

OAK RIDGE INSTITUTE OF SCIENCE AND EDUCATION

OAK RIDGE ASSOCIATED UNIVERSITIES/  
OAK RIDGE NATIONAL LABORATORY  
COMMITTEE ON HUMAN STUDIES  
ACTIVE PROTOCOLS AND RELATED DOCUMENTS  
FILE 3

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*Heyl*

Prussian Blue  
(PB)

Antidotum Thallii-Heyl<sup>(R)</sup>

Radiogardase<sup>(R)</sup>-Cs

Survey about the literature

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## 1. Chemistry

The name Prussian Blue (PB) without further specifications does not indicate which substance is being discussed. Martindale (1982) mentions two substances with the name PB:

- Ferric(III) hexacyanoferrate(II)  
"insoluble PB"  
 $\text{Fe}_4[\text{Fe}(\text{CN})_6]_3$   
Molecular weight: 359.3  
Colour Index No. 77.510  
CAS Registry No. 14038-43-8
  
- Potassium ferric(III) hexacyanoferrate(II)  
"colloidal soluble PB"  
 $\text{KFe}[\text{Fe}(\text{CN})_6]$   
Molecular weight: 306.9  
Colour Index No. 77.520  
CAS-Registry No. 25869-98-1

The above listed chemical formula of both named substances are idealized. Additionally all precipitates of insoluble PB contain nonstoichiometric amounts of potassium, protons and water (Buser et al., 1977; Dvorak, 1971; Ludi, 1983; Nielsen et al., 1987; Nielsen et al., 1988b). Partially the water is adsorbed at the large surface of this pigment, partially it is distributed in cavities of the crystal lattice (zeolitical water), partially it is bound coordinatively (Ludi, 1988). Colloidal soluble PB also may contain additionally nonstoichiometric amounts of cations ( $\text{H}^+$ , alkalimetalions) and anions ( $\text{Cl}^-$ ,  $\text{OH}^-$ ) and water (Bozorgzadeh, 1971; Dvorak, 1970; Dvorak, 1971).

In the literature there are a lot of misunderstands and mistakes in the denomination of the used PB. For example, some authors who used the commercial available PB Antidotum Thallii-Heyl<sup>(R)</sup> with insoluble ferric-hexacyanoferrate as active compound falsely described the chemical formula with  $\text{KFe}[\text{Fe}(\text{CN})_6]$  (Franke et al., 1979; Spoerke et al., 1986). One author is using both formulas,  $\text{KFe}[\text{Fe}(\text{CN})_6]$  as well as  $\text{Fe}_4[\text{Fe}(\text{CN})_6]_3$ , for Antidotum Thallii-Heyl<sup>(R)</sup> in different chapters of the paper (Trenkwalder et al., 1984). Other authors term the drug Antidotum Thallii-Heyl<sup>(R)</sup> "colloidal soluble PB" (Forth et al., 1986; Gansser, 1982; Jax et al., 1973; Kemper, 1979). On the other hand potassium ferric(III) hexacyanoferrate(II) was termed as insoluble (Lehmann et al., 1984). Therefore it is often very difficulty or even impossibility to decide which kind of PB was used in the experiment in reality. More attention has to be paid with respect to the stating, which PB has been used in future publications. This may be done by citing the correct colour index No. and/or the correct chemical name and/or chemical formula and/or the physical nature (insoluble or colloidal soluble).

Ferric(III) hexacyanoferrate(II) which at present is solely available in pharmaceutical preparations (see pt. 2) is insoluble in water and diluted acids [Solubility  $\text{Lp}=10^{-40}$  (Ludi, 1988)].  $^{59}\text{Fe}$ -labelled measurements resulted in a solubility of  $0.7 \mu\text{mol/l}$  (Dvorak, 1970).

2. Monograph of the Bundesgesundheitsamt  
28.05.1990 (BAnz. 29.06.1990)

Effective components

Iron(III)-hexacyanoferrate(II)  $\text{Fe}_4[\text{Fe}(\text{CN})_6]_3$   
(insoluble Prussian blue); ASK-No. 5690

Pharmacology, Pharmacokinetics, Toxicology

Prussian blue has an extremely low solubility and will not be absorbed in a significant amount orally administered. It is binding univalent metal ions, the binding power increases with increasing of the ionic radius of the ions  $\text{Na}^+ < \text{K}^+ < \text{NH}_4^+ < \text{Rb}^+ < \text{Tl}^+ < \text{Cs}^+$ . It will be used in treatment of thallium intoxication and in decorporation respectively in prevention of uptake of radiocesium. The faecal excretion of this ions will be increased by interruption of their enteric cycle. Prussian blue will not be metabolised in the gut.

For acute application in the rat the  $\text{LD}_{50}$  is  $>10$  g/kg body weight, for chronic application  $>1$  g/kg body weight. Chronic application of 1 % of Prussian blue to the food of rats didn't result in pathological changes.

Clinical data

1. Indications: - Thallium intoxication  
- Decorporation respectively prevention of uptake of radiocesium ( $^{134}\text{Cs}$ ,  $^{137}\text{Cs}$ )

2. Contraindications: None

3. Side effects: Prussian blue may cause a harmless dark-staining of the faeces

4. Special preventive remarks for using: None

5. Use in pregnancy and lactation: There are no hesitation in using during pregnancy and lactation

6. Drug and other interactions: Prussian blue may retard the resorption of tetracycline.

7. Dosage and administration: Depending on the severity of intoxication the orally administered daily dose may vary from 3 g to 20 g for adults and children. It should be given continually over the 24-hours-interval. In cases of acute intoxication, in which thallium or radiocesium is still present in the stomach or upper parts of the small intestines, an initial dose of at least 3 g should be given at once.

Prussian blue may be administered either by swallowing the capsules or dispersed in water or mannitol solution using a stomach or a duodenal tube.

The duration of treatment depends on thallium excretion in the faeces or in the detection of radiocesium.

8. Overdosage: None

9. Special caution: None

10. Effects in motorists and in mechanical workers: None

Remarks

In acute thallium intoxication additional clinical procedures such as forced emesis, gastric lavage or hemodialysis may be necessary.

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### 3. Pharmacodynamics

PB has a very high affinity for cesium and thallium. The binding power of univalent metal ions increases with increasing of the ionic radius of the ions  $\text{Na}^+ < \text{K}^+ < \text{NH}_4^+ < \text{Rb}^+ < \text{Tl}^+ < \text{Cs}^+$  (Forth, 1983; Nielsen et al., 1987). Thallium (Forth et al., 1979) and cesium (Nigrovic, 1965) has an entero-enteric cycle. They will be excreted into the intestine and reabsorbed from the gut into the organism. Orally administered PB traps thallium or cesium in the gut, reduces or interrupts its reabsorption from the gastrointestinal-tract and increases so its faecal excretion. The biological half-life of the toxic agents will be reduced. PB itself is not absorbed across the gut wall in a significant amount (see pharmacokinetics).

The mechanism of cesium and thallium-adsorption by hexacyanoferrates is not yet known in full detail (Nielsen et al., 1987). All authors are discussing a chemical ion-exchange as mode of action, non-stoichiometric and stoichiometric cations of the drug are exchanged by thallium- or cesium-ions. After binding of thallium to colloidal soluble and insoluble PB, the content of potassium and hydrogenions was reduced (Dvorak, 1970).  $^{40}\text{K}$  labelled PB showed no more radioactivity after mixing with Tl. The pH value was decreased (releasing of  $\text{H}^+$ -ions) (Dvorak, 1971). However in in-vitro experiments insoluble PB bound more cesium than potassium-, hydrogen- and iron-ions were released. (Nielsen et al., 1987). Therefore an additional, physical adsorption on the large surface, possibly interacting with the water, may be involved (Ludi et al., 1983; Richmond, 1983). This also would explain the influence of the drying procedure on the efficacy (Nigrovic et al., 1966).

Contrary to the chelating agents the mode of action of PB indicates no risk of inversion of gradients of the concentration of the toxic metals between central compartment and the target organs (Chezzi et al., 1979).

The effect of PB in experimental thallium and cesium poisoning has been investigated in various animal studies which are in detail outlined below.

#### Thallium

In vitro thallium was strongly bound to PB (Dvorak, 1970; Dvorak et al., 1971; Kamerbeek et al., 1971b; Lehmann et al., 1984). The adsorption was rather fast, after 10 minutes all thallium was bound (Dvorak et al., 1971). The adsorption of thallium on PB depended on the pH-value of the solution. At a neutral or slightly alkaline pH a maximal adsorption could be detected (Dvorak, 1970).

Concomitantly oral administration of thallium and of PB in rats resulted in a lower uptake of the metal and in a lower content of organs (Dvorak, 1969; Heydlauf, 1969; Rauws, 1974).

In a study by Heydlauf (1969), aqueous solutions of  $^{204}\text{Tl}^+$  as sulphate were administered to male rats ( $n = 5-17$ ) by gastric tube. Aqueous suspensions of ferric ferrocyanide in doses of 0.5-50 g were administered by gastric tube at different times (1-60 min). The maximal protective effect, i.e. approximately ten times lower absorption of  $^{204}\text{Tl}$ , was observed when ferric ferrocyanide was given immediately, although an effect was still seen when ferric

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ferrocyanide was administered at 60 minutes. As expected, there was marked dependence of antidotal efficacy on the dose of ferric ferrocyanide administered.

It was also shown that ferric ferrocyanide was able to remove Tl already adsorbed across the gastrointestinal wall. Immediate begin of PB treatment showed the best results, but a delayed start of therapy was still effectively (Günther, 1970; Heydlauf, 1969).

Carrier-free  $^{204}\text{Tl}$  was injected intravenously and the animals fed with ferric ferrocyanide pellets ad libitum (Heydlauf, 1969). The  $^{204}\text{Tl}$  content of ferric ferrocyanide treated animals was drastically reduced even when treatment was initiated on the 4th day. This was due to markedly enhanced faecal excretion whereas urinary elimination did not reach the control level.

PB (Dvorak, 1969; Günther, 1971; Heydlauf, 1969) reduced the retention of thallium in the body. The excretion in the faeces was increased and decreased in the urine when compared to the control animals (Heydlauf, 1969; Lehmann et al., 1985; Manninen et al., 1976; Rauws, 1974; Van-der-Stock et al., 1978). The cumulative excretion in faeces and urine was increased (Heydlauf, 1969; Lehmann et al., 1985; Rauws, 1974). The biological half-life of thallium in the body was reduced. In dogs the biological half-life was decreased from 6.5 days (measured in control animals) to 2.5 days (animals treated with PB) (Van-der-Stock et al., 1978), in rats it was decreased from 4 days 2 days (Rauws, 1974).

The reduced retention and the increased excretion respectively of thallium by PB resulted in a decrease of the thallium content in liver (Dvorak, 1969; Günther, 1970; Günther, 1971; Heydlauf, 1969; Manninen et al., 1976; Sabbioni et al., 1982), kidney (Dvorak, 1969; Günther, 1970; Günther, 1971; Heydlauf, 1969; Rauws, 1974; Manninen et al., 1976; Sabbioni et al., 1982), skeleton (Heydlauf, 1969) and muscles (Dvorak, 1969; Günther, 1970; Günther, 1971; Heydlauf, 1969; Kamerbeek et al., 1971; Manninen et al., 1976; Rauws, 1974; Rauws et al., 1982).

Kamerbeek et colleagues (Kamerbeek, 1971; Kamerbeek et al., 1971b) showed the influence of PB on the concentration of thallium in the most important target organ, namely the brain. Thirty-five rats, divided into seven groups of five animals, were given 0.075 mM/kg thallos nitrate in 5 % glucose solution by intraperitoneal injection. After 24 hours, one group was sacrificed. Three of the remaining groups were subsequently treated with 50 mg PB suspended in saline, twice daily by gavage. The other groups served as controls. At 48, 72 and 120 hours after administration of thallium, one control and one treated group were killed. The thallium concentration was determined in the brain and in a muscle specimen (quadriceps). After four days of PB therapy the concentration of thallium in the brain of the treated groups was less than half that of the control group. The muscle thallium concentration in the treated group was almost one-fourth of that of the control group. A dose dependent relationship was observed. Also in other experiments reduced thallium levels in the brain were measured (Manninen et al., 1976; Rauws, 1974; Sabbioni et al., 1982).

Because of the non-resorbability of PB the substance persisted in the gastrointestinal-tract and was binding the thallium. Therefore the content of thallium in stomach and colon was increased (Oster et al., 1982; Rauws, 1974; Sabbioni et al., 1982).

In pregnant rats treatment with PB also reduced the Tl-content of placenta as well as of brain and of liver of the fetuses (Sabbioni et al., 1982).

Animal experiments were also undertaken to establish an optimal dosage scheme of PB when used for human thallosis (Kamerbeek, 1971). Five groups of five rats received 0.1 mM/kg thallosis intraperitoneally. After 24 hours four groups were treated by gavage once daily with 10, 50, 250 and 1000 mg/kg PB, suspended in 15 % mannitol. After four days of treatment, the animals were sacrificed and the thallium concentrations were determined in the brain and in a muscle specimen. A daily dose of 250 mg/kg PB appeared to be as effective as 1000 mg/kg/day with respect to Tl-concentration in muscle specimen but with respect to Tl in the brain the highest dosage was more efficacious. In adult human subjects an amount of 20  $\mu$  daily is a manageable quantity. Theoretically larger doses would be even more effective, but the quantities of PB involved would then be impracticable.

It was further shown that enhanced  $^{204}\text{Tl}$ -excretion as a result of ferric ferrocyanide therapy was accompanied by reduced thallium toxicity.  $\text{Tl}_2\text{SO}_4$  (20 mg/kg) was injected intravenously, the LD<sub>50</sub> being 12 mg/kg (Barclay et al., 1953). Twenty rats served as controls. Ferric ferrocyanide was given to 20 animals over a period of 9 days twice daily, each time as a suspension of 50 mg. The mortality in the control series after 36 days was 80 %, the mean lethal time being 6-7 days. All of the ferric ferrocyanide treated rats survived the period and showed no loss of body weight. Treatment with PB increased the LD<sub>50</sub> by a factor 2.3 (Günther, 1971). After application of 30 mg Tl/kg the survival in the control group was 0 %, in the PB group 50 % (Heydlauf, 1969). Kamerbeek (1971) further investigated the protection afforded by PB against thallium toxicity. Two groups of rats were given 0.25 mg/kg thallosis intraperitoneally. Four hours later one group received PB 100 mg/kg in a 15 % mannitol solution by gavage. The other group received mannitol only. This regimen was repeated for 10 days. In the control group, 10 of 20 animals died, while in the treated group only two deaths occurred. In pregnant rats intoxicated with Tl PB also increased the survival rate (Sabbioni et al., 1982). The therapy, however, had to start within 24 hours. Later the thallium induced pathological changes were irreversibly (Günther, 1970; Günther, 1971).

### Cesium

In in vitro studies has been shown to bind to PB (Bozorqzadeh, 1971). The Cs-sorption capacity of various hexacyanoferrates (mmol Cs<sup>+</sup>/g HCF) did not differ significantly (Nielsen et al., 1987).

Administration of a single dose of radiocesium and concomitantly oral application of PB resulted in reducing of the cesium-uptake from the gastrointestinal tract (Brenot et al., 1967; Giese et al., 1970b; Nielsen et al., 1988b; Nigrovic, 1963; Nigrovic, 1965). In piglets PB reduced the  $^{134}\text{Cs}$ -uptake by more than 97 %. The diminution of the  $^{134}\text{Cs}$ -body-burden depended on the dose of administered hexacyanoferrate(II) (Nielsen et al., 1988b). If PB was given as late as 60 min after  $^{137}\text{Cs}$ -administration the enteral  $^{137}\text{Cs}$ -absorption was also suppressed (Nigrovic, 1963). Autoradiography of rats showed, that the radioactivity was limited to the gastrointestinal-tract (Brenot et al., 1967).

Also in a mixture with other substances (for example Ca-alginate, potassium iodide) PB decreased absorption of cesium into the organism and reduced the whole-body-retention (Danetskaia et al., 1977; Kargacın et al., 1985; Kostial et al., 1980; Kostial et al., 1981; Kostial et al., 1983; Ramzaev et al., 1971).

Chronical feeding of rats (Stather, 1972) or piglets (Giese et al., 1970a) with  $^{137}\text{Cs}$ -contaminated food and concomitantly administration of PB resulted in a reduced whole body retention. Most of the applied daily  $^{137}\text{Cs}$ -doses was excreted in the faeces.

After ingestion of radiocesium PB (Bozorqzadeh, 1971; Bozorqzadeh et al., 1972; Giese et al., 1970a; Miller et al., 1974; Nigrovic, 1963; Nigrovic, 1965; Nigrovic et al., 1966; Richmond et al., 1966; Stather, 1972; Wolfsjeffer et al., 1969) decreased the whole-body-retention of the cesiumisotopes. Also in a mixture with other substances PB increased the excretion of the  $^{137}\text{Cs}$  (Kostial et al., 1983). In rats the effect on the whole-body retention was age-dependent. In younger animals the whole body retention was lower than in older animals. Probably because of the higher basal metabolic rate more cesium was excreted into the gut in young animals (Bozorqzadeh, 1971; Stather, 1972).

PB increased the cumulative excretion of incorporated radiocesium in faeces and urine (Brenot et al., 1967; Havlicek et al., 1967; Nigrovic, 1965; Nigrovic et al., 1966). Whereas in untreated animals most of cesium is excreted in the urine, in animals treated with PB the faecal excretion predominates (Brenot et al., 1967; Giese et al., 1970a; Giese et al., 1970b; Miller, 1969; Nigrovic et al., 1966; Richmond et al., 1966; Richmond, 1983). The biological half-life  $t_b$  was reduced (Havlicek et al., 1967; Madshus et al., 1966; Miller et al., 1974; Nigrovic et al., 1966; Richmond, 1983; Strömme, 1983). In rats  $t_b$  was diminished by 50 % ( $\approx 11$  days vs.  $\approx 6$  days) (Miller et al., 1974; Nigrovic et al., 1966), in dogs from 11 to 6.5 days (Madshus et al., 1966).

Oral administration of insoluble PB shortened the stay period of  $^{137}\text{Cs}$  in inmated, pregnant and lactating rats. The deposit of  $^{137}\text{Cs}$  in the embryos or nursed young animals was reduced (Havlicek, 1967).

The efficacy of therapy with PB was time dependent. Start of treatment immediately after intoxication was most successfully (Bozorqzadeh, 1971; Bozorqzadeh et al., 1982), but it was still effectively after a delayed start of 3½ days (Stather, 1972) respectively 6 days (Nigrovic, 1965).

Colloidal soluble PB was more efficiently in increasing the excretion of radiocesium than insoluble (Miller et al., 1969; Seletskaya et al., 1973). In long-term use (after  $\approx 40$  days), however, colloidal soluble PB decreased the excretion comparing the control animals. Insoluble PB did not show this effect (Bozorqzadeh et al., 1972). After exhaustively dialyzation against water to remove possible low molecular impurities this effect of the colloidal PB disappeared. Presumably non-stoichiometric bound hexacyanoferrate(II) salts were resorbed occurring systemically and reacted with endogenous metals in the body to insoluble PB, to which the cesium was absorbed. Because of its insolubility this complex could not be excreted (Miller et al., 1974). The efficacy of the dialysed colloidal soluble PB, however, was only marginal better than that of insoluble PB (Biological half-life: Control 10.51 days, insoluble PB 5.6 days, colloidal PB 4.88 days (Miller et al., 1974)).

The reduced whole-body retention after treatment with PB reduced also the cesium-content in different organs like muscles (Bozorqzadeh, 1971; Bozorqzadeh et al., 1972; Brenot et al., 1967; Kostial et al., 1983; Müller et al., 1974; Stather, 1972; Wolfsieffer et al., 1969), bone (Bozorqzadeh et al., 1972; Müller et al., 1974; Wolfsieffer et al., 1969), carcass (Kostial et al., 1983; Wolfsieffer et al., 1969), liver (Bozorqzadeh, 1971; Müller et al., 1974; Stather, 1942) or kidney (Bozorqzadeh, 1971; Bozorqzadeh et al., 1972; Brenot et al., 1967; Kostial et al., 1983; Müller et al., 1974; Stather, 1972). Due to a different turnover rate of the organs the rate of diminution of Cs in the different organs varied. In the gastrointestinal-tract the cesium content was increased due binding on the non-resorbable PB (Brenot, et al., 1967).

#### 4. Pharmacokinetics

PB is an unresorbable compound acting only in the gastrointestinal tract. To study the degree of resorption of PB from the gastrointestinal tract,  $^{59}\text{Fe}$ -labelled PB was administered to piglets. Low amounts of iron are absorbed from PB. The whole body retention was measured after 14 days (% of applicated doses)

$\text{K}^{59}\text{Fe}[\text{Fe}(\text{CN})_6]$	1.47 %	$^{59}\text{Fe}_4[\text{Fe}(\text{CN})_6]_3$	1.34 %
$\text{KFe}[^{59}\text{Fe}(\text{CN})_6]$	0.2 %	$\text{Fe}_4[^{59}\text{Fe}(\text{CN})_6]_3$	0.15 %

Nearly all of the applicated dose was found in the faeces. (Nielsen et al., 1988a). Application of  $\text{KFe}[^{59}\text{Fe}(\text{CN})_6]$  to rats resulted in 0.03 % whole-body-retention (only in the gastrointestinal-tract) and in traces of radioactivity in the urine (0.14 %). The amount in blood and skeleton was below the detection limit. 99 % of applicated dose was excreted in the faeces (Dvorak et al., 1971; Müller, 1969). After administration  $\text{K}^{59}\text{Fe}[\text{Fe}(\text{CN})_6]$  to rat traces of radioactivity were found in the skeleton (0.11 %) and in blood (0.046 %). The differences in distribution of  $\text{KFe}[^{59}\text{Fe}(\text{CN})_6]$  and  $\text{K}^{59}\text{Fe}[\text{Fe}(\text{CN})_6]$  showed, that no PB will be absorbed, but on the contrary the different ions  $\text{K}^+$ ,  $\text{Fe}^{3+}$  and  $[\text{Fe}(\text{CN})_6]^{4-}$  will be metabolised. No evidence was obtained for decomposition of  $[\text{Fe}(\text{CN})_6]^{4-}$  (Dvorak et al., 1971). Furter studies on the decomposition of PB esp. with respect to the release of cynaide are outlined in section toxicology. Histopathological examination different organs showed no deposits of PB after oral administration of insoluble and colloidal PB (Giese et al., 1970b).

After i.p. administration of  $\text{KFe}[^{59}\text{Fe}(\text{CN})_6]$  the substance will by destructed by the reticuloendothelial system. The first day 40.5 % of the radioactivity was excreted by urine, the content of the faeces was very small. On the second day 42 % were found in the faeces, only traces in the urine. After 4 days the body retention was 4.5 %, most of it in the liver (Müller 1969). I.v.-application of  $\text{KFe}[^{59}\text{Fe}(\text{CN})_6]$  and  $\text{K}^{59}\text{Fe}[\text{Fe}(\text{CN})_6]$  resulted in in an entirely different metabolic behaviour in rats. From  $\text{KFe}[^{59}\text{Fe}(\text{CN})_6]$  more than 50 % of the radioactivity were excreted in the urine, from  $\text{K}^{59}\text{Fe}[\text{Fe}(\text{CN})_6]$  only 0.06 %. The faecal excretion was low for both. The distribution of the radioactivity into the organs after application  $\text{KFe}[^{59}\text{Fe}(\text{CN})_6]$  was similar to that after application of  $\text{K}_4[^{59}\text{Fe}(\text{CN})_6]$  and differed to that of  $\text{K}^{59}\text{Fe}[\text{Fe}(\text{CN})_6]$ . Whereas the radioactivity of  $\text{KFe}[^{59}\text{Fe}(\text{CN})_6]$  persisted in the liver for 8 days, the activity of  $\text{K}^{59}\text{Fe}[\text{Fe}(\text{CN})_6]$  varied from the liver to the blood (Dvorak et al., 1971).

## 5. Toxicology

### Acute Toxicity

After i.p.-administration of ferric(III) hexacyanoferrate(II) to rats the LD<sub>50</sub> was 1.13 mg/g (Brenot et al., 1967). No tissue response could be detected (Migrović et al., 1966). For peroral application the LD<sub>50</sub> is >10 g/kg (NV, 1979).

The test of skin tolerance as well as the eye test in rabbits were without findings (NV, 1979).

PB contains cyanide-ions bound to iron. At extremely low pH values in the presence of oxidizing agents PB decomposes and, under these circumstances, cyanide can be released. Since oral administration of PB is indicated in the treatment of thallium poisoning and cesium incorporation, the possibility of cyanide release must be excluded. To study whether after administration of PB cyanide will be released from the substance <sup>14</sup>C-labelled cyanide was used

1.  $K_4[Fe(CN)_6] \longrightarrow K^+ + Fe^{3+} + [Fe(CN)_6]^{4-}$   
 $Fe_4[Fe(CN)_6]_3 \longrightarrow 4 Fe^{3+} + 3 [Fe(CN)_6]^{4-}$
2.  $[Fe(CN)_6]^{4-} \longrightarrow Fe^{2+} + 6 CN^-$
3.  $CN^- \longrightarrow CO_2 + SCN^-$

In vitro the release of cyanide is negligible (Dvorak, 1970). <sup>14</sup>C-labelled ferric(III) hexacyanoferrate(II) was administered to piglets. No labelled <sup>14</sup>CO<sub>2</sub> was detected in the expired air. This demonstrated, that no significant amounts of cyanide were released from PB in the body. The amount of incorporated ions can be extremely small or even nil (Nielsen et al., 1988a).

### Chronic Toxicity / Mutagenicity / Carcinogenicity

When PB was applied orally to rats for 12 weeks, no significant changes in the increasing of body-weight were determined. Histopathological changes were not detectable in the organs including the gut (Dvorak et al., 1971). For chronic administration of PB to rats the LD<sub>50</sub> is > 1 g/kg (NV, 1979).

Oral application of food containing 1 % of PB during 120 days (Migrović et al., 1966) or during 60 days (Wolfsieffer et al., 1969) resulted in no change of body weight increase. Food consumption and increasing of body weight was unchanged during 10 days (Kostial et al., 1980) or 4 weeks (Kostial et al., 1981). No significant difference of average fluid intake of rats was detected in rats during a 60 day period (Richmond et al., 1966). The well-being and body weight of dogs in no way was affected by PB during 11 days (Nadshus et al., 1966). At autopsy no pathological changes were observed (Migrović et al., 1966).

In humans no significant variations in the potassium level were detected (NV, 1988; Richmond, 1983). As during synthesis PB is saturated with potassium and the binding power increases with increasing of the ionic radius of the ions Na<sup>+</sup> < K<sup>+</sup> < NH<sub>4</sub><sup>+</sup> < Rb<sup>+</sup> < Tl<sup>+</sup> < Cs<sup>+</sup> (Forch, 1983; Nielsen et al., 1987), an influence of PB on potassium and sodium level is not to be expected (Migrović et al., 1966).

## Reproduction Toxicology

PB was used in pregnant rats only within experimental thallium poisoning. The Tl-content of the placenta as well as of brain and liver of the fetuses was reduced by PB (Sabbioni et al., 1982). Also the survival rate of the pregnant rats was increased.

## 6. Indications

### Thallium

The efficacy of PB for treatment of thallium poisonings has been described in various publications. A survey of the literature about treatment with PB in humans after Tl-intoxication is given in table 1. As with antidotes generally clinical experience mainly is based on case reports.

In patients even with severe thallium poisoning published in the literature have all been favourable. Only three deaths were reported (Nielsen, 1974; Van-Kesteren et al., 1980). Two of them have ingested 2400 mg respectively 4000 mg Tl. The lethal dose is about 1000 mg  $Tl_2SO_4$ . One of them died after a second ingestion of thallium (Van-Kesteren et al., 1980). The patients with thallosis exhibited a good clinical response.

Most of the patients, who were treated immediately after Tl-ingestion with PB and other therapeutic regimen, developed no or only traces of thallium induced neurological symptoms, although the thallium levels were high (Graben et al., 1980; Hoppe-Seyler et al., 1975; Stevens et al., 1974; Van-der-Herwe et al., 1972).

Some of the patients, in whom start of treatment was delayed, also recovered uneventfully. However the amelioration progressed sometimes slowly (De-Groot et al., 1985; Ghezzi et al., 1979; Graben et al., 1980; Heath et al., 1983; Richelmi et al., 1980; Schwartz et al., 1988; Stevens et al., 1974, Stevens, 1978). In some patients with severe clinical signs of thallium intoxication the clinical symptoms were not fully reversible at the time of discharge. Neurological disturbances, namely in the legs (Barckow et al., 1976; Heath et al., 1983; Hoppe-Seyler et al., 1975; Kamerbeek et al., 1971b; Muller, 1977; Robb-Smith et al., 1987; Stevens et al., 1974; Van-Hees et al., 1975) and alopecia (Barckow et al., 1974; Nogue et al., 1982; Smith-Pedersen, 1978; Van-Hees et al., 1975) were the most of the remained clinical symptoms.

In the more severe cases of thallium intoxication additional treatment for enhanced elimination was used. If ingestion had occurred within the preceding 48 hours in most cases gastric lavage was carried out. Hemodialysis and forced diuresis are also used in many cases. In very severe cases additionally hemoperfusion was carried out. To increase the faecal excretion laxatives, above all mannitol, was applied. In some cases forced diarrhoea was induced.

### Cesium

The effect of PB on Cs decorporation initially has been studied in volunteer studies (self experiments of the authors) (Madshus et al., 1966; Madshus et al., 1968; Richmond, 1983; Strømme, 1983). 3x1 g PB daily also reduced the long-term biological half-life to one-third. 3x0.5 g

daily, before and concomitantly given with  $^{137}\text{Cs}$ , had no prophylactic effect on body-burden. PB was tolerated without any ill effects except for a slight obstipation. When PB was administered in a daily dose of 2 g divided in 10 single doses for 10 days the biological half-life of  $^{137}\text{Cs}$  was reduced from 115 to about 40 days (Richmond, 1983).

In 4 of 6 volunteers, PB almost completely blocked Cs-uptake from contaminated food. However the preexisting Cs body burden was not substantially decreased. The effect of PB varied individually. The effect was not dose dependent. No adverse effects were observed (Volf et al., 1987).

The PB treatment of 46 patients with incorporated  $^{137}\text{Cs}$  after the radiological accident in Goyana 1987, when 249 persons had been contaminated externally or internally with  $^{137}\text{Cs}$ , is described in the IAEA-Report (NV, 1988). The patients ageing 4 to 38 years were treated with Radiogardase<sup>®</sup>-Cs up to 150 days. The doses ranged from 1 to 10 g daily. PB expedited the decorporation of cesium. Increasing the dose of PB resulted in higher radioactivity in the faecal samples. The in-body-radioactivity was reduced. In a very small number of patients constipation was observed, which could be treated using laxatives.

Five persons had intaked of  $^{137}\text{Cs}$  accidentally. The effective half-life of the cesium depended on the individual. It ranged from 124 to 36 days. The half-life was shorter when the weight of the subject was lighter or the person was younger. PB accelerated the decorporation of cesium. The half-life was reduced to 39 to 16 days (Ma et al., 1985).

For an overview about the clinical use of PB in cesium intoxication see table 2.

## 7. Contraindications/Precautions

It is only effective if the motility of the intestines is intact.

## 8. Adverse effects

Highly doses during treatment over a prolonged period of time may lead to slight obstipation.

## 9. Pharmaceutical incompatibilities and drug interactions

PB given together with tetracycline may retard the resorption of tetracycline.

## 10. Dosage and route

PB is be applied orally. Depending on the severity of thallium poisoning or cesium-incorporation the daily dose may vary from 3 g to 20 g. The higher dose usually is preferred in acute poisoning with thallium. The dose should be continually given over the 24-hours-interval to interrupt the enteral cycle of thallium or cesium in an optimal way.

In cases of acute thallium poisoning, in which thallium is still present in the stomach or upper parts of the small intestines, an initial dose of at least 3 g should be given at once.

The capsules of Antidotum Thalli-Heyl<sup>(R)</sup> and Radiogardase<sup>(R)</sup>-Cs are to be swallowed whole with some liquid or dispersed in warm water and drunk as a solution; this solution may also be administered by way of the stomach tube following gastric lavage. If according to clinical findings an oral ingestion is impossible, application of ferric(III) hexacyanoferrate(II) is recommended by way of the duodenal tube. The duration of treatment depends on thallium identification in the stool by laboratory analysis.

## 11. Remarks

Therapy of thallium poisoning and of ingestion of radioisotopes of cesium is primarily directed to the prevention of absorption from the intestinal tract and to the elimination of the metals from the body. PB became the standard treatment. In severe cases of thallium intoxication additional types of elimination treatment may be necessary.

- Induce emesis, followed by gastric aspiration and lavage.
- Forced diuresis (8-12 l/24h) until urinary thallium excretion is less than 1 mg/24h (De-Groot et al., 1988).
- Charcoal hemoperfusion has been proven to be successful if used within 48 hours of ingestion of thallium and therefore during the distribution phase (De-Groot, 1985). Average blood clearance at a starting blood concentration above 2 mg/l was  $72 \pm 11$  (SD) ml/min, and  $120 \pm 23$  (SD) below this concentration. A saturation of the hemoperfusion column occurs, exchange of the columns is necessary. A charcoal hemoperfusion column has to be used because the clearance achieved with a resin column is zero.
- Hemodialysis has to be reported to be effective in thallium intoxication. Clearance obtained by this technique were 83 ml/min (Pederson et al., 1978) and 111 ml/min (Barckow et al., 1976).

A survey of literature demonstrated, that forced diuresis and hemoperfusion with activated charcoal additionally increases the total clearance of thallium and decreases its biological half-life  $t_{1/2}$  (De-Groot et al., 1988)

- without treatment :  $t_{1/2}$  9.5 to 15 days
- PB only :  $t_{1/2}$   $3.0 \pm 0.7$  days
- PB+forced diuresis :  $t_{1/2}$   $2.0 \pm 0.3$  days
- PB+forced diuresis+hemoperfusion:  $t_{1/2}$   $1.4 \pm 0.3$  days.

## 12. Use in pregnancy and lactation

As PB is not resorbable no teratogenic effects or no appearance in milk are to be expected. Pregnant and lactating women are therefore not considered to be excluded from treatment with PB

## 13. Overdosage

Overdosage by PB has not been described.

## TREATMENT OF HUMAN WITH PRUSSIAN BLUE AFTER THALLIUM INTOXICATION

No. of Patients	Age [years]	Tl-Dosage [µg]	Delay of treatment [days]	Tl-levels at start or day 1 of therapy	Drug	Daily PB-Dosage	Duration of PB therapy [days]	Additive treatment	Outcome	Literature
3		up to 1620	up to 14		6	2x10 g	10 - 14	Mannitol	All patients recovered. The patient with 1.6 g Tl showed some residual neurological disturbances, namely in legs	Kamerbeck et al., 1971
2	26	570	<1	U 13 mg/24h	1	4x3.75 g	13	Gastric lavage, mannitol potassium chloride, activated charcoal, vitamin B, fluid intake	Only traces of neurological damage, which disappeared during the following weeks	Van-der-Herwe 1972
2	22	570	<1	U 3.3 mg/24h	1	250 mg/kg body weight	10	Gastric lavage, mannitol fluid intake	No serious toxic effects of thallium developed	Jax et al., 1973
2	34	405	<1	B 0.9 ppm U 2 ppm F 10 ppm	5	1g every 2 hours	16	Gastric lavage, sodium thiosulfate, enemas, sodium iodide, forced diuresis, hemodialysis dto.		
	54	650	<1	B 0.8 ppm U 5 ppm F 2 ppm	5	1g every 2 hours	24			
1	66	4000		U 43 mg/l	1			Mannitol	Died of bilateral broncho-pneumonia after 21 days	Nielsen 1974
11	35		22	U 1.43 mg/l	2	2x10 g every 2 days	36	Initial treatment with activated charcoal and potassium chloride	Only moderate paresthesias in the legs	Stevens et al. 1974
	30	810	<1	U 1490 µg/24h F 1520 µg/100g	2	2x10 g	11	Gastric lavage	Perfect healthy condition	Barbier, 1974
	33		42	U 500 µg/24h F 1600 µg/100g	2	1x20 g	15		Muscle strength and vision insufficient	
	24	240	<1	U 3220 µg/24h	2	4x5 g	11	Gastric lavage, mannitol	No symptoms of thallosarcosis developed	
	32		94	U 120 µg/24h	2	4x5 g	19	Mannitol	Slight paresthesias of the legs	
	64		28	U 620 µg/24h F 3520 µg/24h	2	4x5 g	11	Mannitol	Only glucose tolerance was slightly pathologic	
	44		62	U 232 µg/l	2	4x5 g	18 + 50 (2 treatment cycle)	Mannitol	Patient recovered well, but slowly	
	45		151	U 215 µg/24h F Constipation	2	4x5 g	45	Mannitol, potassium chloride	Symptoms of thallium intoxication were reversible, but amelioration progressed	

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Ho. of Patients	Age [years]	Tl-Dosage [mg]	Delay of treatment [days]	Tl-levels at start or day 1 of therapy	Drug	Daily PB-Dosage	Duration of PB therapy [days]	Additive treatment	Outcome	Literature
4	49	240	<1	U 2310 µg/24h B 220 µg/l	2	4x5 g	24	Gastric lavage, mannitol potassium chloride	Perfect healthy condition	
	6	180	9	U 840 µg/24h	2	4x1 g	27	Mannitol	The clinical course was very satisfactory	
	2		1	U 180 µg/l	2	4x1.7 g	11	Lactulose, furosemide	No symptoms of thalothoxicosis developed With excellent results	
3	16	607	21	S 600 µg/l	4			Gastric lavage, forced diuresis, hemodialysis	Paresthesias and weakness of muscles in the legs	Hoppe-Seyler et al., 1975
	26	1600	<1	S = 2.7 mg/l	4			Gastric lavage, laxative forced diuresis, hemodialysis	No residual symptoms	
	26	2430	<1	S 3 mg/l	4			Gastric lavage, forced diuresis, hemodialysis, forced diarrhoea	Perfect healthy condition	
1	26	607	2	U 2.39 mg/l F 1.91 mg/100g	1	3g every 4 hours	20	Sorbitol, forced diuresis	Good condition, alopecia, residual symptoms of disturbances in feet	Van-Hees et al., 1975
	25	930	1	U 12.0 mg/l (day 3)	1	3g	45	Gastric lavage, forced diuresis, enemas, hemodialysis	Folliculitis, alopecia, polyneuritis in the area of the lower extremities	Batchow et al., 1976
4	16	300	21	B 600 µg/l	1			Gastric lavage, forced diuresis, hemodialysis, forced diarrhoea		Drasch et al., 1977
	26	1300	<1	B 2.7 mg/l	1			Gastric lavage, catharsis, forced diuresis, hemodialysis		
	26	1000	<1	U 40 mg/24h F 14 mg/24h	1			Gastric lavage, forced diarrhoea, hemodialysis, forced diuresis		
	28	900	2	U 52.4mg/24h	1			Gastric lavage, forced diarrhoea, hemodialysis, forced diuresis		
1	26	~ 4000	2	U 78 mg/l S 5 mg/l	1	2x10 g	14	Laxative, mannitol, forced diuresis	Alopecia, moderate neuropathy cardiovascular symptoms	Muller 1977

No. of Patients	Age [years]	Tl-Dosage [mg]	Delay of treatment [days]	Tl-levels at start or day 1 of therapy	Drug	Daily PB-Dosage	Duration of PB therapy [days]	Additive treatment	Outcome	Literature
1	19	750	4	S 410 µg/l U 40 mg/24h	3	3g	> 49	Forced diuresis, hemodialysis, hemoperfusion, sodium thiosulfate	After 8 months the motor disturbances were reversible	Graben et al., 1978
1	56	1600		U 25 mg/l B 1.2 mg/l	2	4x4 g	19	Gastric lavage, hemodialysis, forced diuresis, laxatives	Slight hair loss, transient paresthesia	Smith-Pedersen et al., 1978
1	41		6	U 2.46 mg/l B 310 µg/l	1	5x5 g	18	Mannitol, potassium chloride	Within one week all symptoms disappeared	Stevens 1978
4	20	400	22		2	250 mg/kg body weight	27	Mannitol, phenobarbital	Totally asymptomatic	Chezzi et al., 1979
	26	400	20		2	250 mg/kg body weight	20	Mannitol	Clear of any symptoms	
	Newborn		16		2	250 mg/kg body weight	19	Mannitol	Clear of any symptoms	
	18		1	F 20 ppm	2	250 mg/kg body weight	12	Mannitol, Gastric lavage catharsis	No clinical symptoms were observed	
10			up to 42		2	1.5 g every 2 hours	up to 28	Forced diuresis, hemodialysis	Immediately treated after the intoxication, the patients were discharged symptom-free. The other patients showed a significant and persistent change for the better.	Graben et al., 1980
	21	600	2	B 1.5 mg/l U 15 mg/l	2	10 g	8	Hemodialysis, forced diuresis	Symptom-free	
	24	= 500	= 14	B 0.07 mg/l U 0.4 mg/l	2	1.5 g every 2 hours			Symptom-free	
1	28	800	4	U 3 mg/l	2	4x5 g	20	Mannitol, glucose, forced diuresis	Asymptomatic	Richelma et al., 1980
18	19 - 58	up to 3000	up to 28	U up to 84 mg/l	2	2x10 g		Mannitol, hemoperfusion, forced diuresis, gastric lavage	One patient died after 4 days. Four months later another patient died after a new ingestion of Tl.	Van-Kesteren et al., 1980
1	32	81	<1	B 415 µg/l	2	250 mg/kg body weight	10	Stomach lavage, hemoperfusion, hexodialysis forced diuresis	Good general condition	De-Baeker et al., 1982
1	37		25	U 3.80 mg/l S 250 µg/l	5	10x0.5 g	32	Forced diuresis	Lack of concentration	Gansser, 1982

No. of Patients	Age (years)	Tl-Dosage [µg]	Delay of treatment (days)	Tl-levels at start of day 1 of therapy	Drug	Daily PB-Dosage	Duration of PB therapy (days)	Additive treatment	Outcome	Literature
1	27	600	2	P 950 µg/l	1	10g every 8 hours during days 1 to 4, and 16 to 19		Forced diuresis, hemodialysis, dithiocarb, mannitol, dithiozone	Alopecia	Hogue et al. 1982
2	58	= 1000	5	B 1.9 mg/l U 30 mg/ml	1	5x4 g	26	Mannitol, forced diuresis, hemoperfusion	Diminished pain perception and abnormal vibration perception in hands and feet	Heath et al., 1983
	28		10	B 0.35 mg/l U 2.7 mg/l	1	5x4 g	5	Mannitol, forced diuresis	Recovered uneventfully	
1	26	> 40	> 40	B 184 µg/l U >3000 µg/24h	5	3x1 g	50	Forced diuresis, vitamin B, analgesics	Residual symptoms of distal polyneuropathy	Trenkwalder et al., 1984
3			< 2	B 1.9-5.8 mg/l P 1.8-5.2 mg/l	1	2x10 g		Mannitol, gastric lavage forced diuresis, hemoperfusion	Fully recovered	De-Groot et al., 1985
9	16 - 70		4 - 7	U 23-2200 µg/ml S 4- 16 µg/ml	6	2g	42	Magnesium sulphate, vitamin B, analgesics, amiloride, hydrochlorothiazide	Fine tremors of the upper limbs, slight incoordination of movements	Pai, 1987
1	1 <sup>o</sup> / <sub>12</sub>		> 10		1		21	Potassium chloride	Alert, ataxic, but walking with help	Kobb-Smith, 1987
1	45	= 200	= 200	U 12.6 mg/l S 85 µg/l	1	4g every 6 hours	12	Mannitol	The patient has recovered	Schwartz et al., 1988
1	37	1130	< 1		5	0.5 g every 4 hours	25	Mannitol, hemodialysis, forced diuresis	In a large measure reduced polyneuropathy	Theilmeyer et al., 1988

Table 1

Treatment of human after thallium intoxication

Drug:

- 1 no specification of the used
- 2 Prussian Blue
- 3 KFe(Fe(CN)<sub>6</sub>)
- 3 Fe<sub>2</sub>(Fe(CN)<sub>6</sub>)<sub>3</sub>
- 4 NaFe(Fe(CN)<sub>6</sub>)<sub>3</sub>
- 5 Antidotum Thallii-Heyl's
- 6 Prussian Blue of BDH London
- 7 Radiogardase-Cs<sup>137</sup>

Tl-levels:

- U Urine
- P Plasma
- S Serum
- B Blood
- F Feces

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# TREATMENT OF CS-INCORPORATION IN HUMANS WITH PRUSSIAN BLUE

No. of Patients	Age (years)	Cs-Isotope	Drug	Daily PB-Dosage	Duration of PB therapy (days)	Additive treatment	Effects of PB	Side-effects of PB	Literature
7		<sup>137</sup> Cs	3	3x0.5g 3x1 g	> 21		3x1 g PB daily reduces the long-term biological half-life of <sup>137</sup> Cs to one-third of its value. 3x0.5g daily resulted only in a small increase of excretion. 3 g PB a day, before and contemporarily given with <sup>137</sup> Cs, had no prophylactic effect on body-burden (Self-experiment)	Without any ill effects except for slight obstipation	Madshus et al., 1966 Madshus et al., 1968 Stromme, 1983
1	37	<sup>137</sup> Cs	3	10x200 mg	10		Administration of PB reduced the biological half-life from 115 days to about 40 days. (Self-experiment)	No constipation, no significant influence on whole body potassium level	Richmond, 1983
5	4 - 38	<sup>137</sup> Cs	1	1 - 3 g	41 - 108		The effective half-life of <sup>137</sup> Cs depended on the individual. Treatment with PB was reducing the half-life. The effectiveness of PB in accelerating the removal of <sup>137</sup> Cs was observable.		Ma et al., 1985
6	28 - 59	<sup>137</sup> Cs <sup>137</sup> Cs	7	4x500 mg 10x200 mg 10x500 mg	14 21 28		In 4 out of 6 volunteers, PB almost completely blocked Cs-uptake from contaminated food. It does not substantially decrease the preexisting Cs body burden. The effect of PB depended on the treated individual.	No adverse effects	Volf et al., 1987
46	4 - 38	<sup>137</sup> Cs	7	1 - 10 g	up to 150	Laxatives	Increasing of radioactivity in fecal samples; increasing of reduction of in-body-radioactivity. Pb expedited the decorporation of <sup>137</sup> Cs.	Constipation in a very small number of patients. No significant variations in the serum levels of potassium	HN 1988

Table 2

Treatment of Cs-Incorporation in humans

Drug: 1 no specification of the used Prussian Blue

- 2 KFe[Fe(CN)<sub>6</sub>]
- 3 Fe<sub>3</sub>[Fe(CN)<sub>6</sub>]<sub>2</sub>
- 4 NaFe[Fe(CN)<sub>6</sub>]
- 5 Antidotum Thallii-Heyl<sup>1,2</sup>
- 6 Prussian Blue of BDH London
- 7 Radioardase-Cs<sup>1,2</sup>

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Norbert Zänker & Partner · Dolmetscher und Übersetzer · Kurfürstendamm 188/189 · 1000 Berlin 15 · Telefon (030) 884 30 250 · Telefax 882 37 37

THE SENATOR FOR HEALTH AND SOCIAL SERVICES

BER

The Senate for Health and Social Services  
An der Urania 12, D-1000 Berlin 30

Ref. No.  
(please quote in  
all correspondence  
IV D 21 - 5373/1  
- Braun -  
Tel.: (030) 21 22  
(switchboa  
(direct): 21 22-  
Ext.: 27 88  
internal (979)

Date: 22 December 1

To Whom It may Concern

In respect of the firm B. Braun Arzneimittel GmbH, Mistelweg  
2 - 6, 1000 Berlin 47, it is herewith certified that

- a) it is authorized to manufacture drugs under the law on the reform of the law governing the manufacture and prescript: of drugs dated 24 August 1987, valid in the Federal Republic of Germany and Berlin (West),
- b) its operations pertaining to the manufacture of drugs are subject to regular official inspection,
- c) it satisfies the GMP-guidelines recommended by the World Health Organization in respect of

injection solutions

which are made available and sold in the Federal Republic Germany including Berlin (West) or exported.

The right to revoke this certificate is reserved.

By order  
(signed) (illegible)  
Jahn, Senate Administrative Officer

(seal) Coat of Arms of Berlin  
The Senator for Health and Social Services  
Berlin  
12

Administrative fee: DM 345.00  
Cost Ref.: 13525 GesUGebo

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(certification overleaf)

1144760

R a d i o g a r d a s e <sup>®</sup> - C s

Capsule

Composition

Each capsule contains  
0,5 g iron(III)-hexacyanoferrate(II)  
(68 %  $\text{Fe}_4[\text{Fe}(\text{CN})_6]_3$ )

Indications

Diminution of the biological half-life of radioactive isotopes of caesium (i.e.  $^{137}\text{Cs}$ ,  $^{134}\text{Cs}$ ).  
Application in cases when persons come into contact with these isotopes.

Side effects

Not known so far.

Comment: Dark colouring of the stool is harmless; it is due to the colour of the substance.

Interactions

Radiogardase-Cs given together with tetracycline may retard the resorption of tetracycline.

Dosage

Adults and children  
in already present caesium resorption  
daily 3 g (6 capsules) Radiogardase-Cs in 6 single doses in a 2 hours interval.

Due to clinical experience an increase of dosage to daily 20 g (40 capsules) Radiogardase-Cs is possible as the non-toxic substance will not be resorbed.

To interrupt the enteral cycle of  $^{137}\text{Caesium}$  in an optimal way the daily dose should be given continually over a 24-hours-interval.

Mode of administration

The capsules are to be swallowed with liquid.

### Properties

The unstable caesium-isotope  $^{137}\text{Cs}$  is considered one of the most dangerous artificial radionuclides. It results highly in atomsplitting, is unhindered resorbed by human beings and animals through the intestines and has a relatively long biological half-life of about 150 days in human beings.

$^{137}\text{Cs}$  Caesium reaches the intestines mostly by way of liver and gall bladder, there it is partially resorbed back through the intestinal mucosa into the circulating blood.

Radiogardase-Cs interrupts this enteral cycle by binding the  $^{137}\text{Cs}$  Caesium present in the intestines complexly and it further prevents its resorption resp. re-absorption, so that  $^{137}\text{Cs}$ -Caesium is excreted with the stool.

The efficacy of Radiogardase-Cs is independent of the time period between the poisoning with  $^{137}\text{Cs}$  and the beginning of the therapy. That is valid also for all other radio isotopes of caesium, e.g.  $^{134}\text{Cs}$ .

### Administration form and package size

30 capsules

# Radiogardase-Cs ( R )

## 1. Composition

One Radiogardase-Cs capsule contains:  
0.5g iron(III)-hexacyanoferrate(II)  
(68% Fe(III)<sub>4</sub>[Fe(II)(CN)<sub>6</sub>]<sub>3</sub>) (insoluble Berlin Blue).

## 2. Indications

Decorporation respectively prevention of uptake of radiocesium  
(<sup>134</sup>Cs, <sup>137</sup>Cs)

## 3. Contraindications

None are known

## 4. Side Effects

None are known

(Remark: Dark coloration of the stools is harmless: it is caused by the color of the substance.)

## 5. Interactions with other Substances

When administered together with tetracycline, Radiogardase-Cs can block tetracycline absorption.

## 6. Individual and Daily Doses

When Cs-resorption has already occurred, the patient (child or adult) should receive 3g of Radiogardase-Cs per day in 6 individual doses of 0.5 g each in two-hour intervals, unless otherwise specified.

Due to the non-resorbability and non-toxicity of the substance, the dose of Radiogardase-Cs can, according to clinical experience, be increased to 20 g/day. In order to optimally interrupt the entersystemic circulation of radiocesium, the daily dose should be evenly distributed throughout the 24-hour time period.

## 7. Type and Duration of Treatment

The long biological half-life of radiocesium must be taken into consideration when determining the length of Radiogardase-Cs therapy.

Capsules should be taken with liquids.

## 8. Emergency Measures, Symptoms and Antidotes

There are no known cases of overdosage or intoxication due to iron(III)-hexacyanoferrate(II).

## 9. Pharmacological and toxicological properties, pharmacokinetic and bioavailability data relevant to therapeutic use.

### *Pharmacologic Properties*

Radiocesium is subject to marked enterosystemic circulation, i.e., resorbed cesium returns to the intestines by back-diffusion and via the gallbladder, where it is again (back)resorbed. The detoxification effects of iron(III)-hexacyanoferrate(II) are based on interruption of the enterosystemic circulation and, therefore, a significant reduction in the biological half-life of radiocesium.

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Iron(III)-hexacyanoferrate(II) has an extremely low solubility product. Splitting and resorption or persorption therefore cannot occur, but rather, the orally administered substance remains in the intestines and is excreted with the feces. Radiocesium present in the intestines, which either has not been resorbed yet or which returned to the intestines via enterosystemic circulation (see above), is bonded to iron(III)-hexacyanoferrate(II) via an ion exchange mechanism. The ion exchange occurs with potassium ions and protons which are available in extra-stoichiometric amounts in iron(III)-hexacyanoferrate(II). Further bonding is possible at vacant sites of the crystal lattice of iron(III)-hexacyanoferrate(II) which can be occupied by cesium ions. After radiocesium has bonded to iron(III)-hexacyanoferrate(II), it can no longer be resorbed or back-resorbed.

Although cesium is normally excreted in urine, fecal excretion of cesium is greatly increased by administration of Prussian Blue. The cumulative total Cs excretion is enhanced.

In self-experiments with humans, the biological half-life of radiocesium was reduced by oral administration of 3 g of iron(III)-hexacyanoferrate(II) per day from 110-115 days to approximately 40 days.

Any (undesirable) bonding with other essential minerals (only the alkali metals Na and K apply here) is improbable. The affinity of iron(III)-hexacyanoferrate(II) to cesium is highest. It has a very much lower affinity for potassium, and the lowest affinity for sodium ( $Cs \gg K > Na$ ). Because of its low affinity for sodium and because of the fact that iron(III)-hexacyanoferrate(II) is already saturated with potassium molecules, it is practically impossible for these metals to bond with the substance, even when cesium is not present.

**Toxicologic Properties; Pharmacokinetics and Bioavailability**  
Iron(III)-hexacyanoferrate(II) is not really subject to any pharmacokinetic factors, since it is not resorbed and does not occur systemically. Due to its non-resorbability, iron(III)-hexacyanoferrate(II) is non-toxic (acute LD-50 > 10 g/kg; chronic LD-50 > 1 g/kg in rats).

Possible decomposition of iron(III)-hexacyanoferrate(II) to form hydrocyanic acid or its salts can be excluded in physiologic conditions, because one would need an extremely low pH and simultaneous absence of oxidants for such a reaction to occur.

#### **10. Additional Remarks**

Not applicable

#### **11. Form of Administration and Package Size**

30 capsules

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Radiogardase-Cs Capsules

1. Appearance / Description

Dark blue, translucent hard-gelatine capsules (size 0) with black violet granular content.

Size:

Diameter: 7,6 mm

Length: 21,8 mm  $\pm$  0,3 mm

2. Average weight of filled capsule

Requirement: 575 mg - 650 mg

2.1 Average weight of capsule filling

Requirement: 475 mg - 550 mg

2.2 Uniformity of weight acc. to DAB 9

Requirement: A maximum of 2 capsule fillings may exceed 7,5 %; however, none should vary from the average fill weight by more than 15 %.

3. Disintegration time acc. to DAB 9

Requirement: max. 30 minutes in water

4. Identification

a. of the active ingredient: Ferric ferrocyanide

A, Heat 0,5 g of capsule filling mass with 5 ml 3 M potassium hydroxide. Brown flocculent ferric hydroxide is formed. After its sedimentation the supernatant appears yellow.

B, Filter the reaction solution (see point A) and acidify 2 ml of the yellow filtrate with conc. hydrochloric acid, then add 0,5 ml of ferric chloride solution 10,5 % (w/v). A blue color or a blue precipitate is produced.

b. of the dye in the hard capsule shell: Indigocarmine

(identical with indigotine C.I. 73015)

Dissolve by heating 1 capsule shell in 50 ml 0,1 N hydrochloric acid. The UV-spectrum of this solution registered from 700 to 240 nm exhibits maxima at around 286 nm and 610 nm.

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5. Assay of content of the active ingredient

Work is to be performed under a fume hood because of evolution of hydrocyanic acid.

Weigh accurately 150 to 200 mg of capsule filling mass and boil with 10 ml conc. sulfuric acid in a Kjeldahl flask for 60 minutes.

After cooling, cautiously and completely transfer the contents of the Kjeldahl flask into a 500 ml Erlenmeyer flask containing 150 ml of dist. water and heat until the solution is clear. Subsequently adjust the pH to 2,5 by dropwise adding sodium hydroxide solution 15 % (w/v).

Add 1 ml hydrogen peroxide solution 30 % (w/w) and stir for 5 minutes. After addition of 1 ml of 5-sulfosalicylic acid solution 5 % (w/v) (indicator) titrate at 40° to 50 °C with 0,1 M disodium edetate to a color change from violet to yellow. Then add another 1 ml of indicator solution, and if the color turns violet again the titration is continued until a permanent change to yellow is obtained.

Each ml of 0,1 M disodium edetate is equivalent to 5,585 mg of iron.

Requirement: 154,7 mg (147,0 - 170,2 mg) of iron per capsule  
is found

Note: This corresponds to 95 - 110 % of the declaration (500 mg ferric ferrocyanide (68 %) per capsule).

March 6, 1991

HEYL *i. R. A. Krämer*  
Chem.-pharm. Fabrik  
Quality Control  
i. A. A. Krämer

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Fun H. Fong/ Dr. Robert C. Ricks  
From: Marta Rivera, Secretary Committee on Human Studies  
RE: Status Report on Active Proposals  
Date: April 28, 1993

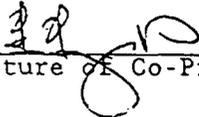
The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposal present a progress report to the Committee on the status of the proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions and add other information you feel pertinent and return by May 14. (If additional space is needed, please use the back of this form or attach extra sheets).

Title of Project: "Use of Prussian Blue for Internal Decontamination of Radiocesium"

Proposal No. 81

  
\_\_\_\_\_  
Signature of Co-Principal Investigator

6/1/93  
\_\_\_\_\_  
Date Signed

  
\_\_\_\_\_  
Signature of Co-Principal Investigator

6 Jun 93  
\_\_\_\_\_  
Date Signed

1. Report progress made in the past year.  
Please see pages attached.
2. Report any complications.  
Please see pages attached.

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Oak Ridge  
Associated Universities Post Office Box 117  
Oak Ridge, Tennessee 37831-0117

To: Dr. Fun H. Fong/Robert C. Ricks  
From: *W.C.*  
Dr. William Calhoun, Chairman  
Committee on Human Studies  
Date: June 29, 1993  
Re: Committee Action on Active Proposals

Your project number 81 "Use of Prussian Blue for Internal Decontamination of Radiocesium" was reviewed and approved for continuation at our last meeting on June 25, 1993.

Progress reports of all active proposals will again be reviewed at our next meeting to be held in the fall of 1993.

/mvr

1144768

Ident No. 81

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS (Draft 12 Jul 91)

TO: COMMITTEE ON HUMAN STUDIES  
Oak Ridge Associated Universities (ORAU)  
and Oak Ridge National Laboratory (ORNL)

REPOSITORY Oak Ridge Inst. of Science & Education  
COLLECTION Medical Sciences Division  
ORAU/ORNL CHS

Date: June 6, 1991

BOX No. \_\_\_\_\_

Principal Investigators: Fun Fong, Jr, MD, FACEP/ Robert C Ricks, PhD

FOLDER ORAU-30019 (2)

Co-Investigators:  

Title of Project: USE OF PRUSSIAN BLUE FOR INTERNAL DECONTAMINATION OF RADIOCESIUM

I. Objective of Experiment:

The objective of the study is to determine the benefits from the administration of Insoluble Prussian Blue,  $Fe_4[Fe(CN)_6]_3$ , to humans who have been internally contaminated with radiocesium. Prussian Blue has been used as a drug cleared for compassionate use in patients contaminated in the 1987 Goiania radiological accident, and an IND for this drug also exists in the U.S. today. The study will quantitate efficacy and a profile of side effects in a larger scale trial.

II. Methods of Procedure:

An investigational new drug application (IND) will be filed by ORAU with the Food and Drug Administration (FDA). Medical-grade Prussian Blue will be obtained from the Heyl Co, a manufacturer based in the Federal Republic of Germany. (See literature information in Appendix 1) Quality control information will be supplied to both the Committee and the FDA, as well as current information available. (See quality control information in Appendix 2) Applications for co-investigators will be solicited from ORAU's existing physician collaborators for DTPA and from other physicians who have a perceived need to treat patients for possible internal contamination with radiocesium. These collaborators, following standard FDA IND protocol, will be required to submit all available treatment and excretion data, along with listed side-effect and other observations to ORAU, who will compile the data and submit the information in an annual report to FDA. The research stimulated will lead to optimization of clinical use and dosage of Prussian Blue. A registry of persons treated with Prussian Blue will be maintained by ORAU as a basis for long term follow-up to determine any delayed effects of this treatment.

III. Possible Hazards and Their Evaluation:

(See Prussian Blue information in Appendix 1)

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Oak Ridge Associated Universities  
Medical Sciences Division (Revision 19 Aug 91)

CONSENT for DECORPORATION THERAPY using Insoluble Prussian Blue,  
An FDA Investigational Drug

INSTITUTION: \_\_\_\_\_ DATE/TIME: \_\_\_\_\_

I may have been exposed to radiocesium and may have been internally contaminated. My participation in Insoluble Prussian Blue therapy is voluntary and I may stop at any time.

I, \_\_\_\_\_, (Patient) authorize Dr. \_\_\_\_\_ (Physician) and his staff to administer decorporation therapy utilizing the drug Insoluble Prussian Blue, ferric (III) hexacyanoferrate (II), in an attempt to (1) determine if a medically significant amount of radiocesium is in my body and (2) to enhance its removal if a medically significant amount is found.

I have been told that the use of Prussian Blue for removal of radiocesium is recommended as the drug of choice by national and international radiation protection councils. The drug is approved for use in Germany and is available throughout Europe. I am aware that there is no other approved treatment for removing radiocesium from my body. My alternatives are, therefore, (1) treatment with Insoluble Prussian Blue or (2) no treatment.

I have been informed that Prussian Blue is not absorbed systemically and works by contact with the Cesium that has been secreted from the gastrointestinal tract preventing the cesium from being reabsorbed by the gut. In past experience the drug reduces the effective biological half-life of cesium in the body by approximately 32%.

Dr. \_\_\_\_\_ (Physician) and his staff have described the potential risks and benefits of decorporation therapy with Prussian Blue and have described what the drug does which is, in my own words, to:

\_\_\_\_\_

I am aware that the human experience with Prussian Blue is limited. I understand that the only known side effects of Prussian Blue is darkening of the stool and possible constipation. I am aware that Prussian Blue is on FDA investigational drug status to help ensure accurate reporting of possible contamination accidents and to record any side effects.

I give permission for information relating to my case to be used in professional medical literature in the interest of increasing medical knowledge. I understand that confidentiality of my identity will be maintained, and I will not be identified in any way. I know that FDA has the right to review my medical records pertaining to Prussian Blue treatment.

I have been told that treatment could require repeated doses of this drug for several months and in some cases years. I am aware that further follow-up visits with my physician will be necessary. Questions regarding current insoluble Prussian Blue research or complications regarding its use may be directed to the Radiation Emergency Assistance Center/Training Site (REAC/TS) through the operator at Methodist Medical Center, Oak Ridge, TN (615)-481-1000.

Patient: \_\_\_\_\_ Witness: \_\_\_\_\_

Relative acting for patient: \_\_\_\_\_ Date/Time: \_\_\_\_\_

Relationship: \_\_\_\_\_ Physician: \_\_\_\_\_

(This form has been approved for use by physicians by the ORAU/ORNL Committee on Human Studies, Oak Ridge, Tennessee)

1144771

ORAU-ORNL COMMITTEE ON HUMAN STUDIES VOTING RECORD

Proposal Number and Title use of Prussian Blue for Internal  
Decontamination of Radiocesium

Principal Investigator Fun Fong R. C. Reick

VOTE OF COMMITTEE

	Signature	Approve	Disapprove	Comment	Date
1.	<i>RSM-7</i>	X			11-21-91
2.	<i>H. Lambert</i>	X			11/21/91
3.	<i>R. Cur</i>	X			11/21/91
4.	<i>G. Davis</i>			Pass (ORAU)	11/21/91
5.	<i>R. D. Lange</i>	X			11/21/91
6.	<i>Howard</i>	X			11/21/91
7.	<i>Fun Fong</i>			Pass (ORAU)	11/21/91
8.	<i>Melvin E. Koon</i>	X			11/21/91
9.	<i>William N. Calhoun</i>	X			11-21-91
10.	<i>Aleksandrovich</i>	X			11-21-91
11.					
12.					
13.					
14.					

Chairman's statement of Committee consensus:

Approved with editing of Consent for

11-21-91  
DATE

U.S. DEPARTMENT OF ENERGY  
FIELD WORK PROPOSAL

**DRAFT**

1. WORK PROPOSAL NO.	2. REVISION NO.	3. DATE	CONTRACTOR NO. 1372.00
4. WORK PROPOSAL TITLE: Occupational Medicine		5. BUDGET AND REPORTING CODE: HA 01 11	
6. WORK PROPOSAL TERM (mm/dd/yy) Begin: 7/90 End: Continuing		7. IS THIS WORK PROPOSAL INCLUDED IN INSTITUTIONAL PLAN? YES	
8. NAME: (First, Last, MI) (FTS number) HEADQUARTERS/OPERATIONS OFFICE PROGRAM MANAGER:  Pettengill, Harry J. (233-3333)	11. HEADQUARTERS ORGANIZATION:  Environment Safety & Health	14. DOE ORGANIZATION CODE:  EH - 40	
9. OPERATIONS OFFICE PROPOSAL REVIEWER:  Cunningham, David C. (624-9276)	12. OPERATIONS OFFICE:  Oak Ridge	15. DOE ORGANIZATION CODE:  OR	
10. CONTRACTOR WORK PROPOSAL MANAGER:  Davis, Glenn (626-3090) PI: Minner, Dale (626-2124)	13. CONTRACTOR NAME: Oak Ridge Associated Universities - Oak Ridge Institute for Science and Education	16. CODE:  36	
17. WORK PROPOSAL DESCRIPTION (A pproach, anticipated benefit in 200 words or less:)  This task provides the DOE Office of Occupational Medicine with technical assistance in the review and assessment of DOE contractor occupational medical programs. It provides assistance in reviewing programs, addressing occupational medicine issues, coordinating activities, providing training, meeting medical and psychological assessment needs of the DOE human reliability programs (PSAP and PAP) and strengthening employee assistance programs. There are six major components, each with one or more projects.			
18. CONTRACTOR WORK PROPOSAL MANAGER:  J. Glenn Davis  _____ (signature) (date)		19. OPERATIONS OFFICE REVIEW OFFICIAL:    _____ (signature) (date)	

20. DETAIL ATTACHMENTS: (See Attachments)

- |   |   |  |
|---|---|--|
| a. <input type="checkbox"/> Facility Requirements | c. <input type="checkbox"/> Approach                          | i. <input type="checkbox"/> Environmental Assessment             |
| b. <input type="checkbox"/> Publications          | f. <input type="checkbox"/> Technical Progress                | j. <input checked="" type="checkbox"/> Explanation of Milestones |
| c. <input type="checkbox"/> Purpose               | g. <input type="checkbox"/> Future Accomplishments            | k. <input checked="" type="checkbox"/> Other (Specify)           |
| d. <input type="checkbox"/> Background            | h. <input type="checkbox"/> Relationship to Other<br>Projects | Foreign Travel   |
|   |   | Capital Equipment  |

1144773

<b>CONTRACTOR NAME:</b> <i>Oak Ridge Associated Universities - ORISE</i>	<b>WORK PROPOSAL TITLE:</b> Occupational Medicine		
	<b>WORK PROPOSAL NO:</b>	<b>REVISION:</b>	<b>DATE PREPARED:</b>

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24. MILESTONES SCHEDULE (Tasks)	DOLLARS (in thousands)		SCHEDULE (date)	
	PROPOSED	AUTHORIZED	PROPOSED	AUTHORIZED
<ul style="list-style-type: none"> <li>Conduct site review of Contractor Occupational Medicine Programs (scheduled by DOE)</li> </ul>	767.0		FY 93	
<ul style="list-style-type: none"> <li>Review Past Medical Activities in the Marshall Islands and propose future medical surveillance</li> </ul>	103.0		June 93	
<ul style="list-style-type: none"> <li>Provide continuing technical assistance for review of reports, proposed rules and orders and related materials.</li> </ul>	59.0		FY 93	
<ul style="list-style-type: none"> <li>Establish and conduct working group meetings on Occupational Medical Issues.</li> </ul>	59.0		FY 93	
<ul style="list-style-type: none"> <li>Compile IND and coordinate therapeutic use of Prussian Blue throughout the DOE System.</li> </ul>	133.0		FY 93	
<ul style="list-style-type: none"> <li>Assist in developing a draft Order - Medical Standards for the Personnel Assurance Program (PAP) &amp; Personnel Security Assurance Program (PSAP)</li> </ul>	74.0		FY 93	

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<b>CONTRACTOR NAME:</b> <i>Oak Ridge Associated Universities - ORISE</i>	<b>WORK PROPOSAL TITLE:</b> Occupational Medicine		
	<b>WORK PROPOSAL NO:</b>	<b>REVISION:</b>	<b>DATE PREPARED:</b>

<b>24. MILESTONES SCHEDULE (Tasks) (Cont'd)</b>	<b>DOLLARS (in thousands)</b>		<b>SCHEDULE (date)</b>	
	<b>PROPOSED</b>	<b>AUTHORIZED</b>	<b>PROPOSED</b>	<b>AUTHORIZED</b>
<ul style="list-style-type: none"> <li>Assist in developing a draft Order - Contractor Psychological Assessment Program and evaluation protocols</li> </ul>	74.0		FY 93	
<ul style="list-style-type: none"> <li>Provide technical input and support assistance for development of a draft manual that establishes standards and guidance for DOE EAPs and to validate methods for evaluating programs.</li> </ul>	162.0		FY 93	
Conduct site review of Contractor Occupational Medicine Programs (scheduled by DOE)	649.0		FY 94	
<ul style="list-style-type: none"> <li>Provide continuing technical assistance for review of reports, proposed rules and orders and related materials.</li> </ul>	43.0		FY 94	
<ul style="list-style-type: none"> <li>Establish and conduct working group meetings on Occupational Medical Issues.</li> </ul>	76.0		FY 94	
<ul style="list-style-type: none"> <li>Compile IND and coordinate the therapeutic use of Prussian Blue throughout the DOE system.</li> </ul>	97.0		FY 94	

<b>CONTRACTOR NAME:</b> <i>Oak Ridge Associated Universities - ORISE</i>	<b>WORK PROPOSAL TITLE:</b> Occupational Medicine		
	<b>WORK PROPOSAL NO:</b>	<b>REVISION:</b>	<b>DATE PREPARED:</b>

<b>24. MILESTONES SCHEDULE (Tasks) (Cont'd)</b>	<b>DOLLARS (in thousands)</b>		<b>SCHEDULE (date)</b>	
	<b>PROPOSED</b>	<b>AUTHORIZED</b>	<b>PROPOSED</b>	<b>AUTHORIZED</b>
<ul style="list-style-type: none"> <li>Assist in developing a draft Order - Medical Standards for the Personnel Assurance Program (PAP) &amp; Personnel Security Assurance Program (PSAP)</li> </ul>	54.0		FY 94	
<ul style="list-style-type: none"> <li>Assist in developing a draft Order - Contractor Psychological Assessment Program and evaluation protocols.</li> </ul>	54.0		FY 94	
<ul style="list-style-type: none"> <li>Provide technical input and support assistance for development of a draft manual that establishes standards and guidance for DOE EAPs and to validate methods for evaluating programs.</li> </ul>	108.0		FY 94	
<ul style="list-style-type: none"> <li>Conduct site review of Contractor Occupational Medicine Programs (scheduled by DOE)</li> </ul>	706.0		FY 95	
<ul style="list-style-type: none"> <li>Provide continuing technical assistance for review of reports, proposed rules and orders and related materials.</li> </ul>	47.0		FY 95	
<ul style="list-style-type: none"> <li>Compile IND and coordinate the therapeutic use of Prussian Blue throughout the DOE system.</li> </ul>	106.0		FY 95	

<b>CONTRACTOR NAME:</b> <i>Oak Ridge Associated Universities - ORISE</i>	<b>WORK PROPOSAL TITLE:</b> Occupational Medicine		
	<b>WORK PROPOSAL NO:</b>	<b>REVISION:</b>	<b>DATE PREPARED:</b>

<b>24. MILESTONES SCHEDULE</b> (Tasks) (Cont'd)	<b>DOLLARS (in thousands)</b>		<b>SCHEDULE (date)</b>	
	<b>PROPOSED</b>	<b>AUTHORIZED</b>	<b>PROPOSED</b>	<b>AUTHORIZED</b>
<ul style="list-style-type: none"> <li>Establish and conduct working group meetings on Occupational Medical Issues.</li> </ul>	82.0		FY 95	
<ul style="list-style-type: none"> <li>Assist in developing a draft Order - Medical Standards for the Personnel Assurance Program (PAP) &amp; Personnel Security Assurance Program (PSAP).</li> </ul>	59.0		FY 95	
<ul style="list-style-type: none"> <li>Provide technical input and support assistance for development of a draft manual that establishes standards and guidance for DOE EAPs and to validate methods for evaluating programs.</li> </ul>	118.0		FY 95	
<ul style="list-style-type: none"> <li></li> </ul>				
<ul style="list-style-type: none"> <li></li> </ul>				
<ul style="list-style-type: none"> <li></li> </ul>				

<b>CONTRACTOR NAME:</b> <i>Oak Ridge Associated Universities - ORISE</i>	<b>WORK PROPOSAL TITLE:</b> Occupational Medicine		
	<b>WORK PROPOSAL NO:</b>	<b>REVISION:</b>	<b>DATE PREPARED:</b>

20. **DETAIL ATTACHMENTS**

*In 1991, DOE established the Oak Ridge Institute for Science and Education (ORISE) with Oak Ridge Associated Universities as the management and operating contractor. All activities described in this Field Work Proposal will be conducted through ORISE.*

The projects making up the six major components in Occupational Medicine are described in detail below. Milestones are defined for each activity in # 24.

I. Occupational Medical Program Reviews

MSD/ORISE provides experienced physicians and nurses to assist in reviewing and evaluating DOE contractor occupational medicine (OM) programs. ORISE will assist in preparation of reports and, upon request, will assist in monitoring responses to recommendations.

In late FY-90 and early FY-91 MSD/ORAU developed a guide which was adopted by DOE and is being used as a part of the review process. It serves as a valuable source of information. This guide will be reviewed and revised in FY-94.

By FY 1994, MSD/ORISE may develop and implement a data management system that abstracts and stores information from program reviews in a computerized system. This data would be used for analysis of the DOE contractor wide OM programs and track recommendations and responses. This data system would be a useful management tool for HQ DOE Office of Occupational Medicine.

MSD/ORISE provides other reviews and evaluations as requested such as a review of past medical evaluations in the Marshall Islands.

MSD/ORISE will provide a monthly status report showing financial and technical progress to Headquarters by the 10th working day each month. This report will include the individuals used, hourly rate, hours worked, and travel expenditures.

II. Coordination of Occupational Medical Issues and Technical Assistance.

MSD/ORISE will provide technical assistance in occupational medicine issues as needed and for assigned organizational (EH-40) projects. Professional medical working group meetings will be arranged and conducted as directed.

The Occupational Medical Program of MSD/ORISE will continue to provide medical expertise in support of other DOE Office of Health programs such as the studies of current and past beryllium workers.

MSD/ORISE will provide a monthly status report showing financial and technical progress to Headquarters by the 10th working day each month. This report will include the individuals used, hourly rate, hours worked, and travel expenditures.

<b>CONTRACTOR NAME:</b> <i>Oak Ridge Associated Universities - ORISE</i>	<b>WORK PROPOSAL TITLE:</b> Occupational Medicine		
	<b>WORK PROPOSAL NO:</b>	<b>REVISION:</b>	<b>DATE PREPARED:</b>

20. **DETAIL ATTACHMENTS (Cont'd)**

III. **Education and Training in Medical Areas**

Assist in the development of education and training syllabuses and modules for the Medical Evaluation Program in Human Reliability, Personnel Assurance Program (PAP), covering the medical, psychological, and substance abuse aspects by March 31, 1993. Arrange and coordinate a workshop with the materials developed, for the physicians, psychologists, and appropriate responsible staff from the five primary PAP sites by June 30, 1993. On topics agreed upon or requested by the Office of Occupational Medicine/EH/DOE, MSD/ORISE develops, manages and implements training activities in an effort to strengthen the DOE OM capabilities.

Assist in the development of education and training syllabuses and modules for the Medical Evaluation Program in Human Reliability, Personnel Security Assurance Program (PSAP), covering the medical, psychological, and substance abuse aspects by June 30, 1993. Conduct a workshop, with the materials developed, for designated physicians, designated psychologists, and other appropriate responsible staff in PSAP programs by September 30, 1993.

Arrange and coordinate the Annual DOE Contractor Occupational Medicine Seminar and Workshop with preliminary plans and agenda completed by March 31, 1993. Under ORISE sponsorship, the scientific sessions of education and training activities will qualify for American Medical Association approved CME Category I credits for participants.

MSD/ORISE will provide a monthly status report showing financial and technical progress to Headquarters by the 10th working day each month. This report will include the individuals used, hourly rate, hours worked, and travel expenditures.

IV. **Medical Evaluation Program for Human Reliability**

MSD/ORISE will assist in the development of a draft DOE Order - Medical Standards for the Personnel Assurance Program for concurrence/nonconcurrence distribution to the appropriate DOE elements by December 31, 1992. MSD/ORISE will also assist in responding to comments and in providing suggested revisions of the draft.

MSD/ORISE will assist in the development of a draft DOE Order - Medical Standards for the Personnel Security Assurance Program for concurrence/nonconcurrence distribution to the appropriate DOE elements by September 30, 1993.

MSD/ORISE will provide a monthly status report showing financial and technical progress to Headquarters by the 10th working day each month. This report will include the individuals used, hourly rate, hours worked, and travel expenditures.

CONTRACTOR NAME: <i>Oak Ridge Associated Universities - ORISE</i>	WORK PROPOSAL TITLE: Occupational Medicine		
	WORK PROPOSAL NO:	REVISION:	DATE PREPARED:

20. DETAIL ATTACHMENTS (Cont'd)

V. DOE Contractor Psychological Assessment Program, Policy, and Standards

Assist in the development of a draft DOE Order - Contractor Psychological Assessment Program, Policy, and Standards for concurrence/nonconcurrence distribution to the appropriate DOE elements by June 30, 1993.

Assist in the development of an evaluation protocol for psychological program reviews for use in the DOE contractor occupational medical program appraisals by September 30, 1993.

MSD/ORISE will provide a monthly status report showing financial and technical progress to Headquarters by the 10th working day each month. This report will include the individuals used, hourly rate, hours worked, and travel expenditures.

VI. Employee Assistance Programs

MSD/ORISE provides assistance in the development of a draft manual with standards and guidance for the DOE Contractor Employee Assistance Programs. The draft is projected to be available for concurrence/nonconcurrence distribution to appropriate DOE elements by December 31, 1992.

Also, MSD/ORISE will assist in the development of EAP evaluation methods for use by reviewers, by September 30, 1993.

In FY-94 reviewers of occupational medicine programs will use the new evaluation methods to assess the DOE contractor employee assistance programs considering scope and content, staffing, how managed, productivity, site quality measures, and costs.

MSD/ORISE will provide a monthly status report showing financial and technical progress to Headquarters by the 10th working day each month. This report will include the individuals used, hourly rate, hours worked, and travel expenditures.

VII. Marshall Island Medical Quality Assurance Project

SUMMARY:

ORISE will provide technical assistance to the Director, Occupational Medicine, DOE/EH/OH in:

- (1) critically reviewing and evaluating the scope, methods and findings of the medical follow-up conducted for DOE by Brookhaven National Laboratory, of residents of the Marshall Islands potentially exposed to radioactive fallout in 1954 as the result of an aberrant atomic test at Bikini Atoll,
- (2) enumerating the scope and magnitude of radiogenic and other chronic disease risks of the 1954 exposures as evidenced by data accumulated to date,
- (3) estimating risks of such outcomes that may be anticipated to occur during the remainder of this population's life span,
- (4) making recommendations for the future clinical surveillance of the population to benefit its individual members, as well as meet any additional needs of DOE.

<b>CONTRACTOR NAME:</b> <i>Oak Ridge Associated Universities - ORISE</i>	<b>WORK PROPOSAL TITLE:</b> Occupational Medicine		
	<b>WORK PROPOSAL NO:</b>	<b>REVISION:</b>	<b>DATE PREPARED:</b>

20. **DETAIL ATTACHMENTS (Cont'd)**

**PROCEDURE:**

ORISE will provide the above assistance by drawing on staff technical and scientific expertise and overall knowledge of DOE's programs in the Marshall Islands to identify, establish and administratively assist an ORISE advisory panel of independent experts in, but not limited to the areas of radiation biology/carcinogenesis, radiation dosimetry, internal medicine, geriatric medicine, radiation epidemiology, information systems, endocrinology/thyroid disease (and perhaps others). ORISE will charge the panel with accomplishing the tasks outlined above.

ORISE assistance also will include recording of the panel's deliberations; retrieval and maintenance of archival; other reference materials and data for the panel's use; drafting of communications for the panel, preparation and publication of the panel's final draft report and its publication after appropriate peer review, as an ORISE document, and appropriate audio-visual and background materials.

Technical assistance also will include support of periodic panel meetings, conferences, presentations and any associated travel.

**PRODUCT:**

ORISE will provide DOE/EH/OH with a credible, independent assessment of the quality of its Marshall Islands clinical surveillance program to date together with assessment of risks of future adverse health outcomes, and recommendations for future program objectives and directions in the form of a published ORISE report. The availability of such a report will enhance the credibility of the Department's clinical surveillance program for this population and serve as a valid, referenceable document for future activities.

**LEVEL OF EFFORT:**

This project will be completed within six months. It will require the services (one day/week) of a maximum of six internationally/nationally recognized scientific/medical experts in the areas of interest. Management and coordination of the panel's activities and other technical assistance will be provided by a senior ORISE/MSD physician with clerical/secretarial and editorial support as necessary.

An initial one-day planning meeting will be followed by 2 two-day working meetings of the panel. These meetings will be held at a mutually convenient location to minimize travel costs. During this meeting, other technical experts (up to a total of four) may be invited to address the panel on specific topics of interest.

This project will be funded under the MSD Occupational Medicine Program.

<b>CONTRACTOR NAME:</b> <i>Oak Ridge Associated Universities - ORISE</i>	<b>WORK PROPOSAL TITLE:</b> Occupational Medicine		
	<b>WORK PROPOSAL NO:</b>	<b>REVISION:</b>	<b>DATE PREPARED:</b>

20. **DETAIL ATTACHMENTS (Cont'd)**

VIII. **Prussian Blue**

**Background**

There has been a long-standing need identified for DOE to make therapy available in the event of internal contamination with radiocesium, a common fission by-product and sealed source component. Although there have been very few cases of radiocesium contamination requiring decorporation, there is an obvious potential for such contamination to occur and a need for specific therapy. Prussian Blue, an ion-binding agent, has been recommended as the drug-of-choice in national and international guidelines for radiocesium decontamination (NCRP 65,1980). Prussian Blue was used efficaciously in the medical response to the 1987 Goiania radiological accident after the MSD-REAC/TS had obtained special permission from FDA in the case of "compassionate use." There has been great interest from current DTPA co-investigators in obtaining pharmaceutical-grade Prussian Blue. Prussian Blue is now under IND status in the US, but the drug is not available to current DTPA co-investigators or DOE contractor sites from the current holder of this Prussian Blue IND. DOE had asked ORAU in 1989 to develop an FDA IND for Prussian Blue, although this request had never been funded. It has been funded in late FY 92 through DOE/Occupational Medicine (EH-43).

**Progress**

An FDA IND application is undergoing compilation, indicating the pharmacological properties, known therapeutic and toxicity data from existing human and animal studies. A informed consent form for administration of Prussian Blue has been prepared and has been approved by the ORAU/ORNL Committee on Human Studies. Securing an initial stockpile of the drug will await FDA approval.

A search for a supplier of Prussian Blue has been conducted. We have determined that it will have to be obtained from the Heyl company in Germany as no pharmaceutical company currently manufactures it in the US. Current DTPA investigators will be surveyed to determine their needs for Prussian Blue and will be invited to become co-investigators on the Prussian Blue IND project, along with other physicians with demonstrated need.

**Objectives**

Management of the Prussian Blue IND will be performed in a procedure identical to that of DTPA. J. Glenn Davis, M.D., Vice-President and Chairman, Medical Sciences Division, will be the institutional sponsor of the IND for Prussian Blue. Fun H. Fong, M.D., Director, Radiation Medicine, and Robert C. Ricks, Ph.D., Director, REAC/TS, will be Co-managers and Co-Principal Investigators of the IND. Dr. Ricks is responsible for the stockpile of Prussian Blue that ORISE maintains and distributes for DOE. He is responsible for labeling and distribution requests for Prussian Blue. Dr. Fong is responsible for all clinical and pharmaceutical matters relating to the management of the IND and is the REAC/TS physician authorized under the IND to administer Prussian Blue as necessary. He is also the REAC/TS clinical contact for all Prussian Blue-related inquiries and requests for assistance. Dr. Fong is responsible for monitoring the quality control needs for maintaining the Prussian Blue IND.

<b>CONTRACTOR NAME:</b> <i>Oak Ridge Associated Universities - ORISE</i>	<b>WORK PROPOSAL TITLE:</b> Occupational Medicine		
	<b>WORK PROPOSAL NO:</b>	<b>REVISION:</b>	<b>DATE PREPARED:</b>

20. **DETAIL ATTACHMENTS (Cont'd)**

Annual usage reports will be compiled from physician Prussian Blue co-investigator usage reports and submitted to FDA as a function of the IND process. Reports of Prussian Blue efficacy and side-effects will be compiled to document an overall drug profile. Quality assurance testing will be performed or documented as necessary.

IX. **Itemized Budget**

	<u>FY 93</u>	<u>FY 94</u>	<u>FY 95</u>
Total	1475.0	981.0	1068.0
Sal	570.0	378.0	413.0
M&S	70.0	47.0	51.0
Prof Serv	231.0	154.0	167.0
Travel	119.0	79.0	86.0
Other	226.0	151.0	164.0
Indirect	259.0	172.0	187.0



Oak Ridge  
Associated  
Universities

Post Office Box 117  
Oak Ridge, Tennessee 37831-0117

Medical  
Sciences  
Division

### ORAU/ORNL COMMITTEE ON HUMAN STUDIES

**TO:** Dr. Fun Fong  
**FROM:** Dr. Karl Hubner/Chairman, Committee on Human Studies  
**RE:** COMMITTEE ACTION ON PROPOSAL  
**DATE:** November 30, 1991

Your project number 81 "Use of Prussian Blue for Internal Decontamination of Radiocesium" was reviewed and approved at our meeting on November 21, 1991. The committee suggests some minor changes be made in the consent form for this project. It is suggested that the route of administration be added and the word "decorporation" be deleted, using instead the term "therapy." Instead of "relative acting for patient," it was suggested "guardian acting for the patient" be used. The paragraph in which the patient is to describe in his or her own words the risks and benefits of this procedure should be deleted and "his" should be changed to the more generic "his or her." Please also make sure the date of the last revision for this consent form be changed to November 21, 1991. Please send a copy of the revised consent form to Ms. Hawkins for the files of the committee.

Progress reports on all active projects will be reviewed at our next meeting to be held in the spring of 1992.

bh

1144784



Oak Ridge  
Associated  
Universities

Post Office Box 117  
Oak Ridge, Tennessee 37831-0117

Medical  
Sciences  
Division

**ORAU/ORNL COMMITTEE ON HUMAN STUDIES**

**TO:** Dr. Fun Fong  
**FROM:** Marta V. Rivera/Secretary, Committee on Human Studies *MVR*  
**RE:** Status Reports on Active Proposals  
**DATE:** May 12, 1992

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 26. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Use of Prussian Blue for Internal Decontamination of Radiocesium

Proposal No. 81

DATE APPROVED: 1991

*Fun Fong*  
Signature of Principal Investigator

*6/26/92*  
Date Signed

1. Report progress made in the past year.  
*See attached*
2. Report any complications.

Proposal No. 81

1. Report progress made in the past year.

*DOE funding has been received to develop the IND for Prussian Blue. A supplier of Prussian Blue has been tentatively identified. An IND is being prepared.*

2. Report any complications.

*Development of the Prussian Blue IND has been more complex than anticipated.*

3. Are there any planned changes?

*No. Progress on the IND document will continue, and the study will be implemented as in the previous report.*

4. Do you wish the project to be continued?

*Yes. Interested DTPA Co-investigators will be polled regarding their interest in becoming a Co-investigator for Prussian Blue. Distribution of Prussian Blue will be to qualified Co-investigators who also display a need for Prussian Blue at their institution.*

5. Comments.



Oak Ridge  
Associated Universities Post Office Box 117  
Oak Ridge, Tennessee 37831-0117

To: Dr. Fun H. Fong/Robert C. Ricks  
From: Dr. Karl Hubner, Chairman  
Committee on Human Studies  
Date: August 5, 1992  
RE: Committee Action on Active Proposals

Your project number 81 "Use of Prussian Blue for Internal Decontamination of Radiocesium" was reviewed and approved for continuation at our last meeting on July 31, 1992.

Progress reports of all active proposals will again be reviewed at our next meeting to be held in the fall of 1992.

/mvr

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ORAU/ORNL COMMITTEE ON HUMAN STUDIES

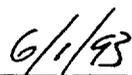
TO: Dr. Fun H. Fong/ Dr. Robert C. Ricks  
From: Marta Rivera, Secretary Committee on Human Studies  
RE: Status Report on Active Proposals  
Date: April 28, 1993

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposal present a progress report to the Committee on the status of the proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions and add other information you feel pertinent and return by May 14. (If additional space is needed, please use the back of this form or attach extra sheets).

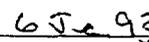
Title of Project: "Use of Prussian Blue for Internal Decontamination of Radiocesium"

Proposal No. 81

  
\_\_\_\_\_  
Signature of Co-Principal Investigator

  
\_\_\_\_\_  
Date Signed

  
\_\_\_\_\_  
Signature of Co-Principal Investigator

  
\_\_\_\_\_  
Date Signed

1. Report progress made in the past year.  
Please see pages attached.
2. Report any complications.  
Please see pages attached.

1144788

Proposal No. 81: Prussian Blue IND application

1. Report progress made in the past year.

*DOE funding is still secure to develop insoluble Prussian Blue as an IND. A supplier of Prussian Blue has been tentatively identified. An IND application is nearing internal review and completion.*

2. Report any complications.

*Development of the insoluble Prussian Blue IND has been more complex than anticipated.*

3. Are there any planned changes?

*No. Progress on the IND document will continue, and the study will be implemented as in the previous report.*

4. Do you wish the project to be continued?

*Yes. Interested DTPA Co-investigators will be surveyed regarding their interest in becoming a Co-investigator for insoluble Prussian Blue. Insoluble Prussian Blue will be distributed to qualified Co-investigators who also display a need for insoluble Prussian Blue at their institution.*

5. Comments.



Oak Ridge  
Associated Universities Post Office Box 117  
Oak Ridge, Tennessee 37831-0117

To: Dr. Fun H. Fong/Robert C. Ricks  
From: *W. Calhoun*  
Dr. William Calhoun, Chairman  
Committee on Human Studies  
Date: June 29, 1993  
Re: Committee Action on Active Proposals

Your project number 81 "Use of Prussian Blue for Internal Decontamination of Radiocesium" was reviewed and approved for continuation at our last meeting on June 25, 1993.

Progress reports of all active proposals will again be reviewed at our next meeting to be held in the fall of 1993.

/mvr

1144790

# PROTECTING HUMAN SUBJECTS



Office of Health and Environmental Research

U.S. Department of Energy

## PROJECT SUMMARY

**Policy:** Research activities that involve human subjects and that are funded by the U.S. Department of Energy (DOE), conducted in DOE facilities, or conducted by DOE personnel must be approved or exempted from review in accord with 10 CFR Part 745. Failure to comply with these regulations may prevent DOE from authorizing or funding an activity, or may lead the Department to suspend or terminate the project.

**Directions:** Institutions must complete this form, providing the data listed below in the format indicated, for each research activity each year. Forms must be sent to the appropriate DOE Field Office, which will forward them to DOE Headquarters (Protection of Human Subjects, Mail Station ER-70, Office of Health and Environmental Research, U.S. Department of Energy, Washington, DC 20585).

1. Project Title Use of Prussian Blue for Internal Decontamination of Radiocesium	
2. Principal Investigator J. Glenn Davis, M.D., M.P.H.	Telephone Number (615) 576-3090
Mailing Address — Include full name of performing institution. Oak Ridge Institute for Science and Education, Medical Sciences Division, Center for Epidemiologic Research, P.O. Box 117, Oak Ridge, TN 37831-0117	
3. Institutional Assurance Number (if issued) MPA 1394	4. Project Number <sup>2</sup> ORAU 81
5. Annual Funding: Give actual funding or check the amount closest to the estimated total for the current Federal fiscal year, whether requested or obtained. Include both direct and indirect costs. <input checked="" type="checkbox"/> Actual Funding \$ 25,000 <input type="checkbox"/> \$10,000 <input type="checkbox"/> \$100,000 <input type="checkbox"/> \$500,000 <input type="checkbox"/> \$1,000,000 <input type="checkbox"/> \$5,000,000	
6. Funding Sources A. Name DOE Program Office (see list in attachment), if applicable. B. Name non-DOE sources of funding (up to two), if applicable.	
A. DOE Program Office Office of Occupational Medicine (EH-43)	
Contact Person Agatha Francis	Telephone Number (301) 903-5591
B. Non-DOE Source N/A	
Non-DOE Source	

<sup>1</sup> Under 10 CFR Part 745, institutions are required to file an assurance of compliance with the regulations with DOE or the Department of Health and Human Services. The Department involved may then issue an assurance number.

<sup>2</sup> Each project must have a unique identification number assigned by the institution—for example, ANL-94/101.

1144791

**7. The Project has been reviewed and approved by the Institutional Review Board (IRB) as required under 10 CFR Part 745.**

**A. Type of Review**

Full Board  
For a list of research not requiring IRB review, see Attachment.

Expedited  
For an explanation of projects that qualify for expedited reviews, see Attachment.

**B. Type of Approval**

New                       Annual Renewal                       Other

**C. IRB Approval Date**  
November 11, 1991; reviewed and approved for continuation annually, most recently June 25, 1993.

**8. This Project involves the following collaborating institutions (list a maximum of two):**

None

**9. Vulnerable Populations**

This project does not involve vulnerable populations.

This project involves the following vulnerable populations:

Minors                       Mentally Disabled                       Prisoners  
 Fetuses, Pregnant Women, In Vitro Fertilization                       Economically or Educationally Disadvantaged

**10. Type of Research**  
Check all categories that apply.

Epidemiology (using personally identifiable data)--  
 Using data collected directly from human subjects.  
 Using existing data.

Diagnostic studies using radiation or chemical agents in tracer amounts.

Therapeutic studies using ~~radiation or~~ chemical agents.

Studies of exposure, effects, health, or monitoring using human urine, blood, other body fluids, cells, or tissues--  
 Specimens collected directly from human subjects for this project.  
 Specimens obtained from secondary sources (e.g., hospitals, laboratories).

Instrument development and testing using human subjects.

Surveys that collect personally identifiable data.

Environmental studies using human subjects to evaluate weatherization options, habitat alteration, or similar.

Other. Please identify \_\_\_\_\_

## 11. Abstract

Provide a brief abstract that includes the following information:

- A. Summarize the objectives and methodology of this research project. (Explain clearly why it belongs in the categories checked in Item 10).

Project supports IND Application to FDA for use of Prussian Blue (Ferric hexacyanoferrate; insoluble Prussian Blue) in treatment of persons internally contaminated with cesium-137.

Physicians designated as authorized co-investigators on the FDA-INDA will administer Prussian Blue as approved to persons contaminated internally with cesium-137 and will monitor its excretion from the body in the feces. The data obtained will be entered into a computerized data base to be designated as a DOE System of Records for evaluation.

- B. Specify the number of human subjects involved each year.

Varies; 0 to  $\geq$  5 annually (estimated).

- C. Describe the involvement of human subjects and the risks, if any, to which they are exposed.

The purpose, potential benefits and risks of this pharmaceutical will be discussed with the patient by the authorized physician and signed informed consent will be obtained prior to administration.

Pharmaceutical grade Prussian Blue is commercially available, fully approved in Europe for treatment of cesium-137-contaminated persons.

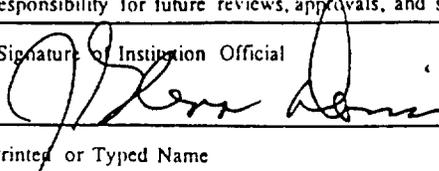
Prussian Blue at approved dose levels may cause harmless staining. No major toxic or other side effects have been observed in humans based on limited use. Available data suggest continued administration or overdosage may cause constipation. Privacy and confidentiality of data collected are assured by the DOE System of Records to the extent possible under law.

- D. List the chemical or radioactive materials, if any, that are used in the study, and identify the route of exposure.

Pharmaceutical grade Prussian Blue is administered orally in treatment for internal cesium-137 contamination.

*See reverse for approval signatures.*

The official signing below confirms that the information provided on this form is correct and that the institution assumes responsibility for future reviews, approvals, and submissions of project summaries, which are all required at least once a year.

Signature of Institution Official 	Date 2/28/94
Printed or Typed Name J. Glenn Davis, M.D., M.P.H.	Telephone Number (615) 576-3090

For DOE USE Only

Date Received by ER-70	Date Accepted _____ Returned to Originator _____
Reason for Return	
DOE Reviewers	

1144794

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

**TO:** Dr. Robert C. Ricks  
**FROM:** Marta V. Rivera/Secretary, Committee on Human Studies  
**RE:** Status Reports on Active Projects  
**DATE:** July 11, 1994

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by **July 20**. (If additional space is needed, please use the back of this form or attach extra sheets. Please include your name, project number, and date on additional sheets).

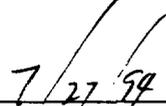
Title of Project: Use of Prussian Blue for Internal Decontamination of Radiocesium

Project No.: ORAU-81

First Approved: June 6, 1991

Most recent re-approval for continuation: June 25, 1993

  
\_\_\_\_\_  
Signature of Principal Investigator

  
\_\_\_\_\_  
Date Signed

1. Report progress made in the past year.  
Draft proposal completed.
2. Report any complications.  
Loss of physician in Radiation Medicine delayed submission.

1144795

3. Are there any planned changes?

Final draft completed and submitted for review early FY 95.

4. Do you wish the project to be continued?

Yes.

5. Comments.

None.

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Robert Ricks  
FROM: Dr. William Calhoun/Chairman, Committee on Human Studies  
RE: COMMITTEE ACTION ON ACTIVE PROJECTS  
DATE: August 31, 1994

Your project number ORAU-81 "Use of Prussian Blue for Decontamination of Radiocesium" was reviewed and approved for continuation at our meeting on July 28, 1994.

This review included an assessment of all existing consent forms used by the investigators. Changes, revisions or modifications to the consent form in use should be submitted to the Committee for review prior to the annual spring meeting. Such forms should be dated and printed on letterhead to show organization/affiliation.

Progress reports of all active projects will again be reviewed at our next meeting to be held in the spring of 1995.

/mvr

1144797

U.S. DEPARTMENT OF ENERGY  
OHER/ER-72  
Washington, DC 20585  
tel 301-903-4731  
fax 301-903-8521

File: 1) HRE Project file  
2) CHS files  
- business  
- protocols  
52, 60, 63, 81

5237

11/28/94

fax t r a n s m i t t a l

to: J. Glenn Davis

fax #: 615-576-3194

from: Susan L. Rose

date: November 23, 1994 4:15 pm

re: Human Subjects

pages: 19, including this cover sheet

NOTES:

Jg

H

D

1144798



**Department of Energy**  
Washington, DC 20585

**TO:** J. Glenn Davis, Oak Ridge  
Bart Gledhill, Lawrence Livermore National Laboratory  
Debra Maresca, Brookhaven National Laboratory  
Joe Furman, Rocky Flats  
Chris Byrne, Lawrence Berkeley Laboratory

**FROM:** Susan L. Rose, DOE

**DATE:** November 23, 1994

**RE:** Intramural Proposal Request from the White House Advisory Committee  
on Human Radiation Experiments

I am forwarding to you a request for information on several projects at your institutions as I received it from the White House Advisory Committee on Human Radiation Experiments (see attachment). While I realize that this is an especially difficult time of year to fill yet another request, I must nonetheless ask you to respond using Federal Express no later the Friday, December 9, 1994. Please send 3 copies of the requested information on each proposal directly to my attention. The committee will be examining contemporary research as part of their charge. I am also faxing to you a few pages from the committees interim report which may shed some light (not much) on this latest request.

**cc:** David Cunningham, Oak Ridge  
Barbara Fitzgerald, BNL  
Vicki Aschenbrenner, Rocky Flats  
Joe Aaron, LBL

1144799



Printed with soy ink on recycled paper



**ADVISORY COMMITTEE ON HUMAN RADIATION EXPERIMENTS**  
1726 M STREET, N.W., SUITE 600  
WASHINGTON, D.C. 20036

**BY FAX**

**TO:** Tara O'Toole, Assistant Secretary for Environment, Safety, and Health  
Ellyn Weiss, Director, Office of Human Radiation Experiments  
Susan Rose, Program Manager, Human Subjects Activities  
Lori Azim  
Marisa Caputo

**FROM:** *sc*  
*for* Donald Weightman

**DATE:** November 16, 1994.

**RE:** Intramural Human Radiation Research Proposal and IRB Materials for the  
ACHRE Research Proposal Review Project

**ACHRE REQUEST 110994-A to 110994-ZD**

Attached please find document requests to DOE from ACHRE staff for materials relating to 30 intramural studies involving research applications of ionizing radiation on human subjects for the ACHRE Research Proposal Review Project. For each study listed, please supply the following:

- Original research protocol/grant application submitted by the investigator to DOE
- Original research protocol/application submitted to Institutional Review Board (IRB)
- Consent form as submitted to IRB
- Consent form as approved by IRB
- IRB disposition letter
- For ongoing studies, any documentation indicating changes to the protocol or consent form over time

Staff asks that you provide these materials no later than November 29, 1994.



The attached requests include the following identifying information about each of the 30 studies sampled from the DOE Database of Research Projects Involving Human Subjects: Title of project, principal investigator, intramural research institution, institutional assurance number (when available), and project number.

The ACHRE Staff has recently implemented a database to be used in tracking the status of agency requests. A unique number is assigned to each request for tracking, monitoring, and managing purposes. Each study listed on the attached request is considered a separate request. It will greatly help this process if you refer to the ACHRE document request numbers in any responses, including all correspondence and documents that you provide to the Committee. For example, reference to a number will allow us to retrieve the name of the staff member who originated the request, so that requests for clarification may be referred quickly to the source of the original question. The numbers are provided above in boldface and on the attached document request before each project's identifying information.

If you have any questions or concerns please contact Sara Chandros at (202) 254-9852. Thank you for your attention to this matter.

**ACHRE Request 110994-A, INTRAMURAL PROPOSAL/IRB MATERIALS FOR RESEARCH PROPOSAL  
REVIEW PROJECT**

**BIODOSIMETRY FOR LOW LEVELS OF IONIZING RADIATION  
RON JENSEN  
LAWRENCE LIVERMORE NATIONAL LABORATORY  
M1415 01-XB  
LLNL-89-111**

**Deadline: 11/29/94**

**ACHRE Request 110994-B, INTRAMURAL PROPOSAL/IRB MATERIALS FOR RESEARCH PROPOSAL  
REVIEW PROJECT**

**US TRANSURANICUM PROGRAM AT ROCKY FLATS  
ROBERT W. BISTLINE  
ROCKY FLATS, INC.**

**RF-94-02**

**Deadline: 11/29/94**

**ACHRE Request 110994-C, INTRAMURAL PROPOSAL/IRB MATERIALS FOR RESEARCH PROPOSAL  
REVIEW PROJECT**

**ROCKY FLATS PLANT MEDICAL MONITORING OF FORMER RADIATION WORKERS  
ROBERT W. BISTLINE  
ROCKY FLATS, INC.**

**RF-94-01**

**Deadline: 11/29/94**

**ACHRE Request 110994-D, INTRAMURAL PROPOSAL/IRB MATERIALS FOR RESEARCH PROPOSAL  
REVIEW PROJECT**

**USE OF PRUSSIAN BLUE FOR INTERNAL DECONTAMINATION OF RADIOCESIUM  
J. GLENN DAVIS  
OAK RIDGE  
MPA 1384**

1144802

ORAU-81

Deadline: 11/29/94

ACHRE Request 110994-E, INTRAMURAL PROPOSAL/IRB MATERIALS FOR RESEARCH PROPOSAL REVIEW PROJECT

PHASE 2 STUDY OF TRISODIUM ZINC (ZN-DTPA) FOR CHELATION OF INTERNALLY DEPOSITED TRANSURANIUM COMPOUNDS; COMPLETION OF DATA IN DATABASE

J. GLENN DAVIS  
OAK RIDGE  
MPA 1394  
ORAU-62

Deadline: 11/29/94

ACHRE Request 110994-F, INTRAMURAL PROPOSAL/IRB MATERIALS FOR RESEARCH PROPOSAL REVIEW PROJECT

US RADIATION ACCIDENT REGISTRY FOLLOW-UP PROGRAM  
SHIRLEY A. FRY  
OAK RIDGE  
MPA 1394  
ORAU-63

Deadline: 11/29/94

ACHRE Request 110994-G, INTRAMURAL PROPOSAL/IRB MATERIALS FOR RESEARCH PROPOSAL REVIEW PROJECT

COMPREHENSIVE EPIDEMIOLOGY STUDY OF DEPARTMENT OF ENERGY ATOMIC WORKERS  
DONNA L. CRAGLE  
OAK RIDGE  
MPA 1394  
ORAU-60

Deadline: 11/29/94

ACHRE Request 110994-H, INTRAMURAL PROPOSAL/IRB MATERIALS FOR RESEARCH PROPOSAL REVIEW PROJECT

1144803

MEASUREMENT OF PLUTONIUM AND METALS IN MAN IN POST-MORTEM HUMAN TISSUES  
EDWARD R. GOZALES  
LOS ALAMOS

LANL-90-03

Deadline: 11/29/94

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ACHRE Request 110994-I, INTRAMURAL PROPOSAL/IRB MATERIALS FOR RESEARCH PROPOSAL  
REVIEW PROJECT

EPIDEMIOLOGIC STUDY OF MORTALITY AND CANCER INCIDENCE AMONG PLUTONIUM  
WORKERS: REPORT COMPLETION  
L. D. WIGGS  
LOS ALAMOS

LANL-91-05

Deadline: 11/29/94

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ACHRE Request 110994-J, INTRAMURAL PROPOSAL/IRB MATERIALS FOR RESEARCH PROPOSAL  
REVIEW PROJECT

MEDICAL FOLLOW-UP OF MANHATTAN PROJECT PLUTONIUM WORKERS  
GEORGE L. VOELZ  
LOS ALAMOS

LANL-91-08

Deadline: 11/29/94

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ACHRE Request 110994-K, INTRAMURAL PROPOSAL/IRB MATERIALS FOR RESEARCH PROPOSAL  
REVIEW PROJECT

A REGIONAL CYCLOTRON-PET CENTER FOR RADIOTRACER RESEARCH AND DEVELOPMENT  
JOANNA S. FOWLER  
BROOKHAVEN  
M-1313-XB  
BNL-CO-11

1144804

Deadline: 11/29/94

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ACHRE Request 110994-L, INTRAMURAL PROPOSAL/IRB MATERIALS FOR RESEARCH PROPOSAL REVIEW PROJECT

PET STUDIES OF BRAIN DOPAMINE IN COCAINE ABUSERS  
NORA D. VOLKOW  
BROOKHAVEN  
M-1313-XB  
BNL-DA-06891

Deadline: 11/29/94

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ACHRE Request 110994-M, INTRAMURAL PROPOSAL/IRB MATERIALS FOR RESEARCH PROPOSAL REVIEW PROJECT

COCAINE ANALOGS FOR PET STUDIES OF SYNAPTIC ACTIVITY  
S. JOHN GATLEY  
BROOKHAVEN  
M-1313-XB  
BNL-CO-14

Deadline: 11/29/94

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ACHRE Request 110994-N, INTRAMURAL PROPOSAL/IRB MATERIALS FOR RESEARCH PROPOSAL REVIEW PROJECT

BODY COMPOSITION AND ETHNICITY III: HISPANIC POPULATIONS  
RUI MEI MA  
BROOKHAVEN  
M-1313-XB  
BNL-DK37362

Deadline: 11/29/94

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ACHRE Request 110994-O, INTRAMURAL PROPOSAL/IRB MATERIALS FOR RESEARCH PROPOSAL REVIEW PROJECT

1144805

**MEDICAL APPLICATIONS OF HIGH PRECISION NEUTRON ACTIVATION**

**RUIMEI MA  
BROOKHAVEN  
M-1313-XB  
BNL-P01 DK42818**

**Deadline: 11/29/94**

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**ACHRE Request 110994-P, INTRAMURAL PROPOSAL/IRB MATERIALS FOR RESEARCH PROPOSAL REVIEW PROJECT**

**BIOMEDICAL RESEARCH GRANT: MEASUREMENT OF MUSCLE MASS BY NEUTRON ACTIVATION ANALYSES**

**RICHARD B. SETLOW  
BROOKHAVEN  
M-1313-XB  
BNL-2807RR05731**

**Deadline: 11/29/94**

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**ACHRE Request 110994-Q, INTRAMURAL PROPOSAL/IRB MATERIALS FOR RESEARCH PROPOSAL REVIEW PROJECT**

**PET STUDIES OF NEUROTRANSMITTER INTERACTIONS IN HUMAN SUBJECTS**

**STEPHEN L. DEWEY  
BROOKHAVEN  
M-1313-XB  
BNL-MH-49936**

**Deadline: 11/29/94**

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**ACHRE Request 110994-R, INTRAMURAL PROPOSAL/IRB MATERIALS FOR RESEARCH PROPOSAL REVIEW PROJECT**

**MEDICAL DEPARTMENT DONATION ACCOUNT: BODY CONTENT STUDIES OF DIALYSIS PATIENTS**

**DARREL D. JOEL  
BROOKHAVEN  
M-1313-XB  
BNL-84021**

1144806

Deadline: 11/29/94

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ACHRE Request 110994-S, INTRAMURAL PROPOSAL/IRB MATERIALS FOR RESEARCH PROPOSAL REVIEW PROJECT

SYNCHROTRON MEDICAL RESEARCH FACILITY  
WILLIAM H. THOMLINSON  
M-1313-XB  
BNL-LS-5

Deadline: 11/29/94

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ACHRE Request 110994-T, INTRAMURAL PROPOSAL/IRB MATERIALS FOR RESEARCH PROPOSAL REVIEW PROJECT

SELECTIVE ATTENTION IN SCHIZOPHRENIC PATIENTS AND NON-SCHIZOPHRENIC SUBJECTS  
JULIANA BALDO  
LBL  
M1349  
LBL-94-1-5

Deadline: 11/29/94

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ACHRE Request 110994-U, INTRAMURAL PROPOSAL/IRB MATERIALS FOR RESEARCH PROPOSAL REVIEW PROJECT

EXPERIMENTAL MEDICINE DEVELOPMENT: NEW DIAGNOSTIC TECHNIQUES AND TRACERS  
HENRY F. VanBROCKLIN  
LBL  
M1349  
LBL-93-6-58

Deadline: 11/29/94

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ACHRE Request 110994-V, INTRAMURAL PROPOSAL/IRB MATERIALS FOR RESEARCH PROPOSAL REVIEW PROJECT

HIPPOCAMPAL METABOLISM IN SCHIZOPHRENIA: A DIAGNOSTIC STUDY  
THOMAS E. NORDAHL

1144807

LBL  
M1349  
LBL-93-6-52

Deadline: 11/29/94

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ACHRE Request 110994-W, INTRAMURAL PROPOSAL/IRB MATERIALS FOR RESEARCH PROPOSAL REVIEW PROJECT

THE METHYL CARBON PATHWAY IN PSYCHOSIS  
THORNTON W. SARGENT, III

LBL  
M1349  
LBL-93-6-67

Deadline: 11/29/94

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ACHRE Request 110994-X, INTRAMURAL PROPOSAL/IRB MATERIALS FOR RESEARCH PROPOSAL REVIEW PROJECT

APOLIPOPROTEIN GENE E (APOE4) IN ALZHEIMER'S DISEASE  
ANANTH ACHARYA

LBL  
M1349  
LBL-93-12-75

Deadline: 11/29/94

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ACHRE Request 110994-Y, INTRAMURAL PROPOSAL/IRB MATERIALS FOR RESEARCH PROPOSAL REVIEW PROJECT

CARDIOVASCULAR FLOW AND METABOLISM  
THOMAS F. BUDINGER

LBL  
M1349  
LBL-93-6-60

Deadline: 11/29/94

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ACHRE Request 110994-Z, INTRAMURAL PROPOSAL/IRB MATERIALS FOR RESEARCH PROPOSAL

**REVIEW PROJECT**

**EXPERIMENTAL MEDICINE CLINICAL: PET STUDIES OF CANCER, CARDIAC, SICKLE CELL, AND  
EPILEPTIC PATIENTS  
THOMAS BUDINGER  
LBL  
M1349  
LBL-93-6-58**

**Deadline: 11/29/94**

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**ACHRE Request 110994-ZA, INTRAMURAL PROPOSAL/IRB MATERIALS FOR RESEARCH  
PROPOSAL REVIEW PROJECT**

**CEREBRAL CHEMICAL PATTERNS IN ALZHEIMER'S DISEASE  
THOMAS F. BUDINGER  
LBL  
M1349  
LBL-93-6-66**

**Deadline: 11/29/94**

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**ACHRE Request 110994-ZB, INTRAMURAL PROPOSAL/IRB MATERIALS FOR RESEARCH  
PROPOSAL REVIEW PROJECT**

**POSITRON 3D IMAGING INSTRUMENT  
STEPHEN E. DERENZO  
LBL  
M1349  
LBL-93-6-58**

**Deadline: 11/29/94**

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**ACHRE Request 110994-ZC, INTRAMURAL PROPOSAL/IRB MATERIALS FOR RESEARCH  
PROPOSAL REVIEW PROJECT**

**HEAVY ION RADIOSURGERY  
RICHARD LEVY  
LBL**

1144809

FYI  
Contemporary Charge from  
Committee Interim Report

- Documents related to DOD's ethics policies (particularly the 1953 Secretary of Defense Directive) to atomic bomb test activities.

In agreeing to search for the information, the agencies and the Committee reserve for future discussion whether particular activities constitute experiments. In conducting the search, the Committee will work with the agencies to ensure that previously retrieved data (such as that assembled for DOD's Nuclear Test Personnel Review) are used efficiently.

Public presentations also spurred Committee consideration of the concept of "experiment of opportunity," that is, situations in which the initial exposure to radiation may have been accidental (or, if premeditated, not for the primary purpose of human subject study), but the opportunity presented by the exposure led to an organized research effort. In discussing the concept, the Committee is mindful that, if only because of staff and resource limits, its mission cannot include the examination of human data gathering solely for safety monitoring purposes. However, the question of the boundary between such data gathering and experiments of opportunity is a focus of inquiry.

## E. THE CONTEMPORARY STORY

As part of its mission, the Committee must establish the current status of the policies and practices related to human radiation research and make recommendations regarding future policies. In an effort to gain insight into this area, the Committee has undertaken three separate research projects aimed at describing contemporary practices related to the ethics of human subject research. The *Subject Interview Study* aims to discover the beliefs and attitudes of research subjects regarding their understanding and voluntary participation in research; the *Research Proposal Review Project* aims to discover the adequacy of current policies and practices in the protection of the rights of the subjects of research; and the *Agency Oversight Review* aims at assessing both the policies and practices of the agencies for oversight of the review and monitoring of human subject research supported or performed by them. The bulk of the work for these projects will be undertaken and completed during the remaining months of the Committee's term. Up to this point, work on the contemporary projects has consisted of seeking administrative approval (through the Office of Management and Budget), designing the projects, requesting the necessary information and materials from agencies, and preparing sufficient staff resources to successfully carry out the projects.

### 1. Subject Interview Study

The purpose of this project is to collect data concerning (1) the extent to which patients of radiation oncology, medical oncology, and cardiology services at both major research institutions and community hospitals believe they are participants in research; (2) the perceived voluntariness of this participation; and (3) subjects' reasons for agreeing to participate. This project will enrich the deliberations of the Committee with direct information about the contemporary experiences of some research subjects.

**Phase III: In-Depth Interviews.** Semi-structured, in-depth personal interviews then will be conducted with 10-15 patients who are participants in research at each of the 15 institutions. An interview guide will be developed with the help of the focus groups, and the same issues covered in the survey will be included in the interviews, with questions posed in an open-ended fashion and followup questions asked based on the subject's responses. Through this process, considerably more attention can be given to the relevant topics, such as the meaning of research participation for subjects.

## 2. Research Proposal Review Project

The project will evaluate the extent to which the rights and interests of persons currently involved as subjects of radiation research conducted or supported by the U.S. Government appear to be adequately protected in the proposal review process, and to compare this level of protection with that afforded the subjects of nonradiation research. The objectives of this project are (1) to determine, based on research proposal and IRB materials, whether harms and benefits, informed consent procedures, and selection of subjects appear to be appropriate; and (2) to determine whether research proposals and IRB materials provide sufficient information to make judgements about the protection of human subjects.

This project involves collecting the necessary documents from agencies and grantee institutions. To achieve these objectives, listings of pertinent research projects will be obtained from the Departments of Defense, Energy, Health and Human Services, Veterans Affairs, and NASA,<sup>14</sup> including:

- All human subject research proposals involving ionizing radiation that were newly approved and funded or renewed by the agency in fiscal year 1993, and a sample of such proposals from previous years.
- Human subject research proposals not involving ionizing radiation that were newly approved and funded or renewed during the same period as the ionizing radiation proposals, for the purpose of creating a comparison group.

Both intramural and extramural proposals in each category will be considered for review. Grantee institutions and the agencies will be asked to provide relevant documents for a sample of the radiation research proposals as well as a parallel sample of non-radiation research. A subset of Committee members and staff will review and evaluate the proposal materials based on evaluation criteria developed by Committee and staff. This team of evaluators will include

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<sup>14</sup> CIA maintains that it neither funded nor performed any human subject research involving ionizing radiation in fiscal year 1993. The Committee is currently determining whether CIA supported such research in 1990-1992.

persons with technical radiation risk and medical expertise, knowledge of the appropriate standards for informed consent and selection of human subjects, and any additional expertise necessary to address the objectives listed above.

### 3. Agency Oversight Review

In an effort to assess both the status and efficacy of current policies regulating human subject research, Committee staff has requested that each of the six agencies identified above (CIA, DOD, DOE, HHS, NASA, and VA) provide information related to oversight of research involving human subjects that it either conducts or supports, including any special procedures for oversight of research involving ionizing radiation. This includes information and materials related to the roles and responsibility of the appropriate office, personnel, process, and authority for oversight of human subject research review in each agency, as well as any applicable rules, regulations, or policies for the conduct, funding, or oversight of human subject research. Agencies also will be asked what procedures would be followed should it be determined that there is a need to bypass applicable research policies or regulations in the conduct of specific research projects. This information will be compiled, analyzed, and recommendations for future policy will be made during the next months of the Committee's work.

## **PART II. THE AGENCY SEARCH PROCESS AND OTHER METHODS OF INQUIRY: THE HUNT FOR PIECES OF THE PUZZLE**

### **A. THE AGENCY SEARCH PROCESS**

When the President established the Advisory Committee on Human Radiation Experiments, he also directed Federal agencies to provide it with the documentary information it needed to do its job. The Interagency Working Group created a subgroup to focus on document location and retrieval. Committee staff works with this group, and its representatives from each agency.

The Interagency Working Group has, collectively, devoted considerable time to these search efforts, which are ongoing. Numerous records collections, encompassing thousands of boxes of potentially relevant files in Federal Records Centers throughout the country, have been identified. Even where relevant collections are identified, however, the search process has been arduous; dozens of boxes may yield only a handful of relevant documents, yet these documents may be of great value. Overall, the level of effort expended by the agencies, and the yield, has been significant.

## 1. Initial Reports

At the Committee's initial meeting, each agency reported on the status of their searches and invited Committee direction for continued search:

- CIA told the Committee in April, 1994 that its search had not found evidence that either showed CIA sponsorship or funding of human radiation experiments or information on human radiation experiments conducted by others.
- In January, DOD components had been charged to locate entities that conducted or sponsored experiments, and documents related to those experiments. DOD reported that many experiments had been identified.
- DOE explained that the first phase of its search was an attempt to inventory all potentially relevant records possessed by the agency and current contractors, in order to identify specific experiments and collections that would merit further review. The second phase would be an attempt to focus, based on what had been found, on the policy or contextual documents surrounding the experiments. (DOE had previously provided documents relating to human radiation experimentation in response to congressional inquiry and other investigations.<sup>15</sup>)
- HHS reported that data on the many thousands of grants for earlier years were limited to skeletal grant records, which did not always make clear whether research involved human subjects. HHS was working on targeted approaches to locate documents of relevance to the Committee and to develop more complete data on intramural research.
- NASA's initial search resulted in the identification of about 200 reports and publications describing six specific studies and three large categories of research.
- VA's initial search focused on a survey of 172 medical centers throughout the country and a review of reports at the central office. There was no formal effort to identify and list experiments. VA told the Committee it would search for further information on its confidential Atomic Medicine Division, which was created in 1947.

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<sup>15</sup> These documents, along with materials collected by DOD relating to the Cincinnati total body irradiation experiments, were the bulk of documentation about specific experiments available at the onset of the Committee's work.

In addition to document searches, a number of the agencies interviewed former officials who might have knowledge of experiments (or related records) and sought to make use of Radiation Helpline telephone information.

## 2. Committee Assessment

In the first days and weeks of work, staff met with the search teams from each agency to learn of progress in and obstacles to the search. Search plans and status, as reported in detailed staff memoranda to the Committee, varied from agency to agency. In most cases, however, their progress demonstrated the inevitable difficulty of retrieving complete, detailed records on specific activities after the passage of up to half a century:

- To the extent experiments had been identified, only fragmentary further information had been provided (or was available).
- The volume of potentially relevant records is enormous, particularly because records often have been consigned to records centers or the National Archives with little useful indexing.
- Agencies had not always searched for headquarters-related documents, including those showing the nature and development of research ethics policies.
- Agencies had not always searched for documents retired to the National Archives (which are technically not within agency possession) and only sporadically searched for documents located in Federal Records Centers.
- While the agency searches produced surprising new information on early ethics policies, there was much less information on the implementation of these policies in the case of particular experiments.
- After the passage of many years, agency components responsible for human experimentation have been renamed, reorganized, or abolished, making it difficult to determine which records collections to search.

## 3. Committee Work with Agencies on Search Strategy

The initial agency searches provided a start in identifying experiments and an appreciation for the difficulty in retrieving substantial data about the experiments. With this data and experience in hand, the Committee sought to determine how to assist agencies in directing the searches. The particulars of these activities are discussed in more detail in Appendix E and in staff memoranda and related Committee discussion concerning each agency.

In general, agencies were asked to refocus their searches. From the "dragnet" searches to identify experiments, it was suggested that focus be placed on identifying and retrieving headquarters-level collections that could provide context for particular experiments. The Committee expected that once more was known about the planning, funding, and use of experiments, it would be able to better advise the agencies on the particular experiments (or groups of them) for which a more intense field-level search would be requested. (It was also expected that the higher-level documents would help identify further experiments.) Agencies also were asked to look for documentation of the development and implementation of ethics policies governing human experimentation.

The Committee's archivists and historians, in conjunction with agency historians and records specialists, identified headquarters-level records collections to be searched and the likely location of these collections in the National Archives or Federal Records Centers. Agencies were also asked to give high priority to locating readily available documentation, such as agency histories, that could serve as guides to further searches.

In summary, and with further detail provided in Appendix E, considerations that were raised with each agency are discussed below.

a. *CIA.*

Documentation provided by DOD and DOE, and located by staff in the National Archives, confirmed that CIA was a participant in the mid-century DOD groups at which biomedical human experimentation, among other matters, was discussed and planned. Other data obtained by the Committee from members of the public confirmed that CIA contracted for work with, at least, DOE radiation research facilities. As a consequence, the Committee has asked CIA to search for documentation related to further evidence of CIA's association with human radiation experimentation.

b. *DOD.*

The Committee proposed that DOD agencies<sup>16</sup> look for headquarters-level planning, programming, and budgeting documentation. The headquarters-level ethics and policy documentation located as a result of this effort did reveal important documentary trails. For example, the records of the Joint Panel on the Medical Aspects of Atomic Warfare include debate on the need for human experimentation, plans for experimentation, and digests of experiments. Similarly, the Armed Forces Medical Policy Council initiated discussions in 1951 that led to both the Secretary of Defense's February 1953 issuance of the top secret version of the Nuremberg Code for human experimentation and to the Joint Panel's consideration of

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<sup>16</sup> Including the Office of the Secretary of Defense and the Defense Nuclear Agency, as well as each of the military services.

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ID:SPF-301 Series

FAX:

PAGE 6

1. **ACHRE Request No. 110994-E (Proposal# 4595360)**  
"Phase 2 Study of Trisodium Zinc (Zn-DTPA) for Chelation of Internally Deposited Transuranium Compounds; Compilation of Data in Database" is missing the following documents:
  - a. Original research protocol/grant application submitted by the investigator to DOE
  - b. Original research protocol/ application submitted to Institutional Review Board
  - c. Consent form as submitted to IRB
  - d. Consent form as approved by IRB
  - e. IRB disposition (approval) letter
  - f. Any documentation indicating changes to the protocol or consent form over time.
  - g. Any current documentation (FY1990- present) concerning this study.
  
2. **ACHRE Request No. 110994-G (Proposal# 7315000)**  
"Comprehensive Epidemiology of DOE Atomic Workers" is missing the following documents:
  - a. Original research protocol/ application submitted to Institutional Review Board (IRB)
  - b. Consent form as submitted to IRB
  - c. Consent form as approved by IRB
  - d. IRB disposition (approval) letter
  - e. Any documentation indicating changes to the protocol or consent form over time
  - f. Any current documentation (FY1990-present) concerning the study
  
3. **ACHRE Request No. 110994-D (Proposal# 5865860)** *ORAU 8/*  
"Use of Prussian Blue for Internal Decontamination of Radiocesium" is missing the following documents:
  - a. Original research protocol/grant application submitted by the investigator to DOE
  - b. Original research protocol/application submitted to Institutional Review Board (IRB)
  - c. Consent form as submitted to IRB
  - d. Consent form as approved by IRB
  - e. IRB disposition (approval) letter
  - f. Any documentation indicating changes to the protocol or consent

form over time.

- g. Any current documentation (FY1990-present) concerning the study

4. **ACHRE Request No. 110994-F (Proposal# 7221060)**

"US Radiation Accident Registry Follow-up Program is missing the following documents:

- a. IRB disposition (approval) letter  
b. Any documentation indication changes to the protocol or consent form over time  
c. Any current documentation (FY1990-present) concerning the study

F. **From Lawrence Berkeley Laboratories**

1. **ACHRE Request No. 110994-Z (Proposal# 2185744)**

"Experimental Medicine Clinical" is missing the following documents:

*This proposal appears to be a program project grant which was originally approved as a Field Task Proposal prior to 1980. Because we are interested in individual studies/projects as opposed to programs, we have pulled this proposal apart into its component projects. We do, however, need the appropriate individual documentation for each "sub"project in order to place it within the parameters of our study. In order to facilitate indexing of these "sub"projects, they are referenced below by name and RMP number (as they have been defined by LBL).*

- a. **RMP 32- "Cognitive Deficits Associated with Depression: A PET Study"** is missing the following documents:
- (1) Original research protocol/ grant application submitted by the investigator to DOE
  - (2) Original research protocol/grant application submitted to Institutional Review Board(IRB)
  - (3) IRB disposition (approval) letter
  - (4) Any documentation indicating changes to the protocol or consent form over time
- b. **RMP 12- "Clinical NMR Imaging of the Brain"** is missing the following documents:

U.S. DEPARTMENT OF ENERGY  
OHER/ER-72  
Washington, DC 20585  
tel 301-903-5037  
fax 301-903-8521

f a x t r a n s m i t t a l

to: ~~J. Glenn Davis~~ Dr. Shirley Fry

fax #: 615-576-3194

from: Sharon Betson

date: February 7, 1995

re: ACHRE Request

pages: 2, including this cover sheet

NOTES: This request is due to Dr. Susan Rose by the 10th of February. It is very important that this deadline is made. If possible, could you please have it here by COB on February 9th. We need to send this information to the Advisory Committee by Special Messenger on Friday morning. If this is going to be a problem, please give me a call. We will only need ONE copy of the project information.

Thank you



**Department of Energy**  
Washington, DC 20585

JAN 17 1995

TO: Extramural:  
Jerry Williams, Los Alamos National Laboratory  
Joe Furman, Rocky Flats, Inc.  
Chris Byrne, Lawrence Berkeley Laboratory  
J. Glenn Davis, Oak Ridge Institute for Science and Education  
Bart Gledhill, Lawrence Livermore National Laboratory  
Debra Maresca, Brookhaven National Laboratory

Intramural:  
Mike Phelps, University of California, Los Angeles

FROM: Susan L. Rose, DOE

RE: Research Proposal Review Project: Follow-up to ACHRE Requests  
110994-A to 110994-ZD and 110994-ZE to 110994-ZX

Evidently our submission was not acceptable to ACHRE. Could you please provide the information requested OR write us a letter stating why the requested information is NOT available. We know you are working another request but I am forced to transmit this one to you, none the less. We need one copy of the requested material by February 10, 1995.

cc: David Cunningham, Oak Ridge  
Barbara Fitzgerald, BNL  
Vicki Aschenbrenner, Rocky Flats  
Joe Aaron, LBL

1144819

experimental design are missing. We would like a *complete* copy of the grant proposal.

- b. ACHRE only received a grant application submitted by New York University for this research. However, ACHRE understood this to be an *intramural* study as this is how it is listed in the DOE Database of Research Projects Involving Human Subjects. If there is an intramural component to this study at Brookhaven, ACHRE needs a full set of the appropriate documents from Brookhaven (see the 6 items listed in the memo accompanying this attachment). If not, ACHRE requests a statement clarifying the situation.

D. From Lawrence Livermore National Laboratory

1. **ACHRE Request No. 110994-A (Proposal# 3860780)**  
"Biodosimetry for Long-term Exposures to Low Levels of Ionizing Radiation" is missing the following documents:
  - a. Original research protocol/ grant application submitted by an investigator to DOE
  - b. Original research protocol/ application submitted to the Institutional Review Board (IRB)
  - c. Consent form as submitted to IRB
  - d. Consent form as approved by IRB
  - e. IRB disposition (approval) letter

*We have only received IRB continuation approval application/approval documents. These documents, however, do not include the actual protocol or consent forms for the study.*

L. From Oak Ridge Associated Universities

*The attachment to the memorandum from ORISE to Susan Rose regarding these documents (dated 12/7/94) indicates that these documents were included in documents previously sent to ACHRE via DOE Oak Ridge Operations. After careful review of the collections that ACHRE received from Oak Ridge Operations, ACHRE staff has discovered that information about these specific experiments is missing. (Other experiments are included in great detail, but ACHRE requires materials related to the research proposal chosen for the Research Proposal Review Project sample.) We ask that complete sets of these Oak Ridge documents as indicated below be sent to ACHRE.*

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