Contaminated ethnic remedy daily for 7 mo from birth	61	Asymptomatic. Metaphyseal sclerosis, anaemia, raised zinc-chelated protoporphyrin	EDTA iv for 5 d, 5 courses DMSA over 6 mo	23 mcg/dL after 6 mo	No info beyond 6 mo
Chin & Charlton, 2004	"Middle school"	Pica; no radio-opaque material in gastrointestinal tract.	173	Asymptomatic; metaphyseal sclerosis, neurodevelopmental delay	Parenteral EDTA and BAL with oral DMSA; then 4 courses of DMSA over 6 mo	39 mcg/dL	No info beyond 6 mo
Gordon et al., 1998	3 y	Pica; paint chips visible on radiograph throughout gastrointestinal tract	550	abdominal pain, vomiting, signs of encephalopathy	WBI for 3 days Parenteral BAL and EDTA 50 for 5 days Once WBI complete, after 3 days, oral DMSA for 20 days	69 mcg/dL at day 23.	No info beyond 23 days.

Table 5 Cases of neonates treated with succimer (DMSA) for lead poisoning due to intrauterine exposure

Reference	Age	Source	Baseline blood lead	Signs & symptoms	Treatment	Peak blood Pb	blood Pb after treatment	Outcome
Tait et al., 2002	Pre-term 24 wks gestation	Maternal use of ethnic remedy containing Pb for 9 years	cord blood = 7.6 micromol/L.	At birth: placid, areflexic, alveolar hypoventilation, no gag reflex, bilateral diaphragmatic palsy. Increase in bone density	Day 1-7: BAL and EDTA day 10-day 30: DMSA, 30 mg/kg/day and again at day 53 5 courses EDTA over 5 mo	11.8 micromol/L	At 5 months corrected age: 0.95 micromol/L	At 5 mo corrected age: neurodevelopmental delay of 2 mo.
Horowitz et al., 2001	Neonate 37 wk 2 d gestation	Source of mother's exposure not known	4 d postpartum 74.7 mcg/dL	Not stated	Day 4-7 BAL and EDTA Day 9-day 28: DMSA Day 77 repeat DMSA.	74.7 mcg/dL	at 196 d(6.5 mo) = 30.5 mcg/dL	Neurologically normal at 6.5 mo
Erdem et al., 2004	Neonate born at term	Mother ingested lead glazed pottery	age 5 mo: 28 mcg/dL	none	At 5 mo 1 course DMSA	28	7 days after treatment: 24 mcg/dL 15 mo after treatment: 9 mcg/dL	Normal growth and development
Powell et al., 2006	Neonate born at 25 weeks	Mother sniffed petrol and had since childhood resulting in encephalopathy and chronic neurological deficits	Cord blood = 3.98 micromol/L	At birth: sleepy, poor sucking, Day 6: temperature instability, dehydration, metabolic acidosis, diarrhoea, no signs of encephalopathy	Day 11– day 20: DMSA.	3.98 micromol/L	After treatment and at 9 mo: < 2 micromol/L	1 yr developmental delay; possible continued exposure

Shamshirzaz et al., 2009	Neonate born at term	Indian herbal preparations, one contained 3,000 mcg/dL lead.	Mother's blood 102 mcg/dL at end of 2 nd trimester; At delivery maternal blood = 35 mcg/dL Cord blood = 54.5 mcg/dL, neonatal blood = 59.8 mcg/dL	Neonate: hypospadias but no other physical abnormalities.	Mother DMSA 500 mg twice daily at beginning of 3 rd trimester' the 3 more courses of DMSA in the first 6 months post-partum. Neonate on day 2 of life DMSA 25 mg orally 3 times days for 5 d, then 25 mg twice daily for 14 d.	102 mcg/dL	normal development at 6 months
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Table 6 Childhood poisoning due to acute ingestion of lead treated with succimer

	age	Source	Delay ingestion to admission	Baseline blood lead mcg/dL	Signs & symptoms	Treatment	Highest blood lead mcg/dL	blood Pb after treatment	Long-term outcome
Dietrich et al., 2000	21 mo	dust from ceiling collapse, History of pica treated with DMSA	< 24h	142	Abdominal pain, loose stools, motor incoordination	Parenteral BAL for 3d then EDTA for 4 d, then DMSA 200mg daily for 24 days. Then another course DMSA after 12 mo	142	42 mcg/dL at 12 mo	At 4 y developmental deficits, behavioural and motor problems
Esernio-Jenssen et al., 1996	3y	Object with 94% lead	4-6 wks	179	abdominal pain vomiting, anaemia	Endoscopy, parenteral BAL and EDTA, intestinal lavage, repeat course BAL and EDTA, followed by "several" courses of DMSA.	179	Not stated	No information
VanArsdale et al., 2004	4y	Object 38.8% Pb	3 wks	123	Abdominal pain, protracted vomiting, decreased urine output, diminished bowel sounds, irritability, weight loss, raised zinc protoporphyrin	Endoscopy. Parenteral BAL and EDTA, followed by DMSA. One repeat course of EDTA and 2 more courses of DMSA	123	< 40 mcg/dL after 2 mo	No information
Mowad et al., 1998	8y	20 fishing sinkers	<1 day	53	None	WBI, colonoscopy, DMSA 1 course	53	3 mcg/dL after 1 mo, 14 mcg/dL after 1 y	No information
Clifton et al., 2002	21 mo	Lead pellets	12 h	47	None	WBI, endoscopy, colonoscopy, DMSA 1 course	48	16 mcg/dL after <1 mo	No information
McKinney et al., 2000	5.5	Lead pellets; and history of pica	13 h	57	Vomiting and Abdominal pain. No biochemical evidence of pre-existing lead poisoning	WBI, and high fibre diet, DMSA 1 course 2273 mcg Pb excreted in the urine during 24 hrs after start of treatment	79	25 mcg/dL at 6 mo	Already had mild developmental and language delays.
St Clair & Benjamin, 2008	8	8 fishing sinkers, possible history of pica	Several days	55	Abdominal pain, nausea, headache. History of ADHD	WBI, DMSA 1 course	55	12 mcg/dL at 462 days	No information

Table 7 Adverse reactions to succimer reported in clinical studies

Ref	Study type	Total Number in study	Number with adverse reactions	Dose of DMSA	Adverse reactions	Length of follow-up
Graziano et al., 1988	Randomized study	21	3	DMSA 1 350 mg/m ² /day for 5 d Or 700 g/m ² /day for 5 d Or 1050 g/m ² /day for 5 days CaNa ₂ EDTA 1000 mg/m ² /day iv for 5 days	One episode of vomiting in 2 children who also received penicillin; and in one child who received high dose.	20 d
Chisolm, 1990	Case series	4		DMSA 1050 mg/m ² /day for 5 d then 350 mg/m ² /day for 5 days. 1 child given a 2 nd course	None reported	
Liebelt et al., 1994	Case series	30	17	DMSA 30 mg/kg/d 5 d, then 20 mg/kg/d for 14 d.	DMSA prematurely discontinued in one patient because of vomiting and diarrhoea. Mild elevation in hepatic aminotransferase in 17 patients. Mean pretreatment ALT: 22 +/- 4mU/ml (ref range 0-22 mU/ml). During or post treatment peak ALT: 26 +/- 3mU/ml (p=0.001).	
Besunder et al., 1995	Retrospective case series	28	1	DMSA 30 mg/kg/d 5 d, then 20 mg/kg/d for 14 d.	No significant adverse effects except neutropenia in one patient (absolute neutrophil count 0.752 x 10 ⁹ /L)	80 d
Besunder et al., 1997	Retrospective case review	45	4	BAL and EDTA (n=23) or DMSA and EDTA (n=22) DMSA 30 mg/kg/d or 1050 mg/d ² /d for 5 d, then 20mg/kg/d or 700 mg/m ² /d for 14 d	alanine aminotransferase increased significantly after 5 days in patients receiving BAL +EDTA but not in those receiving DMSA + EDTA and vomiting during therapy were more frequent in BAL EDTA group compared with DMSA+EDTA group. 4/22 children given DMSA vomited, one child had more than one episode of emesis.	33d
Chisolm, 2000	Open label case series	59	4	DMSA 1050 mg/m ² /d for 5 d, then 700 mg/m ² / for 21-23 d	No adverse reactions. Rising serum alkaline phosphatase activity in 2 children; transient mild depression of serum ceruloplasmin in 1 child which normalized during continued therapy. Eosinophilia in one child	
Graziano et al., 1992		23	1	Study 1 Grp 1 (N=4): EDTA 1000/mg/m ² /d for 5 d Grp2 (n=7): DMSA 1050 mg/m ² /d for 5 d Grp 3 (n=6) DMSA 1050 mg/m ² /d for 5 d, then 350 mg/m ² /d for 14 d Grp 4 (n=6) DMSA 1050 mg/m ² /d for 5 d then 700 mg/m ² /d for 14 d.	Study 1: Slight rise in aspartate aminotransferase and alanine aminotransferase in one child. Not clinically significant and rapidly reversible.	
O'Connor & Rich, 1999	Randomized, double blind, placebo controlled	39		DMSA Children <15kg: 100 mg tid for 5 d, then 100 mg bid for 14 d DMSA Children >15 kg: 200 mg tid for 5 d then 200 mg bid for 14	None	6 mo

Ref	Study type	Total Number in study	Number with adverse reactions	Dose of DMSA	Adverse reactions	Length of follow-up
TLC Trial, 2000	Randomized, double blind with placebo	780		up to three 26 day courses 1050 mg/M2/day for 7 days then 700 mg/M2/day for 19 days	No statistically significant excess of any adverse event in the succimer treated group, for blood counts and liver function tests. More rashes on the scalp in treated group than the placebo group (3.2% v 1.3%, difference 2.2% 95% CI, -0.5 to 6.1%).	
Farrar et al., 1999	Randomized, but not blinded. No placebo	11	1	Grp 1 DMSA 1050 mg/m ² /day for 5 d then 700 mg/m ² /day for 14 d Grp 2. DMSA 1050 mg/m ² /day for 5 d, repeated after a 7 d break	No clinical adverse effects. One child in group 1 had increased serum creatinine (0.4-1.1 mg/dL) during the study, and follow up serum creatinine 0.8 mg/dL.	6 w