See under Atropine Sulfate, p.1221, for details of dosages. As soon as the effects of atropine become apparent, 1 to 2 g of *pralidoxime* chloride, iodide, or mesilate, should be given intramuscularly or intravenously and repeated after 1 hour and then every 8 to 12 hours if necessary. Alternatively, the *BNF* recommends pralidoxime chloride in an initial dose of 30 mg/kg given by intravenous infusion over 20 minutes, or by intravenous injection over at least 5 minutes if pulmonary oedema is present or infusion cannot be given; the initial dose is then followed by intravenous infusion at a rate of 8 mg/kg per hour. In some countries, auto-injectors are available for emergency use containing pralidoxime, either alone or combined with atropine and/or avizafone, a prodrug of diazepam. Typical doses are 600 mg of pralidoxime chloride or 500 mg of pralidoxime mesilate given intramuscularly up to 3 times, depending on symptoms. Another alternative, in severe poisoning, is the use of a continuous infusion of 200 to 500 mg/hour, titrated against response. A maximum dose of 12 g in 24 hours has been suggested. The dose of pralidoxime may need to be reduced in patients with renal impairment.

Treatment should preferably be monitored by the determination of blood-cholinesterase concentrations and clinical symptoms. Patients should be closely observed for at least 24 hours after resolution of symptoms.

Other oximes with cholinesterase-reactivating properties that have been used similarly include asoxime chloride (p.1438), obidoxime chloride (p.1456), and trimedoxime bromide (p.1467).

Organophosphorus poisoning. Oximes such as pralidoxime are widely used in poisoning with organophosphate *pesticides*. Although benefit has been shown in *animal* studies, reviews[1,2] have pointed out that there is little good evidence from human studies to support their use and that randomised controlled studies are needed to confirm their efficacy and safety, as well as the optimum regimens to use. A randomised study[3] in patients with moderately severe poisoning with organophosphorus pesticides found that a continuous infusion of pralidoxime iodide 1 g/hour for 48 hours was more effective than a dose of 1 g every 4 hours.

Cholinesterase reactivators such as the oximes have also been used for poisoning with organophosphate *nerve agents*. Studies in *animals* have suggested that the efficacy of the different oximes depends on the organophosphate involved; asoxime (p.1438) and HLö-7 may be more effective than pralidoxime or obidoxime for poisoning with nerve agents, particularly for soman poisoning.[4]

1. Eyer P. The role of oximes in the management of organophosphorus pesticide poisoning. *Toxicol Rev* 2003; **22:** 165–90.
2. Buckley NA, *et al*. Oximes for acute organophosphate pesticide poisoning. Available in the Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 04/10/05).
3. Pawar KS, *et al*. Continuous pralidoxime infusion versus repeated bolus injection to treat organophosphorus pesticide poisoning: a randomised controlled trial. *Lancet* 2006; **368:** 2136–41.
4. Kassa J. Review of oximes in the antidotal treatment of poisoning by organophosphorus nerve agents. *J Toxicol Clin Toxicol* 2002; **40:** 803–16.

Preparations

USP 31: Pralidoxime Chloride for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Contrathion; ***Braz.:*** Contrathion; ***Canad.:*** Protopam; ***Fr.:*** Contrathion; ***Gr.:*** Contrathion; ***India:*** Neopam; ***Ital.:*** Contrathion; ***Malaysia:*** Pampara; ***NZ:*** Pam†; ***Turk.:*** Contrathion; ***USA:*** Protopam.

Multi-ingredient: ***UK:*** Nerve Agent Antidote L4A1; ***USA:*** DuoDote.

Protamine *(rINNM)*

Protamina; Protaminum.

Протамин
CAS — 9012-00-4.
ATC — V03AB14.
ATC Vet — QV03AB14.

Protamine Hydrochloride *(BANM, rINNM)*

Cloridrato de Protamina; Hidrocloruro de protamina; Protaminihydrokloridi; Protamine, chlorhydrate de; Protamin-hidroklorid; Protamin-hydrochlorid; Protaminhydroklorid; Protamini hydrochloridum; Protamino hidrochloridas.

Протамина Гидрохлорид
ATC — V03AB14.
ATC Vet — QV03AB14.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Protamine Hydrochloride). A mixture of the hydrochlorides of basic peptides prepared from the sperm or roe of suitable species of fish, usually from the families Clupeidae or Salmonidae. A white or almost white hygroscopic powder. Soluble in water; practically insoluble in alcohol. Store in airtight containers.

Protamine Sulfate *(rINN)*

Protamiinisulfaatti; Protamine, sulfate de; Protamine Sulphate *(BAN)*; Protamini sulfas; Protamino sulfatas; Protaminsulfat; Protamin-sulfát; Protamin-szulfát; Protaminy siarczan; Sulfato de protamina.

Протамина Сульфат
CAS — 9009-65-8.
ATC — V03AB14.
ATC Vet — QV03AB14.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.
Ph. Eur. 6.2 (Protamine Sulphate). A mixture of the sulfates of basic peptides prepared from the sperm or roe of suitable species of fish, usually from the families Clupeidae or Salmonidae. A white or almost white hygroscopic powder. Sparingly soluble in water; practically insoluble in alcohol. Store in airtight containers.
USP 31 (Protamine Sulfate). A purified mixture of simple protein principles obtained from the sperm or testes of suitable species of fish. Store at 2° to 8° in airtight containers.

Adverse Effects and Precautions

Intravenous injections of protamine, particularly if given rapidly, may cause hypotension, bradycardia, and dyspnoea. A sensation of warmth, transitory flushing, nausea and vomiting, and lassitude may also occur.

Hypersensitivity reactions can occur; patients at risk include diabetics who have received protamine-insulin preparations, those who have previously received protamine (including those who have undergone procedures such as coronary angioplasty or cardiopulmonary bypass surgery where protamine is frequently used), and those allergic to fish. Protamine is a constituent of sperm and men who are infertile or who have had a vasectomy may also be at increased risk since they may have antibodies to protamine. Anaphylactoid reactions have been reported.

Protamine has an anticoagulant effect when given in the absence of heparin.

When repeated doses of protamine are used to neutralise large doses of heparin, rebound bleeding which responds to further doses of protamine, may occur. Clotting parameters should be closely monitored in patients receiving such prolonged therapy.

◊ In a report on 4 patients given protamine sulfate after cardiac surgery to neutralise the effect of heparin, severe adverse reactions including marked hypotension, vascular collapse, and pulmonary oedema were described.[1] Previous reports of similar reactions to protamine were reviewed. A total of 17 patients had immediate anaphylactic reactions; in 1 patient a complement-dependent IgG antibody-mediated reaction had been demonstrated and 3 patients tested for allergy to protamine had positive skin tests. In 15 of these 17 patients there was evidence of previous exposure to protamine; those with a high risk of sensitisation included leucapheresis donors who had received the drug, diabetics using insulin containing protamine, and patients with fish allergy. Suspected reactions to protamine occurred in a further 10 patients after cardiac surgery. However, these reactions were characterised by severe vascular damage, manifested as noncardiogenic pulmonary oedema or persistent hypotension, and onset was delayed for 30 minutes to several hours. Evidence suggested that these reactions were not antibody mediated; only 2 of 7 evaluable patients had previous exposure. All patients required aggressive therapy.

In a review of the toxicity of protamine,[2] adverse cardiovascular responses were considered to be of 3 types: transient hypotension related to rapid drug administration, occasional anaphylactoid responses, and rarely, catastrophic pulmonary vasoconstriction.

1. Holland CL, *et al*. Adverse reactions to protamine sulfate following cardiac surgery. *Clin Cardiol* 1984; **7:** 157–62.
2. Horrow JC. Protamine: a review of its toxicity. *Anesth Analg* 1985; **64:** 348–61.

Uses and Administration

Protamine is a basic protein that combines with heparin to form a stable inactive complex. Protamine is used to neutralise the anticoagulant action of heparin in the treatment of haemorrhage resulting from severe heparin or low-molecular-weight heparin overdosage. It is also used to neutralise the effect of heparin given before surgery and during extracorporeal circulation as in dialysis or cardiac surgery. Protamine is used in some insulin preparations to prolong the effects of insulin. Protamine is usually given as the sulfate, although the hydrochloride may also be used.

Protamine sulfate is given by slow intravenous injection over a period of about 10 minutes. The dose is dependent on the amount of heparin to be neutralised and ideally should be titrated against the coagulability of the patient's blood. Protamine has weak anticoagulating properties and if given in gross excess its anticoagulant action could be significant. As heparin is being continuously excreted the dose should be reduced if more than 15 minutes have elapsed since intravenous heparin injection; for example, if protamine sulfate is given 30 minutes after heparin the dose may be reduced to about one-half. Alternative regimens may be necessary if heparin has been given subcutaneously or by continuous intravenous infusion. Not more than 50 mg of protamine sulfate should be injected for any one dose; patients should be carefully monitored as further doses may be required.

For *unfractionated heparin* the Ph. Eur. 6.2 specifies that 1 mg of either protamine hydrochloride or protamine sulfate precipitates not less than 100 units of heparin, assayed against a specific reference batch of heparin sodium. One UK manufacturer has stated that each mg of protamine sulfate will usually neutralise the anticoagulant effect of at least 80 international units of heparin (lung) or at least 100 international units of heparin (mucous). In the USA stated values are that each mg of protamine sulfate neutralises about 90 USP units of heparin (lung) or about 115 USP units of heparin (mucous).

For *low-molecular-weight heparins*, protamine neutralises the anti-thrombin activity but only partially neutralises the anti-factor-Xa effect; 1 mg of protamine is stated to inhibit the effects of:

- 71 units of bemiparin sodium
- 80 to 120 units of certoparin sodium
- 100 units of dalteparin sodium
- 1 mg (100 units) of enoxaparin sodium
- 82 units of reviparin sodium
- 100 units of tinzaparin sodium

Haemorrhagic disorders. Endogenous production of heparin-like substances may, rarely, be responsible for some bleeding disorders. It has been suggested that protamine could be useful as a diagnostic aid *in vitro* and could be given intravenously for transient control of bleeding in such patients.[1,2]

1. Tefferi A, *et al*. Circulating heparin-like anticoagulants: report of five consecutive cases and a review. *Am J Med* 1990; **88:** 184–8.
2. Bayly PJM, Thick M. Reversal of post-reperfusion coagulopathy by protamine sulphate in orthotopic liver transplantation. *Br J Anaesth* 1994; **73:** 840–2.

Preparations

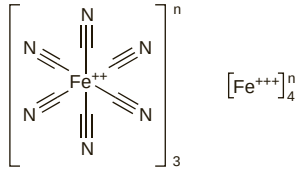
BP 2008: Protamine Sulphate Injection;
USP 31: Protamine Sulfate for Injection; Protamine Sulfate Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Denpru; ***Hong Kong:*** Prosulf; ***India:*** Prota; ***Israel:*** Prosulf; ***UK:*** Prosulf.

Prussian Blue

Azul de Prusia; Berlin Blue; CI Pigment Blue 27; Colour Index No. 77510; Ferric Ferrocyanide; Ferric Hexacyanoferrate (II); Insoluble Prussian Blue; Prussian Blue Insoluble *(USAN)*.

$Fe_4[Fe(CN)_6]_3$ = 859.2.
CAS — 14038-43-8 (insoluble Prussian blue); 12240-15-2 (soluble Prussian blue); 25869-00-5 (soluble Prussian blue).
ATC — V03AB31.
ATC Vet — QV03AB31.



NOTE. Prussian blue is available in a number of forms and it is not always clear from the literature which form is being referred to. CI Pigment Blue 27 has been used for both insoluble ferric hexacyanoferrate (II) (Colour Index No. 77510) and the soluble potassium, sodium, or ammonium ferric hexacyanoferrate (II) salts

Profile

Prussian blue is used in the treatment of thallium poisoning (see p.2400) and for known or suspected internal contamination with radiocaesium. When given orally it forms a non-absorbable complex with thallium or caesium in the gastrointestinal tract and increases their elimination from the body; it may also bind other elements and patients should be monitored for electrolyte imbalances. Prussian blue may cause constipation and a fibre-based laxative is recommended.

The usual dose of Prussian blue is 250 to 300 mg/kg daily, or up to 20 g daily for an adult, given in divided doses either by mouth or by nasogastric or duodenal tube. In the USA, a lower dose of 3 g three times daily for adults, or 1 g three times daily for children, has been recommended. For thallium poisoning, treatment should continue until the urinary excretion of thallium falls to 500 micrograms or less per 24 hours, the urine or blood concentration is less than 10 micrograms/L, or no thallium can be detected in the faeces. For radiocaesium contamination, a minimum of 30 days treatment should be given.

◊ References.

1. Thompson DF, Church CO. Prussian blue for treatment of radiocesium poisoning. *Pharmacotherapy* 2001; **21:** 1364–7.
2. Hoffman RS. Thallium toxicity and the role of Prussian blue in therapy. *Toxicol Rev* 2003; **22:** 29–40.
3. Thompson DF, Callen ED. Soluble or insoluble Prussian blue for radiocesium and thallium poisoning? *Ann Pharmacother* 2004; **38:** 1509–14.

Preparations

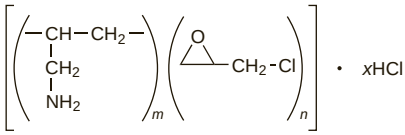
Proprietary Preparations (details are given in Part 3)
Cz.: Radiogardase-Cs; ***Ger.:*** Antidotum Thallii-Heyl; Radiogardase-Cs; ***USA:*** Radiogardase.

Sevelamer *(BAN, rINN)*

Sevelameeri; Sévélamer; Sevelámero; Sevelamerum. Allylamine polymer with 1-chloro-2,3-epoxypropane.

Севеламер

CAS — 52757-95-6.
ATC — V03AE02.
ATC Vet — QV03AE02.



Sevelamer Carbonate *(BANM, USAN, rINNM)*

Carbonato de sevelámero; GT-335-012; Sévélamer Carbonate; Sevelameri Carbonas. Allylamine polymer with 1-chloro-2,3-epoxypropane carbonate.

Севеламера Карбонат

CAS — 845273-93-0.
ATC — V03AE02.
ATC Vet — QV03AE02.

Sevelamer Hydrochloride *(BANM, USAN, rINNM)*

GT16-026A; Hidrocloruro de sevelámero; Sévélamer, Chlorhydrate de; Sevelameri Hydrochloridum. Allylamine polymer with 1-chloro-2,3-epoxypropane hydrochloride.

Севеламера Гидрохлорид

CAS — 182683-00-7.
ATC — V03AE02.
ATC Vet — QV03AE02.

NOTE. The name sevelamer has been used for both sevelamer and sevelamer hydrochloride.

Adverse Effects and Precautions

The most common adverse effects associated with sevelamer are diarrhoea, nausea and vomiting, constipation, headache, cough and other respiratory symptoms, dizziness, hypotension or hypertension, peripheral oedema, pain, and fever. Flatulence, pharyngitis, skin rashes, and pruritus have also occurred; intestinal obstruction and ileus have been reported.

Sevelamer is contra-indicated in patients with hypophosphataemia and in bowel obstruction. Patients with renal impairment may develop hypocalcaemia or hypercalcaemia, and serum-calcium concentrations should be monitored. Serum-chloride concentrations should also be monitored during treatment with sevelamer.

Interactions

Sevelamer has been reported to reduce the bioavailability of ciprofloxacin and should not be taken at the same time. It may also affect the bioavailability of other drugs and should be given at least 3 hours before or 1 hour after drugs for which a reduction in bioavailability could be clinically significant.

Uses and Administration

Sevelamer is a phosphate binder used for hyperphosphataemia in patients with chronic renal failure on haemodialysis. It is given orally as either the carbonate or the hydrochloride. The initial dose is 0.8 to 1.6 g of sevelamer carbonate or sevelamer hydrochloride three times daily with each meal, depending on the severity of hyperphosphataemia. Doses should then be adjusted according to plasma-phosphate concentrations; the usual maintenance dose is from 0.8 to 4 g with each meal.

◊ References.

1. Burke SK. Renagel : reducing serum phosphorus in haemodialysis patients. *Hosp Med* 2000; **61:** 622–7.
2. Qunibi WY, *et al.* Treatment of hyperphosphatemia in hemodialysis patients: The Calcium Acetate Renagel Evaluation (CARE Study). *Kidney Int* 2004; **65:** 1914–26.
3. Almirall J, *et al.* Safety and efficacy of sevelamer in the treatment of uncontrolled hyperphosphataemia of haemodialysis patients. *Nephron Clin Pract* 2004; **97:** c17–c22.
4. Duggal A, *et al.* Novel dosage forms and regimens for sevelamer-based phosphate binders. *J Ren Nutr* 2006; **16:** 248–52.
5. Fischer D, *et al.* Results of a randomized crossover study comparing once-daily and thrice-daily sevelamer dosing. *Am J Kidney Dis* 2006; **48:** 437–44.
6. Suki WN, *et al.* Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. *Kidney Int* 2007; **72:** 1130–7.
7. Tonelli M, *et al.* Alberta Kidney Disease Network. Systematic review of the clinical efficacy and safety of sevelamer in dialysis patients. *Nephrol Dial Transplant* 2007; **22:** 2856–66.
8. Ramos R, *et al.* The Catalano–Balear Peritoneal Dialysis Study Group. Sevelamer hydrochloride in peritoneal dialysis patients: results of a multicenter cross-sectional study. *Perit Dial Int* 2007; **27:** 697–701.
9. Delmez J, *et al.* A randomized, double-blind, crossover design study of sevelamer hydrochloride and sevelamer carbonate in patients on hemodialysis. *Clin Nephrol* 2007; **68:** 386–91.
10. Suki WN. Dialysis Clinical Outcomes Revisited Investigators. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients: results of a randomized clinical trial. *J Ren Nutr* 2008; **18:** 91–8.
11. Goldsmith DR, *et al.* Sevelamer hydrochloride: a review of its use for hyperphosphataemia in patients with end-stage renal disease on haemodialysis. *Drugs* 2008; **68:** 85–104.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Renagel; ***Belg.:*** Renagel; ***Canad.:*** Renagel; ***Cz.:*** Renagel; ***Denm.:*** Renagel; ***Fin.:*** Renagel; ***Fr.:*** Renagel; ***Ger.:*** Renagel; ***Gr.:*** Renagel; ***Hong Kong:*** Renagel; ***Hung.:*** Renagel; ***Irl.:*** Renagel; ***Israel:*** Renagel; ***Ital.:*** Renagel; ***Jpn:*** Renagel; ***Neth.:*** Renagel; ***Norw.:*** Renagel; ***Pol.:*** Renagel; ***Port.:*** Renagel; ***Spain:*** Renagel; ***Swed.:*** Renagel; ***Switz.:*** Renagel; ***Turk.:*** Renagel; ***UK:*** Renagel; ***USA:*** Renagel; Renvela.

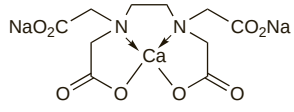
Sodium Calcium Edetate *(BAN, rINN)*

Calcioedetato de sodio; Calcium Disodium Edathamil; Calcium Disodium Edetate; Calcium Disodium Ethylenediaminetetra-acetate; Calcium Disodium Versenate; Calcium édétate de sodium; Calcium EDTA; Disodium Calcium Tetracemate; E385; Edetan sodno-vápenatý hydrát; Edetate Calcium Disodium *(USAN)*; Kalcium-nátrium-edetát; Natrii calcii edetas; Natrii Calcii Edetas Hydricus; Natrio-kalcio edetatas; Natriumkalciumedetat; Natriumkalsiumedetaatti; Sodium, calcium édétate de; Sodium Calciumedetate; Sodu wapnia edetynian; Sodyum Kalsiyum Edetat; Wapniowo-disodowy edetynian. The calcium chelate of disodium ethylenediaminetetra-acetate; Disodium[(ethylenedinitrilo)tetraacetato]calciate(2–) hydrate.

Натрия Кальция Эдетат

$C_{10}H_{12}CaN_2Na_2O_8.xH_2O$ = 374.3 (anhydrous).

CAS — 62-33-9 (anhydrous sodium calcium edetate); 23411-34-9 (sodium calcium edetate hydrate).



NOTE. Do not confuse with sodium edetate; see Inappropriate Administration under Sodium Edetate, p.1464.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 6.2 (Sodium Calcium Edetate). A white or almost white, hygroscopic, powder. Freely soluble in water; practically insoluble in alcohol. A 20% solution in water has a pH of 6.5 to 8.0. Store in airtight containers. Protect from light.

USP 31 (Edetate Calcium Disodium). White, slightly hygroscopic, odourless, crystalline powder or granules. Freely soluble in water. pH of a 20% solution in water is between 6.5 and 8.0. Store in airtight containers.

Adverse Effects

Sodium calcium edetate is nephrotoxic and may cause renal tubular necrosis. Nausea, diarrhoea, and abdominal cramp may also occur. Thrombophlebitis has followed intravenous infusion and may be related to the concentration of the injection. Pain at the intramuscular injection site has been reported. Other adverse effects that have been reported include fever, malaise, headache, myalgia, histamine-like responses such as sneezing, nasal congestion, and lachrymation, skin eruptions, transient hypotension, and ECG abnormalities.

Sodium calcium edetate chelates zinc within the body and zinc deficiency has been reported. Displacement of calcium from sodium calcium edetate may lead to hypercalcaemia.

Effects on the kidneys. Of 130 children with lead poisoning who received chelation therapy with sodium calcium edetate (25 mg/kg intramuscularly every 12 hours) and dimercaprol (3 mg/kg intramuscularly every 4 hours) for a total of 5 days, 21 developed clinical evidence of nephrotoxicity and in 4 severe oliguric acute renal failure began 1 or 2 days after chelation therapy was discontinued.[1] Nephrotoxicity was probably attributable to the use of sodium calcium edetate.

1. Moel DI, Kumar K. Reversible nephrotic reactions to a combined 2,3-dimercapto-l-propanol and calcium disodium ethylenediaminetetraacetic acid regimen in asymptomatic children with elevated blood lead levels. *Pediatrics* 1982; **70:** 259–62.

Precautions

Sodium calcium edetate should be used with caution, if at all, in patients with renal impairment. Daily urinalysis to monitor proteinuria and haematuria and regular monitoring of renal and hepatic function has been recommended.

Sodium calcium edetate can chelate several endogenous metals, including zinc, and may increase their excretion; therapy should be intermittent to prevent severe deficiency developing and monitoring of zinc levels may be required (see below).

Sodium calcium edetate should not be given orally in the treatment of lead poisoning as it has been suggested that absorption of lead may be increased as a result.

◊ Sodium calcium edetate 500 mg/m^2 was given by deep intramuscular injection every 12 hours for 5 days to 10 children with asymptomatic lead poisoning.[1] Blood-lead concentrations decreased to about 58% of the pretreatment values after 5 days and were essentially unchanged for up to 60 hours after the last dose. Sodium calcium edetate also produced a marked fall in the mean plasma-zinc concentration but this rebounded rapidly after the end of treatment. Mean urinary-lead excretion increased about 21-fold during the first 24 hours of therapy and urinary-zinc excretion increased about 17-fold. Sodium calcium edetate had little effect on the plasma concentrations or urinary excretion of copper. The results suggested that careful monitoring of zinc was required during treatment with sodium calcium edetate.

1. Thomas DJ, Chisolm JJ. Lead, zinc and copper decorporation during calcium disodium ethylenediamine tetraacetate treatment of lead-poisoned children. *J Pharmacol Exp Ther* 1986; **239:** 829–35.

Pharmacokinetics

Sodium calcium edetate is poorly absorbed from the gastrointestinal tract. It distributes primarily to the extracellular fluid and does not penetrate cells. It is not significantly metabolised; after intravenous injection about 50% of a dose is excreted in the urine in 1 hour and over 95% in 24 hours.

Uses and Administration

Sodium calcium edetate is the calcium chelate of disodium edetate and is a chelator used in the treatment of lead poisoning (see Treatment of Adverse Effects under Lead, p.2332). It mobilises lead from bone and tissues and aids elimination from the body by forming a stable, water-soluble, lead complex which is readily