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Literature Survey on Decorporation of Radionuclides from the Human Body

E.A. Waller, R.Z. Stodilka, K. Leach and L. Prud'homme-Lalonde

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Literature Survey on Decorporation of Radionuclides from the Human Body

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Abstract

The broad use of radionuclides by many industries has greatly increased the probability of events that could lead to internalized contamination. Examples include accidents and/or intentional damage to nuclear power plants or radiation therapy units in hospitals, the use of radiological dispersal weapons, and lost or stolen radionuclide sources. Developing effective countermeasures requires knowledge of the physical and chemical composition of the radionuclides, their metabolic activities within the body, and methods to expedite their elimination from the body.

This report presents a summary of information pertaining to intake and decorporation of radionuclides from humans. This information would be the first step in establishing a field protocol to guide physicians in military missions. Developing such a guide requires an understanding of the dangers associated with internal radioisotope contamination, decision levels for administering therapy (risk vs. benefit) and protocols for administering therapy. As presented, this study could be used to decide what decorporation pharmaceuticals should be maintained in quantity by the military, and how to best train officers with medical responsibilities.

Résumé

L'utilisation des radionucléides par plusieurs industries a considérablement augmenté la probabilité d'évévements qui peuvent mener à une contamination interne. Les exemples comprennent les accidents ou les dommages intentionnels dans les centrales nucléaires ou dans les unités de radiothérapie dans les hôpitaux, l'utilisation d'armes de dispersion radiologique, et les sources de radionucléides perdues ou volées. Afin de développer des mesures de prévention efficaces, il est nécessaire d'avoir une connaissance de la composition physique et chimique des radionucléides, de leur activité métabolique et des méthodes pour accélérer l'élimination du corps.

Ce rapport présente un résumé des données relatives à l'incorporation et à la décorporation des radionucléides chez les humains. Ces données seraient la première étape dans l'établissement d'un protocole à l'usage sur le terrain par les médecins en missions militaires. Le développement d'un tel guide exige une compréhension des dangers associés à la contamination interne par un radioisotope, des niveaux de décision pour l'administration de la thérapie (risque vs bénéfice) et des protocoles d'administration de la thérapie. Telle que présentée, cette étude pourrait servir à déterminer quels produits pharmacologiques servant à la décorporation devraient être entreposés par les forces armées, et quelle formation devrait être donnée aux officiers avec des responsabilités médicales.

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Executive summary

The potential for exposure to internalized radionuclides has grown exponentially in the last decade. The most important aspect of treating such an exposure is the removal of the radionuclide in order to minimize committed dose. This literature review summarizes decorporation strategies for a variety of exposure scenarios, including radionuclide ingestion, inhalation and wound absorption. However, although medical decorporation is a well-studied endeavour, very few therapeutic drugs are readily available to health care providers.

As with any effort for therapeutic intervention, benefit must be weighted against risk. Certain risk factors that are associated with lung lavage, drug injection and wound excision are presented along with the risk at various levels of committed effective dose from radionuclide exposure. It is concluded that the risk associated with inaction generally outweighs the risk of exercising interventional options. This is sound justification for pursing the most appropriate treatment modality.

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Sommaire

Le potentiel d'une exposition radioactive interne a pris une ampleur exponentielle durant la dernière décennie. L'aspect le plus important dans le traitement de telles expositions est l'extraction du radionucléide afin de minimiser la dose engagée. Cette analyse bibliographique résume les stratégies de décorporation pour une gamme de scénarios d'exposition, comprenant l'ingestion de radionucléide, l'inhalation et l'absorption par blessure. Cependant, même si la décorporation médicale est un domaine d'activités bien connu, très peu de médicaments thérapeutiques sont facilement disponibles aux dispensateurs de soins de santé.

Dans toute intervention thérapeutique, le bénéfice doit être évalué contre le risque. Certains facteurs de risque associés au lavage pulmonaire, à l'injection de médicament et à l'excision d'une blessure sont présentés au même titre que les risques à diverses concentrations de la dose effective engagée d'une exposition à un radionucléide. Il a été établi que le risque associé à l'inaction était généralement supérieur au risque causé par la mise en application des options d'intervention. Ceci justifie la poursuite de la recherche pour la modalité de traitement la plus appropriée.

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1. INTRODUCTION

Most of the scientific experience gained in decorporation of radionuclides is based upon animal experimentation rather than human experience. There are a number of cases that can be specifically referenced that detail internal contamination and/or decorporation therapy. A few significant cases are presented below, with the dominant isotope (with respect to decorporation) presented in brackets.

Radium Dial Painters, US (^{226,228}Ra)

Hanford, WA,US (^{241}Am)

Los Alamos, NM, US (^{239}Pu)

Goiânia, Brazil (^{137}Co)

Chernobyl, Ukraine (^{131}I)

There have been numerous studies conducted around the world regarding the efficiency of various therapeutic drugs for decorporating metals from the body. In general, it has been found that certain decorporation drugs can increase the removal rate of radionuclides from the body, especially if administered within the first few hours post-exposure.

Vivid examples of the affects of the effectiveness of administering a decorporation agent (Prussian Blue) are obtained from the radiological accident in Goiânia, Brazil[1]. On 13 September 1987, a shielded 50.9 TBq (1375 Ci) ^{137}Cs teletherapy source was removed from its protective housing in an abandoned clinic. The source capsule was subsequently ruptured. Four people ultimately died from acute radiation exposure, and 28 people suffered radiation burns. A total of 249 people were found with external contamination, and 46 people were found with internal contamination at high enough levels to warrant decorporation therapy, in the form of Prussian Blue. This accident resulted in the highest levels of ^{137}Cs contamination ever clinically recorded.

The results of fecal analysis showed that Prussian Blue resulted in higher activities of ^{137}Cs in the stool, and whole body counts showed increased removal from the body. The effectiveness of Prussian Blue for one Goiânia patient is depicted in Figure 1. This figure plots the content of radioactive material (in this case, ^{137}Cs) in the body versus time. In the figure, the curve at position "A" is a result of administration of 10 g of Prussian Blue per day. At position "B", the Prussian Blue treatment was ceased, and it is readily observed that the rate of decorporation of ^{137}Cs decreases.

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[1] The Radiological Accident in Goiânia, International Atomic Energy Agency, IAEA STI/PUB/815, Vienna, 1988.

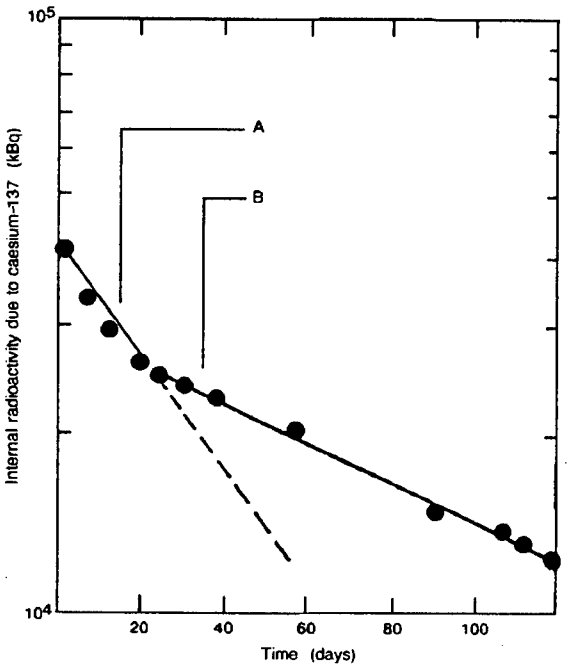

Figure 1- The effect of administering Prussian Blue

For the military application of decorporation agents, consideration must be given to the fact that proper medical care is not available immediately, and therefore special training and protocols must be developed for on-scene treatment. In addition, thought must be given to the fact that it is undesirable to treat a soldier in the field for internal radionuclides, if this treatment is prone to cause further medical problems that will either require more medical attention, or impede the military operation.

This report will discuss various aspects of internal contamination, biological clearance, bioassay, treatment modalities, new trends and military implications of decorporation therapy.

2. Summary of Entry Modes into the Body

2.1 Overview

There are numerous pathways that external radiation and contamination can interact with the human body. The major pathways of military significance are depicted in Figure 2 [1]. Of significance to this work are the pathways that could lead to radionuclides becoming deposited in the human body.

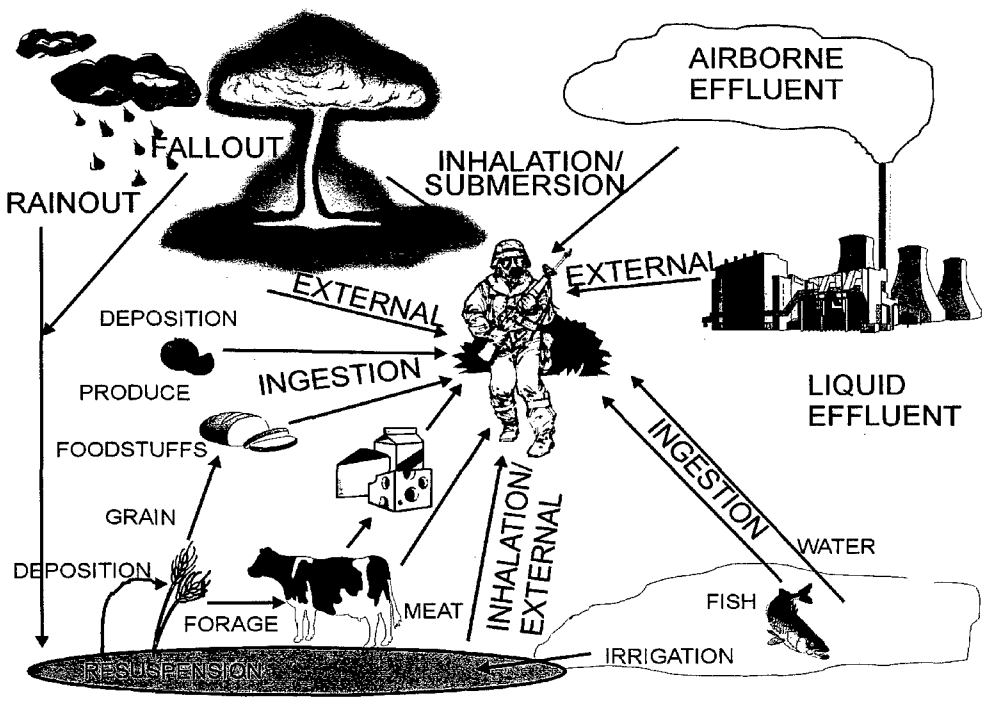

Figure 2 - Exposure pathways

The primary entry routes of radionuclides into the body are:

1. Inhalation;
2. Ingestion;
3. Skin Absorption; and
4. Wound Absorption

With the exception of tritium, skin absorption is not considered to be a significant pathway. Inhalation, ingestion and wound absorption are discussed in the following sections.

2.2 Inhalation Pathway

The inhalation pathway is a result of airborne radioactive gases and particulate. The key to this pathway is that there must be a source of energy causing radioactive material to become airborne, or form a plume. Generally, an explosion or fire will cause a plume.

Inhalation of radioactive contamination associated with an accidental or intentional release of radioactive gas or particulate arises from three primary scenarios:

1. inhalation of particulate or gas while in the plume;
2. inhalation of particulate or gas aloft that precipitates near a breathing space; and
3. inhalation of resuspended particulate.

For military operations, the possibility of chronic resuspension of radioactive contaminant is high due to troop movements and vehicle operations.

The inhalation pathway can dominate during the early stages of a reactor accident, radiological dispersal weapon deployment or nuclear weapon detonation. The intake of radioactive material through inhalation is dependent upon the airborne concentration and the breathing rate of the individual. The uptake, primarily through the lungs, is due to factors such as the deposition site, physical form and chemical form of the contaminant.

2.3 Ingestion Pathway

If there is a potential of eating, drinking or smoking in the presence of loose (removable) contamination, then there is a potential ingestion hazard. For both inhalation and ingestion, the efficiency of the process must be considered. That is, the fraction of radioactive material available for intake must be determined for the given pathway. This fraction can range from zero (no intake) to one (complete intake). For estimating dose, a determination has to be made of the uptake of radioactive material. Again, this fraction can range from zero to one[2].

A generic model of the pathway for a hypothetical ingestion scenario is shown in Figure 3 [2]. The process may be described as follows:

- An item (a) is handled that has loose (removable) contamination;
- The contamination is transferred (b) with an efficiency ($\varepsilon 1$) from the item to the individual's hands;
- The contamination on the hands is then transferred (c) with an efficiency ($\varepsilon 2$) to an item which comes in contact with the mouth (food, drink, cigarette);
- The contaminated product (d) is then placed in contact with the mouth, and the contamination is transferred (known as the intake) from the product into the body, with an efficiency ($\varepsilon 3$)
- The contamination which enters the mouth will travel through the body systems (e), and some will be taken up (based upon the chemistry of the radioisotope) by various body organs, with an efficiency (f1).

If an uptake is known to have taken place, and is quantified using bioassay (urinalysis, fecal assay, whole body counting etc), then it is possible to estimate the intake. It may then be possible to determine the total inventory of radioactive present, by applying the transfer efficiencies ($\varepsilon 1$,$\varepsilon 2$ and $\varepsilon 3$). It is clear that for a hypothetical intake scenario, the transfer efficiencies may be used to estimate the potential uptake, hence estimate the committed dose. It should also be noted that, although a single transfer is considered from the contaminated item to the hands, it is very probably that numerous transfers can take place between the hands and the product (c) and also the product and the mouth (d). Swipes are commonly used to assist quantification of loose (removable) contamination. A value on a swipe corresponds to the first transfer (b) from the source to the hands. For the case of a hypothetical radionuclide ingestion, the transfer efficiencies ($\varepsilon 1$,$\varepsilon 2$ and $\varepsilon 3$) must be estimated.

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[2] The intake to uptake transfer fractions for various internal processes are generally taken into account in dose conversion factors.

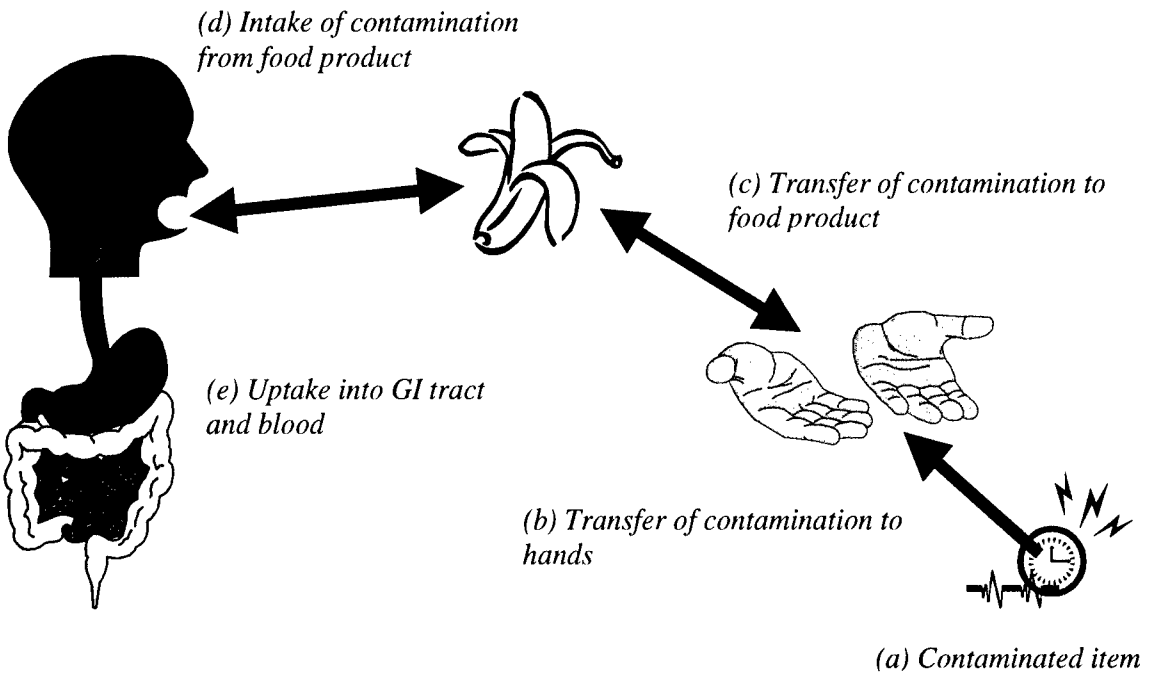


Figure 3 - Model of ingestion pathway from contamination

2.4 Wound Absorption

By definition of a wound, it is likely that treatment of the patient's immediate medical problems will take precedence over wound decontamination. This makes it possible for this radionuclide pathway of entering the human body to exist. The physicochemical characteristics of the radionuclide present will determine the rate at which the contaminant moves from the wound site to more sensitive organs and tissues in the body. There are three general classifications of wounds to consider: abrasion, punctures and lacerations [3].

A contaminated abrasion presents considerable potential for absorption since the surface is often raw and bleeding, and the epidermal barrier is no longer intact. Usually such surfaces can be cleaned with a detergent and, if necessary, a topical anesthetic. After a reasonable effort, there is no need to attempt to remove all contamination since the residue that remains on the surface will probably be incorporated in the scab. When the scab sloughs it should be saved for measurement of radioactivity and proper disposal.

Punctures may result from sharp, contaminated objects contacting the skin at a point. This includes hypodermic needle punctures. In explosions a small missile may be driven through the skin and may leave only a small entry wound. Its exact position may be difficult to locate and thus require considerable surgical extension of the wound.

A simple clean laceration made superficially by a contaminated sharp object is probably the least difficult type of wound in which contamination has to be detected and then decontaminated. Often much of the contamination is deposited on the lips of the wound. When lacerations are ragged and deep, contamination may be deposited in connective tissue with subsequent migration that makes difficult the detection of the contamination. There is also the possibility of direct entry of contamination into a blood vessel or major lymph channel.

3. Factors Affecting Retention Rate and Clearance in Humans

3.1 Overview

Retention rate and clearance are influenced by the mode of entry, the chemistry and solubility of a compound, and the particle size [4]. Some radioactive compounds may not be rapidly absorbed, even though considered to be relatively soluble, because of acidic or caustic properties that fix the material to tissue proteins.

After entrance into the body, a radionuclide will continue to irradiate the surrounding tissues until it is either excreted by some physiological process, principally through the urine or feces, removed by some treatment procedure such as wound debridement or decorporation, or until it becomes inactive through radioactive decay. The internal emitter will be metabolized according to its chemical properties. The metabolism of the radionuclide and its biological half-time are as important as its physical half-life in determining the significance of the exposure. Some radionuclides, such as ^{24}Na, are distributed throughout the body as are the stable isotopes, for example, ^{25}Na. Other radioisotopes, such as ^{131}I, are concentrated in particular organs. In the case of iodine, the thyroid becomes the principal organ involved, often called the "critical organ" because it receives a higher radiation dose or is the site of the most significant biological effect compared to other tissues.

If the radionuclide in question is not absorbed by the body tissues rapidly, knowledge of the transit and clearance times from the pulmonary and gastrointestinal tracts is essential for proper management of that internal contamination. For example, physiological cleansing mechanisms, such as the mucociliary apparatus in the respiratory tract, may be effective in removing radioactive particles in the first few days after exposure. The respiratory tract clearance pathway should not be overlooked in the initial evaluation of an accidental exposure. Similarly, exposure of the gastrointestinal tract by intralumenal radioactive material depends largely on the transit time.

3.2 Inhalation Pathway

There are three major mechanisms that determine the behavior, and in particular the deposition in the respiratory tract, of airborne particles. Gravitational sedimentation and inertial impaction are known as aerodynamic mechanisms and are important for particles with diameters over about 0.5 μm. In contrast, diffusion is a thermodynamic process which becomes more important with decreasing particle size; it is generally important for diameters below about 0.5 μm.

The physical properties of a particle that determine its aerodynamic transport are combined in a single parameter - the aerodynamic diameter - which takes into account

the size, shape, and density of the particle. Similarly, the properties that govern its thermodynamic transport are combined in the thermodynamic diameter which depends on the shape and diffusion coefficient of the particle, as well as the ambient temperature, but is not dependent on the particle density.

Most aerosols encountered in practical situations consist of a distribution (frequently log-normal) of particle sizes. The properties of the aerosol must therefore be characterized by some average of the properties for the individual particle sizes in the distribution. In recent ICRP reports the aerodynamic properties of an aerosol are specified in terms of the Activity Median Aerodynamic Diameter (AMAD). The AMAD is the median aerodynamic diameter of the distribution, thus 50% of the activity in the aerosol is associated with particles which have aerodynamic diameters in excess of the AMAD. Similarly, the thermodynamic properties of an aerosol are described by the Activity Median Thermodynamic Diameter (AMTD) which is defined in an analogous manner to the AMAD.

As noted above, particles with aerodynamic diameters larger than about 0.5 μm are deposited predominantly by aerodynamic processes and particles with aerodynamic diameter less than 0.5 μm are deposited predominantly by thermodynamic processes. Thus, it is appropriate to characterize some aerosols by their AMAD and others by their AMTD.

Inhalation dose coefficients for the public have been calculated using the new model for the Human Respiratory Tract from ICRP Publication 66 [5] which quantifies retention of deposited activity in the various respiratory tract regions. Clearance from these regions is represented by three processes. It is assumed that clearance from the anterior nose is extrinsic (e.g. nose-blowing), and that elsewhere it results from competition between particle transport to the GI tract and lymph nodes, and absorption of material into body fluids. It is assumed, by default, that particle transport rates are the same for all materials, and that the absorption rates are the same in all regions except the anterior nose, where none occurs. It is recommended that material-specific rates of absorption should be used whenever reliable human or animal experimental data exist. For other compounds, default values are recommended for use according to whether absorption is considered to be fast (Type F), moderate (Type M) or slow (Type S), corresponding broadly to inhalation Classes D, W and Y in the ICRP Publication 30 [6] model. It is assumed that clearance rates of all three processes, nose-blowing, particle transport and absorption, are independent of age and sex. For members of the public dose coefficients are based on an Activity Median Aerodynamic Diameter, AMAD, of 1 μm and specified distributions of time spent at four levels of exercise (sleep, sitting, light exercise and heavy exercise). For workers, an AMAD of 5 μm is assumed.

For the calculation of inhalation dose coefficients, allowance has to be made for the absorption of material passing through the GI tract after clearance from the respiratory system. It is considered that for environmental exposure, radionuclides might typically be present as minor constituents of the inhaled particles, and that therefore absorption into body fluids would depend on dissolution of the particle matrix, as well as on the elemental form of the radionuclide. Generally for Type F materials, the

greatest f1 value for the element in ICRP Publication 68 [7] is applied. For Types M and S, default f1 values of 0.1 and 0.01 respectively are applied, unless a lower f1 value for that absorption Type (or for a more soluble Type) was used in ICRP Publication 68, in which case that value is applied. For the remaining 60 elements, the f1 values adopted in ICRP Publication 30 were used.

For radionuclides inhaled in particulate form it is assumed that entry and regional deposition in the respiratory tract are governed only by physical properties of the aerosol such as the size distribution of the aerosol particles. The situation is different for gases and vapours, for which respiratory tract deposition is material-specific. Almost all inhaled gas molecules contact airway surfaces, but usually return to the air unless they dissolve in, or react with, the surface lining. The fraction of an inhaled gas or vapour that is deposited in each region thus depends on its solubility and reactivity. Generally, however, the regional deposition of a gas or vapour cannot be predicted on a mechanistic basis, from knowledge of its physical and chemical properties, but has to be obtained from an in vivo experimental study.

As a general default approach, the ICRP Publication 66 model assigns gases and vapours to three classes, on the basis of the initial pattern of respiratory tract deposition:

- Class SR-0 insoluble and non-reactive: negligible deposition in the respiratory tract.
- Class SR-1 soluble or reactive: deposition may occur throughout the respiratory tract.
- Class SR-2 highly soluble or reactive: total deposition in the extrathoracic airways.

Subsequent retention in the respiratory tract and absorption to body fluids are determined by the chemical properties of the specific gas or vapour. ICRP Publication 68 gives information on the assignment of gases and vapours to these three classes, and for selected Class SR-1 compounds information on fractional deposition and subsequent clearance. Although consideration has to be given to the total respiratory tract deposition, regional deposition does not need to be assessed for such materials, since for the purposes of dose calculation they can be treated as if they were injected directly into body fluids.

3.3 Ingestion Pathway

For exposure of members of the public to radionuclides, ingestion is generally the most significant route of intake. For military theatre personnel, it is assumed that the inhalation pathway is the most significant route of exposure. For extended military operations in a contaminated environment, the ingestion pathway becomes more important for the military theatre. Elements incorporated into food may be more readily absorbed from the gastrointestinal (GI) tract than inorganic forms of these elements. This is taken into account, as far as is possible, in the choice of the recommended fractional absorption, f1, values.

3.4 Clearance

Clearance refers to removal of radionuclides from body compartments, and subsequently from the body. For example, there are several routes of clearance from the respiratory tract. Material deposited in the anterior nose is removed by extrinsic means such as nose-blowing. In other regions clearance is competitive between the movement of particles towards the gastrointestinal (GI) tract and lymph nodes (particle transport), and the absorption into blood of material from the particles in the respiratory tract. Clearance kinetics are expressed in terms of fractional clearance rates. It is assumed that the clearance rates due to particle transport and absorption to blood are independent. Thus the overall rate of clearance from a region is the sum of the rates due to the separate processes.

The rates of clearance from each region, by each route, generally change with time after intake, and will in general be different for material deposited directly in the region during inhalation or cleared into a region following deposition in another region. Indeed, for the latter, the rate of particle transport out of a region depends on the time since the material was transported into the region, but its rate of absorption to blood depends on the time since the material was originally deposited. Thus, the rates of clearance are themselves dependent on the initial pattern of deposition, the time course of intake and the time course of transport from other regions into each region. To take account of this and to simplify calculations, clearance from each region is represented in the model by a combination of compartments. Each compartment clears at a constant fractional rate, such that the overall clearance approximates the required time-dependent behavior.

It is assumed that particle transport rates are the same for all materials. A single compartment model is adequate to describe particle transport of all materials. Reference values of rate constants were derived, so far as possible, from human studies, since particle transport rates are known to vary greatly among mammalian species.

Absorption into blood depends on the physical and chemical form of the deposited material. It is assumed to occur at the same rate in all regions (including the lymph nodes) except the anterior nasal region, where it is assumed that none occurs.

Absorption is a two-stage process: dissociation of the particles into material that can be absorbed into blood (dissolution); and absorption into blood of soluble material and of material dissociated from particles (uptake). The clearance rates associated with both stages can be time-dependent.

The simplest compartment model representation of time-dependent dissolution is to assume that a fraction of the deposited material dissolves relatively rapidly, and the rest dissolves more slowly. In the model, the material deposited in the respiratory tract is assigned to compartments labeled "Particles in initial state" in which it dissolves at a constant rate. Material is simultaneously transferred to a corresponding compartment labeled "Particles in transformed state" in which it has a different dissolution rate. The ratio of these two dissolution rates approximates to the fraction that dissolves rapidly. In different situations, the "Particles in transformed state" may represent the residual material following dissolution of a relatively soluble component or surface layer, or material taken up by macrophages. The essential feature is that it remains subject to particle transport.

Uptake to blood of dissociated material can usually be treated as instantaneous, but in some situations (as for certain gases and vapours), a significant fraction of the dissociated material is absorbed slowly into blood as a result of binding to respiratory tract components. To represent time-dependent uptake, it is assumed that a fraction of the dissolved material is retained in a "bound" state, from which it goes into blood at a given rate, while the remaining fraction goes to blood instantaneously. In the model, material in the "bound" state is not cleared by particle transport processes, but only by uptake to blood. Thus, only one "bound" compartment is required for each region.

It is recommended that material-specific rates of absorption should be used in the respiratory tract model for compounds for which reliable human or animal experimental data exist. For other compounds, default parameters are recommended according to whether the absorption is considered to be fast (Type F), moderate (M) or slow (S), corresponding broadly to inhalation Classes D, W and Y in Publication 30 [6].

Expressed as approximate half-times for one or two components of clearance, these absorption rates correspond to:

Type F (fast)	10 minutes (100%);
Type M (moderate)	10 minutes (10%); 140 d (90%);
Type S (slow)	10 minutes (0.1%); 7000 d (99.9%).

4. Estimating and Confirming Internal Contamination

4.1 Introduction

The greatest body of human experience in the effects of internal emitters has been derived from the early radium exposures. Studies on the long term effects of radium continue to take advantage of the rare opportunity presented by this rather large number of persons exposed to long-lived internal emitters. Our present radiation guide values for bone-seeking isotopes is based on a comparable energy release as delivered by a maximum permissible body burden of 0.1 μg ^{226}Ra plus daughters. In a series of 293 individuals bearing a significant body burden of ^{226}Ra, no malignant tumors have been found where the maximum radium body burden was below 1.2 μCi Ra [8]. It is suspected that the initial amount of radium in the body is a much more important factor in the carcinogenic process than the terminal body content. All studies to date indicate that the permissible guide value for radium is a very safe limit.

Attention should be directed to the fact that internal emitters have not produced pathological effects as a result of acute, accidental exposure. The radium dial painters and uranium miners received multiple exposures over periods of months and years. The atomic energy industries to date have not experienced accidental exposures to internal emitters resulting in any acute or dramatic radiation injury similar to the direct radiation exposures, which produce the dramatic acute radiation syndrome. The concern regarding internal emitters is related more with the continuing internal radiation dose, which may produce late pathological effects. This concern does, in fact, assume the urgency of an emergency due to the need for rapid evaluation and early administration of therapy to reduce the body burden.

A brief review of a few fundamental factors which influence the radiation dose from internal emitters may serve as an introduction upon which to base a discussion of the use of excretion measurements to evaluate acute internal radioisotope exposures. Any radioactive chemical entering the body, whether through the skin, pulmonary or gastrointestinal tract, becomes an internal emitter. It continues to irradiate the tissues until it is either excreted by some physiological process, principally through the urine or feces, or until it becomes inactive through radioactive decay.

Each isotope has a specific physical radioactive half-life (physical half-life, t_{rad}) as well as an independent metabolic rate of disappearance from the body (biological half-life, t_{bio}). The effective half-life (t_{eff}) of the isotope in the body is derived by combining these two disappearance rates as follows:

$$t_{eff} = \frac{t_{rad} \times t_{bio}}{t_{rad} + t_{bio}}$$

The internal emitter will behave in the body according to its chemical and physical properties. Some radioisotopes, such as ^{24}Na, will become generalized throughout the body like its stable isotope. Other radioisotopes such ^{131}I, will be concentrated in particular organs which become the so called "critical organ" due to the concomitant concentration of the radiation dose to this organ. The retention of insoluble particulate inhaled into the lung is determined primarily by the particle size distribution of the aerosol. In this case, the critical organ may be the lung, pulmonary lymph nodes or possibly the lower intestinal tract since a significant percentage of particles are eliminated from the lung and swallowed. Some examples of the critical organs for a few elements are listed in Table 1 [9].

Table 1- Classification of some radionuclides by critical organs

Organ				
Lung	**Bone**	**Thyroid**	**GI**	**Whole Body**
Inhaled	Phosphorous	Iodine	Ruthenium	Carbon
Insolubles	Calcium	Astatine	Silver	Sodium
	Strontium		Rare Earths	Zinc
	Radium		Cobalt	Cesium
	Plutonium (Soluble)		Ingested	
			Insolubles	

The internal dose is influenced markedly by the physical properties of the radiation produced by the particular radionuclide. The alpha emitters become of particular importance as internal emitters due to the intense ionization produced within the short range of its particles. Likewise, the more intense ionization produced by the shorter-ranged beta particles becomes relatively more important in the dose contribution of internal emitters than gamma rays with their lower specific ionization values. It has been demonstrated biologically that alpha particle emitters are more toxic internally than the same μCi quantity of beta emitters. These various physical characteristics of the radiation are important factors in the calculation of the maximum permissible body burdens as recommended by the NCRP and ICRP.

It is apparent that the evaluation of the hazards associated with the internal deposition of radioisotopes is very complex. The principal factors which must be considered will be the amount of isotope absorbed and retained in the body, the character and effective energy of the radiation, the effective half-life and the distribution within the body with particular reference to critical organs.

The principal techniques for estimating the amounts and distribution of radionuclides in the body are by 1) excretion measurements, and 2) whole body counting.

4.2 Clinical assessments

Laboratory tests are done to assess the biological effects of radionuclide intake; to identify abnormalities that might complicate treatment; to locate, identify, and quantify radionuclide contamination; and to provide information useful in intake analysis. The biological and physical samples needed, why they are taken, and how they are handled are presented in Table 2 [10].

Table 2- Clinical laboratory assessments for radiation accidents

Samples Needed	Usage	Protocol
In all cases of radiation injury:		
CBC and differential STAT (follow with absolute lymphocyte counts every 6 hours for 48 hours when history indicates possibility of total-body irradiation)	To assess the radiation dose; initial counts establish a baseline, subsequent counts reflect the degree of injury	Choose an uncontaminated area for veni-puncture; cover puncture site after collection
Routine urinalysis	To determine if kidneys are functioning normally and establish a baseline of urinary constituents; especially important if internal contamination is a possibility	Avoid contaminating specimen during collection; I necessary, give the patient plastic gloves to wear for collection of specimen; label specimen 'Number 1,' with date and time
When external contamination is suspected:		
Swabs from body orifices	To assess possibility of internal contamination	Use separate saline- or water- moistened swabs to wipe the inner aspect of each nostril, each ear, mouth, etc.
Swabs from wounds	To determine if wounds are contaminated	Use moist or dry swabs to sample secretions from each wound, or collect a few drops of secretion from each using a dropper or syringe; for wounds with visible debris, use applicator or long tweezers or forceps to transfer samples to specimen containers which are placed in lead storage containers (pigs)
Skin wipes	To locate contaminated areas	Use filter paper, smear pads, or compresses to wipe sample areas 10cm x 10cm in site

Samples Needed	Usage	Protocol
When internal contamination is suspected.		
Urine: 24-hour specimen x 4 days	Body excreta may contain radionuclides if internal contamination has occurred	Use 24-hour urine collection container
Feces x 4 days	Body excreta may contain radionuclides if internal contamination has occurred	Save excreta in plastic containers in refrigerator or freezer
Vomitus	Body excreta may contain radionuclides if internal contamination has occurred	Save excreta in plastic containers in refrigerator or freezer
Sputum	To assess respiratory tract contamination if inhalation of contaminant was a possibility	Use a 5-percent propylene-glycol aerosol to get a deep cough specimen
Serum creatinine	To assess kidney function if chelation is indicated	Clinical chemistry
Other samples needed		
All irrigating fluids	Radiological assessment	Save in sealed and labeled, glass- or plastic-lined containers

4.3 Comments on Bioassay Samples

4.3.1 Urine

Provided that the sample is collected free from contamination, this is an adequate method of radiobioassay for radiation protection and monitoring of personnel. If a radionuclide is found in urine, there is no doubt that the radionuclide was present in extracellular body fluids. The absence of a positive test for radionuclides by urinalysis **does not**, however, preclude a body burden of any given radionuclide.

4.3.2 Feces

For cases of internal contamination with transportable radionuclides, there is little information relating fecal excretion to the magnitude of the body content. Fecal analysis is most useful in detecting intake of non-transportable material and in providing evidence of the clearance of material from the lungs.

4.3.3 Nasal Discharge

This technique may be used for detecting significant exposures and identifying the radionuclide involved in an accident, but is very difficult to use to obtain information for a body burden.

4.3.4 Sputum

If obtained, may contain insoluble material initially deposited and later eliminated by ciliary action.

4.3.5 Sweat

Sweat may be analyzed to detect tritium oxide.

4.3.6 Breath

Breath may be used to determine ^{14}C (exhaled CO_2) and tritium (exhaled vapour).

4.3.7 Blood and Hair

These samples are not commonly analyzed. In general, blood and hair is analyzed in criticality accidents for neutron activation products. There is little benefit for analyzing these samples with an internal contamination scenario.

4.4 Preventing Contamination Promulgation

For a patient suspected of having a radionuclide intake, consideration must be given to both internal and external contamination. Although decorporation deals strictly with the removal of radionuclides from the body, inadequate decontamination of the patient may lead to resuspension of radionuclides that may be taken in [10].

In general, contaminated wounds and body orifices are decontaminated first, followed by areas of highest contamination levels on the intact skin. The purpose of decontamination is to prevent or reduce incorporation of the material (internal contamination), to reduce the radiation dose from the contaminated site to the rest of the body, to contain the contamination, and to prevent its spread.

4.4.1 External Contamination

Decontamination of the intact skin is a relatively simple procedure. Complete decontamination, which returns the area to a background survey reading, is not always possible because some radioactive material can remain fixed on the skin surface. Decontamination should be only as thorough as practical, and should begin with the least aggressive method and progress to more aggressive ones. Care must be taken to limit mechanical or chemical irritation of the skin. The most simple procedure is to wash the contaminated area gently under a stream of water (being careful not to splash) and scrub at the same time using a soft brush or surgical sponge. Warm (never hot) tap water is used. Cold water tends to close the pores, trapping radioactive material within them. Hot water causes vasodilation with increased area blood flow, opens the pores, and enhances the chance of absorption of the radioactive material through the skin. Aggressive rubbing tends to cause abrasion and erythema and should be avoided.

If washing with plain water is ineffective, a mild soap (neutral pH) or surgical scrub soap can be used. The area should be scrubbed for 3 to 4 minutes, then rinsed for 2 to 3 minutes and dried, repeating if necessary. Between each scrub and rinse, check the contaminated area to see if radiation levels are decreasing. Sodium hypochlorite, diluted 1 to 10 with water, is an effective decontamination agent. A mildly abrasive soap; a 1 to 1 mixture of powdered detergent and cornmeal mixed with water into a paste; a paste of sawdust and water; or a mixture of 65% $NaPO_4$, 5% carboxylmethycellulose, and 30% detergent as a 5% solution in water can be used. More aggressive measures for decontamination include procedures that remove cornified epithelium. Very fine sandpaper can be used on hands or feet. Potassium permanganate (4%) followed by sodium bisulfite (4%) also can be used with caution. *The decontamination procedure stops when the radioactivity level cannot be reduced to a lower level.* Expert advice might be needed to determine an appropriate stopping point. Contaminated hairy areas can be shampooed several times and then rinsed in a 3% citric acid solution. Contaminated hair can be clipped if shampooing is ineffective. Shaving should be avoided since small nicks or abrasions can lead to internal contamination. When shampooing the head, avoid getting any fluids into the ears, eyes, nose, or mouth.

The procedures described above also apply to the decontamination of uninjured accident victims. Small areas (hands, feet, etc.) can be decontaminated using a sink or basin. If extensive body areas are contaminated, the patient can be showered under the direction or with the assistance of a radiation safety officer. Caution the patient to avoid splashing water into the eyes, nose, mouth, or ears. Repeated showers might be necessary, and clean towels provided for drying after each shower. Again, decontamination should be as thorough as practical. Contaminated water can be released directly into the hospital sanitary drain system. No special storage or holding tanks are recommended.

4.4.2 Contaminated Wounds

In a contamination scenario, any wound must be considered contaminated until proven otherwise and should be decontaminated prior to decontaminating intact skin. When wounds are contaminated, the caretaker must assume that uptake (internal contamination) has occurred. Appropriate action is based on half-life, radiotoxicity, and the maximum permissible body burden of the radioactive material. It is important to consult experts as soon as possible and to initiate measures that prevent or minimize uptake of the radioactive material into body cells or tissues.

Contaminated wounds are first draped, preferably with a waterproof material, to limit the spread of radioactivity. Wound decontamination is accomplished by gently irrigating with saline, water, or a 3% hydrogen peroxide solution. Irrigation fluid should be collected and checked with a radiation monitor to judge the effectiveness of decontamination. More than one irrigation is usually necessary. The wound should be monitored after each irrigation. Contaminated drapes, dressings, etc. should be removed before each monitoring for accurate results. When monitoring contaminated wounds or irrigation fluids, gamma radiation is easily detected while beta radiation may prove more difficult to detect. Without special, highly sophisticated wound probes, alpha contamination will not be detected. Following irrigation, the wound is treated like any other wound. If the preceding decontamination procedures are not successful, apply a constriction band to increase blood flow and to help remove contamination from the wound. If this is unsuccessful and the contamination level is still seriously high, surgical decontamination, which is identical to conventional debridement of a wound, must be considered. Debridement should not be initiated until expert medical or health physics advice is obtained. Debrided or excised tissue should be retained for health physics assessment.

Embedded radioactive particles, if visible, can be removed with forceps or by using a water-pik. Puncture wounds containing radioactive particles, especially in the fingers, can be decontaminated by using an "en bloc" full thickness skin biopsy using a punch biopsy instrument.

After the wound has been decontaminated, it should be covered with a waterproof dressing. The area around the wound is decontaminated as thoroughly as possible before suturing or other treatment.

Contaminated burns (chemical, thermal) are treated like any other burn. Contaminants will slough off with the burn eschar. However, dressings and bed linens can become contaminated and should be handled appropriately.

4.4.3 Body Orifices

Contaminated body orifices, such as the mouth, nose, eyes, and ears, need special attention because absorption of radioactive material is likely to be much more rapid in these areas than through the skin. If radioactive material has entered the oral cavity, encourage brushing the teeth with toothpaste and frequent rinsing of the mouth with a 3% citric acid solution. If the pharyngeal region is also contaminated, gargling with a

3% H_2O_2 solution might be helpful. Gastric lavage can be used if radioactive materials were swallowed. Rinsing the nose with tapwater or physiological saline should be tried if the nose is contaminated. Likewise, contaminated eyes should be rinsed by directing a stream of water from the inner canthus to the outer canthus of the eye while avoiding contamination of the nasolacrimal duct. Contaminated ears require external rinsing, and an ear syringe can be used to rinse the auditory canal, provided the tympanic membrane is intact.

4.4.4 Internal Contamination

Once radioactive materials cross cell membranes, they are said to be incorporated. Incorporation is a time-dependent, physiological phenomenon related to both the physical and chemical natures of the contaminant. The rate of incorporation can be quite rapid, occurring in minutes, or it can take days to months. Thus, time can be critical and treatment (decorporation) urgent. Several methods of preventing incorporation (e.g., catharsis, gastric lavage) might be applicable and can be prescribed by a physician. Some of the medications or preparations used in decorporation might not be available locally and should be stocked when a decontamination station is being planned and equipped.

If internal contamination is suspected or has occurred, the caretaker should request samples of urine, feces, vomitus, wound secretions, etc. Whole-body counting and radioassay also can help evaluate the magnitude of the problem and the effect of any treatment. The contaminated patient admitted with an airway or endotracheal tube must be considered to be internally contaminated.

4.5 General Information about Excretion Measurements

The radioactivity measurements of urine, feces, or exhaled air have been used extensively as a means of detecting internal exposures and estimating the radiation dose contribution by the particular radionuclide in the body. These techniques are used primarily when the radiation of the isotope is weakly penetrating so as to preclude the use of external in vivo counting techniques, when external contamination may interfere with accurate external counting, and when it is more convenient than whole body counting to monitor for specific nuclides. An additional value of excretion measurements is the ability to establish excretion rates and modes of elimination for particular exposures and nuclides. The combination of external counting techniques plus excretion measurements provides our best data for estimating dose from internal exposures.

The importance of excretion measurements after accidental exposures is apparent in the admonition to collect all excreta for the purpose of radioactivity measurements; this means retention of all urine and feces for the first few days until preliminary dose estimates are established.

The collection of urine should be a 24-hour composite sample in clean containers. No preservative agent is required or recommended. If the patient has external radioactive

skin contamination care must be taken to avoid contamination of the sample during sample collection. The collection of feces can be best accomplished by use of a plastic bag, which is then placed into a cardboard carton or glass jar with tight fitting tops. Identification of samples as to the specific time of excretion is most important for interpretation.

The time required for analysis will vary markedly depending upon the particular isotope to be measured. The analysis of pure beta and alpha radioisotopes usually require chemical separations and preparations. The length of time for analytical results may therefore be considerable, for example, at least four hours for ^{90}Sr and sixteen hours or more for ^{239}Pu. Gross radioanalysis is not only of no value, it is usually misleading which is even worse. The sample must be sent to a radiochemical laboratory which is prepared to analyze for specific nuclides by gamma spectroscopy, alpha spectroscopy and/or chemical separation techniques.

The time delays introduce a practical problem. The most important first-aid type treatment for internal emitters is best accomplished at the earliest time following an accidental exposure. The immediate treatment decision may have to be based on estimates of field contamination and the physical factors of the accident. This is practical only for treatment procedures which involve no risk to the patient. Other forms of therapy must wait for more quantitative data to be processed.

Collection of excreta samples and measurement of specific nuclides can be done easily and accurately; the disadvantage of excretion measurements is our inability to interpret these measurements accurately. The answer we desire is not the excretion measurement, but the quantity and distribution of the radionuclide remaining in the body. The use of excretion measurements introduces a number of serious interpretation problems which must be considered very carefully each time we use excretion data. Major interpretation problems may arise from the lack of knowledge regarding [9]:

1. identification of the time of the particular exposures;

2. excretion rate of the individual for the particular nuclide; and

3. solubility and retention characteristics of the specific fume aerosol, dust, etc. of the exposure under study.

Each of these areas will be discussed to show why these three points must be appreciated to recognize the large inherent errors in the interpretation of excretion data.

4.5.1 Time of Exposure

The majority of radionuclides which may be absorbed within the body will be excreted at a rate which is variable with time after the exposure. The relationship of the quantity found in a urine sample, for example, and the remaining body burden is meaningful only if the time of exposure is known.

A history of the incident may very well provide the time of an acute single exposure. If the individual is subject to a potential chronic or recurrent exposure condition, the question may arise as to whether some of the material may represent an earlier unknown exposure. An excretion value from an exposure at an earlier time period carries much greater significance for the initial body burden, and hence the radiation dose, than a value in the first couple days post-exposure. Where the exposure has occurred over several weeks or longer, the excretion curve will represent a complex composite of excretion rates from each exposure.

If the time of exposure is unknown, a series of measurements will provide an excretion curve which may be compared with a representative excretion curve for the particular nuclide under similar exposure conditions. The slope of the curve may permit an educated estimate to be made as to the approximate date of exposure. This technique may show a recent exposure in a few days if one is on the steep first part of the curve, but if the curve is flat it may take a number of weeks to establish an accurate slope due to variations between samples.

This simplified explanation of the complex excretion curve is that the initial values on urine or feces samples may at best serve to indicate only whether an exposure has occurred. If the exposure history is complex or unknown, a series of samples is required to attempt to interpret the data. In some instances, the time of exposure will always remain uncertain; this uncertainty will reflect on any interpretation of the data.

4.5.2 Individual Variation

Physicians are familiar with the individual variations encountered in most biological measurements. Most clinical tests are interpreted with a set of values called the "range of normal". This range is expressed frequently as the values found in *95%* of the normal individuals (meaning, plus or minus two standard deviations from the mean value of a group of normals).

One of the most common measurements which physicians interpret daily is the white blood count. A study of a group of approximately 1000 normal individuals in a plant found that the normal count for 95% of these individuals ranged from about 4,000 to 12,000 cells/mm^3. Despite this wide range, it is still found that one normal person out of 20 is outside these values. This situation does not disturb the physician particularly; individual variation is a necessary evil that he recognizes and grants proper allowances.

Another common clinical test is the thyroid uptake of radioiodine. Most textbooks quote 20-40% as the range of normal. Again we see a factor of at least two in the range of values we call normal. The radioiodine that is not incorporated in the thyroid is excreted principally via urine in the first few days. A normal person will excrete from 60 to 80% of the initial dose depending on their particular state of thyroid metabolism. The matter becomes more complicated when the much wider range (0 to 80% uptake) of abnormals existing in a population is included. A series of urinary excretion measurements on an individual exposed to an unknown dose of radioiodine confronts the investigator with a classic problem of selecting an appropriate excretion

curve. The problem may be complicated by such influences on iodine excretion as thyroid surgery, the effect of recent high intake of stable iodides, thyroid medications and other drug influences. Any calculation of the initial unknown burden of radioiodine or thyroid radiation dose made from excretion data only will clearly be subject to the potential influence of all these variables. The biological variation in the urinary excretion of six patients injected with a single dose of soluble uranium (uranyl nitrate) was studied. It was found that a greater number of samples provides a better estimate of dose, but even an average of values can be off by a factor of three to four. It is probable that measurements of other nuclides will have individual variations of at least similar magnitude. Although the excretion curve for uranium has been studied more extensively than other nuclides, we are still limited seriously in the interpretation of excretion data due to these individual variations. Obviously, the use of one or two samples following an acute exposure will have much larger potential for error in the initial evaluation.

4.5.3 Aerosol Characteristics

The most common and important mode of internal deposition of radionuclides in industry is by inhalation. The deposition and absorption of radionuclides via the lung is a complex subject which is only partially understood. The evaluation of excretion data is based on an understanding of the mechanisms of retention, clearance and translocation of inhaled particles.

The fate of the inhaled radioisotope is partially determined by its solubility in body fluids. Although this is largely determined by its chemical composition, it is also dependent on physical properties of the particle, such as size, shape and surface area. In the case of inhaled radionuclides, as may occur around reactors or particle accelerators, the particles may consist of a matrix of various materials with different physicochemical properties from those usually associated with the radioisotope in question.

These characteristics of aerosols involved in personnel exposures are almost always unknown and there is no easy or accurate way to reproduce or study the particular aerosol involved in an exposure after the actual event.

The excretion curves measured after inhalations will reflect all the metabolic, physiological and physical factors involved in determining the fate of particles in the respiratory system. Excretion in the feces will represent the portion which is physically cleared via the trachea and swallowed, plus any soluble material which may be excreted into the GI tract.

The insoluble portion remaining in the lung is not reflected in either excretion mechanism. Unless this lung burden can be measured directly by in vivo counting, there is no accurate means of determining the actual lung component. In these instances, average values of the standard lung model developed by the ICRP are frequently assumed and calculations are made from the excretion values to estimate the unknown quantity left in the lung, which is the critical dose determination in these instances.

It is apparent now that negative urinary measurements following an incident does not rule out the possibility of exposures to the lung. and intestinal tract. The use of fecal samples contributes important information especially on inhalation exposures. However, even with both urine and fecal data, the interpretation of the lung dose is still fraught with uncertainty unless direct counting methods are available to measure the lung burden.

4.6 Whole Body Counting

4.6.1 General

Whole body counting (WBC) is a measurement of photons emitted by radionuclides within the body. The advantage to whole body counting is that it requires no collection of samples. The main disadvantage of whole body counting is external contamination on the patient that will mask the internal contamination component.

Various detectors may be used for whole body counting, described briefly below.

- NaI(Tl) – most common detector; low resolution
- HPGe – becoming more common; high resolution but low efficiency (compared to NaI); requires cooling
- Phoswich – thin NaI(Tl) backed by CsI(Tl), operated in anti-coincidence (i.e. if a photon is detected in the CsI, it must be higher energy and therefore do not count); low background and high efficiency for low energy photons
- Si(Li) – high efficiency, low background due to high resolution for low energy

There are numerous geometries that may be used to perform whole body counting on patients. In general, a prone geometry is preferred due to the reproducibility of this geometry. For specialized counting, a seated geometry may be preferable (for example, wound or lung counting).

Of greatest importance to whole body counting is reduction of background and achieving the lowest possible minimum detectable activity (MDA).

Background counts in a whole body counter generally come from (a) cosmic ray muons and their interaction products, (b) terrestrial gamma-emitting radionuclides (^{40}K, ^{238}U, ^{232}Th and progeny), (c) trace radioactivity in components (^{60}Co in steel, ^{238}U in Be, etc) and (d) natural and fallout radioactivity in subjects (^{40}K, ^{137}Cs, ^{222}Rn and progeny). To determine measurable quantities of radionuclides by whole body counting, it is useful to examine the average body content of some radionuclides normally present and measurable by whole body counting (Table 3).

Table 3- Average body content of some radionuclides measurable by WBC

Radionuclide	Origin	Average Content (Bq)
^{40}K	Natural	3700
^{137}Cs	Global fallout	100
^{214}Pb, ^{214}Bi	Natural	40 or greater

The ^{40}K measurement is a good quality assurance indicator.

There are also numerous radionuclides that exist naturally in the body which are not measurable (in the given quantities) by the whole body counting technique (Table 4).

Table 4- Average body content of some radionuclides NOT measurable by WBC

Radionuclide	Origin	Average Content (Bq)
^{3}H	Cosmic + fallout	30
$^{235,238}U$	Natural	1.5
^{226}Ra	Natural	1
^{228}Ra	Natural	0.4
^{14}C	Cosmic + fallout	3700
$^{239,240}Pu$	Global fallout	0.4
^{90}Sr-^{90}Y	Global fallout	30
^{87}Rb	Natural	700

The detection limit of a whole body counter for a given radionuclide will be a function of the background, including the average normal body content of the radionuclide.

4.6.2 Special External Counting Techniques

Lung Counting – typically used for ^{239}Pu inhalation, but useful for other low-energy (13 ~ 90 keV) photon emitters such as ^{241}Am, ^{210}Pb and ^{238}U. Critical parameter for this type of counting is chest wall thickness. For a ^{239}Pu inhalation from a weapon

scenario, the Am:Pu ratio may be useful, since all nuclear weapons have an exact Am:Pu pedigree.

Skull Counting – used for bone seeking low-energy photon emitters, such as ^{239}Pu, ^{241}Am and ^{210}Pb. Since the skull represents 14% of the skeletal mass and approximately 12% of the total bone surface area, it can be assumed that the skull distribution of activity is representative of the entire skeleton.

Liver Counting – The liver is a deposition site for transuranics, but is difficult to measure for low energy photon emitters due to severe attenuation. Left side of abdomen can be counted to obtain a background,

Wound Counting – used to guide medical treatment and wound excision.

4.7 Internal Dosimetry Techniques

Medical caregivers face a dilemma with respect to internal contamination: "To treat or not to treat". The basis of this dilemma is two-fold:

- Treat early to be effective.
- Don't treat until you know what you are treating.

To be able to treat early, information must be quickly gathered as to the nature of the internal contamination. The primary techniques utlized to determine properties and quantities of internal radioactive contamination are:

- Urine excretion measurements
- Fecal sample measurements
- Direct counting techniques
  - Whole body gamma counting
  - Lung counting
  - Thyroid counting
  - Wound counting

Some initial measurements may be made to assist the primary caregiver as to medical treatment decisions. Some of the relevant data is:

- Air concentration & occupancy time
- Surface activity around the intake site

- Skin contamination levels
- Nasal swab counts
- Wound contamination counts
- Initial urine excretion (selected radionuclides)
- Thyroid uptake (radioiodine)

Some examples of estimation based upon initial measurement data are presented as follows:

Tritium (^3H)

- Empty bladder soon after exposure
- Collect spot urine sample one hour post-void
- Measure tritium concentration (LSC)
- 37 kBq/L ~ 100 μSv whole body

Iodine-131 Intake

Iodine-131 is excreted by the body through urine in the following approximate timeframe

Time (hours)	% Excreted
0 – 4	25
4 – 8	16
8 – 12	10

Therefore, if the activity is estimated during a specified timeframe post-exposure, the initial uptake and intake can be estimated.

Radiocesium Intake

- Measure cesium radioactivity in urine during first three days after exposure
- Approximately 1% of intake will be excreted per day

4.7.1 Special Case: Depleted Uranium

There is increasing interest in determining the concentration of uranium in human systems due to the so-called "Gulf War Syndrome". The connection between potential depleted uranium intake and Gulf War illness is speculative at best, and has not been proven or correlated by either physicians or health physicists.

A recent study by DERA Radiation Protection Services [11] pronounced that

"...it was unlikely that anyone other than those in an armoured vehicle penetrated by a DU projectile, or those spending prolonged periods within a few tens of metres of the point at which a DU penetrator had impacted a hard target, could be exposed to large enough quantities of particulate material for them to have received a radiation dose greater than 20-30 mSv."

In fact, the report goes on to state that using the most recent uranium biokinetics models, the maximum radiation doses would be less than 10 mSv.

However, the question here is not whether it is possible for a radiologically significant exposure to take place, but how could excretion measurements be used to determine uranium intake. Historically, urine samples have been the bioassay method of choice for this monitoring.

A study was performed in Israel [12] to examine the uptake of uranium in volunteers. The volunteers all exhibited normal levels (5-15 ng/L) of uranium in urine, and all ingested a grapefruit drink spiked with 100 □g of uranium (235U/238U = 0.245%). The results of the urine analysis, when normalized to the creatinine levels (as suggested in [6]), indicated that the maximum normal excretion occurred between 6-10 hours after ingestion, and that for the low acute chronic intake, the levels returned to natural abundance within several days.

The main points of the Israeli study are:

1. Diurnal variations in spot urine samples may be significant, and it is therefore recommended that 24 hour urine sample be collected and analyzed;

2. If spot samples must be taken, careful normalization to the creatinine levels must be made; and

3. Urine measurements are ineffective several days post exposure for this ingestion scenario.

The above study did not consider soldiers with retained shrapnel. A study was performed in the US [14] on 33 cohorts who had served in the Gulf War which were wounded while on or in vehicles struck by depleted uranium penetrators. The results indicated that the mean urine excretion of uranium in the cohorts was significantly higher than the control (non-shrapnel containing) group for the time periods 1993/1994 (4.47 vs. 0.03 μg/g-creatinine) and 1995 (6.40 vs. 0.01 μg/g-creatinine). It

was also found in this study that spot urine measurements were well correlated with 24 hours samples. No evidence of a relationship between uranium excretion and renal function was found.

In a study of spot urine samples [15] it was found that although spot urine samples correlated well with 24 hour urine samples at "high" uranium ingestion levels (>0.05 μg/g-creatinine), the correlation declined for levels approaching background (<0.05 μg/g-creatinine).

In the most recent Gulf War veteran cohort study available [16], a total of 169 Gulf War veterans submitted 24 hour urine samples for analysis; they also submitted a detailed questionnaire designed to determine their likelihood for exposure to depleted uranium. The study utlized 0.05 □g/g-creatinine to be the cut-point between "high" uranium and background uranium concentration. A total of 12 individuals (7.1%) exhibited urine uranium values in the high range, whereas the remaining 157 had uranium concentrations in the background range. Investigation of the cohorts in the "high" group lead to the speculation that the observed elevated levels of uranium in urine were caused by DU shrapnel in the soft tissue of that population.

In summary, it is possible to get adequate bioassay data about uranium intake from urinalysis. However, for exposures that do not involve emplacement of particulate in the soft tissue, the window of opportunity for getting useful data is relatively short, and likely on the order of tens of days. This may be illustrated by examining the urinary uranium excretion functions for the three different solubility classes in Figure 4 [17].

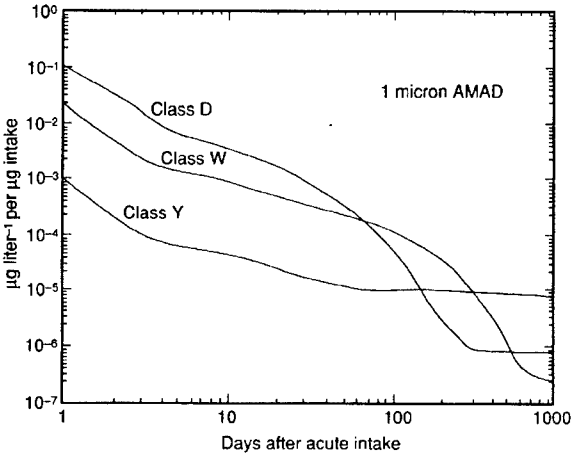


Figure 4 - Urinary uranium excretion after acute intake

4.8 Priorities for Internal Contamination Management

As in the treatment of all medical conditions, triage must take place. The following order of priorities is provided for medical management of internally contaminated personnel.

1. Perform lifesaving measures first! (ABCs – Airway, Breathing, Circulation)
2. Provide contamination control
3. Take accident history from patient and pertinent personnel
4. Identify specific radionuclides involved and potential modes of exposure
5. Estimate potential intake quickly (within a few hours)
6. Attempt to initiate treatment within 3 hours post-exposure
7. Follow-on with detailed dosimetry procedures and analysis

4.9 Summary

There are many considerations for interpreting excretion measurements following radionuclide exposures. It is time to try to isolate a few practical rules for guidance in a sampling program of excreta. A suspected internal radioactivity exposure should be investigated with the following thoughts in mind.

1. The exposure history and mode of exposure is important for interpretation of data.
2. Simple therapeutic procedures for serious internal exposures will generally be more important in the first few hours than waiting for a more comprehensive evaluation of diagnostic measurements.
3. Whole-body counts, plus excretion measurements, provide the best available data for determination of internal doses.
4. Collect 24-hour, composite urine samples and all feces for the first three days following suspected exposures of significance.
5. Avoid contamination of samples.
6. Request analysis for specific isotopes and avoid gross radioactivity measurements.
7. A greater number of samples provides a better estimate of dose.
8. Additional sampling will be based on the results of the initial samples.

9. If there is good excretion data, the dose estimate is still likely to be only within a factor of two or three; whole-body counting data provide much better dose estimates - usually within, ± 33%.

10. Radioactivity measurements of urine samples alone do not rule out the possibility of significant lung or intestinal tract exposure.

5. Chemistry of Chelation and its Role in Decorporation

5.1 Basics of Metal Chelation

5.1.1 Introduction

Complexation is a chemical reaction that produces a bond between a metal atom or ion and a molecule called a *complexing agent.* Complexing agents contain atoms that can "donate" electrons to metals atoms or ions that have a deficit of electrons. As a result of this "donation", a chemical bond is formed. An example of complexation is the well-known reaction between ammonia (complexing agent) and a solution containing copper ions. This reaction produces ammonia complexes of copper and is accompanied by a rapid change in the color of the solution.

If a complexing agent contains two or more electron donor atoms, which can form coordinate bonds with a single metal atom or ion, it is called a *chelating agent*, or *chelant.* After the first such coordinate bond, each successive donor atom that binds creates a ring containing the metal atom. This cyclic structure is called a *chelation complex* or *chelate*, the name deriving from the Greek word chela for the great claw of the lobster [26].

Thermodynamically chelates are usually more stable than regular metal complexes where complexing agents have just one electron donor atom. As a result of this greater stability, equilibrium constants of chelates are usually orders of magnitude higher than those of regular metal complexes.

Once a chelate is formed, it usually has chemical properties different from those for either the free metal ion or the chelant. This is a very important feature that helps dramatically change properties of metal ions and create desirable effects that find their application in metal buffering, corrosion inhibition, solubilization, cancer therapy, etc. [26].

In addition to metals, some non-metals such as iodine can react with chelating agents such as those found in starch and form chelates. In this report, chelation is described mainly with respect to metals; however, the main concepts of it are identical for both metals and non-metals.

Chelates and chelation reactions are very common in nature. They range from biochemical processes in living organisms to interactions between metals and organic matter in the soil to numerous technological purposes (water softening, ore leaching, food preservation, chemical analyses, etc.).

Chelation is a powerful tool in medicine. Examples are treatment of lead poisoning and cancer therapy. Another important medical application of chelation is decorporation of radionuclides from human body, i.e. the subject of this report. The

rationale of decorporation is that the chelating agent will combine with the metal to form a stable complex that can easily be excreted and thus reduce the radiation doses delivered to body tissues [18].

5.1.2 Structure of Chelates

The main feature of any chelate are coordinate bonds between a metal atom or ion, which serves as an electron acceptor, and two or more atoms in the molecule of the chelating agent, or *ligand*, which serve as the electron donors. A chelating agent may be bidentate, tridentate, tetradentate, and so on, depending on whether it contains two, three, four or more atoms capable of simultaneously complexing with the metal atom [26].

In most cases, nitrogen, oxygen and sulfur are principal donor atoms; however, phosphorus, arsenic, and selenium also form chelates. Metals are categorized by coordination numbers which correspond to the number of donor atoms bound to the central metal atom in a particular compound. The most common coordination numbers are four and six. Chelate compounds may be either neutral molecules or complex ions. Ions are associated with appropriate counterions to produce electroneutrality.

Most chelating agents are linear or branched chains. In these chains, the donor atoms are separated by suitable numbers of other atoms to allow the formation of chelate rings. In addition to chain structures, there are other chelating agents where the donor atoms are contained within macromolecular structures. Examples of those are porphine and crown ethers.

5.2 Compounds Having Chelating Properties

Compounds with chelating properties can be found in almost any class of chemical substances containing two or more electron donor atoms. These atoms must be situated in a chelant molecule in places that would allow them to coordinate with the same metal atom. The chelate rings formed contain four or more atoms, with five- or six-atom chelate rings being the most stable and useful.

A vast majority of chelating agents are organic compounds, although there are inorganic chelants such as ammonia and polyphospates. Table 5 (26) provides examples of the most common classes of chelating agents, and Figure 5 depicts the chemical structures of some chelating agents commonly used [27].

Table 5- Examples of chelating agents

Chelating agent	Molecular Formula	Abbreviation
Inorganic chelants		
Ammonia	NH_3	
Sodium tripolyphosphate	$Na_5P_3O_{10}$	STTP
Aminocarboxylic acids		
Ethylenediaminotetraacetic acid	$C_{10}H_{16}N_2O_8$	EDTA
Nitrilotriacetic acid	$C_6H_9NO_6$	NTA
1,3-Diketones		
Acetylacetone	$C_5H_8O_2$	acac
Hydroxycarboxylic acids		
Tartaric acid	$C_4H_6O_6$	
Citric acid	$C_6H_8O_7$	cit
Polyamines		
Ethylenediamine	$C_2H_8N_2$	en
Aminoalcohols		
Triethanolamine	$C_6H_{15}NO_3$	TEA
Aromatic heterocyclic bases		
Dipyridil	$C_{10}H_8N_2$	dipy, bipy
Phenols		
Salicylaldehyde	$C_7H_6O_2$	
Chromotropic acid	$C_{10}H_8O_8S_2$	DNS
Oximes		
Dimethylglyoxime	$C_4H_8N_2O_2$	
Salicylaldoxime	$C_7H_7NO_2$	
Sulfur Compounds		
Dimercaptopropanol	$C_3H_8OS_2$	
Thiourea	CH_4N_2S	
Macrocyclic Compounds		
Dibenzo [18]-crown-6	$C_{20}H_{24}O_6$	
Polymers		
Polyethylenimines	$-(C_2H_5N)_x-$	PEI
Phosphonic Acids		
Ethylenediaminetetra-(methylenephosphonic	$C_6H_{20}N_2O_{12}P_4$	EDTPO
Hydroxyethylenediphosphonic acid	$C_2H_8O_7P_2$	HEDP

Figure 5 - Chemical structure of some chelating agents

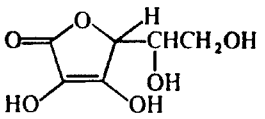
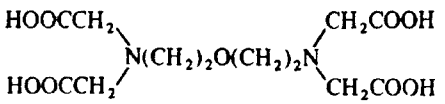
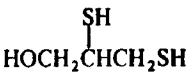
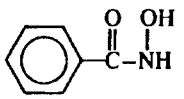
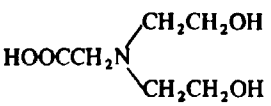
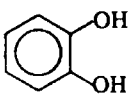
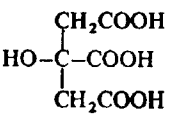
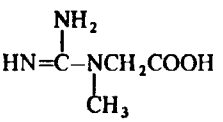
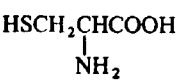
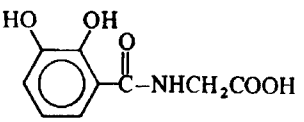
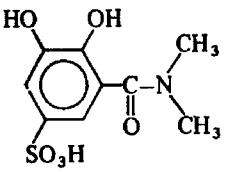
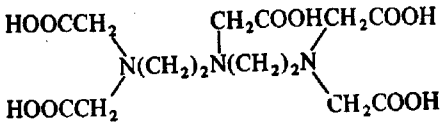
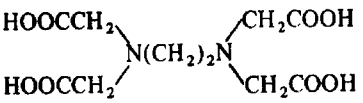
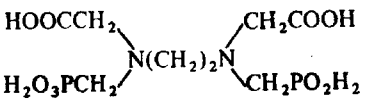
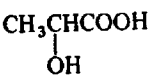
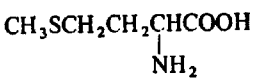
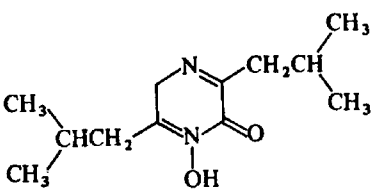
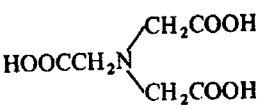
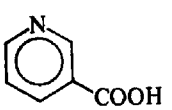
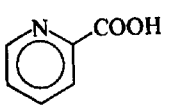
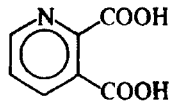
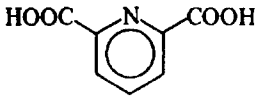
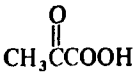
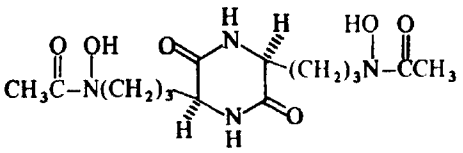
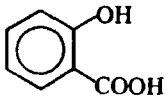
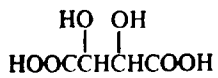
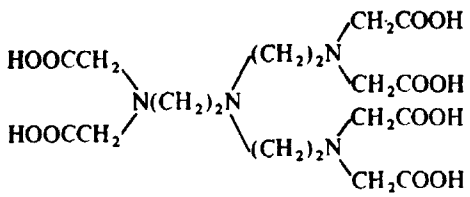
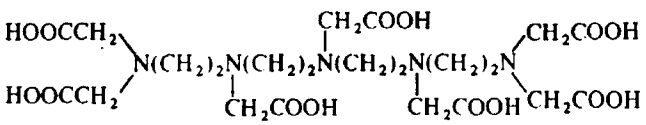
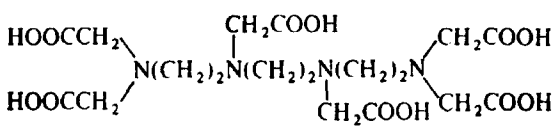
Ascorbic acid	
BAETA	
BAL	
Benzohydroxamic acid	
N, N-Bis(2-hydroxyethyl)glycine	
Catechol	
Citric acid	
Creatine	
Cysteine	
2, 3-Dihydroxybenzoylglycine	

Table 2 (Continued)

DiMeCAMS	
DTPA	
EDTA	
N, N′-Ethylene bis[N-phosphono-methyl]glycine	
Lactic acid	
Methionine	
Neoaspergillic acid	
NTA	
Nicotinic acid	
Picolinic acid	

2, 3-Pyridinedicarboxylic acid	
2, 6-Pyridinedicarboxylic acid	
Pyruvic acid	
Rhodotorulic acid	
Salicylic acid	
Tartaric acid	
TAAHA	
TPHA	
TTHA	

In human decorporation, the most commonly used agent has been diethylenetriaminepentaacetic acid (DTPA) which belongs to the group of aminocarboxylic acids [18, 19 and 23]. In addition to DTPA, other agents such as EDTA [22], phosphonic acids [20 and 24], or chitosan [21] have reportedly been used in treatment. New agents have been evaluated for possible use in decorporation therapy [18, 22 and 25]

In the case of iodine, which is a non-metal, its reaction with poly (n-vinyl-2-pyrollidine) produces stable chelates. These chelates are widely used as disinfectants; however, no reports could be found on their use in decorporation.

5.3 Formation and Stability of Chelates

One of the most important parameters of chelation is the formation or *stability constant.* It is an equilibrium constant of the formation of the chelate complex from the solvated metal ion and its fully dissociated form. The higher the stability constant K the stronger the equilibrium is shifted towards the formation of the chelate. Table 6 (26) illustrates stability constants (expressed in Log K) for some of the commercial chelating agents and metals. The greater the Log K the more stable the chelate.

Table 6- Stability constants for some organic chelants

Metal ion	Log K			
	Citric acid	EDTA	EDTPO	NTA
Fe(III)	10.9	25.1		25.8
Th(IV)		23.2		12.4
Hg(II)		21.8		12.7
Cu(II)	6.1	18.8	23.1	16.3
Pb(II)	5.7	18.0		11.8
Zn(II)	4.5	16.5	18.8	
Co(II)	4.4	16.3	17.1	10.6
Sr(II)	8.6			5.0

The rate of a chelation reaction is another important parameter. Depending on the reaction rate, metals may undergo a chemical transformation fast or it may require a significant time. Chelation is usually instantaneous, especially in case of divalent metal ions. However, some ions of higher valencies, such as Cr(III) and Co(III), react with chelants very slowly.

5.4 Factors Affecting Stability

There are several main factors affecting the stability of chelates. Some of them are associated with chemical properties of either chelating agents or metals; the others are related to conditions of the chemical reaction, such as pH or the presence of competing ions and molecules.

5.4.1 Chemical Composition and Structure of Chelating Agents

The chelant stability is greatly affected by the number of atoms in the chelating ring, with five-and six atom rings being the most stable. The stability of four-atom rings is generally significantly weaker and three-atom rings cannot be formed.

The chemical nature of donor atoms plays an important role. The chelating ability depends not only on what particular donor atom (oxygen, sulfur, or phosphorus) is present but also on what is the chemical group that contains this atom. For example, oxygen can be a part of diketones, hydroxocarboxylic acids, phenols, etc. Each of these chelants will have different ability to bind metals.

5.4.2 pH

Chelating agents, being electron donors, react with protons which are electron acceptors. This reaction, called protonation, usually diminishes the chelating ability. If the pH is low enough, chelates cannot be formed. Protons can therefore be considered competitors to metal ions in their reactions with a chelating agent. Consequently, if the chelating bonds between an ion and a chelating agent are strong, they can withstand the lower pH without being decomposed. On the other hand, chelates with a low stability dissociate even in mild acidic conditions. In the human body, the pH is close to neutral but it changes slightly in different parts of the body and may be quite acidic in the stomach. This change in pH may influence the performance of some of the decorporation agents.

5.4.3 Competing Metals and Chelants

In practically any system where chelation takes place there may be several metals, in addition to the target metal, that can react with a chelating agent. If the chelating agent is not selective it will react with all of these metals. Should one of the competing metals be present in a concentration larger than the concentration of the target metal, the chelant may largely be spent to bind the competing metal. Consequently, there may not be enough of the agent remaining to bind the target metal. It is important therefore that selective chelating agents are used in systems where two or more metals have similar chemical properties. In the case of the human body, calcium, iron, and several other elements may be in a competition with a target metal that needs to be sequestered or removed.

In addition to competing metals, there may be cases, where several compounds, which are present in a system, possess chelating properties and thus can bind the target metal. Examples are amino acids and other constituents of the human body. If the chelating agent that is used in treatment is not strong enough then metals will become bound to the agent rather than body tissues so that the treatment would not be effective.

6. Biological Lifetimes of Radioisotopes in Humans

Some data is included on the biological half-times of various radioisotopes in the human body. The half-times of some commonly found laboratory radionuclides are presented in Table 7 to show the variability of radiological half-life versus retention. It may be seen that some radionuclides are removed by decay before biological processes (such as ^{32}P), whereas the opposite is true for other radionuclides (such as ^{60}Co).

Table 7- Half-lives of some common radionuclides

	Half-life		
	Radiological	**Biological**	**Effective**
H-3	12 years	12 days	12 days
C-14	5560 years	10 days	10 days
P-32	14 days	257 days	14 days
S-35	87 days	90 days	44 days
Co-60	5 years	10 days	9.5 days
Sr-90	28 years	50 years	18 years
I-131	8 days	138 days	7.6 days
Po-210	138 days	60 days	42 days
Ra-226	1620 years	45 years	44 years

Of interest to DND is data regarding tritium, cesium, cobalt, iodine, americium, phosphorus, plutonium, radium, strontium, and uranium. These, and other radionuclides, are discussed in the following section.

6.1 Isotope Specific Data

6.1.1 Hydrogen (Z=1)

The biokinetic model adopted is taken from ICRP Publication 56 [31]. For tritiated water (HTO) it is assumed that 97% of activity equilibrates with body water and is retained with a half-time of 10 days. The remaining 3% is assumed to be incorporated into organic molecules and retained with a half-time of 40 days. For organically bound tritium (OBT) 50% of activity is taken to be retained with the 10 day half-time of water and 50% with the 40 day half-time of organic carbon.

For tritiated gas (HT) it is assumed that 0.01% of the inhaled HT is absorbed and converted to HTO while for tritiated methane it is assumed that 1% is metabolized and behaves as HTO [30].

6.1.2 Carbon (Z=6)

The biokinetic model adopted is taken from ICRP Publication 56 [4] which is the same as in ICRP Publication 30 [32]. The retention is described by a single exponential function. The biological half-time (40 d) is derived using values for the body content and daily balance of carbon, taken from ICRP Publication 23 [33].

For carbon monoxide a 40% deposition is assumed with an instantaneous absorption to blood from where it is excreted with a biological half-time of 200 min [30 and 32]. For carbon dioxide and organic compounds inhaled as vapour it is assumed that all is absorbed instantaneously [30]. For carbon dioxide biological retention half-times of 5 minutes (18%), 1 hour (81%) and 40 days (1%) are assumed [32].

6.1.3 Phosphorus (Z=15)

The biokinetic model adopted is taken from ICRP Publication 30 [34]. Following entry into the transfer compartment 30% of activity is taken to be deposited in bone (^{32}P on bone surfaces) where it is retained with a retention half-time of 1500 days. 55% of activity is deposited in other tissues, of this 40% is retained with a half-time of 19 days and 15% with a half-time of 2 days. The remaining 15% of activity is taken to be excreted promptly (with a biological half-time of 0.5 days).

For activity removed to excretion from systemic compartments, 50% is assumed to be lost to urine and 50% to feces [29]. This will not necessarily be reflected in the predicted values of daily excretion in urine and feces.

6.1.4 Iron (Z=26)

The biokinetic model adopted is taken from ICRP Publication 69 [35]. Following entry into the transfer compartment, most iron is transported to the red bone marrow, incorporated into haemoglobin in newly formed erythrocytes and re-released to the circulation. Smaller amounts of iron are stored in other tissues, principally the liver. Iron from senescent red blood cells is transferred mainly to the red bone marrow, liver and spleen. Losses of iron from the body are largely due to exfoliation of cells from the skin and the GI tract with smaller amounts in sweat, bile and urine.

6.1.5 Cobalt (Z=27)

The biokinetic model adopted is taken from ICRP Publication 67 [36]. Following entry into the transfer compartment, 50% of cobalt is rapidly excreted with a half-time of 0.5 days, 5% is taken up by the liver and 45% is uniformly distributed in all other tissues. Fractions of 0.6, 0.2 and 0.2 are assumed to be lost from the liver and other

tissues with biological half-times of 6, 60 and 800 days, respectively. For activity removed to excretion from systemic compartments, 86% is assumed to be lost to urine and 14% to feces. This will not necessarily be reflected in the predicted values of daily excretion in urine and feces.

6.1.6 Gallium (Z=31)

The biokinetic model adopted is taken from ICRP Publication 30 [32]. Following entry into the transfer compartment, 30% is deposited on bone surfaces, 9% in liver, 1% in spleen, and 60% in all other tissues. Gallium is retained in all organs and tissues with biological half-times of 1 day (30%) and 50 days (70%). For activity removed to excretion from systemic compartments, 50% is assumed to be lost to urine and 50% to feces [29]. This will not necessarily be reflected in the predicted values of daily excretion in urine and feces.

6.1.7 Strontium (Z=38)

The biokinetic model adopted is taken from ICRP Publication 67 [36]. This model describes in detail the kinetics of alkaline earth elements in bone, which is the main site of deposition and retention, and also considers retention in soft tissues and routes of excretion. It takes account of initial uptake onto bone surfaces, transfer from surface to bone volume and recycling from bone and soft tissues to blood. It also describes the excretion pathways for which no constant ratio is used.

6.1.8 Zirconium (Z=40)

The biokinetic model adopted is taken from ICRP Publication 67 [36]. Following entry into the transfer compartment, 50% of systemic zirconium is retained on bone surfaces with a half-time of 10,000 days (related to the rate of bone remodelling), and the other 50% is distributed throughout all other tissues and is retained with a biological half-time of 7 days. For activity removed to excretion from systemic compartments, 83% is assumed to be lost to urine and 17% to feces. This will not necessarily be reflected in the predicted values of daily excretion in urine and feces.

6.1.9 Niobium (Z=41))

The biokinetic model adopted is taken from ICRP Publication 56 [31]. Following entry into the transfer compartment, 0.4 is deposited in mineral bone, 0.2 in liver, 0.03 in kidneys, and 0.37 in all other tissues. The retention is described by a two-component exponential function for all tissues and organs, with biological half-times of 6 days (50%) and 200 days (50%). ^{95}Nb in the skeleton is assumed to be distributed over bone surfaces. For activity removed to excretion from systemic compartments, 83% is assumed to be lost to urine and 17% to feces [36]. This will not necessarily be reflected in the predicted values of daily excretion in urine and feces.

6.1.10 Technetium (Z=43)

The biokinetic model adopted is taken from ICRP Publication 67 [36]. Following entry into the transfer compartment, 0.04 of technetium is taken up by the thyroid gland and retained with a half-time of 0.5 days. Further fractions of 0.1 and 0.03 are assumed to be translocated to the stomach wall and liver, respectively, and the remaining fraction is assumed to be uniformly distributed in all other tissues. Biological half-times for the retention of technetium in all tissues other than the thyroid are taken to be 1.6, 3.7 and 22 days applying to fractions of 0.75, 0.2 and 0.05, respectively. The biological half-time in blood is assumed to be 0.02 days. For activity removed to excretion from systemic compartments, 50% is assumed to be lost to urine and 50% to feces. This will not necessarily be reflected in the predicted values of daily excretion in urine and feces.

6.1.11 Ruthenium (Z=44)

The biokinetic model adopted is taken from ICRP Publication 56 [30]. For ruthenium absorbed to body fluids data have shown that the subsequent tissue distribution is fairly uniform. A model using a three-term retention expression is recommended: 35% of activity is retained with a biological half-time of 8 days, 30% with 35 days and 20% with 1000 days . The biological half-time in body fluids is taken to be 0.3 days, and 15% of systemic activity is assumed to be excreted directly. For activity removed to excretion from systemic compartments, 80% is assumed to be lost to urine and 20% to feces. This will not necessarily be reflected in the predicted values of daily excretion in urine and feces.

6.1.12 Antimony (Z=50)

The biokinetic model adopted is taken from ICRP Publication 69 [35]. From that part of antimony entering the circulation, a fraction 0.2 is rapidly excreted, 0.4 is taken up by bone surfaces, 0.05 by the liver and the remaining fraction of 0.35 is uniformly distributed throughout all other organs. For all tissues, fractions of 0.85, 0.1 and 0.05 are assumed to be retained with biological half-times of 5, 100 and 5,000 days, respectively. For activity removed to excretion from systemic compartments, 80% is assumed to be lost to urine and 20% to feces. This will not necessarily be reflected in the predicted values of daily excretion in urine and feces.

6.1.13 Iodine (Z=53)

The biokinetic model adopted is taken from ICRP Publication 56 [31]. It is assumed that of iodine reaching blood a fraction of 0.3 is accumulated in the thyroid gland and 0.7 is excreted directly in urine. The biological half-time in blood is taken to be 0.25 days. Iodide incorporated into thyroid hormones leaves the gland with a half-time of 80 days and enters other tissues where it is retained with a half-time of 12 days. Most iodide (80%) is subsequently released to blood and is available in the circulation for

uptake by the gland and urinary excretion; the remainder (20%) is excreted in feces in organic form.

The biokinetic model for iodine assumes that 0.3 is taken up by the thyroid and the remainder is excreted in urine. In fact, there are relatively large variations, depending on many parameters like stable iodine content in common food and thyroid dysfunctions. For example, current uptake values for a European euthyroid adult are in the range 0.20 - 0.25. However in countries with iodine deficiency in food this value is considerably higher. Pathological states of the thyroid may result in uptake values from 0 - 0.05 (blocked thyroid) to greater than 0.5. When such cases are suspected, then individual values should be introduced in the dose calculation, especially in case of accidental exposure, where a precise assessment is needed.

6.1.14 Cesium (Z=55)

The biokinetic model adopted is taken from ICRP Publication 56 [31]. Following entry into the transfer compartment cesium is taken to be distributed uniformly throughout all body tissues; 10% of activity is assumed to be retained with a biological half-time of 2 days and 90% with 110 days. For females however, the half-time for the long-term component is significantly less than for males [30 and 37]. There is also evidence that in some countries the mean biological half-time of cesium in adult males is shorter than 110 days. Additionally, there is information that a small part of activity is retained with a longer biological half-time of about 500 d [37]. For activity removed to excretion from systemic compartments, 80% is assumed to be lost to urine and 20% to feces [36]. This will not necessarily be reflected in the predicted values of daily excretion in urine and feces.

6.1.15 Cerium (Z=58)

The biokinetic model adopted is taken from ICRP Publication 56 [31]. Following entry into the transfer compartment cerium is taken to be distributed in skeleton (bone surfaces; 30%), liver (50%), and other tissues (20%). The retention half-time is taken to be 3500 days in all tissues. For activity removed to excretion from systemic compartments, 10% is assumed to be lost to urine and 90% to feces [36]. This will not necessarily be reflected in the predicted values of daily excretion in urine and feces.

6.1.16 Thallium (Z=81)

The biokinetic model adopted is taken from ICRP Publication 30 [32]. Following entry into the transfer compartment thallium is taken to be distributed instantaneously within the kidneys (3%) and all other organs (97%). Thallium in all tissues is assumed to be retained with a biological half-time of 10 days. For activity removed to excretion from systemic compartments, 50% is assumed to be lost to urine and 50% to feces [29]. This will not necessarily be reflected in the predicted values of daily excretion in urine and feces.

6.1.17 Lead (Z=82)

The biokinetic model adopted is taken from ICRP Publication 67 [36]. The model uses the structure of the alkaline earth model [36]; it describes the kinetics of lead in bone, which is the main site of deposition and retention, and also considers retention in liver and other soft tissues as well as routes of excretion. It takes account of initial uptake onto bone surfaces, transfer from surface to bone volume and recycling from bone and other tissues to plasma.

6.1.18 Polonium (Z=84)

The biokinetic model adopted is taken from ICRP Publication 67 [36]. Following entry into the transfer compartment polonium is taken to be distributed to liver (30%), kidneys (10%), red bone marrow (10%), spleen (5%) and all other tissues (45%). The retention half-time for polonium is taken to be 50 days for all tissues. For activity removed to excretion from systemic compartments, 33% is assumed to be lost to urine and 67% to feces. This will not necessarily be reflected in the predicted values of daily excretion in urine and feces.

6.1.19 Radium (Z=88)

The biokinetic model adopted is taken from ICRP Publication 67 [36]. The model describes the kinetics of radium in bone, which is the main site of deposition and retention, and also considers retention in liver and other soft tissues as well as routes of excretion. It takes account of initial uptake onto bone surfaces, transfer from surface to bone volume and recycling from bone and other tissues to plasma.

6.1.20 Thorium (Z=90)

The biokinetic model adopted is taken from ICRP Publication 69 [35] and is based on the actinide model of ICRP Publiation 67 [36]. It takes account of the initial deposition in bone, liver, gonads and other tissues, and allows for transfer of activity from bone surfaces to bone volume and marrow, recycling of activity between tissues, as well as loss by excretion. The biological half-life of ^{230}Th and ^{232}Th is the same, and is assumed to be 8,000 days for thorium in bone (70 percent of the uptake goes to bone), 700 days for thorium in the liver (4 percent of the uptake goes to liver) and 700 days in all other tissues and organs (16 percent of the uptake goes to these locations). The remaining 10 percent is assumed to be excreted with a half-life of 0.5 days. These values are based on animal experiments and, although expected to be close, are not exact numbers.

6.1.21 Uranium (Z=92)

The biokinetic model adopted is taken from ICRP Publication 69 [35] and is based on the alkaline earth model of ICRP Publiation 67 [36]. The model describes in detail the kinetics of uranium in bone, which is the main site of deposition and retention, and

also considers retention in liver, kidneys and other soft tissues as well as routes of excretion. It takes account of initial uptake onto bone surfaces, transfer from surface to bone volume and recycling from bone and other tissues to plasma.

6.1.22 Neptunium (Z=93)

The biokinetic model adopted is taken from ICRP Publication 67 [36] and is based on the actinide model. It takes account of the initial deposition in bone, liver, gonads and other tissues, and allows for transfer of activity from bone surfaces to bone volume and marrow, recycling of activity between tissues, as well as loss by excretion.

6.1.23 Plutonium (Z=94)

The biokinetic model adopted is taken from ICRP Publication 67 [36] and is based on the actinide model [36]. It takes account of the initial deposition in bone, liver, gonads and other tissues, and allows for transfer of activity from bone surfaces to bone volume and marrow, recycling of activity between tissues, as well as loss by excretion.

6.1.24 Americium (Z=95)

The biokinetic model adopted is taken from ICRP Publication 67 [36] and is based on the actinide model. It takes account of the initial deposition in bone, liver, gonads and other tissues, and allows for transfer of activity from bone surfaces to bone volume and marrow, recycling of activity between tissues, as well as loss by excretion.

6.1.25 Curium (Z=96)

The biokinetic model adopted is taken from ICRP Publication 71 [30] and is identical to the americium model of ICRP Publication 67 [36]. It takes account of the initial deposition in bone, liver, gonads and other tissues, and allows for transfer of activity from bone surfaces to bone volume and marrow, recycling of activity between tissues, as well as loss by excretion.

7. Current Standard Therapies in Decorporation

7.1 Introduction

Nasal swabs are used in nuclear facilities as an early, rough indication of whether inhalation of radionuclides, especially alpha emitters, may have occurred. This procedure consists of swabbing the nasal membranes of each nostril separately with a moist cotton applicator or a moistened filter paper strip wound around a swab stick. Radioactivity in the swipe samples are measured using laboratory type counters such as liquid scintillation counters, proportional counters, etc. Extremely rough estimates can sometimes be made immediately by placing the swabs directly in front of a thin window GM probe. If the two sides do not have approximately the same activity, the result may represent contamination from hands or face rather than an inhalation exposure.

Decisions to treat should be made at the earliest possible time, because the effectiveness of treatment (decorporation) for many radionuclides can drop dramatically within just a few hours. There is no standard protocol that designates when treatment is indicated, however experience has shown that there is not sufficient time for detailed dose assessments. The decision to treat is a subjective judgment. Based on the available data at the time, one might think of the potential exposure as being high, medium, or low. "High" might be exposures of 10 or more times the annual occupational guidelines and "low" might be exposures below the guidelines. Do not permit significant delays, such as several hours, to obtain whole-body counts or results from urine or fecal samples if it is thought the dose could be high. The risk from the initial treatments of internally-deposited radionuclides is nil or very small. Treatment can be started despite the many uncertainties that are always present when such decisions must be made.

After initial treatment has begun, there is time available to get more detailed measurements of external and internal contamination. Emergency planning will reduce the evaluation time required because the plan should list and make arrangements for sources of appropriate instrumentation, dosimetry and analytical chemistry services. Medical and health physics experts can also be brought in for consultation and advice at this time.

7.2 Treatment Procedures and Drugs

The following sections summarize the principal procedures and drugs used to reduce doses from internal contamination by radionuclides [38]. More extensive discussion, including more specific dose recommendations, is available in NCRP Report 65 [39].

7.2.1 Reduction of Uptake

The procedures that may prevent or reduce uptake of radionuclides into the body include skin decontamination, proper management of contaminated wounds, and reduction of gastrointestinal absorption.

During the immediate aftermath of an intake, such simple procedures as irrigation of the nose, mouth, and pharynx, removal of gastric contents, and the use of purgatives should not be overlooked. Any reduction in the residence time of the radioactivity in the gastrointestinal tract will reduce the resultant dose and absorption.

The administration of a laxative such as magnesium sulfate (15 g in 100 ml water) will reduce the residence time of radioactive material in the lower segment of the large intestine. Magnesium sulfate may also produce relatively insoluble sulfate with some radionuclides, such as radium or strontium.

Several compounds can be used to reduce the gastrointestinal uptake of specific radionuclides. Most notable examples are Prussian Blue (1 g in water 3 times per day) for cesium, thallium, or rubidium; aluminum-containing antacids (100 ml aluminum phosphate gel or aluminum hydroxide) for strontium; and barium or magnesium sulfate for strontium or radium. Phytates found in grains, especially oats and soybean products, form insoluble salts of calcium, magnesium, zinc, and iron.

Prussian Blue has been well tolerated in humans. Constipation has been the only noted side effect. Unfortunately, it is not currently available in pharmaceutical grade in the U.S. nor is it approved by the U.S. Food and Drug Administration for medicinal use. Some firms have prepared their own supply for use as part of emergency plans. It is approved as an investigational new drug (IND).

In animal studies, the use of expectorants and/or aerosol therapy, including use of hypertonic saline, hygroscopic agents, detergent mixtures, and mucolytic agents, have not been effective in removing inhaled particulates. In view of these discouraging results, use of expectorant drugs and inhalants are not recommended as therapy after inhalation of radioactive particles.

7.2.2 Contaminated Wounds

In the event of severe injuries associated with radioactive contamination, the first consideration of the attending physician should be for the patient's general welfare. Emergency procedures to control hemorrhage, to restore respiratory and circulatory function, and to alleviate pain are obviously a first order of business, even if the contamination levels are high. Most contaminated wounds, often relatively trivial injuries, will involve relatively low radiation levels.

The level of contamination and effectiveness of decontamination must be measured by means of some type of radiation instrumentation. For beta-gamma radiation, a portable survey meter is usually adequate. Alpha emitters present more difficult monitoring problems and special wound counters are generally necessary.

The first decontamination procedure should be an immediate rinsing of the wound with running tap water or saline irrigation in such a manner that the water flows away from the wound. Use of a pulsating water jet stream may be helpful. Application of a tourniquet frequently is mentioned as a useful procedure to reduce the uptake of radioactive materials, but in practice it is seldom used or needed.

Wound excision has been used primarily to remove long-lived alpha contaminants, such as ^{239}Pu. Excision has not been used often for beta-gamma contamination. Small quantities of alpha contamination, such as 74 Bq or less of ^{239}Pu, do not need to be excised. A significant loss of function due to the excision is usually not justified for decontamination purposes. Frequently, chelation therapy is done simultaneously in cases involving radionuclides for which such treatment is helpful.

7.2.3 Blocking and Diluting Agents

A blocking agent saturates the metabolic processes of a specific tissue with the stable element and thereby reduces the uptake of the radioisotopes. Stable potassium iodide (300 mg) given to prevent the uptake of radioiodine in the thyroid is an example of a blocking agent. To be effective, stable iodide must be administered in a rapidly absorbed form soon after exposure to the radionuclide. Only about 50% of the uptake is blocked if treatment is delayed by 6 hours, which may be compared with about 90% reduction if started in less than one hour. Little reduction is achieved if the delay is 12 hours or more. Once started, continuation of stable iodide administration (300 mg daily, which translates to a dose of 390 mg KI) for 7 to 14 days will prevent recycling of the radioiodine into the thyroid.

Isotopic dilution is achieved by the administration of large quantities of the stable element or compound similar to the radionuclides being treated. The presence of a large quantity of the stable element dilutes the smaller quantity of the radioisotope. For example, forcing fluids to tolerance (minimum of 3-4 liters daily) reduces the biological half-time of tritium (radioactive hydrogen) in the body due to dilution and enhanced turnover time of water.

Displacement therapy is a special form of dilution therapy in which a stable element of a different atomic number successfully competes with a radionuclide for uptake sites. An example is the use of calcium to reduce the deposition of radiostrontium in the bone.

Other examples of blocking or diluting agents are strontium lactate or strontium gluconate for radiostrontium; oral phosphate for ingested radiostrontium; and oral or intravenous calcium for radiostrontium or radiocalcium. Oral administration of zinc or potassium may be used as a diluting agent for their respective radioisotopes.

7.2.4 Mobilizing Agents

Mobilizing agents are compounds that increase a natural turnover process, thereby releasing some forms of radionuclides from body tissues and enhancing elimination

from the body. An example is ammonium chloride, which acts as a mobilizing agent for radiostrontium in the body. Other examples of mobilizing agents are diuretics for sodium, chlorides, potassium, and tritium (radioactive hydrogen); and parathyroid extract for calcium, phosphorus, and strontium.

7.2.5 Chelating Agents

Several chemical compounds are known to enhance the elimination of metals from the body by chelation, a process by which organic compounds (ligands) exchange less firmly bonded ions for other inorganic ions to form a relatively stable non-ionized ring complex. This soluble complex is excreted readily by the kidney. Chelation therapy is most effective when it is begun immediately after exposure while the metallic ions are still in extracellular fluids before incorporation into cells.

The principal chelate used for the removal of radionuclides is DTPA, diethylenetriaminepentaacetic acid. It is effective for transuranic metals (plutonium, americium, curium, californium, and neptunium), the rare earths (such as cerium, yttrium, lanthanum, promethium, and scandium), and others (such as zirconium and niobium).

The effectiveness of DTPA in enhancing excretion of plutonium is affected principally by the chemical form of the plutonium. For exposures to insoluble forms of plutonium, such as plutonium oxide, DTPA is not effective because only tiny amounts of plutonium are present in the blood and extracellular fluids soon after exposure. Soluble compounds of plutonium, such as the nitrate, are taken up much more rapidly in blood, where it is available for chelation. Data from persons treated with Ca-DTPA within about 3 hours of

exposure indicate that about 60% or more of soluble forms of plutonium are removed.

Two forms of DTPA are available for clinical use, the calcium salt (Ca-DTPA) and the zinc salt (Zn-DTPA). Zn-DTPA, which is less toxic than Ca-DTPA, is recommended for longer term treatment and pregnant women. Ca-DTPA is more effective than Zn-DTPA in rats when given promptly after exposure to transuranium metals. Thus, Ca-DTPA is generally the preferred form of the drug used during the first day or two after exposure.

The recommended dose of DTPA is 1g delivered once per day and may be repeated on 5 successive days per week. The dose should not be fractionated. It can be given either intravenously or by aerosol inhalation. The intravenous administration of 1 g DTPA in 250 ml normal saline or 5% glucose in water over 30 minutes has been the usual procedure. An alternate procedure, 1 g diluted in 10 or 20 ml normal saline and injected intravenously by syringe over 5 minutes, is preferred by some physicians. In either case, care should be taken to avoid extravasation outside the vein. Aerosol administration is done with 1 g Ca-DTPA placed in a nebulizer and the contents inhaled over a 15 to 20 minute period.

No serious toxicity in man has been reported as a result of either Ca-DTPA or Zn-DTPA in recommended doses. Long-term, low dose administrations in man, 1 g Ca-DTPA per week, caused no adverse effects after four years. Ca-DTPA binds trace metals present in the body, such as zinc and manganese. It is the reduction of these two metals that apparently accounts for toxicity seen after high doses in animal experiments. Very large doses (greater than about 100 times the clinical human dose range) can produce severe lesions of the kidneys, intestinal mucosa, and liver in animals. Teratogenesis and fetal death have occurred in mice when similarly high doses were given throughout gestation.

DTPA should not to be used in minors. Significant leukopenia, thrombocytopenia, or impaired kidney function are also contraindications. Blood counts and clinical urinalyses should be taken. Blood pressure should be checked during infusion. DTPA should be discontinued if diarrhea occurs.

Zn-DTPA is less well suited for aerosol administration than Ca-DTPA because of a reported metallic taste. It is prudent not to use the inhalation route in persons with preexisting pulmonary disease.

Both Ca-DTPA and Zn-DTPA are approved as Investigational New Drugs (IND) in the United States.

7.2.6 Lung Lavage

Deposition of radioactive particles in the lung is a common mode of accidental exposure of humans to radionuclides. Insoluble particles, once inhaled into the lung, are dissolved slowly and translocated to other organs over many months and years.

Lavage of the trachcobronchial tree has shown promise in animal studies as a possible treatment technique for individuals who have inhaled relatively insoluble particles of radioactive material. The procedure requires placement of an endotracheal tube in the trachea and major bronchi under a general anesthesia and then the lung can be lavaged with isotonic saline. It is used as a standard medical procedure in persons with chronic lung diseases. Dogs treated after inhaling insoluble radioactive particles have shown reductions of their lung burdens from about 25 to 50% (average of 44% in eight dogs) after five lavages of each lung, 10 total. Radiation pneumonitis and early deaths were prevented in 75 % of the treated dogs in contrast to the untreated dogs. In baboons, 60 to 90% of the lung burdens of plutonium oxide was removed by 10 pulmonary lavages.

Possible use of this experimental technique in man requires a careful risk/benefit assessment. The risk lies primarily in the administration of a general anesthetic. Thus, this technique should be considered only in high exposures in which a reduction of 25 to 50% of the dose could be expected to prevent acute or subacute effects, such as radiation pneumonitis or fibrosis. To date, it has been used only once in a human for radionuclide inhalation. It should be recognized that the procedure's risk is immediate, whereas late effects of radiation dose to the lung may occur many years later.

7.3 Therapy for Selected Elements

Brief comments are presented for a few elements that have important radioisotopes. This section discusses only drug therapy and does not go into other important aspects of medical management of radiation cases, such as psychological support for the patient [38].

7.3.1 Knowledge Bases for Decorporation Therapy

Much of the understanding about the mechanisms of decorporation therapy is taken from animal studies. The advantages of animal studies are that known amounts of radioactivity as a defined chemical form can be administered under controlled conditions. The amounts retained in various body tissues or excreted in urine and feces can be readily determined. For research purposes the radionuclides are normally administered as soluble forms, usually the nitrate or citrate. However, conclusions reached from these studies are not necessarily appropriate for industrial, environmental or military theatre scenarios. Ultimately, the optimal treatment protocol will be influenced by the extent and rate of dissolution of the radionuclide at the deposition site, the reactions of dissolved forms with biological ligands at the site, the rates of absorption into the blood and the tissue distribution after absorption.

For investigative purposes, both radionuclides and chelating agents are often administered by intravenous injection. This procedure, while being convenient for investigating and screening new substances, may not lead to reliable conclusions concerning their practical field application (for example, inhalation or wound contamination).

An important consideration in the design of studies with laboratory animals is that the mass of the material in the lungs or wound is a realistic representation of likely human accidents. For example, if unit mass were deposited in the lungs of a rat, the equivalent amount in the human lungs would be about three orders of magnitude greater, reflecting the difference in tissue mass between the species. To correlate the animal exposure with human intake, the fractional deposition in the respiratory tract would also need to be considered. In this case the difference between the amount measured in the alveolar interstitial region of the rat lung after exposure, and the equivalent human intake could differ by up to about twenty thousand. Clearly if animal studies were conducted with say ^{239}Pu in order to simulate inhaled ^{239}Pu by workers then the equivalent human intake could be unrealistically high. Moreover, physico-chemical reactions, such as hydrolysis, which would be unlikely in humans after realistic accidents, could occur in animals, hence resulting in misinterpretation of the experimental data. To overcome this difficulty, radionuclides with a higher specific activity, such as ^{238}Pu, are frequently used. Similar considerations to those described for plutonium will also apply to other elements. Excessive amounts of uranium administered to animals could result in precipitation reactions in lung fluid or at wound sites. Also of relevance in this context is thorium, since workers are potentially exposed in different circumstances to ^{228}Th and ^{232}Th. The large difference in specific activity will have a substantial effect on the efficacy of chelation.

Much of the research activity in decorporation involves testing new substances likely to be superior to those in clinical use. In such cases the experimental design should always permit a direct comparison to be made with the recommended agent of choice. In general, current protocols for the administration of chelating agents to humans involve intravenous injection or infusion. It is important that research studies with either new, or existing, compounds should address other routes of intake such as inhalation, wound infiltration and oral administration.

In the following sub-sections, decorporation modalities are presented for selected elements. The data is based upon both human experience and animal studies (40), and as such incorporates elements of both medical clinical experience and animal research.

7.3.2 Americium

For decades, the chelating agent of choice for increasing the excretion of plutonium and americium from the body has been diethylenetriaminepentaacetic acid (DTPA). The trisodium calcium salt, $CaNa_3$-DTPA (referred to hereafter as Ca-DTPA) is normally used for early treatment and the zinc salt, whereas $ZnNa_3$-DTPA (Zn-DTPA) is used when extended or protracted treatment is necessary.

Irrespective of the route of intake, Ca-DTPA or Zn-DTPA are normally administered to humans by slow intravenous injection, although protocols exist for inhalation, wound infiltration and oral intake. In general the administration of these substances by whatever route is not completely effective and there may be a need to continue treatment for weeks or months, or even years after severe accidents. Thus the development of superior substances remains an important aspect of radiological protection for workers.

It has been recognised for the past decade that the most likely alternative substances to Ca-DTPA or Zn-DTPA would be analogues of siderophores (see Section 10.2.3 for a discussion of current research in siderophores). Siderophores are sequestering agents produced by microorganisms in order to obtain Fe(III) from their environment. The rationale for this approach was that in mammals, the biokinetics of the actinides are associated with the Fe(III) transport and storage systems and that the formation constants of the actinide-ligand complexes are much higher than with DTPA. Initially, the tetracatechoylate enterobactin analogue named 3,4,3-LICAM(C) appeared to have much potential. However, the plutonium chelate was found subsequently to be unstable at the pH of tubular urine, and there were undesirable side effects produced in the kidneys. Moreover, 3,4,3-LICAM(C) was less effective for inhaled plutonium than DTPA, and only enhanced minimally the excretion of americium.

Three other siderophore analogues were also considered worthy of more detailed investigation. These were a dihydroxamic acid of DTPA, code named DTPA-DX, a hydroxypyridinone derivative of desferrioxamine, DFO-HOPO and a linear hydroxypyridinone derivative 3,4,3-LIHOPO, or more correctly, 3,4,3-LI(1,2 HOPO). After the intravenous injection of both ^{238}Pu and the ligands in mice, all three were more effective than DTPA. Importantly, they appeared to be of low toxicity in mice. Subsequent studies with rats showed that after the inhalation of ^{238}Pu and ^{241}Am as

nitrates, DTPA-DX was as effective as DTPA for removing ^{241}Am from the body but less effective for ^{238}Pu. While DFO-HOPO was considerably more effective than DTPA after the intravenous injection of ^{238}Pu, it was inferior to DTPA for inhaled ^{238}Pu, and did not significantly enhance the excretion of ^{241}Am after either mode of intake.

However, the potential of 3,4,3-LI(1,2-HOPO) suggested by the initial intravenous experiments has been confirmed, and at present this substance is the most effective yet used for the decorporation of plutonium and americium after either inhalation or wound contamination; it is also appreciably more effective than DTPA after oral administration.

7.3.3 Californium

See Section 7.3.16 (Transuranic Elements).

7.3.4 Cerium

See Section 7.3.13 (Rare Earths).

7.3.5 Cesium

Prussian Blue (ferric ferrocyanide), 1 g given orally with water three times daily, should reduce the biological half-time from the usual 70 days to 35-50 days during the period of administration.

7.3.6 Cobalt

Whatever the route of internal contamination, the recommended treatment is the slow intravenous injection of DTPA or EDTA, although the inhalation of DTPA can be considered after inhalation of cobalt. The administration of these chelates can be accompanied by the sublingual injection of cobalt gluconate as an isotopic dilution agent.

7.3.7 Curium

See Section 7.3.16 (Transuranic Elements).

7.3.8 Iodine

Stable KI or NaI (390 mg of KI, which incorporates a dose of 300 mg stable iodine) should be administered orally as soon as possible, and continued daily for 7 to 14 days to prevent recycling of the radioiodine. For administration of stable iodide to the general public as a prophylactic measure after an accidental release of radioactive iodine, smaller doses are recommended – 130 mg KI tablets for adults and children

and one-half tablet (65mg KI) for children under 6 months of age. Crush tablets to enhance the rate of absorption. Success depends upon early administration of the drug, preferably within 1 to 4 hours of exposure. Little effectiveness is expected if given as late as 12 hours.

7.3.9 Lanthanum

See Section 7.3.13(Rare Earths).

7.3.10 Phosphorus

Aluminum hydroxide (100 ml) antacids will reduce gastrointestinal absorption. Phosphate (1 g) will act as a diluting agent.

7.3.11 Plutonium

See Sections 7.3.2(Americium), 7.3.16(Transuranic Elements), and 7.3.19(Special Case: Plutonium).

7.3.12 Radium

Magnesium sulfate (15 g in 100 ml water) will reduce absorption of radium from the gastrointestinal tract. No effective therapy is available after absorption and deposition of the radium in bone. Administration of ammonium chloride and calcium may increase urinary excretion of radium slightly.

7.3.13 Rare Earths

Chelation with DTPA should start as soon after exposure as possible.

7.3.14 Strontium

Aluminum phosphate gel or aluminum hydroxide antacids (100 ml), if given shortly after ingestion, will reduce absorption from the gastrointestinal tract. Administration of strontium (500-1500 mg strontium lactate orally each day or 600 mg strontium, gluconate intravenously daily up to 6 days) or large doses of oral or intravenous calcium combined with oral ammonium chloride (1 to 2 g four times/day) will enhance urinary excretion of strontium. This treatment needs to be started as soon as possible after exposure.

7.3.15 Thorium

The recommended chelate for thorium is also DTPA. However, studies in animals have shown that it is ineffective when the amounts deposited in the lungs simulated accidental human exposures to the Annual Limit on Intake for ^{232}Th. Treatment with

DTPA was moderately effective in the rat after intravenous, subcutaneous or intramuscular injection and by a combination of intramuscular and oral administration, provided very low masses of thorium (^{234}Th) were used and the ligand was administered promptly. The siderophore analogue 3,4,3-LI(1,2-HOPO) developed for the treatment of plutonium and americium has also been shown to be the most effective substance tested so far for the decorporation of thorium after inhalation, or wound contamination.

7.3.16 Transuranic Elements

Chelation with DTPA should start as soon after exposure as possible, preferably within the first hour or two. The dose is 1 g Ca-DTPA or Zn-DTPA per day (usually 5 days per week) by IV administration or aerosol inhalation. Animal data suggests aerosol administration may be advantageous for inhalation cases, but this remains unconfirmed. A therapeutic trial dose of DTPA, combined with monitoring of the urine for significant excretion of plutonium or other transuranic element, can be used to determine the effectiveness of chelation therapy. Results should be monitored with plutonium excretion data from urine samples to determine when chelation treatment is no longer worthwhile. After high exposures, the treatment may be continued for many months. A model developed for plutonium excretion after DTPA treatment that suggests an optimal dosage schedule is provided with administrations of DTPA on days 1 (immediately after exposure), 2, 4, 7, and 15 after exposure.

7.3.17 Tritium

Force fluids to tolerance of patient up to about two weeks. The length of treatment will depend on the estimated dose determined by measurements in daily urine samples. The normal 10-12 day biological half-time should be reduced to six days or less.

7.3.18 Uranium

Soluble compounds of uranium are nephrotoxic. The recommended substance for uranium decorporation is sodium bicarbonate despite the possibility of undesirable side effects such as hypokalaemia and alkalosis. Since there appears to be no substantive evidence that bicarbonate is effective, several alternative substances have been investigated in animals. Amongst these were phenolic chelating agents. While one of the most promising substances, sodium 4,5-dihydroxybenzene-1,3-disulphonate (Tiron) was shown to avert uranium poisoning in mice, and to a lesser extent in rats, prompt administration was required (within minutes) and it was ineffective after a few hours. Moreover, after the administration of sub-lethal amounts of uranium to rats, its excretion was not enhanced appreciably by the Tiron.

Since uranium has a known affinity for phosphonic acid, another approach has been to investigate the efficacies of polyarninophosphonic acids, bisphosphonates and phosphoalkylphosphinates. These substances are known to complex uranium, and some are also being investigated for other medical uses, such as bone marrow suppressing agents. In many cases large reductions in the kidney and skeletal contents

have been observed when the substances have been administered immediately after uranium. Under more meaningful conditions relevant to human treatment, (for example, delays of an hour or more), their efficacy is poor.

Much of the current research on uranium decorporation concerns the evaluation of analogues of siderophores, particularly multidentate catecholate and hydroxypyridonate ligands after their intravenous or intraperitoneal injection. Reductions in the kidney content of about an order of magnitude compared with controls were observed for some of them after prompt administration, e.g. 3,4,3-LI(1,2-HOPO), 4-LI(Me-3,2-HOPO). However, when treatment is delayed for 30 min or more, it is largely ineffective. In this respect the behavior of the siderophore analogues is similar to the phosphonates. It is noteworthy that under the same conditions of evaluation that the phosphonates and siderophore analogues are much superior to sodium bicarbonate and DTPA.

It is concluded that, at present, no effective chelating agents are available for uranium.

7.3.19 Special Case: Plutonium

A wealth of data has been collected over the years on chelating plutonium from animals and humans. Much of the work in this area was driven by the use of plutonium in weapons manufacturing. The special case of plutonium is presented as a model for chelation research.

While not the most toxic, plutonium is the most likely transuranic element to be encountered [41]. In addition to the several kilograms of naturally occurring plutonium, about 5,000 kg of plutonium has been released during nuclear weapons testing and nuclear fuels reprocessing. Fortunately, the viable routes of plutonium contamination are limited to direct physical transport, since the inability of plutonium to cross physiological membranes prevents its concentration in the food chain. The concentration of plutonium in plants is 10^{-4} to 10^{-6} of the surrounding soil. Further, only 0.03% of ingested Pu(IV) citrate is absorbed by the gastrointestinal tract of mammals, while much smaller amounts of less stable chelates, simple salts, or insoluble compounds of plutonium are absorbed. Similarly, insignificant amounts of plutonium are absorbed through intact skin during long exposures to highly acidic plutonium solutions. Thus human contamination by environmental plutonium would seem to be limited to the direct ingestion or inhalation of plutonium resuspended from soil. However, there continues to be concern that naturally-occurring chelating agents might complex plutonium sufficiently strongly to change this view. Occupationally, plutonium has gained admittance to humans principally through inhalation and wounds.

The biological behavior of plutonium is dependent on the chemical form. Insoluble compounds of plutonium, such as oxides, fluorides, and hydroxides, largely remain in the lung or at the site of an intramuscular wound. Particles of these insoluble compounds may be slowly transported to the lymph nodes, and a small portion may react with biological ligands to form soluble complexes that are transported by the circulatory system. Extremely small particles of PuO_2 when inhaled as aerosols are

rapidly absorbed from the lung and enter the circulation as low molecular weight complexes. Plutonium chelates are quickly and completely absorbed from the site of entry, but metabolically inert complexes, such as Pu-DTPA, are rapidly and nearly quantitatively excreted. Complexes of metabolizable ligands, such as citrate and ascorbate, are not excreted, but give up their plutonium to plasma proteins. Other compounds of plutonium such as hydrolyzable chelates and simple salts are partially absorbed into the circulation. Much larger amounts of Pu(III) and Pu(VI), which hydrolyze less readily than Pu(IV), are absorbed. The remainder hydrolyzes to form an insoluble deposit, which behaves as described above.

While the hydrolytic behavior of the oxidation state determines the amount and the rate of plutonium absorbed from the lungs or from a wound, the tissue distribution of the absorbed Pu is indistinguishable when Pu(III), Pu(IV), or PU(VI) is administered to rats. Thus, once plutonium enters the circulation its behavior is independent of its original oxidation state. Biologically plutonium behaves like thorium, which is stable in solution only as a tetravalent ion. While the biological behavior of Am(III) and Cm(III) is similar to plutonium, there are significant differences in the binding to endogenous ligands, biological transport, distribution, and rate of elimination. In contrast to tri- and tetravalent actinides, the oxocations, as exemplified by the uranyl ion, are rapidly absorbed from lungs and wounds, and the majority of the absorbed uranium is rapidly excreted as a uranyl-bicarbonate complex.

Although there is no direct measurement of the oxidation state of plutonium in biological fluids, redox potentials, complexation and hydrolysis strongly favor Pu(IV) as the dominant species.

Plutonium which is absorbed into the circulatory system of mammals, either by injection of a metabolizable complex or by solubilization of plutonium deposited in a wound or in a lung, is quickly and strongly bound to transferrin, the iron transport protein found in the plasma of mammals. Small amounts of plutonium are associated with other macroglobulins or complexed with low molecular weight substances such as citrate, sugars and peptides. While the exact nature of the binding of Pu(IV) to transferrin is unknown, it appears to be bound by the same sites that bind iron. As with iron, bicarbonate is required in the formation of the Pu-transferrin complex. Plutonium is displaced by Fe(III) and does not bind to iron saturated transferrin. Titrimetric experiments show that transferrin specifically binds Th(IV) at the same sites as Fe(III). Further, the half-life for the removal of plutonium from circulation nearly equals that of iron, such that after 1 h 70% of the injected plutonium is still in circulation. In contrast, 86% of the injected Am(III) or Cm(III) is removed from the blood within 1 min. Thus, the trivalent actinides are not complexed by transferrin, but are weakly associated among various plasma proteins. The complexation of plutonium by transferrin effectively prevents its excretion, but small amounts are excreted as the citrate complex in the urine.

Colloids and particles of insoluble plutonium compounds which enter the circulatory system are not complexed by transferrin, but accumulate primarily in the liver. Small amounts are also found in the spleen and bone marrow. These organs have a high concentration of reticuloendothelial cells, which act as filters to consume rapidly any

colloidal particles. While the extent of hydrolysis depends on the oxidation state, a portion of an intravenously injected, hydrolyzable salt of plutonium, such as the nitrate or the chloride, forms insoluble colloids of hydrolyzed plutonium that are removed mainly by the liver. The remainder is complexed and transported by transferrin.

Circulating as the Pu-transferrin complex, plutonium is initially distributed throughout the body, but is eventually deposited as single atoms primarily on bone surfaces close to the marrow and the circulatory system. Initially the plutonium appears to bind to the glycoproteins present in the organic matrix of bone. These proteins contain many free carboxyl groups and bind plutonium stronger than a 30-fold excess of bone mineral or any other protein investigated, including transferrin. The carboxyl groups of the proteins appear to be important in binding Pu(IV), but not Am(III) or Cm(III), which are less strongly bound. The trivalent actinides are uniformly distributed on all bone surfaces and tend to deposit on bone mineral to a greater extent than plutonium.

Once deposited on bone, plutonium is not released until the bone is physically destroyed. It may become buried under a new layer of mineral or may be taken up by special cells that digest foreign materials. As these cells die, the plutonium accumulates in immobilized deposits of hemosiderin, an insoluble iron storage protein that contains a large core of polymeric iron hydroxides and phosphates. These deposits are located close to the bone surfaces in the reticuloendothelial cells of the bone marrow.

In addition to deposition on bones, smaller, but significant amounts of circulating plutonium is deposited in the liver. Initially the plutonium is distributed throughout the liver, where it is bound principally in the cytosol of cells to an unidentified protein that has the chromatographic characteristics of γ–globulin. Within several days, the plutonium becomes associated with subcellular structures, where it is primarily bound to ferritin, a soluble iron storage protein. Small amounts of plutonium are associated with other proteins located on the subcellular structures such as glucose-6-phosphatase, cytochrome-c-oxidase, aryl-sulphatase, acid-phosphatase and unknown glycoproteins. In an attempt to minimize their toxic effects, other toxic metals are similarly immobilized on subcellular structures.

As the liver cells die, the plutonium accumulates in the hemosiderin of the reticuloendothelial cells. As in the bone marrow and the liver, plutonium in the spleen and the adrenal glands is also localized with hemosiderin. Incorporation of plutonium into hemosiderin or the mineral matrix of bone is not permanent, but the mechanisms of release are not known. However, it is more probable that released plutonium will be complexed by transferrin and re-deposited instead of excreted. In fact, the human iron transport system is so efficient in preventing plutonium excretion that only 20-30% of the plutonium injected into humans was excreted during 27.4 years. In view of the role of iron transport and storage proteins in the mammalian metabolism of plutonium, it is not surprising that the highest uptake of plutonium occurs in plants grown in iron deficient conditions (meaning that if a plant is iron deficient, it will readily uptake plutonium substitutionally).

The most promising approach to the removal of incorporated plutonium uses chelating agents to form soluble, excretable complexes of plutonium. Sodium citrate was the first complexing agent to be tested for plutonium removal. Although plutonium is naturally excreted as the citrate complex, the rapid metabolism of sodium citrate and its complexes decreases its effectiveness as a chelating agent. Administration of sodium citrate within 2 h after the injection of plutonium increased urinary excretion several fold, but the increase was not sufficient to be of practical importance. However, the excretion of thorium was increased from the control value of 28% to 47% of the injected thorium by treatment with sodium citrate 30 min after the injection of thorium.

The limited success with sodium citrate led to the trial and error testing of other chelating agents. Despite the fact that hard Lewis acids such as plutonium do not bind strongly to sulfur ligands, the success of 2,3-dimercapto-1-propanol (BAL) as an efficient chelator for arsenic led to testing its ability to remove actinides. As expected on a chemical basis, excretion of plutonium was not enhanced by treatment with BAL, methionine, or cysteine. Several other sulfur containing compounds were also found to have a negligible effect on the excretion of lanthanides. Similar results were obtained for biologically occurring complexing agents, such as ascorbic acid, nicotinic acid and creatine, as well as for nitrilotriacetic acid (NTA), and picolinic acid. However, since 70% of the yttrium administered simultaneously with therapeutic doses of ethylenediaminetetraacetic acid (EDTA) was excreted from rats in 24 h, the use of EDTA was suggested for plutonium removal. Rats receiving plutonium followed by EDTA in the first 24 h excreted ten times the plutonium of the control group. Another study showed that an injection of EDTA immediately following the plutonium increased the urinary excretion in rats from the control value of 6% to 51 % of the injected plutonium. As with zirconium, a large dose of EDTA administered 30 days after the plutonium did not significantly decrease the body burden of plutonium in rats.

The additional carboxylic acid group present in diethylenetriaminepentaacetic acid, DTPA, relative to EDTA increases the stability of its actinide complexes, while the complexation of calcium remains nearly constant. Thus, the octadentate DTPA was found to be superior to EDTA or zirconium, and slightly more effective than BAETA, in the removal of plutonium from animals. Prompt administration of a single dose of DTPA caused the excretion of 89% of the injected plutonium from pigs during the following six days, compared to 3% excreted by controls. DTPA injected in dogs (1/2 h) or in mice (1 h) following the plutonium promoted the excretion of 60-65 % of the injected plutonium during 24 h, compared to 2% and 6% excreted in untreated dogs and mice. A further delay in treatment results in less plutonium removal such that only 15% of the injected plutonium was excreted by beagles during the first day following DTPA treatment given two hours after the plutonium.

Delayed treatment with multiple doses of DTPA removes moderate amounts of plutonium from animals. Treatment of swine on five successive days two months after plutonium contamination removed 11-19% of the plutonium. The body burden of rats was reduced to 60% of the controls by treatment with DTPA administered on day 6, 8 and 11 after the plutonium injection. The largest decrease of plutonium was found in

the soft tissues, but skeletal removal was more difficult, and the moderate amounts removed may not significantly reduce the number of bone tumors formed.

Further increasing the number of carboxyl groups of a polyaminocarboxylic acid did not significantly increase plutonium removal. Triethylenetetraaminehexaacetic acid, TTHA, and DTPA were nearly equally efficient at plutonium removal, but TTHA was reported to be more toxic. Due to the formation of multinuclear complexes, the additional increase in the number of carboxyl groups in tetraethylenepentaaminehеptaacetic acid, TPHA, resulted in a chelating agent significantly poorer in plutonium removal than DTPA, but still more effective than EDTA. Although tri(2-aminoethyl)aminehexaacetic acid, TAAHA, and TTHA each have six carboxylic acid groups, TTHA is better able to encapsulate the metal ion and removes much more thorium from rats than does TAAHA. As with EDTA, the complete phosphorylation of DTPA decreases its ability to remove plutonium.

The stability of the calcium complex of the naturally-occurring iron sequestering agent desferrioxamine B, DFOA, is much less than that of DTPA. Although the stability of its Fe(III) chelate is not much greater than that of DTPA, DFOA is significantly more efficient in iron decorporation, primarily due to its decreased affinity for calcium. If administered within 1 hour after an injection of plutonium, DFOA is more effective than DTPA in promoting the excretion of plutonium. However, the ability of DFOA to decorporate plutonium decreases more rapidly than DTPA as elapsed time between contamination and treatment increases; DFOA treatment begun 4-7 days after contamination was ineffective. Prompt treatment with DFOA reduced bone deposition to 1/2 the amount in DTPA treated rats, while the metabolism of DFOA deposits more plutonium in the liver, and the low pH of the kidneys causes the release of more plutonium from the more basic hydroxamic acid groups of DFOA. Combined treatment of DFOA and DTPA removed the greatest amount of plutonium, as the plutonium freed by destruction of the Pu-DFOA complex in the liver and the kidney is recomplexed by DTPA.

The additive effect of DTPA and DFOA has prompted studies of the plutonium removal exhibited by other combinations of chelating agents. The simultaneous local administration of citric acid or 2,6-pyridinedicarboxylic acid in conjunction with DFOA or DTPA increased the amount of plutonium nitrate absorbed and excreted from an intramuscular site compared to using DFOA or DTPA alone. Tartaric acid, 2,3-pyridinedicarboxylic acid, lactic acid or pyruvic acid had no effect when administered with DTPA or DFOA. Citric acid or 2,6-pyridinedicarboxylic acid when administered alone solubilized much of the plutonium from the intramuscular site, but the plutonium was redeposited in other body tissues instead of excreted. With the hope of enhancing systemic plutonium removal by the formation of mixed ligand complexes, catechol, salicylic acid and benzohydroxamic acid were administered simultaneously with DTPA, but the amount of plutonium removed did not increase.

While DTPA is currently the reagent of choice in reducing the body burden of actinides, it is most effective in removing monomeric plutonium from the circulation system - thus preventing the deposition of plutonium in body tissues - which requires prompt treatment. DTPA removes very little hydrolyzed thorium or plutonium

colloids or polymers. The decreasing efficacy of plutonium removal as the time between contamination and treatment increases indicates that the plutonium deposited in intracellular sites is unavailable for complexation. Metabolic experiments show that intravenously injected EDTA or DTPA mix rapidly with extracellular fluid, but are unable to cross cell walls.

Very few cases of accidental plutonium contamination are likely to create a high blood level of plutonium. Only very small amounts of plutonium compounds are absorbed from the gastrointestinal tract. A maximum of 2% of ingested Pu(Vl) citrate or 0.03% Pu(IV) citrate, and much less of most other compounds, was absorbed by rats. This absorption was reduced by a factor of 10 by the oral administration of ion exchange resin. Only a small amount of an intramuscular deposit of plutonium nitrate was removed by an intravenous injection of DTPA, while a local application of DTPA 1 h after contamination removed 80-90% of the plutonium. However, much less was removed by a local DTPA treatment applied 21 days after contamination, during which time the plutonium had formed insoluble, polymeric hydroxides. DTPA is totally ineffective in removing insoluble plutonium compounds as PuO_2 from intramuscular sites or from lungs. These conditions are best treated by surgical excision of contaminated tissue, lung lavage, or other methods of direct physical removal.

Protracted DTPA therapy removes plutonium as it is liberated from cells by natural processes or solubilized by body fluids from intramuscular or lung deposits. The slowness of these processes requires DTPA administration over long periods of time to remove significant quantities of plutonium. The usefulness of such therapy may be of little value in preventing cancer caused by the plutonium. Thus, there has been much emphasis applied to the development of a lipophillic chelating agent. Thus far, very limited success has been realized in this area.

7.4 Common Medications Having Chelating Effects

There are numerous common medications that may be used as chelating agents in a military field deployment. Some of these agents are outlined in Table 8 through Table 11 [42].

Table 8- Drugs with non-specific chelating effects

Anti-inflammatory drugs	Steroids
Salicylates	Cortisone, Hydrocortisone
Indocin	
Aminopyrine	**Psychic Drugs**
Tylenol	Chloropromazine
Butazolidin Group	Dilantin

Table 9- Common drugs with chelating effects

Drug	Chelate
Hygroton	^{86}Ru
Phosphajel	$^{85,90}Sr$
Gaviscon	$^{85,90}Sr$
Neutraphos	^{32}P

Table 10- Anti-microbial drugs with specific chelating effects

Drug	Chelate
P-Aminosalicylic Acid	Fe, Cu
Bacitracin	Zn
Isoniazid	Fe, Cu, Mn, Co
Kanamycin	Ca
Neomycin	Fe, Al
Novobiocin	Mg
Penicillin	Co
Polymyxin	Mg, Mn, Ca, Fe
Streptomycin	Mn
Tetracycline	Fe, Mg, Mn, Mo, Al, Ca

Table 11- Common foods with chelating effects

Foodstuff	Chelate
Cabbage	^{131}I, ^{99}Mo, ^{75}Se
Eggs	^{59}Fe
Soybean	^{65}Zn, ^{59}Fe
Vitamin C	STOP taking for ^{59}Fe

7.5 Summary

Table 12 summarizes some important decorporation agents [43]. See Section 12 for an explanation of the acronyms.

Table 12- Medications and mechanisms of decorporation

		Applications in		
Radionuclide	**Medication**	**Ingestion/Inhalation**	**Wound**	**Principle of Action**
Iodine	KI	130 mg (tabl) stat. followed by 130 mg q.d. x 7 if indicated	Same	Blocking
Rare earths Plutonium Transplutonics Yttrium	DTPA	1 gm Ca-DTPA in 500 ml 5-percent D/W i.v. over 60 min;. or 1 gm (4ml) in 6 ml 5% D/W by slow i.v. injection (1 min)	Irrigate wound with 1 gm of Ca-DTPA in 250 ml D5W	Chelation
Polonium Mercury Arsenic Bismuth Gold	BAL	One ampoule (=300 mg) i.m. q4 hrs. for 3 days (first test for sensitivity with 1/4 amp.)	Same	Promotes excretion
nium	Bicarbonate	Slow i.v. infusion of bicarbonated physiological solution (250 ml at 14 percent)	Slow i.v. infusion of bicarbonated physiological solution (250 ml at 14%) and wash with bicarbonate	Alkalinization of urine; reduces chance of ATN
Cesium Rubidiu Thallium	Prussian Blue [Ferrihexacyano-Ferrate (II)]	1 gm in 100-200 ml water p.o. t.i.d. for several days	Same	Mobilization from organs and tissues - reduction and absorption
Radium Strontium	Ca-gluconate Ammonium chloride	May be tried; 20-percent Ca-gluconate 10 ml i.v. once or twice daily 3 gm t.i.d. p.o.	Same Same	Displacement Demineralizing agent
Tritium	Water	Have patient drink 6-12 litres of water per day	Same	Isotopic dilution
Strontium Radium Calcium Barium	$BaSO_4$ Sodium alginate	100 gm $BaSO_4$, in 250 ml of water 10 gm in a large glass of water	Same Same	Reduces absorption Inhibits absorption
Copper Polonium Lead Mercury Gold	D-penicillamine	1 gm i.v. q.d. or 0.9 gm p.o. q4-6 hrs.	Same	Chelation

8. Adverse Health Effects Associated with Decorporation Therapy

There have not been an abundance of adverse health affects associated with decorporation therapy in humans. Although there is discussion about the possible toxic effects of Ca-DTPA therapy, adverse reactions have only been observed in treatments on rats, at relative doses much higher than required for adequate chelation.

In the following sections, some data is presented to assist the care provider in determining causalities of treatment modalities with decorporation therapies.

8.1 Specific Therapies

8.1.1 Ca-DTPA

Ca-DTPA can deplete the body of zinc and, to a lesser extent, manganese with repeated dosing. The amount of zinc lost is determined by the amount of DTPA and the frequency of dosage. By depletion of these essential trace metals, Ca-DTPA can then interfere with necessary mitotic cellular processes, over long time periods.

No serious toxicity in human subjects has been reported as a result of over 4500 Ca-DTPA administrations in recommended doses. When given repeatedly, with short intervals for recovery, Ca-DTPA treatment may cause nausea, vomiting, diarrhea, chills, fever, pruritus, and muscle cramps in the first 24 hours. Anosmia was observed in one individual after 123 g of Ca-DTPA over twenty-seven months of therapy and possibly could have been related to zinc depletion. After 100 days of no further DTPA administration, the patient's sense of smell improved. Urinary zinc excretion studies suggest that the zinc supply is quickly replenished during this treatment regimen and that any partial depletion of zinc stores, if it occurs at all, would be transient.

Ca-DTPA is approximately 10 times more effective than Zn-DTPA for initial chelation of transuranics; therefore, Ca-DTPA should be used whenever larger body burdens of transuranics are involved. Ca-DTPA is the form of choice for initial patient management unless contraindicated. Approximately 24 hours after exposure, Zn-DTPA is, for all practical purposes, as effective as Ca-DTPA. This comparable efficacy, coupled with its lesser toxicity, makes Zn-DTPA the preferred agent for protracted therapy.

Ca-DTPA should not to be used as a chelator for uranium or neptunium. Internal contamination with uranium is currently treated by alkalizing the urine with bicarbonate in order to promote excretion. DTPA has also been postulated to form an unstable complex with neptunium, which may increase bone deposition of this actinide

8.1.2 Zn-DTPA

No serious toxicity in humans has been reported as a result of over 1000 Zn-DTPA administrations in recommended doses. When given repeatedly, with short intervals for recovery, Zn-DTPA treatment may cause nausea, vomiting, diarrhea, chills, fever, pruritus, and muscle cramps in the first 24 hours

Zn-DTPA should not to be used as a chelator for uranium or neptunium. Internal contamination with uranium is currently treated by alkalizing the urine with bicarbonate in order to promote excretion. DTPA has also been postulated to form an unstable complex with neptunium, which may increase bone deposition of this actinide.

8.1.3 Dimercaprol (BAL)

Although BAL is a very powerful chelating agent, especially for arsenic and mercury poisoning, it can have some serious side-effects. BAL treatment may cause nausea, vomiting, burning of lips and throat, salivation, abdominal pain, anxiety, weakness and unrest. Potential effects to the nervous system include headache, conjunctivitis, lacrimation and tingling of the hands. Cardiovascular effects may include a rise in blood pressure and tachycardia. Other miscellaneous effects may include burning sensation in penis, sweating of the forehead and hands, feeling of constriction in chest and throat, pain at the site of injection and renal damage. The risk of toxicity of this drug increases when taken with iron.

8.1.4 Desferal (Deferoxamine Mesylate)

Desferal has been used in the treatment of iron toxicity. The injection can be very painful.

8.1.5 Prussian Blue - Ferric(III) hexacyanoferrate(II)

The medical consideration to using high doses during treatment over a prolonged period is slight obstipation. In addition, the patient will observe blue stool, which may be a psychological consideration.

8.1.6 Penicillamine

This drug is a standard therapy for Wilson's Disease and severe rheumatoid arthritis. Penicillamine treatment may cause nausea, vomiting, gastric pain, diarrhea, altered taste perception and oral ulcerations. Nervous system effects include muscle weakening and tinnitus. Various hematological effects include bone marrow depression, leukopenia, thrombocytopenia, red cell aplasia, agranulocytosis and aplastic anemia.

8.2 Allergic Reactions

8.2.1 Potassium Iodide (KI)

The use of KI in Poland after the Chernobyl accident provides useful information regarding its safety and tolerability in the general population. Approximately 10.5 million children under age 16 and 7 million adults received at least one dose of KI. The side effects among adults were generally mild and not clinically significant. Side effects included gastrointestinal distress, which was reported more frequently in children (up to 2 percent) and rash (~1 percent in children and adults). Two allergic reactions were observed in adults with known iodine sensitivity [45].

8.2.2 Penicillamine

Persons who are allergic to penicillin, may likely be allergic to penicillamine.

8.3 Chemical Toxicity

Before considering the chemical toxicity of decorporation agents on the human body, a comparison of the acute toxicities of various actinide-based substances (in mice) are presented in Table 13 [44].

Table 13 - Acute chemical toxicities of some compounds

Substance	LD50/30 mmole/kg	Relative toxicity
NaCl	44.52	1
$CaCl_2$	2.50	18
$ZrOCl_2$	0.96	46
$CrCl_3$	0.90	49
$ThCl_4$	0.89	*50*
AlC_{13}	0.80	56
$Fe_2(SO_4)_3$	0.42	106
Pb $(acetate)_2$	0.37	120
$ZnCl_2$	0.18	247
TlCl	0.10	445
$CdSO_4$	0.033	1349
UO_2Cl_2	0.021	2145
$HgCl_2$	0.020	2283
^{239}Pu(IV)Citrate	0.0047 (rat)	9400
	0.0013 (dog)	
Strychnine	0.0015	30000
Botulinus Toxin A	3×10^{-9} mg/kg	

It may be seen that the acute chemical toxicity of tetravalent actinides, as exemplified by Th(IV), is similar to Cr(III) or Al(III). However, the acute toxicity of ^{239}Pu(IV) is

similar to strychnine, which is much more toxic than any of the non-radioactive metals such as mercury. Although the more radioactive isotopes of the transuranium elements are more acutely toxic by weight than plutonium, the acute toxicities of ^{239}Pu, ^{241}Am, and ^{244}Cm are nearly identical in radiation dose, ~100 pCi/kg in rodents. Thus, the extreme acute toxicity of ^{239}Pu is thought to be attributed to its high specific activity of alpha emission.

Unlike organic poisons, biological systems are unable to detoxify metal ions by metabolic degradation. Instead, unwanted metal ions are excreted or immobilized. Unfortunately, only a small portion of absorbed tetra- or trivalent actinide is eliminated from a mammalian body during its lifetime. The remaining actinide is distributed throughout the body but is especially found fixed in the liver and in the skeleton. While the ability of some metals to do damage is greatly reduced by immobilization, local high concentrations of radioactivity are produced by immobilized actinides, thereby increasing the locally absorbed radiation dose and the carcinogenic potential. Thus the long-term, chronic toxicity is much greater than the immediate, acute toxicity

Primarily through the induction of bone cancer or tumors of blood forming tissue, very low doses of ^{239}Pu significantly shorten the life span of laboratory animals. While mice suffered no ill effects from plutonium doses less than 1/1000 of the acutely toxic dose (~ 1 μg/kg), a dose of 0.26 μg/kg given to dogs increased the incidence of bone cancer from 1/10,000 to 1/3 and decreased their lifespan 14%. Lung cancer formed in all dogs that inhaled 1 μg/kg of plutonium oxide, but their lifespan was not significantly shortened. Removal of very small amounts of actinides from the body is therefore an essential component of treatment for actinide contamination, particularly Pu(IV)

Zn-DTPA is some 30 times less toxic than Ca-DTPA to mice when given daily at high doses. Acutely lethal doses of Zn-DTPA are estimated at >20 mmol/kg or 10 g/kg in the adult male mouse. In animal and in human studies, in contrast to experience with Ca-DTPA, there has been no observed decrease in Zn or Mn in the liver, small intestine, or in the kidneys.

8.4 Psychological Stress

Numerous articles have been written on the psychological factors affecting the radiation accident patient [46]. It suffices to say here that the care-provider must be sensitive to the psychological requirements of the patient, and of other soldiers that may have concerns about their health. It is also worthy to note that psychological stress can often manifest as physical symptoms (such as nausea), and the care-provider must be aware of this.

9. Military Theatre Considerations for Administrated Therapies

9.1 Speed of Treatment

During the past fifty years a great deal of work has been devoted to developing methods for increasing the naturally slow rate of elimination of plutonium, and other actinides, from the human body by the administration of chelating agents. The rationale is that the agent will combine with the metal to form a stable complex that can easily be excreted and thus reduce the radiation doses delivered to sensitive cells and thereby the risk of late radiation effects, such as cancer. The most widely used agent has been DTPA; however, this agent is of only limited effectiveness, especially at times longer than a few days after contamination. The same may be said about blocking and reduction agents, such as KI or Prussian Blue. Therefore, for effective field treatment of incorporated radionuclides, speed of treatment delivery is of the essence.

In general, if pharmacological treatment is not administered within the first 6 hours post-exposure, then time may be taken to determine the optimum decorporation route on a risk-benefit scale. It is recommended, therefore, that decorporation therapy agents be included as part of the NBC medical kit, and attending personnel be instructed on how, when and why to administer the appropriate treatment.

9.2 Medical Condition

There are a few medical condition considerations which need to be taken into account for field treatment of contamination injuries. Decorporation treatment must come secondary to performing life-saving actions on an injured soldier. In addition, knowledge of a soldier's medical history with respect to pharmacological sensitivities may assist the care provider in determining the interaction of the decorporation agent with the overall health of the patient.

Triage of patients based primarily upon overall medical condition and secondarily upon initial bioassay indicators, is crucial to the overall medical health of the deployment. Field personnel must be trained on medical and radiological triage.

9.3 Contraindications

Administration of decorporation agents should be with a knowledge of contraindications to drug therapy. For example, a soldier with a severe allergy to iodine would not be a good candidate for iodine prophylaxis from a reactor release scenario.

In addition, a general rule of thumb is that the patient will tell the care provider of how a treatment is affecting them. If the treatment is doing more immediate medical harm,

then a decision must be made by a medical expert, with the assistance of health physics support, whether or not to continue therapy. Field personnel administering decorporation treatments must be trained to observe contraindications.

9.4 Bioassay

There is no way to determine whether a given decorporation treatment is being effective without bioassay. It is important to get an initial estimate of internal contamination levels, and monitor closely discharges of radioactive material through the fecal and urine streams.

For military operations in environments with potential radiological contamination scenarios, bioassay should be an integral part of the deployment. In addition, field personnel attending to the medical conditions of soldiers must be aware that nasal swabs, body swipes, and urine/fecal collection may prove to be very important to both the medical and tactical assessment of the local conditions. Field personnel must be trained in obtaining, labeling and storing these samples.

9.5 Mobility of Therapies

For a military deployment, it is often impossible to treat a patient in a sterile environment. In addition, all of the equipment that would be available in a civilian hospital will not be available in a military theatre, nor would it have the same mobility as military medical equipment.

For the most part, decorporation therapies are administered orally, intravenously or intramuscularly. There is, therefore, very little equipment required for administration of the therapy. However, consideration must be given to the absolute number of required therapies. For example, a five day military theatre treatment of DTPA would require approximately 2 ampoules of Ca-DTPA and 3 ampoules of Zn-DTPA per soldier believed to have incorporated (applicable) radionuclides. Therefore, consideration must be given *a priori* to the number of potential patients, the number of field personnel providing the medical care, and the storage and distribution of the pharmacy. This can be a formidable task for a large number of personnel, because the therapies lose effectiveness rapidly the longer they are administered post-exposure.

9.6 Cost/Risk-Benefit

In addition to considering the medical implications of decorporation therapy, consideration must be given to the monetary cost of maintaining a pharmacy of decorporation therapies, versus the risk of administering the therapies in the field.

10. Current Research Areas Relating to Decorporation

This section will focus on various agents being investigated, or that have been investigated, for decorporation therapy. It should be noted that new molecular constructs are being investigated continuously for their application to decorporation.

10.1 Colloidal Scavenging Agents

These agents attempt to remove a metal based on the premise that an innocuous metal ion with metabolic properties similar to the radionuclide will displace the radionuclide from body tissues (similar to an ion exchange resin).

Because of its low toxicity in rodents and its rapid elimination from the body, zirconium was the most promising of the metals tested. Typically, 50-60% of the injected plutonium was rapidly excreted in the urine of rats which received an injection of 40-50 mg of zirconium in the form of zirconyl citrate within one hour of the plutonium administration, while only 1-2% of the injected plutonium was excreted by untreated rats. Prompt treatment with zirconyl citrate was reported to remove up to 90% of the injected plutonium from dogs. However, the amount of excreted plutonium dropped rapidly as the time between treatment and plutonium administration increased. When two hours elapsed between plutonium and zirconyl citrate injections, only 10% of the injected plutonium was excreted. Treatment with zirconyl citrate 2½ years after the plutonium injection in dogs increased the excretion of plutonium 10-15 fold, but the initial level of excretion was so low that the additional amount of plutonium removed was negligible.

These results indicate that zirconyl citrate is effective only in the removal of plutonium from the circulation system and not from body tissues. This is consistent with the reduction of plutonium in the blood of treated rats to 50% of the control value after five minutes and to 10% after 1 h. The actual mechanism of plutonium removal probably involves the hydrolysis of zirconium to form colloidal aggregates of zirconium hydroxides and phosphates. Other hydrolyzable metals, such as plutonium and thorium, either co-precipitate with the zirconium or are absorbed by the colloids, which act as carriers. In an analogous manner, the high affinity of Pu(IV) for colloidal iron hydroxide probably explains the strong association of Pu(IV) to ferritin and to iron storage pigments such as hemosiderin. As predicted by this mechanism, manganese, iron, titanium, aluminum and thorium, metals which hydrolyze under physiological conditions, also serve as carriers. However, not all of these metals promoted plutonium excretion. The larger colloids do not pass through the kidneys, but are filtered from the blood by organs such as the liver, spleen and bone marrow. Thus thorium and aluminum, which hydrolyze to form large polymers, prevent the deposition of plutonium on the skeleton, but cause an increase in the amount of plutonium deposited in the liver.

Prompt administration of polymeric phosphates have also been successful in increasing plutonium excretion from laboratory animals. Hexametaphosphate was found to reduce bone absorption of plutonium by a factor of three, but this was

accompanied by an increase in the liver burden of plutonium. Thus, it seems likely that plutonium and polymeric phosphates form colloids that behave similarly to those formed with zirconium, except that the phosphates are more toxic. Alternatively, phosphate groups may bind to bone. Pretreatment with ethane-1-hydroxy-1,1-diphosphoric acid or dichloromethylenediphosphoric acid inhibited the mineralization and growth of bone as well as the skeletal uptake of plutonium [47].

10.2 Chelators

10.2.1 Polyaminopolycarboxylic Acids

For many years the chemistry of the polyaminopolycarboxylic acids was dominated by their analytical uses and by investigations of the chelates formed with transition elements. The organic chemistry, other than the various basic syntheses, was neglected. In 1956 it was reported that these compounds were more or less totally lacking in organic chemistry. This observation, which was based upon the failure to produce anhydrides and acid chlorides, is now known to be incorrect. Although all attempts to produce acid chlorides have failed - even the action of oxalyl chloride on the anhydrides, an established procedure, was ineffective - the preparation of bisanhydride is now an established route to a variety of derivatives. Other derivatives that can be formed are hydrazides and esters.

The first organic derivative of DTPA to be screened for medicinal application was the pentaethyl ester which was examined for ability to reduce hepatic deposits of plutonium in mice. Although superior to DTPA in removing plutonium from mice, this derivative was too toxic for further use.

Other lipophilic derivatives of EDTA and DTPA were synthesized by condensing the bisanhydride of the former with phosphatidylethanolarnine to give PE-EDTA whereas that of the latter was condensed with 11-aminoundecanoic acid to give Puchel. PE-EDTA failed to mobilize plutonium from the hamster, although studies with PE-[^{14}C]EDTA established the uptake of the radiolabel into the liver.

In contrast to PE-EDTA, Puchel mobilized plutonium from the liver of Syrian hamsters but was ineffective in mobilizing thorium from the rat. Studies with tritium labelled Puchel in the hamster, the rat and the rabbit showed different rates of clearance. In the rat and the rabbit - species which possess a gallbladder in contrast to the hamster - there was a rapid clearance of the chelating agent through the liver into the small intestine. In the hamster the chelating agent accumulated in the liver before being discharged into the small intestine. It is possible that these differences in hepatic clearance influence the mobilization of plutonium from the livers of hamsters and rats.

10.2.1.1 NTA

The chemical nitrilotriacetic acid (NTA) has been utilized for many years in the detergent manufacturing industry. Just over 100 years elapsed between the synthesis of NTA and the beginnings of alarm over its presence in the environment. Initially

concern over eutrophication arising from phosphate-based detergents led to extensive use of NTA as a detergent builder and the conjecture that there would be a buildup of it in the environment. In recent years this concern has led to NTA having perhaps the most comprehensive database for any synthetic organic chemical that has widespread application in consumer products. This extensive research indicates that concern over the levels of NTA is unnecessary. Ingestion of large quantities of NTA brings about increases in zinc and manganese in some species. Other than a slight increase in clearance of magnesium, NTA has no effect upon clearance of endogenous metal ions from mice.

10.2.1.2 EDTA

EDTA, first synthesized in 1935, was first used as a calcium-sequestering agent in the textile industry. However, in the mid-1940s EDTA rapidly became an intensely investigated substance. In addition to being examined for ability to clear toxic metals from the body it was also used to treat several other conditions. These other applications, however, are now known to be of little or no value.

As EDTA forms stable complexes with a number of physiologically important elements (Ca, Mn, Cu, Zn, Fe), it might be expected to mobilize these elements when used to treat toxic metal poisoning. Several studies have established that there is a mobilization of manganese and zinc. It is possible that the loss of zinc and manganese affects the synthesis of DNA. Depletion of zinc as a consequence of the ingestion of Ca-EDTA by pregnant rats results in impaired reproduction and congenital malformation. In computer simulation models EDTA in plasma exists mainly as the calcium chelate (85%) whereas the zinc chelate represents only 14%.

In the US there is mild opposition to chelation therapy, which is based upon the potential for damage to the kidneys.

10.2.1.3 DTPA

DTPA is superior to EDTA as an agent for removing many of the toxic metals. This superiority does not originate entirely from the greater hard base characteristics of DTPA which arise from the additional acetate moiety. DTPA has been replaced by DFOA as the treatment for iron-overload conditions. In the US, calcium and zinc salts are both approved for human use and are only available for countering uptake of transuranics. The superiority of DTPA over EDTA for polyvalent cations such as the lanthanides and the actinides arises from the potential octadenticity of DTPA as opposed to the hexadenticity of EDTA. The successful use of DTPA in reducing the ^{241}Am burden in a worker who became peppered with ^{241}Am-contaminated fragments in an incident in the US in 1976 testifies to the value of chelation therapy. Intensive therapy prevented 99% of ^{241}Am which entered the bloodstream from becoming deposited in the internal organs.

The manifestations of the toxicity of DTPA arise from depletion of transition elements. Administration of DTPA as its zinc salt suppresses its toxicity. Computer

simulation studies of the chelates formed in plasma identify Zn-DTPA as the major form, 96%, whereas Ca-DTPA accounts for 3%.

The high hydrophilicity and corresponding low lipophilicity of both EDTA and DTPA result in very low uptake of these chelating agents into cells. In an endeavour to increase intracellular uptake of DTPA, mice were injected with liposomally-entrapped DTPA which had hepatic accumulations of ^{239}Pu. Although this was an effective treatment for mice it proved to be unsatisfactory for hamsters, and therefore only weak conclusions can be made.

10.2.1.4 DCTA, HEDTA, TTHA

As these chelating agents became available 25-30 years ago they were met with much acclaim. HEDTA as a decorporation agent of iron is inferior to DFOA and a recommendation that TTHA be used as an orally-acting therapy for the transuranics has never become practice.

10.2.1.5 EHPG

Ethylenebis[(O-hydroxyphenyl)glycine]was originally synthesized many years ago, and has been used to model the metal coordination sites of transferrin. The ester derivatives of EHPG have proved to be effective in test animals for the reduction of iron overload. It has been suggested that EHPG could be used to mobilize aluminum in aluminum-induced neuro-biological disorders.

10.2.1.6 Iminodiacetic Acids

Iminodiacetic acids have a long record of study in medicinal chemistry, starting over 25 years ago when radiolabeled forms were shown to be taken up into newly formed bone. The uptake into bone was attributed to chelation with calcium.

In more recent years a wide variety of iminodiacetic acids (in excess of 65), have been used to chelate predominantly ^{99m}Tc, although ^{103}Ru has also been screened. The structures of these chelating agents have been selected to achieve a biodistribution of the chelated radiocation to a variety of organs. In some cases studies with ^{14}C-labeled iminodiacetic acids have revealed clearance patterns which are not displayed by the ^{99m}Tc chelates: a predominantly urinary clearance was noted for ^{14}C-N-(2,6-dimethylphenylcarbamoylmethyl)iminodiacetic acid, whereas the ^{99m}Tc chelate underwent predominantly hepatobiliary clearance.

10.2.1.7 Polyaminophosphonic Acids

Polyaminopolyphosphonic acids have attracted intermittent interest since the early applications of chelating agents in medicine. First synthesized 30 years ago, ethyl-enediaminetetraphosphonic acid (EDTMP) has only recently been examined for ability to inhibit dental calculus and caries in dogs and rats.

The observations that pyrophosphate and the geminal 1,1-bisphosphonate chelates of ^{99m}Tc are taken up by bone led to the polyaminopolyphosphonates also being screened for bone scintigraphic potential. It was reported that EDTMP chelates of ^{111}In and ^{113m}In had bone uptake comparable to that of ^{85}Sr. EDTMP was shown to be marginally superior to diethylenetriaminepentamethylene phosphonic acid (DTPMP). DTPMP is no more effective than DTPA at removing skeletally incorporated ^{239}Pu. Even less effective is a partially lipophilic form of polyaminopolyphosphonic acid.

10.2.1.8 1,1-Bisphosphonates

The 1,1-bisphosphonates have attracted considerable interest in the last 15 years or so because of their uptake by bone, an uptake which is a consequence of their structural similarity to bone-seeking pyrophosphate.

The early promise of pyrophosphate as a modulator of the biochemistry of bone was not fulfilled because of its ready hydrolysis. As molecular models indicated that 1,1-bisphosphonates might exhibit some pharmacological responses in bone, a program of syntheses has been in place for many years.

Briefly, the bisphosphonates inhibit soft tissue calcification. Bisphosphonates, such as HEBP, inhibit the mineralization of cartilage, bone and dentine. Prolonged administration of HEBP to man at oral doses of 10 mg/kg for more than one month affects the mineralization of hard tissues. It has been suggested that the differences in physiological properties of the bisphosphonates arise from the ability to form bidentate-bidentate and bidentate-tridentate bridged structures. No doubt the affinity of bisphosphonates for calcium must be considered an important factor in their biochemical actions.

Bisphosphonates have several important clinical applications which can be divided roughly into two categories. Firstly, their use in regulation of calcium kinetics. Secondly, the exploitation of their bone-seeking properties to carry ^{99m}Tc and other γ-emitting radionuclides to bone. In the first category, the bisphosphonates are now extensively used to control diseases with increased bone destruction. Foremost amongst these diseases is Paget's disease, a condition of uncertain aetiology and which is marked by excruciating pain in the bones. In many patients treated with HEBP at the rate of 20 mg/kg-d, normal values of alkaline phosphatase and hydroxyproline can be achieved within 3 to 6 months.

Preliminary clinical findings established that this treatment was well tolerated and did not affect the levels of calcium and phosphate in blood. Promising results have been reported for the use of HEBP in primary hyperparathyroidism and tumoral osteolysis, two diseases also characterized by increased bone resorption. In the treatment of ectopic calcification the use of bisphosphonates has not fulfilled the early hopes which were held for them. However, the bisphosphonates could prove useful in the prevention of heterotropic calcification as found in patients with spinal cord injury or in the treatment following total hip replacement. Good results have also been obtained against dental calculus and this had led to the use of bisphosphonates in toothpastes.

The anti-arrhitic properties attributed to bisphosphonates have prompted an expansion of the syntheses of bisphosphonates.

10.2.1.9 8-Hydroquinolines

The well-established chelating properties of oxines have been exploited in NIDM. Oxine is an effective agent for transporting ^{111}In into leucocytes and granulocytes which are then used to detect abscesses. Other developments are the radiolabeling of platelets with the oxine of ^{68}Ga, for detecting thrombosis or artherosclerosis; the radiolabeling of lymphocytes with ^{111}In for detection of cardiac rejection, and lymphography with ^{99m}Tc-Sn oxine radiocolloids. In addition, studies have been done of the interaction of lipophilic chelators with the malaria parasite. A number of chelating agents - hydroxamic acids, catechols, dithiocarbamic acids and substituted 8-hydroxyquinolines have been screened as anti-malarials.

10.2.1.10 Polyaminopolycarboxylic Acids in NIDM

EDTA and DTPA were among the first chelating agents screened in non-invasive diagnostic medicine (NIDM), typically in nuclear medicine. However, their current use is limited with the development of chelating agents designed for selective uptake into specified regions of the body. The extensive excretion of DTPA by glomerular filtration makes it an ideal agent, for instance radiolabelled with ^{113m}In for determining the glomerular filtration rate. When immobilized on macromolecules DTPA is also a suitable chelating agent for use in NIDM.

As fatty acids are taken up into the myocardium, similar polyaminopolycarboxylic acids, radiolabelled them with ^{99m}Tc and ^{57}Co, may be utilized for myocardial imaging. These chelators, which posses chelating characteristics similar to DTPA, have a low uptake into the heart (< 0.94%) but show uptake into the liver of 16%.

The use of DTPA in NIDM has not been restricted to nuclear medicine. The distribution of chelates in areas of high vascularity or expanded interstitial space has been exploited in magnetic resonance studies. Numerous investigators have used gadolinium(III)-DTPA to study the magnetic relaxation times of normal and infarcted myocardium, to study cerebral tumours, and to study both cerebral and cervical intraspinal tumours. Its potential for detection of human breast carcinoma has also been noted. As an alternative to Gd-DTPA, Cr-EDTA, which is well tolerated by dogs and rats, could be used. As an alternative to chelators labeled with paramagnetic cations, spin-labeling with bispiperdinyl nitroxyl derivatives of EDTA and DTPA has been examined.

10.2.2 Macromolecules

Investigations of the complexation of polyvalent cations by biomacromolecules, particularly metalloproteins, have been conducted for many years. Investigations of the binding of polyvalent cations by synthetic polymers are more recent.

Macromolecule chelating agents (MCA) are represented by a wide variety of structures:

1. Mercaptodextrans, disulphide-reducing polythiols formed by thiolation of dextran;

2. Various polyacryls bearing DFOA; polyvinylamine-vinyl (2,3-dihydroxy-5,6-dimethylbenzenesulphonamide)-vinyl sulphonic acid;

3. Various polysaccharides bearing DTPA;

4. Proteins bearing DTPA, pAPhEDTA or DFOA;

5. Poly-(EDTA-cys2), formed by polymerizing EDTA-cys2 by production of disulphide; and

6. Hydroxamic acids linked by oligomethacroyl units.

The immobilization of low molecular weight chelating agents on macromolecules received an initial impetus with the synthesis of pAPhEDTA. Over the years pAPhEDTA, and related forms, have been coupled to a series of macromolecules and other chemicals and evaluated for potential as diagnostic agents for detection of tumours and for studying dysfunction of organs. Diazotized pAPhEDTA coupled to proteins such as human serum albumin (HSA) and fibrogen can be monitored in experimental animals and humans through the chelation of ^{111}In. The plasma disappearance rate in humans of the HSA-chelate is similar to that found for radioiodinated HSA.

There have been many procedures developed for immobilizing chelating agents on macromolecules. For example, a mixed acid anhydride procedure may be used to couple DTPA to proteins, or DTPA bisanhydride may be reacted with cyanogen bromide-activated cellulose bearing 1,6-diaminohexane as a spacer arm. It has been demonstrated that antibodies derivatized with DTPA-bisanhydride retain their capacity for interaction with the antigen. In addition to immobilization of DTPA, the immobilization of DFOA on human immunoglobulin has been achieved by coupling reactions using glutaraldehyde or carbodiimide. The labeling of monoclonal antibodies with radionuclides such as ^{67}Ga, ^{111}In and ^{113m}In through chelation by immobilized chelating agents will facilitate the detection of specific tumours. In an extension of this procedure it has been proposed that tumours could be destroyed by a radiotherapeutic procedure which carries the β-emitting radionuclide ^{90}Y into the tumour bound as the DTPA chelate coupled to a monoclonal antibody, although it must be cautioned that potential of tumour killing by using radiolabeled antibodies may result in over-exposure. For example, if a 60 Gy dose in 7 days was sufficient for tumour sterilization, this would result in a whole body dose of 14.3 Gy for chelated ^{90}Y. The maximum reasonable whole body dose is 2 Gy.

The use of MCAs is not restricted to radiopharmacy. This technique has been exploited by use as a contrast agent Mn^{2+} bound by DTPA immobilized on the

monoclonal antibody antimyosin. The extent of infarcted myocardium was determined with 2 mg of antibody bearing 50 ~μg Mn^{2+}. It is to be expected that many more similar contrast agents await development, and will extend magnetic resonance imaging.

The uses of MCAs in medicine, other than in NIDM, are limited. MCAs have been examined for ability to suppress gastrointestinal (GI) uptake of radiocations and cations of toxic elements. In the 1960s alginates, incorporated into bread, were shown to suppress GI-uptake of ^{90}Sr in experimental animals. Several years later it was demonstrated that DTPA immobilized on cellulose also brought about suppression of GI-uptake of alkaline earth radiocations.

Although not in the strictest sense MCAs, there has been success using thiol-bearing polymers to suppress enterohepatic recirculation of methylmercury. For example, Iraqi farmers and other villagers who consumed seed grain which had been treated with a mercury-based fungicide have been successfully treated in this fashion.

10.2.3 Microbial

Microorganisms are important sources of many chelating agents, particularly ferric-selective ones. Chelating agents of microbial origin range from what could be considered as a substituted iminodiacetic, that is pyridine-2,6-dicarboxylic acid, through the calcium-specific ionophores to the ferric-selective ones, chemicals which generally possess either catechol or hydroxamic acid properties.

10.2.3.1 Ionophores

Predominant in this category are the calcium-specific ionophores calcimycin, lasalocid and ionomycin, one of the few naturally-occurring 1,3-diketones. These ionophores have been used in investigations of the role of calcium in secretory cells such as mast cells and β–pancreatic cells. Although it complexes several divalent cations, antibiotic M144255 has a high affinity for zinc and thus has been given the trivial name zincophorin. Zincophorin, like several other ionophores, exhibits anti-coccidial activity against *Eimcria tenella* in chicks. It is also active against Gram-positive bacteria.

10.2.3.2 Siderophores

The hydroxamates have been the more extensively investigated of the two kinds of siderophores. For many years, DFOA has been used in the treatment of siderosis.

Current research into synthetic ferric-selective chelating agents has become extensive. The ineffectiveness of DFOA in removing aged deposits of iron has lead to investigations into new methods of drug delivery as well as modifications of the structure. Liposomally entrapped DFOA was an ineffective therapy when administered orally or via the intraperitonal cavity, but when given intravenously the treatment doubled the clearance of ^{59}Fe from mice. In clinical trials of DFOA

entrapped in red cell ghosts a much greater clearance of iron was observed than that achieved by slow subcutaneous infusion of DFOA.

In addition to being used to mobilize iron, DFOA has been examined as an anti-inflammatory agent for the treatment of rheumatoid arthritis which may be precipitated by the increased stores of iron which accompany hyposideraemic anemia. The mobilization of iron from patients with rheumatoid arthritis indicates that it may be possible to limit damage to the synovial membrane, by oxygen free radicals of oxygen, by removing iron deposits from the synovial membrane.

Soon after the introduction of DFOA to pre-clinical studies it was evaluated for ability to mobilize ^{239}Pu(IV) in experimental animals. As it was not superior to DTPA there were no further studies with it. In a lipophilic form N-stearoyl DFOA was also ineffective as a mobilizing agent for ^{239}Pu(IV), as was rhodotorulic acid. The greater chemical stability of rhodotorulic acid and the ease with which it can be obtained in high purity has resulted in it being evaluated as a potential agent for treating transfusional siderosis. Rhodotorulic acid has been shown to be only 16% more effective than DFOA in humans. As it causes local inflammatory reactions it is unlikely to replace DFOA.

The extensive reliance upon renal dialysis to prolong the lives of people suffering from kidney failure has led to diseases caused by uptake of aluminum from the dialyzate. The use of aluminum-free dialyzate has led to many fewer reports of dialysis dementia and dialysis osteomalacia. Several studies have demonstrated the clinical efficacy of DFOA in combating these two diseases. Investigation of bone samples removed from the iliac crest before and after treatment for osteomalacia have given conflicting results on the mobilization from aluminum in bone.

The response of bacteria to iron-depleted media is well-characterized as the release of the siderophores. Less well known is the response of microorganisms in rich media to the presence of toxic cations. The response of *Pseudomonus aeruginosa* CSU and *P. aeruginosa*-PAO-1 to uranyl and thorium salts added to iron-deficient and iron-supplemented media has been investigated. Analyses of the ultrafiltered culture media showed that both actinides induced the formation of complexing agents. In the presence of iron, both uranyl and thorium salts induced the formation of chemicals containing hydroxamate and phenol catechol functions. Preliminary analyses of a thorium-induced chemical indicated it was a pyochelin. It is possible that these thorium-binding chelating agents could be used to mobilize intracellularly accumulated plutonium.

Many new siderophores are being investigated currently. Investigations of the kinetics of the reaction of new siderophores with iron-saturated transferrin showed a rapid formation of a ternary complex with transferrin, followed by a slow step in which the ferric siderophore was released from the apoprotein. The ferric-chelating properties of several siderophores were investigated and following order of effectiveness for removing iron from transferrin was found: (1) enterobactin, (2) MECAMS, (3) MECAM, (4) LICAMS, (5) DFOA, and (6) TRIMCAMS.

The chemistry of the biomimetic siderophores used to remove transuranics is actively being investigated. The problem is to remove plutonium(IV) and americium(III) from serum, where they are bound to transferrin, and from the parenchymal cells of the liver. An additional target for depletion of the transuranic is the surface of bone where both radionuclides deposit. The decorporation of the skeletally accumulated transuranics is only feasible if chelation therapy quickly follows uptake of the elements. Once the radiocations are incorporated into the bone matrix they become inaccessible to chelating agents until the bone matrix is reworked by the osteoclasts.

Ligands have been examined for their ability to mobilize plutonium and americium varied from the CYCAM, LICAM and MECAM series to a macromolecular form bearing 14 catecholamide properties. An extensive study identified 3,4,3-LICAMS as the most effective chelator for incorporated ^{239}Pu. This may be exemplified in Figure 6 which compares 3,4,3-LICAMS with the calcium salt of DTPA for ^{239}Pu injected into mice. Substitution of alkyl groups on the terminal nitrogens increased lipophilicity but was found to hinder chelation and delay excretion of the radionuclides. For the inhaled transuranics (as opposed to injected transuranics, as depicted in Figure 6) which are the principal forms which could lead to contamination in the workplace, DTPA proved to be superior to 3,4,3-LICAMS, although both chelating agents were equally effective at clearing the circulating radionuclides from the blood.

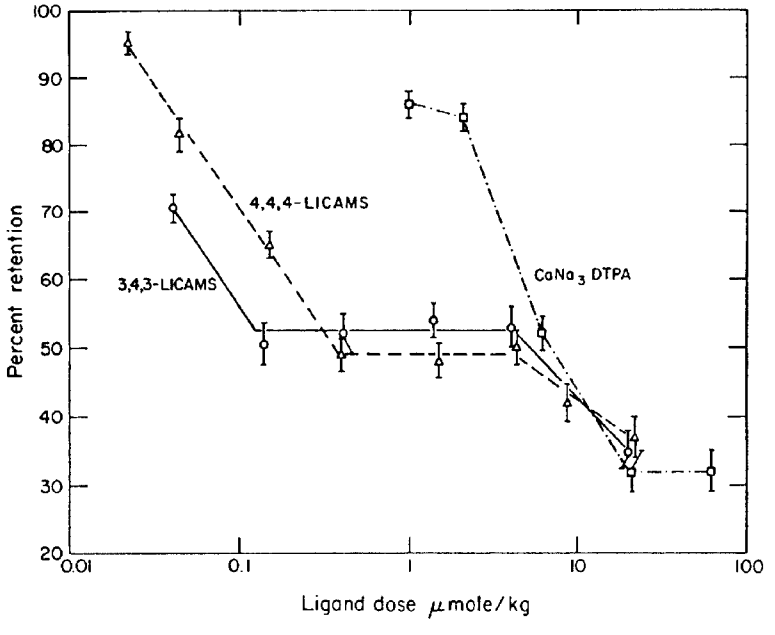


Figure 6 - Decorporation of ^{239}Pu in rats

10.2.3.3 3,4,3-LI(1,2-HOPO)

As was previously discussed in Section 7.3.2, one of the most promising therapeutic drugs investigated for decorporation, and an alternative to DTPA, is the siderophore analogue 3,4,3-LI(1,2-HOPO). In a recent study (49), the decorporation drugs DTPA and 3,4,3-LI(1,2-HOPO) were investigated in rats for their relative efficacies for removing americium, plutonium, uranium and thorium.

In general, 3,4,3-LI(1,2-HOPO) was more effective at removing radionuclides from the body than other decorporation agents. Using injected and wound contaminated uranyl nitrate in rats, the uranium retention was estimated for various treatments. Some results, adapted from [49], are presented in Table 14, where the retention was normalized to a control group. It may be seen that in both the injected uranyl nitrate case and the wound contaminated case, LIHOPO exceeds the performance of both DTPA and sodium bicarbonate.

It should be noted, however, that although LIHOPO outperforms both DTPA and sodium bicarbonate as a chelating agent, it still does not remove enough of the uranium to be considered an effective chelator. LIHOPO was found to perform much better in decorporating plutonium and americium, and considerably less effective for thorium.

Table 14- Efficacies of LIHOPO as a decorporation agent for uranium

Injected Uranyl Nitrate		
Treatment	*Retention (% of injected)*	
	Lungs	*Total body*
LIHOPO	38 +/- 2	40 +/- 2
DTPA	79 +/- 3	79 +/- 2
Wound contaminated with Uranyl Nitrate		
Treatment	*Retention (% of injected)*	
	Kidneys	*Fermora (bone)*
LIHOPO	21 +/- 4	61 +/- 8
$NaHCO_3$	76 +/- 20	102 +/- 25

10.2.3.4 Siderophores in NIDM

The use of DFOA in radiopharmacy has been principally restricted to enhancing the clearance of circulating ^{67}Ga which has not been taken up into tumours and abscesses, thus enhancing the images. In human studies DFOA accelerated the clearance of ^{67}Ga from the blood but tumour images were not necessarily improved. As its N-succinyl derivative, the DFOA complex of ^{67}Ga has been shown to have potential for measuring renal tubular secretion.

The potential of the LICAM and MECAM series in nuclear medicine has been demonstrated. The introduction of isopropyl moieties onto nitrogens to give 3,4-DiP-LICAMS and TiP-MECAMS resulted in ^{67}Ga and ^{111}In chelates which were cleared primarily through the kidneys. In contrast, the less polar 3,4-Di-LICAM chelates were cleared through the liver. As 3,3-LICAMC cleared ^{67}Ga from blood, where it is associated with transferrin, it could be of value for reducing the radiation burden from ^{67}Ga, which is otherwise unsatisfactorily slow to clear.

10.2.4 Other Agents

10.2.4.1 Crown Ethers and Cyptands

The synthesis of crown ethers in 1967 fortunately occurred about the same time as naturally occurring lipophilic metal-binding agents were being identified as products of microbial growth.

The search for medicinal applications of crown ethers and cryptands has so far led to only a few pre-clinical studies. Many of the crown ethers and natural ionophores are toxic. Presumably the toxicity arises from the slow leakage of potassium out of cells and of sodium into cells. Antibacterial activity has been noted for several crown ethers and found to parallel potassium transport. The established coccidiostatic activity of ionophores has led to the screening of crown ethers for coccidiostatic activity. As yet the synthetic ionophores have shown no evidence of superiority over their natural product counterparts.

In a search for crown ethers with lowered toxicity levels, several silacrowns have been prepared. The introduction of two siloxyl oxygen atoms modifies the binding alkali metal ions, a phenomenon which arises from the lower basicity of the siloxyl oxygen atoms. Investigations of their hydrolytic stability established that they were susceptible to hydrolysis in normal saline. Incorporation of hydrolytically labile bonds into ionophores may lead to decreased but acceptable levels of toxicity and thus ionophores of medicinal value.

In the early 1960s when there was concern over levels of ^{90}Sr in the atmosphere, various research programs were directed at producing acceptable decorporation techniques. The problems are obvious: as the divalent cations of calcium and strontium have similar ionic radii - 9.9 nm and 11.3 nm, respectively, the selectivity of chelating agents for strontium must be considerably greater than that for calcium to ensure that calcium is not depleted and that tetany is not induced. All attempts to mobilize radiostrontium from the body without mobilization of calcium have by and large failed.

10.2.4.2 Polyamines

The polyamines fall into a category between hard and soft bases. Their primary use is in the treatment of Wilson's disease. Although cyclic polyamines such as 1,4,8,11-tetraazacyclotetradecane (cyclam) have high copper-binding formation constants their enhancement of copper clearance does not merit use in decorporation.

In NIDM cyclic polyamines may find clinical use as complexing agents for ^{99m}Tc which when chelated by cyclam is cleared through the liver and kidneys of the

unanaesthetized mouse. There is also data which indicates that manganese(II)-cyclam is more effective than gadolinium(III)-DTPA as a contrast agent.

10.2.4.3 Phosphinepolyacetic Acids

Phosphinotriacetic acid ($P(CH_2COOH)_3$) and ethylenediphosphine-tetraacetic acid (EDTPA) are structural analogues of NTA and EDTA. The presence of phosphorus confers considerable softness upon the molecules. As these chelating agents possess both hard and soft donors they could be of use in chelation therapy for toxic metals and NIDM. The chelates of Ca(II), Mn(II), Zn(II), La(III) and Pb(II) are of limited stability, with bonding only through the carboxyl groups. With the exception of Pb(II) and Cd(II), there is no coordination of phosphorus. A rapid intermolecular exchange characterized these complexes. In contrast the chelates of Fe(II), Co(II), Ni(II), Pd(II), Pt(II) and Hg(II) were stable and kinetically inert to intermolecular exchange.

10.2.4.4 Thiosemicarbazones

The aromatic and heteroaromatic thiosemicarbazones are powerful chelating agents. They have had a role as antiviral agents in the 1950s to reduce the severity of vaccinia infections of chick embryos and mice. The thiosernicarbazones have been used prophylactically to prevent outbreaks of smallpox in persons who had been in contact with the disease.

The chelating properties of the thiosemicarbazones are regarded as their main chemotherapeutic principle. In the case of the acetylpyridine thiosemicarbazones, only the 2-substituted derivative shows any appreciable antiviral activity. The absence of any significant antiviral activity in the 3- and 5-substituted derivatives supports the hypothesis that a metal chelate is formed between the ring nitrogen and the thiosemicarbazone. This prophylactic has been used successfully in the treatment of people who had been exposed to smallpox-infected patients. It is assumed that its copper(II) chelate binds to nucleic acids in-vitro under conditions in which there is no significant binding of aquated copper(II) ions. It is possible that the copper chelate is bound to an mRNA which is synthesized late in the infective cycle. It is also known that the thiosemicarbazone acts only in the final process of infection and is active even after the synthesis of viral DNA has ceased. As the smallpox virus contains appreciable amounts of copper(II), it is possible that its chelation is part of the mode of action. The other thiosemicarbazones are less well studied and as yet the link between antiviral action and chelation is not fully established. It has been proposed that the chelation of iron(II), a cofactor of ribonucleoside diphosphate reductase, could be the principal mode of action of the thiosemicarbazones.

10.2.4.5 2,3-Dimercaptans

The best known Dimercaptan, BAL, has a long history in the treatment of heavy metal poisoning. BAL is an oil-soluble and foul-smelling drug which is unpleasant to take and which is not without serious side-effects.

For several years now 2,3-dimercaptopropanesulphonic acid (DMPS) and 2,3-dimercaptosuccinic acid (DMSA) have been the alternatives to BAL. In contrast to BAL, both of these chelating agents are less toxic, much more soluble in water, and hence have limited solubility in lipids, and are effective when taken orally. The use of both DMSA and DMPS in combating heavy metal poisoning has been examined, specifically for mobilizing inorganic mercury, cadmium, arsenic, copper, lead, gold and antimony.

N-(2,3-Dimercaptopropyl)phthalamidic acid (DMPA) has been shown to form relatively stable complexes with cadmium, zinc and mercury. DMPA has also been shown to enhance fecal and urinary excretion of mercury in mice and arsenic in mice and rabbits. For the decorporation of arsenic, taken in as arsine, the administration of 3-(tolylthio)propane-1,2-dithiol has been proposed.

10.2.4.6 D-Penicillamine

D-Penicillamine, first introduced in 1956 as a therapeutic agent to counter Wilson's disease, has also been used to treat lead and mercury poisoning.

Dithiocarbamic Acid

Diethyldithiocarbamic acid (DDTC) has been used to combat nickel poisoning arising from intake of nickel carbonyl. In addition to chelation of nickel(II), DDTC has been examined for ability to mobilize other soft acids. Unfortunately DDTC brings about an unwanted mobilization of cadmium to testes, lung, brain, heart and muscles. As this unwanted redistribution can be attributed to the marked lipophilicity of the complex, attention has been directed towards the more water soluble dithiocarbamates. Polar dithiocarbamates do not bring about a redistribution of cadmium to those organs which receive increased cadmiun after therapy with DDTC. In cadmium loaded mice substantial reductions in both the kidney (71%) and liver (40%) levels were achieved after treatment with N-methy-D-glucamine dithiocarbarnate. The efficacy of these dithiocarbamates in countering the uptake of other soft acids remains undemonstrated. Equally these dithiocarbarnates might also serve as alternatives to DDTC in other areas.

11. Conclusions and Recommendations

This report serves as a literature review of available and clinically tested decorporation agents for radionuclide ingestion, inhalation and wound absorption scenarios. Although many therapeutic drugs were described in the body of this report, very few are actually available to physicians and health physics personnel.

Protocols for treating patients with internal contamination are described in NCRP Report No.65. Therein lies advice on appropriate treatment modalities for various radionuclide forms. This reference is invaluable to the health care provider as it is structured for quick reference in emergency situations.

The benefit for using any specific treatment for internal radionuclides must be weighed against the risk from performing the same treatment. Certain risk factors that may be associated with lung lavage, drug injection and wound excision are presented along with the risk of various levels of committed effective dose in Table 15. It may be seen that the risk associated with not performing a given therapy generally outweighs the risk of performing the therapy. This is sound justification for pursing the most appropriate treatment modality.

Table 15- Medical risk factors associated with internal contamination therapy

Action	Risk of	Risk Factor
General anaesthesia	Medical complications, coma, death	1 in 50,000
Intravenous injection	Air-bubble embolism	1 in 20,000
Wound excision	Loss of use of extremities	1 in 40
20 mSv effective dose (50 y)	Fatal cancer	1 in 1000
200 mSv effective dose (50 y)	Fatal cancer	1 in 100
1 Sv effective dose (50 y)	Fatal cancer	1 in 20

It is recommended that DRDC Ottawa pursue the status of co-investigator for Investigational New Drugs (IND) related to decorporation therapy. An appropriate first step would be for DRDC Ottawa to align with the Radiation Emergency Assistance Center and Training Site (REAC/TS) in Oak Ridge, Tennessee as a co-investigator of Ca- and Zn- DTPA. In addition, due to the recent animal decorporation successes of siderophore analogues, specifically 3,4,3-LI(1,2-HOPO), effort should be made in acquiring or synthesizing this drug for decorporation research.

12. Selected Glossary of Terms

Anosmia - loss of the sense of smell

b.i.d. - twice per day (*bis in die*)

BAL - British Anti-Lewistite

Canthus - corner of the eye in proximity to the ear duct

Catharsis - cleansing or purging

CBC - complete blood count

Ciliary action – motion of fluid in and around the eye caused by the cilia

CNS - central nervous system

Cocci - pertaining to a spherical bacterial cell

Conjunctivitis - inflammation around the eyes, including thick sticky morning discharge

Cornified – thickened skin caused by a buildup of dead epithelium cells

Creatine – a nitrogenous compound formed by metabolic processes in the body

Creatinine – substance formed from the metabolism of creatine, commonly found in blood, urine and tissue

d - day

Debridement - to remove dirt, foreign objects, damaged tissue etc from a wound

Decorporation – a chemical acceleration of the removal of radioactive atoms from the body, using chelating agents or other administered pharmaceutical agents (*Health Phys., Vol. 78, No .5, pp. 563-565, 2000*).

Diaphoresis - sweating (*dia+pherein*)

Distal - farthest point away from the centre point or centre-line

Edema - swelling (*oidema*)

Endotracheal - within or through the trachea (*endon+tracheia*)

Epithelium - covering of the internal and external organs of the body (*epi+thele*)

Erythema - reddness (*erythros*)

Eschar - scab or dry crust resulting from a chemical burn, infection, of skin disease

Eutrophication - water rich in plant nutrients but deficient in oxygen

Glomerulus - structure composed of blood vessels or nerve fibres

Gram-positive - referring to a positive indication, via violet stain, of some strands of pathogenic bacteria (Gram-negative refers to bacteria that do not stain violet)

h - hour

Hct - hematocrit

Hgb - hemoglobin

Hypertonic – having a greater concentration of solute than another solution (for example, a hypertonic saline solution may contain 1 – 15% sodium chloride, as compared to normal saline at 0.9%)

i.m. - intramuscular

i.v. - intravenous

inj. - injection

Intake - the quantity of radioactive material entering the body via inhalation, ingestion, absorption or wounds

Intralumenal – inside a cavity or channel within the body

Intraperitoneal – into the peritoneal (abdominal) cavity

KI - potassium iodide

Lacrimation - excessive amount of tear production

Lavage – washing

Leukopenia – abnormal decrease in the number of white blood cells (< 5000 cells/ mm^3)

Ligand - molecule, ion, or group bound to the central atom of a chemical compound; organic molecule attached to a specific site on a surface.

n.p.o. - nothing by mouth (*nihil per os*)

Nadir - the lowest point

Nebulizer – a device for producing a fine spray

Necrosis - local tissue death (*nekros+osis*)

Nephrotoxic – toxic or destructive to the kidney

Obstipation - extreme or persistent constipation

Oliguria - diminished capacity to pass urine (*oligos+ouron*)

p.o. - orally (*per os*)

p.r.n. - when required (*pro re nata*)

Pruritus - itching (*prurire*)

q. - each, every (*quaque*)

q.d. - every day (*quaque die*)

RBC - red blood cell

Renal - pertaining to the kidney

Sepsis - infection (*sepein*)

Stat. - Immediately (*statim*)

Syncope - brief lapse in consciousness (*synkoptein*)

t.i.d. - 3 times/day (*ter in die*)

tabl – tablet

Teratogenesis – development of physical defects in the embryo

Thrombocytopenia – abnormally low number of platelets in the blood

Transferrin - trace protein present in blood, essential in the transport of iron. Main function is to move iron from the intestine to the bloodstream.

Uptake - quantity of radioactive material transferred from the site of intake to body organs or tissue (uptake is a fraction, up to 1, of the intake)

Vasodilation - widening of blood vessels (*vas+dilatare*)

WBC - white blood cell

Wilson's Disease - rare, inherited disorder of copper metabolism, in which copper slowly accumulates in the liver and is released and taken up by other parts of the body. This disease can affect the brain, liver and kidneys.

Wound - any physical injury causing a break in the skin

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Annex A – Radionuclide properties[3]

Table 16 - Properties of some selected radionuclides

			Dominant emissions - MeV		
Radionuclide	**Mode of Decay**	**Half-life**	**α**	**β (max)**	**γ**
H-3	β–	12.28 y		0.018601	
C-14	β–	5.73E+3 y		0.15640	
P-32	β–	14.29 d		1.7104	
K-40	β–	1.277E+9 y		1.31160	1.4608
Co-60	β–	5.271 y		0.3179	1.1732, 1.3325
Sr-90	β–	28.6 y		0.5460, 2.2839	
I-129	β–	1.57E+7 y		0.15242	0.02978, 0.03360
I-131	β–	8.04 d		0.60632	0.36448
Cs-137	β–	30.17 y		0.51150	0.66165
La-140	β–	40.22 h		1.2388,1.3482, 1.6770,	0.3288,0.4870, 0.8159,1.5965
Po-210	α	138.37 d	5.3045		
Ra-226	α	1.6E+3 y	4.7845		
Th-230	α	7.7E+4 y	4.6875		
Th-232	α	1.4E+10 y	4.0100		
U-234	SF	2.45E+5 y	4.7758		0.0130
U-235	α, SF	7.04E+8 y	4.396		0.0130, 0.4138, 0.1837
U-236	α, SF	3.42E+6 y	4.494		
U-238	α, SF	4.47E+9 y	4.196		
Pu-238	α, SF	87.75 y	5.499		0.0136
Pu-239	α, SF	2.41E+4 y	5.1554		
Pu-241	β–	14.4 y		0.0208	
Am-241	α, SF	432.2 y	5.486		0.0139, 0.0595

[3] In the table, the dominant (~ 10% probability of emission or greater)particle energies are presented for select radionucleides.

Annex B – Decorporation Drugs

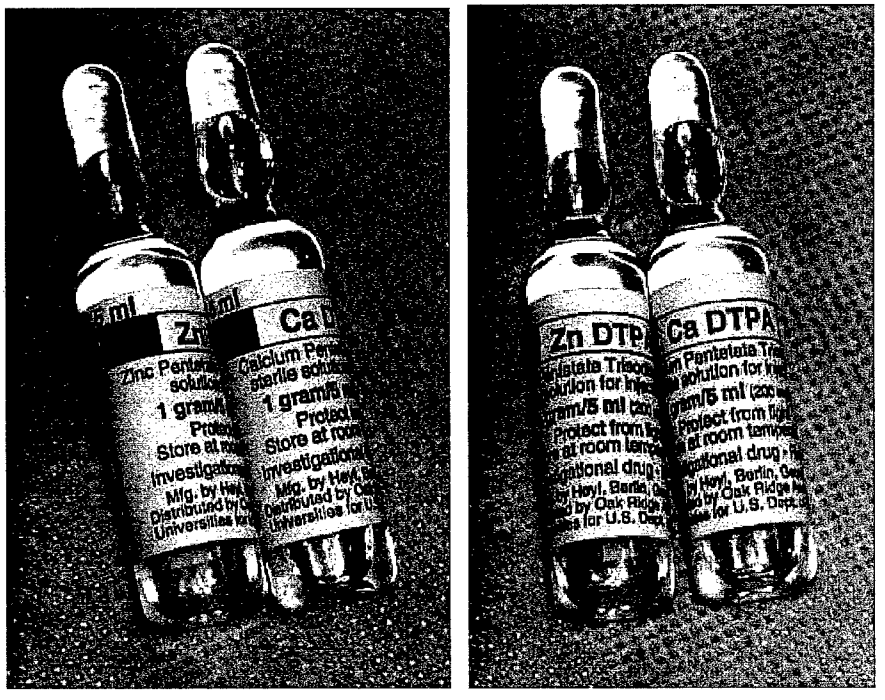

Figure 7- Ampoules of Ca- and Zn- DTPA

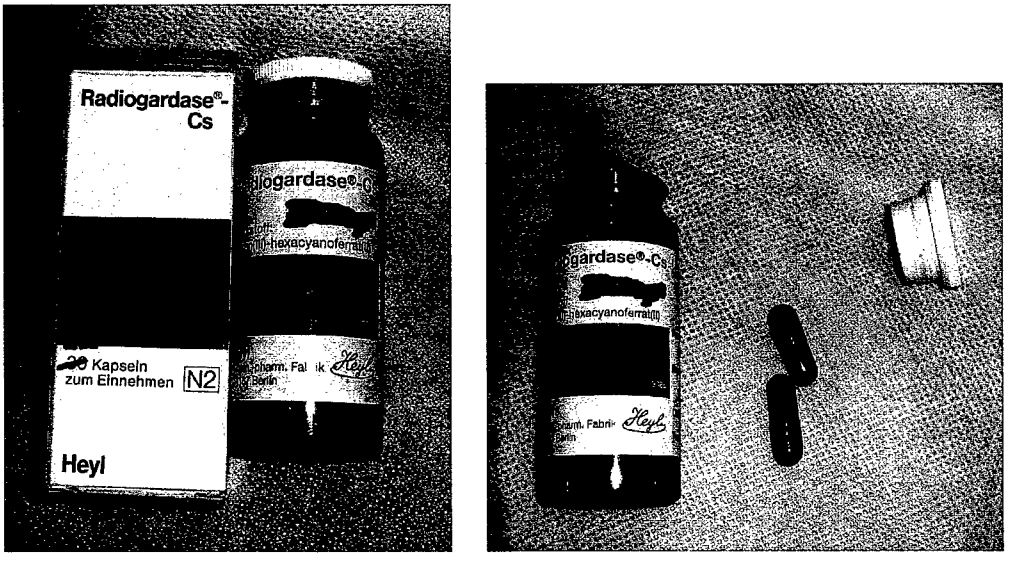

Figure 8- Prussian Blue

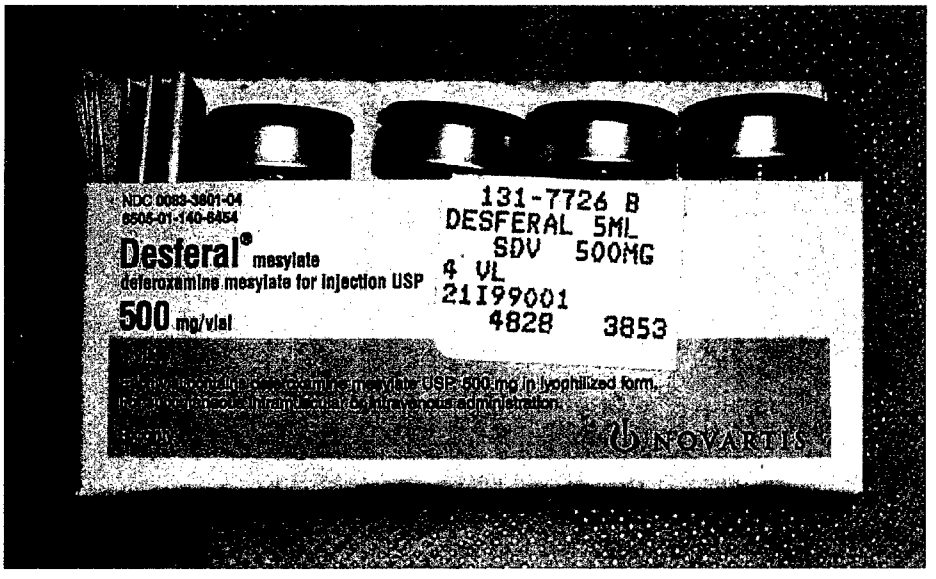

Figure 9- Desferal

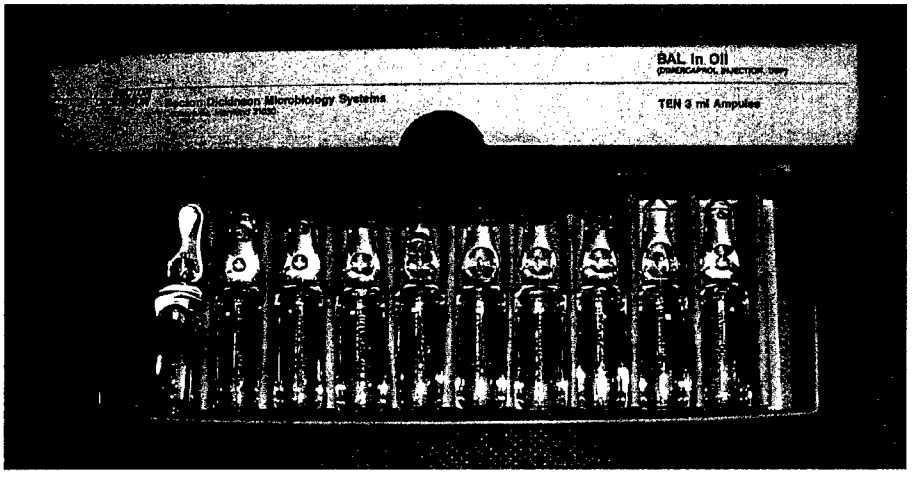

Figure 10- BAL

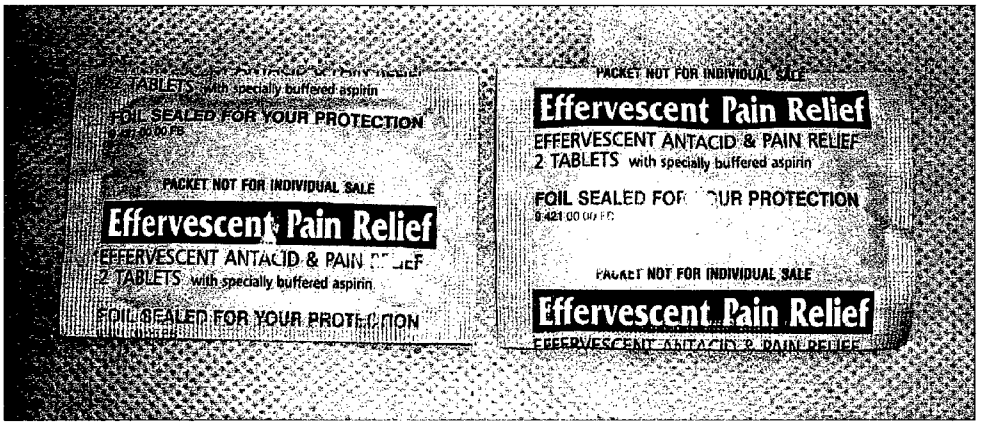

Figure 11- Common antacid

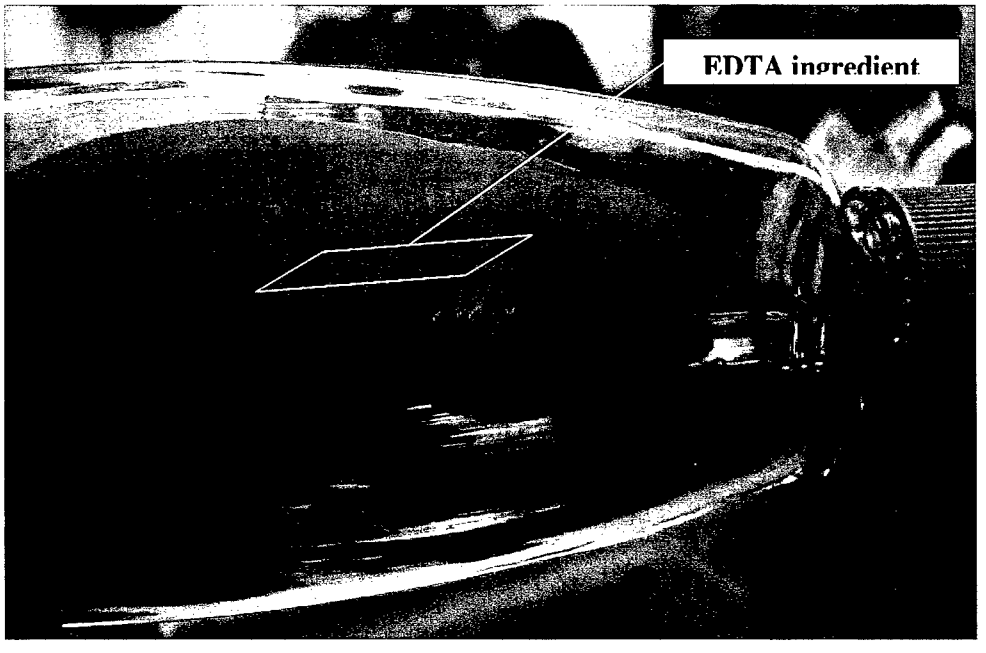

Figure 12- EDTA in common shampoo

Note: The bottle of baby shampoo is presented herein to show that some commonly found household items may contain EDTA, however it is not necessarily suggested that this item be used for internal chelation. Many other common foodstuffs, such as salad dressing, margarine, sandwich spreads, mayonnaise, processed fruits and vegetables, canned shellfish and soft drinks can contain EDTA salts. EDTA is used as a food preservative primarily to bind free metal ions that cause changes in color and taste.

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(U) The broad use of radionuclides by many industries has greatly increased the probability of events that could lead to internalized contamination. Examples include accidents and/or intentional damage to nuclear power plants or radiation therapy units in hospitals, the use of radiological dispersal weapons, and lost or stolen radionuclide sources. Developing effective countermeasures requires knowledge of the physical and chemical composition of the radionuclides, their metabolic activities within the body, and methods to expedite their elimination from the body. This report presents a summary of information pertaining to intake and decorporation of radionuclides from humans. This information would be the first step in establishing a field protocol to guide physicians in military missions. Developing such a guide requires an understanding of the dangers associated with internal radioisotope contamination, decision levels for administering therapy (risk vs. benefit) and protocols for administering therapy. As presented, this study could be used to decide what decorporation pharmaceuticals should be maintained in quantity by the military, and how to best train officers with medical responsibilities.

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contamination, radionuclide, decorporation, depleted uranium

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