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TECHNICAL REPORT

Cesium-137 Decorporation Model

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CONVERSION TABLE

Conversion factors for U.S. customary to metric (SI units of measurement)

MULTIPLY TO GET	BY BY	TO GET DIVIDE
angstrom	1.000 000 x E-10	meters (m)
atmosphere	1.012 25 x E +2	kilo pascal (kPa)
bar	1.000 000 x E + 2	kilo pascal (kPa)
barn	1.000 x E – 28	meter ² (m ²)
British thermal unit (thermochemical)	1.054 350 x E + 3	joule (J)
calorie (thermochemical)	4.184 000	joule (J)
cal (thermochemical)/cm ²	4.184 000 x E-2	mega joule/m ² (MJ/m ²)
curie	3.7000 000 x E + 1	giga becquerel (GBq)*
degree (angle)	1.745 329 x E – 2	radian (rad)
degree (Fahrenheit)	Tk = (t +459.69)/1.8	degree kelvin (K)
electron volt	1.602 19 x E – 19	joule (J)
erg	1.000 000 x E – 7	joule (J)
erg/sec	1.000 000 x E – 7	watt (W)
foot	3.048 000 x X-1	meter (m)
foot-pound-force	1.355 818	joule (J)
gallon (U.S. liquid)	3.785 412 x E – 3	meter ³ (m ³)
inch	2.540 000 x E -2	meter (m)
jerk	1.000 000 x E + 9	joule (J)
joule/kilogram (J/kg) (absorbed dose)	1.000 000	Gray (Gy)**
kilotons	4.183	terajoules
kip (1000 lbf)	4.448 222 x E + 3	newton (N)
kip/inch ² (ksi)	6.894 757 x E +3	kilo pascal (kPa)
ktap	1.000 000 x E +2	newton-second/m ² (N-s/m ²)
micron	1.000 000 x E – 6	meter (m)
mil	2.540 000 x E – 5	meter (m)
mile (international)	1.609 344 x E + 3	meter (m)
ounce	2.834 952 x E – 2	kilogram (kg)
pound-force (lbf avoirdupois)	4.448 222	newton (N)
pound-force inch	1.129 848 x E – 1	newton-meter (N*m)
pound-force/inch	1.751 268 x E + 2	newton-meter (N/m)
pound-force/foot ²	4.788 026 x E – 2	kilo pascal (kPa)
pound-force/inch ² (psi)	6.894 757	kilo pascal (kPa)
pound-mass-foot ² (moment of inertia)	4.214 011 x E – 2	kilogram-meter ² (kg*m ²)
pound-mass/foot ³	1.601 846 x E + 1	kilogram/m ³ (kg/m ³)
rad (radiation absorbed dose)	1.000 000 x E – 2	Gray (Gy) **
rem (roentgen equivalent man)		Sievert (Sv) ***
roentgen	2.579 760 x E – 4	coulomb/kilogram (C/kg)
shake	1.000 000 x E – 8	second (s)
Slug	1.459 390 x E + 1	kilogram (kg)
Torr (mm Hg, 0 degrees C)	1 333 22 x E – 1	kilo pascal (kPa)

* The Becquerel (Bq) is the SI unit of radioactivity: 1 Bq = 1 event/s.

** The Gray (Gy) is the SI unit of absorbed radiation.

*** The Sievert (Sv) is the SI unit of dose equivalent.

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Preface

The research and development work, described in this report was conducted under subcontract for Gryphon Scientific, LLC for the Joint Science and Technology Office (JSTO) of the Department of Defense (DoD) Chemical and Biological Defense (CBD) Program. JSTO is also the Chemical/Biological Technologies (CB) Directorate in the Research and Development (RD) Enterprise of the Defense Threat Reduction Agency (DTRA). Contract HDTRA1-10-C-0025 is titled *Medical Countermeasures for CBR Agents*.

This project was initiated by Ms. Nancy Nurthen, of the Information Systems Capability Development Division (J9-CB) and continued by Dr. Christopher Kiley. It was funded under DTRA Contract Number HDTRA1-10-C-0025 to Gryphon Scientific, LLC, with subcontractor Applied Research Associates, Inc. (ARA). The target application for the product of this contract is under the auspices of the Joint Project Manager for Information Systems (JPM IS) of the Joint Program Executive Office for Chemical and Biological Defense (JPEO-CBD).

Section 1.

Executive Summary

A model for Prussian Blue treatment of internal cesium-137 (Cs-137) contamination was developed to predict the efficacy of various treatment regimens. The baseline uptake and decorporation model was developed by implementing an inhalation exposure model and a physiologically-based biokinetic model for cesium distribution. A treatment model for Prussian Blue decorporation of Cs was developed, along with a radiation dosimetry model for calculating doses; these models were integrated with the baseline model. The composite Cs decorporation model presented in this work estimates cesium absorption, distribution, retention, excretion, and response to Prussian Blue treatment in adult healthy males after an inhalation (or ingestion) exposure. The model further estimates the acute red bone marrow dose and the whole body effective dose as a function of time. The results of the model compare favorably with human data and provide estimates within the uncertainty limits of alternative models developed by the International Commission on Radiological Protection (ICRP) and the National Council on Radiation Protection and Measurements (NCRP). Calculations from the model may be used to analyze consequences of exposure to Cs-137 and the effect of treatment, based on different initiation and duration times. The model may facilitate interpretation of Cs-137 bioassay data and aid in treatment planning. The Cs decorporation model is a valuable tool for assessing the effects of exposure to Cs-137 and subsequent Prussian Blue treatment.

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Section 2.

Introduction and Purpose

Accurate modeling of medical countermeasure efficacy against chemical, biological and radiological agents (CBR agents) is essential to understanding the vulnerability of our warfighters on the modern battlefield. In helping to calculate the benefit of countermeasures, modeling can inform data-driven purchasing decisions and logistical tradeoffs. In this study, Gryphon Scientific and Applied Research Associates, Inc. (ARA) have developed models to predict the efficacy of medical countermeasures in preventing casualties and reducing the severity and duration of illness caused by CBR agents.

This report (prepared by ARA) is one of five, describing the medical countermeasure models constructed for this project. This volume focuses exclusively on the modeling approach, parameters, and calculations used for the medical countermeasure model (MCM) for cesium-137 (Cs-137) exposure. The composite model includes the appropriate parameters necessary for calculating the impact of Prussian Blue (PB) countermeasure treatment on Cs-137 exposure.

This paper presents an inhalation exposure model for calculating the absorbed fraction of cesium-137 from a given air concentration. The paper also presents a biokinetic model for calculating the distribution of cesium-137 within the body, a Prussian Blue model for binding and removal of cesium-137 circulating through the gastrointestinal tract, and a radiation dose model for calculating the absorbed radiation dose in the whole body and to the critical organ, the red bone marrow. Each model approach is described and justified along with the assumptions and key parameters that are implemented in each model. The composite model connects each set of calculations and is collectively used to calculate the committed radiation dose, which can be related to potential adverse health effects. The radiation dose with and without PB treatment can be calculated and compared to determine efficacy of treatment. Different treatment initiation times and treatment duration times can be evaluated to determine the impact of different treatment scenarios on radiation dose.

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Section 3.

Background and Methodology

3.1 Importance of Cesium-137

Because of its long half-life (30.2 years) and penetrating photon emission, cesium-137 is commonly used in irradiators for blood irradiation or for use in research. Irradiators using Cs sources are common in hospitals, blood banks, universities and other research facilities that often have minimal security. According to a National Research Council (NRC 2008) committee, the U.S. inventory of Cs-137 included approximately 2.8 million Curies. The most common form of cesium used for radiation sources is a pressed powder of cesium chloride (CsCl). Since the powder is easily dispersible and highly soluble, inhalation and biological absorption of CsCl could easily result in significant internalization of the radionuclide, if an exposure occurred. CsCl is also available in fairly high specific activity and includes a β -emission whose energy is readily absorbed in the body. Collectively, these attributes led the NRC committee to rank Cs-137 as one of the highest security risks for the U.S. (2008).

3.2 Cesium-137 Decorporation

The pharmaceutical countermeasure Prussian Blue (PB, Radiogardase®) is the only FDA-approved decorporation agent for cesium-137. Prussian Blue capsules contain insoluble ferris hexacyanoferrate (II) crystalline powder that is not absorbed or digested. The drug's clearance from the body is dependent on gastrointestinal (GI) transit time. The mode of action of PB is through high affinity binding of cesium that is circulating through the GI tract via ion exchange, absorption, and mechanical trapping in the crystal lattice. The cesium bound by PB is prevented from further recirculation and excreted through the GI tract. The recommended dosing regimen is three grams of Prussian blue administered three times a day.

Human and animal data indicate that PB effectively increases the rate of elimination of cesium-137, which then reduces the radiation dose absorbed by the body. While PB reduces the absorbed radiation dose, it does not treat the effects of radiation dose, such as hematopoietic cell damage and loss. The benefit of PB treatment is dependent on the total Cs-137 absorbed into the body, the time of PB administration, and the duration of treatment. The parameters necessary for calculating the effect of PB countermeasure treatment of cesium-137 exposure is further described in the following sections.

A block diagram of the composite modeling is outlined in Figure 1. The first input into the model is from the exposure scenario providing either the radioactivity air-concentration of Cs-137 or a mass air-concentration with an appropriate specific activity conversion. The model can accommodate the air concentration input parameter with specific particle sizes or a particle size distribution. The fraction of the air concentration that is inhaled is calculated based on the particle size, the ambient air speed, and the breathing rate. Next, the model calculates the fraction of inhaled material that is deposited in the respiratory tract. The model assumes that the Cs deposited in the respiratory tract is rapidly transferred to the blood stream. A biokinetic model then determines the systemic distribution of cesium is distributed throughout the body based on a blood flow and tissue-specific retention. This allows for steady-state equilibrium of Cs to be

quickly reached. The countermeasure treatment model calculates cesium extraction from the small intestine as each dose of Prussian Blue is administered. The biokinetic model redistributes the remaining Cs throughout the body accordingly and provides adjusted tissue concentrations. The radiation dosimetry model calculates the red bone marrow dose and the effective whole body-dose. Calculations are based on the quantity of Cs distributed to each tissue and retained in each specific organ over a given time period.

The following sections provide specific details on the inhalation exposure model, the cesium biokinetic model, the Prussian Blue treatment model, and the radiation dose models included in the composite Cs-137 decorporation model.

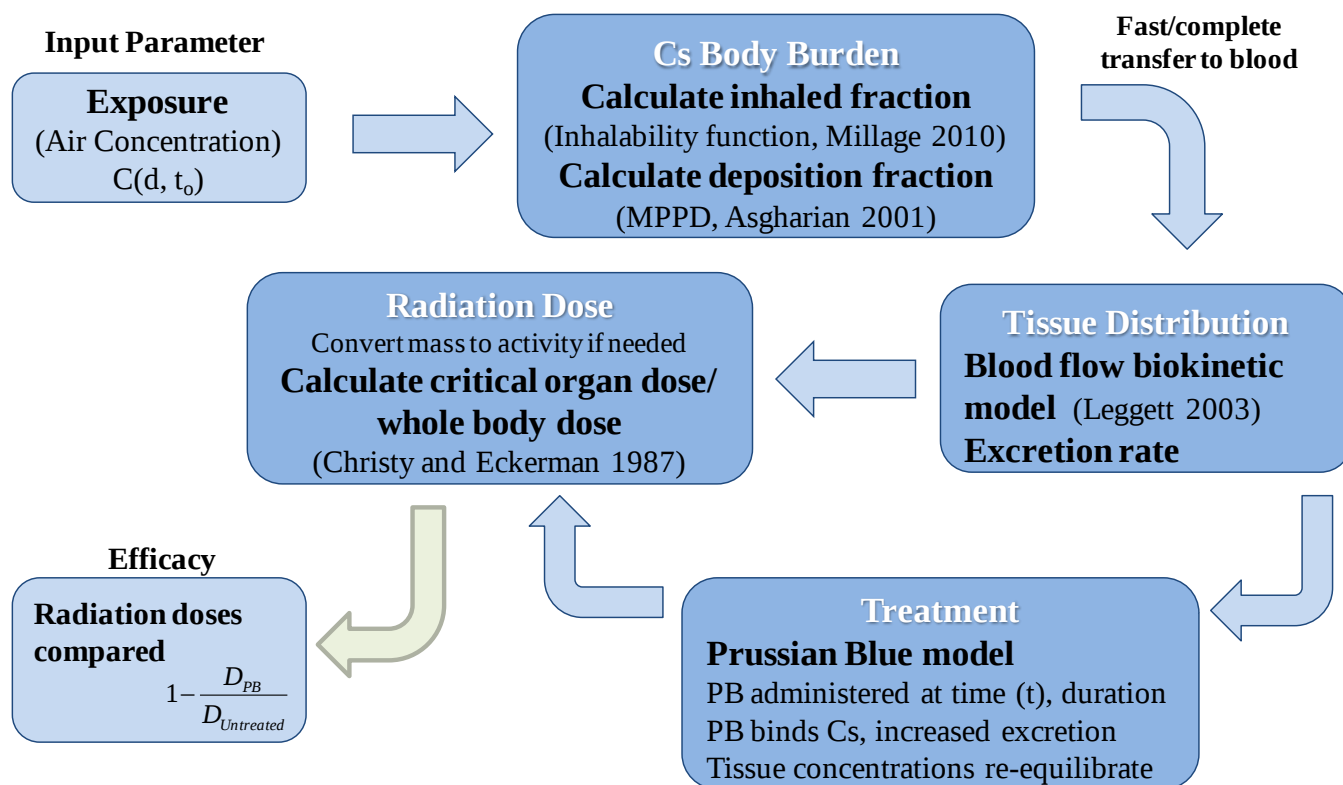


Figure 1. Composite Cs-137 Decorporation Model Components

Section 4.

Cesium-137 Decorporation Model

4.1 General Assumptions

4.1.1. Physical and Chemical Form

Mono-dispersed particle sizes, ranging from 1 – 100 μm , can be modeled. Particles in this range generally deposit in different areas of the respiratory tract; larger particles will preferentially deposit in the upper respiratory tract and extrathoracic region, while small particles can reach the lower respiratory tract and pulmonary regions. These parameters are estimated using the respiratory model described below. This approach will allow us to examine the influence of particle size on deposition and dose.

Because of cesium chloride's (CsCl) is most commonly used in industrial radiation sources, and is easily dispersed, highly soluble, and ranked as a high priority national security risk (NRC 2008), it was chosen as the chemical form of cesium to be used in this modeling effort. Since CsCl is relatively soluble, rapid and nearly complete absorption from both the respiratory and gastrointestinal tracts is observed.

4.1.2. Inhalation Exposure

One of the most likely exposure battlefield scenarios for Cs-137 is use of a radiological dispersal device (RDD), in which case inhalation will be the predominate route of exposure. Therefore, the model assumes aerosolized particulate exposure. The exposure will result in an inhaled fraction and small ingested fraction; however both fractions are readily absorbed. Hence, for the RDD scenario, the deposition of Cs-137 is assumed to be only in the respiratory tract (modeled as the lung in the model) where fast and complete absorption occurs. For radionuclides that are not readily absorbed, more detailed evaluation of the deposition fractions is required. This is due to particle size and deposition location significantly impacting the absorption of less soluble radionuclide substances.

4.1.3. Ingestion Exposure

Given the RDD scenario, ingestion is not considered a stand-alone route of exposure. Other scenarios may exist in which a significant amount of radioactive cesium is ingested. The decorporation model may be adjusted to accommodate an ingestion scenario. This is accomplished by inputting the dose ingested. For the case of ingestion, the entire dose can be assumed to be from ingestion with the fast and complete absorption occurring from the stomach.

4.2 Inhalation Exposure Model

The cesium body-burden after an exposure to a given air concentration is calculated by considering the inhaled fraction of that exposure and the amount of the inhaled fraction that is deposited into the different regions of the respiratory tract. Both of these parameters are dependent on particle size distribution and can provide a more accurate representation of the

amount of cesium retained from the exposure. An overview of the inhalation model used to calculate the cesium body-burden is provided in Figure 2.

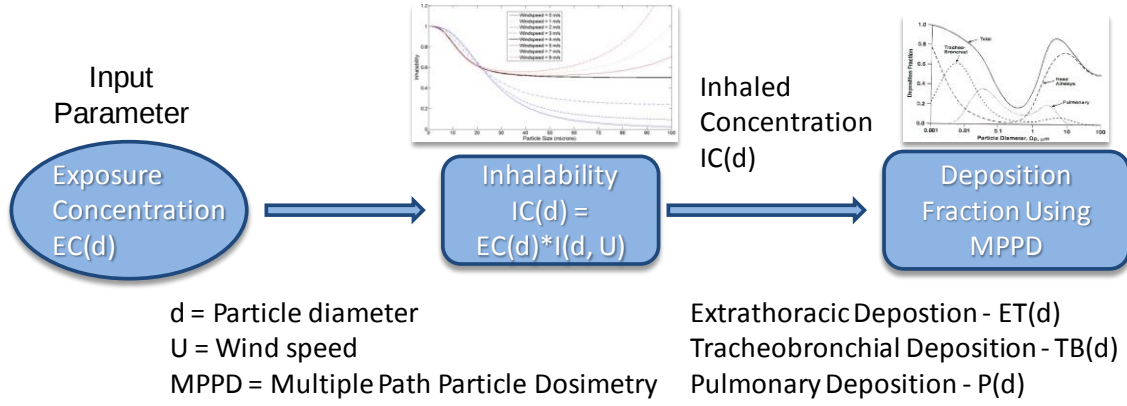


Figure 2. Inhalation Model

4.2.1. Inhaled Fraction

The inhaled fraction, $I(d_{ae})$, is determined by the particle size and air concentration:

$I(d_{ae}) = C_{inspired}(d_{ae}) / C_{ambient}(d_{ae})$ where $I(d_{ae})$ is the inhaled fraction by aerodynamic particle size (d_{ae}) and C is the particle concentration.

Inhalability is a measure of the air concentration of material that is inhaled, relative to the concentration in the ambient air; inhalability only refers to the intake process and does not account for deposition. A recent review examined the data from inhalability measurements and current mathematical models of inhalability (Millage 2010). Based on this review, the proposed mathematical model provides the best description of the data across a variety of conditions, while minimizing mathematical inconsistencies. The inhalability model is a function of both particle size (d_{ae}) and ambient wind speed (U) (wind speed can play a significant role in how much particulate material can be inhaled). The equation also takes into account the fraction of inhalation that is nasal (f_N) or oral (f_O). The nasal versus oral fraction can depend on breathing rate; most people breathe 100% through their nose until their breathing rate reaches 35 liters per minute and then they begin breathing through their mouth, as well.

Three equations are used to create a piecewise continuous model of inhalability to include the effects of wind speed, particle size and breathing function; each equation describes different wind speed regimes. The first equation is for still air, i.e. wind speed is zero.

$$I_{Still}(d_{ae}) = f_N \left[1 - \left(\frac{1}{1 + 6.809 \cdot 10^3 d_{ae}^{-2.736}} \right) \right] + f_O \left[\frac{1 + 0.44}{1 + 0.44 \exp(0.0195 d_{ae})} \right]$$

The next equation is for winds speeds (U) greater than zero, but less than or equal to 4 meters per second (m/s).

$$I_{0 < U \leq 4 \text{ m/s}} = (1 - J) \left\{ f_N \left[1 - (1 + \exp(8.826 - 2.736 \ln d_{ae}))^{-1} \right] + f_O \left[\frac{1.44}{1 + 0.44 \exp(0.0195 d_{ae})} \right] \right\} \\ + J \left\{ 1 - 0.5 \left[1 - (7.6 \times 10^{-4} (d_{ae})^{2.8} + 1)^{-1} \right] + 1 \times 10^{-5} U^{2.75} \exp(0.055 d_{ae}) \right\}$$

$$J = \frac{U^{2.75}}{4^{2.75}}$$

where:

The final equation is for wind speeds greater than 4 m/s and less 10 m/s.

$$I_{4 < U \leq 10 \text{ m/s}}(d_{ae}) = 1 - 0.5 \left[1 - \frac{1}{7.6 \times 10^{-4} (d_{ae})^{2.8} + 1} \right] + 10^{-5} U^{2.75} \exp(0.055 \cdot d_{ae})$$

Note that these equations are not applicable for particle sizes greater than 100 microns in aerodynamic diameter. Often particles larger than a few microns are ignored because the general thought is that they will not be inhaled; however, larger particles can be inhaled and while they may not reach the pulmonary region, they can deposit in the extrathoracic region and be absorbed into the bloodstream. As an example, based on the equation shown above, in a moderate wind environment of 4 meters per second approximately 60% of 22 micron particles will be inhaled.

4.2.2. Inhaled Concentration

The inhaled concentration, $IC(d)$, is the ambient or presented concentration of radioactive particulate in the air multiplied by the inhalability function:

$$IC(d) = EC(d) \cdot I(d, U),$$

where EC is the exposure concentration by particle size diameter, d , and I is the inhalability function in terms of particle size diameter, and wind speed, U . The resultant inhaled value is the radioactive material concentration that actually enters the nasal or oral cavities; it does not take into account the fraction of the material that is deposited in the respiratory tract.

4.2.3. Wind Speed

If wind speed conditions are known, the model will allow a user-specified value; otherwise a default ambient air speed value of 4 m/s will be used.

4.2.4. Deposition Fraction

The deposition fraction is the fraction of inhaled radioactive material that is deposited in the respiratory tract. The Multiple-Path Particle Dosimetry (MPPD) model is a widely-used, fast-running, GUI-driven, Java-based set of algorithms that can calculate the deposition and retention of both mono-dispersed and poly-dispersed particulates and aerosol droplets in human respiratory tracts (Asgharian 2006a, Asgharian 2006b, Asgharian 2006c). The human respiratory model includes both single-path, symmetrical calculations as well as several multi-path variations of limited-asymmetric, asymmetric and stochastic models. The limited-asymmetric model uses a 5-lobed model with subsequent symmetric airways. An age-dependent set of lung morphologies is also available. The model can calculate deposition in three regions, extrathoracic (ET), tracheobronchial (TB) and pulmonary (P), or by specific airway generation, shown in Figure 3. The solubility of Cs-137 accounts for deposition in these three regions that adequately correlates with the available human response data. However, as we further develop models for other isotopes, such as materials that are insoluble, it will be more important to have a more detailed assessment of deposition location. Since MPPD does not rely entirely on a simple, symmetrical model, such as that used in the International Commission on Radiological Protection (ICRP) Publication 66 (1994), the model can account for specific lobal deposition in the asymmetric model as well as generation-by-generation deposition throughout the respiratory tract. Results of the deposition and retention calculations using MPPD have been favorably compared with experimental data from both rats and humans (Raabe 1976, Heyder 1986). Results were published that indicate the asymmetrical model used in the MPPD is effective at modeling clearance (Asgharian 2001). In addition, MPPD includes a set of stochastically generated lung models that can be used to provide an estimate of the uncertainty associated with respiratory tract deposition.

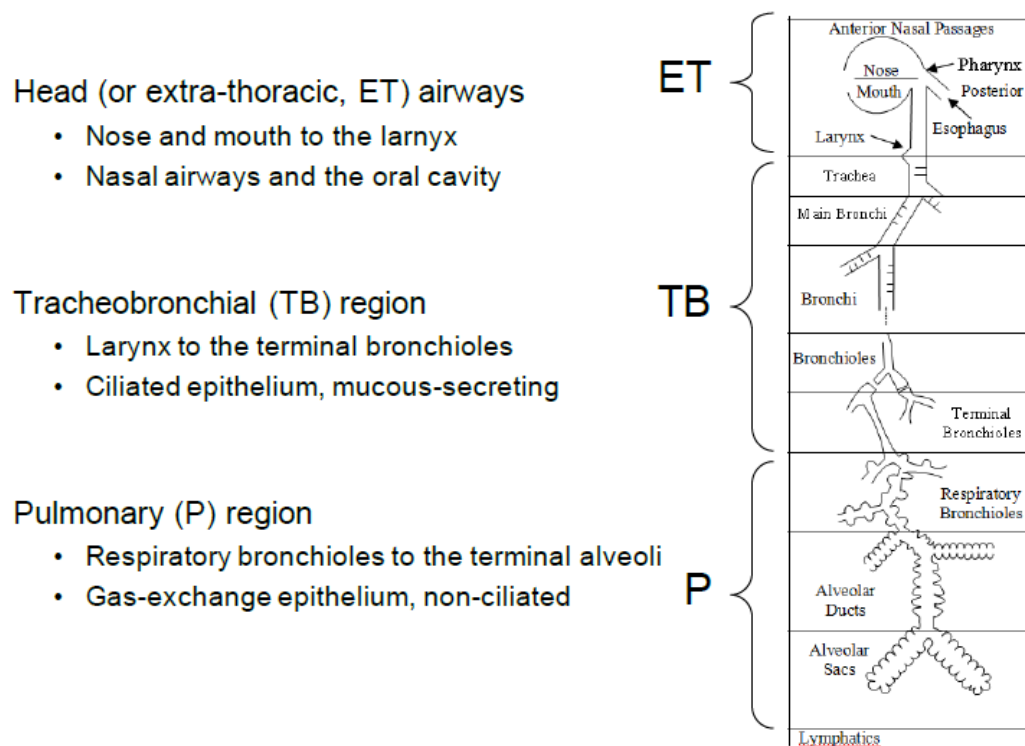


Figure 3. The Three Functional Regions of the Respiratory Tract (Asgharian 2006a)

As an example, we noted earlier that in an area with an ambient wind of 4 m/s, approximately 60% of particles of 22 microns would be inhaled. Using MPPD, we calculated that of the particles inhaled, approximately 94% would deposit in the ET region, 5.4% would deposit in the TB region and 0.0002% would deposit in the pulmonary region, and the remaining 0.3% exhaled.

4.2.5. Absorption

Absorption from both the respiratory and gastrointestinal tracts is assumed to be relatively fast and complete (100%), due to the high solubility of cesium chloride (NCRP 2009). CsCl is considered a category F material by ICRP (1994), which exhibits fast absorption of 100% absorption within one day.

4.3 Cesium Biokinetic Model

The distribution of cesium throughout the body's tissues is calculated according to a cesium-specific biokinetic model developed by Leggett et al. (2003) shown in Figure 4. This model is based on blood flow and tissue kinetics described by the parameters listed below. The physiologically-based model developed by Leggett was chosen because it is the most detailed model available for cesium and is an improvement over the ICRP model (1989), which only accounts for two compartments. The physiologically-based model allows more detailed and accurate dosimetry calculations for the whole body and enables the calculation of doses to specific tissues. Specific tissue doses are critical in determining acute effects from radiation for which dose to critical organs must be examined. Detailed tissue transport data obtained from the biokinetic model also enable the calculation of the amount of cesium available for removal by Prussian Blue treatment.

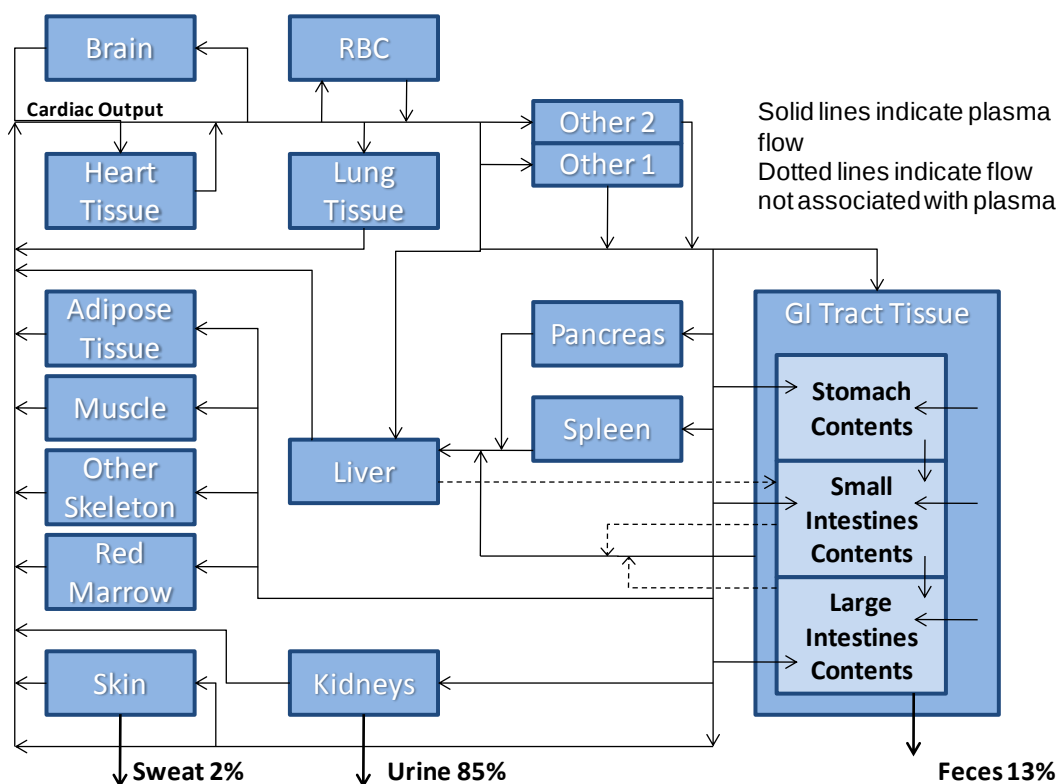


Figure 4. Cesium Biokinetic Distribution Model (Leggett 2003)

The rate of transfer of Cs from plasma into a tissue is calculated from the blood flow rate to that tissue (BF), a tissue and element-specific extraction fraction (E_{T-Cs}), and cardiac output (CO).

4.3.1. Blood Flow Rates

Reference values for standard cardiac output (6500 mL/min, or 1766 plasma volumes/day) and blood volume (5300 mL), according to ICRP Publication 89 (2002), were used in developing compartmental blood flow rates (Table 1). Leggett and Williams developed values for regional blood volumes and the distribution of cardiac output to support revision of the Reference Man model (ICRP 2002), based on additional analysis of blood flow data (Leggett 1995).

Table 1. Tissue Blood Flow (Leggett 2003)

Compartment	Blood Flow: Fraction of CO
Adipose tissue	0.05
Brain	0.12
GI tract tissues	0.15
Heart	0.04
Kidneys	0.19

Liver – arterial	0.065
Liver – portal	0.19
Lungs	0.025
Skeletal muscle	0.17
Red marrow	0.03
Bone and other tissue	0.02
Skin	0.05
Spleen	0.03
Pancreas	0.01
Other	0.05

The Cs biokinetic model allows incomplete, tissue-dependent extraction of material during passage through the circulation and return of material from tissues to plasma. The model performs this function by accounting for the blood flow rate to different tissues, tissue-specific extraction fractions, and transfer coefficients.

4.3.2. Tissue-Specific Extraction Fractions

The tissue-specific extraction fraction is the fraction of cesium extracted by the tissue in passage from the arterial to venous plasma. The Cs biokinetic model estimated values, shown in Table 2, based on extensive review of human and animal autopsy data, *in vitro* experiments simulating Cs transport through potassium channels, and *in vitro* tissue selectivity experiments (Leggett 1995, 2003). The parameters estimated by Leggett provide accurate model outputs, as tested against case study data.

Table 2. Cs Tissue-Specific Extraction Fractions (Leggett 2003)

Tissues	Extraction Fraction
Kidneys, GI tract, heart	0.2
Liver, skin	0.05
Brain	0.002
All other tissues	0.1

The Cs tissue-specific extraction values in Table 2 are used to calculate the fraction of cesium transferred into a tissue. Subsequent calculations are made for the fraction of Cs that can transfer back out of the tissue. The extraction fraction is used to calculate transfer coefficients.

4.3.3. Transfer Coefficients

The transfer coefficients, *TC*, for the flow of cesium from plasma to tissue and the return, are mathematically derived from the fractional blood flow, cardiac output, and the tissue-specific extraction fractions described in the following equations:

Plasma to tissue: $TC_{P-T} = E_T \cdot BF_T \cdot CO$

Tissue to plasma: $TC_{T-P} = CsF_P \cdot TC_{P-T} / CsF_T$

where E is the extraction fraction, BF is blood flow, CO is cardiac output, TC is transfer coefficient, CsF is the cesium fraction at equilibrium, and subscripts T and P are tissue and plasma, respectively.

4.3.4. Untreated Excretion Rates

The biokinetic model provides excretion rates for urine, feces, and sweat. The model yields excretion rates in terms of plasma volume, per day, as follows:

Day 1:+	3.9 plasma volumes/day
Day 2:+	3.5 plasma volumes/day
Day 3+:	3.3 plasma volumes/day

The urinary fraction of excreted cesium predicted by the model is approximately 0.86 at equilibrium.

4.4 Prussian Blue Treatment Model

Prussian Blue (PB) is not absorbed from the gastrointestinal tract into the blood stream. Based on animal studies, 99% of the ingested compound is excreted, unchanged in the feces (HelTex pharmaceutical insert). PB simply passes through the gastrointestinal (GI) tract where it may bind with cesium as shown in Figure 5. PB treatment or decorporation of Cs can easily be modeled by following its transit through the GI tract. The treatment model is linked with the cesium biokinetic model to correlate cesium concentration in the small intestines over the time period for which PB passes through the small intestines. The Cs is bound by PB and removed through the GI tract, and the biokinetic model allows for re-equilibration of Cs throughout the body. One key component of the treatment model is the enterohepatic circulation of cesium between the liver and the GI tract and the movement of Prussian Blue through the GI tract, which determines the amount of Cs that can be removed. The time of PB administration and the duration of treatment play a critical role in the efficacy of PB treatment, as illustrated by the composite model in the next section.

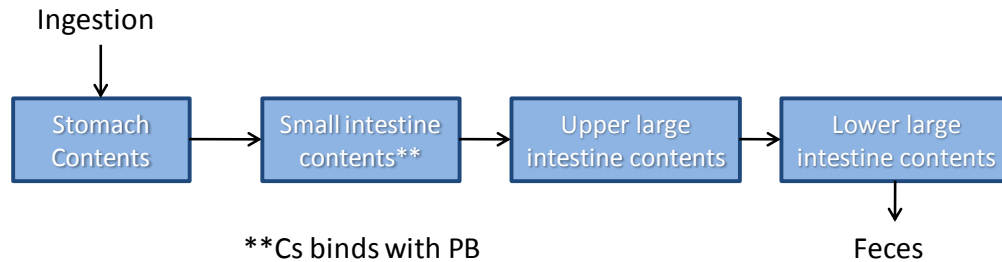


Figure 5. GI Tract Model for Prussian Blue Treatment

4.4.1. Route of Administration

The only effective route of administration for Prussian Blue is oral administration (HelTex, FDA). Treatment administration is a fixed parameter in the model.

4.4.2. Formulation, Dose, and Time Course

The formulation of PB is insoluble crystals contained in 500 mg capsules with an enteric coating, which are taken orally. This is a standard formulation, which is treated as a fixed parameter in the treatment model.

The recommended dose for Prussian Blue is 3 grams, three times per day. PB treatment of cesium internal contamination is based on the dosage, such that it is in vast excess compared to the cesium present in the GI tract. In most documented cases, different treatment regimens (1-3 grams, 3 to 4 times per day) were not found to affect the retention of Cs in persons during periods of continuous treatment (Madshus 1966, 1968, Ye 1981, Ma 1983, Tang 1988, Farina 1991, Lipsztein 1991, Melo 1994). The data suggests that multiple doses of at least 1 gram of PB per day results in complete removal of cesium entering the GI tract. Actual PB dosing could vary, depending on available resources. The treatment model was designed to optimally calculate Cs retention, excretion, etc. based on 3 grams of Prussian Blue administered 3 times per day. However, lower PB doses of 1 gram, 3 times per day may be used with the model reliably. Evidence shows that as little as 1 gram three times a day is as equally effective (Farina 1991, Lipsztein 1991, Melo 1994). There was insufficient data to model the response of Prussian Blue treatment on Cs retention at suboptimal dosing regimens (i.e. less than 1 gram PB, three times per day).

The duration of treatment, in days, is an input variable for the treatment model. The effect of treatment duration can be examined with the model, with longer treatment courses having a greater impact on total radiation dose.

4.4.3. Time from Exposure to Treatment

The time from exposure to initiation of treatment is an input variable parameter in the model. Using the Cs biokinetic model enables the dose calculation to be made as a function of Cs concentration in the body integrated over time. When PB treatment begins, cesium concentration is reduced and fast re-equilibration is assumed. Since radiation dose is calculated based on the Cs concentration over time, it can be seamlessly calculated in the model, regardless of PB treatment start time or duration. The impact of time from exposure to initiation of treatment can be examined with the model. The greatest impact on dose reduction is observed when treatment begins soon after exposure.

4.4.4. Gastrointestinal Tract Transit Times

PB is not absorbed from the gastrointestinal (GI) tract into the blood stream, but simply moves through the GI tract and is not metabolized. Animal studies indicate 99% of the ingested compound is excreted, unchanged in the feces; therefore, PB simply passes through the gastrointestinal (GI) tract where it may bind cesium. The movement of PB is modeled as a function of its transit time through the GI tract. Reference values developed by the ICRP (2006) for the transit times of the different parts of the GI tract are listed in Table 3. The values chosen by ICRP were based on an extensive review of the literature and were developed specifically for

application in internal nuclide contamination. The alimentary tract model has undergone extensive critical review and the reliability of this model has also been evaluated and reviewed (Leggett 2007).

Table 3. Gastrointestinal Tract Transit Times (ICRP 2006)

Compartment	Transit Times	
	Male	Female
Mouth	15 sec	15 sec
Esophagus	45 sec	45 sec
Stomach	75 min	105 min
Small Intestines	4 hr	4 hr
Right colon	12 hr	16 hr
Left Colon	12 hr	16 hr
Rectosigmoid	12 hr	16 hr

The transit times for adult males were examined, since the biokinetic model parameters are based on an adult male. Transit times based on the intake of solid material were considered since PB is administered as solid pills containing the insoluble compound. The actual transit time for any individual is highly variable and depends on a number of other parameters, including consumption of food.

As discussed in the next section, the variability observed in data from humans treated with PB after internal contamination of cesium is extremely large with estimated Cs half-times, ranging from 10 to 70 days during treatment (Madshus 1966, 1968, Ye 1981, Ma 1983, Tang 1988, Farina 1991, Lipsztein 1991, Melo 1994). This variation could not be correlated with any measured biological parameters (age, weight, gender; Lipsztein 1991, Melo 1994). Therefore, we assume that at least a portion of the variability observed is associated with variations in an individual's transit time.

Originally, the transit time for the small intestines alone was examined for incorporation into the treatment model. However, using the 4-hour transit time for the small intestines underestimated PB removal of Cs as compared to the studies referenced above. It is reasonable to assume the half-time of the PB in the stomach (75 minutes) can impact the time PB first begins to be released into the small intestines and its total effective time in the GI tract, during which it binds to Cs. Therefore, the transit time of PB in the gastrointestinal tract was critically examined and optimized, according to the observed human data.

4.4.5. Cesium Decorporation

Using the cesium biokinetic model, the quantity of cesium in the small intestines may be calculated over the period of time that Prussian Blue coincides in that compartment. The quantity of cesium available for binding by Prussian Blue is dependent on the quantity of cesium circulating through the small intestines over the specified time period that the PB passes through

the small intestines. This amount of cesium entering the small intestines is dependent on the relevant cesium transfer coefficients (see Table 4).

Table 4. Flow of Cesium Into the Small Intestines

Source	Substance	Cs Transfer Coefficient (d ⁻¹)
Plasma	Secretions	0.645
Plasma	Pancreatic juices	0.387
Liver	Bile	0.116
GI tract wall	Sloughed cells	0.108
Plasma	Brunner's gland secretions	0.016

For each PB treatment, the amount of cesium entering the small intestines is integrated over the established transit time to determine the total cesium bound by PB. That quantity is deducted from the total body-burden of cesium and the cesium retained in the body is then re-equilibrated according to the biokinetic model.

4.4.6. Optimizing PB Transit Time

Different effective dwell times for Cs in the small intestines were examined in the treatment model. The model, as described above, is constructed such that all Cs entering the small intestines during the transit time of PB is removed. Cs retention under PB treatment (assuming 3 doses per day) was examined starting with the ICRP (2006) transit time for the small intestines, (4 hours) and increasing until PB is continually present in the small intestines, with a dwell time of 8 hours. The scenario examined the relative Cs with treatment at day 15 to allow enough time for the Cs to establish equilibrium before testing the treatment model. Figure 6 shows the comparison of Cs retention with different effective dwell times for PB in the small intestines.

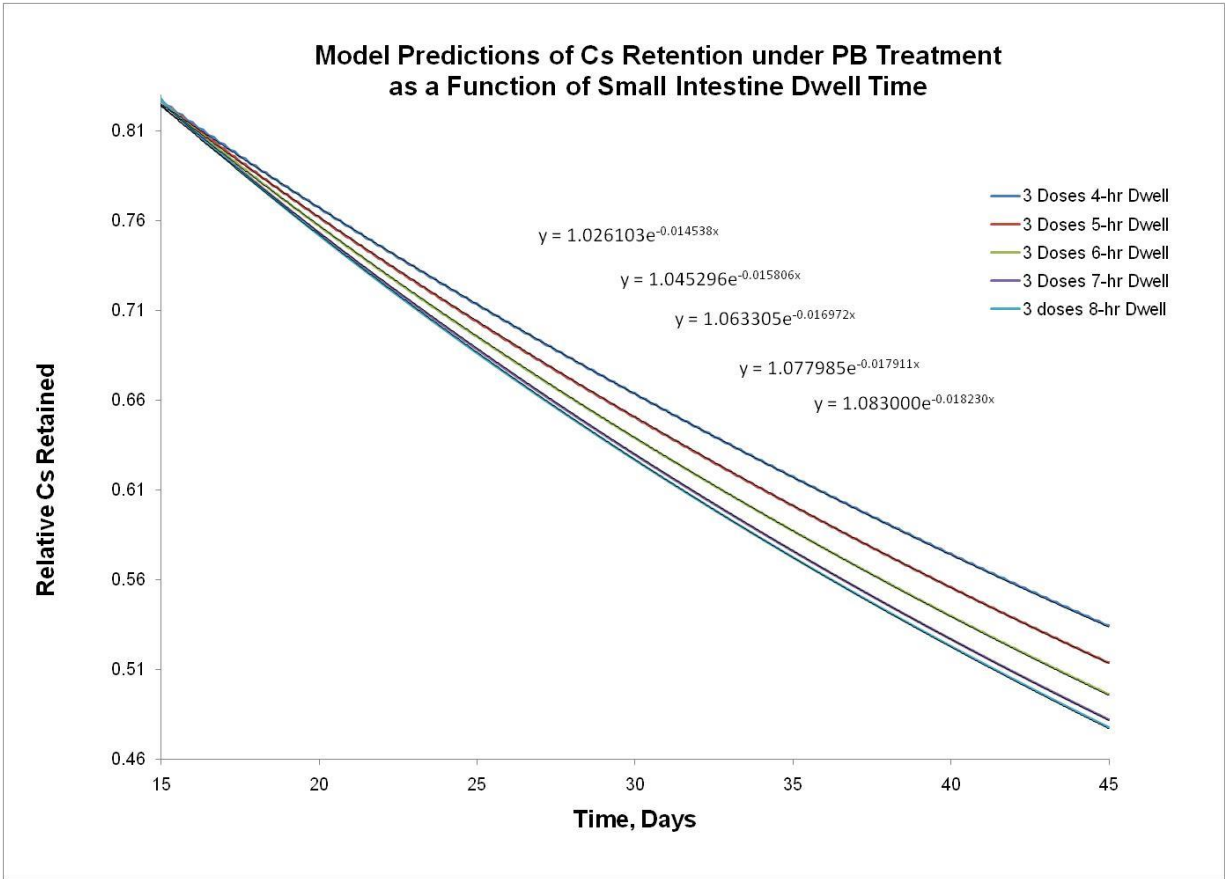


Figure 6. Cs Retention During PB Treatment with Different Dwell Times

The curves were fit to an exponential function and Cs half-times were calculated from the exponential terms. Then, Cs was compared to reported values from the literature, listed in Table 5 (Madshus 1966, 1968, Ye 1981, Ma 1983, Tang 1988, Farina 1991, Lipsztein 1991, Melo 1994).

Table 5. Cs Half-Times During PB Treatment

Cs half-time during PB	Reference	Cs half-time during PB	Reference
40 days	Madshus 1966	47.7 days	Model, 4-hr dwell
31 days	Madshus 1968	43.8 days	Model, 5-hr dwell
70	Ye 1981	40.8 days	Model, 6-hr dwell
16-39	Ma 1983	38.7 days	Model, 7-hr dwell
50 days	Richmond 1983	38.0 days	Model, 8-hr dwell
29-48 days	Tang 1988		
44.4 days	Lipsztein 1991		
10-36 days	Melo 1994		

The half-time of Cs under virtually continuous PB presence in the small intestines (i.e. 3 grams, 3 times per day, assuming a dwell time of 8 hours), according to our model, provides estimates that are within the expected range based on human data. PB treatment of cesium internal contamination is based on the administration of PB, such that it is in vast excess compared to the cesium present in the GI tract. In most cases reported in the literature, different treatment regimens (1-3 grams, 3 to 4 times per day) were not found to affect the retention of Cs in persons during periods of continuous treatment (Madshus 1966, 1968, Ye 1981, Ma 1983, Tang 1988, Farina 1991, Lipsztein 1991, Melo 1994). The data suggests that a treatment of multiple doses of at least 1 gram of PB per day results in the complete removal of cesium entering the GI tract. By extrapolation, estimating the longest possible transit time for PB in the small intestines in our model, 8 hours, allows for complete removal of Cs during regular PB treatment. Therefore, the value for the PB dwell time in the small intestines incorporated in the model is 8 hours. Using these parameters, as shown in Table 5, yields a treated Cs half-time of 38 days.

Cs retention is modeled using the half-time of Cs during Prussian Blue treatment (3 grams, 3 times per day) with the chosen dwell time for the small intestines (8 hours), according to our model. Cs retention was then compared to other half-times reported in the literature (Figure 7). The dotted lines represent the average half-time observed from the specific studies. The shortest and longest half-times observed in any of the studies (10 days and 70 days, respectively) are also included for reference.

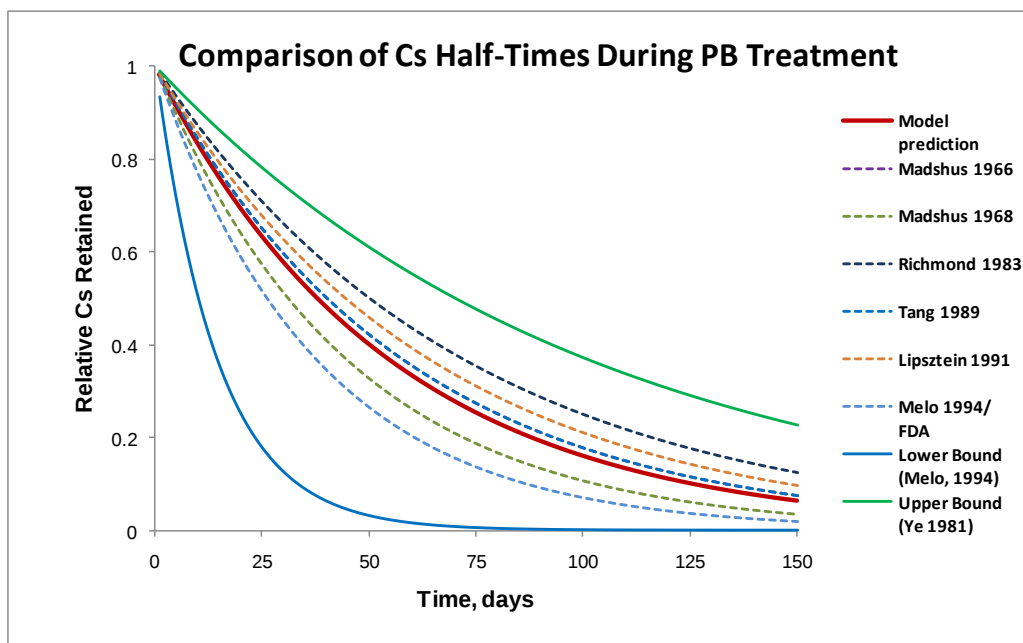


Figure 7. Comparison of Cs Half-Times During PB Treatment According to Human Data and Model Predictions

The parameters chosen for our model provide reliable predictions of the average response to PB treatment. The parameters are based on the cumulative observed data in humans. However, some data indicates that a greater amount of Cs than predicted in our model can be removed upon PB treatment in select individuals (Ma 1983, Tang 1988, Melo 1994). Since our model removes virtually all of the Cs entering the small intestines during treatment, Cs removal beyond this point must be accounted for by individual variation in transfer of Cs to the small intestines. Melo (1994) also postulated that the metabolism of Cs changes during PB treatment resulting in an increased excretion into the small intestines. However, there is not adequate data to determine if either hypothesis is sound.

4.4.7. Toxicity/Side Effects

There is limited data on the side effects of short term use of PB; however, gastrointestinal distress and constipation were reported in some patients. Furthermore, limited data exist on the side effects of extended use of PB. Thus far, extended use can result in hypokalemia, due to binding and removal of potassium (HelTex pharmaceutical insert). A review of animal and human data noted that no significant toxicity was observed in animal and human experimental and therapeutic studies (Pearce 1994). Therefore, for the purposes of this work, toxicity can be considered negligible and side-effects are of limited concern.

4.5 Radiation Dose Model

The radiation dose delivered to the critical target organ (the red bone marrow) for acute effects is calculated based on the cesium burden in each of the tissues and the amount of energy absorbed in the critical target organ from all sources. The method used for this calculation is sometimes referred to as the Medical Internal Radiation Dose (MIRD) method. The method

utilizes tabularized data that are computational estimates of the amount of energy deposited in a specific organ, based on the amount of energy emitted from radioactive material that is located within another organ (Snyder 1978). Due to the complex nature of the human anatomy, these Specific Absorbed Fractions (SAFs) in each of the tissues require detailed radiation transport calculations as described below. The dose to specific target organs requires an integrated calculation, based on the dose rate as a function of time, resulting from the time dependent Cs-137 body-burden. Since Cs-137 emits both a photon and a β -particle (electron), the dose to the bone marrow will include contributions from photons emitted from all organs. Also, Cs within the red bone marrow will further emit photons and β -particles.

In addition to the organ-specific dose calculation, we present a method for approximating the 50-year committee effective dose equivalent (CEDE). The CEDE is the dose calculation that is commonly used for radiation protection associated with internal hazards and it is also the unit upon which most long-term or cancer incident rates are based. Acute dose calculations are generally considered to be associated with the dose accumulated over the first thirty days; the majority of the total dose accumulated will occur during this time period. The body-burden, and the associated dose accumulation rate, will decrease with time as a result of radioactive decay, natural elimination and accelerated elimination resulting from Prussian Blue treatment.

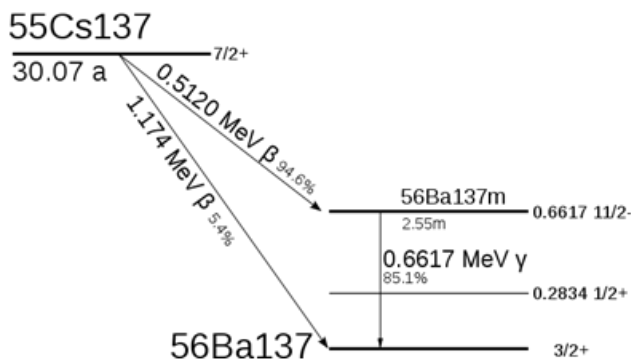


Figure 8. Decay Scheme for Cs-137

4.5.1. Organ-Specific Acute Doses

The decay scheme illustrated in Figure 8 shows all of the decay paths for Cs-137. The predominant mode of decay for Cs-137 is with a 0.521 MeV (peak energy) β -particle emission to meta-stable Ba-137; Ba-137 decays by emitting the 0.662 MeV γ -ray that is commonly associated with Cs-137. Since the Cs will be distributed by the bloodstream to most organs throughout the body, determining how much energy is absorbed by specific organs is complex. The dose delivered to each given organ is a result of energy emitted from all organs, including self-absorption in the same organ. High-fidelity phantoms were created to facilitate calculating these doses and both Monte Carlo and discrete calculation methods were implemented. Oak Ridge National Laboratory (Christy 1987a) generated a set of Specific Absorbed Fractions (SAFs) that provides an energy-dependent means of calculating the dose absorbed by an organ, as a function of the energy emitted by another organ. For example, an average decay of a Cs-137 atom emits a single 0.186 MeV β -particle and a 0.662 MeV photon. Therefore, for every Becquerel (1 disintegration per second) of activity in a given organ, the 0.186 MeV of electron

energy and 0.662 MeV of photon energy is emitted per second. By interpolating the SAF tables, the fraction of the energy, from a given emission, deposited in another (or the same) organ can be calculated. The contributions from all organs to a specific target organ are summed. For Cs-137, the red bone marrow is considered the most critical target organ for predicting acute radiation effects, in specific hematopoietic syndrome. The calculation is summarized in the following equation:

$$D_{BM}(t) = \sum_{t_0}^t \left[\sum_{i=1}^N \left(\frac{A_{Cs,t}^i \cdot \bar{E} \cdot SAF(O_i \Rightarrow BM)}{M_{BM}} \right) \right] \cdot \Delta t$$

where:

$D_{BM}(t)$ = Dose delivered to bone marrow at time t

$A_{Cs,t}^i$ = Activity of Cs as a function of time

$\bar{E}$ = Average energy emitted per decay

Δt = Time step increment

$SAF(O_i \Rightarrow BM)$ = Specific Absorption Fraction from Organ i to bone marrow

M_{BM} = Mass of bone marrow

The SAF values for the 0.662 MeV photon are shown in Table 6 for each source organ, with the red bone marrow as the target organ. Some assumptions were necessary to harmonize the SAF values given by Christy (1987a) with the Cs tissue content provided by the Leggett (2003) model. The brain had minimal Cs content, and no SAF value was reported for that organ, assuming there is no dose to red bone marrow from the brain.

Table 6. Photon SAF Values for Cs-137 for Red Bone Marrow

Organ	SAF	Organ	SAF
Plasma	0.004298	Lower lg. int. wall	0.009655
RBC	0.004298	Pancreas	0.006999
Heart	0.00543	Spleen	0.004468
Lung	0.005454	Liver	0.004298
Other 1	0.004298	Kidneys	0.008254
Other 2	0.004298	Adipose	0.004298
Stomach	0.003881	Muscles	0.004483
Sm. intestines contents	0.008141	Other skeleton 1	0.00989
Upper lg. int. contents	0.006779	Other skeleton 2	0.0022959
Lower lg. int. contents	0.009655	Red marrow	0.02239
Sm. Intestine wall	0.008141	Skin	0.002423
Upper lg. int. wall	0.006779	Urinary bladder	0.003792

The mean-free path of a 0.186 MeV β -particle is approximately 2.5 mm in water (which approximates tissue), so β -particles will almost exclusively deposit their energy within the organ of origin. The red bone marrow is a complicated case because of the intricate nature of the structure in and around the blood forming region. The region has distinct discontinuities, due its porous nature; therefore, secondary electrons generated from electron and photon interactions may not deposit their energy in the local area. As a result, more sophisticated analysis is required to estimate the energy deposited from primary radiation interactions. Oak Ridge National Laboratory provided data on the absorbed fraction calculation for electrons emitted in the trabecular bone region, developed using multiple methods (Christy 1987). The absorbed dose fractions provided allow us to calculate the dose to active marrow, based on cesium trapped in both the trabeculae and the active marrow. The cesium content in the bone, provided as “other skeleton” in the physiological model, is divided by a factor of two, to account for the Cs content in the trabecular portion of the bone. The absorbed dose fraction for red marrow self-absorption from the β -particle is 0.873 and for the trabecular contribution, 0.396.

4.5.2. Effective Whole-Body Equivalent

While it is imperative to understand doses to specific organs for acute effects, most predictors of long-term effects, such as cancer induction from internally deposited radioactive material, are based on the concept of a 50-year committed whole-body dose. In other words, the model considers the radiation dose that the body will accumulate over a 50-year period, following the uptake. This dose value is based on the estimated dose delivered to specific organs or tissues. The resultant dose is then multiplied according to a specified tissue weighting factor (ICRP 1991). While our model approximates the calculation of dose to a specific organ as a function of activity in other organs, performing this calculation from all organs, to all organs, and appropriately weighting the results is not practical. SAF values are not available for all tissue

contributions in the biokinetic model. Too many assumptions would be required for the calculation, and the resulting uncertainty in this calculation would be significant. However, we approximate the dose using tabulated estimates of 50-year committed doses from inhalation and ingestion uptakes of Cs-137. By using some basic assumptions, we developed a method for the incremental accumulation of whole-body equivalent dose, thereby estimating the whole-body effective dose over time and the 50-year committed dose.

The NCRP suggests that the uptake from ingestion of Cs in soluble form is effectively 100%. They further estimate a 50-year effective dose equivalent of 8.9E-09 (Sv/Bq) (NCRP 2009). The 50-year dose is estimated based on the ICRP model of Cs retention and elimination for an adult (ICRP 1989) that takes the form of a sum of two exponentials:

$$R(t) = ae^{(-\frac{0.693t}{T_1})} + (1 - a)e^{(-\frac{0.693t}{T_2})}$$

Where:

$R(t)$ = Retention rate

$a = 0.1$

$T_1 = 2 \text{ Days}$

$T_2 = 120 \text{ Days}$

Assuming ingestion of cesium results in 100% uptake; we use this retention equation and assume the cesium delivers a “dose equivalent rate” proportional to the amount of cesium retained in the body at time t . We further assume the cesium is in equilibrium throughout the body at all times; in other words, the proportion of cesium in any given organ is constant at all times. We then calculate a dose-rate conversion factor. The equilibrium assumption is reasonable, since our model is based on a chemically-soluble form of cesium, CsCl, which is rapidly distributed via the bloodstream. The dose rate is proportional to the amount of cesium in the body, and the 50-year committed dose per unit activity is calculated by taking the integral of the cesium retention calculation and multiplying it by a dose rate conversion factor:

$$D_{50} = \int_0^{50} C \left[ae^{(-\frac{0.693t}{T_1})} + (1 - a)e^{(-\frac{0.693t}{T_2})} \right] dt,$$

where C is the dose-rate conversion factor in Sv/Day/Bq. Based on the NCRP estimate of 8.9E-09 Sv/Bq for the 50-year committed dose equivalent, then $C = 6.2\text{E-}11$ (Sv/Day/Bq). Using this conversion factor, we can estimate the accumulation of dose equivalent as a function of the cesium retained in the body at any given time, regardless of the elimination rate. This allows us to compare accumulated doses with and without Prussian Blue treatment.

4.6 Efficacy

The efficacy of Prussian Blue treatment can be evaluated in terms of overall dose reduction and prevention of acute and long-term health effects.

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Section 5.

Preliminary Model Results

The results obtained from the preliminary implementation of the model are presented in this section. Final results may vary upon final implementation in stand-alone code and software, due to the precise numerical solutions used in the final code for the integrations required within the various models.

5.1 Preliminary Implementation

A number of the calculations required in the Cs decorporation model involve several differential equations and the integration of values over time. Many of the differential equations are interconnected and certain calculations require simultaneous numerical solutions to provide the appropriate outputs. Therefore, Berkley Madonna™ v. 8.3.18 software, licensed by Robert Macey and George Oster of the University of California, was used to solve the differential equations contained within the overall model. The integration method used was the 2nd order Runge-Kutta method and a time-step interval of 0.0001 days was employed for most calculations. For 50-year calculations, a smaller time step of 0.05 days was used for optimal model performance.

Final software will have the model coded autonomously from Berkley Madonna™ and incorporate numerical solutions for the differential equations independently.

5.2 Model Outputs

The Cs decorporation model can be used to calculate a number of time dependent parameters. The initial conditions currently assumed are that Cs intake is through inhalation with complete and fast absorption, although the model can be easily adapted to accommodate an ingestion exposure. The Cs physiological model requires an input for the initial dose of cesium in activity or mass and a time interval in days. The outputs from this portion of the model describe the levels of cesium in tissues or excretion in units, to use as the input dose, and the rate is per day (ex. mCi/day):

- Cs in plasma, brain, heart, red blood cells, lungs, GI tissue, small intestines, large intestines, pancreas, spleen, liver, kidneys, adipose, red bone marrow, skeleton other than red bone marrow, skin, urinary bladder
- Total Cs in the body
- Cs excretion in urine, feces, sweat
- Total Cs excreted

Certain tissue values are used as input parameters for the radiation dose calculations. For radiation dose calculations, the input dose must be in radioactive units (mCi) providing an output in absorbed radiation dose (mGy or mSv). If mass is used as the input, the specific activity of the exposure material can be used to convert the input into activity. The red bone marrow calculation is derived from the summation of the SAF values from relevant target organs as described in

section 4.5.1 and integrated over the time period specified. The whole-body effective dose is calculated based on the decay-corrected total cesium activity and the constant for the whole-body effective dose over the time period specified as described in section 4.5.2. In general, the red bone marrow dose is used to estimate risk of acute health effects (hematopoietic syndrome). The whole-body effective dose is used to calculate the 50-year dose to evaluate long-term carcinogenic health risk.

Treatment with Prussian Blue is modeled by using the following input parameters: dose of Prussian Blue in milligrams of material, which results in a vast excess of Prussian Blue in the GI tract as compared to Cs, the doses per day, treatment start-time relative to the initial intake of cesium, and the duration of PB treatment. Standard treatment of Prussian Blue is 3000 mg administered 3 times daily and is suggested for use in the model. The outputs of the model are the same as those listed above.

Untreated and treated courses, as well as different treatment initiation and durations, can be evaluated and compared, to determine doses and dose reductions that may be obtained in different scenarios. The data generated from different scenarios are detailed below in order to illustrate the reliability and utility of the Cs decorporation model developed in this work.

5.2.1. Cesium Tissue Distribution

The model allows for an examination of the simple distribution of cesium throughout the body. Figure 9 illustrates cesium distribution in selected tissues over 30 days in an untreated scenario with 1mCi inhaled Cs-137 total lung deposition. As indicated in research (Leggett 2003), cesium has an initial affinity to muscle tissue compared with other tissues. This illustration also shows how cesium is redistributed from the lungs after the initial inhalation exposure. The distribution of cesium reaches a steady-state relatively quickly.

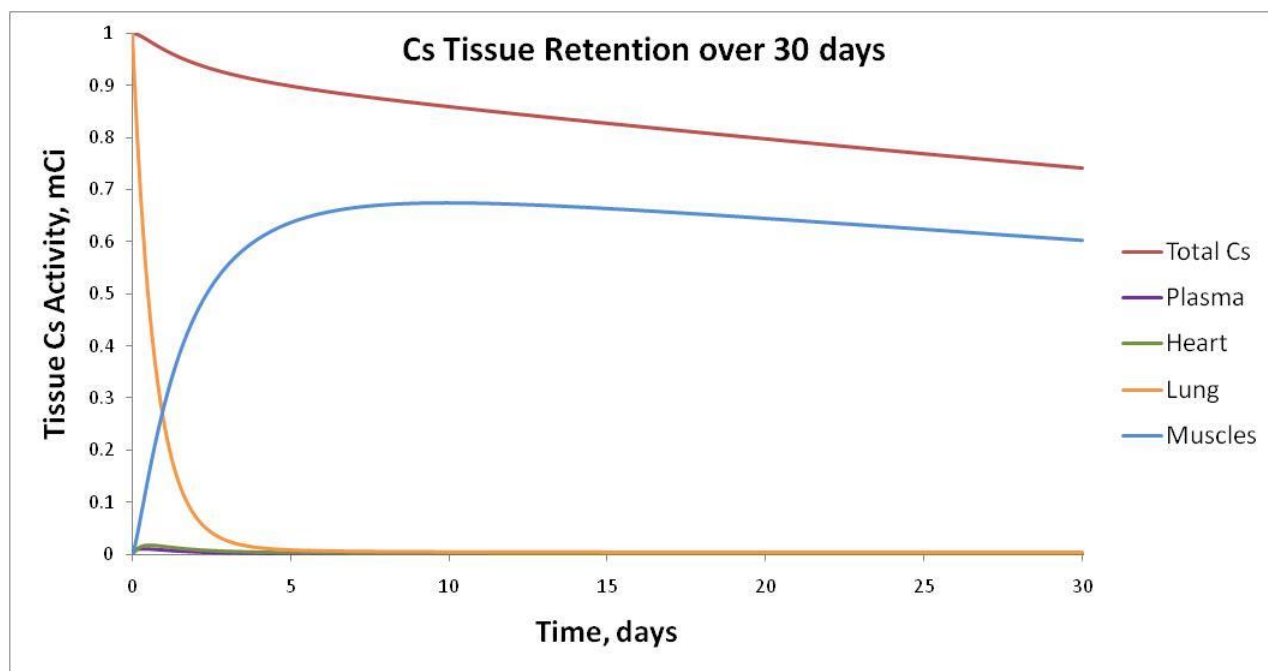


Figure 9. Cesium Retention in Selected Tissues Over 30 Days

The total Cs in Figure 9 is calculated by summing the Cs present in all of the tissues represented in the model for each time step. Additional organ and tissue distributions that could not be easily displayed in Figure 9 are illustrated in Figure 10. These tissues experience an initial increase in activity as the cesium redistributes from the lungs and then quickly declines. Cesium distribution in the early time period when its activity and concentration are highest is critical for accurately calculating dose to the red bone marrow.

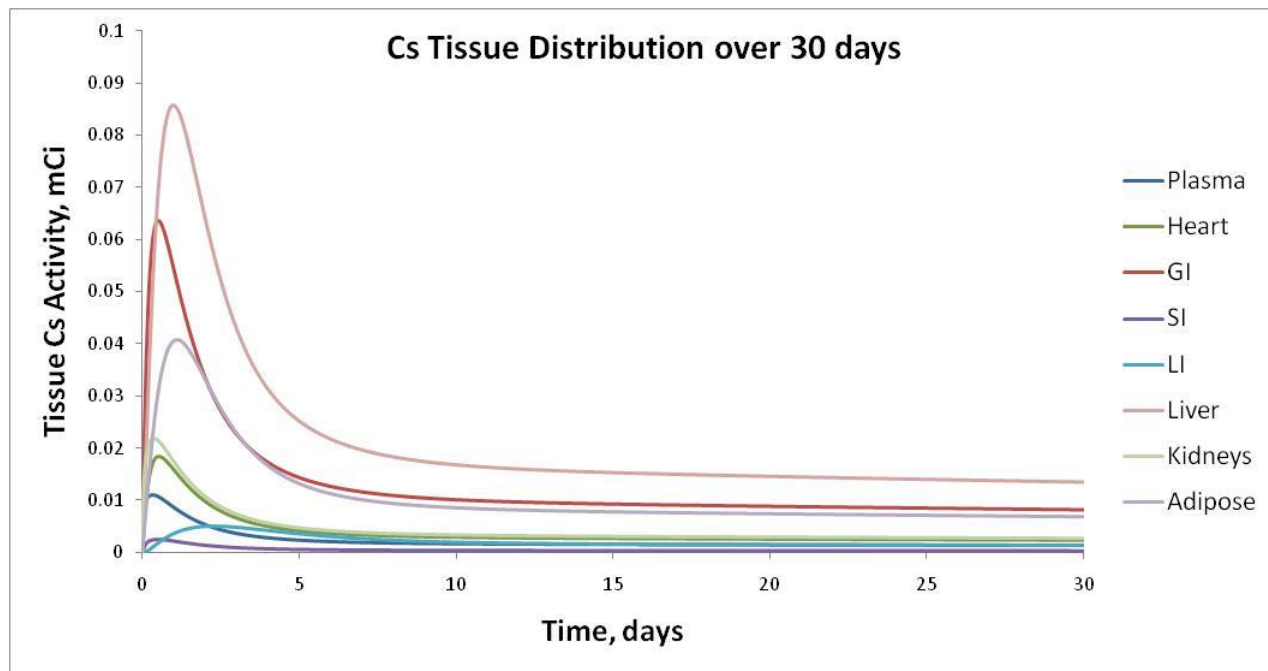


Figure 10. Cs Distribution for Selected Tissues Over 30 Days

5.2.2. Comparison of Predicted Cesium Retention to Human Data and Published Models

Data collected on humans indicates large variability in retention, based partially on age, gender, and body weight. Since the model incorporated in this work is based on adult male physiological parameters, our retention values are compared to human data (Lloyd 1973, Melo 1997) for adult males and the ICRP model (1989) for adult males.

The physiological model developed by Leggett and implemented in the Cs decorporation model was compared to human data from several studies of healthy adult males (Leggett 2003). This comparison of data is shown in Figure 11. The data is represented by four subjects of a controlled study by Richmond (1962), five controls in a study by Lloyd (1972, 1973), and five non-chelated men in Goiânia accident (Melo 1997, 1998). While significant individual variability exists, the model adequately represents the general whole-body retention of cesium in adult males.

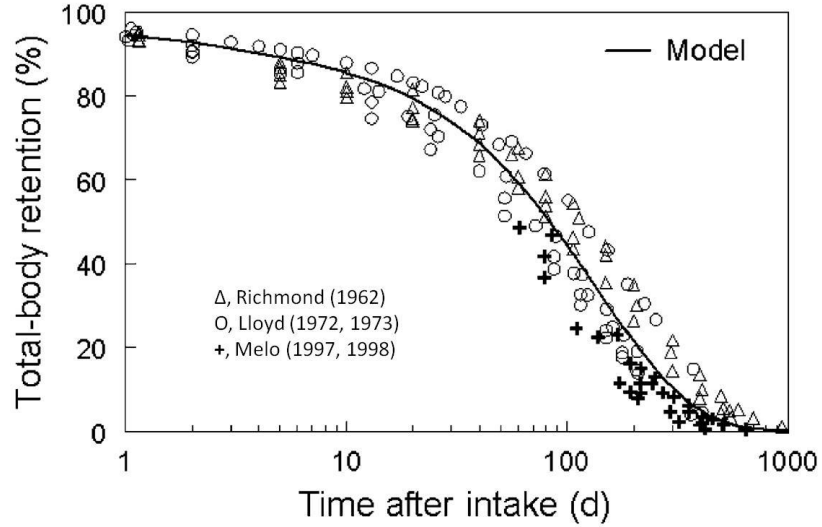


Figure 11. Model Predictions of Cs Retention (Leggett 2003)

Based on the human and animal experimental data, a whole-body retention function for cesium was determined to have a short-term and long-term component in a number of studies (Boecker 1969, Lloyd 1973, Leggett 1986, Melo 1997). As described in section 4.5.2, Cs retention has been described by the following function:

$$R(t) = ae^{-\frac{0.693t}{T_1}} + (1 - a)e^{-\frac{0.693t}{T_2}},$$

where R is retention as a function of time in days, a is the fraction of Cs exhibiting a short retention time, and T_1 and T_2 are the retention half-times for the short and long-term components, respectively. Again, the half-times and overall cesium retention differs among individuals and has significantly different values between gender and among different age groups. The simplified biokinetic model adopted by the ICRP (1989, 1993) has age-specific values for the coefficients and half-time terms. These terms were also estimated from data collected on individuals, such as that collected in the Goiânia, Brazil accident. For the purposes here, the terms for healthy adult males are evaluated.

The coefficient and half-time terms were extrapolated from our Cs decorporation model by using a curve fit to the data output of total cesium retention over time in the form of the function listed above. The coefficient a is 0.1 and the short-term and long-term half-times are 4.3 and 97.8, respectively. The terms of the retention function are compared to those established by individual bioassay data (Lloyd 1973, Melo 1997) as well as those adopted by the ICRP (1989), shown in Table 7.

Table 7. Comparison of Cs Retention Parameters

Reference	a	T_1 (days)	$(1-a)$	T_2 (days)
ICRP 1989	0.1	2	0.9	110
Lloyd 1973 (1)	0.15	2.1	0.85	90.4
Lloyd 1973 (2)	0.09	0.9	0.91	91.7
Lloyd 1973 (3)	0.12	2.4	0.88	79.5
Lloyd 1973 (4)	0.19	3.8	0.81	81.5
Lloyd 1973 (5)	0.08	1.5	0.92	140
Melo 1997 (ave)	0.15	3	0.85	90
Cs Decorporation Model	0.1	4.3	0.9	97.8

The Cs decorporation model described here is in agreement with other published models and human data. The short-term half-time from our model is slightly longer than other models (4.3 days, as compared to 2-3 days in most cases), due to the lag-time in absorption and redistribution from the lungs that is applicable in our model. The comparison studies predominately include ingestion or injection, which exhibit faster uptake and redistribution.

The predicted Cs retention from our model is compared to data from individual adult males from the Goiânia, Brazil Cs-137 accident and the average observed Cs retention of those seven individuals. Figure 12 shows strong agreement between observed and predicted Cs retention.

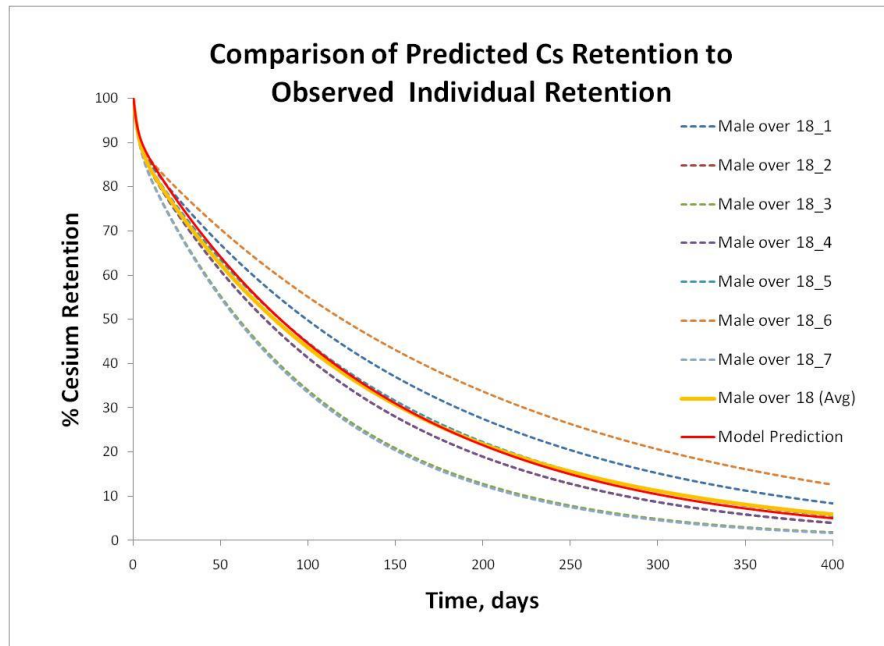


Figure 12. Model Compared to Individual Retention Accident in Goiânia, Brazil (Melo 1997)

Finally, the cesium retention curve generated from our Cs decorporation model is plotted as a function of time in Figure 13 and compared to the retention curves obtained from the ICRP model (1989) and Melo's (1997) model. The retention curves illustrate strong agreement between the three models. However, the long-term half-time currently used by ICRP is higher than the average observed in the human data (Melo 1997) and as predicted in the physiological model (Leggett 2003). This will result in more conservative (higher) radiation dose estimates for the 50-year committed dose (see section 4.5.2).

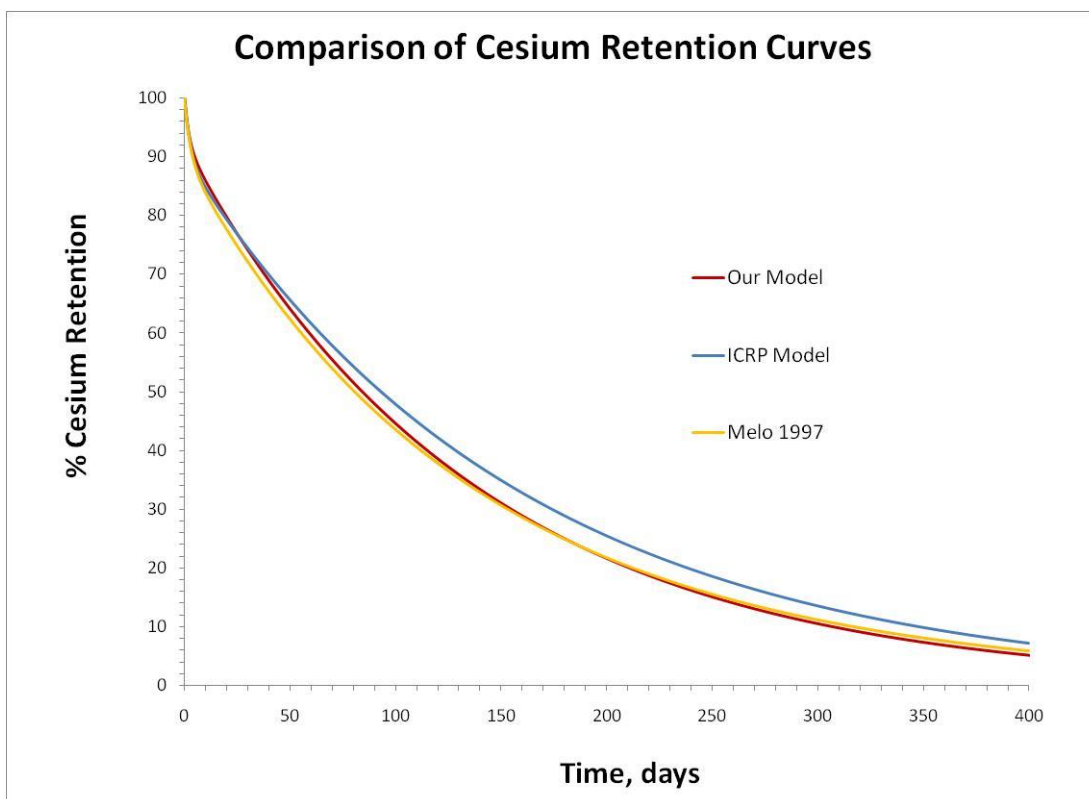


Figure 13. Comparison of Cesium Retention Curves from Three Models

5.2.3. Prussian Blue Decorporation of Cesium

Prussian Blue treatment effectively reduces the amount of cesium in the body by binding the cesium circulating through the GI tract, as described in section 4.4.5. The Prussian Blue predominately binds cesium during its transit through the small intestines and fast re-equilibration to the steady-state is assumed. This action is illustrated in Figure 14, which shows cesium whole-body retention after 1mCi lung deposition in the untreated case. Then, the Prussian Blue treatment case, which begins at day 3 after exposure and the standard dosing (3 grams, 3 times daily) lasts for a duration of 7 days. The red curve shows a rapid decline of cesium after treatment is initiated. When treatment is discontinued at day 10, after the 7-day course, the slope of the treated curve resumes the shape of the untreated curve and is parallel to it.

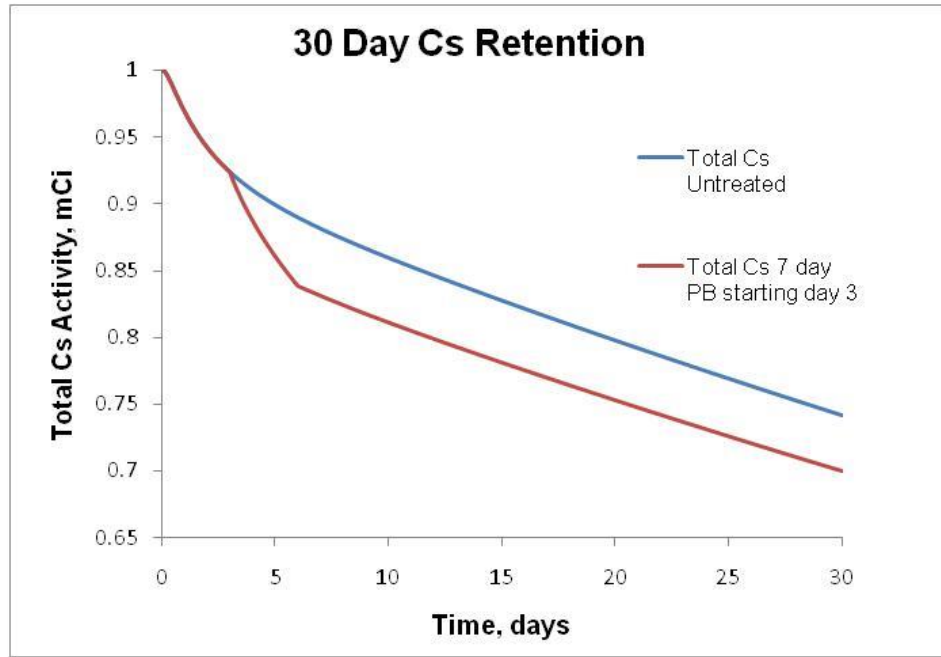


Figure 14. Total Cs Retention With and Without Treatment

The predicted retention of Cs during the course of treatment is compared to the retention curves of treatment for the adult males of the Goiânia, Brazil accident (Lisztein 1991, Melo 1994). These data show that our model predicts Cs retention during PB treatment within the range of what is observed in adult males, in Figure 15. In the two studies, the average data for adult males had Cs half-times at 58 days (n=9, Lisztein 1991) and 26 days (n=11, Melo 1994).

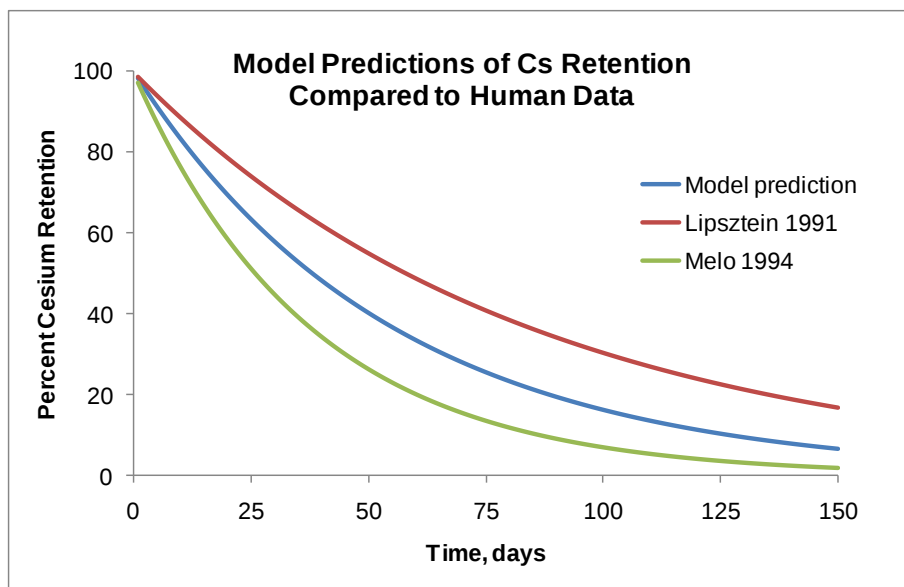


Figure 15. Model Predictions of Cs Retention After Treatment

As described in section 4.4.6, large individual variability is observed in the retention and clearance of cesium with PB treatment. The reported Cs half-time under treatment is 9 to 72 days (Melo 1994). Since several studies were not able to correlate Cs retention rates with any of the biological parameters measured within the studies, improvements on the treatment model are difficult unless individual bioassay data becomes available. Then, estimates could be improved on, on a case-by-case basis.

5.2.4. Cesium Excretion Rates

The Cs decorporation model determines the excretion rate of cesium in urine, feces, and sweat in untreated and treated scenarios. Using the same scenario as section 5.2.1, Figure 16 compares the 30-day total excretion and route- specified excretion to a treatment scenario involving standard PB administration beginning at day 3 and continuing for 30 days. A dramatic increase is observed in total Cs excretion after Prussian Blue treatment begins. Since Prussian Blue acts only in the GI tract, the predominant route of excretion changes from the urine in the untreated case to the feces in the treated case, (Farina 1991). This change in excretion route is important when interpreting bioassay data (Lipsztein 1991b). For example, if only urine is monitored after an exposure and during treatment, the results may be difficult to interpret since the actual urinary output of Cs after treatment is actually lower than the urinary output in the untreated case, due to the increased fecal excretion.

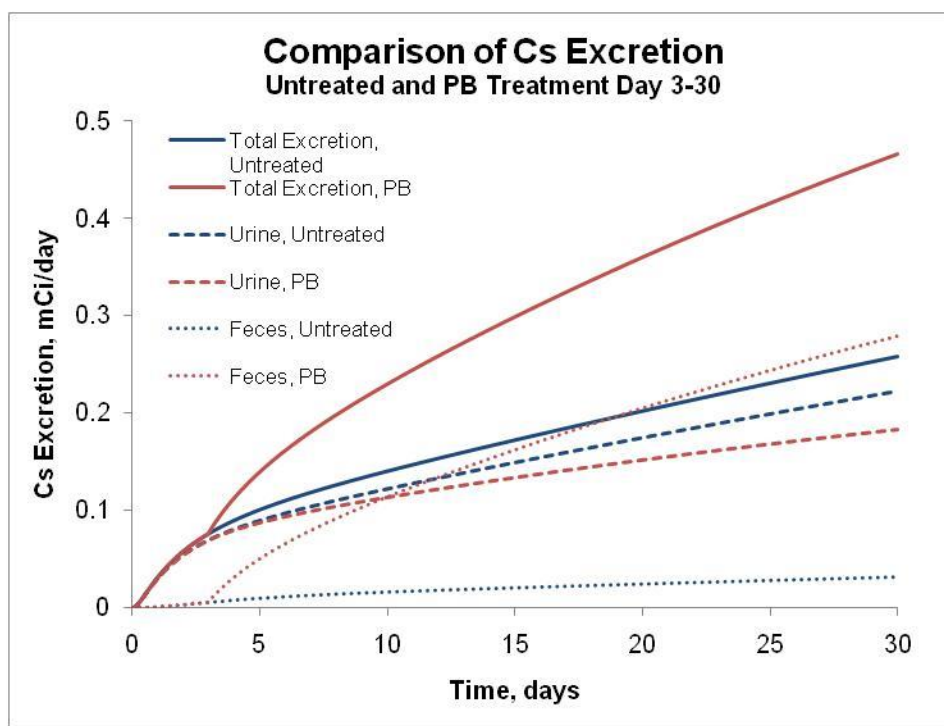


Figure 16. Cs Excretion With and Without Treatment

5.2.5. Cesium Acute and Whole-Body Effective Doses

The model may be used to calculate acute doses to the critical target organ (the red bone marrow) and the whole-body effective dose. Since Cs has a β -particulate component, a high radiation dose delivered directly to the red bone marrow is possible. Therefore, the red bone marrow is the critical organ for which acute effects could be observed from exposure to Cs-137, in the form of hematopoietic syndrome.

The acute red bone marrow dose and the whole body effective dose for an intake/lung deposition of 1mCi of Cs-137 in an untreated case are shown in Figure 17.

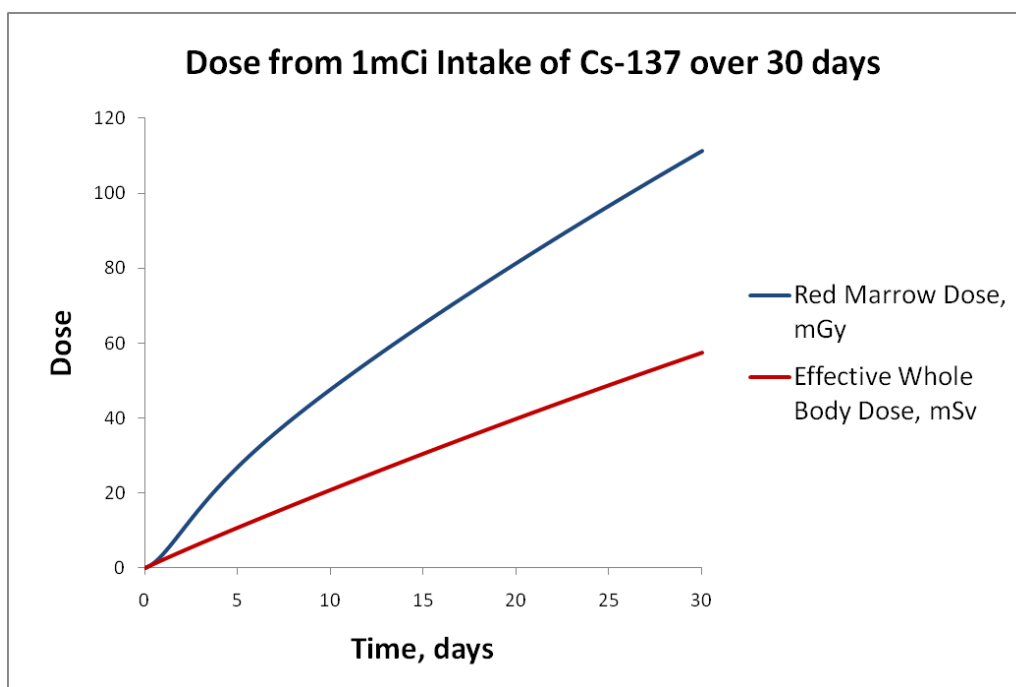


Figure 17. Radiation Dose from Cs-137 Over 30 Days

The effective whole-body dose illustrated in Figure 17 has a lower value than the acute red bone marrow dose. It is important to differentiate between what the acute and effective dose reference. The acute dose refers to the total energy deposited in a particular organ, which is most appropriate for referring to acute effects (i.e. cell death, which results in organ dysfunction leading to morbidity and mortality). While the effective dose calculation can be made for earlier time points, the effective dose concept was developed to relate long-term health effects, such as carcinogenesis. For this relationship, tissues must be weighted, since different tissues have different dose response to carcinogenesis. This weighting results in averaging the dose over the whole body according to tissue-specific sensitivities and calculating the effective-whole body dose.

The long-term health risk to cancer is most often evaluated calculating the 50-year committed whole-body effective dose. Table 8 shows the predicted cumulative radiation dose to the red bone marrow and the whole-body effective dose in treated and untreated scenarios. The

treated scenarios involve treatment start time at 3 days post-exposure and durations of one week and 30 days.

Table 8. 50-Year Radiation Doses from Cs-137 in Untreated and Treated Cases

Dose	Untreated	PB at Day 3, 7-day Course	PB at Day 3, 30-day Course
Red Marrow, mGy	507	457	370
Effective Whole Body, mSv	290	262	212

The data in Table 8 illustrates a 9% reduction in the 50-year committed dose by using Prussian Blue treatment early on, for only 7 days. The 30-day course of PB further reduces the committed dose by 27%.

5.2.6. Evaluation of Efficacy

The efficacy of Prussian Blue treatment can be evaluated based on the concept of dose reduction. The example above, in Table 8, provides a good example of how a comparison of doses after PB treatment can evaluate efficacy. This type of analysis also allows an end-user to determine how long PB treatment administration is justified. The dose reduction from treatment is further illustrated in Figure 18, which shows the dose accumulated over 90 days in untreated and treated cases. The treated cases assume treatment starting day 3 and continuing for either 7 or 30 days. A significant reduction in dose is observed with treatment of only 7 days. Dose is further reduced with longer treatment times.

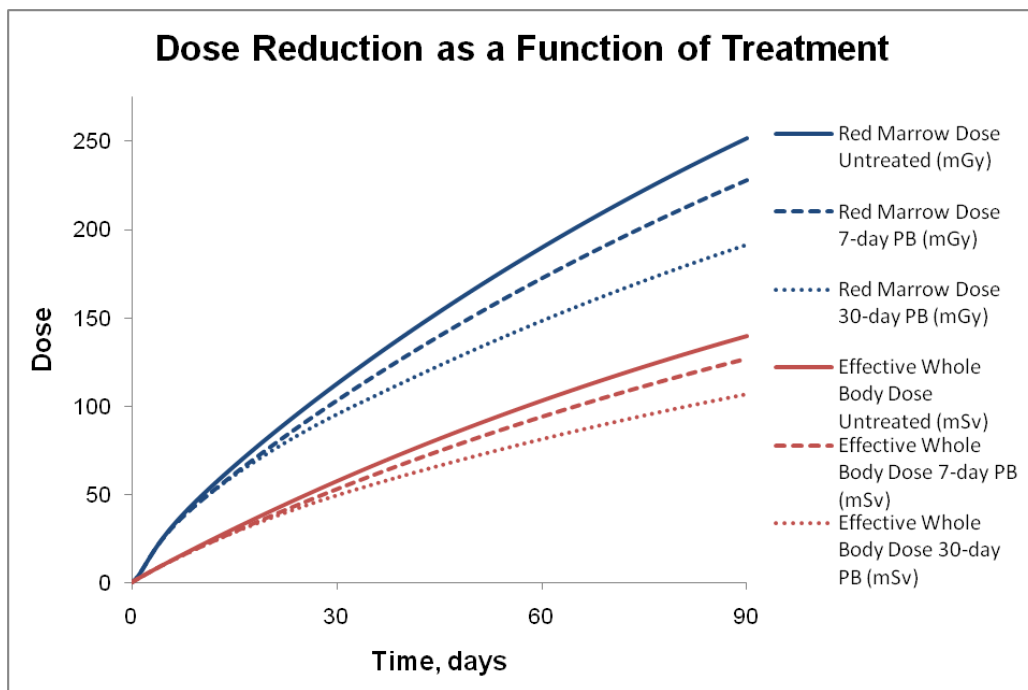


Figure 18. Doses from Cs-137 Over 90 Days in Treated and Untreated Cases

The dose saving reduces dramatically with time, which illustrates that the majority of the dose absorbed by the body is received very early after an exposure. The time of treatment with PB can have a significant impact on the overall dose resulting from Cs exposure. Therefore, another important aspect to consider in efficacy evaluation is the impact of the lag-time between an exposure and the initiation of treatment. In the example, shown in Table 9, the 90-day dose from 1 mCi of Cs-137 is reduced more dramatically the sooner treatment begins. Efficacy of treatment drops off with greater lag-times in treatment initiation.

Table 9. Doses After 90 Days from 1mCi Cs-137 Exposure in Untreated and 30-Day PB Treated Subjects with Different Treatment Initiation Times

Dose	Untreated	PB at day 14, 30-day course	PB at day 7, 30-day course	PB at day 3, 30-day course	PB at day 1, 30-day course
Red Marrow, mGy	252	207	200	191	179
Effective Whole Body, mSv	140	116	111	107	100

Dose reduction is further examined in Table 10 where the 50-year effective whole-body dose versus treatment initiation time and duration of treatment are presented.

Table 10. 50-Year Committed Whole-Body Effective Doses (mSv)

Duration of PB, days	<u>Treatment Initiation Times (days post exposure)</u>						
	0	30	60	90	120	150	180
0	290	290	290	290	290	290	290
30	188	231	243	252	260	266	271
60	152	198	216	231	242	252	260
90	131	178	200	218	232	244	253
120	119	167	192	211	226	239	249
150	111	160	186	207	223	236	247
180	107	156	183	204	221	234	246

The data illustrate that earlier treatment initiation enables greater reduction of dose. Likewise, longer courses of PB generally provide greater dose reduction. However, at later treatment initiation times, dose reduction is not as significant, even with longer treatment durations. The dose reduction factors for these same data may be calculated by dividing the treated dose by the untreated dose. The dose reduction factors for the different treatment courses, summarized in Table 10, are listed in Table 11.

Table 11. Dose Reduction Factors for Different Treatment Regimens

Duration of PB, days	<u>Treatment Initiation Times (days post exposure)</u>						
	0	30	60	90	120	150	180
0	1	1	1	1	1	1	1
30	0.65	0.80	0.84	0.87	0.90	0.92	0.93
60	0.52	0.68	0.74	0.80	0.83	0.87	0.90
90	0.45	0.61	0.69	0.75	0.80	0.84	0.87
120	0.41	0.58	0.66	0.73	0.78	0.82	0.86
150	0.38	0.55	0.64	0.71	0.77	0.81	0.85
180	0.37	0.54	0.63	0.70	0.76	0.81	0.85

The values in Table 11 may be converted to estimates of efficacy by subtracting the dose reduction factors from one. The efficacy values are shown in Table 12. The higher values indicate more effective treatment and greater efficacy. Earlier treatment combined with longer duration affords the greatest dose reduction and efficacy.

Table 12. Efficacy of Different Treatment Regimens

Duration of PB, days	<u>Treatment Initiation Times (days post exposure)</u>						
	0	30	60	90	120	150	180
0	0	0	0	0	0	0	0
30	0.35	0.20	0.16	0.13	0.10	0.08	0.07
60	0.48	0.32	0.26	0.20	0.17	0.13	0.10
90	0.55	0.39	0.31	0.25	0.20	0.16	0.13
120	0.59	0.42	0.34	0.27	0.22	0.18	0.14
150	0.62	0.45	0.36	0.29	0.23	0.19	0.15
180	0.63	0.46	0.37	0.30	0.24	0.19	0.15

Section 6.

Next Steps

Each of the components of the Cs decorporation model, which are the inhalation exposure model, the cesium biokinetic model, the Prussian Blue treatment model, and the radiation dose models. These components will be consolidated into a single set of codes and integrated into user-friendly software, for use in scenario simulations. The results presented here provide an indication of the utility of the composite model and a sample of the type of data that can be generated.

As previously mentioned, large individual variability was observed in human data collected, to date, regarding cesium absorption, retention, and response to treatment. Although beyond the scope of the current effort, certain aspects of individual variability could be addressed in the Cs decorporation model presented here. For example, the distribution of cesium is known to be dependent on age, gender, and body size/composition. Distribution is partially due to the differences in the relative size of the tissues and partially due to differences in metabolism. Physiological data exists for age and gender specific variances. Certain extrapolations can be made mathematically for body size and composition. Therefore, the physiological model for cesium, as well as the PB treatment model, could be refined to account for physiological differences in distribution and retention of cesium, so that additional age and gender specific data could be generated. Likewise, the absorption of radiation is impacted by the differential tissue distribution of radioactivity. Furthermore, long-term health risks vary among different ages and between genders. Model refinements would also enable more precise health risk assessments outside of the “healthy, adult male”.

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Section 7.

Conclusions

The Cs decorporation model presented in this work estimates cesium absorption, distribution, retention, excretion, and response to Prussian Blue treatment in adult healthy males after an inhalation (or ingestion) exposure. The model further estimates the acute red bone marrow dose and the whole-body effective dose as a function of time. The results of the model compare favorably with both human data and alternative models developed by the ICRP and NCRP. Calculations from the model may be used to analyze consequences of exposure to Cs-137 and the effect of treatment based on initiation and duration times. The model may facilitate interpretation of Cs bioassay data and aid in treatment planning. The Cs decorporation model is a valuable tool for assessing the effect of exposure to Cs-137 and Prussian Blue treatment.

The model could be further improved by incorporating age and gender specific parameters and data, which would enable more precise calculations for additional segments of the population.

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Section 8.

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Section 9.

Definitions, Acronyms, and Abbreviations

AMedP-8	Allied Medical Publication 8
ARA	Applied Research Associates, Inc.
DTRA	Defense Threat Reduction Agency
DoD	Department of Defense
FDA	Food and Drug Administration
GI	Gastrointestinal tract
Gryphon	Gryphon Scientific, LLC
ICRP	International Commission on Radiological Protection
JPEO-CBD	Joint Program Executive Office for Chemical/Biological Defense
JPM-IS	Joint Program Manager Information Systems
JSTO	Joint Science and Technology Office
MCM	Medical Countermeasure Model
MPPD	Multiple-Path Particle Dosimetry
NCRP	National Council on Radiation Protection and Measurement
PB	Prussian Blue
PBPK/PD	Physiologically Based Pharmacokinetic/Pharmacodynamic
SAF	Specific absorbed fraction