

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-626

MEDICAL REVIEW

**MEDICAL OFFICER REVIEW
PRUSSIAN BLUE**

IND: 51, 700
Drug: Generic: Prussian Blue, Berlin Blue
Chemical: Ferrichexacyanoferrate $\text{Fe}_4[\text{Fe}(\text{CN})_6]_3$
Trade: Radiogardase- _____

Pharmacological Category: Radioprotector

Route of Administration: Oral

How supplied: Gelatin capsules with 500 mg ferrichexacyanoferrate

Proposed Dose: 3 g PO TID (adults and adolescents),
1 g PO TID (children 4-12)

Proposed Indications:

- 1) Enhancement of the excretion of Cs-137 in patients with known or suspected internal contamination with Cs-137
- 2) Enhancement of the excretion of thallium in patients with known or suspected internal contamination with thallium

Sponsor: Oak Ridge Institute for Science and Education (ORISE)
Manufacturer: Heyl GMBH (Germany)
Related Drugs; _____

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EXECUTIVE SUMMARY

Recommendation:

Prussian Blue should be approved for marketing for the following indications

Approval is contingent upon the provision of adequate chemistry and manufacturing controls data, and upon acceptable commitments for post approval studies. These commitments include the following.

1. Epidemiological, longitudinal follow-up of patients treated with PB is needed to assist in determining how long patients should be treated. These data should be in the form of a patient registry that follows patients for life. This registry should be maintained and analyzed by the NDA holder.
2. _____
3. Dose adjustment for pediatric patients from neonates to 2 years.
4. _____
5. _____

Summary of Clinical Findings

^{137}Cs is a γ emitting radioactive isotope, with a physical half-life of 30 years. It is present in nuclear weapons fallout, nuclear reactor cores and spent reactor fuel rods. It is used in clinical, laboratory and industrial sealed radiation sources as ^{137}Cs chloride, a soluble powder. Its widespread availability makes it a possible component in a so called "dirty bomb" in which radioactive material is dispersed in a populated area with conventional explosives. ^{137}Cs chloride has been shown, in animal experiments, to be readily absorbed from the GI tract and distributed uniformly throughout the body. It is slowly eliminated from the body with an effective half-life ranging from 40 to 140 days in adult humans. The toxicity of ^{137}Cs results from its radioactivity, not from its chemical properties.

The most important source of clinical data on the treatment of ^{137}Cs contamination with Prussian Blue is the 1987 incident in Goiania, Brazil, in which 249 people were contaminated, of whom 46 were treated with Prussian Blue. Data from this incident

showed that patients who receive a radiation absorbed dose of 1 Gy or more, from internal ^{137}Cs are at high risk of developing acute bone marrow failure. Morbidity and mortality increase with increasing dose. At doses above 5 or 6 Gy bone marrow failure becomes 100% lethal. Treatment options for bone marrow failure are limited in these patients since patients who are still internally contaminated can not receive a bone marrow transplant. For doses below 1 Gy the principal toxicity is radiation induced cancer, which may not occur for years or even decades after exposure. The excess cancer risk is believed to be proportional to the radiation absorbed dose. For adults receiving photon irradiation, the excess cancer mortality has been estimated to be about 0.04 per Gy (4 excess cancer deaths in a population of 100 persons each receiving a whole body dose of 1 Gy)[Hall E, Radiobiology for the Radiologist, 4th edition, J Lippincott Co. Philadelphia, Pa, 1994]

^{137}Cs is eliminated in both the urine and the bile, but most of the cesium carried in the bile to the small intestine is reabsorbed from the intestines (entero-hepatic circulation). The only effective means of treating contamination with any radioactive isotope is to increase the rate at which the isotope is eliminated from the body. Prussian Blue, given orally, increases the rate of elimination of ^{137}Cs by binding it in the GI tract so that it is eliminated with the Prussian Blue in the feces.

Thallium is a highly toxic heavy metal which has been used, in the past, as rat poison, and which undergoes a similar entero-hepatic circulation as cesium.

Insoluble Prussian Blue is an insoluble ferrocyanide compound, which binds both cesium and thallium in the gut, interrupting the entero-hepatic circulation, increasing the rate of fecal elimination and decreasing the effective whole body half-life. On the basis of animal studies and anecdotal clinical data, Prussian Blue has been generally recognized by the medical community as an effective treatment for thallium poisoning and ^{137}Cs contamination, since the 1960s. Prospective clinical trials have never been performed to demonstrate the safety and efficacy of Prussian Blue in humans.

Clinical and pre-clinical literature on the use of Prussian Blue for the treatment of ^{137}Cs and thallium contamination were reviewed. Data is available from retrospective analyses of Prussian Blue treatment of a total 65 patients with ^{137}Cs contamination, 7 normal volunteers who voluntarily ingested tracer doses of ^{137}Cs , and 34 patients with thallium poisoning. Of these the critical information is derived from 46 patients who were contaminated with ^{137}Cs in an accident in Goiania, Brazil. Pre-clinical data are also available on rats, dogs and farm animals treated with Prussian Blue for ^{137}Cs contamination.

Clinical data consistently demonstrates the safety and efficacy of Prussian Blue treatment for cesium and thallium contamination. Prussian Blue was found to be effective in increasing the rate of elimination of ^{137}Cs from the body. In the Goiania patients, Prussian Blue was found to reduce the ^{137}Cs whole body effective half-life (see appendix 2) by 69% in adults, by 46% in adolescents and by 43% in children. In other studies, Prussian Blue was found to reduce the whole body effective half-life in patients by a factor of 3. Prussian Blue treatment reduced the half-life of thallium by about 2/3.

Prussian Blue appeared to be well tolerated and the only adverse events reported were cases of mild to moderate constipation, which were effectively treated with a high fiber diet. Asymptomatic biochemical hypokalemia was reported in 3 Goiania patients while under treatment with Prussian Blue, but these patients were also taking diuretics. The hypokalemia was successfully treated with potassium supplements.

Experiences were similar in pediatric patients from 4-12 years, adult patients up to 49 years and in pregnant women. Collectively, the data are sufficient to support treatment of Prussian Blue at a dose of 3-10 g/day PO in divided doses in adults and at a dose of 1-3 g/day in children and adolescents. Treatment should begin immediately after suspected contamination occurs.

INTRODUCTION:

Type of NDA Submission

Although the data have been reviewed as an NDA. At this point, the Prussian Blue is still under IND. The database consists entirely of papers from the published literature from 1967 to 2001. Except for the data generated from the incident at Goiania the published clinical reports are anecdotal with each publication reporting on, at most, a handful of patients contaminated with ^{137}Cs or Thallium. No prospective clinical trials have been performed by the sponsor or reported in the clinical literature. Controlled clinical trials are not possible since it would be unethical to deliberately contaminate human subjects with ^{137}Cs . All published clinical reports, including the reports from Goiania, are retrospective analyses. The quality and reliability of the data varied from publication to publication.

In the Goiania incident, exposure to ^{137}Cs varied greatly from patient to patient. Dosing with Prussian Blue was individualized by the treating physicians. Some details of treatment, such as treatment duration, are not available for most patients. There was minimal long-term follow-up, so that the success of treatment in reducing the incidence of radiation induced cancer, can not be assessed. Effectiveness of the treatment was determined by the increase in the rate of elimination (decrease in the effective whole body half-life) of ^{137}Cs , which was used as a surrogate for improved clinical outcome.

There was no systematic monitoring for adverse events in any of the published reports. The safety of Prussian Blue can only be assessed from pre-clinical data and from the absence of any clinical reports of serious or severe adverse events attributed to Prussian Blue. However in the most heavily contaminated individuals, who would have received the highest doses of Prussian Blue and have been treated for the longest times, any toxicity of Prussian Blue may have been masked by the acute radiation toxicity of the ^{137}Cs .

Because of the nature of the data on which this review is based, the standard format for clinical NDA reviews would not be appropriate in this case. Because the nature and

quality of the data differed greatly from publication to publication, it would be difficult to combine the results of these publications in a single integrated summary of safety or efficacy. In this review the material in each publication is discussed separately.

The key publications were the 2 IAEA reports and the 5 journal articles concerning the Goiania incident. The Goiania data represents the only systematic attempt to collect and analyze data on a substantial number of patients treated with Prussian Blue for ^{137}Cs contamination. Other publications are either anecdotal reports, review articles or foreign language articles with little detail given on either the methods or the results of treatment. The articles on thallium poisoning are also anecdotal. Some articles report on as few as 1 or 2 patients. Thallium was used in the past as rat poison, but has not been used for that purpose, in the US for many years. Consequently, cases of thallium poisoning are now extremely rare.

Material reviewed:

- Two International Atomic Energy Agency Monographs and five journal articles concerning 46 patients treated with Prussian Blue for ^{137}Cs contamination the Goiania incident,
- Four journal articles concerning 26 other patients and normal volunteers treated with Prussian Blue for ^{137}Cs contamination.
- Three journal articles concerning the treatment of 34 patients for acute thallium poisoning
- Nine pre-clinical journal articles concerning the treatment of rats, dogs and domestic farm animals, with Prussian, blue for ^{137}Cs contamination.

Background

^{137}Cs is a fission fragment that is present in nuclear reactor cores and in spent nuclear fuel rods. It is also used in medicine as a radioactive source in teletherapy (external beam) radiotherapy treatment machines and in sealed sources used for brachytherapy (radioactive implants). It is also used in sealed sources in industry. It has a half-life of 30 years and emits a 661 Kev photon as well as a 1 Mev and a 0.5 Mev β . Cesium is an alkali metal that lies under sodium and potassium in the periodic table. It crosses the cell

membrane more slowly than potassium. ^{137}Cs chloride, when ingested, is rapidly absorbed from the GI tract and is deposited uniformly throughout the body. Elimination is bi-exponential with about 10 % of the ingested dose eliminated rapidly in the urine in 2-3 days. The other 90% is eliminated with a biological half-life of several months, in adults. The slow component represents both fecal and urinary elimination of cesium deposited in tissues. The long half-life is partly a consequence of recycling whereby cesium is reabsorbed from the gut, absorbed from the portal vein by the liver and excreted back into the gut in the bile. A small, but detectable amount of radioactivity may remain in the body indefinitely.

When ingested, insoluble Prussian Blue colloid can break the entero-hepatic cycle by binding cesium in the gut so that the bound cesium is eliminated with the insoluble Prussian Blue in the feces. The average effective half-life of the slow component of elimination can thereby be reduced by about a factor of 3.

Since ^{137}Cs is deposited uniformly throughout the body the radiation absorbed dose distribution will be uniform. The probability of bone marrow death or severe bone marrow suppression is determined by the whole body radiation absorbed dose (Gy). The radiation absorbed dose is proportional to the product of the initial whole body activity and the effective half-life. For long-lived isotopes such as ^{137}Cs , the effective half-life is essentially equal to the biological half-life (see appendix 2). The objective, of treatment of internal contamination, is to decrease the biological half-life and thereby to decrease the radiation absorbed dose. Treatment can not effect the radiation absorbed dose already received before treatment is started and therefore it is essential to begin treatment of contaminated individuals as quickly as possible. Since elimination takes time, the patient will still receive additional radiation absorbed dose while under treatment, and will still be contaminated for some time after treatment is initiated

Prussian Blue is insoluble, is not absorbed from the GI tract, and is not pharmacologically active. When ingested it is eliminated unchanged in the feces. Prussian Blue is known to bind both cesium and thallium. Thallium salts are known to be highly toxic and have been used, in the past, as rat poison. A dose of 1 gm of thallium is lethal in man. There

have been numerous reported cases of thallium toxicity due to accidental or intentional ingestion of thallium salts, usually as the result of either homicide or suicide attempts. Prussian Blue has been used as an antidote for thallium poisoning for many years. The usefulness of Prussian Blue in the decontamination of internal contamination with ^{137}Cs , has been known since Madshus and Stromme tested it on rats, dogs and themselves, after voluntarily ingesting a trace dose ($1\mu\text{Ci}$) of ^{137}Cs , in 1968.

The largest series of patients treated for internal contamination with ^{137}Cs resulted from the incident at Goiania Brazil in 1987. In this incident, the source assembly from an abandoned ^{137}Cs medical teletherapy unit was removed by scavengers and sold as scrap. The source capsule was breached and the cesium chloride powder, which glowed in the dark, was distributed to friends and relatives. Some food was contaminated. Before the authorities became aware of the situation, 249 individuals had been contaminated with soluble ^{137}Cs -chloride powder. Treatment was given to the 46 patients with the highest internal contamination. Four (4) of these patients died of radiation induced bone marrow failure.

Given the safeguards in place for the handling of radiation sources, it is extremely unlikely that a similar incident would occur in the US. However, since September 11, 2001 there has been increasing concern about the possibility of a deliberate release of radioactive material into the environment by terrorists using a so called "dirty bomb" (radioactive material dispersed in a populated area by conventional explosives). Cesium-137 would be of particular concern since it is used as soluble ^{137}Cs chloride in medical cesium sources. It would therefore be prudent to have drugs available that could be used for the treatment of ^{137}Cs contamination.

REVIEW OF THE LITERATURE

THE GOIANIA INCIDENT: INTERNATIONAL ATOMIC ENERGY AGENCY (IAEA) REPORTS

1) **The Radiological Accident in Goiania: Report of the Review Meeting on the Goiania Accident Rio de Janeiro 18-22 July 1988**-International Atomic Energy Agency Vienna 1988 ISBN 92-0-129088-8.

Type of Study: Retrospective analysis of all aspects of the 1987 Goiania incident.

2) **Dosimetric and Medical Aspects of the Radiological Accident in Goiania in 1987** Gustafsson M., Turai I. IAEA-TECDOC-1009 International Atomic Energy Agency, Vienna (1988).

Type of Study: Retrospective crossover study of persons exposed to ^{137}Cs in the 1987 Goiania incident. The primary efficacy variable is whole body half-life of ^{137}Cs .

Reviewer's Comment: As there is considerable overlap in the information provided in these two International Atomic Energy Agency Monographs, they are reviewed together. The Radiological Accident in Goiania: Report of the Review Meeting on the Goiania Accident Rio de Janeiro 18-22 July 1988 is a general description of the incident and its aftermath. Dosimetric and Medical Aspects of the Radiological Accident in Goiania in 1987 as its title implies, concentrates on the medical and technical aspects of patient treatment. There is also some overlap in the information presented in these monographs and the journal literature on the Goiania incident discussed below

Also, in the latter article treatment efficacy was assessed by comparing in each patient, the whole body effective half-life during Prussian Blue treatment to the whole body effective half after treatment had been discontinued. Whole body effective half-life is a surrogate variable. A clinically significant outcome variable would be survival, or decreased cancer incidence. While it is known, from radiation dosimetry models, that

radiation absorbed dose is proportional to effective half-life, and it is generally believed that cancer risk increases linearly with radiation absorbed dose, a direct correlation between effective half-life and either survival or excess cancer risk has not been shown in this study

The Incident: In 1985 a clinical ^{137}Cs teletherapy machine was abandoned when a radiotherapy institute, in the city of Goiania, Brazil, moved to new quarters. The source containing 1375 Ci of ^{137}Cs -chloride powder was left in place, in the machine. In 1987, scavengers, looking for scrap metal, removed the source assembly and sold it to a junk-yard. The junk-yard owner attempting to dismantle the source assembly, breached the source capsule releasing ^{137}Cs chloride powder. The powder was seen to glow blue in the dark (the blue glow was later found to be Cerenkov radiation in water that had condensed on the cesium chloride), and family and friends came to look and take small amounts of powder away with them. Powder was given to children to play with. People ate with contaminated hands. It was not until about two and a half weeks after the source capsule was breached that authorities became aware of the incident and began to initiate radiation safety measures and medical treatment of irradiated and contaminated individuals. By that time, 249 people had become contaminated. Whole body radiation absorbed dose estimates were obtained by analysis of chromosome aberrations in cultured peripheral lymphocytes. Individuals were found to have received whole body radiation absorbed doses up to 7 Gy.

Reviewer's comment: The use of chromosome aberrations in cultured peripheral lymphocytes (in vivo dosimetry) is a standard method of estimating radiation absorbed dose in the absence of a direct measurement of radiation exposure (e.g. by film badge). The LD_{50} dose for bone marrow death in humans is 4 Gy. It is therefore possible that one or more of the Goiania patients who died, may have already received a lethal dose of whole body radiation before Prussian Blue treatment could be started. This illustrates the need to begin treatment as soon as possible. The only possible treatment for someone who has received a lethal dose of whole body radiation is bone marrow transplant, but, of course, this can not be done while the patient is still contaminated. Bone marrow transplant was not attempted on any of the Goiania patients. Patients who have received

a high but sub-lethal dose of radiation may require supportive care for severe bone marrow depression in addition to the Prussian Blue treatment to eliminate the isotope from the body.

Patient Screening and Pharmacokinetics: Screening patients for ^{137}Cs internal contamination was initially performed by in vitro assay of radioactivity in feces and urine. Total urine and feces from hospitalized patients were collected. Counts were obtained with a NaI(Tl) detector and ^{137}Cs activity was determined. All existing whole body counters in Brazil had been designed only for determination of low level contamination, and the activities in the Goiania patients were too high for these systems. A special whole body counter for in vivo measurement was designed and constructed in a Goiania hospital but this counter was not functional until about a month and a half after the incident. There was an overlap period during which both in vivo (whole body counter) and in vitro (feces and urine) measurements were obtained. There was good agreement between the effective whole body half-lives obtained from in vivo and from in vitro data. Animal data has suggested that 10% of the activity is eliminated rapidly by fast component of elimination with a short half-life, T_1 , of about 3 days while 90 % of the isotope is eliminated with a longer half-life, T_2 , of several months.

Reviewer's Comment: The rapid component of elimination may represent elimination from the blood while most of the ^{137}Cs has not yet been distributed from the vascular compartment to other body compartments. Once the ^{137}Cs has been uniformly distributed through the whole body, the rate limiting step in the slow elimination phase may be the leakage of the isotope from the other body compartments back into the vascular compartment. Cesium is in the same part of the periodic table as Potassium, which is an intra-cellular ion. It is rapidly pumped from the serum to the intracellular compartment and leaks only slowly back into the vascular compartment.

Because of the delay in reporting the incident, all information on the fast component of elimination in the Goiania patients was lost. The data below therefore refers to the slow component only. It was noted that 4 patients a still had measurable ^{137}Cs activity at 4

years post exposure, suggesting that a small amount of isotope may be eliminated very slowly with a half-life measured in years.

Reviewer's comment: The data is insufficient to even attempt to quantify this very slow component of elimination, but the amount of isotope involved is likely to be negligible.

The Goiania data were used to determine the intermediate half-life (T_2) in humans. This is shown in table 1 below. The mean half-life is longer in males than in females. The half-life in children is variable increasing with weight.

Table 1: Whole body intermediate half-life (T_2) of ^{137}Cs in days (untreated) obtained from data on 57 Goiania patients			
	Mean	SD	Range
Adult Males (n=15)	89	21	66-141
Adult females (n=15)	63	15	39-90
Infants (age 2-6 mos.)			15-20
Children (infants + children n = 27)	Intermediate between infants and adults and dependent body weight*		

*For children between 5 and 10 years old and a weight between 16 and 30 kg, the half-life in days can be fitted to the equation $T_2 = 4.9W^{0.693}$ with a correlation coefficient, $r^2 = 0.99$

Treatment with Prussian Blue: The primary route of excretion of ^{137}Cs is in the urine. ^{137}Cs is also excreted by the liver in the bile but most of this is reabsorbed from the gut (entero-hepatic circulation). Without treatment 80% of the excreted ^{137}Cs is in the urine and 20% is in the feces. Prussian Blue is given orally and is not absorbed from the gut. Prussian Blue binds ^{137}Cs , interrupting the entero-hepatic circulation and increasing the elimination of ^{137}Cs in the feces. Of the 249 persons contaminated, 46 individuals were determined to have sufficient internal contamination to require Prussian Blue treatment.

Reviewer's Comment: The fact that only 46 individuals were treated with Prussian Blue, implies that a decision was made to treat only the most heavily contaminated individuals, even though ^{137}Cs contamination, at a low level may carry an increased risk of cancer or

leukemia. The cutoff level of contamination, at which patients were treated with Prussian Blue, was not stated

Treatment was started, at the earliest 10, days after ingestion. The adult doses were 3, 6 or 10 gm/day, PO in divided doses, depending on the level of contamination. The dose was increased to 20 gm/24 hrs. in 4 patients but was immediately reduced when the patients developed "gastric distress".

Reviewer's comment: The term "gastric distress", used in these reports, is not defined, but it could presumably refer to epigastric pain or to nausea and vomiting. The duration of treatment with Prussian Blue is not discussed. Some patients may have had their dose of Prussian Blue reduced as the amount of residual activity decreased. Presumably treatment was individualized and depended on the level of contamination and the response to treatment. The criterion for terminating Prussian Blue treatment is not stated. Whether treatment was stopped abruptly, or whether the dose was decreased with time is not discussed. The total length of treatment presumably varied from patient to patient.

Evaluation of Efficacy of Prussian Blue Treatment: Pharmacokinetic data and whole body counts were obtained both during Prussian Blue treatment and after treatment had stopped. It is therefore possible to compare effective half-lives in the same patient, while being treated and while not being treated. A significant increase in the effective half-life occurred when treatment was discontinued. It is assumed that the post treatment half-life would be the same as the half-life for an untreated patient.

Reviewer's comment: Since the effective half-life under treatment, was compared, for each patient, with the effective half-life after treatment was stopped, this can be considered a crossover study with each patient serving as his/her own control.

Values for the effective half-life during treatment and after the discontinuation of treatment are shown in table 2, for different age groups and for different doses of Prussian Blue.

Group	Age	Dose gm/day	No. of Pts.	Under Treatment T _{1/2}	Post-Treatment T _{1/2}
Adults	> 18	3	6	25 ± 9	80 ± 15 (all 26 adult patients)
Adults	>18	6	10	25 ± 15	
Adults	>18	10	5	26 ± 6	
Adolescents	12-14	< 10	5	30 ± 12	62 ± 14
Children	4-9	< 3	7	24 ± 3	42 ± 4

Prussian Blue reduces the whole body half-life of ¹³⁷Cs by 69% in adults, by 46% in adolescents and by 43% in children. The half-lives under treatment for adults, adolescents and children are comparable while the untreated half-life is significantly shorter in adolescents and children than in adults.

The fact that Prussian Blue increases the rate of fecal elimination of ¹³⁷Cs can be verified by considering the ratio of the rate of elimination in the feces to the rate of elimination in the urine (the feces to urine ratio). The feces to urine ratio has been obtained for 10 patients who received different doses of Prussian Blue. Some patients received more than one dose at different times, so the data base includes 4 patients who received 10 g/day, 10 patients who received 6 g/day 6 patients who received 3 g/day and 6 patients receiving no treatment. The results are given in table 3.

Prussian Blue dose gm/day	No Treatment	3	6	10
Number of patients	6	6	10	4
Feces/Urine Ratio	0.23 ± 0.44	1.5 ± 0.35	1.9 ± 0.50	4.6 ± 1.1

Thus the feces/urine ratio increases with increasing dose of Prussian Blue. This increase, however, does not result in a shorter half-life with increasing dose above 3 g/day (table 1). A likely explanation is that the increased rate of fecal elimination results in a decrease in serum concentration which in turn results in a decreased rate of urinary elimination. The increase in the feces/urine ratio results from both an increase in the rate of fecal elimination and a decrease in the rate of urinary elimination while the total rate of elimination is relatively independent of dose. The feces to urine ratio is not a good indicator of the effectiveness of different doses of Prussian Blue.

Reviewer's comment: The results for different doses of Prussian Blue are not strictly comparable, since it may be the case that the patients with the largest amount of internal contamination received the highest doses of Prussian Blue. It should not therefore be concluded, from the data in table 1, that the lower doses of Prussian Blue are adequate in all cases.

Toxicity of Prussian Blue: The only side effect of Prussian Blue that is mentioned, for doses of 10 g/day or less is "intestinal constipation" which occurred in the majority of patients. The severity of this complication or variation of the incidence with Prussian Blue dose is not discussed. As previously noted, patients given a dose of 20 g/day developed "gastric distress".

Reviewer's comment: Constipation during Prussian Blue treatment will increase the time that ¹³⁷Cs bound to Prussian Blue remains in the intestines and will therefore increase the radiation absorbed dose to the intestines. For this reason, constipation during Prussian Blue treatment should be treated with laxatives. The term "gastric distress" is not defined, but could presumably refer to epigastric pain or nausea and vomiting. Obviously, standard methods of reporting adverse events, such as the COSTART system, have not been used in the Goiania literature.

¹³⁷Cs Contamination and Pregnancy One woman ingested 0.2MBq (0.005 mCi) Cs 137 during the 4th month of pregnancy. Because of the low dose this patient was not treated with Prussian Blue. The woman was followed during pregnancy and the mother

and baby were followed after delivery. There was no change in the woman's whole body half-life at delivery, the half-life being 46 days both before and after delivery. At delivery, the whole body activity was measured in the mother, the infant and the placenta. The activity concentration in the mother, baby and placenta were 912, 971, and 919 Bq/kg respectively, indicating that the ^{137}Cs passes easily through the placenta and is equally distributed through the maternal fetal and placental tissues. The infant was breast fed for the 60 days and during this time the total body activity in the infant did not change, indicating that ^{137}Cs lost in the urine and feces was replaced by an equal amount in the breast milk. After weaning, the infant's time activity curve ran parallel to the mothers with a half-life of 43 days.

Reviewer's comment: Since there is no mention of clinically significant pregnancy complications or birth defects, that could be attributed to the ^{137}Cs contamination, it can be assumed that there were none. This would not be surprising in view of the very small amount of activity ingested. In retrospect, the decision not to treat this pregnant woman with Prussian Blue may have been justified. However because of the radiation dose received in-utero, both from internal contamination and from isotope in the mother, the child may have an increased lifetime risk of cancer, and there may be a risk of genetic defects in future generations. Since there is only a single individual involved, this increased risk could not be quantified, even if this individual were followed for life. The constant whole body activity, in the infant, during breast feeding, makes it prudent for women who are internally contaminated with ^{137}Cs to refrain from breast feeding. A small number of pregnant women were exposed to radiation from fallout in the Chernobyl accident. There is evidence from Chernobyl, suggesting retarded mental development and behavior problems in children exposed to radiation in-utero. However there is no discussion of any assessment of mental development for the individual exposed in- utero at Goiania.

A second woman was contaminated with 300 MBq (8 mCi) ^{137}Cs and was treated with Prussian Blue. She became pregnant 3 years and 8 months after contamination. At this time the retained activity was low but still measurable. At birth the concentration of ^{137}Cs in the mother was 13 times higher than in the infant, which is probably due to the

very slow rate of elimination of residual activity ($T_{1/2} = 475$ days) at 3-4 years post ingestion

Reviewer's comment: This case illustrates that, even after ingestion of a substantial dose of ^{137}Cs , a woman who is treated with Prussian Blue, does not necessarily become sterile. Once again, the absence of discussion of any notable pregnancy complications or birth defects, makes it likely that there were none.

The whole body radiation absorbed doses, from internal ^{137}Cs , for 21 individuals treated with Prussian Blue, were calculated. These doses ranged from 0.97 Gy to 0.0046 Gy. The doses that they would have received without Prussian Blue treatment were also calculated and these ranged from 5.0 Gy to 0.022 Gy. The LD_{50} for bone marrow death is 4 Gy. The factor by which the whole body radiation absorbed dose was decreased by Prussian Blue treatment ranged from 1.7 to 6.2.

Radiation absorbed doses were also obtained from cytogenetic analysis for 129 patients. These doses would not necessarily correspond to doses calculated for internal contamination since many patients received external radiation from handling the ^{137}Cs source as well. Of the 129, 105 had received doses between 0.1 and 0.49 Gy. The remaining 24 patients received doses of 0.5 to 5.99 Gy. No patient received a whole body dose greater than 6 Gy. Of these 14 patients developed severe bone marrow depression characterized by leucopenia, thrombocytopenia and bone marrow hypoplasia. The eight patients with the most severe cases were treated with G-CSF. Treatment also included gut sterilization with oral antibiotics, treatment of fever with triple IV antibiotics and transfusion with irradiated blood products as needed. Despite this treatment, 4 of these 8 patients died, 2 from generalized internal bleeding and 2 from antibiotic resistant klebsiella infections. The 4 patients who died had all received whole body radiation doses of between 4 and 6 Gy.

Follow-up 1989-1997: The most severely exposed patients (number not specified) were followed with quarterly peripheral blood counts and yearly bone marrow aspirate and biopsy. All but four patients have normal blood counts. The four patients have mild and transient leukopenia, with a normal appearing marrow and no clinical symptoms. A number of patients developed GI complaints such as heartburn dyspepsia and nausea, but since most patients were heavy smokers and drinkers, ate spicy food and came from an area where intestinal parasites were endemic, these complaints may not be the result of radiation exposure. One patient died of end stage liver failure in 1994, but his condition was diagnosed as alcoholic liver disease. All 9 males who had received a whole body dose of 1 Gy or higher were oligospermic or azospermic. However one woman who had received a whole body dose of 1Gy became pregnant and gave birth in 1992.

Reviewer's Comment: Although data from 8 years of follow-up were reported, there is no mention of cases of leukemia or of solid tumors developing in these patients> It is possible that there were none. The small number of patients and the rather short follow-up period may have been inadequate to observe and increased incidence of malignancy over background

Reviewer's assessment: It is not ethically acceptable to deliberately contaminate humans with ^{137}Cs in order to perform prospective randomized controlled clinical trials. Therefore the best human data on the efficacy of Prussian Blue will come from retrospective analyses of data on accidentally contaminated patients who have been treated with Prussian Blue. Such studies can not, of course, be powered to achieve statistical significance. No formal statistical analysis has been performed on this data. The small number of patients, the individualization of patient treatment and the fact that all data was not available for all patients, would make a statistical analysis problematical in any event. The Goiania incident was the only incident in which a large number of individuals became contaminated with large doses of pure ^{137}Cs . The data set is, of course, incomplete. Authorities were not informed of the situation until two and a half weeks after people became contaminated and there is therefore no clinical pharmacokinetic data on the early rapid excretion of ^{137}Cs , in the urine, which is seen in animal experiments.

The whole body scanner was not available until one and a half months after the incident and in vitro data on feces and urine only is available from before that time. The Goiânia incident was a medical emergency in which the first priority was patient treatment, not gathering data for future publication. Most data is reported for only a subset of the 46 patients who were treated with Prussian Blue.

The data presented in these monographs clearly demonstrate the safety of Prussian Blue and the efficacy of Prussian Blue in increasing the rate of fecal excretion of ^{137}Cs and thereby decreasing the whole body effective half-life and the whole body radiation absorbed dose. These data, however provides little guidance on the specifics of treatment. Dosing was apparently ad hoc with different patients receiving different doses for differing periods of time. The dose and duration of treatment were presumably determined on the basis of the degree of contamination, but the criteria by which the dose and the duration of treatment was decided, are not discussed. The data does offer some guidance on dosing. Doses of 3 gm/day to 10 gm/day, in divided doses, are well tolerated with minimal side effects. A dose of 20 gm/day causes "gastric distress" (presumably epigastric or abdominal pain, the underlying cause is unclear). The data suggests that increasing the dose above 3 gm/day increases the feces to urine ratio without further decreasing the effective half-life. A dose of 3 gm/day may be adequate for all patients but without further information about how the dose for each individual patient was chosen, such a conclusion is, at best, tentative. The daily dose should not exceed 10 gm in adults, 6 gm in adolescents and 3 gm in children. The duration of treatment remains unclear.

The life threatening acute toxicity of ^{137}Cs contamination is bone marrow failure. Patients who survive bone marrow depression will recover and return to normal lives, except for sterility in males. The primary objectives of treatment should be to remove ^{137}Cs from the body as quickly as possible and to provide the necessary care during the bone marrow nadir. Even if a suitable matched donor is readily available, bone marrow transplant may not be feasible in patients who are internally contaminated with ^{137}Cs .

PUBLICATIONS IN REFEREED JOURNALS CONCERNING THE
GOIANIA INCIDENT

3) Studies of Cs Retention in the Human Body Related to Body Parameters and Prussian Blue Administration: Lipsztein J, Bertelli L, Oliveria C, Dantas B: Health Physics 60; 57-61 (1991)

Type of study: Retrospective analysis of data from 37 Patients treated with Prussian Blue in the Goiania incident. The primary efficacy variable is whole body half-life of ^{137}Cs

Purpose: To evaluate in vivo data on 37 Goiania patients (19 males and 18 females) treated with Prussian Blue. To compare half lives with and without treatment with Prussian Blue and to asses the influence of age, height, weight, sex and total ingested activity on the whole body half-life of ^{137}Cs .

	<i>Males</i>	<i>Females</i>	<i>Total</i>
<i>Adults</i>	8	10	18
<i>Children</i>	11	8	19
<i>Total</i>	19	18	37

Reviewer's comment: *How these 37 cases were selected from the 46 patients who were treated with Prussian Blue is not clear*

Methods: Internal contamination was monitored for the first one and a half months by in vitro assay of urine and feces. After that time period, a whole body counter was available and was used to measure whole body activity directly. By the time the whole body counter was used, all external contamination of skin and wounds had been removed, so internal contamination alone was monitored. Patients were treated with Prussian Blue at doses of 1,1.5, 3, 4, 6 or 10 gm/day, depending on age and level of contamination. Time activity curves were determined for each patient both during Prussian Blue treatment and after treatment had been discontinued

Results: The time activity curves both during and after treatment were consistent with decay of activity by first order kinetics (single exponential) and the effective half lives were determined by a least squares fit. The after treatment half lives ranged from 66 to 106 days with a mean of 83 days in adult males. The effective half-life in adult females ranged from 39 to 106 days with an average of 65.5 days. In children the half-life was highly dependent on age, height and weight. In all cases, the effective half-life during Prussian Blue treatment was shorter than the effective half-life after treatment had been discontinued. Prussian Blue reduced the half-life by an average factor of 0.76 for patients treated with 3 gm/day, by a factor of .69 for patients treated with 6 gm/day and by a factor of 0.67 for patients treated with 10 Gm/day. There was a strong positive correlation between untreated half-life and age, height and weight.

Author's conclusion: Prussian Blue reduced the effective half-life of ^{137}Cs by 32% in adult males and females and by 12% in children

Reviewer's assessment: Prussian Blue reduced the whole body effective half-life of ^{137}Cs . In every patient who was treated with Prussian Blue. However the untreated half-life and the effect of Prussian Blue were highly variable from patient. The untreated half-life was highly correlated with age weight and height.

4) Application of In Vivo Bioassay for ^{137}Cs During the Emergency Phase of the Goiania Accident: Lipsztein J., Bertelli L., Mello D., Azeredo A., Juliao L., Santos, S: Health Physics 60: 43-49 (1991)

Type of study: Retrospective study of patients contaminated in the Goiania incident. Primary efficacy variables are rates of fecal and urinary excretion of ^{137}Cs

Purpose: To study the pattern of urinary and fecal excretion of ^{137}Cs and to develop a mathematical model that can be used to determine the total ingested activity and the total radiation absorbed dose received

Methods: A bi-exponential time activity curve is assumed in order to use the rate of elimination in feces and urine to project the time activity curve back to the time of ingestion. Assuming all decay activity is deposited in the body, the total energy deposited is just the integral of the time activity curve multiplied by the energy per decay. Dividing by the body weight, the radiation absorbed dose is obtained.

Reviewer's comment: For these calculations the authors used the same bi-exponential function for all patients even though there is a large variation in half-life from patient to patient. The average body weight for each age group was used, instead of each patient's actual body weight. The resulting doses must be considered to be rough estimates. No attempt was used to compare these results with doses estimated by cytogenetics

Results and author's conclusions After administration of Prussian Blue in doses of 3 gm/day or higher, feces became the primary route of elimination of ^{137}Cs . Prussian Blue, when given in the right dosage, proved to be a very good decontaminant, removing ^{137}Cs in the feces.

Reviewer's assessment: this paper discusses the same patient population as the previous paper and reaches the same conclusion

5) Clinical and Hematological aspects of ^{137}Cs : The Goiania Accident: Brandao-Mello C., Oliveria A, Valverde N., Farina R., Cordeiro J; Health Physics 60: 43-49 (1991)

Type of study: Retrospective analysis of clinical data

Purpose: To study the clinical course of the 20 patients who required hospitalization in the Goiania incident. The primary outcome variable is the whole body radiation absorbed dose

Methods: 20 patients involved in the Goiania incident required hospitalization for bone marrow depression. 14 patients, who required a high degree of supportive care, were transported to a specialized unit in Rio de Janeiro. The other 6 patients were hospitalized in Goiania. There were 15 males and 5 females. Ages ranged from 6 to 59 years. Whole body radiation absorbed doses were estimated using an in vitro cytogenetic assay. Adults received 3-10 gm/day Prussian Blue and children received 1-3 gm/day. Infection precautions were taken, infections were treated with appropriate antibiotics and patients received packed cell and platelet transfusions as needed. Eight patients with the most severe bone marrow depression were treated with recombinant GM-CSF.

Results: The radiation absorbed doses for this group ranged from 0.6 Gy to 7.0 Gy.

Reviewers comment: The patients with the lowest whole body doses in this group may have received high local doses from external ^{137}Cs and may have been hospitalized for severe radiation burns etc. The fact that some patients may have received both a uniform whole body dose from ingested ^{137}Cs and a non-uniform dose from external ^{137}Cs may explain why the whole body dose was not always predictive of the bone marrow toxicity.

Of the 8 patients who received G-CSF, the four patients who responded survived and recovered normal peripheral blood counts. The four patients who did not respond died, two from diffuse internal hemorrhage due to low platelet counts and two from antibiotic resistant klebsiella infection due to neutropenia. The patients who died had received whole body doses of between 4.5 and 6.0 Gy. Two patients who received doses of 6.2 and 7.0 Gy were among the survivors. All other patients in the group received doses of 4.4 Gy or less. There were four patients who received doses of 1.1 Gy or less. All four remained hematologically normal. Sperm counts were obtained from nine adult male patients. All nine were azoospermic or oligospermic, with reduced motility and abnormal spermatozoa

Author's conclusions: The critical phase of acute radiation toxicity consisted of the hematological syndrome only. Symptoms of GI syndrome or CNS syndrome were not identified. Four patients died during the first month after the incident from diffuse

internal hemorrhage or infection resulting from bone marrow failure. All other patients recovered. Treatment with G-CSF would be effective only if there were surviving bone marrow stem cells. If all stem cells are killed the marrow can not recover. Whole body dose estimates from cytogenetics and from pharmacokinetic data were useful in predicting bone marrow depression. Decorporation of ^{137}Cs was successfully achieved by Prussian Blue

Reviewer's assessment. This data indicated that patients with high internal contamination with ^{137}Cs , will need, not only emergency treatment with at least 3 Gm/day of Prussian Blue, but also specialized supportive care during their bone marrow nadir, including protection against infection, multiple red cell and platelet transfusions and recombinant G-CSF. Such care is best delivered in a bone marrow transplant unit or a chemotherapy unit, where physicians and nursing staff are experienced in treating patients with severe bone marrow depression. Patients who receive a whole body dose of 4 Gy or higher are at high risk of death from bone marrow failure despite treatment., while patients with whole body doses of 1 Gy or less are likely to remain asymptomatic with normal peripheral counts. The only risk to patients who recover from bone marrow depression will be long term carcinogenic and genetic effects. No data indicating an increased cancer risk in the Goiania patients was presented in any of the publications concerning the Goiania incident. The fact that males, who received high radiation doses, were oligospermic makes the issue of genetic defects in the progeny of these individuals moot

6) Medical Aspects of ^{137}Cs Decorporation: The Goiania Radiological Accident:

Farina R., Brandao-Mello C., Oliverira A. Health Physics 60: 63-66 (1991)

Type of study: Retrospective study of 42 Goiania patients treated for ^{137}Cs contamination with Prussian Blue, diuretics water overload and induced sweating. The primary efficacy variables are the rates of elimination of ^{137}Cs in the urine, feces and sweat

Methods: 42 patients treated with Prussian Blue were studied. 10 patients also received diuretics, 12 patients received PO water overload and 10 patients had sweating induced either by exercise or in a sauna.

Reviewer's comment: Whether the same patients received two or all three of these additional treatments, is not mentioned.

The number of patients receiving various maximum doses of Prussian Blue is given in table 5

Maximum Dose Received gm/day	Number of Patients
0.67	4
3	19
4	1
5	9
10	9

Results: Diuretics were ineffective in eliminating ¹³⁷Cs. Sweat induced patients had measurable radioactivity on their clothes or on the floor of the sauna but the amount was not quantified. Constipation (mild in 7 patients and moderate in 3 patients) occurred in 10 patients treated with Prussian Blue but this was successfully treated with a high fiber diet. Three patients developed hypokalemia, with serum potassium levels of 2.5 to 2.9. (normal range is 3.5-5)

Reviewer's comment The authors state that hypokalemia was "without clinical repercussions", but since there is no mention of cardiac monitoring, asymptomatic arrhythmias or other EKG changes may have been missed. Since these patients also had acute radiation syndrome and were being treated with diuretics, the hypokalemia can not be definitely attributed to Prussian Blue. Nevertheless monitoring serum electrolytes during Prussian Blue treatment would be prudent.

Hypokalemia was successfully treated with oral or IV potassium supplement. At 6 months follow-up, 11 patients complained of epigastric pain but these patients also had stools positive for intestinal parasites, which are endemic in this area of Brazil. Prussian Blue reversed the feces to urine ratio from 1:4 to 4:1.

Authors conclusion: "Prussian Blue is a real antidote" for ^{137}Cs deposited in the body. It "is well tolerated when given orally, even using high doses". Intestinal constipation is a side effect, of Prussian Blue treatment that can be treated with a high fiber diet. Diuretics and water overload are ineffective in removing ^{137}Cs from the body. The effect of induced sweating could not assessed quantitatively

Reviewer's assessment: Prussian Blue is an effective treatment for ingestion of ^{137}Cs but it may induce constipation or low serum potassium. Constipation should be treated with a high fiber diet or mild laxatives if necessary, to reduce the time that ^{137}Cs bound to Prussian Blue remains in the intestines. Serum potassium should be monitored in all patients receiving 3 gm/day or more of Prussian Blue, and low serum potassium should be treated with oral potassium supplements. For severe or persistent cases of low serum potassium, patients should be monitored with a Holter monitor.

7) ^{137}Cs Internal Contamination Involving a Brazilian Accident and the Efficacy of Prussian Blue Treatment: Mello D., Lipsztien J., deOliveria C., Bertelli L: Health Phys 66: 245-252 (1994)

Type of study: Retrospective analysis of clinical data. The primary efficacy variable is whole body half-life of ^{137}Cs

Purpose: analysis of pharmacological data from Goiania patients during the first two months after the incident.

Methods: During the first two months after exposure data on the Goiania patients was obtained from in-vitro data from feces and urine only. 15 adult patients were selected for this study.

Results: The whole body ^{137}Cs half-life, under Prussian Blue treatment, as estimated from urine and fecal data was 10-36 days, compared to IRCP values of 50-150 days for untreated patients. These values were smaller than the half-lives estimated from whole body counting data after 32 months, but this might reflect poor compliance with Prussian Blue treatment after patient's discharge from hospital. The radiation absorbed dose can be obtained by integrating the time activity curve and will depend on the length of treatment. Using these values for the half-life under treatment the reduction in the radiation absorbed dose ranged from 51% to 84%.

Author's conclusions: A significant reduction in the radiation absorbed dose was achieved with 2 months treatment with Prussian Blue.

Reviewer's assessment: The radiation absorbed dose will be proportional to the area under the time activity curve. If t_1 is the half-life before treatment, and t_2 is the half-life during Prussian Blue treatment, then the maximum possible effect is achieved if treatment is started immediately after ingestion and continued indefinitely, in which case, the whole body radiation absorbed dose would be reduced by a factor of $r = t_2/t_1$. If treatment is delayed or stopped early, dose reduction would be less. To achieve a significant effect, treatment should be continued for at least one under treatment half-life, t_2 , and preferably for several half-lives. It is disconcerting to learn that estimates of under treatment half-lives are different when estimated from in vitro data on urine and feces or by whole body counting.

PRUSIAN BLUE CLINICAL LITETATURE OTHER THAN GOIANIA

- 1) **Increased Excretion of ^{137}Cs in Humans by Prussian Blue:** Madhus K., Stromme A.: Z. Naturforsch. 23b 391-392 (1968)

Type of study: Prospective uncontrolled Phase I study. The primary efficacy variable is whole body half-life of ^{137}Cs

Purpose: To study the effect of Prussian Blue treatment on normal volunteers who deliberately ingested trace amounts of Cs- Prussian Blue, TID.

Methods: The authors state "*Encouraged by the observation that neither rats nor dogs showed any ill effects which could be thought to be toxic effects of Prussian Blue, we determined to try it out on ourselves*". The authors and 5 other male physicians each ingested 1 μCi ^{137}Cs . Activity was monitored with serial whole body counts. Two months later these seven normal subjects were treated with 1 gm Prussian Blue, PO, TID. They also tried ingesting ^{137}Cs and Prussian Blue simultaneously.

Reviewer's comment: *The authors do not discuss, and may not have been aware, of the possible long term toxic effects of even small doses of ^{137}Cs*

Results: When ingested simultaneously, Prussian Blue did not prevent absorption of ^{137}Cs from the gut. However Prussian Blue treatment after ^{137}Cs was already absorbed reduced the average whole body half-life from 94 days to 31 days

Author's conclusion: A dose of 1 gm TID per day of Prussian Blue reduced the whole body half-life of ^{137}Cs by a factor of 3.

Reviewer's assessment: *This was probably the first clinical study to demonstrate the efficacy of Prussian Blue in the elimination of Cs-137.*

2) **Increased Excretion of ^{137}Cs in Humans with Prussian Blue:** Stromme A.
Symposium on Diagnosis and treatment of Deposited Radionuclides, Kornberg H.,
Norwood W., Eds. :

*Reviewer's comment: This publication presents the same clinical data as the paper
by Madhus and Stromme above. Two additional observations are made:*

- a) The Prussian Blue used in this study was made in the author's laboratory
- b) Prussian Blue can be given for "a little more than 3 weeks" without ill effects

3) **Management of Persons accidentally Contaminated with Radionuclides:
Recommendations of the National council on Radiation Protection and
Measurements National council on Radiation Protection and Measurements
(Unpublished Report, 1979)**

Type of study: Review article.

Methods: Data from 19 cases of ^{137}Cs internal contamination, treated with Prussian
Blue, reported in the literature, are discussed. Contamination ranged from $< 1 \mu\text{Ci}$ to
 $30 \mu\text{Ci}$

Results: Whole body half-lives ranged from 68 to 155 days in adults and from 12
days to 57 days in children. Prussian Blue is "relatively harmless and well tolerated
by man" and reduces the half- life of ^{137}Cs to about one third its untreated value.

Reviewer's assessment: The discussion of Prussian Blue treatment of ^{137}Cs is
contained in a larger article discussing treatment of patients contaminated with
several radionuclides. No details about any single case of ^{137}Cs contamination are
given.

- 4) **A Decrease in Dose of Internal Irradiation with Cs Radionuclides Using Ferrocyanide (Prussian Blue):** K Korzun V: Izdatelstvo Medinskaia Moskva 36: 23-27 (1991)

Reviewer's comment: This article is in Russian with a very short English summary

Author's conclusion: Adding Prussian Blue to some foodstuffs can reduce the intake, from the gut, of ^{137}Cs , in areas contaminated by the Chernobyl accident

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

PRECLINICAL STUDIES WITH PRUSSIAN BLUE AND ¹³⁷Cs

- 1) **Increased Excretion of ¹³⁷Cs in Humans by Prussian Blue:** Madhus K., Stromme A. Z. Naturforsch. 23b 391-392 (1968)

Reviewer's comment: This paper contains both clinical and animal data, and has been previously discussed in the clinical section

Purpose: to study the efficacy of Prussian Blue treatment in dogs and rats internally contaminated with ¹³⁷Cs

Methods: Prussian Blue was given to both rats and dogs who had previously ingested ¹³⁷Cs

Results: Prussian Blue reduced the biological half-life of ¹³⁷Cs in rats by 50 % and in dogs from 11 days to 6.5 days

Author's conclusion "Encouraged by the observation that neither rats nor dogs showed any ill effects which could be thought to be toxic effects of Prussian Blue, we determined to try it out on ourselves".

Reviewer's assessment: No details of the rat and dog studies are given. The fact that the half-life of ¹³⁷Cs is so much shorter in dogs than in humans is surprising

- 2) **Studies of Any Toxicological Effects of Prussian Blue in Mammals- A Review:** Pearce J.: Food and Chemical Toxicology 32 577-582 (1994)

Type of study: Review of published clinical and pre-clinical data

Reviewer's Comment: This is a review article that discusses both human and animal data. The human data discussed is the data from Madhus and Stromme, and from the Goiania incident, that has already been discussed in the clinical section.

Methods: Published data on oral Prussian Blue are reviewed

Results: Humans: The human data has previously been discussed in the clinical section

Laboratory Rodents: There were no toxic effects when rats were given Prussian Blue 100 mg/day for 11 days or when young rats were given diets containing 1% Prussian Blue for 120 days. **Dogs:** 1.5 gm/day and 3 gm/day of Prussian Blue, PO for 10 days was given to 3 month old German Shepherd dogs without noticeable toxicity.

Ruminants: When C-

14 labeled Prussian Blue was given PO to Dairy cows, between 91% and 102% of the activity was recovered in the feces. Sheep were given PO Prussian Blue, 5gm per day for 15 days and then sacrificed. No histological changes were seen in any tissues examined

Author's conclusion: Prussian Blue has no adverse effect on animal health. The consumption of products from Prussian Blue treated animals would not be expected to have adverse effects on human health.

Reviewer's Assessment: The lack of toxicity of Prussian Blue in animals makes the toxicity in humans less likely

3) A method of Simultaneous Decrease in Strontium, Cesium and Iodine Retention After Oral Exposure in Rats :Kostial K., Vanucek M., Tominac C: Int. J Radiat Biol. 37: 347-350 (1980)

Type of study: Prospective preclinical Study in rats

Methods: Treatments to be studied were Sodium Alginate, Iron Ferrocyanide (Radiogardase, Prussian Blue) and Sodium Perchlorate. Isotopes studied were Sr-90, ¹³⁷Cs and I-131,

Rats were given in their drinking water $3\mu\text{Ci } ^{137}\text{Cs}$, or $30\mu\text{Ci I-131}$ through a stomach tube or $0.\mu\text{Ci /ml Sr-84}$ in drinking water. They were then treated with Sodium Alginate, Prussian Blue and Sodium Perchlorate, as single agents and in combination with each-other

Results: Sr-84 concentration in the femur was reduced by a factor of 3 to 5 by Sodium Alginate. Radiocesium concentration in the muscle was greatly reduced by Prussian Blue treatment. Radioiodine concentration in the thyroid was reduced y treatment with Sodium Perchlorate. Giving the treatment agents in combination did not significantly reduce the effectiveness of the individual agents

Author's conclusion: There is no appreciable interference between treatments.

Reviewer's assessment: **The importance of this paper is that it notes the effectiveness of sodium alginate in the treatment of Sr-90 contamination.** In a nuclear reactor accident, or the explosion of a nuclear device, individuals will be exposed to many fission fragments simultaneously. To reduce the patient's radiation dose it is necessary to remove as many of the long-lived isotopes as possible. Among the more significant long lived fission fragments are Sr-90, ^{137}Cs and I-131. Today the generally accepted treatment for I-131 contamination is Potassium Iodide, as the non-radioactive iodine competes with I-131 for thyroid uptake. The data on sodium Perchlorate are therefore not particularly useful. As noted in this review there are many publications demonstrating the efficacy of Prussian Blue, and this paper has little to add. The observations concerning sodium Alginate (a product derived from seaweed) and Sr-90 is intriguing, but much more data is required before this agent can be recommended for use in humans.

4) **Comparative Toxicity and Efficacy of 4 Ferrocyanides in the Decontamination of Radioactive Cesium-134:** Brenot A, Rinaldi R: *Pathologie et Biologie* 15: 55-59; 1967

Reviewer's Comment: This article is in French with a one paragraph English summary.

Type of study: Prospective Preclinical study of the efficacy of Ferrocyanate salts (Prussian Blue) in rats

Methods: Iron, Calcium, Bismuth and Cobalt ferrocyanide salts were given PO to rats that had previously ingested Cs-134 chloride

Results: 95% of the radioactivity is eliminated within 3 days. All four salts were equally effective but the cobalt salt was least toxic.

Reviewer's assessment: Results of this 35 year old paper seem to contradict results of more recent publications and therefore should be taken with a grain of ferrocyanate salt. No one is currently proposing to use the cobalt salt of Prussian Blue. Only the calcium and zinc salts are proposed for clinical use. All other studies have found an under treatment half-life for ¹³⁷Cs much longer than 3 days. (¹³⁷Cs should have exactly the same pharmacokinetics as Cs-134)

5) **Accelerating the Turnover of Internally Deposited Radiocesium** (review)

Richmond C. In: *Proceedings of the Symposium on Diagnosis and Treatment of Deposited Radionuclides:* Kornberg H, and Norwood W Eds. Excerpta Medica foundation, Amsterdam, (1968)

Type of study: Review of the experimental literature of ¹³⁷Cs decontamination

Results: A number of agents, including hormones, diuretics, cold cesium, potassium and Prussian Blue have been used tried to accelerate the removal of ¹³⁷Cs from the body. Except for Prussian Blue, all are ineffective. 100 mg/day PO Prussian Blue for

11 days was found non toxic in rats. 2.5 Gm/l in drinking water for 60 days was well-tolerated in rats and decreased the urine to feces excretion ratio by a factor of 20. In a healthy 37 year old man (patient? normal subject?) who had ingested an unspecified dose of ^{137}Cs , 2 gm/day Prussian Blue, PO in ten 200 mg doses reduced the biological half-life from 140 days to 50 days.

Reviewer's assessment: This article does not provide all of the relevant details of the studies that are discussed. It is therefore difficult to evaluate. It does support the conclusion that Prussian Blue is safe and effective for removing ^{137}Cs from the body

6): **An Estimate of the Protective Action of Prussian Blue, Sodium Alginate and Calcium Phosphate According to Tumor Appearance in Single and Chronic Exposure to Strontium-90, and ^{137}Cs Mixture:** Danetskaia E., Lavrentev L., Zapolskaya N., Teplykh L. Izdatelstvo Meditsina Leningradskoe 23 57-61 (1977)
(Russian with 1 paragraph English summary)

Type of study: Prospective preclinical study in rats

Methods: Rats were internally contaminated with 0.8 mCi ^{137}Cs and 2.0 mCi Sr-90. Rats were then given PO 50 mg Prussian Blue, 800 mg sodium alginate and 258 mg calcium phosphate.

Results: Compared to contaminated rats who did not receive treatment, treated rats had one half as many malignant tumors and a life expectancy that was 120 days longer. The absorbed dose (activity?), of ^{137}Cs , was reduced by 17 times and the strontium in the bones by for 4 times.

Reviewer's assessment: With only a one paragraph summary, it is difficult to determine precisely what methods were used and the dose and duration of treatment. It is therefore difficult to assess the quantitative results. Qualitatively this paper supports the conclusions that Prussian Blue is effective in reducing contamination with ^{137}Cs

and that sodium alginate is effective in reducing contamination with Sr-90 This is the only paper to show directly that Prussian Blue treatment can reduce cancer incidence

7) Intestinal absorption of Iron from Fe-59 labeled hexocyanoferrates

Nielsen P., Fischer R., Gabbe. E., Heinrich H., Pfau A. Aznem-Forsch 38 1469-1471
(1980)

Type of study: Prospective pre-clinical study in piglets

Methods: Fe-59 and C-14 labeled Prussian Blue was given PO to 4 month old piglets kept in metabolic cages

Results 0.1 to 1% of the Fe-59 activity was recovered in the urine. The activity of exhaled C-14 labeled CO₂ was indistinguishable from background

Author's conclusion: The amount of Cyanide ions absorbed is at least two orders of magnitude below the LD₅₀ dose.

Reviewer's assessment: If CN ions were absorbed the carbon would be oxidized to CO₂. The fact that labeled CO₂ is undetectable puts an upper limit on the amount of CN absorbed> This upper limit is 2 orders of magnitude below the LD₅₀ dose. Since only 0.1-1% of the Fe-59 label is recovered in the urine, > 99% of the PO Prussian Blue is excreted in the feces.

8) Hexacyanoferrate II als Thallium-Antidote: Dvorak P.: *Arzneim. Forsch.* 12 1886-1888 (1970) (German with 1 paragraph English summary)

Type of study: In vitro study

Results and conclusions: Solubility is 1-3 µmol/l. Disintegration to CN⁻ is negligible.

Reviewer's Assessment. The low solubility and the lack of disintegration into iron and cyanide, help explain the low toxicity of Prussian Blue.

- 9) **Hemodialysis as a Potential Method for the Decontamination of Persons Exposed to Radiocesium:** Verzijl J., Wierckx F vanDijk A., Savelkoul T., Glerum J.: Health Physics 69: 543-548 (1995)

Type of study: In vitro study.

Methods: Both pasteurized plasma solution and whole blood, contaminated with ^{137}Cs were run through an artificial kidney device using commercially available dialysis fluid

Results and conclusions: hemodialysis can rapidly remove ^{137}Cs from plasma and blood> A Prussian Blue ion exchange column can remove ^{137}Cs from dialysis fluid

Reviewer's Comment: This experiment suggests that Hemodialysis, could be used as an alternative or an adjuvant to Prussian Blue treatment. However if the rate limiting step in decontamination is the release of ^{137}Cs from cells into plasma, Dialysis would not be expected to add much to Prussian Blue treatment. Since this a is an in vitro study only, additional pre-clinical studies would be required before this approach could be used in humans.

PRUSSIAN BLUE AS TREATMENT FOR THALLIUM POISONING.

Reviewer's Comment: Thallium has been used in the past as a rat poison. Cases of life-threatening human ingestion are usually cases of attempted homicide or attempted suicide. The mean lethal dose in humans is about 900 mg of ionized thallium. Prussian Blue is the generally accepted method treatment for thallium ingestion. The mechanism of action is similar to that with ¹³⁷Cs, Prussian Blue binds to thallium in the gut, increasing fecal excretion and breaks the cycle of enteric-hepatic circulation. While the literature on thallium poisoning can not be used to support the efficacy of Prussian Blue in treating ¹³⁷Cs contamination, it can provide additional data on the safety of Prussian Blue in humans

- 1) **Thallium Intoxication: An Evaluation of therapy:** vanKesteren R., deGroot G., vanHeijst A: Intensivmed. 17: 293-297 (1980)

Type of study: Retrospective study of patients treated with Prussian Blue for thallium poisoning. The primary efficacy variable is whole body half-life of thallium

Methods: The cases of 18 patients treated with Prussian Blue, 10 g BID, for thallium poisoning, at the University of Utrecht, between 1971 and 1978, were reviewed.

Results and conclusions: Prussian Blue reduced the biological half-life of thallium from an average of 8 days to an average of 3 days. No toxicity attributable to Prussian Blue was seen.

- 2) **Treatment of Thallium Poisoning** (letter to the editor): Barbier F. Lancet 7886: 965 (1974)

Type of study: Retrospective study of patients treated with Prussian Blue for thallium poisoning.

Methods: cases of 15 patients treated for thallium poisoning were reviewed

Results and author's conclusions: No side effects were noted

3) Akut Thalliumforgiftning og Behandling med Berlinblat (Acute Thallium Poisoning and Treatment with Berlin Blue, in Danish with 1 paragraph summary):
Nielsen J.: Ugeskrift for Laeger 136: 2930-2931 (1974)

Type of study: Retrospective clinical study of a single patient

Methods: The case of a single patient treated with Prussian Blue for thallium poisoning. The patient received 250 mg/kg/day Prussian Blue

Reviewers comment: This would amount to 17.5 g/day, Prussian Blue, in a 70 kg patient

Results and conclusions: Although the patient died of thallium poisoning, no side effects of Prussian Blue were noted

4) The Toxic Emergency :Thallium; Hoffman, R: Emergency Medicine June 1994 127-128

Type of study: Discussion of a case of four individuals treated with activated charcoal and diuresis, after eating candy containing thallium

Author's conclusion "Speculative treatments include Prussian Blue, a substance not yet approved by the FDA"

5) Management of Thallium Poisoning: Pau, P. HKMJ (Hong Kong Medical Journal?): 316- 318 (2000)

Type of study: Retrospective analysis of a single a case of thallium poisoning

Methods: A 67 year old woman with thallium poisoning was initially treated with activated charcoal, 5 days after ingestion. She was found to have persistent neurological symptoms at 6 weeks and was then given Prussian Blue 4gm q8h
Neurological symptoms persisted

Author's Conclusion: "Thallium may cause prolonged neurological damage if detoxification therapy is not commenced within 72 hours.

6) **Thallium Poisoning:** Moore, D. BMJ 306: 1527-1529 (1993)

Type of study : Retrospective analysis of two cases of thallium poisoning

Methods: Two men with thallium poisoning were treated with Prussian Blue 250 mg/kg/day divided into 4 doses

Results: One man had persistent neurological symptoms while the other had only minimal symptoms

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CONCLUSIONS

- 1) There is sufficient data in the published literature to conclude that Prussian Blue is both safe and effective for the treatment of contamination with ^{137}Cs . Data is reported on 46 patients treated with Prussian Blue as a result of the Goiania incident. This data is contained in two large monographs published by the International Atomic Energy Agency in Vienna, and in five papers published in refereed journals. Additional data on the treatment of 19 patients and 7 normal human volunteers is contained in three additional journal articles. The safety database is enhanced by data on 34 additional patients treated for thallium poisoning with Prussian Blue. Although these publications all describe retrospective studies, and the number of patients is small compared to a typical Phase 3 clinical trial, the evidence is compelling. The only complaint attributed to Prussian Blue treatment at doses up to 10 gm/day, in adults, was mild to moderate constipation, which could be successfully treated with a high fiber diet. Three of the 46 patients developed asymptomatic hypokalemia, (serum potassium 2.5-2.9, normal value 3.5-5) which was successfully treated with oral or IV potassium supplements. Patients given 20 gm/day Prussian Blue complained of "gastric distress". Prussian Blue increased the rate of fecal excretion and reduced the whole body half-life of ^{137}Cs for every patient for which data on these parameters were available. Reducing the half-life reduces the whole body radiation absorbed dose, which should, in turn, reduce the risk of bone marrow suppression and radiation induced cancer. In this retrospective study each patient served as his/her own control. For each patient the half-life during treatment was compared to the half-life after treatment had stopped, which was assumed to be equal to the half-life if no treatment had been given.
- 2) The optimal dose and dosing schedule has not been determined. For doses up to 10 gm/day in divided doses, there was no other complaint other than mild to moderate constipation. Patients who received 20gm/day experienced

“gastric distress” requiring that dosing at this level be stopped but “gastric distress” is not defined or described. Three patients, 6.5% of patients receiving 10 g/day or less, developed asymptomatic hypokalemia. For doses of Prussian Blue, between 3 gm/day and 10 gm /day, the fecal/urine ratio increased with increasing dose, but there was no further decrease in the whole body half-life for doses above 3 gm/day.

- 3) The parameter most closely correlated with the clinical outcome of ^{137}Cs contamination is the whole body radiation absorbed dose in Gy. The data from Goiania indicates that a whole body dose of 4-5 Gy or greater carries a high risk of death from bone marrow failure. Doses between 1 and 4 Gy are associated with life threatening bone marrow depression with severity increasing with increasing dose. Patients who received a whole body dose of less than 1 Gy may be asymptomatic and have normal peripheral blood counts. These patients are still at risk of increased cancer incidence due to radiation exposure, but since there is no published data on the excess cancer risk in persons ingesting ^{137}Cs , this risk can not be quantified.
- 4) In order to treat patients effectively, an accurate determination of the whole body activity is helpful. Treatment planning was hampered in the Goiania incident by the lack of a whole body counter for one and a half months after the incident. If a whole body counter is not available, whole body activity should be estimated using urine and fecal counts
- 5) Pre-clinical data supports the conclusion that Prussian Blue is safe and effective in treating ^{137}Cs contamination. Prussian Blue is insoluble, it is not absorbed from the gut, and the amount of cyanide released from Prussian Blue ingested by laboratory animals is undetectable. Prussian Blue has been shown to consistently decrease the whole body half-life of ^{137}Cs in dogs, rats and farm animals. Prussian Blue, sodium alginate and calcium phosphate, given together, have been shown to reduce the incidence of malignant tumors and to increase the life expectancy in rats internally contaminated with ^{137}Cs and Sr-

90. However since three agents are given together, it can not be determined from this data, how much each agent is responsible for this effect

- 6) Sodium alginate has been shown to be an effective treatment for Sr-90 contamination [A Ivanikov et al; Radiobiologica. 33:297-301(1993)]. Sodium alginate is derived from brown seaweed and is available commercially in pharmaceutical grade.
- 7) Clinical data supports the conclusion that Prussian Blue is a safe and effective treatment for thallium poisoning. Prussian Blue has been shown to reduce the serum half-life of thallium from 8 days to 3 days No treatment related complications have been reported in patients who wave been treated with Prussian Blue for thallium poisoning.
- 8) Clinical outcome is most closely correlated with the radiation absorbed dose. While data demonstrates that Prussian Blue decreases the effective half-life of ¹³⁷Cs, on average, by a factor of 3, there is no discussion of how that reduction in half-life would lead to a reduction in the whole body radiation absorbed dose. The reviewer has therefore constructed a simple mathematical model to address this question. (see appendix 3)

RECOMMENDATIONS

- 1) Prussian Blue should be approved for marketing for the following two indications

2)

DRAFT
LABELING

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

APPENDIX 1
GLOSSERY OF TERMS AND UNITS

ACTIVITY:

Radioactive decays per unit time

Units: Becquerel (Bq) 1 Bq = 1 decay per second

megabecquerel (MBq) 1 MBq = 10^6 Bq

1 MBq = 10^6 decays per second

Curie (Ci) 1 Ci = 3.7×10^{10} decays per second

millicurie (mCi) 1 mCi = 1/1000 Ci

1 mCi = 3.7×10^7 decays per second

1 mCi = 37 MBq

The unit of activity used in this review is mCi

HALF-LIFE ($t_{1/2}$)

The time it takes for activity to decay to $\frac{1}{2}$ of its initial value

The definitions and relationships between physical half-life, biological half-life and effective half-life are discussed in appendix 2. Unless otherwise stated, the term "half-life" as used in this review refers to effective half-life. Units used for half-life are seconds minutes hours days or years

RADIATION ABSORBED DOSE:

Energy deposited in tissue per unit mass of tissue

Units: Gray (Gy): 1 Gy = 1 Joule per kilogram (J/kg)

Rad: 1 Gy = 100 Rad

The unit of radiation absorbed dose used in this review is Gy

Clinical and biological effects in any organ are determined by the radiation absorbed dose to that organ

APPENDIX 2 HALF-LIFE

Physical half-life....tp, Biological half-life....tb Effective half-lifete

The radioactivity in the body of a contaminated individual decreases through two processes. The radioactive isotope physically decays at a constant rate characterized by the physical half-life t_p . The physical half-life is a physical constant that does not change. In the simplest cases, the radioactive material is also removed from the body by first order kinetics (a single exponential function) characterized by the biological half-life, t_b . The biological half is dependent on physiological processes and is variable from individual to individual and may vary with time in the same individual. The biological half-life can be altered by treatment. The object of treatment is often to shorten the biological half-life and speed the elimination of the isotope from the body. Both these processes contribute to the decrease with time of the patient's radioactivity, a process characterized by the effective half-life t_e . There is a simple relationship between the effective half- life, the biological half-life and the physical half-life given in eq. A1

$$A1) \quad (1/t_e) = [(1/t_p) + (1/t_b)]$$

The effective half-life is always shorter than either the physical half-life or the biological half-life. If the biological half-life is reduced, than the effective half-life is reduced. For Cs-137, the physical half-life is 30 years and the biological half-life in man is several months. When the biological half-life is very much shorter than the physical half-life, then the biological half-life and the effective half-life are virtually identical.

The half-life calculated directly from sequential whole body counts, or from urine and fecal data is the effective half-life. Physical half lives can be looked up in

physics text books. If the physical and effective half-lives are known then the biological half-life can be calculated using equation A1

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APENDIX 3

LITERATURE DATABASE

PAPERS DISCUSSED IN THE REVIEW

CLINICAL TREATMENT OF ^{137}Cs CONTAMINATION: THE GOIANIA INCIDENT

1) **Title: The Radiological Accident in Goiania**

Journal Reference: Report of the Review Meeting on the Goiania Accident
Rio de Janeiro 18-22 July 1988-International Atomic Energy agency Vienna
1988

ISBN 92-0-129088-8

Number of Patients: 42

Condition: ^{137}Cs -internal contamination

Dose: 1-10 gm/day PO

Other treatments: Diuretics (17 patients)

Efficacy Increasing doses of Prussian Blue lead to increase in ^{137}Cs
elimination in the feces

Reported Side Effects: constipation in a small number of patients

2) **Title: Dosimetric and Medical Aspects of the Radiological accident in
Goiania in 1987**

Authors: Gustafsson M., Turai I.

Journal reference: IAEA-TECDOC-1009 International Atomic Energy
Agency, Vienna (1988)

Number of patients 46

Dose: 1-3 gm/day (children), 3, 6 or 10 gm daily (adults) in divided doses

Efficacy: Prussian Blue reduced the biological half-life of ^{137}Cs by an average of 69% in adults and 43% in children. Prussian Blue is more effective when administered immediately after cesium uptake-

Side effects: mild to moderate constipation

3) Title; Studies of Cs Retention in the Human Body Related to Body Parameters and Prussian Blue Administration

Authors Lipsztien J., Bertelli L., Oliverira A., Dantas, B.

Journal reference: Health Physics 60: 57-61 (1991)

Number of patients: Data from 18 females and 19 males, (37 patients total)

Condition: ^{137}Cs ingestion

Dose: 1, 1.5, 3, 4, 6 or 10 gm/day, depending on age and contamination level

Other treatment: Not discussed

Efficacy evaluation: ^{137}Cs was eliminated by first order kinetics both with and without Prussian Blue. Prussian Blue reduced the average whole body half-life of ^{137}Cs by 32% in children and male adults and by 12% in female adults. Half-life was strongly correlated with weight, height and age

Side effects: Not discussed

4) Application of In-Vivo Bioassay for ^{137}Cs During the Emergency Phase of the Goiania Accident

Authors . Lipsztien J., Bertelli L., Mello D., Azeredo A., Juliao L., Santos, S

Journal reference: Health Physics 60: 43-49 (1991)

Number of patients: Not stated

Dose: Not specified

Other treatment: Not discussed

Efficacy evaluation: A mathematical model was used to estimate whole body ingested activity and evaluate the efficacy of Prussian Blue in removing ^{137}Cs from the body, using data on activity in urine and feces After administration of Prussian Blue in doses of 3 gm/d or greater, feces became the predominant route of excretion of ^{137}Cs

Side effects: Not discussed

5) Title; Clinical and Hematological aspects of Cs-137: The Goiania Accident

Authors: Brandao-Mello C., Oliveria A, Valverde N., Farina R., Cordeiro J.

Journal reference: Health Physics 60: 43-49 (1991)

Number of patients: 249 patients were contaminated 50 required medical supervision 20 required hospitalization

Dose: Not specified

Other treatment: Diuretics, water overload, exercise to induce sweating

GM-CSF (8 patients)

Efficacy evaluation: 14 patients developed bone marrow failure 4 died

Side effects: Not discussed

6) Title; Medical Aspects of Cs-137 Decorporation: The Goiania Radiological Accident

Authors Farina R., Brandao-Mello C., Oliverira A.

Journal reference: Health Physics 60: 63-66 (1991)

Number of patients: 33 adults, 13 children total 46

Condition: ^{137}Cs ingestion

Dose: 3-4 gm/day in divided doses to adults with lower whole body burden

4-10 gm/day to adults with highest whole body burden

1-1.5 gm/day to children

Other treatment Diuretics, increased oral fluid intake, induced perspiration

Efficacy evaluation: Prussian Blue reversed the urine to fecal elimination ratio from 4 :1 to 1: 4

Side effects: Constipation, otherwise well tolerated.

7) Title: Cs-137 Internal Contamination Involving a Brazilian Accident and the Efficacy of Prussian Blue Treatment

Authors: Mello D., Lipsztien J., deOliveria C., Bertelli L.

Journal Reference: Health Phys 66: 245-252 (1994)

Number of Patients 15 patients with internal ^{137}Cs Contamination in the Goiania incident
Condition: ^{137}Cs internal contamination
Dose: 3-10 Gm/day in adults
Efficacy: ^{137}Cs half-life reduced to 10-36 days from 50-150 days. Whole body radiation absorbed dose reduced by an average of 71%..
Reported Side Effects: Not Discussed

8) **Title; Clinical and Hematological aspects of Cs-137: The Goiania Accident**

Authors: Brandao-Mello C., Oliveria A, Valverde N., Farina R., Cordeiro J.
Journal reference: Health Physics 60: 43-49 (1991)
Number of patients: 249 patients were contaminated 50 required medical supervision 20 required hospitalization
Dose: Not specified
Other treatment: Diuretics, water overload, exercise to induce sweating
GM-CSF (8 patients)
Efficacy evaluation: 14 patients developed bone marrow failure 4 died
Side effects: Not discussed

CLINICAL TREATMENT OF ^{137}CS CONTAMINATION (GENERAL)

9) **Title: Increased Excretion of Cs-137 in Humans by Prussian Blue**

Author: Madhus K., Stromme A.
Journal Reference: Z. Naturforsch. 23b 391-392 (1968)
Number of Patients: 7 normal human male subjects
Condition: voluntary ingestion of trace dose ($1\mu\text{Ci}$) ^{137}Cs
Dose: 1 gm TID
Efficacy: Biological half-life reduced by 2/3
Reported Side Effects: none reported

10) **Title: Increases Excretion of Cs-137 in Humans with Prussian Blue**

Author: Stromme A.

Journal Reference: Symposium on Diagnosis and treatment of Deposited Radionuclides, Kornberg H., Norwood W., Eds.

Number of Patients: 7 normal human male subjects (*Reviewer's comment: These are the same seven subjects discussed in reference 1 above.*)

Condition: voluntary ingestion of trace dose ($1\mu\text{Ci}$) ^{137}Cs

Dose: 1 gm TID

Efficacy: Mean ^{137}Cs biological half-life reduced from 94 days to 31 days

Reported Side Effects: No toxicity noted when taken for 3 weeks by human volunteers. No toxicity noted in rats or dogs

11) **Title: Management of Persons accidentally Contaminated with Radionuclides: Recommendations of the National council on Radiation Protection and Measurements**

Author: National council on Radiation Protection and Measurements

Journal reference: Unpublished Report

Number of patients: 19 cases of minor contamination ($1\mu\text{Ci}$ to $30\mu\text{Ci}$) reported in the literature in the 1960s

Condition ^{137}Cs internal contamination

Dose: Not specified

Other treatment: Not specified

Efficacy evaluation: Biological half-life reduced by about a factor of 1/3

Reported Side effects: "relatively harmless and well tolerated by man"

12) **Title: A Decrease in dose of Internal Irradiation with Cs Radionuclides Using Ferrocin (Prussian Blue) [in Russian with English abstract]**

Author: Korzun V.

Journal Reference: Medinskaia Radiologija 26: 23-27 (1991)

Number of patients: not specified

Condition: Cs ingestion from Chernobyl reactor accident

Dose: Unspecified dose included in food

Efficacy evaluation" Ferrotin containing foodstuffs achieve a considerable reduction in Cs contamination"

Reported side effects; not discussed

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PRE-CLINICAL LITERATURE DATABASE FOR PRUSSIAN BLUE

13) Title: Increased Excretion of Cs-137 in Humans by Prussian Blue

Author: Madhus K., Stromme A.

Reviewer's comment: This paper contains both clinical and animal data

Journal Reference: Z. Naturforsch. 23b 391-392 (1968)

Animal species: rats and dogs

Condition: ¹³⁷Cs ingestion

Dose: Not stated

Efficacy: Prussian Blue reduced the biological half-life of ¹³⁷Cs by 50% in rats and by 40% in dogs

Toxicity : not discussed

14) Title: Studies of Any Toxicological Effects of Prussian Blue Compounds-

A Review

Reviewer's Comment: This is a review article that discusses both human and animal data

Author: Pearce J.

Journal reference: Food and Chemical Toxicology 32 577-582 (1994)

Animal species laboratory rats, dogs sheep cattle

Condition : ¹³⁷Cs ingestion

Dose: 1.5 – 3gm/d x 20-22 days

Other treatment: None

Efficacy Evaluation: Prussian Blue prevented tissue uptake of PO ¹³⁷Cs and increased clearance of ¹³⁷Cs in rats

Toxicity: Other than a slight decrease in Hgb (4.6%) and in liver iron stores (17%), no toxic effects were observed by observation or histological examination of sacrificed animals

15) Title: A method of Simultaneous Decrease in Strontium, Cesium and Iodine Retention After Oral Exposure in Rats

Authors: Kostial K., Vanucek M., Tominac C

Journal Reference: Int. J Radiat Biol. 37: 347-350 (1980)

Animal Species: Rats

Condition : ^{137}Cs ingestion

Dose: With food 1.25 gm/100gm food

Efficacy evaluation: Cesium retention decreased by factor of 19-51

Toxicity: not discussed

**16) Title: Toxicite et Efficacite Comparees de Quatre Ferrocynures dans la Decontamination du Cesium Radioactif [French with English abstract]
(Toxicity and efficacy of 4 Ferrocyanides in the Decontamination of Radioactive cesium)**

Authors: Brenot A., Rinaldi, R

Journal reference: Pathologie et Biologie 15 55-59 (1967)

Animal species: Wistar rat

Condition ^{137}Cs ingestion

Dose 50 mg/kg

Efficacy evaluation: 94.6% of cesium dose eliminated in 3 days

Toxicity: not discussed

17) Title: Accelerating the Turnover of Internally Deposited Radiocesium

Authors: Richmond C

Journal reference: In 1963 Annual Report to Congress of the Atomic Energy Commission

Animal species: Review of Experimental Literature

Condition: ^{137}Cs ingestion

Dose: 100 mg/day x 11 days

Efficacy evaluation: Urine/feces ratio decreased by factor of 20

Toxicity: No toxicity observed

18) Title: An Estimate of the Protective Action of Prussian Blue, Sodium Alginate and Calcium Phosphate According to Tumor Appearance in Single and Chronic Exposure to Strontium -90, and Cs-137 Mixture. [Russian with English abstract]

Authors: Danetskaia E., Lavrentev L., Zapolskaya N., Teplykh L.

Journal reference: Izdatelstvo Meditsina Leningradskoe 23 57-61 (1977)

Animal species Rat

Condition : ^{137}Cs ingestion

Dose 50 mg

Efficacy evaluation: Absorbed dose reduced by factor of 17

Toxicity : not discussed

19) Title: Intestinal absorption of Iron from Fe-59 labeled hexocyanoferrates

Authors: Nielsen P., Fischer R., Gabbe., E., Heinrich H., Pfau A.

Journal reference Aznem-Forsch 38 1469-1471 (1980)

Animal species: Piglets

Condition : ingestion of ^{59}Fe and ^{14}C labeled $\text{Fe}[^{59}\text{Fe}(^{14}\text{CN})_6]$

Efficacy evaluation: not discussed

Toxicity: 0.20% of ^{59}Fe was absorbed from the gut. $^{14}\text{CO}_2$ from the metabolism of ^{14}CN was below the level of detectability indicating undetectable levels of absorbed free CN

20) Title: Hexacyanoferrate II als Thallium Antidotre [German with English abstract]

Author: Dvorak P.

Journal reference: Arzneim. Forsch. 12 1886-1888 (1970)

Animal species: none , in vitro study

Condition: none

Dose: none specified

Efficacy evaluation: non, in vitro study

Toxicity: Solubility of Prussian Blue is 1-3 $\mu\text{mol/l}$. CN from disintegration is negligible

21) Title: Hemodialysis as a Potential Method for the Decontamination of Persons Exposed to Radiocesium

Author: Verzijl J., Wierckx F vanDijk A., Savelkoul T., Glerum J.

Journal Reference: Health Physics 69: 543-548 (1995)

Number of Patients: In Vitro Study none

Condition: Blood Contaminated with ¹³⁷Cs

Dose: N/A

Efficacy : Hemodialysis can remove ¹³⁷Cs from Pasteurized plasma solutions.

Prussian Blue ion exchange columns can remove ¹³⁷Cs from dialysis fluids

Reported Side Effects: N/A

CLINICAL DATABASE ON THE TREATMENT OF THALLIUM POISONING WITH PRUSSIAN BLUE

22) Title: Thallium Intoxication: An Evaluation of therapy

Author: vanKesteren R , deGroot G., vanHeijst A.,

Journal Reference: Intensivmed. 17: 293-297 (1980)

Number of Patients: 18 Patients (16 suicide attempts, 2 homicide attempts)

Condition Thallium intoxication

Dose: 10 gm BID in Duodenum by NG tube

Other treatments Mannitol, Forced diuresis

Efficacy evaluation: 17 patients survived, 1 patient died

Whole body half-life reduced to 3 ± 0.7 days with Prussian Blue alone

Side effects: Not discussed

23) Title: Treatment of Thallium Poisoning (letter)

Author: Barbier F.

Journal Reference: Lancet 7786: 965 (1974)

Number of Patients 11

Condition: Thallium poisoning

Dose: 88 to 416 mg/kg/day

Efficacy Evaluation: Not discussed

Reported Side Effects: None

24) Title: Akut Thalliumforgiftning og Behandling med Berlinblat [in Danish with English abstract] (Acute Thallium Poisoning and Treatment with Berlin Blue)

Author: Nielsen J.

Journal Reference: Ugeskrift for Laeger 136: 2930-2931 (1974)

Number of Patients 1

Condition Intentional Thallium Poisoning (suicide attempt)

Dose: 250 mg/kg daily

Other treatments: Mannitol

Efficacy evaluation: Patient died

Side effects: Not discussed

25) Title: Successful Recovery of a Patient with Thallium Poisoning

Authors: Vrij A., Cremers H., Lustermans F.

Journal Reference: Netherlands Journal of Medicine: 47 121-126 (1995)

Number of patients: 1

Condition: Thallium Poisoning

Dose: 250 mg/kg/day

Efficacy evaluation: Patient survived

Side effects Persistent constipation

26) Title: The Toxic Emergency: Thallium

Authors: Hoffman R

Journal Reference: Emergency Medicine, June, 1994 127-128
Number of patients: 4
Condition: Thallium Poisoning
Dose: Treated with activated charcoal and diuresis
Efficacy evaluation: Prussian Blue is a “speculative” treatment not approved by the FDA
Side effects N/A

27) Title: Thallium Poisoning

Authors: Moore D
Journal Reference: BMJ306: 1527-1529 (1993)
Number of patients: 2
Condition: Thallium Poisoning
Dose: 250 mg/kg/day divided doses
Efficacy evaluation: Neurological symptoms persisted in 1 patient
Side Effects: Not discussed

PAPERS NOT DISCUSSED IN THE REVIEW

28) Title: Hemodialysis as a Potential Method for the Decontamination of Persons Exposed to Radiocesium

Author: Verzijl J., Wierckx F., Hennen L vanDijk A., Glerum J
Journal Reference: Health Phys 69: 521-529 (1995)
Number of Patients Computer simulation based on animal data
Condition: ¹³⁷Cs contamination
Dose: N/A
Efficacy Hemodialysis can remove ¹³⁷Cs from the body more rapidly than oral Prussian Blue
Reported Side Effects N/A

29) Title: An Evaluation of the Efficacy of Charcoal Hemoperfusion in the Treatment of Three Cases of Thallium Poisoning

Authors: deGroot G., vanHeijst A., vanKesteren R., Maes R.

Journal Reference: Arch Toxicol 57: 61-66 (1985)

Number of Patients: 3

Condition: Thallium poisoning

Dose: 10g BID

Other treatments: Charcoal hemoperfusion, gastric lavage and forced diuresis

Efficacy evaluation: Thallium serum half-lives in the 3 patients reduced to 25 hr, 35 hr, and 41 hr respectively

Reported side effects: not discussed

30) Title: Toxokinetic Aspects of Thallium Poisoning: Methods of Treatment by Toxin Elimination (review article)

Authors deGroot G., vanHeijst A

Journal Reference: The science of the Total Environment 71: 411-418 (1988)

Number of Patients 1

Condition Thallium Poisoning

Dose 10g BID intraduodenally by NG tube

Other treatments Forced diuresis,

Efficacy evaluation: clearance increased to 170 ml/min

Reported side effects: not discussed

31) Title: Prussian Blue Treatment of Radiocesium Poisoning (review article)

Authors Thompson D

Journal Reference: Pharmacotherapy 2001: 21: 1364-1367

Condition ¹³⁷ Cs contamination

Dose: 3-10 g/day

Efficacy: Prussian Blue can reduce the effective half-life in humans by 43%

32) Title: Successful Recovery of a Patient with Thallium Poisoning

Authors: Vrij A., Cremers H., Lustermans F.

Journal Reference: Netherlands Journal of Medicine: 47 121-126 (1995)

Number of patients: 1

Condition: Thallium Poisoning

Dose: 250 mg/kg/day

Efficacy evaluation: Patient survived

Side effects Persistent constipation

33) Title: Management of Thallium Poisoning

Authors: Pau P

Journal Reference: Hong Kong Medical Journal, 2000 316-318

Number of patients: 1

Condition: Thallium Poisoning

Dose: 4g TID

Efficacy evaluation: Treatment started 6 weeks after contamination did not relieve neurological symptoms

Side effects: Not discussed

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Patricia Stewart
9/15/03 05:04:13 PM
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