CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-626

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

IND 51,700

Title: Insoluble Prussian Blue-Radiogardase®.

Reviewer: Alfredo R. Sancho, Ph.D.
Submission Date: 17 October 1996
Final Review Date:
Assigned Date: 31 October 2001
Draft Review Date: 17 July 2002
Revised Review Date: 30 August 2002
Dose: 1 to 9 g PO daily depending on the severity of thallium and/or cesium toxicity.
Indication: Enhancement of cesium and thallium excretion from the body by means of ion-exchange.
Sponsor: J. Glenn Davis, MD, MPH

EXECUTIVE SUMMARY

The biological effect of ionizing radiation can be described in terms of direct and indirect physiochemical effects. In the case of direct physiochemical effects, the ionization of a molecule brings about a reorganization of the electrons on which its cohesion is based, rendering it susceptible to the breaking of chemical bonds and thereby its destruction. Depending on the role this molecule has in the cell, the effect can be devastating. Indirect physiochemical effects, involves the production of the aqueous free radicals $OH^{\cdot}$ and $H^{\cdot}$, as following the ionization of the water content of most human tissues.

A radioprotectant is a substance, which if introduced immediately after or soon after a radiation exposure, attenuates or suppresses the symptoms caused by it and diminishes the expected radiation associated with the risk of cancer. There are two main types of radioprotectants, chemical and biological.

Insoluble Prussian Blue (PB), ferric hexacyanoferrate, $Fe_4[Fe(CN)_6]_3$ is a drug that enhances excretion of isotopes of cesium (Cs) and thallium (Tl) from the body by means of ion exchange "capture" within the lumen of the gastrointestinal tract. The sponsor provided a selected bibliography on insoluble Prussian Blue being used in cesium and thallium decorporation therapy. The principal objective of this application is to make insoluble PB, also known as *Radiogardase®*, available for the medical treatment of patients who have been internally contaminated with radio-cesium. A secondary objective is to assess the supporting information for quantitative efficacy and to establish a drug profile based on published literature. Insoluble PB has been recommended for years as the drug of choice by national and international radiation protection societies for use in treating internal contamination with radiocesium. In 1987, the FDA temporarily cleared this product for compassionate use in patients contaminated in the radiological accident in Goiânia, Brazil. Insoluble PB is currently under an IND. Under the general investigational plan proposed, the IND collaborators will be required to submit all available treatment and bioassay data, along with listed side-effects and other observations to Oak Ridge Associated Universities/Oak Ridge National Laboratory (ORAU/ORNL), who will compile the data and submit necessary IND information in an annual report to the FDA. The research stimulated will lead to optimization of the dose and dosage regimen for PB by itself or co-administered with outer radioprotectants. This IND application is structured to also allow the use of PB for treatment of the relatively rare cases of radio-thallium exposure.

Oak Ridge Associated Universities (ORAU) is a private, non-profit consortium of 88 colleges and universities established in 1946 with a mission to provide and develop capabilities critical to the nation's technology infrastructure, particularly in energy, education, health, and the environment. ORAU manages and operates the Oak Ridge Institute for Science and Education (ORISE) for the US Department of Energy (DOE). ORISE is responsible for programs in education, training, medical sciences, and the environment. ORISE has been mandated by DOE to make Insoluble Prussian Blue available for DOE facilities that employ individuals who work with cesium radioisotopes.

The following sections are a summary of findings from the reviewed published literature and the proposed package insert. The totality of the published literature reviewed for this document was provided

in part by the sponsor and supplemented by literature searches by this reviewer via Medline search engine. The key supporting articles are identified and listed in this document. Treatment usually continues until evidence of Tl or Cs contamination is no longer present in the urine or feces. The dose depends on the level of poisoning with Tl or Cs; but there is a wide range of doses in humans. Prussian blue presence in the body depends on the GI tract transit time; yet, it is not absorbed through the intestinal wall. It is recommended by this reviewer that PB be co-administered with other radioprotectants (i.e., Zn-DTPA, KI) so to increase the efficiency of both products in the elimination of radio-elements accidentally introduced into humans.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics Division of Pharmacological Evaluation II has reviewed the information and data submitted with IND 51,700 on 17 October 1996 along with current published literature. It is recommended that the co-administration of PB with other radioprotectants (i.e., Zn-DTPA and KI) be the standard procedure for patients exposed to one or more known or unknown radio-elements. Although the dose and dosing regimen is not clearly established in the literature, these are dependent on the amount and type of radio-element contamination. Detection and monitoring methods for early and effective identification and quantification of the radio-element contaminants should also be in place so to aid in the dose and dosing regimen determination. In summary, the obtained information and data adequately addresses the needs from the Clinical Pharmacology and Biopharmaceutics perspective. The labeling changes as covered under the Labeling Recommendations section of this review (page 12) should be communicated to the sponsor.

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SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

RADIATION BIOLOGY – GENERAL CONSIDERATIONS

During a radiologic accident, the radio-exposure can be of internal and/or external type. External radio-exposure (temporal limited exposure) is not the focus of this document. Internal radio-exposure (continuous exposure), which is the focus of this document, takes place in four stages:

- the deposition of a radio-element at some place of entry,
- its penetration into the body by passage into the blood or lymph,
- homogenous distribution within the body (influence by blood flow) or concentration in one or more organs (following a particular pathway) designated as "critical organs", and
- elimination (effective half-life).

The penetration by the radio-element can be through the respiratory, digestive, transcutaneous, and/or direct wound route. It can be through one or more routes, simultaneously or staggered. Once inside, the radio-element, may distribute itself in a homogenous manner affected by its own chemical properties (e.g., solubility, oxidation state) and blood flow through the various organ-tissues but not following a particular metabolic pathway (e.g., ^{24}Na, ^{36}Cl, or tritium). It can also concentrate in particular organ-tissues ("critical organs") following specific pathways; such as in the case of ^{131}I that predictably favors the thyroid.

Any radio-element that does not tend to concentrate in a particular organ-tissue is eliminated rapidly usually via the kidneys or lungs. If the radio-element is not commonly found in the body it will behave like those elements with similar chemical properties that are normally found in the body (i.e., plutonium, strontium, barium, and cerium behave like calcium by favoring the bone mass). Overall, the "disappearance" of the radio-element from the body depends on its *effective half-life*, which is a function of the *physical half-life* (radioactivity or physical decay) and *biological half-life* (distribution, uptake, and elimination).

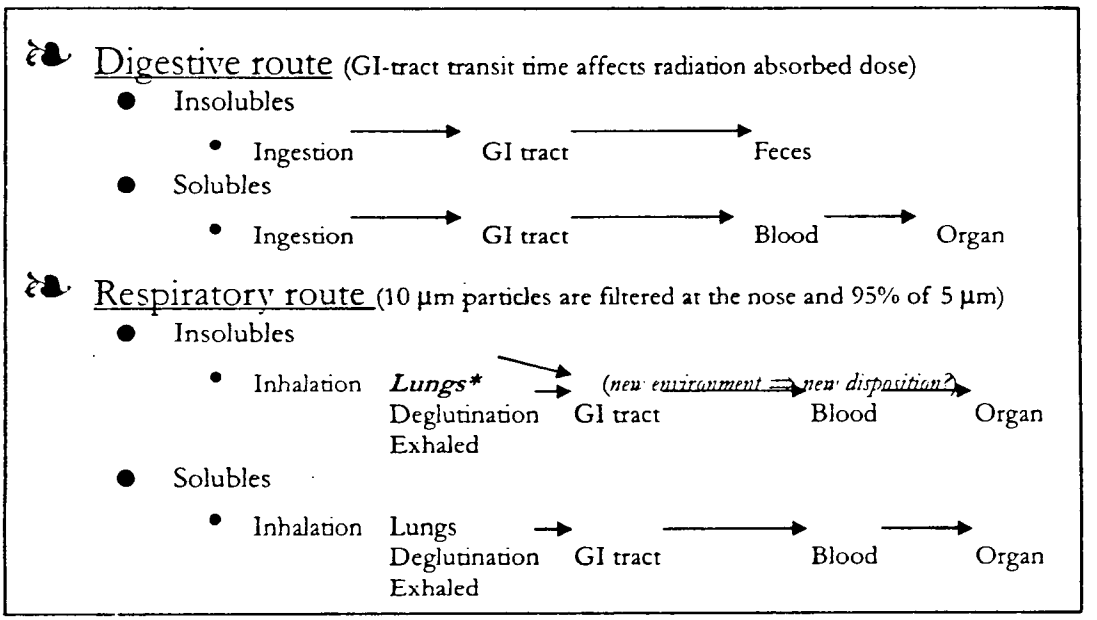
Accidents or otherwise incidents leading to internal radiation exposure from radio-elements can be of chronic or acute modalities. Chronic internal exposure is defined as "*the delivered dose equivalent for the whole body or for a critical organ, during a chronic internal radio-exposure by a given radio-element*". The contributing factors in chronic internal exposure are the daily intake of the radio-element, the effective half-life of the radio-element, and the mode and energy emission of the radio-element. Acute internal exposure is defined as "*caused by an accidental absorption, inhalation, ingestion, and/or direct passage into the body in a very short time of a radio-element with a given radioactivity (A), localized in a given organ (q_o), which can be determined by the radioactivity in the blood passing through that organs ($f'x$)*". The relationship of these three parameters is described by the following formula:

$$q_o = f'_x * A$$

Ingestion of radio-elements can be from contaminated mucous from the upper respiratory tract and contaminated food and water. Solubility of the radio-elements is the major factor in determining the absorption and distribution within the body. Fission products of uranium and plutonium are oxides and do not dissolve well. As oxides, strontium and barium are about 10% soluble and after entering the blood will go into the bone mass; while iodine being much more soluble, once it enters the blood, goes directly to the thyroid [*Glasston and Dolan, 1977*]. While large amounts of radio-elements pass through the kidneys, they do not greatly affect this organ for the residence time is brief; as compared to the gastrointestinal tract, particularly the large intestine, for which the residence time can be long [*Dunning, 1957*].

Inhalation of radio-elements, if due to an explosion, will be of a particle nature. These particles will range in size from 2 um to 1 cm, with the 10 um the most hazardous. The nose will filter out 95% of particles larger than 10 um. Soluble and insoluble particles entering the lungs will behave differently [*ICRP, 1968*]. Generally, 25% of the inhaled soluble particles will be exhaled; 50% will remain in the

upper respiratory tract and swallowed within 24 hrs; and, 25% will be absorbed. Of the inhaled insoluble particles, 25% are exhaled; 50% remain in the upper respiratory tract and swallowed within 24 hrs; 12.5% remain in the deep respiratory tract and eliminated with a biological half-life of 120 days. The following diagram depicts the general flow of particles through the different entry routes depending on their solubility characteristics.



There are several systems of classification for radio-elements. One such classification system segregates the radio-elements into "transferable elements" and "non-transferable elements". Transferable elements are soluble in the physiochemical conditions characteristic of biological media and are rapidly metabolized in the organ-tissues (i.e., chemical analogues, alkalines, earth-alkalines, carbon, iodine, etc.). The non-transferable elements are composed of either insoluble elements at all pH (e.g., metals, calcinated oxides) or of elements soluble only under acid pH and whose salts hydrolyze if the pH rises leading to hydroxides, which are polymerized and are cations with valence greater than II (i.e., plutonium).

A different classification system for radio-elements is based on their physical decay or half-lives, Group 1 (relatively short physical half-life, e.g., ^{131}I), Group 2 (relatively long physical half-life, e.g., ^{90}Sr, ^{89}Sr, ^{137}Cs, ^{140}Ba), Group 3 (rare earth with physical long half-life, e.g., ^{91}Y, ^{144}Ce), and *Others* (^{14}C, tritium).

Another issue to consider when classifying radio-elements is the various types of radiation. There are three main types of radiation: Alpha (α), Beta (β), and Gamma (γ). Alpha particles, because of their relatively large size and extremely high energy, produce localized tissue damage. Gamma radiation, because of its greater ability to penetrate tissue, at the time of interaction will produce less damage per unit path length than alpha particles. High energy gamma radiation may leave the body without interacting with tissue. Beta radiation is comparable in damage to gamma, but it will travel less than gamma; therefore, producing relatively high average radiation absorbed doses.

There are no standardized treatment procedures or protocols for radiation exposure. The purpose of any treatment procedure is to prevent or reduce the incorporation of the radio-element into critical organs. Treatment procedures will include external decontamination, stable iodine administration (Lugol solution, tablets of sodium or potassium iodide, 100 mg for 10 days), and avoidance of any food that may contain ^{131}I, ^{134}Cs, and ^{137}Cs such as milk, meats, and leafy greens.

TECHNICAL BACKGROUND

Currently, insoluble Prussian Blue (PB) is only supplied by the German company, HEYL Chemisch-pharmazeutische Fabrik GmbH & Co. KG under the name of *Radiogardase®*. Its characteristics are:

Name	Ferric(III) hexacyanoferrate(II)
Formula	Fe4[Fe(CN)6]3
Molecular weight	859.3
Color index	No. 77.510
CAS registry	No. 14038-43-8

All precipitates of insoluble PB contain non-stoichiometric amounts of potassium, protons, and water [*Buser et. al., 1977; Dvorak, 1971; Ludi, 1983; Nielsen et. al., 1988b*]. It is insoluble in water and dilute acids [Solubility $L_p = 10^{-40}$ (*Ludi, 1988*)]. ^{39}Fe-labelled measurements indicated a solubility of 0.7 umol/l [*Dvorak, 1970*]. Insoluble PB contains cyanide ions that can readily bind to iron. At extremely low pH in the absence of oxidizing agents, PB decomposes and under these circumstances, cyanide can be released.

The mechanism of action of insoluble PB for cesium and thallium "capture" (adsorption by hexacyanoferrates) is not fully understood [*Nielson et. al., 1987*]. It is speculated that it is a chemical ion-exchange, in which non-stoichiometric and stoichiometric cations of the drug are exchanged by thallium and cesium ions. After binding of thallium to insoluble PB, the content of potassium and hydrogen is reduced [*Dvorak, 1970*]. Insoluble PB labeled with ^{40}K demonstrated no additional radioactivity after mixing with thallium, but the pH value was decreased from release of H+ ions [*Dvorak, 1971*]. In-vitro experiments using insoluble PB bound more cesium atoms than the total number of potassium-, hydrogen-, and iron-ions released [*Nielsen et. al., 1987*]. The effect of insoluble PB in experimental thallium and cesium poisoning has been investigated in several animal species.

Cesium-137 (^{137}Cs) is a common fission by-product material, a frequent active component of sealed sources, and an important radionuclide in radiation oncology. The use of ^{137}Cs falls under the jurisdiction of the Nuclear Regulatory Commission (NRC). It can be found in hospitals used for performing gynecological brachy-therapy or intestinal therapy of solid rumors. It has a physical half-life of 30.15 ±0.06 years with a Beta energy peak at 174.0 keV.

Thallium-201 (^{201}Tl) has a physical half-life of 3.041 ±0.004 days with energy electron, photon and gamma (167.4 keV) emissions. Thallium poisoning leads to neurological disturbances, namely in the legs, and alopecia constitutes most of the remaining clinical symptoms.

BIOLOGICAL BACKGROUND

Insoluble Prussian Blue, Ferric(III) hexacyanoferrate(II), is not absorbed through the gastrointestinal wall. Therefore, its disposition within the body depends on the gastrointestinal tract transit time.

Insoluble PB forms insoluble complexes in the gut lumen, with thallium or cesium ions exchanging for potassium ions in the molecular lattices. This effectively reduces enteric reabsorption of cesium or thallium; thus enhancing faecal excretion.

Thallium and cesium distributes in the same way as potassium because it has a similar charge and ionic radius. Potassium supplementation may be required during treatment to eliminate thallium or cesium. Early potassium supplementation may raise intracellular free thallium ion concentrations resulting in hyperexcitability and restlessness. The International Atomic Energy Agency (1988) recommended the use of insoluble PB in cases of ^{137}Cs contamination, and it predicts a reduction of the ^{137}Cs effective half-life in the organism to one-third of the initial value.

The formation of bile appears to take place in the canaliculi of the liver. Bile flow is the result of secretory activity of the hepatic cells lining the bile canaliculi. During the passage of the bile through the biliary duct free exchange of compounds to and from blood occurs. It is here where the Cs and Tl capture occurs. The transport into bile requires active secretion. The bile is stored in the gallbladder from which up to 90 percent of the water is reabsorbed. The liver produces 0.5 to 1 liter of bile per day, which is emptied into the duodenum. The bile secretion is regulated principally by humoral mechanisms. However, nervous regulatory influences exist. The magnitude of bile production depends on the type of food consumed. Food rich in protein results in increased bile secretion, food rich in fat in some increased secretion, and carbohydrates have hardly any influence. Two hormones, secretin and cholecystokin, are involved in the regulatory mechanism. Both are extracted from the duodenal mucosa, intestinally absorbed and reach the liver via the blood.

The normal total blood thallium concentration in humans is under 2 ug/l and concentrations greater than 100 ug/l are toxic. The toxicokinetics of thallium in humans are described by a three compartmental model [*Moore D., 1993*]. The first phase, which lasts about four hours, represent intravascular distribution. The second phase lasts 4-48 hours during which thallium is distributed into the central nervous system. In general the distribution phase is completed within about 24 hours. The elimination phase starts about 24 hours after ingestion and its duration depends on the therapeutic intervention used. Thallium or thallous ions are secreted into the small and large bowel but there is some enteral reabsorption. Intestinal secretion of thallium is the primary mechanism of thallium elimination with minimal secretion occurring in the bile. The fecal to urinary excretion ratio of thallium is about 2:1. The elimination half-life of thallium without treatment is about eight days.

Cesium compounds are readily secreted into the gut. It enters the blood-stream and is distributed throughout the body. Cesium follows the movement of potassium in the body and competes with potassium for transport across cell membranes. Potassium traverses cell membranes more rapidly than ^{137}Cs, with greater differences occurring for passive transport and for rapidly exchanging tissues (predominantly the viscera) [*Leggett, 1986*]. Without treatment, the main (~80%) pathway of ^{137}Cs excretion is through glomerular filtration in kidneys [*Lessard et. al., 1987*]. Fecal excretion (~20%) is due, in part, to excretion via the biliary system into the intestine since the liver concentration of ^{137}Cs is high; however, a high amount of cesium is reabsorbed in the intestine [*Rosoff et. al., 1963*]. The rate of cesium secretion will depend partly on its turnover rate in body tissues, particularly muscle, which accounts for a large proportion of the total body ^{137}Cs activity. The turnover rate of cesium in muscle tissues of young animals is faster than that of older animals; therefore, insoluble PB was more effective in the treatment of young rats [*Stather, 1972*]. This could also be valid for children of early age, possibly due to their higher basal metabolic rate [*Kostial K. et. al., 1980*]. Different mathematical models have described cesium-137 retention in the body. In these models, many factors such as age [*Bengtsson et.al., 1964*], gender, body weight [*Eberhardt, 1967; Cryer and Baverstock, 1987; Menlo, 1997*], total body potassium content [*Lloyd et.al., 1973*] concentration of aldosterone [*Rundo and Turner, 1992*], and others

have influenced ^{137}Cs retention. Based on animal and human data, the International Commission on Radiological Protection (ICRP) has adopted the following parameters for ^{137}Cs retention in humans:

Age	Range of body weight (kg)	Parameters of ^{137}Cs retention			
		a_1	T_1 (days)	a_2	T_2 (days)
3 months	6	-	-	1	16
1 year	9.8	-	-	1	13
5 years	19	0.45	9.1	0.55	30
10 years	32	0.30	5.8	0.70	50
15 years	55	0.13	2.2	0.87	93
Adults	70	0.10	2	0.90	110

CLINICAL PHARMACOLOGY

Insoluble Prussian Blue (PB) has a very high affinity for cesium and thallium. Thallium [*Forth et. al., 1979*] and cesium [*Nigrovic, 1965*] metabolism follows an entero-enteric cycle. These ions are ordinarily excreted into the intestine, reabsorbed from the gut into the blood, then to the bile, and then excreted again into the gastrointestinal tract. Orally administered PB "traps" thallium or cesium in the gut. Thus, biological half-life of thallium and cesium is significantly reduced after decorporation therapy with PB. Insoluble PB itself is not absorbed across the gut wall in significant amounts.

Various animal studies have been conducted to verify that PB is not absorbed once orally administered. From these studies, there was no evidence of PB absorption, instead different ions associated with the radiolabeling of PB [K^+, Fe^{3+}, and $[Fe(CN)_6]^{4-}$] were metabolized. In humans, no significant variation in the potassium levels were detected [*Richmond, 1983*]. A 14-day whole-body retention was measured (% of administered dose) following the oral administration of ^{39}Fe-labelled PB (four distinct chemical species) to piglets [*Nielsen et. al., 1988a*]:

$K^{39}Fe[Fe(CN)_6]$	1.47%
$^{39}Fe_4[Fe(CN)_6]^3$	1.34%
$Fe_4[^{39}Fe(CN)_6]^3$	0.15%
$KFe[^{39}Fe(CN)_6]$	0.2%

In a retention study with rats where $KFe[^{39}Fe(CN)_6]$ was orally administered, 0.03% of dose was retained in the gastrointestinal (GI) tract; 0.14% was found in the urine; and, 99% was excreted in the feces [*Dvorak et. al., 1971*]. In another study with rats, $K^{39}Fe[Fe(CN)_6]$ was administered and 0.11% was found in the skeleton and 0.046% was found in the blood. Overall, no evidence was found of $[Fe(CN)_6]^{4-}$ decomposition and absorption [*Dvorak et. al., 1971*]. Histopathological examination of different organs showed no deposits of PB after oral administration of insoluble.

After intraperitoneal administration of $KFe[^{39}Fe(CN)_6]$ the substance was eliminated by the reticuloendothelial system. The first day 40.5% of the administered dose was excreted via the urine, with trace amounts in the feces. On the second day, 42% was found in the feces, with trace amounts in the urine. After four days, the body retention was 4.5% with most of it in the liver [*Muller, 1969*].

After intravenous administration of $KFe[^{39}Fe(CN)_6]$ and $K^{39}Fe[Fe(CN)_6]$ into rats, resulted in a different metabolic behaviour. While more than 50% of $K^{39}Fe[Fe(CN)_6]$ was excreted via the urine; only 0.06% of $KFe[^{39}Fe(CN)_6]$ was found in the urine. The fecal extraction for both was low [*Dvorak et. al., 1971*].

The LD_{50} based on rat data was calculated to be greater than 10 g/kg for orally administered doses and 1.13 mg/g for intraperitoneally administered doses [*Brenot et. al., 1967*].

DOSAGE

The recommended dosage is dependent on the severity of the thallium poisoning or cesium incorporation. In the reviewed literature, insoluble PB has been given from 3 to 20 g daily, divided into several doses (i.e., 2 to 4 times a day). In the case of Goiânia, Brazil there was a "*general tendency*" to keep increasing the dosage over time (3, 6, 10, and 20 g/day PO QID).

Treatment length usually continues until evidence of thallium or cesium contamination is no longer present in the urine or feces (i.e., urine with <1 mg/24h for thallium) [*Atsmon J. Et. al., 2000*]. The higher dose usually is used for acute poisoning with thallium.

Several reviewed articles mention ancillary treatment procedures applied in conjunction with administration of insoluble PB. These ancillary procedures included gastric lavage or induced emesis (i.e., if thallium ingestion was within 48 hours); hemodialysis, forced diuresis, and charcoal hemoperfusion in severe cases of intoxication with thallium. The use of laxatives (i.e., mannitol) to increase fecal excretion was also noted in several articles.

In a related publication by Melo *et.al.* (1994), the authors state that there was no statistically significant difference in biological half-lives due to the differences in dosages of insoluble PB that were prescribed to the patients. There was no discussion of findings by the authors of any correlation between the difference doses and the reduction in the biological half-live of either thallium or cesium. The following table is an example of the higher dose ranges found in the literature and the proposed package insert for treating Thallium and Cesium toxicity in both children and adults.

Source	**Thallium**		**Cesium**	
	Children	*Adults*	*Children*	*Adults*
Proposed Package Insert	3-20 g/day TID	3-20 g/day TID	3-20 g/day TID	3-20 g/day TID
ORISE IND application	3-20 g/daily	3-20 g/daily	3-20 g/daily	3-20 g/daily
IAEA Report – Goiânia	N/A	N/A	1-10 g/daily	1-10 g/daily

Some of the reported dosing schemes included an initial single "loading" dose of 1-3 g for both Thallium and Cesium poisoning. In all treatments, the dosing continued until no evidence of either contaminant was present in the feces and urine of patients. The appropriate daily dose of PB is based on the suspected or estimated level of internal ^{137}Cs contamination, e.g., 3 g daily for low level accidents; 3-10 g daily for intermediate or moderate levels; and, 10-20 g daily for high levels of internal contamination.

OVERDOSING

No studies on over-dosage of insoluble PB have been conducted. Adverse events related to overdosing of PB (doses greater than 10 g/day) have been mainly transient gastrointestinal discomfort, i.e., gastritis, constipation, and diarrhea.

PEDIATRIC POPULATION

There is limited information on pediatric population that has been contaminated with cesium and treated with insoluble PB. In the 1987 Goiânia accident, children (n=7) ages 4 to 9 years of age (14-27 kg) received three gm PB daily, and adolescents (n=5) ages 12 to 14 years (31-58 kg), received 10 gm PB daily. For children ranging from 7-12 years old, biological half-lives were in agreement with estimated retention model by Leggett [*Leggett, 1986*]. For children between 1 and 5 years old, the biological half-life values were almost twice those proposed by Leggett (1986). The following table shows the Goiânia children and adolescent data, including the daily dose corrected for weight, effective half-life during and after PB treatment, and the Percent Difference in the effective half-life between PB treatment and no treatment. The data demonstrated that within the group of children (4-9 yrs of age), PB response (reduction of ^{137}Cs effective half-life, $T_{1/2}$) was similar, 21-27 days (mean of 24 days, S.D., 2.6). While the data from the adolescents (12-14 years of age) had a greater variability in reducing ^{137}Cs effective half-life in response to PB treatment, 17-45 days (mean of 30 days, S.D., 12.0).

Gender	Age	Weight	Daily dose	Weight corrected daily dose	$T_{1/2}$ w/PB	$T_{1/2}$ w/o PB	% Difference
	(yrs.)	*(kg)*	*(gm)*	*(gm/kg)*	*(days)*	*(days)*	
f	4	14	3	0.214	21	39	0.18
f	5	20	3	0.150	22	42	0.20
f	7	22	3	0.136	21	42	0.21
m	7	23	3	0.130	27	47	0.20
m	7	23	3	0.130	23	33	0.10
m	6	26	3	0.115	25	46	0.21
m	9	27	3	0.111	27	44	0.17
m	12	31	10	0.323	25	49	0.24
m	14	38	10	0.263	24	43	0.19
m	13	52	10	0.192	45	65	0.20
m	13	55	10	0.182	17	78	0.61
m	13	58	10	0.172	41	75	0.34

PREGNANCY AND LACTATION

Insoluble PB is not absorbed from the GI tract; therefore, teratogenic effects or appearance in breast milk is not expected.

DRUG-DRUG INTERACTIONS

Very limited information on drug-drug interactions was found in the reviewed literature. A single mention of drug-drug interaction was found, tetracycline resorption was found to be retarded. The

simultaneous dosing of multiple radioprotectants in humans has not been evaluated in detail. There is a mention of such scenario in the animal model using rats, with three radioprotectants (calcium alginate, PB, and potassium iodide) and three radio-elements (^{85}Sr, ^{137}Cs, and ^{131}I). Long term use of some of these radioprotectants may be an issue such as in the case of potassium iodide may lead to hypothyroidism.

FOOD EFFECT

Food effect studies performed in humans or animals to assess Prussian blue efficacy when given with meals were not identified in the literature. In animal toxicology studies, Prussian blue was found to not be significantly absorbed into the blood. Thus, food effect on Prussian blue absorption are not relevant.

The purpose of a food effect study would be to determine the effect of the presence or absence of food on the ability of Prussian blue to capture cesium or thallium in the lumen of the gastrointestinal tract and increase their fecal excretion; thus interrupting their enterohepatic recirculation.

By interrupting the enterohepatic recirculation of cesium or thallium, it leads to a reduction of cesium or thallium in the blood, reducing the effective half-life of the contaminant. Therefore, theoretically, to increase the efficacy of Prussian blue in capturing cesium or thallium, it could be given with meals, for meals would stimulate bile excretion from the gall bladder coinciding with the presence of Prussian blue in the small intestine.

QUESTION BASED REVIEW

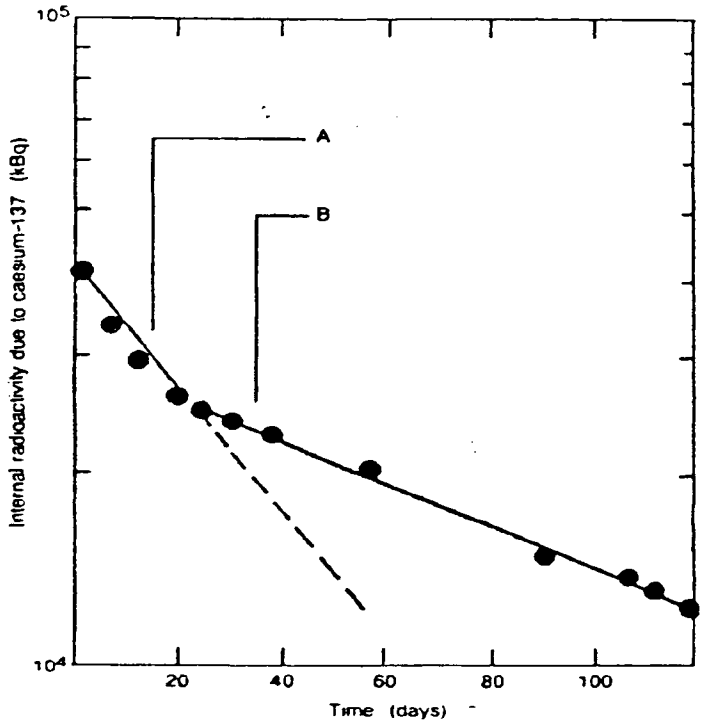
Are there any references to animal models that demonstrate PB efficacy?

There are several literature articles where animal models demonstrate Prussian Blue efficacy as a non-absorbed heavy metal trapper within the Gastrointestinal tract. As an example the following two studies are mentioned:

- A rat model with thallium as the intoxicant was used to compare the efficacy of Prussian Blue and various other products at 8-days post exposure [*Lehmann P.A., et.al., 1985*]. In this study, PB alone increased total elimination of thallium from 53% (control group with no treatment, n=10) to 82% (n=8) and the combination of PB+furosemide increased total elimination to 92% (n=8).
- For cesium, a rat model was used to compare the efficacy of Prussian Blue and other non-absorbed metal trapper products [*Nigrovic V., 1965*]. An increase of renal elimination of ^{137}Cs in humans given diuretics was found to be ineffective; therefore, PB was used to interrupt the reabsorption or "enteral cycle" of cesium from the gut. At 7-days post exposure, the control group had 80% of ^{137}Cs in the body as compared to the group treated with PB, 20-25%.

Are there any references to human data that demonstrate PB efficacy?

The results of fecal analysis from those patients contaminated with ^{137}Cs in Goiânia, Brazil and treated with Prussian blue resulted in higher activities of ^{137}Cs in feces, and whole body radioactivity counts showed increased removal from the body. This figure plots the whole body content of radioactive material from one Goiânia patient, ^{137}Cs, in the body (kBq) on the *y*-axis versus time in days on the *x*-axis. In the figure, the curve segment "A" shows the content of radioactive material, ^{137}Cs, in the whole body while under Prussian blue treatment of 10 gm daily. The curve segment "B" shows the content of radioactive material, ^{137}Cs, in the whole body after Prussian blue has been terminated.



Comparisons of whole body ^{137}Cs radiation content during and after Prussian blue treatment.

A – ^{137}Cs whole body radiation content (kBq) DURING PB 10 gm/day.

B – ^{137}Cs whole body radiation content (kBq) AFTER PB treatment is terminated.

Dotted line – *extrapolated* decrease in ^{137}Cs whole body radiation content (kBq).

Is there a set dose for Prussian blue (PB)?

The PB doses mentioned in the reviewed literature used to treat thallium or cesium exposure varied widely. It is clear that to reach maximal efficacy of PB, an optimal and constant concentration of PB needs to be maintained in the gut during the entire treatment period. In animal models (e.g., rats) a high dose of PB (e.g., 50 mg/day) for a long period of time (e.g., 17 days) did not lead to body mass or weight loss (under free food and water conditions). It seems that the time of treatment initiation is not as critical as the dose and duration of treatment. In the same animal model, extremely high PB doses (i.e., 100 mg/day) did not demonstrate a dramatic increase in efficacy over 50 mg/day doses. There is a publication [*Proceedings, Fd Cosmet Toxicol, 1959*] that estimates the human dose of PB to be 0.25 mg/kg/day based on the "customary" 100-fold safety factor over the no-effect level in rats for 90 days, 25 mg/kg/day.

Is there any evidence of the efficacy of PB in preventing the passage of thallium or cesium into breast milk?

While there are no direct studies in humans to evaluate this issue, there is study in a sheep model that provides evidence that PB does limit the transfer of cesium into breast milk [*Ioannides et.al., 1991*]. Female sheep, ewes, consumed an average of 2740 Bq [1 Becquerel (Bq) = 2.7 x 10-11 Curie (Ci)] from ^{137}Cs contaminated wheat and grass for two months. Half of the ewes (n=5) were given PB in solution (5 L/day at 1 g/L concentration) for 23 days. The milk from treated ewes had an 85% reduction of cesium contamination.

Are there examples of simultaneous multiple drug dosing?

Using an animal model, rats (n=121), a combination of calcium alginate, PB, and potassium iodide was used to evaluate drug combination efficacy against simultaneous multiple isotope exposure, ^{85}Sr, ^{137}Cs, and ^{131}I [*Kostial K. et. al, 1981*]. The mixture reduced *whole body retention* of ^{85}Sr by 10 times, ^{137}Cs by 93 times, and ^{131}I by 5 times (134 times in the thyroid), as compared to the control group. The author reported that there was no apparent interference in efficacy between the three radioprotectants used simultaneously and used separately. No major differences between the control and test groups were found in their body weight, hematological profile, trace element, or bone parameters. Although no pathophysiological changes were found, long term use of some of these radioprotectants may be an issue, for example potassium iodide may lead to hypothyroidism.

In another publication [*Kargacin et. al., 1985*] the authors combined oral administration (PO) of calcium alginate, PB, potassium iodide with intraperitoneal administration of Ca-DTPA or oral administration of Zn-DTPA in rats (n=36). The administration of high doses of Ca-DTPA lead to the loss of zinc and manganese mainly from the small intestine, skeleton, pancreas, and testes. Long term dosing (~10 days) of Ca-DTPA lead to mobilization or binding of endogenous essential trace metals in exchange for calcium and a consequent impairment of metal-controlled or activated systems. On a similar dosing regimen length and total dose, Zn-DTPA has lower toxicity shown by a lower mortality, absence of kidney, liver or small intestine lesions.

Is there documentation on the plausible side-effects of PB?

Extensive number of published studies using a wide range of doses and oral dosing regimens have not provided evidence of side-effects or adverse events beyond minor or mild transient gastrointestinal discomfort.

Is there a linear dose response for PB?

In a study using rats (n=40) exposed to ^{137}Cs, it was demonstrated that there is dose linearity from 1 to 50 mg/day, but little improvement between 50 to 100 mg/day [*Nigrovic V. et.al., 1965*].

Dosing	Body weight (gm)	Percent Injected Dose - % ID (range)	Percent of Control
Control – 0 mg/day	219	58.1 (63.3 – 53.4)	100
1 mg/day	215	9.42 (13.2 – 6.72)	16
10 mg/day	203	1.17 (1.64 – 0.84)	2
50 mg/day	186	0.57 (0.80 – 0.41)	1
100 mg/day	188	0.52 (0.73 – 0.37)	0.9

Are there other effective treatments to reduce cesium or thallium exposure?

Various treatments have been tested to eliminate cesium exposure with no conclusive nor reproducible results. These include administration of stable potassium (Mraz F., et. al., 1957; Richmond C.R., et.al., 1961; McNeill K.G., et. al., 1961; and Wasserman R.H., et. al., 1963), stable cesium (Kurlandskaya E.B., et. al., 1957; Ogawa E., et.al., 1958; Moskalev Y., et. al., 1961; and Furchner J.E., et.

al., 1962), diuretics (Rama-Sastry B.V., et. al., 1962; Rosoff B., et. al., 1963; and Rama-Sastry B.V., et. al., 1964), enzymes inhibitors (Richmond C.R., et. al., 1961), hormones (Dorfman R.I., et. al., 1949; Mraz F., et. al., 1956; and Mraz F., et. al., 1958), natural food products (Mraz F., et. al., 1957), ion exchangers (Mraz F., et. al., 1957), EDTA (Fateyeva M.N., et. al., 1960; and Geller L.I., et. al., 1963), and organic acids and salts (Takamiya K., 1960; Ryabova E.Z, et. al., 1958; Nigrovec V., 1963; and Nigrovic V., 1965).

From the database of reviewed published articles, which are identified as critical articles?

- Ionnides K.G., Mantzios A.S. and Pappas C.P. *Influence of Prussian Blue in reducint transfer of Radiocesium into Ovine milk.* Health Phys 60(2): 261-264, 1991
- Kargacin B., Maljkovic T., Blansua M., Kostial K. *The influence of a composite treatment for internal contamination by several radionuclides on certain health parameters in rats.* Arh Hig Rada Toksikol 36: 165-172, 1985
- Karcigan B. and Kostial K. *Reduction of ^{85}Sr, ^{137}Cs, ^{131}I and ^{141}Ce retention in rats by simultaneous oral administration of calcium alginate, ferrihexacyanoferrate(II), KI and Zn-DTPA.* Health Phys, 49 (5): 859-864, 1985
- Kostial K. et. al. *A mgethod for a simultaneous decrease of strontium, cesium and iodine retention after oral exposure in rats.* Int J Radiat Biol 37(3): 347-350, 1980
- Kostial K., Kargacin B., Rabar I., Blanusa M., Maljkovic T., Matkovic V., and Ciganovic M. *Simultaneous reduction of radioactive strontium, caesium and iodine retention by single treatment in rats.* Sc Tot Envir 22(1): 1-10, 1981
- Nigrovec V. *Correspondence: Enhancement of the excretion of radiocaesium in rats by ferric cyanoferrate (II).* Int J Rad Biol 7(3): 307-309, 1963
- International Atomic Energy Agency *The Radiological Accident in Goiania* IAEA STI/PUB/815, Vienna, 1988.

LABELING RECOMMENDATIONS

The sponsor provided a copy of their proposed *Package Insert* dated 06 December 2001. It described the mechanism of action and site of action of PB on both Cesium and Thallium internal contamination. There is a section in which the pharmacokinetic profile of Prussian Blue is described as well as the efficacy of PB in reducing the total radioactivity exposure. In the Summary of Administration section of the proposed Package Insert, there are Therapy Guidelines described in detail to help in selecting the appropriate dose and dosing regimens.

It is recommended that the sponsor add the following text to the Clinical Pharmacology section of the proposed package insert:

Insoluble Prussian Blue, Ferric(III) hexacyanoferrate(II), after oral ingestion is not absorbed through the intact gastrointestinal wall. Its clearance from the body depends on the gastrointestinal tract transit time.

PHARMACOKINETICS:

Absorption/Elimination:

In animal studies of pigs (n= 38), after a single dose of 40 mg of labeled Prussian Blue, 99% of the administered dose was excreted unchanged in feces. Absorption from multiple doses has not been studied.

2 page(s) of revised draft labeling has been redacted from this portion of the review.

CONCLUSIONS

- The **effectiveness of insoluble PB in the treatment of ^{137}Cs intoxication is clearly established** by comparing the biological half-life of ^{137}Cs in subjects not treated with insoluble PB against those treated with insoluble PB [*Melo et. al., 1994*]. Patients receiving insoluble PB, on average, ^{137}Cs biological half-life was reduced at least by one-third to half, 10-36 days versus 50-150 days, respectively [*ICRP No.30, 1979*].
- There is **no standardized pattern for treating patients** with insoluble PB. The dose and treatment duration varies depending on the level of toxicity, the toxic compound (cesium or thallium), and the overall clinical assessment of the patient. Ancillary treatment include gastric lavage or induced emesis (i.e., if thallium ingestion was within 48 hours); hemodialysis, forced diuresis, and charcoal hemoperfusion in severe cases of intoxication with thallium; and, the used of laxatives (i.e., mannitol) to increase fecal excretion.
- The **transient time of a dose of insoluble PB in humans is not available** in the reviewed literature. It is important to time the dosing of insoluble PB with normal billiary excretion (main route of excretion of ^{137}Cs, Moore *et. al.*, 1962) or an artificially induced billiary excretion (with high fat and high protein meals or with drug products that can induce billiary excretion).
  - Standard procedure in Nuclear Medicine or Radiology to study billiary function is to administer a small fatty, high protein meal approximately 15-minutes before image acquisitions [*Keyes et. al., 1975*]. It is suggested to increase the efficacy of insoluble PB in capturing any Cs or Tl contaminants, a small fatty, high protein meal be ingested before insoluble PB dosing to stimulate billiary excretion. There are approved drug products will also stimulate billiary excretion.
- The reviewed literature delineates **thallium and cesium metabolism differences** which lead to slight differences in treatment with insoluble PB. These differences should not affect the dose or dosing regimen and the use of PB in conjunction with other radioprotectants, such as Zn-DTPA.
- **No studies on overdose** of insoluble PB have been conducted in humans. The maximum tolerated dose should be considered for patients with severe acute thallium and/or cesium toxicity. Insoluble PB seems to not move from the gut lumen into the blood stream, hence it has been assumed to be relatively safe.
- **No well-controlled studies in children** were found in the reviewed literature. Based on case studies of 137-Cesium contaminated children (ages ranging 1-12 years). The biological half-life of cesium did not agree with the previously estimated and published values. [*Leggett, 1986*] This data showed

that Leggett's model may not be accurate for the children ages ranging 1 to 5 years. Further studies and a re-evaluation of the model needs to be completed. The dosing range for children in the reviewed literature has been the same as for adults, 2 to 20 g/day QID PO for several weeks until evidence of thallium or cesium contamination is no longer present in the urine or feces.

- **No studies in pregnant women, or breast-feeding mothers** have been conducted. Due to the characteristics of insoluble PB not being absorbed from the gut lumen into the blood stream, it has been assumed to be relatively safe.
- **Pertaining renally impaired and/or hepatically impaired patients,** no data was available nor have well controlled studies been conducted. Cesium will be excreted via both of the renal and fecal routes of elimination depending on the treatment applied. The effect of renal and/or liver impairment on the efficacy of insoluble PB to treat 137Cs is not assessed in any of the reviewed articles.

/S/

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Cc: HFD-160 51,700 IND (1X); DIV.FILE (1X); STEWART (1X); SANCHO (1X)
HFD-870 JHUNT (1X); MALINOWSKI (1X)
HFD-850 SHUANG
CDR Attn.: Barbara Murphy

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Appendix 1.

COMMON TERMS

Chronic dose – Means a person that received a radiation dose –internal or external source- over a long period of time.

Acute dose – Means a person that received a radiation dose –internal or external source- over a short period of time.

Somatic effects – Are effects from some agent, like radiation, that are seen and measurable in the casualty in response to the agent.

Genetic effects – Are effects from some agent, like radiation, that are seen in the offspring of the individual who received or was exposed to the agent. The agent must be encountered pre-conception.

Teratogenic effects – Are effects from some agent, like radiation, that are seen in the offspring of the individual who received or was exposed to the agent. The agent must be encountered during the gestation period.

Stochastic effects – Are effects that occur on a random basis with its effect being independent of the size of dose. The effect typically has no threshold and is based on probabilities, with the chances of seeing the effect increasing with dose (e.g., cancer).

Non-Stochastic effects – Are effects that can be related to the dose received or exposed. The effect is more severe with a higher dose, i.e., the radiation skin burn gets worse with an increase in radiation dose. It typically has a threshold, below which the effect will not occur.

Gray (Gy) – Is a unit used to measure a quantity called "absorbed dose". This relates to the amount of energy actually absorbed in some material, and is used for any type of radiation and any material. One gray is equal to one Joule (J) of energy deposited in one Kilogram (kg) of a material. The unit Gy can be used for any type of radiation, but it does not describe the biological effects of the different radiations. Absorbed dose is often expressed in terms of hundredth of a gray, or centi-gray (cGy). One gray is equivalent to 100 rads.

Sievert (Sv) – Is a unit used to derive a quantity called "equivalent dose". This related the absorbed dose in human tissue to the effective biological damage of the radiation. Not all radiation has the same biological effect, even for the same amount of absorbed dose. Equivalent dose is often expressed in terms of millionths of Sv, or micro-Sv (uSv). To determine equivalent dose (Sv), multiply the absorbed dose (Gy) by a quality factor (Q) that is unique to the type of incident radiation. One Sv is equivalent to 100 rem.

Becquerel (Bq) – Is a unit used to measure "radioactivity". One Bq is that quantity of a radioactive material that will have 1 transformation in one second. Often radioactivity is

expressed in larger unit like: thousands (kBq), one million (MBq), or even billions (GBq) of a Becquerel. As a result of having one Becquerel being equal to one transformation per second, there are 3.7×10^{10} Bq in one curie.

Roentgen (R) – Is a unit used to measure a quantity called "exposure". This can only be used to describe an amount of gamma and X-rays, and only in air. One roentgen is equal to depositing in dry air enough energy to cause 2.58 E-4 coulombs per kilogram. It is a measure of the ionizations of the molecules in a mass of air. The main advantage of this unit is that it is easy to measure directly, but it is limited only for deposition in air, and only for gamma and x-rays.

Rad (Radiation Absorbed Dose) – Is a unit to measure a quantity called "absorbed dose". This related to the amount of energy actually absorbed in some material, and is used for any type of radiation and any material. One rad is defined as the absorption of 100 ergs per gram of material. The unit rad can be used for any type of radiation, but it does not describe the biological effects of the different radiations.

Curie (Ci) – Is a unit used to measure "radioactivity". One curie is that quantity of radioactive material that will have 37,000,000,000 transformations in one second. Often radioactivity is expressed in smaller units like: thousands (mCi), one millionths (uCi), or even billionths (nCi) of a curie. The relationship between Becquerels and Curies is: 3.7×10^{10} Bq in one Ci.

APPENDIX 2.

ACUTE RADIATION SYNDROME (ARS) SYMPTOMOLOGY

Radiation exposure greater than 1 Gy may lead to Acute Radiation Syndrome (ARS). ARS follows a predictable pattern after substantial exposure or contamination. The following table categorizes symptoms based on different radiation dose ranges (i.e., subclinical, sublethal, and lethal) for patients exposed to external or internal absorbed radiation.

Phase of Syndrome	Features	Subclinical range		Sublethal range		Lethal range	
		0-1 Gy	1-2 Gy	2-6 Gy	6-8 Gy	6-30 Gy	>30 Gy
Initial or prodromal	Nausea, vomiting Time of onset	None	5-50 % 3-6 hrs	50-100 % 2-4 hrs	75-100 % 1-2 hrs	90-100 % <1 hr	100 % <1 hr
	Diarrhea Time of onset			<10 % (Moderate) 3-8 hrs	>10 % (Severe) 1-2 hrs	100% (Severe) <1 hr	
	Headache Time of onset		Slight	50 % (Moderate) 4-24 hrs	80 % (Moderate) 3-4 hrs	80-90 % (Severe) 1-2 hrs	
	Body temperature Time of onset			80-100 % (fever) 1-3 hrs	100 % (high fever) <1 hr	100 % (high fever) <1 hr	
	Duration Lymphocyte count		<24 hrs	<24 hrs <1000 at 24 hrs	<48 hrs <500 at 24 hrs	<48 hrs	
	CNS function	No impairment	No impairment	Routine task performance Cognitive impairment for 6-20 hrs	Simple and routine task performance Cognitive impairment >24 hrs	Progressive incapacitation	
Latent	Duration	>2 weeks	7-15 days	0-7 days	0-2 days	None	
Manifest illness	Signs and symptoms	None	Moderate leukopenia	Severe leukopenia, purpura, hemorrhage, pneumonia, hair loss after 3 Gy		Diarrhea, fever, electrolyte disturbance	Convulsions, ataxia, tremor, lethargy
	Time of onset		>2 weeks	2 days – 2 weeks		2-3 days	
	Critical period		None	4-6 weeks		5-14 days	1-48 hrs
	Organ system	None		Hematopoietic and respiratory (mucosal)		GI tract (mucosal)	CNS
Hospitalization	% Duration	0	<5 % 45-60 days	90 % 60-90 days	100% 90+ days	100 % 2 weeks	100 % 2 days
Fatality		0 %		0-80 %	90-100 %	90-100 %	
Time to death				3 weeks – 3 months		1-2 weeks	1-2 days

Acute radiation exposure can begin to cause death at doses of 1.5 Gy to the whole body. The LD 50/60 (radiation dose which would expect to kill 50 percent of the target population in 60 days) for

patients with acute radiation exposure receiving "minimal" treatment would be ~3.5 Gy and those receiving "supportive " treatment would be ~5 Gy. Organ systems damaged, in order of increasing radiation dose, are the blood-forming system, the gastrointestinal tract, and the nervous and circulatory systems.

Delayed effects from radiation include cancer and cataract formation, which may occur several years after exposure. Delayed effects may be observed in persons who survive high-dose radiation exposure or have received doses of radiation over time. Many delayed effects are referred to as stochastic effects because the probability of the effect and not the absolute appearance of the effect increases with radiation dose.

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