

# Modeling of DTPA decorporation therapy – still puzzling after all these years

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## Abstract:

Incorporations of some actinides (Pu/Am/Cm) can be treated by i.v. injections of Ca- or Zn- salts of di-ethylene-Triamin-Pentaacetic-Acid (DTPA). An enhanced urinary and fecal excretion and thus a reduction of the body burden can be observed after the injections. Multiple injections are used in the decorporation therapies, which in some cases use total amounts as high as 500g of DTPA within several years without adverse side effects.

The principle behind the enhancement of the excretion is the in-vivo formation of stable complexes of the radionuclide with DTPA. These An-DTPA-chelates mask the actinide from the biokinetic processes in the body and are rapidly excreted. After this basic idea was stated in the 1940s by Kety et al., several chelators including Citrates or EDTA have been studied. DTPA which has become available in the 1960s showed to be the most effective chelator and was used since then.

A modeling of the observed biokinetics is required for assessing the doses averted by the therapy. Primarily in the 1970s various studies in several species of experimental animals have been conducted to understand and improve DTPA therapy. The results of these and newer studies as well as human case studies after incidents have been used as database for modeling decorporation therapy. Today in the 2010s several case specific models exist in the literature as well as a generic empirical model. The latter can only describe the urinary excretion pattern as a mathematical function being used for a rough assessment of the dose using a “reduced intake”. Even after more than 50 years of using DTPA decorporation therapy no generic model exists, which can describe the biokinetics of the radionuclides under therapy and be used for accurate dose assessment. Several hypothesis and approaches in modeling are currently followed. One of the many problems for the understanding and modeling of DTPA decorporation therapy are the still unknown sites of chelation, i.e. which parts of the biokinetic system the An is removed from and with which efficacy. Another puzzling point is the identification of the bio-ligands and other molecules competing for the DTPA or the An and their influence on the therapy. The database still needs to be widened by targeted experiments to answer such more specific questions.

## Keywords:

DTPA, decorporation, actinide, biokinetic, modeling

## Introduction

Handling of open radionuclides bears the non-negligible risk of incorporation, even if appropriate safety measures are taken. If Plutonium or other actinides are incorporated in the body they might deliver significant radiation doses to the person. This is due to the fact that these nuclides are physically and biologically long-lived and (with few exceptions) emit alpha-particles which have a high Linear Energy Transfer (LET). Radiation doses caused by the Intakes of activity need to be assessed in order to estimate the risk associated to the incorporation incident, to decide about further measures to be taken and to show compliance to legal regulations and dose limits. Standard techniques of internal dosimetry are applied in the assessment. For Plutonium and Actinides usually urinary or fecal samples are collected and radiochemically analyzed. The results of these monitoring measurements are interpreted by applying biokinetic models, which mathematically describe the behavior of the radionuclide inside the body and give predictions about the distribution and excretion patterns to be observed. The “standard” or reference biokinetic models used in dose assessments have been published by the International Commission on Radiation Protection [1] and were adopted into local legislation for most countries.

If a significant radiation dose is expected from the intake, medical countermeasures to reduce the radiation dose may be considered. Lung lavage or wound excision to remove activity from the initial contamination site can only be done if a significant part of the activity is still at the site of intake. Pharmaceuticals that block the uptake of activity to organs or that enhance the excretion may be used as decorporation therapy when the activity has already been transferred to the body system. For incorporated actinides a chelation therapy with DTPA is the only treatment available nowadays. An enhanced urinary excretion (and thus a reduced body burden) of the actinide can be observed in the days following an injection or infusion of DTPA. A realistic assessment of the treatment effect in terms of averted doses is currently not possible because the perturbation of the biokinetic system cannot be described with the reference models for actinide biokinetics. Usually estimates of the dose due to a reduced body burden are made; in some special cases, mostly in case-specific scenarios, models are applied in the interpretation of decorporation therapy data [2].

## Biokinetics of Plutonium and Actinides

Research on the metabolism of plutonium (and actinides) in man is done since the 1940s. Langham et al. [3] were the first that did injection experiments with Plutonium in human. The latest studies on human volunteers have been published by Talbot et al. in 1993 and Newton et al. in 1998 [4,5]. The US Transuranium and Uranium Registries (USTUR) [6] are devoted to the study of the biokinetics of actinides in man. Here for some cases also autopsy data of incorporation cases are available. Another resource of data, which has become available lately, is the so called “Mayak Worker cohort”, consisting of workers of the Mayak PA in Russia. A new model of Plutonium biokinetics developed by Leggett et al. [7] is based on these data. Additionally, data obtained from animal experiments are extensively used in biokinetic modeling. Plutonium and Americium biokinetics has been studied in Beagles, small rodents and rats. The Transfer of these animal data to human must be done carefully and inter-species variations must be taken into account.

Plutonium (which can be seen as example for most other actinides) circulates in blood and accumulates in liver and bones. Retention times in the body or these organs are in the order of magnitude of tens of years. Small amounts of the incorporated plutonium are excreted via urine and to a lesser extent in feces [1,8]. The earliest models aimed at describing excretion and retention (i.e. body burden) by simple mathematical equations such as power functions [3] or sums of exponential terms [9,10]. More complex models use compartmental formalism [11]. Here mathematically the body is divided in several compartments (which can be organs, groups or parts of organs or tissues). These are treated as kinetically homogenous units; i.e. every particle entering a compartment is instantaneously available

for further transport. The structure of the models identifies the compartments and the pathways along which the nuclide is transported. Models of actinide biokinetics use compartments representing the skeleton, liver, blood and other soft tissues. The nuclide content of the compartments can then be described by a set of coupled differential equations. The assumption of linear kinetics implies that the transfer rates are proportional to the amount of nuclide available in the compartments. The proportionality constants are called transfer coefficients. For models of Actinide biokinetics the proposed values range from the order of  $10^{-5}$  to the order of  $10^{+1}$ , due to the different “velocities” of the processes driving the biokinetic behavior. The complete compartmental model is defined by the model structure (including its interpretation) and the set of transfer coefficients. The model can be solved numerically to calculate retention and excretion functions [11]. Due to the complexity of the models (typically 20 or more compartments are involved) analytic solutions are not used, although computer algebra tools able to calculate the exact solutions of the models [12] are available.

The current “reference” models were published by the ICRP in 1992 [1]. A newer model of Plutonium biokinetics has been published by Leggett and coworkers in 2005 [7]. All recent models use the compartmental formalism.

### **(DTPA-)Decorporation Therapy**

The basic principle of decorporation therapy with chelating agents was presented in 1942 by Kety [13]. The metal ion is mobilized by a complexing agent by forming a complex (chelate). Bound in the chelate the metal is no more available for its “standard” metabolic processes. The complexes are quickly eliminated by natural routes. An enhanced excretion of the metal can be observed in the first days after a treatment. Series of multiple injections are used in the decorporation therapies, which in some cases use total amounts as high as 500 g of DTPA within several years. As consequence a radiation dose in proportion to this additional decorporation of the contaminant is averted by the therapy. One problem of chelation therapy is the missing selectivity of most of the chelating agents. Chelates are formed with all metals available in the body, thus the levels of essential and trace metals might also be reduced and need to be monitored during the therapy [2].

Decorporation treatments using chelators have been applied since the 1950s [14, 15]. Several chelating agents (e.g. Zr-Citrate or EDTA) have been tested. DTPA (DiethyleneTriaminePentaacetic Acid) has proved to be an “optimal” chelator for treatment of incorporation cases with plutonium (and most other transuranium elements). Currently there are no scientifically based rules for an optimized treatment schedule. In-house protocols are used by the different institutions. Usually the trisodium salts of Ca- or Zn-DTPA are injected or slowly infused intravenously (iv-DTPA). Interestingly the two salts of DTPA differ in toxicity and decorporation efficacy. Powder formulations of DTPA salts may be applied via inhalators as first measure in cases of actinide deposition in the lungs. Only sparse side actions of DTPA-therapy have been reported. Short-lasting irritations of the skin were observed in few cases. One case with repeated treatments of overall more than 500 g of DTPA showing no side effects of DTPA has been reported by Breitenstein [16]. The use of pentetate calcium trisodium injection (Ca-DTPA) and pentetate zinc trisodium injection (Zn-DTPA) are approved in the U.S. by the Food and Drug Administration (FDA) for treating certain kinds of radiation contamination [17]. In Germany Ca-DTPA and Zn-DTPA are approved pharmaceuticals as well, but in most European countries DTPA is still not approved as „regular“ drug and may only be used by named experts as kind of „experimental therapy“. Several reviews and guidelines on decorporation focused on the medical aspects of the therapy are available in literature [2, 18, 19,20].

New chelating agents such as Hydroxypyridonates (e.g. 3,4,3-LI(1,2-HOPO)) have been and still are synthesized and studied for their therapeutical efficacy [21]. Several of these “optimized” chelating agents and galenic forms (such as pills for oral application or encapsulation in liposomes [22]) have been studied in the past 50 years, but none has shown a higher efficacy than iv-DTPA. Thus injection

of DTPA has become the de facto standard therapy after incorporation of actinides. Any new drug developed is compared to iv-DTPA. After the discovery and first application of chelating agents [13] lots of research activities have been devoted to understanding, developing and optimizing of decorporation therapy. Most of these were focusing on the development of new agents studying their efficacy or the medical aspects of the therapies (e.g. developing optimal therapeutic regimes). Only few studies were done about biokinetic modeling of the therapies, e.g. [23,24]. Experimental and theoretical studies were conducted mainly in the 1960s and 1970s [15]. In the following decades interest and funding diminished but never came to a complete stop. Recently decorporation of actinides from humans has become a “hot” topic in research again, because mass casualty scenarios with incorporation of actinides in members of the public have become imaginable. Here countermeasures, which are rapidly and easily applicable also to large groups of people, are required.

### **Models of DTPA decorporation therapy**

Models of decorporation therapies are required for two reasons. The treating physician needs to have a quick way to evaluate the outcome of the therapy and plan the further treatment. The dosimetrist needs a method to interpret the monitoring data disturbed by the therapy in order to calculate a resulting dose. Several approaches to the modelling of DTPA decorporation therapy can be found in Literature. These models range from simple empirical interpretations of the observed urinary excretion pattern to modifications of the compartmental models describing the actinide’s biokinetics.

#### Empirical models

Jech et al. [25] state that the effect of chelation has ceased 100 days after application of DTPA. Thus monitoring data sampled at long times after the infusions can be interpreted using the standard models. The result will be a “reduced” intake, decorporation efficiency cannot be described with this “model”. Only if undisturbed measurements before the therapy are available an overall effect in terms of removed activity can be estimated. Hall et al. [26] developed an empirical model, which is able to calculate urinary excretion curves of Plutonium after chelation therapy. The authors assume that some amount  $Q$  of Plutonium is available for chelation and that the Pu-DTPA complexes do not affect the original biokinetics. Additional terms  $i_c(t)$  are added to the original empirical curve  $i_i(t)$  (which is then further calculated using an intake reduced by  $Q$ ). Considering the observed pattern after therapies with two distinguishable half-lives, a sum of two exponential functions is suggested by the authors for  $i_c(t)$ . The parameters of these functions can be estimated by fitting to the observed data. Both models can only give the overall reduction of effective dose, but no information about redistribution of Pu after chelation and dose reduction in the target-organs (liver, skeleton) is given by the model.

#### Compartmental models

Several authors added the effect of DTPA to existing compartmental models by modifications of these. A simple mechanistic model is presented by LaBone [27]. He uses the ICRP 66 model [1] and implements the chelation by stopping the model at the time of chelation, removing parts of the compartmental contents from the model, letting these be excreted with their own excretion function (the same function used in Hall’s method). The model is then restarted with the reduced compartment contents. The excretion of chelate and the excretion of plutonium are added to get the total excretion. This model is a kind of transfer of the Hall-Model to the compartmental world. The excretion rate of “pure” Pu is decreased and an extra-function for the Pu-DTPA excretion is added.

Other approaches modify the models by adding extra compartments describing DTPA complexes or accelerating selected transfer rates between the compartments of the model. In a publication of Bailey et al. [28] a wound incorporation case was interpreted by adding compartments representing the kinetics of DTPA and Plutonium bound to DTPA. Chelator and chelate are assumed to be removed through urinary excretion with the same fractional clearance rate. Parameter values have been based on the

work of Hall et al. [26] and were adjusted to the data interactively. Fritsch et al. [29] model decorporation therapy by adding up to three DTPA-compartments (associated with blood + ST0) clearing to urine to the different Pu-Models and fitting the rates. Each injection clears 90% of Pu in (blood + ST0) and 3 to 30% of Pu in liver. These models are used to interpret a wound incorporation case. The model of Leggett and co-workers [7] suits better the analysis of DTPA effect on Pu excretion than the ICRP 67 model [1] or the Luciani and Polig model [30]. James et al. [31] apply multiplication factors to the rate-constants of the ICRP67 model to reproduce the effect of chelation therapy in a USTUR donor. In this case besides the urinary excretion data, the organ contents (autopsy results) are used in a least square fit of the new transfer coefficients. The CONRAD/EURADOS group coupled a model of DTPA-biokinetics [32] to a model of Plutonium biokinetics [7] using second order differential equations. These are interpreted as direct implementation of the in-vivo chelation reaction in terms of the compartmental models [33].

### **Some open questions in modeling of decorporation therapy**

The central question of compartmental models of DTPA therapy is the identification of the parts of the models which are affected by DTPA (i.e. compartments which are decorporated or transfer rates which are accelerated). The puzzling point here is the distribution volume of the chelating agent. A frequent assumption in modelling of decorporation therapy is that DTPA is distributed in the extracellular fluid space [33]. An intracellular decorporation [34], induced by the tiny fraction of DTPA which is said to enter cells, is an alternative approach. This explains a delayed chelation of new actinide deposits and assuming that chelation occurs only in extracellular compartments, liver and at the site of conatmination, a similar modelling approach could describe several cases of Pu/Am inhalation after repeated DTPA treatment [35].

Even if the different parts of compartmental models, which are affected, are identified, the question of the kinetics of the decorporation process remains open. The biokinetics of DTPA in the body are very fast processes, compared to the ones driving Plutonium biokinetics. Within the first day after injection more than 99 % of the DTPA is excreted from the body [33]. The enhancement of urinary excretion of Plutonium can be observed for longer times. The molecular excess of DTPA compared to the Actinide (usually millimoles of DTPA and pico- or nanomoles of the Actinide are inside the body) might help explaining this.

The in-vivo formation of the Actinide-DTPA complexes is one of the processes, which needs to be depicted in the model. The chemistry of this reaction has been studied in vitro [15, 20] and stability constants of the complexes were derived. In vivo several competitors for the reactants need to be considered in the modelling. DTPA is not selectively binding the actinides, but chelates any available metal, while the actinides in the body will bind to bioligands (such as Transferrin). For example, the speciation of plutonium inside the body needs to be considered explicitly. In animal experiments often Citrates were used. This might not be representative for other forms of the Actinides (such as Nitrates), because Citrate is one of the bioligands “competing” for the Actinide in blood. The whole complex biochemical environment and its influences on the chelation need to be understood for deriving a complete, generic model of decorporation therapy. A similar issue is the differences between the two forms of DTPA (Zn- and Ca-) for the in-vivo chelation reaction.

Any model will be used for an estimation of the doses. Obviously any changes in the model will be reflected in the doses. The simple empirical models are only able to calculate the amount of intake removed by the therapy (often in terms of a reduced “apparent intake”); doses are then estimated by applying the dose coefficients calculated with the undisturbed reference models. This insinuates that the distribution pattern of the actinide under therapy does not differ from the undisturbed one. Animal experiments show varying efficacies for different organs [15]. From a scientific point of view it is preferable to have a compartmental model which describes the processes in a mechanistic way. The

structure of undisturbed biokinetics needs to be described, as well as the changes in the model (in structure and in parameter values) caused by the injection of DTPA. This will facilitate a more accurate estimation of the doses by calculating “correct” retention and excretion functions.

### Conclusion and outlook

Even after more than 50 years of using DTPA decorporation therapy no generic model exists, which can describe the biokinetics of the radionuclides before, during and after therapy and thus be used for an accurate dose assessment. Only case specific models and empirical descriptions are available. Several hypothesis and approaches in modeling are currently followed. One of the many problems for the understanding and modeling of DTPA decorporation therapy are the still unknown sites of chelation, i.e. which parts of the biokinetic system the actinide is removed from and with which efficacy. Another puzzling point is the identification of the bio-ligands and other molecules competing for the DTPA or the actinide and their influence on the therapy. The complex biochemical environment needs to be understood to model the in-vivo chelation. The database for the modeling still needs to be widened by targeted experiments to answer such more specific questions.

The only human data available under therapy are excretion data, which represent the output of the system under study. Parts of the system itself cannot be observed in-vivo since external counting is not possible for most actinides. The one exception is Am-241 which emits 60 keV photons, being able to penetrate the body. If this data is available still the observed “organ” needs to be assigned to one or more of the compartments of the model. The monitoring data could give guidance for the modelling process. However, one has to take into account the difficulties assigned with external organ counting (in radiation protection use), which will make the interpretation even more complicated. Autopsy data such as the ones used by James et al. [31] are the only source of human information for studying the changes in distribution of plutonium under therapy. Unfortunately these data are seldom available and they only represent the net outcome of the whole therapy and will not help to understand changes of decorporation efficacy with time as reported by some authors [36].

In order to derive a model that is not a purely mathematical fit of the observed data, the interpretations of urinary excretion and autopsy data need to be made very carefully and always based on knowledge and understanding of the physiological resp. biochemical processes.

Having a (generic) model describing the effects of DTPA on the biokinetics of plutonium and other transuranium elements would help optimizing the treatment strategy and thus maximize the dose averted and minimize the health effects of the incorporation. This may become an important point even beyond the radiation protection of workers in the nuclear industry with reference to mass casualty scenarios with malevolent internal contamination the non-exposed population with actinides.

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