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## Treatment of Radiological Contamination: A Review

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### Abstract

After nuclear accidents, people can be contaminated internally via ingestion, inhalation and via intact skin or wounds. The assessment of absorbed, committed doses after internal exposure is based on activity measurement by *in vivo* or *in vitro* bioassay. Estimation of dose following internal contamination is dependent on understanding the nature and form of the radionuclide. Direct counting methods that directly measure  $\gamma$ -rays coming from within the body or bioassay methods that measure the amount of radioactive materials in urine or feces are used to estimate the intake, which is required for calculating internal exposure doses. The interpretation of these data in terms of intake and the lifetime committed dose requires knowledge or making assumptions about a number of parameters (time, type of exposure, route of the exposure, physical, biological and chemical characteristics) and their biokinetics inside the body. Radioactive materials incorporated into the body emit radiation within the body. Accumulation in some specific organs may occur depending on the types of radioactive materials. Decorporation therapy is that acceleration of the natural rate of elimination of the contaminant will reduce the amount of radioactivity retained in the body. This article presents an overview of treatment of radiological contamination after internal contamination.

Keywords: radionuclide, internal contamination, bioassay methods, decorporation therapy.

### 1. Concepts of Medical Treatment of Radiological contamination

In case of accidents involving nuclear reactors, industrial, or medical sources, internal radioactive contamination can arise. Radioactive contaminants may be released into the air and then breathed into the lungs, or may get into the body through ingestion, injection, skin or through an open wound (1).

The distribution of the radioactive contaminant, is determined by its physical and chemical form and associated *in vivo* solubility (2).

In case of ingestion, radioactive contaminant passes through the gastrointestinal tract and a fraction of the radionuclide may be absorbed depending mainly on chemical form, the remainder is excreted in the feces. For soluble chemical compounds such as tritium, iodine or cesium, the fraction absorbed can be very high, but for insoluble chemical compounds such as plutonium or uranium, the fraction absorbed can be very low (3,4). The absorbed radionuclide is

circulated via the bloodstream, it will then be deposited in specific organs and further excreted via the urine and feces (3).

In case of inhalation, fractions of inhaled contaminant, depending on particle size, are deposited in different regions of the respiratory tract (nasopharyngeal, tracheobronchial and pulmonary regions) and the fraction not deposited is exhaled. The regional deposition of the inhaled contaminant is influenced by the characteristics of the inhaled material and by the anatomic and physiologic status of the subject. Once deposited, the elimination and systemic absorption of the contaminant are governed by the sites of deposition and by the physical and chemical properties of the inhaled contaminant. Radioactive contaminants deposited initially on the ciliate epithelium of the respiratory tract are cleared by mucociliary followed by swallowing and passage through the gastrointestinal tract. Retention of material deposited initially beyond the level of the ciliate epithelium is influenced by the solubility of the material in the body fluids (5). If the inhaled contaminant is soluble in body fluids, significant absorption to the bloodstream can occur through the tissue of the upper

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respiratory tract. Soluble materials (such as  $^{137}\text{Cs}$  or  $^{90}\text{Sr}$ ) are mainly absorbed into the bloodstream. Relatively insoluble forms are retained in the pulmonary region for longer times and are subject to removal (5,6,7).

Absorption through intact skin or wound are additional routes by which radionuclides contaminant can enter the body. While much of the material may be retained at the wound site, soluble material can be transferred to the blood and hence to other parts of the body. Insoluble material will be slowly translocated to regional lymphatic tissue, where it will enter in the systemic circulation. A fraction of insoluble material can be retained at the wound site or in lymphatic tissue and can potentially also irradiate locally (1,8).

Radioactive contaminants incorporated into the body emit radiation within the body. Accumulation in some specific organs may occur, depending on the types of radioactive contaminant (9). For example, strontium, having similar properties to calcium, tends to accumulate in calcium rich parts such as bones once it enters the body (10); cesium, because of its properties similar to potassium, tends to distribute throughout the body. Iodine, a constituent element of thyroid hormones, tends to accumulate in the thyroid, whether it is radioactive iodine or stable iodine (11).

As long as these radioactive contaminants remain in the body, they may pose significant long term health risks (development of cancers of the lung, liver, thyroid, bone...) (1).

The effective method of reducing these long term health risks is removal of the radioactive contaminants from the body by medical treatments. Treatments are available for limiting or removing internal contamination depending on the type of radioactive material involved (1, 12).

The goals of internal decorporation are to reduce absorption or to enhance excretion of radioactive contaminants. Treatment is most effective if it is started as soon as possible after contamination. Decorporation consists to remove radioactive contaminants from the body (1, 12,13).

The radiation exposure is quantitated by the committed dose, which is defined as the total effective dose due to radionuclide intake absorbed over 50 years after the incident (70 years for children) (14). The determination of the committed effective dose requires the measurement of radioactivity in the body by whole-body counting or radionuclide excretion measurements in urine or feces, followed by internal dosimetry calculations (15). Computations are based on complex kinetic models describing the absorption, distribution and elimination of a defined radionuclide, in combination with a dosimetric model describing the absorption of energy in the different organs and tissues due to the radioactive decay (16).

## 1.1 Methods to measure internal contamination

The radioactive burden depends on type and amount of intake radionuclide and intake route (e.g. inhalation, ingestion, or wound absorption). Therefore, appropriate measurement methods and biosamples for the assessment should be selected by considering intake route, biokinetics, and excretion route of radionuclide and sample availability (3, 4).

Direct or indirect measurement methods are available for the radionuclides in the human body: *in vivo* bioassays are commonly used to measure radioactive materials in the human body directly via whole-body or organ counting (lung, thyroid, liver and skeleton). *In vitro* bioassay analysis is an example of an indirect method that is used to measure radioactive contaminant in the human body fluids via excreta (e.g. urine and faeces, blood, nose blows, or sweat (3,17).

Direct methods consist of the measurement, with external detectors, of the radiation emitted by the radionuclides deposited inside the body (18). They can only be used for radionuclides emitting penetrating radiation, i.e. X-rays, gamma emitter with a sensitive low-energy photon detector. Lung burden can only be measured accurately by *in vivo* counting (19).

Once in the body, radioactive contaminant may be transported to various sites (eg, bone marrow), where it continues to emit radiation until it is removed or decays. Therefore, it is essential to know which radioactive contaminants are involved, their chemical behavior, and biodistribution. Internal contamination should be treated in several ways, depending on the route of entry and chemical properties of the material (5, 18).

Urine analysis for radioactive contaminant provides a useful assessment of the existing systemic burden. Urine analysis can be particularly useful when equipment and facilities for external detection of radionuclides are not available on a routine basis (18,19). Except when 24-hour samples are collected, some correction of the concentration measurement may be required to account for abnormal conditions of high or low fluid intake or excessive loss of water by perspiration. This correction is frequently made by relating the specific gravity. Urine sample (first 24 hours) may be of little value, as they may comprise residual bladder and bowel contents present prior to exposure or redistribution and excretion of absorbed radionuclide. As described in the literature which deals with DTPA therapy, which shows that DTPA treatment significantly influences internal dose estimations (20).

Feces analysis is another means of obtaining an indirect assessment of the body burden of an internally deposited radionuclide. It can be useful in detecting and quantifying an inhalation exposure to a relatively insoluble form of

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radionuclide, because clearance via feces is the predominant excretion mode in such a situation (17). Nevertheless, this method carries significant uncertainty as stated by EURADOS where it described that the transit time through the alimentary tract is subject to large inter/intra subject variations (21).

Another possible means of estimating the internal contamination in an individual is to measure the radionuclide content of a blood sample. Blood samples show less fluctuation in radionuclide content than do urine samples, but the sensitivity of the analysis is limited, due to the amount of blood that can be withdrawn from an individual, particularly in the event of an accident with severe injury (17,18).

## 1.2 Estimation of internal dose

Many factors can influence the amount of radioactive contaminant deposited in the body. These factors include chemical form, route of intake, elapsed time from intake, organs containing the radioactive contaminant, particle size, physical and biological half-life. Complex mathematical models have been developed that take each of these factors into account (1, 16, 22).

A dose value is derived from this measurement by means of biokinetic and dosimetric models which describe the behaviour of radionuclides in the body of a reference man and the subsequent absorption and deposition of energy (22).

Dosimetric models represent the anatomy of the body and predict the interactions in the transport of the radiation from the source regions to the radiosensitive target regions (4, 22). The deposited energy is provided by computational anthropomorphic phantoms consistent with the volumes and densities of organs in a reference person (23).

Biokinetic models describe the uptake of radionuclides to the body, their retention, transfer to other body regions and their excretion. They are built from the follow-up of incidental or volunteer intake of radionuclides, animal experiments, basic physiological data and chemical analogies (16).

Biokinetic models are mathematical models describing the distribution, retention and elimination of the incorporated radioactivity, and enable calculation of retention curves and number of transformations in each source region, as well as the profiles of activity excretion in urine and faeces (3,5, 16).

Different software can be used to evaluate the intake of radioisotopes as well as the committed effective dose. Taurus or Miodose computer programs, which are commercial softwares that reflect the latest recommendations from the International Commission on Radiation Protection (ICRP),

can be widely applied worldwide because they are easy to use, and make it simple to evaluate the uncertainties and intakes of the measured samples. The validity of the models, tools and methods used is periodically evaluated in intercomparison exercises at national and international levels (22, 24, 25).

The International Commission on Radiological Protection (ICRP) and the National Council on Radiation Protection (NCRP) have developed biokinetic models to describe absorption processes: the respiratory tract model the gastrointestinal tract model and the wound model (5, 6, 12).

A number of organisations, including ICRP, IAEA and NCRP, have provided relevant recommendations on action levels to be used following a radiation emergency, that correspond to doses where actions such as medical assessment should be considered. Dose estimation is modelled using bioassay results and reference tables, manual and computer calculations (12).

The effects on the human body vary depending on the types and energy quantities of radiation even if the absorbed doses are the same. Doses weighting health effects of respective types of radiation are equivalent doses for a tissue or organ. The effective dose was developed for exposure management in radiological protection (1).

To manage the radiation exposure of the general public or workers, the committed dose recommended by the ICRP is typically evaluated. Because the internal exposure is maintained over time after intake (50 years for adults, and 70 years for children), the internal exposure is evaluated using the committed dose. The committed effective dose is calculated as the product of the intake estimate and the committed effective dose coefficient (14, 25, 26).

## **2. Current decorporation strategies after intake of Radionuclides**

### *2.1 General approaches*

Reduction of internally deposited radionuclides can be accomplished by means of general processes, including reduction of absorption and internal uptake, enhanced elimination and excretion of absorbed radionuclides (27,28, 29, 30).

Bronchial lavage has been proposed as a treatment method for contamination of the airways. The greatest utility of bronchial lavage is for patients with high levels of contamination that may lead to long-term pulmonary fibrosis. The procedure has complications, and its utility and effectiveness in various other situations are debated (1, 31).

Decorporation is the action, mediated by biological processes and facilitated by chemical agents, by means of which incorporated radionuclides are removed from the human body (1, 32, 33). Current methods to remove radioactive contaminants from the body include :

-Chelation at the site of entry or in body fluids followed by rapid excretion (e.g., calcium or zinc DTPA for americium, californium, plutonium, and yttrium)

-Saturation of the target organ (eg, potassium iodide for radioactive iodine isotopes)

-Acceleration of the metabolic cycle of the radionuclide by isotope dilution (e.g., water for  $^3\text{H}$ )

-Precipitation of the radionuclide in the intestinal lumen followed by fecal excretion (e.g., oral calcium, sodium alginate or aluminum phosphate solutions for  $^{90}\text{strontium}$ )

-Ion exchange in the gastrointestinal tract (e.g., Prussian blue for  $^{137}\text{cesium}$ ).

Decorporation treatment should begin at the earliest time after exposure, however, there is no consensus when to start the treatment (32,33,34, 35). In suspected situation of accidental contamination and periodic control (occupational exposure) decorporation treatment should start as soon possible, even if radionuclide intake is just suspected. Treatment should be discontinued once internal dosimetry results are available and the committed effective dose has been shown to be not significant. In some countries, decorporation treatment only start when the relevant committed effective dose has been confirmed according the results of internal dosimetry (13, 35).

The urgency of using specific treatment depend on the type and amount of the radionuclide, its chemical form (eg, solubility, affinity for specific target organs), the route of contamination (eg, inhalation, ingestion, contaminated wounds) (29, 35).

## 2.2 examples of drugs currently used in decorporation treatment

Medical therapy with a chelating agent is most effective when it is begun immediately after exposure while the radionuclide is still in bloodstream and before intake within cells or deposition in organs (such as bone or liver for plutonium, for example). As example DTPA is effective in removing many of the actinides (plutonium, americium, californium, curium, ...) (12). Nevertheless, DTPA should not be used to chelate uranium or neptunium because it is not effective (36, 37). DTPA comes in two forms: calcium (Ca-DTPA) and zinc (Zn-DTPA). Both forms work by binding to radioactive as

plutonium, americium. These radioactive complexes (radionuclide bound to DTPA) are then passed from the body in the urine. DTPA works best when given shortly after radioactive plutonium, americium, and curium have entered the body. DTPA is usually injected intravenously but may also be administered by inhalation. Intravenous administration is typically 1 g CaDTPA or ZnDTPA in 250 ml normal saline or five percent glucose in water given over one hour in a single daily dose. The dose may be repeated on 5-6 successive days. Aerosol inhalation is usually 1 g CaDTPA or ZnDTPA placed in a nebulizer (38).

Authors demonstrated that after inhalation contamination by actinide in rat, most of the activity was retained at the entry site. DTPA treatment via injection had no significant effect on removing in lung compared with untreated animals. Recent studies establish the better efficacy of nebulized DTPA compared to its intravenous injection for removing plutonium from lung. In case of systemic retention in skeleton or liver, the excretion of actinide was enhanced irrespective of the contamination route or DTPA treatment regimen (38, 39, 40).

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, up to 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 (40, 41).

Other methods to remove radioactive contaminants from the body include the saturation of the target organ (eg, potassium iodide for iodine isotopes). If the isotope is concentrated by a particular organ in the body, the concentrating organ can be saturated with a nonradioactive isotope. The thyroid gland cannot make the difference between stable and radioactive iodine and it will absorb both. When a person takes KI, the stable iodine in the medicine gets absorbed by the thyroid. Because KI contains so much stable iodine, the thyroid gland becomes saturated and cannot absorb any more iodine, either stable or radioactive for the next 24 hours (11, 42).

KI (potassium iodide) blocks radioactive iodine from entering the thyroid. Stable iodine is most effective if given less than 12 h prior or up to 2 h after radioiodine exposure (11, 42).

Potassium iodide can be given either in tablet form or as a supersaturated solution (dosage for adult > 70 kg, 130 mg of KI) and a single dose of stable iodine is sufficient. Authors showed that the early administration of KI is more efficient to reduce the absorbed dose in the thyroid. When KI is administrated within 2 h after the intake of radioiodines, the protective effects are 78.9% and 74.3% for  $^{131}\text{I}$  and  $^{133}\text{I}$ , respectively (43). Repeated doses should only be considered in the case of prolonged radioiodine exposures that cannot be avoided (44).

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Adults older than 40 years should not take KI unless contamination with a very large dose of radioactive iodine is expected with a risk of hypothyroidism. Adults older than 40 years have the lowest chance of developing thyroid cancer after contamination with radioactive iodine. Moreover adults older than 40 are more likely to have allergic reactions to or adverse effects from KI (44). Side effects included gastrointestinal distress, which was reported more frequently in children (up to 2 %) and rash (1% in children and adults). Two allergic reactions were observed in adults with known iodine sensitivity (44).

Blocking the absorption of radioactive contaminant is also a method to remove radioactive contaminants, such as the use of Prussian Blue. Prussian blue is currently approved by the FDA and ANSM in France, for the treatment of internal contamination with radioactive cesium and thallium. The drug is administered orally and binds cesium or thallium in the intestinal tract during enterohepatic circulation. The resulting complex shifts excretion from the urine to the feces reducing the effective time of residence of the radioactive element inside the body (12, 45, 46). The daily dose in adults is 3 g for at least 30 days. Dosage can vary between countries (11, 45). The duration of therapy is guided by the amount of radioactive cesium or thallium that is being removed. Prussian blue reduces the biological half-life of cesium from about 110 days to about 30 days (46).

Other medicine drugs are used as treatment for internal contamination and are listed by national and international organizations. In some countries, chelators with Dimercaprol or DMSA (dimercaptosuccinic acid or succimer), are also considered necessary for radiological emergencies (13, 29, 35).

Dimercaprol (BAL™) forms stable chelates with mercury, lead, arsenic, gold, bismuth, chromium, and nickel. Administered by intramuscular injection, Dimercaprol should be useful in accelerating removal of ionic metals (1). Unfortunately, dimercaprol is a toxic drug and must not to be used for patients with hepatic or renal failure (35, 47, 48).

DMSA (dimercaptosuccinic acid) has been the alternative to Dimercaprol. In contrast to Dimercaprol, DMSA is less toxic, much more soluble in water, and hence has limited solubility in lipids, and is effective when taken orally (10 mg/kg per day in adult). The use of DMSA in decorporation of heavy metal poisoning has been examined, specifically for mobilizing inorganic mercury, cadmium, arsenic, copper, lead, gold and antimony (31, 35, 48, 49, 50, 51).

Penicillamine is an amino acid, derived from the degradation of penicillin, chelates with copper, iron, mercury, lead, gold, and possibly other heavy metals. It is superior to dimercaprol and Ca-EDTA for removal of copper. The incidence of adverse effects with penicillamine is low. The most common and serious are hypersensitivity reactions manifested by a maculopapular or erythematous rash. One fatal case of granulocytopenia has been reported. Penicillamine is given orally 250 mg four times daily on an empty stomach between meals and at bedtime (49, 52, 53, 54).

Deferoxamine (DFOA) has been used effectively in treatment of acute iron poisoning and chronic iron overload. DFOA is given by intravenous injection, never exceed 80 mg/kg of body weight per total dosage. Toxic reactions, usually manifested as a generalized erythema, flushing, tachycardia, urticarial, or sudden hypotension, are serious enough to contraindicate use of DFOA in treatment of mild iron poisoning (1, 29).

EDTA is primarily to treat lead poisoning. It can also be used to chelate zinc, copper, cadmium, chromium, manganese. EDTA is nephrotoxic and must be used with extreme caution in patients with pre-existing renal disease (1, 50).

Other non specific treatments also exist, such as adsorptive agents like aluminum phosphate or alginate which may be used to reduce gastrointestinal uptake of radionuclides. Aluminum phosphate gel may be particularly beneficial in case of strontium intake. Laxatives like magnesium sulfate may decrease the residence time of radioactivity in the gut, thus lowering the local radiological dose as well as the gastrointestinal absorption (29).

### **3. Conclusion**

Internal exposures are generally more complex to manage than external exposures. Internal emitters indeed present particular aspects which distinguish them from the case of external exposures. The dose assessment is complicated by the fact that internal exposures from incorporated radionuclides are often accompanied by external exposures from various possible sources (1).

The determination of the internal exposures requires the identification of the radionuclide; the measurement of radioactivity in the body by whole body counting or excretion

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measurements in urine or feces, depending on the radionuclide involved, and computations on the basis of the adequate biokinetic and dosimetric models (2).

Internal dosimetry requires the measurement of radioactivity in the body at the time of the examination. In a second step, the initial radioactivity intake at the time of the incident is calculated using the most suitable biokinetic model. In the last step, this activity is used to compute the committed effective dose. Depending on the method (whole-body counting, radio-toxicological method), the availability of the measurement equipment, the number of patients and logistics, internal dosimetry may take days or even weeks before results are available (1).

The ICRP has developed and published the reference biokinetic models for use in radiation protection. It distinguishes models for the main routes of intake: inhalation and ingestion, which predict the kinetics and magnitude of absorption from the site of entry to the circulation, and systemic models that describe the distribution and clearance of radionuclides in the systemic circulation (3, 4, 5).

Dosimetric models represent the transport of radiation recorded in nuclear databases from their point of emission, following the nuclear transformation of a radionuclide, to the radiosensitive regions of the body. Combined with biokinetic models they can predict the doses absorbed by the tissues and the committed effective dose following the intake of a radionuclide (15).

The current decorporation therapies are consisting in chelation, e.g. formation of a stable complex with the radionuclide, which is rapidly excreted; inhibition or reduction of the absorption of the radionuclide from the gastrointestinal tract or block the uptake to organs or blood. Some examples of the three therapies are: the use of salts of DTPA for decorporation of actinides, the use of Prussian Blue to block absorption of caesium from the gastro-intestinal tract, and the use of potassium iodide, to block thyroid uptake of radioisotopes of iodine (1, 29).

Even for these three molecules highly used, a need for harmonisation between organizations and countries could contribute to improve the administration of the treatments.

The application of decorporation therapy must be balanced against the toxicological risks imposed by the drugs used. Therefore, decorporation is mainly applied in cases where significant doses are expected. These treatments are very effective at binding isotopes, but they also bind nonradioactive isotopes as well. If these compounds are to be used, close management of electrolytes and essential trace elements will also be required.

It could be justified to start therapy without knowing the committed effective dose to avoid delays. This approach has been recommended by the French authority for nuclear safety

(29). The guidelines recommend starting decorporation treatment after the identification of the radionuclide "a priori".

Although the indication of decorporation therapy clearly depends on the committed effective dose, the decision when to start the treatment must be taken individually by the physician on a case-by-case basis.

There are other drugs available approved by FDA or ANSM for other indications, not related to internal contamination. Some authorities, such as the National Council on Radiation Protection and Measurements and International Atomic Energy Agency, have reported recommended decorporation agents for each radionuclide. However, few drugs are approved by the FDA, ANSM, and many are off-label-use agents (DMSA, Dimercaprol, EDTA).

For a certain number of radionuclides, there is no treatment available.

The assessment of therapeutic efficacy is not conclusive for all radionuclides, and recommendations vary. For DTPA, the recommended maintenance dose is 0.5-1 g (14 mg/kg in children) of DTPA administered intravenously once a day, administered over days, months, or years, depending on the level of internal contamination. DTPA is also effective when co-administered by nebulizer. Further research is needed to improve the current practice in decorporation therapy, including dose administration, regimen, route of administration, such as use of liposome containing DTPA to improve the delivery in lung after nebulisation (55, 56, 57).

Ideally, a decorporation agent should be able to chelate and eliminate a range of radionuclides, effective for radionuclide contamination by different routes (inhalation, ingestion and dermal), orally administered, effective when administration is delayed long after radionuclide exposure, and are safe for all potential populations including infants, children and the elderly.

Finally important studies have been launched for expanding the range of treatments. Some molecules already authorized as therapeutic drugs have been investigated for improving decorporation of radionuclides. For example penicillamine, recommended to treat Wilson's disease, leading to copper overload, has been evaluated for decorporation of polonium or cobalt. Preclinical studies were undertaken on rodents (58). Otherwise candidates molecules such as hydroxypyridinone are still investigated for their affinity, complexation stability, specificity with lanthanides and actinides (59). But such studies should demonstrate the efficacy of the molecules to decrease the radionuclide burden in the deposit organs and increase the excretion without toxicity.

In conclusion, there is a need for research in new decorporation agents, pharmaceutical reformulations of existing agents, and extension of the labeled indications for existing treatments.

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