9 Decorporation of radionuclides

This Chapter first provides an overview of the factors which influence the treatment of persons internally contaminated with radionuclides and of the available methods of treatment. However it is devoted mainly to the decorporation of tritium, strontium and iodine isotopes and the actinides plutonium, americium, thorium and uranium which continue to be a matter of concern. Important cases published in the scientific literature are summarised and progress made in research studies designed to optimise treatment for different chemical forms of the actinides reviewed. The Chapter concludes with priorities for future research and an extensive bibliography.

List of symbols and abbreviations

a	Year (annum)
ALI	Annual Limit on Intake
Bq	Becquerel
CED	Committed Effective Dose
DTPA	Diethylenetriaminepentaacetic acid
EDTA	Ethylenediaminetetraacetic acid
EHDP	Ethane-1-hydroxy-1,1,-biphosphonate
EU	European Union
ICRP	International Commission on Radiological Protection
ID	Injected Dose
ILD	Initial Lung Deposit
i.p.	Intraperitoneal injection
i.v.	Intravenous injection
$\log \beta$	The overall stability constant for a metal-ligand complex or chelate
N	Number of observations
ORAU	Oak Ridge Associated Universities
SD	Standard Deviation
SE	Standard Error of the Mean
Sv	Sievert
TBP	Tri-butylphosphate
ξ	Mean (average)

9.1 Introduction

Several useful handbooks and reviews on the decorporation of radionuclides from the body have been published over the years [78V1, 80N1, 84W1, 92B1, 00H1]. However, in the course of time, views and opinions change on the need for treatment, the radiation doses at which treatment should be considered or implemented, the most appropriate substance to be used and the optimum treatment regimen. The purpose of this Chapter is to review and update these issues with particular emphasis on hydrogen (tritium), strontium, iodine, caesium, plutonium, americium, thorium and uranium. These elements are amongst those of most concern as a consequence of accidents and incidents involving radioactive materials. Priority is given to uptakes resulting from inhalation and wound contamination.

The Chapter commences with an overview of factors that affect the efficacy of treatment, treatment decisions, decision levels and the perception of risk (Section 9.2). This is followed by summaries of the various methods of treatment (Section 9.3), the efficacies of chelating agents for different chemical forms of the actinides (Section 9.4) and recent developments in this field (Section 9.5). Much of the Chapter is devoted to the most effective treatment regimens for different chemical forms of the elements considered here, as identified by both human experience and animal studies (Section 9.6). The Chapter concludes with suggestions for future research (Section 9.7) and a comprehensive bibliography (Section 9.8).

9.2 General considerations

9.2.1 Factors affecting the efficacy of treatment

The efficacy of treatment using chelating agents can be affected by the mode of intake, mass and physico-chemical form of the contaminant, the reactions of the radionuclide with biological ligands at the site of entry in the blood and at the sites of secondary deposition, the absorption kinetics of the radionuclide into the blood, the method and duration of treatment and the mole ratio of the radionuclide to chelating agent.

In principle, the efficacies of clinically approved chelating agents are best evaluated after accidental human exposure. In practice this may be difficult for some radionuclides, notably the actinides, owing to uncertainties in the physico-chemical form, pattern of intake, and assessment of intake. Moreover, the chelating agent may not have been administered by the most appropriate route or the optimum protocol adopted. Animal studies, when properly executed, need not suffer these disadvantages and moreover are likely to be the only effective means for evaluating new substances and protocols.

The method of administration favoured by most physicians is slow intravenous injection or infusion since it is considered that chelation will be most effective when the radionuclide is present in circulating blood. In general, this is not true. Many studies with laboratory animals have shown that chelating agents are most effective for biologically soluble forms of radionuclides when they are present at the site of deposition, for example in the lungs or at a wound site. In these circumstances, local administration of the chelate is almost certainly the best option. However, when absorption into the systemic circulation occurs over an extended period then continual intravenous infusion, either directly or as a consequence of oral administration may be the most effective regimen. For inhaled biologically insoluble materials, bronchopulmonary lavage may be the only viable method of treatment (see Sections 2.3.1, 2.4)

9.2.2 Factors influencing treatment decisions

The aim of treatment is to reduce the risk of deleterious effects to the patient, usually cancer, by reducing the radiation dose. However, for some compounds of uranium considerations of chemical toxicity may over-ride radiotoxicity.

It is most important that the organisation or industry should have a clear policy concerning treatment and that all personnel are familiar with this policy. This should state that the final responsibility for treatment must always rest with the physician or appointed doctor. Nevertheless, in formulating policy several points should be addressed, such as:

- Does the maximum credible dose warrant treatment?
- What are the uncertainties in the assessment of intake and dose?
- Can any intake of sufficient magnitude to require treatment be rapidly confirmed?
- Is the material amenable to treatment?
- What is the likely reduction in dose?
- Has the age and general health of the individual been taken into account?
- What is the psychological condition of the individual?
- Is the outcome of treatment likely to be beneficial when compared with the potential risks ?

9.2.3 Decision levels

An important aspect of radiological protection for the organisation or industry concerned is that there should be a clear policy concerning treatment and that all personnel are familiar with this policy. The International Commission on Radiological Protection (ICRP) in Publication 60 [91I1] advises against the application of current dose limits for deciding on the need for, or scope of, treatment whilst recognising that at some level of dose treatment should occur. Hence a clear distinction must be drawn between the dose limit and decisions concerning treatment.

Nevertheless, in practice, treatment decisions, other than for soluble compounds of uranium, will usually be related to the effective dose limits recommended by the ICRP, namely 20 mSv a^{-1} averaged over a defined period of 5 a with a further provision that the dose should not exceed 50 mSv in a single year [91I1, 96O1]. Since in many countries the annual dose limit is restricted to 20 mSv a^{-1}, this value forms the basis of the decision levels suggested here. It is recognised that there are likely to be differing views on the magnitude of such decision levels. The recommendations given below are the same as those given in recently published EU reports on decorporation from the human body [92B1, 00W11].

9.2.3.1 Inhalation

For intakes of biologically soluble material, treatment should not be considered when the assessed dose is below 20 mSv.

For assessed doses between 20 mSv and 200 mSv, treatment should be considered [92B1, 00W1]. Although clinical effects from the intake are unlikely, psychological factors will probably be important. Single or short-term administration will usually be sufficient. However, if the assessed dose is greater than 200 mSv, then extended or protracted treatments should be considered depending on the magnitude [92B1, 00W1].

For intakes of biologically insoluble material such as ^{239}Pu dioxide, the treatment of choice is bilateral pulmonary lavage but should only be undertaken if there is a likelihood of deterministic effects [92B1, 00W1]. It has been suggested that lung lavage should be considered only when the estimated lung dose is

likely to exceed 5 Sv within a few weeks. It should be noted that whilst this procedure is considered to be of low risk [95D1], attributable to mortality from general anaesthesia [00W1], the lung content will be reduced only by about two-fold [89N1].

Biologically soluble compounds of low enriched, depleted or natural uranium are potentially nephrotoxic. The basis for current limits on intake is a maximum kidney concentration of 3 μg g^{-1} [73S2, 96H]. It can be deduced, using the ICRP human respiratory tract model [94ICRP] and the systemic model for uranium [95ICRP], that this value will be attained after acute inhalation of 30 mg and 230 mg of a very soluble (Type F) or a moderately soluble (Type M) compound, respectively, of uranium [97S1, 98S2].

9.2.3.2 Wound contamination

After a serious accident involving injury and wound contamination, necessary life-saving procedures must take precedence over decontamination. For accidents involving biologically soluble forms of radionuclides, the first approach should be to reduce contamination by copious washing with water. However, if radioactivity has entered the systemic circulation, similar criteria to those described previously for inhalation should apply.

For wounds contaminated with insoluble materials, washing with copious amounts of water should again be considered first. In many cases deposits at wound sites can be removed by surgical excision. Under these conditions it is considered inappropriate to recommend decision levels since many physicians would wish, provided there is little risk of functional impairment, to remove the radioactivity until it is below the limit of detection, perhaps a few tens of Bq or less. When, there is a risk of impairment, a balanced judgement must be made by the physician, preservation of normal function always being the primary objective.

9.2.3.3 Ingestion

For radionuclides that are extensively absorbed into the bloodstream such as ^{3}H and ^{137}Cs, the criteria for treatment should again be the same as for inhaled soluble compounds. For ingested insoluble materials the dose to the lower intestine may be large, with the possibility of deterministic effects. In these circumstances the use of cathartic or binding agents to accelerate faecal excretion should be used.

9.2.4 Perception of risk and its implications

Rather than have a series of risk coefficients for different individuals in different circumstances, the most conservative approach will be considered here, i.e. the risk for members of the public. The probabilities assumed by ICRP for the risk of radiation induced stochastic effects in members of the public are illustrated in Table 9.1, which shows that the overall risk of health detriment from stochastic effects will be 7.3 %/Sv [91I1].

Table 9.1. The nominal probabilities for radiation induced harmful effects (from ICRP Publication 60, 1991); [91I1].

	Risk [%/Sievert]			
	Fatal cancer	Non-fatal cancer	Serious hereditary effects	Total
General public	5.0	1.0	1.3	7.3

Since decisions on treatment will be based on the net benefit to the patient, it is more appropriate to consider the overall risk rather than only the risk from fatal cancers. For the suggested decision levels of 20 mSv and 200 mSv, the overall risks from stochastic effects are 0.15 % (~1 in 700) and 1.5 % (~1 in 70). However, other risks to be addressed include the following.

9.2.4.1 The risk from the administration procedure

The route of administration carrying the most significant risk is intravenous injection, in which an air embolism, leading to serious cardiovascular or neurological effects, or to death is likely to occur in 1 in 20,000 injections (0.005 %) [00W1]. Minor, and reversible, adverse reactions are known to occur in 1 in 40 injections [00W1]. Clearly the likelihood of adverse effects would be increased by repeated administration.

For treatment of inhaled insoluble materials by whole lung lavage, the risks are considered to be essentially those of a general anaesthetic- between 1 in 50,000 (0.002 %) and 1 in 200,000 (0.0005 %) [00W1]. It is considered that this level of risk justifies the use of lavage to reduce potential deterministic effects, but only for lung doses in excess of 5 Sv [00W1].

9.2.4.2 The risk from adverse effects of the therapeutic agent

This is difficult to quantify, and reference to well defined case histories provides the best information. For example, other than for uranium, the agent of choice for most actinides is DTPA and the usual human dosage is 0.5 to 1 g of the calcium or zinc salt. In France, over 500 workers have been given a single dose by slow intravenous infusion and over 200 workers have received multiple doses of DTPA without adverse effects [87B1]. The Oak Ridge Associated University (ORAU) Registry reported that between 1958 and 1987, 485 patients received a total of 3,077 dosages of DTPA, about two-thirds of them as the calcium salt. Minor transient effects were observed in 12 patients, but no serious or long term effects were reported [87B1]. In the Hanford americium accident, 583 g of DTPA, primarily as the zinc salt were administered to an individual over a 4-year period without any observed toxic effects [89B1].

9.2.4.3 The reduction in risk from treatment

This is again difficult to quantify since it will depend amongst other things on the biokinetics of different chemical forms of the radionuclide, the method of administration of the chelating agent, and the frequency and duration of treatment. The spectrum may range from marginal to almost complete removal of the radionuclide from the body. In broad terms, the extent of removal will reflect the reduction in risk.

9.2.4.4 The risk to the patient in the absence of treatment

Clearly, the risk coefficients for health detriment and the risks associated with the various treatment procedures referred to above will affect the decision making process. It should be noted that when the estimated doses are less than about 20 mSv, the risk of treatment may surpass the anticipated benefit.

9.2.5 Approaches to treatment

In broad terms, there are two alternative approaches on which treatment decisions are based. For convenience these are referred to here as urgent and precautionary.

The urgent approach is advisable when a potentially serious intake is suspected but which would take time to confirm. In this approach the chelating or complexing agent should be administered as a single dose as soon as possible. The desirability of further administrations would be decided when additional information on the physico-chemical form of the contaminant, individual monitoring data (whole-body monitoring or bioassay data as appropriate) or the psychological reaction of the patient becomes available. The advantage of this approach is that if a high uptake is confirmed, therapy, at least in most cases, will have commenced at the optimum time. The disadvantage is that if the uptake was not confirmed, or was trivial, or the material was not amenable to effective chelation therapy, then the patient might have been subject to an unnecessary, albeit small, risk. It should also be remembered that even the single administration of a chelating agent may substantially delay the accurate assessment of uptake, particularly if this is from excretion monitoring, and may increase stress to the patient. On the other hand, treatment often reduces stress to the patient.

In the precautionary approach, treatment is withheld until uptake is confirmed. The decision to treat can then be based on the likely magnitude of the uptake and probable reduction in risks of late effects. Although confirmation of small uptakes can take some time, the advantage of the precautionary approach is that should the intake be unconfirmed, or assessed as low, then any risks associated with treatment will have been avoided. The disadvantage of this approach is that should the estimated uptake be above the decision level, then the efficacy of treatment is likely to be reduced appreciably.

Other than for lavage, which can be delayed for a few weeks without reduced effectiveness, the authors do not favour one approach over another. They leave any decisions to the professional judgement of the physician and radiological health-team who will have considered all the options based on local knowledge.

9.3 Methods of treatment

This Section considers in some detail the different treatment regimens suitable for removing radionuclides from the body, but with emphasis on tritium, iodine, strontium, caesium, and the actinides plutonium, americium, thorium and uranium.

9.3.1 Non-specific procedures

These procedures can be applied to any radionuclide and any radioactive compound. They include gastric lavage to remove material from the stomach; copious washing of a wound; the administration of laxatives for cleansing the gastrointestinal tract; surgical incision for removing material from a wound; and pulmonary lavage for removing insoluble material from the lungs.

9.3.1.1 Removal from the gastrointestinal tract

Non-specific procedures can be effective when used immediately after ingestion of radioactive material which is rapidly absorbed from the gastrointestinal tract or which may result in a high dose to the intestine.

Orally administered antacids or adsorbents are useful for reducing the uptake of soluble forms of radionuclides from the gastrointestinal tract. The substances recommended have been used frequently in clinical practice and they represent virtually no risk to the patient after short- term administration. Suitable laxatives, such as sodium or magnesium sulphate, will be desirable for reducing irradiation of the lower large intestine irrespective of the chemical form. Enemas or colonic irrigation may also be used for the same purpose.

Specifically, aluminium phosphate or aluminium hydroxide is suitable for strontium (and barium and radium) [69S2, 92B1], whilst Prussian Blue (ferric ferrocyanide) $[Fe_4(Fe(CN_6)_3]$ will bind caesium (and rubidium and thallium) in the gut by ion exchange. Prussian Blue thus renders caesium insoluble in the intestinal lumen and prevents initial absorption from the gut. By breaking the secretion–reabsorption cycle, its continuous administration will reduce appreciably the systemic content of the element. At the recommended human dosage, usually 3 g d^{-1}, Prussian Blue has no known toxicity [92B1]. The oral administration of alginate has been investigated for strontium [64W1, 67H1 68C1], barium [72H2] and radium [72V1].

9.3.1.2 Lung lavage

Lung lavage is used to remove alveolar macrophages from the lungs in which particulate material is entrained. During a lavage procedure, both lungs will be treated alternately under a single general anaesthesia with multiple washes of warm isotonic saline whilst oxygen is administered to the other lung. The procedure can be repeated if necessary after 3-4 days. The technique should not be performed before the particles in the upper airways have been cleared naturally, but it remains a viable option up to several weeks after exposure. However the total amount of material which can be removed from the lungs does not generally exceed 50 % [89N1]. The risk associated with lavage is mainly that of general anaesthesia. However, it has been suggested that it should only be used on healthy people and where the radiation dose over a period of a few weeks is likely to exceed 5 Sv [00W1].

9.3.2 Procedures to enhance systemic radionuclide excretion

As indicated previously the procedure of choice will be determined by the biokinetic behaviour of the contaminant and the different mechanisms by which excretion can be enhanced e.g. by the use of diluting, immobilising or chelating agents.

9.3.2.1 Diluting and immobilising agents

An important example of a diluting agent is the enhancement of tritiated water excretion by means of forced fluid intake, often in combination with a diuretic, under medical supervision. In these circumstances, the biological half-time of ^3H in the body, usually about 10 d, can be reduced by about two-fold during the period of treatment; the reduction in the committed effective dose is somewhat less due to the short period of treatment [71L1, 72H1, 86L1].

Another important example is the reduced deposition of iodine in the thyroid by the administration of stable iodide or iodate immediately after intake of the radio-isotope.

The most effective treatment regimen for systemic radio-strontium appears to be the prompt intravenous or oral administration of stable alkaline earth metal salts, usually as their gluconates [80N1, 84W1, 92B1]. Similarly, attempts can be made to dilute, and hence reduce the systemic deposition of cobalt and radium isotopes by the administration of stable isotopes, or analogous elements.

At present the best available treatment for systemic caesium is the oral administration of Prussian Blue, which immobilises the element in the gastrointestinal tract (see 9.3.1.1). However, even with extended administration the reduction in dose is likely to be only about 2 to 3 fold [94M1, 98I1].

9.3.2.2 Chelating agents

The formation of radionuclide complexes in the body that lead to their excretion via the kidneys and urine, and/or liver and faeces is the most appropriate procedure for many radioactive heavy metals, in particular the lanthanides and actinides. The chelates most widely used for enhancing the excretion of plutonium, americium and thorium isotopes are the trisodium calcium or zinc salts of diethylaminetriaminepenta-acetic acid, referred to hereafter as CaDTPA and ZnDTPA. The former is normally used for initial and single administration, but since it can remove the essential biometals iron, manganese and zinc from the body, the zinc salt is preferred for extended or protracted administration. The mode of action of DTPA is the formation of chemically stable complexes of radionuclides in the extracellular fluids, most potently lung fluid and blood, that are rapidly excreted in the urine and, to a lesser extent, the faeces without being reabsorbed. DTPA is normally administered by slow intravenous infusion or injection at dosages of 15-30 μmol kg^{-1} body mass (0.5-1 g for a body mass of 70 kg). Alternatively, it can be administered as an aerosol or orally, usually at a similar dosage. For wound contamination, local infiltration of the substance is likely to be most effective, but because severe pain is likely to be associated with the intramuscular injection of the DTPA, a local anaesthetic, e.g procaine should be added to the solution. No serious side effects have been observed in humans treated with DTPA [87B1, 89B1, 98 G1] (see Section 9.2.4).

There is no evidence that DTPA is effective for significantly enhancing the removal of uranium from the body. In some guidebooks, the recommended agent is sodium bicarbonate. However, this is not supported by controlled studies with laboratory animals under realistic conditions e.g. with delays between exposure and treatment of 30 min or more.

Chelation therapy is not an option for the alkaline earth elements strontium, barium or radium since EDTA (ethylenediaminetetraacetic acid), DTPA, and most other chelators, form stronger complexes with calcium, than with strontium, barium or radium. Thus calcium will be complexed preferentially, and no useful enhancement of the excretion of the other alkaline earth metals will be achieved. This point is illustrated by the stability constants given in Table 9.2. The stabilities are expressed as the overall constant β which is the product of the formation constants for each of the individual metal-ligand reactions involved in the formation of the chelate of interest. For convenience the values are given as log β, the negative logarithm of the constant.

Table 9.2. Stability constants log β (see text) for the complexes between the alkaline earth metals and EDTA and DTPA [74M1]

Element	log β	
	EDTA	DTPA
Ca	10.69	10.83
Sr	8.73	9.77
Ba	7.86	8.78
Ra	7.1	[7.9]*

* Estimated value.

9.4 General comments on the efficiacy of chelating agents for the actinides

In general, the greatest problems posed in decorporation of radionuclides from the human body involve the actinide elements. Most of the research conducted in the last decade or so has also concentrated on these elements. This Section concerns the authors' responses to some of the most frequently asked questions on the efficacy of chelating agents for the actinides.

9.4.1 What are the factors that govern the efficacy of chelating agents ?

The efficacy of treatment can be influenced by the mode of intake, mass and physico-chemical form of the contaminant, the reactions of the radionuclide with biological ligands at the site of entry, the absorption kinetics of the radionuclide into the blood, the method and duration of treatment, the formation constant of the metal-ligand complex and the ligand-metal mole ratio.

The mass of the material deposited in the respiratory tract or at a wound site is an important consideration for predicting the likely efficacy of treatment in human beings and for designing animal studies. This is particularly relevant for plutonium, americium and thorium which hydrolyse readily at physiological pH, but will also be important for uranium which can precipitate as phosphate in the lungs. In animal studies, ^{238}Pu is used frequently for providing mass concentrations of Pu in the respiratory tract which simulate human exposures to ^{239}Pu (see Section 9.6) more realistically.

Clearly the physico-chemical form will also dictate the availability of the radionuclide to react with the chelator and thus to enhance excretion. For different materials, the efficacy may be influenced by the ultrafine component, the rate of dissolution of the particles *in-vivo*, the reaction of the radionuclide with biological ligands at the site of deposition and in systemic tissues, its rate of absorption into the blood and the tissue distribution. The influence of some of these factors are described in more detail in Section 9.6.

The overall efficacy of treatment will also be influenced by the mode of intake of the radionuclide and the chelating or complexing agent. Invariably, the most likely routes of internal contamination result from inhalation and wound contamination. After inhalation, chelating or complexing agents could in principle be administered as an aerosol, by intravenous injection or infusion, or orally. The choice between the methods will depend on the biokinetics of the contaminant, and whether the substance will cross the air-blood barrier or gut wall in sufficient amounts. After wound contamination, chelating agents could be administered by intravenous injection or infusion, or by local injection. The data obtained from animal studies suggests that local injection is the preferred method (see Section 9.6)

9.4.2 Can the efficacy of treatment be predicted from animal studies ?

Yes, provided the aerosol characteristics, the mass concentrations of the appropriate chemical forms at the site of deposition and the mode of uptake represent a realistic accident scenario. In many cases this may involve the use in animals of a higher specific activity isotope e.g. ^{238}Pu rather than ^{239}Pu. Any conclusions reached purely on the basis of intravenous injection experiments should be treated with caution. The differences in the distribution pattern of the radionuclide between species and in their absorption rates to blood should also be recognised. For example, after the inhalation of a moderately absorbed compound such as plutonium nitrate, the retention half-time of plutonium would be greater in the human lungs than in the rat lungs and the fraction of absorbed plutonium deposited in the human skeleton would be less than in the rat skeleton. On both counts, the overall efficacy of say DTPA would be expected to be higher in the human than in the rat (see Section 9.6).

9.4.3 Are chelating agents always most effective when the radionuclides are present in circulating blood ?

No! Ultimately the efficacy of the chelate will be influenced by the biokinetics of the contaminant, and this should be taken account of in designing the treatment regimen. Often, for radionuclides that are biologically soluble such as plutonium and americium nitrate, chelating agents will be most effective when they are deposited at the same site as the contaminant, e.g. in the lungs or at a wound site. However, for radionuclides which are absorbed into the blood at a moderate rate over a period of time, such as with $^{238}PuO_2$ and $^{241}AmO_2$ after inhalation, then it may be more productive to complex the radionuclide in the blood so as to prevent its deposition in systemic tissues such as liver and bone. This may require the continual infusion of the chelate, or its oral administration in drinking water over weeks or months.

9.4.4 Is DTPA effective for all actinides ?

No! The major successes in animal studies have been with biologically soluble or moderately soluble forms of plutonium and americium referred to above. However at present the administration of DTPA cannot be considered an effective method of treatment for soluble thorium, uranium and neptunium compounds after inhalation or wound contamination under realistic conditions [00S1, 00S2].

9.4.5 Will the administration of chelating agents result in enhanced tissue deposition ?

There appears to be no evidence from either human or animal studies that this is an important consideration when DTPA is used for the decorporation of plutonium and other actinides. However this may not be true for other chelators, particularly when they are unstable at physiological pH. For example, research studies with the siderophore analogue 3,4,3-LICAM(C) indicated enhancement of plutonium deposition in the kidneys [89S2, 89D2], whilst some phosphonates increase substantially the deposition of uranium in the liver [98H1].

9.4.6 Is the administration of sodium carbonate effective for uranium ?

The administration of sodium bicarbonate has been recommended in various guidebooks and handbooks for the decorporation of uranium [80N1, 84W1, 92B1]. The evidence available suggests it is not effective, and in view of the possible side effects such as hypokalaemia and respiratory acidosis its use should be re-considered for human treatment. Whilst alternative substances such as tiron and some polyphosphonic acids and the siderophore analogue 3,4,3-LI (1,2-HOPO) have been suggested, the experimental data show that apart from instantaneous administration they are only partially effective, and usually high dosages are required [98H1]. The effective decorporation of uranium remains an important problem in radiological protection.

9.4.7 Must chelating agents be administered promptly to be effective ?

In most cases, yes! It is particularly effective for soluble compounds of plutonium and americium deposited in the lungs or at wound sites [00S2, Section 9.6]. Prompt administration will minimise deposition in systemic tissues such as liver and bone from where appreciable removal is exceedingly difficult. However, the lung content can still be reduced appreciably should treatment be delayed for several days, although the evidence available suggests that this is not true for wounds [00S2, Section 9.6]. For other chemical forms of plutonium and americium such as $^{238}PuO_2$ and $^{241}AmO_2$, prompt administration will have little effect, and extended treatment as described above, and in Section 9.6 will be more appropriate.

If effective chelators were available then prompt treatment is essential for soluble uranium compounds after inhalation and wound contamination in order to mimimise the nephrotoxic effect.

9.4.8 Is intravenous injection the best mode of administration ?

This method, favoured by many clinicians, is the means by which most chelating agents can be administered rapidly. Whilst, in principle, an even more rapid response and greater efficacy (Section 9.6), could probably be achieved with an aerosol form self-administered with a spinhaler, there is some doubt about the extent of aerosol deposition in the lungs, and the procedure may be in contravention of the standing instructions of the employing organisation which would require that a medical officer administers the substance. However in accidents involving wound contamination, or after intakes requiring the extended administration of chelates, then intravenous injection would not be the most appropriate method, and in such cases local and oral administration respectively would need to be considered.

9.4.9 How can judgements on efficacy be made ?

In the emergency planning stage by consulting the scientific literature on the biokinetics of the same or similar material to ascertain the absorption kinetics, and whether human or animal data are available to indicate the likely efficacy of treatment and the optimum treatment regimen. After the accident from assessments of intake, and retention and excretion data using the most appropriate methods e.g. chest monitoring, wound monitoring, bioassay.

9.4.10 When should treatment start ?

This will depend on the biokinetics of the contaminant. In most cases, whatever the radionuclide and the route of contamination, treatment should begin as soon as possible. Delays of a few days would be appropriate if lung lavage is considered an option (Section 9.2), and might not be critical for compounds such as $^{241}AmO_2$ which dissolve fairly slowly in the lungs (see Section 9.6).

9.4.11 When should treatment stop ?

Several criteria are possible. One, when it is evident that the excretion of the contaminant is low compared with that expected from the estimated internal deposit. This judgement may not be straightforward. For example, a substantial increase in the urinary excretion rate above background may still represent a very small fraction of the uptake. On the other hand, an apparent lack of early success does not preclude the effectiveness of extended therapy, as described for $^{241}AmO_2$ (Section 9.6). Two, when the dose or risk has been reduced to an acceptable level (Section 9.2), taking account of the psychological needs of the patient.

9.4.12 For which materials are chelating agents likely to be effective ?

In the context of this Section, effective treatment implies that the reduction in the committed effective dose is likely to be at least two-fold, and hopefully much greater. Judgements on the efficacy of treatment can be based on the published biokinetic behaviour of known chemical forms in animals, and knowledge of the treatment regimens which can be effective for known soluble or moderately soluble forms; these

are described in more detail in Section 9.6. Whilst ligands currently approved for human use must be of prime consideration, account should be taken of experimental studies with new substances which may appear to be appreciably superior (Section 9.6)

- Provided the criteria affecting decision levels are met (Section 9.2.3), treatment is expected to be effective for ^{238}Pu and ^{239}Pu inhaled or deposited in wounds as a pure chemical form, e.g. nitrate or tributylphosphate, provided that treatment commences early and continues for a few weeks (see Section 9.6)
- ^{239}Pu inhaled as an oxide with a large ultrafine component (ca 50 % by activity), such as Pu-Na mixed oxide aerosols [78S1, 79S1 80M1]
- $^{238}PuO_2$, provided treatment is extended over many months in order to chelate the Pu arising from the dissolution of fragmented particles [80 S1, 83M1]
- ^{241}Am inhaled or deposited in wounds as a pure chemical form of the nitrate, provided treatment commences early and continues for a few weeks (see Section 9.6)
- ^{241}Am present in residues resulting from the refining of Pu metal, provided treatment continues for a few weeks [87S1]
- ^{228}Th inhaled or deposited in wound sites as the nitrate, provided treatment commences promptly and continues for a few weeks (see Section 9.6)
- In principle inhalation and wound contamination of ^{237}Np and ^{239}Np. However no effective clinically approved substance is currently available [00S1]
- In principle, uranium inhaled or deposited in wounds as ammonium diuranate, trioxide, nitrate, tributylphosphate, hexafluoride and tetrafluoride, octoxide and dioxide inhaled as ultrafine particles. However no effective clinically approved substance is currently available [00S1]

9.4.13 For which materials are chelating agents unlikely to be effective ?

Based on extensive biokinetic studies in laboratory animals to which the appropriate literature references are given, it is considered that treatment is unlikely to be effective for

- ^{238}Pu and ^{239}Pu nitrate intermixed with corrosion products or building dust [87S1, 94M2]
- $^{239}PuO_2$+ $^{241}AmO_2$ formed by calcination at high temperatures where ^{241}Am is present as a decay product of ^{241}Pu [87S1, 95S1]
- ^{239}Pu present in residues resulting from the refining of plutonium metal [87S1]
- ^{239}Pu present in residues arising from the corrosion of magnox fuel [89S1]
- ^{232}Th nitrate , fluoride, hydroxide or dioxide [00S2, 93M1]
- ^{237}Np or ^{239}Np dioxide [96I1]
- uranium octoxide or dioxide, unless there is a substantial ultrafine component [94A1, 95S1, 96I1, 98A1]
- For other materials of potential concern it is recommended that further research on the absorption kinetics in laboratory animals is undertaken in order to make judgements of the likely efficacy of treatment.

9.4.14 Is lung lavage more effective than chelation treatment for inhaled materials ?

Only if they are essentially insoluble, or dissolve slowly in the lungs over a long period of time. However, it should be remembered that at best, lung lavage will remove about one half of the radioactivity. The method would be inappropriate for biologically soluble forms of plutonium and americium. However for high uptakes of thorium nitrate and $^{241}AmO_2$, the choice between chelation treatment and lavage is more difficult to determine.

9.5 Recent developments

No significant developments in enhancing the excretion of tritium, radiostrontium, radioiodine or caesium from the body have taken place for many years. For ^{3}H and radioiodine, it is difficult to envisage how those procedures in current use can be improved.

Recent developments in decorporation therapy have focussed primarily on the actinides. This is because the efficacy of DTPA for a variety of chemical forms of plutonium, americium and thorium taken into the body by various routes has not been fully examined, or treatment using the usual route of intake, intravenous infusion, has not been completely effective. In addition, no effective agent for uranium appeared to be available. All this work has been reviewed in more detail elsewhere [94S1, 98S1, 98 S2, 00S1,00S2]

9.5.1 Plutonium and americium

It has been recognised for many years that anologues of siderophores were likely to be more effective than DTPA. Siderophores are sequestering agents produced by microorganisms in order to obtain Fe(III) from their environment. The basis for this approach was that since the biokinetics of the actinides in mammals are associated with the Fe(III) transport and storage systems, then the formation constants of the actinide complexes with siderophore derivatives would be much higher than with DTPA. This was subsequently found to be the case. Many siderophore analogues such as a linear catechoyl amide code-named 3,4,3-LICAM(C), a dihydroxamic derivative of DTPA, DTPA-DX, a hydroxypyridinone derivative of desferrioxamine, DFO-HOPO, a hydroxypyridonate code-named 3,4,3-LI(1,2-HOPO) and ligands containing the isomer 3,2-HOPO have been synthesised and tested for the decorporation of plutonium and americium, usually after their intravenous injection as citrates [98D1]. However, animal experiments involving inhalation and simulated wound contamination using different chemical forms of these elements, and administration of the ligand by different routes, showed repeatedly that 3,4,3-LI(1,2-HOPO) was substantially superior to DTPA (see Section 9.6). Whilst in the early stages the synthesis of 3,4,3-LI(1,2-HOPO) was difficult and expensive, this difficulty has now been largely overcome [98B1]. However it has not yet been approved for human use and studies on optimising treatment for different chemical forms of plutonium and americium with DTPA remain an important aspect of decorporation therapy.

9.5.2 Thorium

Studies with rats have shown that DTPA is ineffective for ^{232}Th when deposited as nitrate in the lungs in amounts that correspond to the annual dose limit for workers. At low masses of thorium, as ^{234}Th, DTPA is moderately effective after simulating wound contamination by subcutaneous or intramuscular injection, provided it is administered within minutes. However the most effective ligand developed so far for the decorporation of thorium after inhalation and wound contamination is 3,4,3-LI(1,2-HOPO). More information on the most effective treatment protocols is given in Section 9.6.

9.5.3 Uranium

Soluble compounds of uranium are nephrotoxic [89D1, 89L1]. Hence it is important that treatment should be prompt and effective. Several substances have been investigated in animals. These have included phenolic compounds such as Tiron, polyaminophosphonic acids, bisphosphonates, and phosphoalkylphosphinates, and more recently the siderophore analogues 3,4,3-LI(1,2-HOPO) and

4-LI(Me-3,2-HOPO). Some of these compounds can reduce the kidney content by about an order of magnitude compared with untreated animals when the uranium and ligand are administered almost simultaneously, or within a few minutes. However the efficacy falls sharply with any delay in administration and they are ineffective beyond about 30 minutes post exposure.

9.6 Optimum treatment protocols

This Section reviews human data where sufficient good quality information is available. However important data are often obtained from controlled studies with laboratory animals. This procedure is particularly useful since more than one regimen can be compared for the same exposure scenario, and new agents can be compared directly with the current clinically approved substance.

The emphasis is placed on inhalation, wound contamination and ingestion. Whilst intravenous injection of both radionuclides and ligands are used widely in the testing of new substances in animals, this route of contamination is not important from the standpoint of accidental exposure. However, it is considered here when data on the other modes of intake are unavailable. In addition it should be borne in mind that the high efficacy of a ligand observed after intravenous injection of a radionuclide does not necessarily mean that this will be the case after inhalation or wound contamination. Conversely, the efficacy may be higher after these routes of intake than after intravenous injection of the radionuclide.

9.6.1 Tritium

9.6.1.1 Human data

Incidents involving the uptake of substantial amounts of HTO are rare. The following case is included because it resulted in a substantial intake, about 35 GBq, and the treatment regimen used represents the optimum that can be achieved in practice [86L1]. The individual was encouraged to increase fluid intake soon after the accident and under medical supervision in hospital, forced diuresis was commenced 100 h after the accident and continued for 4 d. Diuresis was induced by an intravenous infusion of 7 litres per day, alternating 1 litre of isotonic saline with 1 litre of 5 % glucose, both being supplemented by 20 mM of potassium chloride, and further enhanced by giving 40 mg furosimide intravenously each day. In the 4 d of diuresis, which was considered the maximum medically justifiable, 15 GBq of ^{3}H was excreted in the urine. It was calculated that the above treatment regimen reduced the radiation dose from 800 mSv to 470 mSv. Had forced diuresis commenced immediately after the accident, the dose would be about 410 mSv. Thus for treatment of incorporated ^{3}H, the maximum reduction in dose is unlikely to be more than two-fold [86L1].

The authors are unaware of any definitive human or animal data on other chemical forms of tritium.

9.6.2 The alkaline earth elements, strontium, barium and radium

The substances recommended for minimising uptake from the human gastrointestinal tract, and hence systemic deposition, are strontium gluconate (isotope dilution), barium sulphate (insoluble sulphate by ion exchange), magnesium sulphate (laxative), colloidal aluminium phosphate (antacid) [80N1, 84W1, 92B1].

A number of animal studies showed that sodium alginate when given simultaneously or immediately after oral intake of strontium (or baium or radium) was able to reduce intestinal absorption and thus retention of the element [72H2, 72H3, 71V1, 77V1, 78V1, 80K1] with little effect on calcium absorption. A similar effect in humans was reported by Hesp and Ramsbottom [65H1].

Much attention has been paid to methods for enhancing the natural excretion of ^{90}Sr from the body, these include the administration of diuretics, hormones and the administration of a variety of complexing agents [68V1, 68W1, 68S1]. However, none of these have suggested a clinically useful procedure and it is difficult to conceive how the efficacy of removing radiostrontium from the body can be improved with currently available agents and approaches. Some of the substances tested are given in Table 9.3.

Table 9.3. Compounds which have been investigated for the ability to mobilize radiostrontium in animals or humans

Substance	Reference	Substance	Reference
Calcium gluconate	68S2, 68V1	Pilocarpine	68S1, 68S2
Strontium gluconate	68S2, 68V1	Parathyroid hormone	68S1
Ammonium chloride	68S1, 68S2	L-Triiodothyronine	68W1
Citrate	68S1	Oestradiol	68W1
Polyphosphates	68S1	Hydrocortisone	68W1
Fluoride	68S1	Alginate	65H1, 68H1, 71V1
Salicylate	68S1	Chlorothiazid (Saluric®)	68S2
Phytate	68S1	Mercurihydrin	68S2
Alginate	68S1		

9.6.2.1 Human data

In human volunteer studies Spencer et al [67S1, 67S2, 69S2] found that aluminium phosphate effectively inhibited the absorption of radiostrontium from the human gastrointestinal tract.

Aluminium phosphate is used clinically for the treatment of colitis, however, the recommended method of administration is by enema and the only listed pharmaceutical preparation is an aqueous solution containing 6.5 % $AlPO_4$ (Phosphalugel-Klys® 00R1). For the immediate treatment of an accidental oral intake of radiostrontium or radium an appropriate volume of this solution could, with caution, be administered orally.

In one study [69S2], a single oral dose of aluminium phosphate gel ranging from 300 ml to 100 ml (100 ml contained 886 mg aluminium and 1016 mg phosphate) was administered to 12 healthy adults immediately before an oral administration of ^{85}Sr half-way through breakfast. The amount absorbed, 3.6±0.5 % (mean ± se) was substantially less than in untreated controls, 28.8±1.9 %. In the same study using 9 volunteers, the amount of ^{45}Ca absorbed in treated and control volunteers was much higher and more variable, 27.0±3.0 % and 45.0±4.2 % respectively. Increasing the dosage of the gel from 100 ml to 300 ml had little effect on absorption in either case.

Vanderborght et al [72V1] administered 15 g sodium alginate per day in bread to a woman who had been contaminated accidentally with $^{226}RaSO_4$. The faecal excretion appeared to be enhanced for several days, suggesting that absorption of the isotope from the intestine would have been reduced. However, this was a single case and any alginate-induced increase in faecal excretion could only be deduced by comparison with published data from persons contaminated under different circumstances.

Sodium alginate is a polysaccharide isolated from seaweed and containing guluronic and mannuronic acid residues; it forms very viscous solutions and is not easy to administer in the required amounts. For many of the studies reported the alginate was incorporated into bread, [71V1] at a level of 5 % alginate. However, today a number of alginate-containing pharmaceutical preparations are licensed for human use; for example Gaviscon®, is available as tablets containing 500 mg alginate, 100 mg aluminium hydroxide, 25 mg magnesium trisilicate and 170 mg sodium bicarbonate. Such preparations could be used safely for the immediate treatment of an oral intake of a strontium, barium or radium.

9.6.2.2 Animal data

Humphreys et al [72H1] studied the effect of a single feed of bread containing 5 % of different alginates on the whole-body retention of orally administered ^{47}Ca, ^{85}Sr, ^{133}Ba and ^{226}Ra in mice. Sodium alginate had no significant effect on the retention of ^{47}Ca, but that of ^{85}Sr, ^{133}Ba and ^{226}Ra were reduced by factors of 5, 9 and 9, respectively. Harrison [68H1] also reported that the addition of 10 % of sodium alginate to the diet decreased the absorption of orally administered ^{85}Sr in rats by factors of 4-5 without influencing the absorption of ^{45}Ca. Kestens et al [80K1] fed sodium alginate containing bread daily to mice for 3 months following intraperitoneal injection of ^{226}Ra and studied the retention of the radionuclide in the femur. The ^{226}Ra activity of the femurs was slightly reduced in the alginate-treated animals but the amount of radium removed was independent of the injected dose that varied by a factor of 4. The reduction in femur content presumably reflects decreased uptake due to reduced reabsorption of strontium excreted into the gut, this was reflected in an increased faecal excretion in the treated animals.

A reduction in the absorption of ^{226}Ra and ^{85}Sr in mice following administration of aluminium phosphate was reported by Kesley et al. [72K1].

9.6.3 Iodine

The substances recommended for human use are potassium iodide or iodate. These can be given orally in the form of a suspension, or as Lugol's solution which contains 50 mg iodine and 100 mg potassium iodide per ml [80N1, 84W1, 92B1]. One blocking dose of 300 mg potassium iodide, if given within 30 min, will prevent further uptake by the thyroid. However, it may be advisable to administer 100 mg for a further few days to prevent recycling of the radio-iodine. Potassium iodate, at similar doses, can be given as an alternative to iodide. For current guidelines on iodine prophylaxis, and reviews of treatment efficacy, the reader is referred to three recent publications [99H1, 99W2, 00G1].

9.6.3.1 Human data

One of the best examples of the efficacy of prompt and delayed treatment has used human volunteers [67R1]. This work showed that if iodide administration is delayed by 6 h, the thyroid uptake is blocked by only about 50 %, is whilst after 12 h, the uptake of iodine by the thyroid is scarcely affected by the treatment.

If stable iodide is given after the first 24 h, there may be a prolonged retention of radio-iodine by the thyroid due to the suppression of thyroid hormone release. Further, besides diluting the radio-iodine, treatment with stable iodide and the massive increase in the iodine pool in the body also inhibits thyroid metabolism. Under treatment with 300 mg sodium iodide followed a few daily doses of 100 mg, toxic reactions are rare, although a few individuals may be over sensitive to iodide and develop angioedema. If a reaction occurs, symptoms should disappear within a few days after cessation of treatment. Iodide should also be administered with caution to persons with goitre or being treated for hyperthyroidosis because the condition may exacerbate to thyrotoxicosis. This condition may also result if individuals have a low dietary intake of iodine. Some people are allergic to large doses of iodide and such cases should be treated with perchlorate.

9.6.4 Caesium

The substance recommended for the decorporation of caesium isotopes is Prussian Blue [80N11, 84W1, 92B1].

9.6.4.1 Human data

One of the major and most comprehensively investigated accidents involving internal contamination with ^{137}Cs occurred in Goiania in 1987 [94M1, 98I1]. Prussian Blue was administered orally to 46 individuals. The dosages administered ranged from 1 to 3 g d^{-1} for children, and from 3 to 10 g d^{-1} for adolescents and adults. In general treatment commenced about 10 d after exposure and continued over a period of about 3 weeks for children and over periods ranging from 3 weeks to 3 months for adults. During the administration of the chelate, the mean retention half-times of ^{137}Cs in the body were, on average, 43 %, 45 % and 69 % respectively of the values after termination of treatment. The committed effective doses were reduced by between 1.7 fold and 6.2 fold, with a median value of 2.1 fold [94 M1, 98I1]. These results are summarised in Table 9.4. The reduction in dose appeared to be independent of the dosage of Prussian Blue, and the age of the patient [94M1, 98I1]. Reductions in doses of 2 to 3 fold have also been found after other accidental intakes involving caesium isotopes [96M1, 85M1, 88T1].

Table 9.4. Committed whole body doses for individuals treated with Prussian Blue in the Goiania accident [94M1, 98I1, 00S2]

Subject	Sex	Age [y]	Weight [kg]	Dose[(1)] [mSv]	Dose[(2)] [mSv]	Ratio[(3)]
1	F	5	17	180	360	2.0
2	F	6	20	120	220	1.8
3	M	7	26	120	210	1.8
4	M	8	23	46	90	2.0
5	M	8	25	140	240	1.7
6	M	10	27	140	250	1.7
7	M	13	31	180	350	2.0
8	M	13	38	700	1200	1.8
9	M	13	55	200	670	3.3
10	M	13	55	22	39	1.7
11	M	14	58	35	68	1.9
12	M	19	50	140	290	2.0
13	M	23	66	910	5000	5.5
14	M	28	69	970	3800	4.0
15	F	29	66	850	3100	3.6
16	M	32	61	370	1400	3.7
17	M	33	80	49	140	2.7
18	F	36	58	160	390	2.4
19	M	41	63	300	1900	6.2
20	M	43	73	200	800	4.0
21	M	46	64	46	220	4.8

[1])With Prussian Blue treatment, [2])Without Prussian Blue treatment, [3])Reduction in dose with treatment.

9.6.4.2 Animal data

Many studies on the efficacy of Prussian Blue have been undertaken in laboratory animals [94M1, 96M1, 98I1], however in view of the detailed human studies that have been published they are not described here.

In the last decade or so, work on improving the decorporation of caesium has involved investigations of other hexacyanoferrates [90D1, 93D1, 91N1]. However, at present they do not appear to be significantly more advantageous than Prussian Blue and it is difficult to see how substantial improvements can be made.

9.6.5 Plutonium and americium

The currently recommended substances for enhancing biologically soluble forms of plutonium and americium are CaDTPA or ZnDTPA (see Section 9.3).

9.6.5.1 Human data

Well-documented studies on the treatment of plutonium and americium after inhalation and wound contamination have been published in the scientific literature. Perhaps the most notable example on the efficacy of treatment is that often referred to as the Hanford americium accident, in which an individual sustained an intake of about 41 MBq ^{241}Am by inhalation and wound contamination resulting from the explosion of an ion-exchange column [83B1, 89B1].

Briefly, in the absence of treatment, the bone and liver deposits were each predicted to be about 18,500 kBq, resulting in life-threatening doses of 0.07 Gy d^{-1} and 1 Gy d^{-1} respectively [89B1]. The minimum ^{241}Am contents of these tissues after an initial intravenous adminstration of CaDTPA followed by the protracted administration of ZnDTPA by the same route, were about 220 and less than 4 kBq about 2 years after the accident. The values then increased to about 350 and 20 kBq by the 10th year as the frequency of treatment was reduced. In total 583 g of DTPA was administered. Importantly no toxic side effects were observed. The individual died 11 years after the accident from a medical condition unrelated to the accident. A summary of the tissue content and excretion of ^{241}Am is given in Table 9.5.

Table 9.5. Summary of tissue content and excretion of ^{241}Am [89B1]

Time	Organ content [kBq]				Cumulative excretion [kBq]	
	Skin	Lungs	Bone	Liver	Urine	Faeces
Day 0	185,000				4,800	0
Day 3	26,000	960	480	1,400	5,000	4,700
Day 10	14,000	290	320	590	22,000	6,800
Day 60	5,500	74	250	150	31,000	7,000
1 year	1,300	74	230	150	33,000	7,000
2 years	740	55 [1)]	220	ND	34,000	7,000
5 years	196	ND	280	9.6 [2)]	34,000	7,000
7 years	190	ND	NM	17	5.4 [3)]	1.4 [3)]
10 years	110	ND	350	19	4.8 [3)]	0.036 [3)]
11 years	NM	AS	NM	23 (AS)	NM	NM

[1)] not detected at 3 years
[2)] increase in liver content due to reduction in DTPA treatment
[3)] values per year based on 1-2 assays per year
ND not detectable, NM not measured, AS measured in autopsy sample

A good example of the comparative efficacies of surgical treatment and the efficacy of DTPA after the intake of ^{239}Pu oxalate through a puncture wound in the hand has also been reported [74S1]. It was estimated that the wound was contaminated with 525 kBq of ^{239}Pu. Cleaning the wound immediately after the accident removed 144 kBq Pu. Continual monitoring of the wound with a probe showed that by 15 d, about 285 Bq remained. During this time 17 kBq had been removed with surgical dressings and 16 kBq

was excreted in urine as a consequence of repeated DTPA treatment. The monitoring data implied that 37-74 kBq had been transferred to systemic tissues. A wide excision of the wound area performed in hospital 15 d after the accident removed a further 255 kBq of ^{239}Pu from the hand. Subsequent measurements with a wound probe indicated that about 67 kBq remained at the wound site. In all there were five courses of chelation therapy which commenced 40 minutes after the accident and were spread over a period of 163 d. It was estimated that this treatment caused the elimination of 21 kBq of Pu in addition to the 0.7 kBq that would be expected in its absence. Whilst the overall efficacy of treatment with DTPA cannot be quantified due to the uncertainty in the estimate of systemic content, a reduction of 21 kBq would, based on the current ICRP model for ^{239}Pu [93I1], imply an averted dose of 10.5 Sv [00P1].

The published information on the effectiveness of oral treatment for inhaled plutonium and americium is sparse. In general, it appears to have been useful for treating accidental intakes by workers [60N1, 67L1, 77S1]. However, uncertainties in the chemical forms of these actinides, the amounts inhaled and the delays between exposure and treatment make assessments of its potential efficacy difficult. Importantly however, the DTPA appeared to be of low toxicity; in one case 249 g of the free acid were administered over a period of 16 weeks without any apparent side effects [67L1].

There are of course many other examples of the treatment of humans after accidental exposure to plutonium and americium, published in the scientific literature. In many of these cases the administration was only partially effective [60N1, 69S1, 72J1, 73S2, 76O1, 77S1, 80P1, 80V1, 89C1, 94W1]. In part this may have been due to uncertainty in the chemical form of intake or exposure pattern, the implementation of treatment regimens which may not have been optimised, or simply that the chemical form was not amenable to treatment. Animal studies when properly executed need not suffer these disadvantages. Moreover, such studies may also be used to evaluate alternative methods of treatment or new substances.

9.6.5.2 Animal data

9.6.5.2.1 Inhaled plutonium and americium nitrate

Most animal experiments have been conducted with plutonium nitrate. In these circumstances it is important that the mass concentrations of plutonium in tissues at the site of entry simulate a realistic accident scenario, say intakes corresponding to doses up to two orders of magnitude greater than the annual limit. Otherwise, the experimental data may provide information which could prejudice the use of the ligand or the mode of administration.

Animal studies have shown that the administration of DTPA as an aerosol, by injection or orally in drinking water can substantially reduce the lung deposit and hence systemic deposit of plutonium and americium.

Information on the efficacy of inhaled DTPA in the rat after the inhalation of ^{238}Pu and ^{241}Am nitrate is given in Tables 9.6 and 9.7 respectively. The tables show that concentrations of the chelate well below the usual human dosage removed nearly all the contamination from the lungs. The small amounts retained in other body tissues probably resulted from absorption and deposition in systemic tissues before the commencement of treatment. It is noteworthy that the inhalation of DTPA was almost as effective as repeated injection of the substance. These results contrast sharply with those obtained in the rat after intakes in which the mass concentrations in the lungs were about 100 times higher. Under these conditions aerosol DTPA was completely ineffective [77Bal].

Other studies, with the hamster, have shown that plutonium and americium can also be near-quantitatively removed from the lungs (i.e 1-3 % of controls) when either aerosol DTPA (2μmol kg^{-1}) or the combined administration of aerosol (2μmol kg^{-1}) and injected (30 μmol kg^{-1}) was delayed for up to 11 days after exposure. However in these cases, the total body contents of plutonium and americium could be up to 30 % and 54 % of controls respectively, reflecting the difficulty in removing systemic deposits that had accumulated before the commencement of treatment [00S2].

After inhalation of plutonium as nitrate by rats and treatment by intravenous injection, the siderophore analogue 3,4,3-LI(1,2-HOPO) is appreciably more effective than DTPA, particularly after repeated administration (Table 9.8). Under similar conditions of exposure and treatment, the ligands were considered similarly effective for americium (Table 9.9).

The oral, and intraperitoneal, administration of DTPA has also been shown to be an effective method of treatment in rats after the inhalation of plutonium and americium as their nitrates (Tables 9.10 and 9.11). Importantly, a ZnDTPA concentration an order of magnitude higher than that reported here did not result in any observed histopathological changes to the liver, kidneys or gastrointestinal tract. It is also noteworthy that the higher ZnDTPA concentration did not improve its efficacy. The low toxicity of DTPA after oral administration is consistent with the data obtained from human [67L1] and other animal [80T1, 90T1] studies.

The intravenous infusion and repeated injection of DTPA after the inhalation of plutonium nitrate by dogs [92G1] have also been shown to be an effective method of treatment (Table 9.12).

Tables 9.6 to 9.12, see pages 9-21 and 9-22

9.6.5.2.2 Inhaled tributyl phosphate

Studies on the efficacy of injected DTPA and 3,4,3-LI(1,2-HOPO) have been undertaken after inhalation by the rat. The repeated intraperitoneal injection of CaDTPA proved to be an effective treatment regimen (Table 9.13). In another study involving a higher lung deposit and a shorter period of treatment (Table 9.14), the reduction in the plutonium contents of the lungs and systemic tissues were less, but the study emphasised the higher efficacy of 3,4,3-LI(1,2-HOPO).

Table 9.13. Efficacy of injected DTPA on retention of ^{238}Pu in rats after inhalation as TBP [85S2, 00S2]

	% controls at 28d ($\xi \pm$ SE, N=5)[1]	
Treatment	Lungs	Total body
CaDTPA[2]	4.3 ± 0.7	16 ± 2
ZnDTPA[2]	2.5 ± 0.6	15 ± 2
ZnDTPA[3]	4.2 ± 0.8	26 ± 2

Initial lung deposit 384 Bq ^{238}Pu, 0.59 ng Pu.
Equivalent intake of Pu-239 by workers 0.86×10^4 ng or 1.98×10^4 Bq, i.e. 32 ALIs (CED 640 mSv).
[1])% inhaled activity in controls at 1 d, lungs 23.1 ± 1.8, total body 62.0 ± 3.0.
% inhaled activity in controls at 28 d, lungs 9.5 ± 1.0, total body 43.1 ± 2.7.
[2])30 μmol kg^{-1} CaDTPA or 200 μmol kg^{-1} ZnDTPA injected i.p. at 30 min, 6 h, 1 d, 2 d, 5 d, and then every 3-4 d to 26 d.
[3])Treatment regimen as for (a) but delayed for 1 d.

Table 9.14. Efficacy of injected 3,4,3-LI(1,2-HOPO) and CaDTPA on retention of ^{238}Pu in rats after inhalation as TBP [93P1, 00S2]

	% controls at 7d ($\xi \pm$ SE , N=4)	
Treatment	Lungs	Skeleton
iv injection[1]		
LIHOPO	27 ± 2	12 ± 3
CaDTPA	30 ± 1	22 ± 2
im + iv injection[2]		
LIHOPO	28 ± 2	2.9 ± 0.9
CaDTPA	45 ± 2	14 ± 2

[1]) Initial lung deposit 5200 ± 400 Bq, 8.1 ng Pu.
Equivalent intake of Pu-239 by workers 1.18×10^5 ng or 2.72×10^5 Bq, i.e. 435 ALIs (CED 8.7 Sv)
Administration of 30 μmol kg^{-1} after 1 h
Liver contents were 6.0 ± 0.7 % and 17.5 ± 3.4 % of those in controls after administration of LIHOPO and DTPA respectively.
[2]) Initial lung deposit 34000 ± 3000 Bq, 53 ng Pu.
Equivalent intake of Pu-239 by workers 7.70×10^5 ng or 1.78×10^6 Bq, i.e. 2840 ALIs (56.8 Sv)
Administration of 30 μmol kg^{-1} after 1h (iv) and 1 d and 2 d (im).
Liver contents were 1.7 ± 0.2 % and 8.1 ± 2.2 % respectively of those in controls after administration of LIHOPO and DTPA respectively.

Table 9.6. Efficacy of aerosol and injected DTPA on retention of ^{238}Pu in rats after inhalation as nitrate [85S1, 00S2]. ξ = arithmetic mean, N = number of observations.

	% controls at 28 d ($\xi \pm$ SE, N=5)[1]	
Treatment[2]	Lungs	Total body
Aerosol[3]	2.1 ± 1.1	7.6 ± 1.2
Aerosol plus injection[4]	1.1 ± 0.1	4.2 ± 0.7
Injection only[5]	4.4 ± 2.4	5.7 ± 1.4

Initial lung deposit, 505 ± 37 Bq, 0.78 ng Pu.
Equivalent intake of ^{239}Pu by workers 1.13×10^4 ng or 2.61×10^4 Bq, i.e. 42 ALIs (CED 840 mSv).
[1]) % ILD in controls at 28 d; lungs, 29.3 ± 3.8, total body, 45.1 ± 5.8.
[2]) DTPA administration at 30 min, 6 h, 1 d, 2 d, 3 d, 5 d and then twice weekly to 27 d; first administration CaDTPA, then ZnDTPA.
[3]) Inhalation, 2 µmol kg^{-1}.
[4]) Inhalation, 2 µmol kg^{-1}and intraperitoneally (i.p.) injection, 30 µmol kg^{-1}
[5]) i.p. injection, 30 µmol kg^{-1}

Table 9.7. Efficacy of aerosol and injected DTPA on retention of ^{241}Am in rats after inhalation as nitrate [85S1, 00S2]

	% controls at 28d ($\xi \pm$ SE, N=5)[1]	
Treatment[2]	Lungs	Total body
Aerosol[3]	2.3 ± 0.5	3.7 ± 0.6
Aerosol plus injection[4]	1.6 ± 0.3	2.9 ± 0.5
Injection only[5]	5.0 ± 2.1	3.6 ± 0.9

Initial lung deposit, 350 ± 25 Bq, 2.8 ng Am.
Equivalent intake of ^{241}Am by workers 4.05×10^4 ng or 5.09×10^6 Bq, i.e. 6870 ALIs (CED 137 Sv).
[1]) % ILD in controls at 28 d; lungs, 14.3 ± 1.8, total body 30.9 ± 4.1.
[2-5]) Treatment regimens as given in Table 9.7

Table 9.8. Efficacy of injected 3,4,3-LI(1,2-LIHOPO) and DTPA on retention of ^{238}Pu in rats after inhalation as nitrate [92S1, 00S2]

	% controls at 7d ($\xi \pm$ SE, N=4)[1]	
Treatment[2]	Lungs	Total body
LIHOPO[3]	11 ± 1	11 ± 1
DTPA[3]	16 ± 2	18 ± 2
LIHOPO[4]	1.8 ± 0.3	11 ± 1
DTPA[4]	12 ± 1	4.5 ± 0.4
LIHOPO[5]	24 ± 2	27 ± 2

Initial lung deposit, 600 ± 25 Bq, 0.92 ng Pu.
Equivalent intake of ^{239}Pu by workers 1.34×10^4 ng or 3.08×10^4 Bq i.e. 49 ALIs (CED 980 mSv).
[1]) % ILD in controls at 7 d: lungs, 64.6 ± 4.4, total body 86.3 ± 4.8.
[2]) DTPA, 30 µmol kg^{-1} administered by intraperitoneally (i.p.) injection; first administrations CaDTPA then ZnDTPA .
[3]) 30 min only.
[4]) 30 min, 6 h, 1 d ,2 d ,3 d.
[5]) 1d only.

Table 9.9. Efficacy of injected 3,4,3-LI(1.2-HOPO) and DTPA on retention of ^{241}Am in rats after inhalation as nitrate [92S1, 00S2]

	% controls at 7d ($\xi \pm$ SE, N=5)[1]	
Treatment[2]	Lungs	Total body
LIHOPO[3]	41 ± 4	31 ± 3
DTPA[3]	21 ± 2	15 ± 1
LIHOPO[4]	13 ± 2	11 ± 2
DTPA[4]	13 ± 2	9 ± 1
LIHOPO[5]	81 ± 8	64 ± 4

Initial lung deposit, 623 ± 25 Bq, 4.97 ng. Am.
Equivalent intake of ^{241}Am by workers 7.22×10^4 ng or 9.05×10^6 Bq, i.e. 12,230 ALIs (CED 244 Sv).
[1]) % ILD in controls at 7 d : lungs, 40.4 ± 3.7, total body, 71.5 ± 4.4.
[2-5]) Treatment regimen as in Table 9.8

Table 9.10. Efficacy of oral and intraperitoneally (i.p.) injected ZnDTPA on retention of ^{238}Pu and ^{241}Am in rats after inhalation as nitrate: prompt administration [95G1, 00S2]

	% controls at 21 d ($\xi \pm$ SE, N=4)[1]	
Treatment[2]	Lungs	Total body
Plutonium		
Oral[3]	2.2 ± 0.4	8.8 ± 1.5
Oral[4]	2.2 0.3	7.8 ± 0.8
i.p[5]	1.7 ± 0.3	5.2 ± 0.7
Americium		
Oral[3]	3.6 ± 0.6	6.0 ± 0.6
Oral[4]	3.2 ± 0.3	4.8 ± 0.5
i.p[5]	1.7 ± 0.6	2.5 ± 0.4

Initial lung deposit, Pu 676 ± 96 Bq, 1.04 ng Pu , Am, 354 ±49 Bq , 2.82 ng Am.
Equivalent intake by workers: ^{239}Pu 1.51×10^4 ng or 3.49×10^4 Bq, i.e. 56 ALIs (CED 1120 mSv); ^{241}Am 4.10×10^4 ng or 5.14×10^6 Bq, i.e. 6950 ALIs (CED 139 Sv).
[1]) % ILD in controls at 21 d: Pu, lungs, 41.0 ± 3.6 , total body 63.9 ± 4.7;
Am, lungs, 20.1 ± 1.6, total body 51.7 ± 4.
[2]) Treatment commenced 1 h after exposure.
[3]) 950 µmol kg^{-1} d^{-1} for 21d.
[4]) 95 µmol kg^{-1} d^{-1} for 21d.
[5]) 30 µmol kg^{-1} twice weekly for 21 d.

Table 9.11. Efficacy of oral and intraperitoneally (i.p.) injected ZnDTPA on retention of ^{238}Pu and ^{241}Am in rats after inhalation as nitrate: delayed administration [93S1, 00S2]

	% controls at 28 d ($\xi \pm$ SE , N=4)[1]	
Treatment[2]	Lungs	Total body
Plutonium		
Oral[3]	6.1 ± 0.4	19 ± 3
Oral[4]	6.2 ± 0.3	17 ± 2
i.p[5]	11 ± 1	25 ± 4
Americium		
Oral[3]	3.6 ± 0.6	23 ± 3
Oral[4]	3.2 ± 0.3	20 ± 3
i.p[5]	1.7 ± 0.6	29 ± 4

Initial lung deposit, Pu 676 ± 96 Bq, 1.04 ng Pu , Am, 354 ± 49 Bq , 2.82 ng Am.
Equivalent intake by workers: ^{239}Pu 1.51×10^4 ng or 3.49×10^4 Bq, i.e. 56 ALIs (CED 1120 mSv); ^{241}Am 4.10×10^4 ng or 5.14×10^6 Bq, i.e. 6950 ALIs (CED 139 Sv)
[1]) % ILD in controls at 28 d: Pu, lungs, 30.7 ± 2.7, total body 60.0 ± 4.9; Am, lungs, 14.8 ± 1.0, total body 51.3 ± 3.8.
[2]) Treatment commenced 7 d after exposure.
[3-5]) Treatment as given in Table 9.10.

Table 9.12. Efficacy of injected CaDTPA on retention of ^{238}Pu in dogs after inhalation as nitrate [93G1, 00S2]

	% controls at 64d ($\xi \pm$ SD, N=2)[1]	
Treatment	Lungs	Total body
DTPA injections[2,3]	20 ± 6	22 ± 4
DTPA infusions[4,5]	22 ± 6	17 ± 2

[1]) Initial lung deposit, 16-26 kBq.
% initial deposit in controls after 64 d , lungs 10.8 ± 2.9, liver 31.3 ± 4.6 , bone 30.5 ± 3.3 total body 76 ± 4.
[2]) CaDTPA i.v. (30µ mol. kg.$^{-1}$) after 1 h, 1 d , 2 d, 3 d, 4 d, and ZnDTPA twice weekly thereafter.
[3]) Liver and bone content reduced to 8.3 ± 4.2 % and 36 ± 5 % of controls.
[4]) CaDTPA i.v. after 1 h ,then subcutaneous infusion with ZnDTPA (30 µmol kg^{-1} d^{-1}) from 1 d.
[5]) Liver and bone content reduced to 3.8 ± 1.4 % and 28 ± 6 % of controls.

9.6.5.2.3 Inhaled plutonium dioxide

Under normal conditions the soluble or ultrafine component of ^{239}Pu dioxide aerosols would be expected to be appreciably less than 1 % [72ICRP]. Hence the administration of DTPA by whatever route would have little impact on reducing the committed effective dose.

However the presence of other metals during the formation of the aerosol, particularly those of low atomic weight such as sodium, can substantially increase the ultrafine component, and in such circumstances the administration of the ligand will be much more effective [80S1]. The experimental data are summarised in Table 9.15.

The absorption of ^{238}Pu into blood after the inhalation of $^{238}PuO_2$ is governed by the formation of particles about 1 nm in diameter by radiolytic fragmentation. The transportable fraction arising from this process is retained in part in the lungs from where it can be mobilised by DTPA [82S1]. The experimental data summarised in Table 9.16 illustrate that DTPA was effective for removing Pu from the lungs as judged by the appreciable increase in urinary excretion. On the other hand the reduction in the body content after treatment was only about 20 % as a consequence of the competing action of mucociliary clearance. It is concluded that the protracted treatment required for a small reduction in the lung content would be unlikely to be used in humans, where for large intakes lung lavage would be more beneficial.

Table 9.15. Efficacy of injected CaDTPA on retention of Pu and Am in hamsters after inhalation of a mixed aerosol of PuO_2 (+AmO_2) and Na_2O, Pu:Na atomic ratio 1:30 [80S1]

	% controls at 30 d ($\xi \pm$ SE, N= 8) [1]	
Treatment [2]	Lungs	Total body
Pu	33 ± 6	22 ± 3 [c]
Am	40 ± 7	20 ± 3 [d]

[1]) Initial deposit, 3.6 kBq kg^{-1} body mass;
% ILD in controls at 30 d; Pu: lungs 27.4 ± 4.6, total body 81.2 ± 8.2, Am: lungs 21.0 ± 3.0, total body 83.0 ± 8.5
[2]) DTPA, 30 μmol kg^{-1} andimistered i.p. at 3 h, 1 d, 2 d, 4 d.
[3]) % controls in liver and bone, 13 ± 3 and 17 ± 4 respectively
[4]) % contols in liver and bone, 11 ± 2 and 16 ± 3 respectively

Table 9.16. Efficacy of DTPA on retention and excretion of ^{238}Pu in the hamster after inhalation as $^{238}PuO_2$ [82S1]

Treatment	% body deposit at 7 d ($\xi \pm$ SE, N=4 - 6) [1]			
	Lungs	Systemic	Urine	Faeces
% ILD at 154 d				
aerosol DTPA [2]	31.5 ± 2.7	4.0 ± 0.2	23.5 ± 1.0	41.0 ± 3.6
controls	39.2 ± 1.1	3.1 ± 0.4	2.8 ± 0.2	54.9 ± 1.4
% ILD at 147 d				
aerosol [2]+ i.p [3] DTPA	30.8 ± 1.4	4.1 ± 0.1	29.6 ± 0.7	35.5 ± 2.4
controls	37.7 ± 1.1	7.6 ± 0.6	5.2 ± 0.5	49.5 ± 0.8

[1]) Initial body content of $^{238}PuO_2$ at 7 d, 510 ± 40 Bq, of which 98.8 % was in the lungs.
[2]) DTPA administration, 2 μmol kg^{-1} commenced 7 d after exposure and continued at weekly intervals to 147 d
[3]) DTPA injections, 26 μmol kg^{-1}, commenced 10 d after exposure and continued at weekly intervals until 143 d

9.6.5.2.4 Inhaled americium dioxide

The efficacy of DTPA for inhaled $^{241}AmO_2$ has been investigated after administration as an aerosol and intraperitoneal injection in the hamster [84S1] and by intravenous injection and infusion using implanted osmotic pumps in the dog [88G1]. All methods of administration were moderately effective (Tables 9.17, 9.18). The latter treatment was particularly impressive since it virtually prevented the deposition of ^{241}Am in systemic tissues. Implanted osmotic pumps in humans for long periods may be impracticable. However the data obtained for ^{241}Am nitrate after the oral administration of DTPA referred to above suggest that this could be an alternative mode of administration for inhibiting systemic deposition.

Table 9.17. Efficacy of injected ZnDTPA for ^{241}Am nitrate and $^{241}AmO_2$ inhaled by the hamster [84S1, 00S2]

	% controls at 74 d ($\xi \pm$ SE, N=5)	
Treatment	Lungs	Total body
Am nitrate[1]		
Injection[3]	3 ± 1	13 ± 1
Inhalation[4]	3 ± 1	54 ± 4
Am dioxide[2]		
Injection[3]	14 ± 2	16 ± 2
Inhalation[4]	27 ± 4	56 ± 4

ILD 150 Bq or 80 Bq at the commencement of treatment.
[1]) % ILD in controls at 74 d, lungs, 19.8 ± 2.6, total body, 54.4 ± 2.6.
[2]) % ILD in controls at 74 d, lungs, 25.2 ± 2.4, total body, 58.6 ± 3.1.
[3]) Zn DTPA injected intaperitoneally at weekly intervals from 4 d to 67 d at a dosage of 200 µmol kg^{-1}.
[4]) Zn DTPA inhaled at weekly intervals from 4 d to 67 d at a dosage of 2 µmol kg^{-1}.

Table 9.18. Efficacy of CaDTPA on retention of ^{241}Am in dogs after inhalation of AmO_2 [88G1, 00S2]

	% controls at 64 d ($\xi \pm$ SD, N=2)[1]	
Treatment	Lungs	Total body
DTPA injections[2,3,5]	63 ± 25	29 ± 10
DTPA infusions[4,5]	30 ± 9	11 ± 3

[1]) Initial lung deposit, 17-39 kBq.
% initial deposit in controls after 64 d, lungs 24.5 ± 2.5, liver 25.1 ± 3.4, bone 21.8 ± 4.2, total body 76.7 ± 7.8.
[2]) CaDTPA i.v. (30 µmol kg^{-1}) after 1 h, 1 d, 2 d, 3 d, 4 d, and ZnDTPA twice weekly thereafter.
[3]) Liver and bone content reduced to 4.7 ± 3.2 % and 18 ± 4 % of controls.
[4]) CaDTPA i.v. after 1 h ,then subcutaneous infusion with ZnDTPA (30 µmol kg^{-1} d^{-1}) from 1 d.
[5]) Liver and bone content reduced to 0.43 ± 0.28 % and 1.7 ± 0.7 % of controls.

9.6.5.2.5 Wound contamination with plutonium and americium nitrate

For the purpose of investigating new or alternative treatment protocols, human wounds are usually simulated in animals by subcutaneous or intramuscular injection of radionuclides. The ligands have been administered as either a single and repeated local administration or combinations of local and intraperitoneal injections, intravenous injection and oral administration. In general, local administration has proved to be most effective and intravenous injection ineffective.

The comparative efficacies of 3,4,3-LI(1,2-HOPO) and DTPA in rats after the intramuscular injection of plutonium and americium nitrate are shown in Tables 9.19 and 9.20. The data show that virtually all of the plutonium and americium were removed from the body by a single local injection of 30 µmol kg^{-1} of 3,4,3-LI(1,2-HOPO). The retention of plutonium and americium in the body using a similar treatment protocol with DTPA were about 30 and 20 times more respectively.

The efficacy of both ligands falls appreciably with delayed administration. However the retention of plutonium and americium at the wound site and in the total body is still about 3 to 4 times less with 3,4,3-LI(1,2-HOPO) than with DTPA (Tables 9.21, 9.22).

The high efficacy of 3,4,3-LI(1,2-HOPO) after wound contamination has also been reported elsewhere [96V1].

Table 9.19. Efficacy of injected 3,4,3-LI(1,2-HOPO) and DTPA on retention of ^{238}Pu after intramuscular injection as nitrate: prompt treatment [93S1, 00S2]

	% controls at 7 d ($\xi \pm$ SE, N=4)[1]	
Treatment	Wound site	Total body
LIHOPO[2]	4.8 ± 0.4	5.9 ± 0.5
LIHOPO[3]	0.9 ± 0.1	0.9 ± 0.1
LIHOPO[4]	0.6 ± 0.1	1.0 ± 0.1
DTPA[5]	33 ± 2	32 ± 1
LIHOPO [6]	33 ± 3	33 ± 2

[1]) Injected activity 190 ± 5 Bq , 0.3 ng Pu.
% injected activity in controls at 7 d, wound site 70.2 ± 1.7 total body 95.7 ± 1.0.
[2]) 3 µmol kg^{-1} locally at 30 min.
[3]) 30 µmol kg^{-1} locally at 30 min.
[4]) 30 µmol kg^{-1} at 30 min, plus i.p. at 6 h, 1 d, 2 d and 3 d.
[5]) as (4) with CaDTPA for local injection and ZnDTPA for i.p.
[6]) 30 µmol kg^{-1} i.v. at 30 min.

Table 9.20. Efficacy of injected 3,4,3-LI(1,2-HOPO) and DTPA on retention of ^{241}Am after intramuscular injection: prompt treatment [93S1, 00S2]

	% controls at 7 d ($\xi \pm$ SE, N=4)[1]	
Treatment	Wound site	Total body
LIHOPO[2]	8.5 ± 0.1	8.8 ± 0.6
LIHOPO[3]	0.6 ± 0.1	0.8 ± 0.1
LIHOPO [4]	0.4 ± 0.1	1.2 ± 0.1
DTPA[5]	27 ± 3	22 ± 2
LIHOPO[6]	43 ± 4	39 ± 2

[1]) Injected activity 200 ± 5 Bq , 1.6 ng Am.
% injected activity in controls at 7 d, wound site 70.5 ± 2.6 total body 96.8 ± 2.0.
[2-6]) Treatment protocols as given in Table 9.19

Table 9.21. Efficacy of injected 3,4,3-LI(1,2-HOPO) and DTPA on retention of ^{238}Pu after intramuscular injection: delayed treatment [94G1, 00S2]

	% controls at 7 d ($\xi \pm$ SE, N=4)[1]	
Treatment	Wound site	Total body
LIHOPO [2]	1.0 ± 0.1	1.2 ± 0.1
CaDTPA[2]	39 ± 2	31 ± 2
LIHOPO [3]	17 ± 1	15 ± 1
Ca DTPA [3]	71 ± 2	76 ± 2
LIHOPO [4]	24 ± 1	23 ± 1
CaDTPA[4]	75 ± 2	81 ± 2

[1]) Injected activity 200 Bq , 0.3 ng Pu.
% injected activity in controls at 7 d, wound site 68.4 ± 0.9, total body 97.2 ± 1.3.
[2]) 30 µmol kg^{-1} locally at 30 min.
[3]) 30 µmol kg^{-1} locally at 6 h
[4]) 30 µmol kg^{-1} at 1 d.

Table 9.22. Efficacy of injected 3,4,3-LI(1,2-HOPO) and DTPA on retention of ^{241}Am after intramuscular injection: prompt and delayed treatment [94G1, 00S2]

	% controls at 7 d ($\xi \pm$ SE, N=4)[1]	
Treatment	Wound site	Total body
LIHOPO [2]	0.7 ± 0.1	1.0 ± 0.1
CaDTPA[2]	28 ± 2	25 ± 2
LIHOPO[3]	15 ± 1	13 ± 1
CaDTPA[3]	69 ± 2	68 ± 2
LIHOPO[4]	23 ± 1	22 ± 1
CaDTPA[4]	72 ± 2	73 ± 2

[1]) Injected activity 200 Bq, 1.6 ng Am.
% injected activity in controls at 7 d, wound site 71.4 ± 1.1, total body 97.0 ± 1.0.
[2-4]) Treatment protocols as given in Table 9.21.

9.6.5.2.6 Wound contamination with plutonium tributylphosphate (TBP)

The protocols used have in broad terms been similar to those used for plutonium nitrate. A summary of the data obtained after the intramuscular injection of plutonium-TBP is given in Table 9.23. They show that the removal of plutonium from the wound site and systemic tissues is considerably less than for plutonium nitrate. This is attributed in part to the greater mass of plutonium deposited, but clearly the influence of chemical form is also important. It is noteworthy that the skeletal and liver contents after the administration of 3,4,3-LI(1,2-HOPO) are 3 to 4 times less than with DTPA.

Table 9.23 Efficacy of injected 3,4,3-LI(1,2-HOPO) and DTPA on retention of ^{238}Pu after intramuscular injection as TBP [95P1, 00S2]

	% controls at 7 d ($\xi \pm$ SD, N=6)[1]	
Treatment	Wound site	Total body
Local injection		
LIHOPO[2]	73 ± 24	60 ± 20
CaDTPA[2]	71 ± 15	72 ± 15
Iv injection		
LIHOPO[2]	86 ± 13	70 ± 13
CaDTPA[2]	100 ± 22	87 ± 15

[1]) % injected activity in controls at 7 d, wound site 71.1 ± 9.8 , total body 97.6 ± 8.9.
[2]) 30 μmol kg^{-1} CaDTPA after 30 min.

9.6.6 Thorium

The recommended substance for thorium isotopes is DTPA (see Section 9.3). The authors are unaware of any definitive human data which demonstrates the efficacy of the substance.

9.6.6.1 Animal data

9.6.6.1.1 Inhalation of thorium nitrate

Studies in rats [91S1] have shown that DTPA is poorly effective when the amounts of ^{232}Th simulated acute intakes equivalent to the dose limit, even when the substance was injected at dosages of 300 and 1000 μmol kg^{-1} (Table 9.24). It is noteworthy that treatment is unlikely to be implemented for intakes of less than 10 times the dose limit (see Section 9.2). Compared with the human equivalent dosage of DTPA, the increase in efficacy for ^{232}Th using 3,4,3-LI(1,2-HOPO) could only be considered marginal (Table 9.25).

The efficacy of DTPA increased to a moderate extent when substantially lower mass concentrations of thorium were used, as with ^{228}Th. (Table 9.26). However the most effective treatment to date has involved the repeated injection of 3,4,3-LI(1,2-HOPO) whereby the thorium content of the lungs was reduced to 17 % of that in controls (Table 9.24). The results obtained with 3,4,3-LI(1,2-HOPO) suggest that the ineffectiveness of DTPA is unlikely to be due to the formation of hydrolysis products in the lungs.

9.6.6.1.2 Wound contamination with thorium nitrate

Simulated wound studies in rats have been undertaken mainly with the high specific activity ^{228}Th isotope. The data given in Table 9.27 show that 7 to 8-fold reductions in the body content occur after the prompt local injection of 3,4,3-LI(1,2-HOPO) followed by repeated administration at the same dosage. Under the same conditions, the reduction after DTPA administration was about 2-fold. The table also shows that the efficacy of both ligands is reduced appreciably when treatment is delayed only by 1 day. Based on other data with plutonium and americium [00S2], it is unlikely that intravenous or intraperitonal injections alone would have any beneficial effect.

Table 9.24 Efficacy of single and repeated DTPA administration on retention of ^{232}Th in rats after inhalation as nitrate [(1)] [91S1]

	% controls at 7 d ($\xi \pm$ SE, N=4)[(2)]	
Treatment [(3)]	Lungs	Total body
CaDTPA, [(4)]	75 ± 8	74 ± 8
CaDTPA[(5)]	66 ± 7	65 ± 8
Ca+ ZnDTPA[(6)]	66 ± 9	65 ± 8
CaDTPA [(7)]	98 ± 10	97 ± 10

[1]) initial lung deposit of $^{230+232}$Th, 586 ± 16 Bq; 6.46 ± 0.18 µg Th
[2]) % of ILD in control animals at 7 d: lungs 76.2 ± 5.2, total body 82.0 ± 5.4
[3]) chelates administered intraperitoneally
[4]) 300 µmol kg^{-1} administered at 30 min only
[5]) 1000 µmol kg^{-1} administered at 30 min only
[6]) 1000 µmol kg^{-1} CaDTPA administered at 30 min and 300 µmol kg^{-1} ZnDTPA at 1 d, 2 d and 3 d
[7]) 1000 µmol kg^{-1} administered at 1 d only

Table 9.25 Efficacy of injected 3,4,3-LI(1,2-HOPO) and DTPA on retention of ^{232}Th in rats after inhalation as nitrate[(1)] [91S1, 98S2]

Treatment	% controls at 7 d ($\xi \pm$ SD, N=4)[(1)]	
	Lungs	Total body
LIHOPO [(2)]	93 ± 7	87 ± 5
LIHOPO [(3)]	73 ± 6	69 ± 5
ZnDTPA [(3)]	93 ± 6	91 ± 5

[1]) Initial lung deposit, 4.2 µg Th
Equivalent intake of Th by workers 61 mg or 247 Bq ^{232}Th, i.e. 0.36 ALI for ^{232}Th (CED 7.2 mSv)
% ILD in controls at 7 d: lungs 69.9 ± 4.5, total body 78.1 ± 4.6
[2]) 30 µmol kg^{-1} i.p. after 30 min
[3]) 30 µmol kg^{-1} i.p. after 30 min, 6 h, 1 d, 2 d and 3 d

Table 9.26 Efficacy of injected 3,4,3-LI(1,2-HOPO) and DTPA on retention of ^{228}Th in rats after inhalation as nitrate [98S1, 00S2]

	% controls at 7d ($\xi \pm$ SD, N=4)[(1)]	
Treatment	Lungs	Total body
LIHOPO[(2)]	36 ± 3	29 ± 2
LIHOPO[(3)]	17 ± 2	17 ± 2
DTPA[(3)]	73 ± 4	78 ± 3

[1]) Initial lung deposit, 4 ng Th
Equivalent intake of Th by workers, 58 mg or 4.18×10^4 Bq ^{230}Th and 1.74×10^9 Bq ^{228}Th i.e. 59 ALIs ^{230}Th (CED 100 mSv) and 2×10^6 ALIs ^{228}Th (2000 Sv)
% ILD in controls at 7 d: lungs 50.7 ± 1.9, total body 69.9 ± 3.5.
[2]) 30 µmol kg^{-1} i.p. after 30 min
[3]) 30 µmol kg^{-1} i.p. after 30 min, 6 h, 1 d, 2 d, 3 d

Table 9.27 Efficacy of injected 3,4,3-LI(1,2-HOPO) and DTPA on retention of ^{228}Th after intramuscular injection: prompt and delayed treatment [95S1, 00S2]

	% controls at 7 d ($\xi \pm$ SE, N=4)[(1)]	
Treatment	Wound site	Total body
LIHOPO [(2)]	14 ± 1	20 ± 1
CaDTPA[(2)]	60 ± 3	65 ± 3
LIHOPO[(3)]	12 ± 1	15 ± 1
Ca DTPA[(3)]	50 ± 3	55 ± 2
LIHOPO[(4)]	38 ± 2	40 ± 2
CaDTPA[(4)]	79 ± 3	79 ± 2

[1]) Injected activity 600 Bq ^{228}Th, 0.1 ng Th.
% injected activity in controls at 7 d, wound site 64.8 ± 1.5, total body 91.5 ± 1.7.
[2]) 30 µmol kg^{-1} locally at 30 min
[3]) 30 µmol kg^{-1} locally at 30 min and then by ip injection at 6 h, 1 d, 2d and 3d after exposure.
[4]) 30 µmol kg^{-1} at 1 d and then by i.p. injection at 6 h, 1 d, 2 d and 3 d later.

9.6.7 Uranium

At the present time no agent can be recommended for the removal of uranium from the systemic circulation. Uranium complexation by sodium bicarbonate has been proposed for reducing the systemic deposit [80N1, 84W1, 92B1]. However, this is not supported by controlled studies with laboratory animals under realistic conditions e.g. with delays between exposure and treatment of 30 min or more.

The recommended dose is 250 cm^3 of 1.4 % sodium bicarbonate (42 mmol) administered by slow intravenous infusion, with further infusions on subsequent days if necessary [92B1]. Since the plasma bicarbonate concentration is held more or less constant at ~25 mmol dm^{-3}, and its turnover time is fairly rapid, it appears unlikely that the slow infusion of a further 42 mmol would lead to a sufficiently large and sustained increase in plasma bicarbonate concentration to significantly enhance the excretion of uranium. It should also be noted that alkalosis, respiratory acidosis and hypokalaemia may result from such treatment.

The authors are unaware of any definitive human data which demonstrates the efficacy of bicarbonate, or indeed any other substance.

9.6.7.1 Animal data

9.6.7.1.1 Injection of uranium

Other than the octoxide and dioxide, uranium compounds formed in the nuclear fuel cycle are readily absorbed into the blood after inhalation e.g. ammonium diuranate, uranyl nitrate, uranium tetrafluoride. Since the role of treatment will be to minimise nephrotoxocity in the early lung clearance phase, the administration of uranium by intravenous injection would be appropriate for evaluating the likely efficacy of various treatment regimens.

Since there appears to be no substantive evidence that the administration of sodium bicarbonate is an effective method of treatment, several alternative substances have been investigated in animals. Some of these such as tiron, certain phosphonates and hydroxypyridonate derivatives have caused large reductions in the kidney and skeletal contents of uranium when administered simultaneously or within minutes [00S2, 00S3]. However under more realistic conditions when delays between exposure and treatment may be 30 minutes, or probably longer, they are poorly effective. The efficacies after immediate and delayed treatment for some selected substances are shown in Tables 9.28 and 9.29. Notably, Table 9.29 also demonstrates the poor efficacy achieved with sodium bicarbonate.

9.6.7.1.2 Wound contamination

The ligand 3,4,3-LI(1,2-HOPO) has been shown to be the most effective yet tested for plutonium, americium and thorium after inhalation and wound contamination. However the data in Table 9.29 show that it is only moderately effective even when administered immediately after the uranium. Under more realistic conditions of exposure and treatment it is poorly effective. The immediate administration of the bisphosphonate EHBP, (ethane-1-hydroxy-1,1-bisphosphonate) has been shown to prevent death in animals [94U1, 00M1]. However, the prevention of death in an acutely poisoned animal is not a reliable indicator of the effect of a chelator at the much lower level of human contamination that would be expected in any likely industrial accident, further the doses of EHBP used were more than 100 times those used in the treatment of human disease. The data given in Table 9.30 demonstrates that the efficacy of EHBP again falls rapidly with time. The main interest in EHBP is that some preparations have been licensed for other medical purposes, and hence its toxicity and metabolism are well known.

It is concluded that at present no effective substance is available for the treatment of internal contamination by uranium.

Table 9.28 Efficacy of injected polyphosphonic acids on retention of uranium [92G1, 98H1, 00S2]

	% controls at 4 d ($\xi \pm$ SE, N=4)[1]	
Treatment	Kidneys	Total body
Immediate		
HMDTMP[2]	8 ± 1	31 ± 3
DTPMP[2]	8 ± 1	32 ± 3
Delayed 30 min		
HMDTMP[2]	60 ± 8	81 ± 6
DTPMP[2]	70 ± 9	86 ± 6

[1]) ID 300 Bq ^{233}U, Ligand:uranium mol ratio 1.5×10^4
% ID in controls, kidneys, 9.9±0.9, total body, 27.3±1.3
[2]) 300 µmol kg^{-1} of hexamethylenediaminetetra-meyhylene-phosphonic acid or diethylenetriamin-epentamethylene-phosphonic acid.

Table 9.29 Efficacy of injected 3,4,3-LI(1,2-HOPO) and sodium bicarbonate on retention of uranium [95H1, 98 H1, 00S2]

	% controls at 24 h ($\xi \pm$ SE, N=5)[1]	
Treatment	Kidneys	Femora (Bone)
Uranium im Chelate im[2]		
LIHOPO	23 ± 3	46 ± 5
$NaHCO_3$	87 ± 5	67 ± 22
Uranium im, chelate ip[3]		
LIHOPO	54 ± 9	82 ± 13
$NaHCO_3$	64 ± 13	114 ± 33
Uranium iv, chelate iv[4]		
LIHOPO	21 ± 4	61 ± 8
$NaHCO_3$	76 ± 20	102 ± 25

[1]) Initial deposit, 0.84 µmol kg^{-1}.
[2]) Treatment immediate. % ID in controls, kidneys 18.2, femora 1.4.
[3]) Treatment after 30 min. % ID in controls, kidneys 15.5, femora 1.25.
[4]) Treatment immediate. % ID in controls, 15.3, femora 2.2. LIHOPO, 30 µmol kg^{-1}, $NaHCO_3$, 640 µmol kg^{-1} in all cases.

Table 9.30 Removal of intramuscular ^{233}U from rats by intramuscular injection of EHBP [98H1, 00S2]

	% controls at 24 h[1]	
EHBP	Kidneys	Total body
5 min	24 ± 7	70 ± 9
30 min	55 ± 21	89 ± 12

[1]) Mean ± standard error, n=5
U injected 0.02 µmol kg^{-1}, 1.5 kBq kg^{-1}, ligand to U molar ratio, 5000.
% initial deposit in controls: kidneys, 14.1 ± 2.9, total body 54.6 ± 6.0
EHBP = ethane-hydroxy-1,1-bisphosphonate

9.7 Future research needs

For insoluble substances deposited in the lungs or in wounds, decorporation procedures involving lung lavage and surgical excision respectively are the most appropriate. Increasing the expertise in the treatment of obstructive lung disease should increase the availability of the lavage procedure after major accidents. However, it is difficult to perceive what improvements could be made to increase the efficacy of lavage, and surgical excision, other than through good medical practice and medical-team training.

Likewise, it is difficult to envisage what improvements can be made to increase the elimination of tritium and iodine isotopes from the body beyond those procedures described earlier.

The decorporation of caesium becomes an important issue in major radiation accidents e.g. contamination of members of the public from leaking radiotherapy sources, fission product release in a nuclear accident. The commonly used decorporating agent, Prussian Blue, is of only limited efficacy and it is recommended therefore that more effective agents are developed and tested.

Within the last decade in particular, considerable progress has been made in evaluating treatment regimens and developing new chelating agents for the decorporation of plutonium, americium, and high specific activity forms of thorium. Animal studies have shown that some of these ligands are much superior to DTPA, comprehensive toxicity testing has not yet been undertaken, and for practical purposes DTPA must at present remain the agent of choice for these elements. It is essential, however, that patients who receive DTPA therapy are followed up in order to establish the efficacy of the treatment regimen for the particular physico-chemical form.

Little progress has been made on the decorporation of uranium. In view of the large scale and widespread use of the element, this should be viewed with some concern. It is recommended that research to find new methods for the decorporation of uranium should be expedited.

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