IPCS EVALUATION OF ANTIDOTES FOR POISONING BY METALS AND METALLOIDS

PRUSSIAN BLUE

Potassium ferric (III) hexacyanoferrate (II) (colloidal soluble Prussian Blue, KFe[Fe(CN)₆] and ferric (III) hexacyanoferrate (II) (insoluble Prussian Blue, Fe₄[Fe(CN)₆]₃)

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1. Introduction

Prussian blue was first prepared in 1704 and used principally as an inorganic pigment (Faustino, 2008). Work in the 1960s investigated the use of Prussian blue as an antidote for thallium poisoning and a decorporation agent for radiocaesium (caesium-134 and caesium-137). From the 1970s Prussian blue was recommended as an antidote in thallium intoxication and it is now routinely used for this purpose. Further studies into its use for increasing the elimination rate of radiocaesium were undertaken following the Chernobyl nuclear reactor accident in 1986 but it was only after Goiânia incident in 1987 that it was used in the management of a large scale radiation accident (Faustino, 2008).

There are two forms of Prussian blue, ferric (III) hexacyanoferrate (II) (insoluble Prussian blue) and potassium ferric (III) hexacyanoferrate (II) (soluble or colloidal Prussian blue). It is essential to be specific about which form of Prussian blue has been used in future publications. The different forms should be identified by citing the correct chemical name and/or chemical formula and/or the physical nature (insoluble or colloidal soluble).

Prussian blue is given orally and acts via ion exchange, adsorption and mechanical trapping to bind thallium and caesium within its crystal lattice, interrupting their enterohepatic circulation, enhancing faecal elimination and reducing body burden.

Insoluble Prussian blue is used to treat patients with known or suspected internal contamination with radioactive caesium, radioactive thallium and non-radioactive thallium, to increase their rates of elimination. Prussian blue can reduce the biological half-life of radiocaesium by about a third. There is one report where Prussian blue has been used for the treatment of non radioactive caesium toxicity (Thurgur et al., 2006) and rubidium has also been shown to bind to Prussian blue (Hoffman, 2006).

Prussian blue is well tolerated but can result in constipation. It is essential to treat constipation as it will decrease elimination of thallium and caesium and some authors advise administration of Prussian Blue with laxatives to prevent constipation.

2. Name and Chemical Formula of Antidote

There are two forms of Prussian blue, ferric (III) hexacyanoferrate (II) (insoluble Prussian blue) and potassium ferric (III) hexacyanoferrate (II) (soluble or colloidal Prussian blue).

<table>
<thead>
<tr>
<th>Potassium ferric (III) hexacyanoferrate (II)</th>
<th>Ferric (III) hexacyanoferrate (II)</th>
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</thead>
<tbody>
<tr>
<td><strong>Synonyms</strong></td>
<td><strong>Molecular formula</strong></td>
</tr>
<tr>
<td>colloidal soluble Prussian blue,</td>
<td>KFe[Fe(CN)₆]</td>
</tr>
<tr>
<td>SPB, potassium ferric ferrocyanide,</td>
<td>Fe₄[Fe(CN)₆]₃</td>
</tr>
<tr>
<td><strong>Molecular weight</strong></td>
<td>306.9</td>
</tr>
<tr>
<td></td>
<td>859.3</td>
</tr>
</tbody>
</table>
Prussian blue is a non-stoichiometric compound and the chemical formulae for both forms shown above are therefore idealized. Additionally all precipitates of insoluble Prussian blue contain nonstoichiometric amounts of potassium, protons and water (Dvořák, 1971; Nielsen et al., 1987; Nielsen et al, 1988b). The water is partially adsorbed at the large surface of this pigment, partially distributed in the cavities of the crystal lattice (zeolithical water) and partially coordinatively bound (Ludi, 1988). Colloidal soluble Prussian blue may additionally contain nonstoichiometric amounts of cations (H⁺, alkali metal ions) and anions (Cl⁻, OH⁻) and water (Bozorgzadeh, 1971; Dvořák, 1970; Dvořák, 1971).

Insoluble Prussian blue is the only commercially available pharmaceutical preparation however in the literature there is confusion over the two available forms of Prussian blue and inconsistencies in the nomenclature of Prussian blue (Hoffman, 2006). For example, some authors who used the commercially available Prussian blue Antidotum Thallii-Heyl® containing insoluble ferric hexacyanoferrate have incorrectly described the chemical formula as KFe[Fe(CN)₆] (Franke et al., 1979) or named the compound as potassium ferric ferrocyanide (Spoerke et al., 1986). In another report both formulae are used KFe[Fe(CN)₆] and Fe₄[Fe(CN)₆]₃ for Antidotum Thallii-Heyl® (Trenkwalder et al., 1984). In other cases the drug Antidotum Thallii-Heyl® is described as "colloidal soluble Prussian blue" (Jax et al., 1973; Kemper, 1979; Gansser, 1982; Forth, 1986) or potassium ferric (III) hexacyanoferrate (II) is described as insoluble (Lehmann & Favari, 1984). As a result it is often very difficult or impossible to determine which form of Prussian blue was used.

Where possible, the two forms of Prussian blue are identified here as soluble Prussian blue and insoluble Prussian blue.

### 3. Physico-chemical Properties

<table>
<thead>
<tr>
<th></th>
<th>Potassium ferric (III) hexacyanoferrate (II)</th>
<th>Ferric (III) hexacyanoferrate (II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS Registry No</td>
<td>12240-15-2</td>
<td>14038-43-8</td>
</tr>
<tr>
<td>Colour Index No.</td>
<td>77520</td>
<td>77510</td>
</tr>
<tr>
<td>RTECS number</td>
<td></td>
<td>LJ82000000</td>
</tr>
<tr>
<td>Structural diagram (ChemIDplus Lite)</td>
<td>[Image]</td>
<td>[Image]</td>
</tr>
</tbody>
</table>
Melting point: Not available.

Solubility: Potassium ferric (III) hexacyanoferrate (II) is colloidally soluble in water, ferric (III) hexacyanoferrate (II) is insoluble in water and diluted acids (solubility product $=10^{-40}$, i.e. practically insoluble) (Ludi, 1988). $^{59}$Fe-labelled measurements resulted in a solubility of 1.1 µmol/L for potassium ferric (III) hexacyanoferrate (II) and 0.7 µmol/L for ferric (III) hexacyanoferrate (II) (Dvořák, 1970).

Optical properties: Not available.

pH: Not available.

pKa: Not available.

Stability in light: Prussian blue should be stored in tightly closed containers protected from light.

Thermal stability: Not available.

Refractive index: Not available.

Specific gravity: 1.8

Loss of weight on drying: Potassium ferric (III) hexacyanoferrate (II) 6-15% loss of weight on drying at 150°C. Ferric (III) hexacyanoferrate (II) 28-34% loss of weight on drying at 105°C.

Excipients and pharmaceutical aids: In both pharmaceutical preparations, Antidotum Thallii-Heyl® and Radiogardase®-Cs, ferric (III) hexacyanoferrate (II) is provided as 500mg of Prussian blue powder in gelatine capsules with 0-38mg of microcrystalline cellulose. The powder may vary in coarseness and colour shade (Heyl, 2004).

Pharmaceutical incompatibilities: None known.

Binding to some therapeutic drugs and essential nutrients is possible. Insoluble Prussian blue may bind electrolytes in the gastrointestinal tract. Hypokalaemia (potassium 2.5-2.9) was reported in 3 of 42 patients (7%) treated with insoluble Prussian blue (Heyl, 2004; Thompson & Callen, 2004; Thompson & Church, 2001). There are some anecdotal reports of Prussian blue decreasing the bioavailability of oral tetracycline and the serum levels and, or clinical response to critical orally administered products should be monitored (Heyl, 2004).

4. Synthesis and Pharmaceutical Formulation

4.1 Routes of Synthesis

Both substances can be synthesized according to the method of Dvořák (1969). The basic chemicals needed are the same for both substances. However, the salt ultimately formed will depend on the ratio of the raw materials and the way in which they are added to each other.
FeCl₃ + K₄[Fe(CN)₆] \rightarrow KFe[Fe(CN)₆] + 3 KCl

4 FeCl₃ + 3 K₄[Fe(CN)₆] \rightarrow Fe₄[Fe(CN)₆]₃ + 12 KCl

**Raw materials:**
Ferric chloride (FeCl₃) and potassium ferrocyanide (K₄[Fe(CN)₆])

Water suitable for injection or of comparable quality (i.e. water with cation and anion concentrations equal or less than water for injection).

**Synthesis:**

(a) Basic solutions

Dissolve appropriate amounts of FeCl₃ and K₄[Fe(CN)₆] in water so that the molar ratio of the two solutions is 2.0. This means that when a 0.2 M ferric chloride solution has been prepared, the molarity of the K₄[Fe(CN)₆] solution should be 0.1 M.

(b1) Potassium ferric (III) hexacyanoferrate (II)

It is essential that the final stoichiometric ratio Fe³⁺/ [Fe(CN)₆]⁴⁻ in the reaction mixture equals 0.33. When 1 litre of 0.2 M ferric chloride solution is used, then (1000 x 0.2)/(0.33 x 0.1) 6060 ml of a 0.1 M [Fe(CN)₆]⁴⁻ solution is necessary. The quantity of [Fe (CN)₆]⁴⁻ is added drop wise to the ferric chloride solution whilst stirring vigorously. Centrifuge at 120000g after one hour standing. Wash the precipitate three times with water and centrifuge after each washing step. Dry the precipitate obtained after the last washing step at 105 °C until the weight remains constant.

To remove possible low molecular impurities some authors have dialysed the colloidal soluble Prussian blue exhaustively against water (Müller et al., 1974; Nielsen et al., 1987; Nielsen et al., 1988a; Nielsen et al., 1988b).

(b2) Ferric (III) hexacyanoferrate (II)

It is essential that the final stoichiometric ratio Fe³⁺/ [Fe(CN)₆]⁴⁻ in the reaction mixture equals 1.33. When 1 litre of 0.2 M ferric chloride solution is used, then (1000 x 0.2)/(1.33 x 0.1) 1504 ml of a 0.1 M [Fe(CN)₆]⁴⁻ solution is necessary. The quantity of [Fe(CN)₆]⁴⁻ is added drop wise to the ferric chloride solution whilst stirring vigorously. Filter standing for one hour. Wash the precipitate and filter three times after each washing step. Dry the precipitate obtained after the last washing step at 105 °C until weight remains constant. The drying process influences the efficacy of the substance (Nigrović et al., 1966). The effectiveness of Radiogar®-Cs in binding caesium was higher than that of the ferric (III) hexacyanoferrate (II) synthesized by the authors (Nielsen et al., 1987). Among other things this can be attributed to a special drying procedure.

After synthesis as described, and after one year's storage in tightly closed containers at room temperature, neither substance showed any significant decomposition into cyanide ion (Dvořák, 1970). The effectiveness of ferric (III) hexacyanoferrate (II) was not decreased after storage during one year (Nigrović et al., 1966).
4.2 Manufacturing processes
Not known.

4.3 Presentation and formulation
Prussian blue is available as Radiogardase®-Cs (Radiogardase® in the United States of America) and Antidotum Thallii-Heyl® distributed by Heyl Chemisch-pharmazeutische Fabrik GmbH, Berlin, Germany.

Both products are available in bottles of 30 hard gelatine capsules, each containing 0.5 g of insoluble Prussian blue.

5. Analytical Methods

5.1 Quality control procedures for the antidote and/or its formulation

5.1.1 Test for the presence of colloidal Prussian blue:
A mixture of 10 g insoluble Prussian blue and 50 ml of distilled water is shaken and filtered using a membrane filter. The filtrate should show no blue colouration (absence of colloidal soluble Prussian blue).

5.1.2 Test for the presence of insoluble Prussian blue:
Shake 100 mg of colloidal soluble Prussian blue with 20 ml of water. An intensely dark blue solution is obtained. Precipitation should not occur before a standing time of two days has passed (test to exclude the insoluble form).

5.1.3 Test for the presence of hexacyanoferrate (II) and hexacyanoferrate (III):
The filtrate is then mixed with the hydrochloric acid salt of ferrous ammonium sulphate ((NH₄)₂Fe (II)(SO₄)₂) or ferric ammonium sulphate ((NH₄)Fe (III)(SO₄)₂). The absence of blue colour indicates that K₃[Fe (III)(CN)₆] is less than 5 ppm and K₄[Fe (II)(CN)₆] is less than 20 ppm respectively.

5.1.4 Test for iron content:
500 mg Prussian blue in 50 ml water are shaken and filtered. Compared with an iron standard solution the iron content should be not more than 100 ppm.

5.1.5 Test for heavy metal content:
After digestion of Prussian blue with concentrated sulphuric acid the heavy metal content (measured as lead) should be less than 50 ppm. Arsenic content must be less than 5 µg/g.

5.1.6 Removal of oxalic acid:
Prussian blue may contain oxalic acid, originating from the manufacturing process. Shake 1 g of Prussian blue with 10 ml sodium acetate solution (Dutch Pharmacopoeia, 1966). Centrifuge and filter the upper layer through a paper filter folded three times. Add to 5 ml filtrate 1 ml of calcium acetate solution (Dutch Pharmacopoeia, 1966). No precipitate of calcium oxalate should occur after 24 hours. Since no oxalic acid is used in the above specified synthesis, quality control for this acid may be omitted provided that the raw materials do not contain it. The commercially available pharmaceuticals Prussian blue in Antidotum
Thallii-Heyl® and Radiogardase®-Cs do not contain oxalic acid.

### 5.2 Methods for identification of the antidote

Detection of ferric (III) and hexacyanoferrate (II) ions: 500 mg of Prussian blue is heated in 5 ml of 3M potassium hydroxide resulting in decomposition to brown, flocculent ferric hydroxide. After deposition the supernatant fluid appears yellow (K₄[Fe(CN)₆]). After filtration, 2 ml of the fluid is acidified with concentrated hydrochloric acid and mixed with a FeCl₃ solution and this will result in blue colouration or formation of a blue precipitate.

### 5.3 Methods for analysis of the antidote in biological samples

Not applicable.

N.B. It is often stated that Prussian blue is not absorbed to any significant extent however anecdotal reports suggest prolonged therapy results in a blue discolouration of sweat and tears suggesting some absorption.

### 5.4 Analysis of the toxic agents in biological samples

#### 5.4.1 Analysis of thallium in urine, plasma and erythrocytes

Thallium can be measured by spectrophotometry, flame atomic absorption spectrophotometry (AAS) and electrothermal atomic absorption spectrophotometry (ETAAS) (Moffatt et al, 2004).

**5.4.1.1 Spectrophotometry**

A spectrophotometric method was described by de Wolff and Lenstra (1964). It involves the determination of thallium at 550nm using rhodamine ‘B’ or brilliant green and can be used on urine and on blood diluted with water. The limit of quantification is approximately 50µg/L (Moffat et al, 2004). This method is described in the Thallium Poisons Information Monograph (IPCS, 1990).

Another spectrophotometric method is described by Flanagan et al (1995). In this method a pink-red colour indicates the presence of thallium at concentrations of 1mg/l or more. A calibration graph of absorbance against thallium concentration in standard samples can be used to measure the thallium concentration more precisely. The limit of sensitivity is 0.1 mg/L.

**5.4.1.2 Atomic Absorption Spectrophotometry**

Flame AAS can be used to measure thallium in plasma, blood or urine by extracting it as a pyrrolidine dithiocarbamate complex in an organic solvent (de Groot et al, 1985). The lowest quantifiable concentration is at least 0.2 mg/l and depends on the atomic absorption spectrophotometer used. Linearity is up to 5 mg/l. Higher concentrations can be measured by diluting the sample under investigation with blank sample. This method is described in the Thallium Poisons Information Monograph (IPCS, 1990).

ETAAS has been used for monitoring occupational exposure and has a limit of detection of less than 1 µg/L (Moffat et al, 2004).

#### 5.4.2 Analysis of caesium in biological samples

Caesium-134 and caesium-137 decay by emitting beta particles and these nuclides are
detected using gamma spectrometry.

Specialist advice is essential for dose assessment following a radiation accident as this assists in determining appropriate management and the expected clinical course. Radioactivity measurements of the wound (if applicable), skin or chest (following inhalation), nasal swabs, urine and faeces are also used to assess dose. In many cases the victim is not wearing a dosimeter (and this only measures external exposure not the internal dose). In addition the standard models for calculating intake from routine occupational exposures may not be applicable and individual-specific models may have to be developed and applied for internal dose calculations (Toohey, 2003).

A quantitative baseline of the internal contamination of radiocaesium should be obtained by appropriate whole body counting and/or by bioassay, or faeces/urine sample whenever possible to obtain the following type of information to establish an elimination curve:

- Estimated internalised radiation contamination of caesium, and
- Rate of measured elimination of radiation in the faeces (Heyl, 2004).

6. Shelf-life

The pharmaceutical products of Prussian blue should be stored in the dark at 25 °C; occasional variations of temperature within the range 15 to 30 °C are permitted (Heyl, 2004). For the pharmaceutical preparations Antidotum Thallii-Heyl® and Radiogardase®-Cs the shelf-life is given as five years.

7. General Properties

Orally administered Prussian blue binds thallium or caesium in the gut and increases the concentration gradient, enhancing elimination by gut dialysis. Thallium (Forth & Henning, 1979) and caesium (Nigrovic, 1965) also undergo enterohepatic circulation and Prussian blue interrupts their reabsorption from the gastrointestinal tract thereby increasing faecal excretion. Prussian blue therefore reduces the biological half-life of caesium and thallium.

The mechanism of caesium and thallium adsorption by hexacyanoferrates is believed to involve chemical ion exchange whereby nonstoichiometric and stoichiometric cations of the drug are exchanged by thallium or caesium ions. The affinity of Prussian blue increases as the ionic radius of the cation increases, so Prussian blue preferentially binds caesium (ionic radius 0.169 nm) and thallium (0.147 nm) over potassium (0.133 nm) and sodium (0.116 nm) (Forth, 1983; Nielsen et al., 1987). An influence of Prussian blue on potassium and sodium levels is therefore not expected (Nigrovic et al., 1966). Rubidium (ionic radius 0.148) has also been shown to bind to Prussian blue (Hoffman, 2006).

Evidence is provided by a number of experimental studies. After binding of thallium to colloidal soluble and insoluble Prussian blue, the content of potassium and hydrogen ions was reduced (Dvorak, 1970). ⁴⁰K labelled colloidal Prussian blue showed no radioactivity after mixing with thallium. The pH value was decreased, indicating release of H⁺ ions (Dvorak, 1971). In in vitro experiments insoluble Prussian blue bound more caesium than potassium, and hydrogen and iron ions were released.
There may be other mechanisms in addition to ion exchange. Nielsen et al. (1987) found that colloidal soluble Prussian blue released more potassium than it adsorbed caesium, suggesting that an additional, physical adsorption on its large surface, possibly interacting with water, may be involved (Ludi, 1983; Richmond, 1968). Yang et al (2008) found that the binding capacity of insoluble Prussian blue for thallium decreased as the water content of Prussian blue was decreased. Forms of Prussian blue with a smaller crystal size, and therefore a larger surface area, have a higher adsorptive capacity and antidotal efficacy for thallium (Kravzov et al., 1993; Yang et al, 2008).

Non-dialyzed colloidal soluble Prussian blue initially proved to combine with thallium much more effectively than ferric (III) hexacyanoferrate (II) in vitro as well as in vivo (Dvořák, 1969; Dvořák, 1970; Kamerbeek et al., 1971). This greater binding was not only the result of the larger surface area of the colloidal soluble preparations (Dvořák, 1970), but also because of the larger amount of extra-stoichiometric potassium in these preparations (Dvořák, 1971). The sodium salt-derived preparation did not meet these requirements (Rauws et al., 1979), and subtle differences in the dimensions of the crystal lattice might also play a role (Keggin & Miles, 1936; Kravzov et al, 1993).

Colloidal soluble Prussian blue may, however, present problems. The production of a standard colloidal soluble Prussian blue was found to be difficult resulting in a different toxicity of the different preparations (Dvořák et al., 1971). Long-term treatment of rats with non-dialysed colloidal soluble Prussian blue resulted in actual caesium retention in the body in treated rats compared to control animals (Bozorgzadéh & Catsch, 1972; Müller et al., 1974). Dresow et al., (1993) investigated the effect of soluble and insoluble Prussian blue in rats, pigs and humans and concluded that for medical use in man, a separation of the low molecular weight compounds from crude commercial preparations is recommended.

Following the introduction of colloidal potassium ferric (III) hexacyanoferrate (II) as an antidote for thallium poisoning in 1970 (Kamerbeek, 1971; Kamerbeek et al., 1971), the results of treatment with potassium ferric (III) hexacyanoferrate (II) as well as with ferric (III) hexacyanoferrate (II) in patients with severe thallium poisoning published in the literature have been associated with a favourable outcome, particularly when it is used early. Treatment with Prussian blue in patients with thallotoxicosis can be life-saving but it does not improve all the clinical signs, such as neurological signs or alopecia, particularly in late-presenting patients.

Thompson & Callen (2004) reviewed the English language literature concerning the efficacy of soluble and insoluble Prussian blue and its use as a therapeutic agent in radioceasium and thallium poisoning. They noted that most of the evidence describing the efficacy of Prussian blue for radioceasium poisoning is based on the use of the insoluble form, whilst similar evidence for thallium poisoning involves the use of the soluble form. They concluded that while there is sufficient evidence that the insoluble form of Prussian blue is effective in radioceasium poisoning, there is a lack of analogous data supporting its use in thallium poisoning. The authors acknowledged that further research is needed to determine the significance of any differences between the two forms of Prussian blue and whether their physicochemical differences have any effect on outcomes in human poisoning is currently unknown. However, the commercial products in current use are formulated with the insoluble form of Prussian blue and most data collated from future use is likely to refer to this form only.
8. In Vitro Studies

8.1 In vitro binding of caesium

Various in vitro studies have shown that Prussian blue binds caesium (Bozorgzadéh, 1971; Nielsen et al., 1987; Verzijl et al., 1992; Faustino et al., 2008).

*In vitro* binding of caesium to insoluble Prussian blue is affected by pH, exposure time, storage temperature (affecting moisture content) and particle size. The lowest caesium binding was at pH 1.0 and 2.0 and the highest at pH 7.5. Dry storage conditions results in loss of moisture from Prussian blue which causes a negative effect on caesium binding capacity. There is batch to batch variation in particle size and variation in binding capacity. At 1, 4 and 24 hours it was determined that caesium binding increases as particle size decreases. The maximum caesium binding capacity of insoluble Prussian blue was approximately 715 mg/g (Faustino et al., 2008).

In a study comparing the binding capacity of soluble and insoluble Prussian blue, the binding of caesium-137 was greater with insoluble Prussian blue (Radiogardase®-Cs) and was pH-dependent for both formulations. The maximum binding capacities for insoluble Prussian blue were 87 mg/kg at pH 1.0, 194 mg/g at pH 6.5, and 238 mg/g at pH 7.5. For soluble Prussian blue the maximum binding capacities were 48 at pH 1.0, 73 mg/g at pH 6.5, and 78 mg/g at pH 7.5 (Verzijl et al., 1992).

Nielsen et al. (1987) investigated caesium binding by various hexacyanoferrate compounds (iron, copper, cobalt, nickel, zinc, manganese) at pH 1.2 and 6.8. All the compounds bound caesium; potassium copper hexacyanoferrate (II) and potassium zinc hexacyanoferrate (II) were the most efficient at pH 1.2 and 6.8. These compounds had twice the binding capacity of soluble and insoluble Prussian blue. These authors also demonstrated that whey contaminated with caesium-134 and caesium-137 was almost completely decontaminated by dialysing a whey suspension against a buffer solution containing insoluble Prussian blue. The whey had been produced from the milk of South German cows contaminated in the summer of 1986 following the Chernobyl accident.

8.2 In vitro binding of thallium

*In vitro* studies have demonstrated that thallium binds to both soluble (Dvořák, 1970; Kamerbeek et al., 1971; Krazov et al., 1993) and insoluble Prussian blue (Dvořák, 1970; Yang et al., 2008). The adsorption is rapid: after 10 minutes all thallium was bound (Dvořák et al., 1971). The effectiveness of soluble Prussian blue (as measured by mg of thallium/mg Prussian blue or % adsorbed) was higher than that of insoluble Prussian blue (Dvořák, 1970; Kamerbeek et al., 1971). *In vitro*, thallium binds more strongly to Prussian blue than to activated charcoal (Kamerbeek et al., 1971).

As with caesium, the thallium binding capacity of Prussian blue is affected by pH, exposure time, storage temperature (affecting moisture content) and particle size. The adsorption of thallium on Prussian blue depended on the pH-value of the solution and a maximal adsorption could be detected at a neutral or slightly alkaline pH (Dvořák, 1970). In the *in vitro* study by Yang et al. (2008) the maximum thallium binding capacity of insoluble Prussian blue was approximately 1400 mg/g at pH 7.5 after 24 hours. The lowest binding occurred at pH 1.0 at 1 hour and thereafter, binding increased as pH increased (determined
up to pH 7.5). The binding constant was higher for fully hydrated Prussian blue compared to
Prussian blue which had been dried for 24 hours and the smaller the particle size the higher
the binding constant.

An in vitro study examined the adsorption of thallium-201 by insoluble Prussian blue to
investigate the use of Prussian blue in reducing the radiation burden in thallium-201
myocardial scintigraphy. The maximum adsorption peaked at approximately 30 minutes
irrespective of the concentration (1, 10 or 100 mg or Prussian blue in 5 mL of water). It
reached a plateau at 30 to 60 minutes with no further increase in adsorption of thallium until
4 hours. The rate of absorption was constant for up to 1 hour but slowed down thereafter.
Thallium-201 removal increased from 46 to 95% when the pH was increased from 2.0 to 8.0.
In the most favourable conditions the maximal adsorption capacity was 5000 MBq of
thallium-201/g of Prussian blue and maximal adsorption occurred at 30 minutes (Bhardwaj
et al., 2006).

9. Animal Studies

9.1 Pharmacodynamics

9.1.1 Caesium

A number of animal studies have examined the impact of Prussian blue on the absorption of
caesium, its effect on the enhancement of excretion (or reduced retention) of caesium and
the impact of these actions on final outcomes.

9.1.1.1 Prevention of absorption/uptake from gut

Administration of a single dose of radiocaesium and concomitant oral dosing of Prussian
blue resulted in reduction of caesium uptake from the gastrointestinal tract (Brenot &
Rinaldi, 1967; Dresow et al., 1990, 1993; Giese & Hantzch, 1970; Nielsen et al., 1988b;
Nigrović, 1963; Nigrović, 1965). In piglets potassium ferric (III) hexacyanoferrate (II) and
ferric (III) hexacyanoferrate (II) reduced the caesium-134 uptake by more than 97%. The
diminution of the caesium-134 body burden depended on the dose of administered
hexacyanoferrate (II). The difference between the colloidal and insoluble Prussian blue
compounds in decreasing enteral absorption of caesium-134 was small (Nielsen et al.,
1988b).

If Prussian blue was given as late as 60 minutes after caesium-137 administration the enteral
caesium-137 absorption was also suppressed (Nigrović, 1963). Autoradiography of rats
showed, that the radioactivity was limited to the gastrointestinal-tract (Brenot & Rinaldi,
1967).

In rats administered a composite treatment mixture containing calcium alginate, potassium
iodide and insoluble Prussian blue in their diet and exposed to various radionucleotides, the
Prussian blue, even as a component of the mixture, decreased the absorption of caesium into
the organism and reduced the whole-body retention (Kargacin & Kostial, 1985; Kostial et
al., 1980; Kostial et al., 1981; Kostial et al., 1983).

In a study in pigs the animals (82 kg) were fed twice daily with pellet food and 500 mL of
milk together with 200 g of radiocaesium-contaminated whey powder. Prior to each feeding
the pigs were given 0.5g, 1.5g or 2.5 g of soluble Prussian blue, insoluble Prussian blue or ammonium iron hexacyanoferrate (II) \((\text{NH}_4\text{Fe[Fe(CN)]}_6)\) in gelatine capsules. The animals were slaughtered after 27 days of feeding. All compounds were found to be effective at reducing caesium-134 and caesium-137 absorption. Administration of increasing quantities of the compounds resulted in a dose-dependent reduction in the radioactivity of the tissues tested. Soluble Prussian blue and ammonium iron hexacyanoferrate were more effective, possibly due to more favourable distribution of colloidal soluble compounds in the gastrointestinal tract (Dresow et al., 1993). Similarly, soluble Prussian blue and ammonium iron hexacyanoferrate were most effective in rats (260 to 280 g) given 0.5 mg of Prussian blue in water 2 minutes before 0.5 mL of water containing a tracer dose of caesium-134, by gastric tube. There was almost complete blockade of radiocaesium absorption as judged by urinary excretion and whole body retention measured 7 days after ingestion. Insoluble Prussian blue was less effective (Dresow et al., 1993).

9.1.1.2 Enhancement of decorporation (reduced retention)

Chronic feeding of rats (Dresow et al., 1993; Stather, 1972) or piglets (Dresow et al., 1993; Giese et al., 1970) with caesium-137 contaminated food and concomitantly administration of Prussian blue resulted in reduced whole body retention. Most of the daily caesium-137 dose was excreted in the faeces.

After ingestion of radiocaesium, administration of insoluble Prussian blue (Bozorgzadêh & Catsch, 1972; Dresow et al., 1990; Nigrović, 1963; Nigrović, 1965; Nigrović et al., 1966; Stather, 1972;) and colloidal soluble Prussian blue (Bozorgzadeh, 1971; Bozorgzadêh & Catsch, 1972; Dresow et al., 1990; Giese et al., 1970; Müller et al., 1974) decreased the whole-body-retention of the caesium isotopes. Also in a mixture with other substances Prussian blue increased the excretion of the caesium-137 (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 caesium was excreted into the gut in young animals (Bozorgzadeh, 1971; Stather, 1972).

Prussian blue increased the cumulative excretion of incorporated radiocaesium in faeces and urine (Brenot & Rinaldi, 1967; Nigrović, 1965; Nigrović et al., 1966). Whereas in untreated animals most caesium is excreted in the urine, in animals treated with Prussian blue faecal excretion predominates (Nigrović et al., 1966; Brenot & Rinaldi, 1967; Müller, 1969; Giese et al., 1970; Giese & Hantzsch, 1970; Richmond, 1968). The biological half-life was reduced (Madshus et al., 1966; Nigrović et al., 1966; Havliček et al., 1967; Havliček, 1968; Müller et al., 1974; Richmond, 1968; Strömme, 1968). In rats the half-life was reduced by 50% (11 days compared to 6 days) (Nigrović et al., 1966; Müller et al., 1974), and in dogs from 11 to 6.5 days (Madshus et al., 1966).

Colloidal soluble Prussian blue was more efficient in increasing the excretion of radiocaesium than the insoluble form (Müller, 1969). In long-term use however, colloidal soluble Prussian blue decreased the excretion compared with control animals. Insoluble Prussian blue did not show this effect (Bozorgzadêh & Catsch, 1972). After thorough dialysis with water to remove any possible low molecular impurities this effect of the colloidal Prussian blue disappeared (Müller et al., 1974). The efficacy of the dialyzed colloidal soluble Prussian blue, however, was only marginally better than that of insoluble Prussian blue (biological half-lives: control 10.51 days, insoluble Prussian blue 5.6 days, colloidal Prussian blue 4.88 days) (Müller et al., 1974).
The efficacy of therapy with Prussian blue is time-dependent. The best effect resulted in administration of Prussian blue 2 minutes before application of caesium (Dresow et al., 1990). Start of treatment immediately after intoxication was also successful (Bozorgzadèh, 1971; Bozorgzadèh & Catsch, 1972), but it was still effective after a delayed start of 3.5 days (Stather, 1972).

The reduced whole-body retention of caesium after treatment with Prussian blue can also be seen in individual organs. This reduced caesium content of the different organs has been reported in muscle (Bozorgzadèh, 1971; Bozorgzadèh & Catsch, 1972; Brenot & Rinaldi, 1967; Kostial et al., 1983; Müller et al., 1974; Stather, 1972; Wolsieffer et al., 1969), bone (Bozorgzadèh & Catsch, 1972; Müller et al., 1974; Wolsieffer et al. 1969), carcass (Kostial et al., 1983; Wolsieffer et al. 1969), liver (Bozorgzadèh, 1971; Müller et al., 1974; Stather, 1972) and kidney (Bozorgzadèh, 1971; Bozorgzadèh & Catsch, 1972; Brenot & Rinaldi, 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 caesium in the different organs varied. In the gastrointestinal-tract the caesium content was increased due to binding on the non-resorbable Prussian blue (Brenot & Rinaldi, 1967).

After 15 days of dietary acclimatization to insoluble Prussian blue as 1% of their food, rats were given intraperitoneal casesium-137. The animals were killed 30 days later. There was significant reduction in the retention of caesium-137 in the carcass, femur and muscle (Wolsieffer et al., 1969).

Oral insoluble Prussian blue was given to rats in drinking water (400 mg/kg/day) for 11 days which was started immediately after an intravenous injection with caesium-137. On evaluation at 11 days Prussian blue had increased the faecal excretion of caesium-137 5-fold and this consequently also reduced urine excretion. There was also reduced retention of Cs-137 in all the tissues tested (blood, liver, kidneys, spleen and skeleton) (Le Gall et al., 2006).

Oral administration of insoluble Prussian blue shortened the retention of caesium-137 in mated, pregnant and lactating rats and the deposition of caesium-137 in the embryos and nursed young animals was reduced (Havliček, 1967; Havliček, 1968).

The effect of Prussian blue provided in drinking water to rats of various ages, on the excretion of intraperitoneally administered caesium-137 was investigated. In 19-week old rats the body burden of caesium-137 was reduced to 34% of the controls 1 week after injection whilst in 9-week and 4-week old rats, the corresponding values were 28% and 9% respectively. Tissue analysis suggested that the rate limiting factor of excretion of caesium-137 during Prussian blue therapy was the turnover rate of caesium-137 in muscle tissue. The turnover rate of caesium-137 in muscle tissues of young animals is faster than that of older animals and this is reflected in an increased efficacy of Prussian blue in removing caesium-137 from the younger animals (Stather, 1972).

**9.1.1.3 Impact on outcomes**

Richmond & Bunde, (1966) investigated the effect of three different concentrations of Prussian blue on caesium-137 contaminated rats. Each rat (approximately 92 days old with and average bodyweight of 372g) received approximately 0.84 microcurie of caesium-137, the rats were then measured 30 minutes later for total body activity and then returned to their respective cages. Insoluble Prussian blue was incorporated into their drinking water which
they had free access to over the following 60 days. The concentrations of Prussian blue in the water were 0, 0.025, 0.25 and 2.5 g/L, and the estimated daily dose of Prussian blue was 0, 0.9, 8.5 and 84 mg/rat, respectively. There was significant reduction in the whole body retention of caesium-137 with continuous ingestion of Prussian blue at 0.25 and 2.5 g/L, but no effect was observed at 0.025 g/L. Retention of caesium was described in 3 exponential terms and the third component had a half-life of 8.77 days in high-dose Prussian blue rats compared to 14 days in control rats. The authors concluded that the rate of caesium-137 secretion would depend partially on the turnover rate in body tissues, particularly muscle, which accounts for a large proportion of the total body caesium-137 activity.

The effect of Prussian blue was studied in sheep fed wheat and grass contaminated with caesium after the Chernobyl accident. The lactating sheep (average 35 kg) were given 0.5 kg of wheat (average radiocaesium content 1684 ± 17 Bq/kg) and 200 g (9840 ± 442 Bq/kg) daily. The average milk yield was 110 g per day. When the radiocaesium content of the milk had reached a state of equilibrium half the animals were given colloidal Prussian blue, 5 g in 5 L of drinking water for 23 days. The colloidal Prussian blue settled in the container and the drinking water had to be stirred repeatedly during the day and it took about 2 days before the sheep became used to the water. Treatment with Prussian blue reduced the radiocaesium content of the milk by approximately 85% and the effect was seen within a few days of the start of treatment (Ioannides et al., 1991).

The role of Prussian blue in removing caesium-137 internal contamination from rats was studied to evaluate the possible side effects caused by chronic consumption on various biomarkers for exposure. Rats of two age groups (growing rats (2-months old) and adult rats (4-month old)), were observed over a 60 day period having had either caesium-137 alone, Prussian blue alone, or a combination of both, administered at different time intervals (e.g. both given simultaneously or with a time lapse between). The authors reported that in both growing and adult rats Prussian blue administration, particularly when given before or immediately after Caesium-137 intake, could eliminate the effects of caesium-137 irradiation on red blood cell count and haemoglobin content, and on serum levels of: total proteins (in adult rats only), globulins (in adult rats only), creatinine, urea, urea nitrogen, ALT activity, T3, and T4. When given one or seven days post caesium-137 irradiation, Prussian blue eliminated the effects of caesium-137 treatment on serum cholesterol, serum calcium and serum bilirubin, in both growing and adult rats (Fekry et al., 2003).

The efficacy of insoluble and colloidal soluble Prussian blue in removing a single dose of internally deposited caesium-134 was compared in rats (6 rats in each experimental group). Prussian blue was administered twice daily and treatment started immediately after injection of caesium-134. For the first few days the colloidal form initially showed greater efficacy in removing the caesium but with continuous administration it brought about a complete blockage of caesium-134 excretion from the liver, spleen and skeleton. This was attributed to in vivo disintegration of the colloidal compound yielding free \([\text{Fe(CN)}_6]^{4-}\) which when absorbed from the gut reacts with endogenous metal ions. The authors highlight the practical clinical consequences of this finding in that the insoluble compound should be the antidote of choice for caesium-134 toxicity; the slight transient superiority of the colloidal form is over-shadowed by its untoward long-term effect (Bozorgzadéh & Čatsch, 1972).

9.1.2 Rubidium
There is limited information on the decorporation effect of Prussian blue in rubidium exposure. Rats were fed insoluble Prussian blue in their food (as 5%) from 2 days before an
intraperitoneal injection of rubidium-86. Prussian blue reduced the half-life of rubidium-86 from 10.3 days to 1.7 days, reducing the whole body retention to 9% that of controls after 7 days (Stather, 1972).

9.1.3 Thallium

9.1.3.1 Prevention of absorption/uptake from gut
Concomitant oral administration of thallium and of Prussian blue in rats resulted in a lower uptake of the metal and lower concentrations found in organs (Dvořák, 1969; Heydlauf, 1969; Rauws, 1974). Soluble Prussian blue was more effective than the insoluble Prussian blue (Dvořák, 1969).

In a study by Heydlauf (1969) aqueous solutions of thallium-204 sulphate were administered to rats by gastric tube. Aqueous suspensions of ferric cyanoferrate (II) (insoluble Prussian blue) in doses of 0.5-50 g were then administered by gastric tube 1 to 60 minutes later. The maximal protective effect, i.e. approximately ten times lower absorption of thallium-204, was observed when Prussian blue was given immediately, although an effect was still seen when Prussian blue was administered at 60 minutes. As expected, there was a marked dependence of antidotal efficacy on the dose of Prussian blue administered.

9.1.3.2 Enhancement of decorporation (reduced retention)
It was also shown that insoluble Prussian blue was able to remove thallium across the gastrointestinal wall. Carrier-free thallium-204 was injected intravenously and the animals fed with Prussian blue pellets at will (Heydlauf, 1969). The thallium-204 content of Prussian blue treated animals was drastically reduced even when treatment was initiated on the fourth day. This was due to markedly enhanced faecal excretion whereas urinary elimination did not reach the control level.

Insoluble Prussian blue (Heydlauf, 1969) as well as colloidal soluble Prussian blue (Dvořák, 1969; Günther, 1971) 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 & Favari, 1985; Leloux et al. 1990; Manninen et al., 1976; Rauws, 1974; van der Stock & de Schepper, 1978). The cumulative excretion in faeces and urine was increased (Heydlauf, 1969; Lehmann & Favari, 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 Prussian blue) (van der Stock & de Schepper, 1978), in rats it was decreased from 4 days to 2 days (Rauws, 1974).

A study in rats demonstrated that soluble Prussian blue increased excretion of thallium and reduced the LD$_{50}$ but only if started within 24 hours of exposure. Thereafter thallium-induced pathological changes were irreversible (Günther, 1971).

The reduced retention and the increased excretion of thallium by Prussian blue results in a decrease of the thallium content in liver (Dvořák, 1969; Günther, 1971; Heydlauf, 1969; Kravzov et al., 1993; Manninen et al., 1976; Rios & Monroy-Noyola, 1992; Sabbioni et al., 1982), kidney (Dvořák, 1969; Günther, 1971; Heydlauf, 1969; Kravzov et al., 1993; Manninen et al., 1976; Rauws, 1974; Rios & Monroy-Noyola, 1992; Sabbioni et al., 1982), skeleton (Heydlauf, 1969) blood (Rios et al., 1991), heart (Kravzov et al., 1993; Rios & Monroy-Noyola, 1992) and muscles (Dvořák, 1969; Günther, 1971; Heydlauf, 1969;
9.1.3.3 Impact on outcomes

Kamerbeek et al. (Kamerbeek, 1971; Kamerbeek et al., 1971) showed the influence of Prussian blue on the concentration of thallium in the brain. Thirty-five rats, divided into seven groups of five animals, were given 0.075 mM/kg thallous 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 Prussian blue 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 Prussian blue 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 (Kravzov et al., 1993; Leloux et al., 1990; Manninen et al., 1976; Rauws, 1974; Rìos et al., 1991; Rìos & Monroy-Noyola, 1992; Sabbioni et al., 1982).

Trying to establish an optimal dosage scheme for use of Prussian blue in human thallotoxicosis, Kamerbeek (1971) gave five groups of five rats 0.1 mm/kg thallous nitrate intraperitoneally. After 24 hours four groups were treated by gavage once daily with 10, 50, 250 and 1000 mg/kg Prussian blue, 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 Prussian blue appeared to be as effective as 1000 mg/kg/day with respect to thallium-concentration in muscle specimen but with respect to thallium in the brain the highest dosage was more efficacious.

Kamerbeek (1971) further investigated the protection afforded by Prussian blue against thallium toxicity. Two groups of rats were given 0.25 mg/kg thallous nitrate intraperitoneally. Four hours later one group received Prussian blue 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.

It was further shown that enhanced thallium-204 excretion as a result of Prussian blue therapy was accompanied by reduced thallium toxicity (Kravzov et al., 1993; Rìos et al., 1991; Rìos & Monroy-Noyola 1992). Treatment with potassium ferric hexacyanoferrate (II) (colloidal soluble Prussian blue) increased the LD$_{50}$ by a factor 2.3 (Günther, 1971). After application of 30 mg thallium/kg the survival in the control group was 0% and in the Prussian blue group 50% (Heydlauf, 1969).

After intraperitoneal injection of thallium (32 mg/kg) on day 1, a group of 16 rats was given soluble Prussian blue (50 mg/kg orally twice daily), D-penicillamine (intraperitoneal injection 25 mg/kg) or a combination of the two from days 2 to 5. The mortality in the different treatment groups by day 6 was: control group 87.5%, Prussian blue group 56.25%, D-penicillamine group 100% and Prussian blue + D-penicillamine group 25%. Only the combination of antidotes produced a significant difference in mortality compared to controls. Prussian blue alone protected against thallium-induced neurotoxicity (as measured by the number of altered Purkinje cells) but the effect was greater with combined Prussian blue + D-penicillamine. D-penicillamine alone did not protect against thallium-induced changes in
Purkinje cells (Barroso-Moguel et al, 1994).

9.2 Pharmacokinetics

9.2.1 Oral

There is limited information on the pharmacokinetics of Prussian blue as these compounds are very poorly absorbed from the gastrointestinal tract. Most studies have been performed with iron-59 or carbon-14 labelled Prussian blue examining intestinal absorption and bioavailability of iron and cyanide (see section 9.4 for studies on assessment of cyanide toxicity).

The release of iron from potassium ferric (III) hexacyanoferrate (II) and ferric (III) hexacyanoferrate (II) was examined in piglets. The compounds were labelled with iron-59 in the ferric or ferrous position. When labelled in the ferric position only 1.47% of the iron was absorbed from potassium ferric (III) hexacyanoferrate (II) and 1.34% from ferric (III) hexacyanoferrate (II), as determined by the whole-body retention 14 days after oral dosing. Only 0.2% and 0.15%, respectively, of the iron was absorbed from the ferrous position. Most of the dose was excreted in the faeces; 0.1 to 1% of the iron-59 was in the urine but it could not be determine how much of may have been due to faecal contamination (Nielsen et al., 1988a). This study suggests that iron is not significantly absorbed from Prussian blue.

Administration of labelled (59Fe, 14C) Prussian blue to rats resulted whole-body retention of 0.03% of the dose (only in the gastrointestinal tract) and in traces of radioactivity in the urine (0.15%). The amount in blood and skeleton was below the detection limit. After administration of iron-59 labelled potassium ferric (III) hexacyanoferrate (II) (K59Fe[Fe(CN)6]) to rats traces of radioactivity were found in the skeleton (0.11% of the administered dose) and in blood (0.046%). Again, with radio-labelled iron in the ferric and ferrous positions, the differences in distribution showed that Prussian blue is not absorbed, but the different ions K+, Fe3+ and [Fe(CN)6]4- are metabolized instead. No evidence was obtained for decomposition of [Fe(CN)6]3+ (Dvořák et al., 1971). Histopathological examination of organs showed no deposits of Prussian blue after oral administration of insoluble and colloidal soluble Prussian blue (Giese & Hantzsch, 1970).

9.2.2 Parenteral

After intraperitoneal administration of radio-labelled colloidal soluble Prussian blue the substance is eliminated by the reticuloendothelial system. On the first day 40.5% of the radioactivity was excreted in the urine, the content in the faeces was very small. On the second day 42% was found in the faeces with only traces in the urine. After 4 days the body retention was 4.5%, mostly in the liver (Müller, 1969).

Intravenous administration of KFe[59Fe(CN)6] and K59Fe[Fe(CN)6] resulted in entirely different metabolic behaviour in rats between the two forms. With potassium ferric (III) hexacyanoferrate (II) labelled in the ferrous position (KFe[59Fe(CN)6]) more than 50% of the radioactivity was excreted in the urine, by contrast when labelled in the ferric position (K59Fe[Fe(CN)6]) only 0.06%. The faecal excretion was low for both. The distribution of the radioactivity into the organs after administration of KFe[59Fe(CN)6] differed from that of K59Fe[Fe(CN)6]. Whereas the radioactivity of KFe[59Fe(CN)6] persisted in the liver for 8 days, the activity of K59Fe[Fe(CN)6] varied from the liver to the blood (Dvořák et al., 1971).

9.3 Toxicology
9.3.1 Acute toxicity

**Ferric (III) hexacyanoferrate (II)**

**Oral:**

According to a Soviet study, 8g/kg body weight was not lethal to laboratory animals (presumed to be rats or mice) and produced no clinical signs of toxicity (BIBRA, 1997)

**Intraperitoneal administration:**

- LD$_{50}$ rat: 1.13 mg/g body weight (Brenot & Rinaldi, 1967).
- LD$_{50}$ rat: 2.1 g/kg body weight (BIBRA, 1997).
- LD$_{50}$ mouse: 2 g/kg body weight (BIBRA, 1997).

Rats or mice given lethal doses suffered inertia, breathlessness and sluggishness with excess blood in the liver, spleen and kidney (BIBRA, 1997).

**Potassium ferric (III) hexacyanoferrate (II)**

In studies by Dvořák et al. (1971) the lethality of intravenous injection of 1 mg of colloidal soluble Prussian blue in rats varied from 0% to 100%, despite the same manufacturing processes. Some animals became unwell within 15 minutes and developed respiratory distress. A blue colouration was noted in the lungs at post-mortem examination. This variation in toxicity was thought to be due to differences in the degree of dispersion of the Prussian blue in the solution of each batch.

**Pigment blue 27**

Oral LD$_{50}$ rat: >5g/kg body weight (BIBRA, 1997).

9.3.2 Chronic toxicity

In rats colloidal soluble Prussian blue given as 2% of drinking water for 12 weeks resulted in no significant body weight changes or histopathological changes in the organs, including the gut (Dvořák et al., 1971). Similarly, sheep (average weight 35 kg) given colloidal soluble Prussian blue, 5 g in 5 L of drinking water daily for 23 days had no change in body weight (Ioannides et al., 1991).

There were no significant differences in average fluid intake in rats given insoluble Prussian blue in drinking water (0.025, 0.25 or 2.5 g/L) for 60 days. The estimated daily dose of Prussian blue was 0.9, 8.5 and 84 mg/rat, respectively (equating to 2.4, 23, 226 mg/kg) (Richmond & Bunde, 1966).

Oral insoluble Prussian blue caused no adverse effects and no impairment of growth in young rats when given as 1% of the diet for 120 days (Nigrović et al., 1966) or as 1% of their food for 60 days in rats (Wolsieffer et al., 1969). Also in rats, food consumption and body weight were unchanged during 9 days of treatment with a mixture of sodium alginate (daily consumption 2 g), insoluble Prussian blue (250 mg) and sodium perchlorate (100 mg) (Kostial et al., 1980) or during 4 weeks treatment with a mixture of calcium alginate (average 4.8 g/day), insoluble Prussian blue (average 0.8 g/day) and potassium iodide (0.0048 g/day) (Kostial et al., 1981).
There were no adverse effects in dogs (7 to 8 kg) given oral insoluble Prussian blue (3 or 6 doses of 0.5 g daily) for 11 days. The doses equate to approximately 200 and 400 mg/kg, respectively (Madshus et al., 1966). At autopsy no pathological changes were observed (Nigrović et al., 1966).

9.3.3 Reproductive toxicology and teratogenicity
There is no information available on the reproductive toxicity of Prussian blue.

In pregnant rats intoxicated with oral thallium soluble Prussian blue started 8 hours later increased the survival rate, reduced the thallium content of the placenta by 5-fold and in the foetuses reduced the thallium content of the brain and liver (Sabbioni et al., 1982).

9.3.4 Genotoxicity
No information available.

9.4 Assessment of possible cyanide toxicity
Prussian blue contains cyanide ions bound to iron. At extremely low pH values in the presence of oxidizing agents Prussian blue decomposes and, under these circumstances, cyanide can be released. Since oral administration of Prussian blue is indicated in the treatment of thallium poisoning and caesium incorporation, various studies have examined the possibility of cyanide release from these hexacyanoferrate compounds.

When gastric juice (pH 2) and soluble Prussian blue were incubated for 4 hours no cyanide was detected. Similarly no cyanide was detected when the study was conducted with 0.1 N hydrochloric acid at room temperature. Cyanide was only detected when this last experiment was repeated at 100 °C (Kamerbeek, 1971). Other in vitro studies have also shown that the release of cyanide is negligible (Dvořák, 1970).

Verzijl et al. (1993) studied in vitro cyanide release of four Prussian blue salts, potassium ferric (III) hexacyanoferrate (II), ferric (III) hexacyanoferrate (II) and ammonium ferric (III) hexacyanoferrate (II), both unpurified and purified compounds (that is, with and without 33% ammonium chloride as a manufacturing impurity). These salts were added to water, artificial gastric (pH 1.2) or intestinal (pH 6.8) juices and the content flasks were allowed to stand for 5 hours, protected from light, at 37°C. Cyanide was detected in all tests and the quantity released ranged from 22 to 535 µg/g of Prussian blue in water, 64 to 418 µg/g in artificial gastric juice and 15 to 58 µg/g in artificial intestinal juice. For all salts tested the release of cyanide was greatest in artificial gastric juice than the other test media. The unpurified ammonium ferric (III) hexacyanoferrate (II) released the most cyanide and ferric (III) hexacyanoferrate (II) (insoluble Prussian blue) the least in all test media.

In an in vitro study the release of cyanide from insoluble Prussian blue was measured over a pH range of 1.0 to 12 following incubation for 1 to 48 hours in a shaking water bath at 37°C (Yang et al., 2007). Five batches of active pharmaceutical ingredients were tested and three batches of drug product. The release of cyanide was both pH-dependent and incubation-time dependent. The greatest release occurred at pH 1.0 with a gradual decline as the pH increased to 7.0. At this pH the lowest quantity of cyanide was released and as the pH increased again the cyanide concentration also increased. Increasing the incubation time at different pH also increased the amount of cyanide released. The highest cyanide concentration occurred when Prussian blue was incubated at pH 1.0 for 48 hours. The
authors concluded that, based on a dose of 17.5 g of Prussian blue per day, a total of 1.5-1.6 mg of cyanide would be released, which was well below the minimum toxic dose of cyanide of 14.4 mg.

The release of cyanide from potassium ferric (III) hexacyanoferrate (II) and ferric (III) hexacyanoferrate (II) was examined in piglets. The compounds were labelled with carbon-14 in the cyanide group. No carbon-14 dioxide was detected in expired air after ferric (III) hexacyanoferrate (II), indicating that the quantity of cyanide released is very small or nil (Nielsen et al., 1988a).

10. Volunteer Studies

10.1 Pharmacokinetics

There is very little published pharmacokinetic data on Prussian blue in humans.

10.1.1 Release of iron and cyanide from Prussian blue

Three volunteers (all male, 36 years, 81 kg; 38 years, 81 kg; 45 years, 70 kg) were given radio-labelled soluble Prussian blue (500 mg) to determine the release of iron and cyanide in humans in vivo. The compound was labelled with iron-59 in the ferric or ferrous position and carbon-14 in the cyanide group. Only 0.22% of iron (II) and <0.04% of iron (III) was absorbed. Only 2 mg of non-complex bound carbon-14 labelled cyanide was absorbed. This is a factor of 20 to 100 below the lethal dose of 0.5 to 3.5 mg cyanide/kg in humans (Nielsen et al., 1990a).

10.2 Caesium

10.2.1 Studies on absorption

In a series of volunteer studies on the effect of Prussian blue on the pharmacokinetics of caesium the studies involved self-dosing by the study authors. These authors (to include 8 observations, 5 volunteers undertook the study once and one author repeated the experiment twice) showed that 3 g daily of Prussian blue given before caesium-137 did not reduce caesium absorption. The increase in caesium-137 excretion was small following 0.5 g of Prussian blue three times daily (Madshus & Strömme, 1968).

In 6 volunteers a preliminary study showed that insoluble Prussian blue (4 x 0.5 g or 10 x 0.2 g daily for 2 to 3 weeks) did not fully block caesium uptake from contaminated food (Volf et al., 1987).

Two male volunteers (age 36 and 38 years, both 81 kg) ingested three single test meals consisting of 170 g of milk labelled with a tracer dose of caesium-134 along with bread, margarine and cheese 10 minutes after ingestion of 1 g of Prussian blue in gelatine capsules. Both forms of Prussian blue were equally effective in reducing radiocaesium absorption. The absorption of radiocaesium from the meal judged by urinary excretion of caesium-134 and whole body retention 14 days after administration was reduced from 100.9% (control without Prussian blue) to 5.6% by soluble Prussian blue and to 6.4% by insoluble Prussian blue (Dresow et al., 1993). In a similar study in two male adult volunteers, the ingestion of Prussian blue ten minutes before eating a test meal containing caesium-134 labelled milk (along with bread, margarine and cheese) reduced the caesium absorption more than the
simultaneous administration of Prussian blue along with the labelled test meal. Administration of Prussian blue prior to the meal reduced absorption of the radiocaesium to 3-10% of the ingested dose whereas simultaneous ingestion of Prussian blue and the test meal only reduced absorption to 38-63%. The 100% control was the absorption rate of the radiocaesium test meal alone without Prussian blue (Nielsen et al., 1991).

10.2.2 Studies on decorporation/excretion

In a series of volunteer studies on the effect of Prussian blue on the pharmacokinetics of caesium the studies involved self-dosing by the study authors. Studying the decorporation of caesium involved ingestion of Prussian blue (3 g daily as 2 or 3 doses for several weeks) in 2 adult males given 180 days after ingestion of caesium-137 and it was found to reduce the biological half-life of caesium from the pre-treatment values of 110 and 115 days to 40 days. The only adverse effect was mild constipation (Madshus et al., 1966).

In five cases when Prussian blue (1g three times daily) was given several months after caesium ingestion the biological half-life of caesium was reduced on average from 94 to 31 days, that is, to one third of its original half-life (Madshus & Strömme, 1968; Strömme, 1968).

A 37-year-old male was given oral caesium-137 for 24 days followed by 2 g of insoluble Prussian blue (as 10 x 200 mg daily over a 9 hours period) from day 12 to day 17 then after a rest period of 2 days was given Prussian blue for another 5 days. The biological half-life of the caesium was reduced from 140 days to approximately 50 days. There was no constipation and no change in whole-body potassium values (Richmond, 1968).

Fifteen Chinese exchange students in Bulgaria were exposed to caesium-134 and 137 released following the accident at the Chernobyl Nuclear Power Station in April 1986, and following their return to China in June they were assessed for contamination. In three volunteers the biological half-life of caesium ranged from 42 to 71 days. Insoluble Prussian blue (1 g three times daily for 6 days repeated for 3 courses with a 6 day rest period in between) was given from day 114 to 145 after exposure. This reduced the half-life of caesium and enhanced elimination (Tang et al., 1988).

10.3 Rubidium exposure

There are no volunteer studies on the effect of Prussian blue in rubidium exposure.

10.4 Thallium poisoning

There are no volunteer studies on the effect of Prussian blue in thallium exposure.

Bhardwaj et al. (2006) studied the effect of insoluble Prussian blue on whole body radioactivity in two patients following thallium-201 myocardial scintigraphy. Each patient had two sessions of scintigraphy, one with and one without Prussian blue (100 mg 3 times daily after meals for 3 days), so each patient acted as their own control. In the first patient whole body radioactivity was reduced by 18 and 30% after 24 and 48 hours, respectively, of oral Prussian blue therapy. The second patient developed constipation and did not pass any stools after oral Prussian blue for 48 hours. The whole body radiation counts were similar to those when Prussian blue was not given but there was a concentration of radioactivity in the colon suggesting that the radioactivity was unavailable for resorption.
11. Clinical Studies – Clinical Trials

There are no controlled clinical trials on the use of Prussian blue in human thallium poisoning or radiocaesium decorporation.

12. Clinical Studies - Case Reports

12.1 Decorporation of radiocaesium

12.1.1 Goiânia incident, Brazil, 1987

At the end of 1985 a private radiotherapy institute moved premises and left a caesium-137 teletherapy unit behind. The building was partly demolished and in 1987 two men removed the source assembly head from the machine thinking it may have scrap value but without being aware of what it was. They took this home and tried to dismantle it during which they ruptured the source capsule. This contained caesium chloride which is highly soluble and easily dispersed. After the rupture the source capsule was sold for scrap to a junkyard dealer. He observed that the material glowed blue in the dark and over the next 5 days this was a source of interest to family and friends. During this time several individuals started to become unwell with gastrointestinal signs and eventually the source capsule was suspected and it was taken to the public health department. This triggered a major response to the incident. In total 112,000 people were assessed and 249 were found to contaminated either internally or externally with caesium-137. Some had very high exposure due to eating with contaminated hands or rubbing the glowing material over their body. Twenty patients developed bone marrow suppression. Eight developed acute radiation syndrome (Brandão-Mello et al., 1991) and four of these victims died within 4 weeks of their admission to hospital (IAEA, 1988). Prussian blue (Radiogardase®-Cs) treatment was given to 46 patients (aged 4 to 46 years) for up to 150 days. The adults were initially given 3 g daily and the 13 children were given 1 to 1.5 g daily. These doses were later increased to 10 g and 3 g daily, respectively, when it was established that larger doses resulted in higher radioactivity of faecal samples. In four cases 20 g of Prussian blue was given over 24 hours. Of 46 patients, 10 developed mild to moderate constipation and this was managed with a high fibre diet or laxatives (Farina & Brandão-Mello, 1991). Prussian blue treatment significantly increased the rate of faecal caesium excretion and reduced whole body retention of caesium (IAEA, 1988). The physiological faeces to urine excretion ratio of caesium was 1:4 and this was changed to 4:1 with Prussian blue treatment (Farina & Brandão-Mello, 1991). In 15 adult patients who received Prussian blue the body burden of caesium-137 was reduced by 51% to 84% with an average of 71% within the first 2 months after exposure. This dose reduction was independent of the Prussian blue dose in the range of 3 to 10 g/day (Melo et al., 1994).

In vivo data from patients internally contaminated with caesium-137 in the Goiânia accident was analysed to compare the half-life of caesium-137 with and without Prussian blue treatment. Additionally the possible influences of various body parameters (age, height, weight and radioactivity) on the half-lives were evaluated. Subjects were monitored using a whole-body counter and the findings are from data collected for the period of one year post the accident. Patients under treatment had previously followed different Prussian blue dosing patterns but during the monitoring period received 3 g/day, 6 g/day or 10 g/day. Caesium-137 elimination from the body followed first order kinetics with or without Prussian blue
therapy. Without Prussian blue treatment the half lives of caesium-137 in the 10 adult females studied varied widely (range 39 to 104 days; mean: 65.5 days) with less variation seen in the 8 adult males (66 to 106 days; mean: 83 days). Overall Prussian blue reduced the half-life of caesium-137 by about 32%. The actual calculations showed that for those subjects receiving 3 g/day of Prussian blue the mean reduction was 28%, it was 31% in those receiving 6 g/day and was 32% in subjects receiving 10 g/day. The strongest parameter influencing the half-life in both males and females was body weight. Height and age were correlated to the half-lives through their correlation to the weight parameter but were not additional variables. Investigating the estimated caesium-137 body burden at the initial time of elimination found an inverse relationship between initial activity and half-life: the larger the initial body burden, the faster the nucleotide removal from the body. The influence of this parameter was much weaker than that of body weight (Lipsztein et al., 1991).

12.1.2 Chernobyl incident, 1986

Measurements were made on 15 Chinese subjects internally contaminated with radionucleotides released from the Chernobyl accident on 26th April 1986. The students had been visiting Sofia, Bulgaria from 19th April until 23 May 1986 and monitoring was done on their return to Beijing. Internal contamination with radioactive caesium (caesium-134 and caesium-137) was measured in all 15 students. The measured activity in the body for the 15 volunteers ranged from 68-840 Bq for cesium-137 and 110-630 Bq for caesium-134. The estimated intakes were calculated and ranges were 95-1200 Bq (Caesium-137) and 170-930 Bq (Caesium-134). The biological half-life was calculated for three volunteers along with the effect of Prussian blue on their rate of elimination of radiocaesium. Prussian blue was given at doses of 1g three times a day for a 6 day course, 3 courses in total were give with a 6 day time interval between each course. The biological half-life of the radiocaesium ranged from 43-71 days. Prussian blue was given to the three volunteers in the period of 114-141 days after contamination and the body retention of radiocaesium declined more rapidly following Prussian blue administration than in those of controls (Tang et al., 1988).

12.1.3 Other case reports

Five persons, two adults (aged 34 and 38 years, weight 56 and 55 kg) and three children (aged 4 to 11 years; weight 13.5 to 34 kg) accidentally received caesium-137 chloride for approximately 20 days (no details given). The patients were evaluated as soon as the accident was discovered and started on Prussian blue. The adults received 3 g daily from days 35 to day 128 or 143. The children received 1, 1.5 or 2 g daily from days 35 to 86, 76 or 99. The half-life of the caesium was very variable and was 124, 54, 61, 36 and 36 days without treatment. With Prussian blue treatment the half-life of caesium was 38, 39, 25, 17 and 16 days, respectively (Ma et al., 1985).

12.1.4 Non-radioactive caesium

A 65 year old woman presented to a hospital accident and emergency department with a one day history of recurrent fainting. The patient claimed to have essential hypertension and was having treatment for this from her family doctor. Six months prior to her presentation she had been diagnosed with rectal cancer and liver metastasis and she had experienced frequent episodes of watery diarrhoea in the past 4 weeks. On admission her blood pressure was 138/55 mmHg, pulse 52/min regular, temperature 36.8°C, respiratory rate 18/min and blood glucose 10.7 mmol/L. She developed and episode of Torsades de points (TDP) polymorphic ventricular tachycardia with transient loss of consciousness during initial assessment. The arrhythmia spontaneously converted back to normal sinus rhythm in about 10 seconds. Her electrocardiogram (ECG) showed QT prolongation with a corrected QT interval of 620 ms
calculated by Bazett’s formula. Serum electrolytes showed mild hypokalaemia (2.8mmol/L) whilst serum magnesium and serum calcium were normal. She was treated with intravenous magnesium sulphate and vigorous potassium replacement however there was no improvement in the QT prolongation after these therapies. At this stage it was discovered that in the previous 6 weeks the patient had been taking anticancer naturopathic drugs obtained from an alternative medical centre in Hong Kong. A detailed drug history was obtained. Her medications included methyldopa, Dologesic™ (dextropropoxyphene 32.5mg and paracetamol 325mg) and Lomotil™ (diphenoxylate 2.5mg, atropine 0.025mg) all prescribed by her family physician. In addition, a bottle of herbal powder (1 teaspoon taken daily), 3 oral medications including “Gigamax” (labelled as multivitamins), Slow K™ (slow release potassium supplement) and “multi-C” were prescribed by the naturopathic practitioner. On the basis of the clinical findings and along with previous case reports of caesium chloride use in anticancer therapy, the diagnosis of caesium poisoning was highly suspected. Whole blood and serum were assayed and the serum caesium concentration was elevated markedly at 288µmol/L (normal range 0.0045-0.0105µmol/L). Whole blood arsenic concentration was normal. One of the naturopathic medicines (“multi-C”) was found to contain 89% caesium chloride by weight. No undeclared contents or toxins were found on analysis of the herbal powder “Gigamax” and Slow K™ tablets. The patient was hospitalized for 2 weeks with intensive cardiac assessment and monitoring. The use of naturopathic medicines was stopped after hospitalization. Oral Prussian blue 3g 3 times daily was started on day 7 after hospital admission and continued for 4 weeks (day 7 to day 34). Hypokalaemia was noticed during Prussian blue therapy and an oral potassium supplement was given to keep the serum potassium concentration at around 4mmol/L. Serial serum and urine caesium concentrations were measured. The calculated serum half-life of caesium was shortened from 61.7 days to 29.4 days with Prussian blue therapy. The corrected QT interval of her ECG returned to normal baseline on day 27 (Chan et al. 2009).

Thurgur et al. (2006) report a case where Prussian blue was used in the treatment of non-radioactive caesium. The patient was a 58 year old female with chronic caesium toxicity from the use of caesium chloride as an alternative cancer therapy. High levels of caesium are arrhythmogenic and this patient showed recurrent syncpe, polymorphic ventricular tachycardia, hypokalaemia, and a QT prolongation of 690 ms. Along with conventional measures Prussian blue was used to treat her caesium toxicity. The Prussian blue treatment decreased the half-life of caesium from 86.6 days to 7.9 days, with associated normalization of QT interval and cardiac rhythm.

12.2 Rubidium
There are no reports on the use of Prussian blue in rubidium exposure in humans.

12.3 Thallium poisoning
Reference values for thallium (Walker, 1998):

<table>
<thead>
<tr>
<th></th>
<th>Blood</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 nmol/L (&lt;1 µg/L)</td>
<td>&lt;5 nmol/L (&lt;1 µg/L)</td>
<td></td>
</tr>
</tbody>
</table>

A 45 year old man with no significant medical history was hospitalized with peripheral neuropathy and paraesthesia of the extremities of all 4 limbs for 2 days. Clinical examination revealed an erythematous popular rash on the face and folliculitis on the lower limbs associated with hyperaesthesia of the feet and hands. An electromyogram showed severe polyneuropathy. The patient had a cardiac arrest 9 days after admission followed by
post-anoxic coma. The patient worked in a technical crystals factory and handled thallium, bromide, caesium and iodide. The urinary thallium concentration measured twenty days after his cardiac arrest was 5118µg/g of creatinine. Despite the late diagnosis treatment with insoluble Prussian blue (Radiogardase™) was started 2 weeks later (42 days from his original admission to hospital) and continued for 24 days at a dose of 6g three times daily. Urinary thallium concentrations decreased from 1333µg/g of creatinine to 166µg/g of creatinine. After evaluation of the efficacy of the treatment a second course of Prussian blue therapy was started at 77 days post admission and continued for 1 month when the patient died. The urinary thallium concentration decreased from 86µg/g of creatinine to 3µg/g of creatinine (Villa et al., 2009).

Ten members of two families (family A and family B) sought treatment at a health care facility in Baghdad, Iraq. All patients were experiencing vomiting, abdominal pain and dysphagia. Over the next 4 days, 5 of the patients developed neurological signs and symptoms of varying severity (pain, abnormal sensations and weakness—particularly of the lower limbs). Four days after admission biological samples and a sample of a cake that all 10 patients had consumed were submitted for toxicology testing. Thallium was detected in both the biological samples and the cake. On the eighth day after admission one of the patients, a child aged 11 years, died and two days later the 9 surviving patients were evacuated to Jordan for Prussian blue therapy which was not available in Iraq. A second patient, a 2 year old child died soon after arrival in Jordan, prior to receiving therapy. Prussian blue therapy was begun in the 8 surviving patients, now 11 days after they had eaten the cake. Two of these 8 patients were already comatose with severe cerebral oedema and subsequently died. Over the next thirty days, all 6 long-term survivors developed hair loss and 5 of the 6 survivors developed muscle weakness and spasticity of the lower limbs, with differing severity. An epidemiological investigation was started and it was discovered that the fathers of the two families were both board members of an Iraqi sporting club and had attended a routine board meeting on the day before hospital attendance in the club’s conference room. The cake, prepared by a local bakery and pre-divided into 10 pieces, had been delivered to the board meeting as a gift from a former board member. However the cake arrived late, after most board members had already left the meeting so no cake was eaten then. The two members that remained (the fathers of the two families) divided the cake and took the halves home to their families and it was eaten by both families at home that evening. Family A comprised seven members (parents and five children) and family B comprised five members (parents, two children and an uncle). Ten cases of abdominal pain, vomiting and dysphagia were identified among family members who consumed any amount of the cake. No other board members or their families were ill and no similar illnesses were reported at the health facility in Baghdad or at any nearby health facilities. Food exposure histories were collected in Jordan through interviews with family members. Ten people who ate portions of the cake became unwell; neither of the two persons who did not eat cake became unwell, however one of the two had tasted some of the cake icing and although asymptomatic, his blood and urine samples tested positive for thallium. A more rapid onset of illness occurred in adults and in persons who ate the most cake. Fatality was not significantly associated with sex, age, the amount of cake eaten, or the time to illness onset. Quantitative thallium levels were determined from blood and urine samples of nine patients taken on day 16 after eating the cake. Thallium was detected in all nine patients; the median blood thallium level was 289µg/L (range 53-1,408 µg/L; reference range expected <2µg/L), and the median calculated 24 hour urine excretion of thallium was 3063 µg/L (range 542-12,556 µg/L; reference range expected <5µg/L). Blood thallium levels correlated weakly with the amount of cake reported to have been eaten (CDC., 2008)
A previously healthy forty-year old male was admitted to hospital complaining of progressive weakness of his limbs, repeated vomiting and recurrent episodes of confusion. He had initially presented to the hospital six weeks previous to this admission complaining of thirst, nausea, vomiting, dizziness, paraesthesias and arthralgias (predominantly of the lower limbs). The paraesthesias were not described as ascending or notably painful. A supine blood pressure of 180/90mmHg and a mild fever were the only physical findings noted. Neurological examination showed the cranial nerves to be intact and the results of muscle strength tendon reflex and cerebellar function tests were normal. There was no evidence of impaired superficial or position senses. The results of a complete blood count and blood chemistry tests were normal. He was discharged and symptomatic treatment (non-steroidal anti-inflammatory drugs) was prescribed. Two weeks before the present admission he returned complaining of general weakness, anxiety, myalgias (particularly of the legs), delayed growth of facial hair after shaving and thirst. Physical examination and routine laboratory tests were again normal. His symptoms were diagnosed as “non-specific”, partly attributed to stress. On his present final presentation he was alert and complained of double vision. Physical examination revealed hyperhidrosis, tachycardia (100beats/min) and supine blood pressure of 140/100 mmHg. Alopecia of the scalp was noted but eyebrows, eye lashes and body hair were intact. Neurological assessment disclosed horizontal and upbeat nystagmus, severe weakness of the lower extremities (more prominent proximally), bilateral absence of Achilles tendon reflexes, and lower limb ataxia. He did not complain of extreme pain and no objective signs of sensory changes were detected. He was found to have raised blood alanine aminotransferase and raised aspartate aminotransferase. There was no evidence of proteinuria. Lumbar tap revealed an elevated protein. Electroencephalogram showed persistent generalized slowing; the electromyogram displayed bilateral, severe, lower limb motor axonal neuropathy. Rapid deterioration of his neurological state was observed over the next few days, including flaccid paraparesis, lower limb areflexia, severe sensory impairment, mild distal arm and neck weakness, as well as occasional urinary and faecal incontinence. Visual disturbance progressed from impaired colour vision and decreased acuity to optic disc atrophy. Cognitive disturbances and hoarseness were also noted. Sural nerve biopsy showed early acute axonal degeneration with no evidence of vasculitis. At this stage he was started on intravenous immunoglobulin as a variant of Guillain-Barré syndrome (Millar-Fisher type) could not be excluded, and alternative causes were explored. Several days later thallium poisoning was diagnosed as heavy metal urinalysis showed renal thallium excretion of 7mg/24 hours. Prussian blue was administered (250mg/kg/day, dissolved in 15% mannitol) daily through a nasogastric tube, along with forced diuresis. At this stage Mees’ lines appeared on his nail beds. No improvement in his general state was noted within the next two weeks. He became drowsy, required respiratory assistance and subsequently developed aspiration pneumonia. The suspicion of cardiotoxicity was raised by elevations of alanine aminotransferase, aspartate aminotransferase and creatine phosphokinase (MB fraction) levels however this was not substantiated by electrocardiographic follow-up and echocardiography. There was swelling and pain in his right knee, however, some clear fluid drained was inconsistent with any particular diagnosis. Rheumatoid factor was mildly elevated, without any other supporting evidence of concurrent arthritic disease. His condition stabilized over the next weeks and there was a gradual decrease in thallium urinary output (table below). He was transferred to a rehabilitation hospital after forty two days. A follow-up examination 3 months later the alopecia and Mees’ lines had completely resolved. There were no cognitive disturbances, his proximal strength was restored and his colour vision was normal. Decreased visual acuity and bilateral drop-foot were still evident however and the patient had only a vague
recollection of his period in hospital.

<table>
<thead>
<tr>
<th>Hospitalization day</th>
<th>Daily excretion (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>18</td>
<td>7.6</td>
</tr>
<tr>
<td>19</td>
<td>3.2</td>
</tr>
<tr>
<td>21</td>
<td>5.6</td>
</tr>
<tr>
<td>24</td>
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<td>25</td>
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</tr>
<tr>
<td>28</td>
<td>2.5</td>
</tr>
<tr>
<td>38</td>
<td>0</td>
</tr>
</tbody>
</table>

(Atsmon et al., 2000)

A 67 year old woman was admitted to a county hospital because of acute pain in the chest, abdomen and lower limbs. The pain in the lower limbs was described as burning and severe. There was no vomiting or diarrhoea. The patient was discharged after 3 days with the cause of her illness undetermined. The patient then presented one week later to a private clinic because of persistent symptoms. Physical examination showed mild tenderness over the abdomen and electrocardiography showed non-specific T-wave inversion in the anterior waves. Routine urinalysis results were normal and laboratory tests showed normal blood cell counts, blood glucose level and kidney and liver function. The patient was treated symptomatically with analgesics. She was soon readmitted to hospital because of fainting spells and persistent symptoms. The patient suspected she was being poisoned. Paranoid psychosis and trichotillomania were diagnosed and she was admitted under restraint to the psychiatric department for observation. After being discharged home at week 5, the woman then re-presented at the private clinic. According to the patient the pain had become less severe. Physical examination showed diffuse alopecia which had started 2 weeks after the onset of the initial symptoms. Thallium poisoning was suspected. Urinalysis showed a thallium level of 8.56µmol/L (normal level, 0.003µmol/L; a level of 0.98µmol/L is toxic). The case was reported to the police and the prime suspect was the patient’s 73 year old cohabitant. A dose of activated charcoal was given in the emergency department of a nearby district hospital and the patient was discharged home with a 2-week supply of succimer (2,3-dimercaptosuccinic acid) (no reason for this was given). At follow-up at week 6 however, it was found that the pain in her chest, abdomen and lower limbs had subsided, but symptoms of peripheral neuropathy had emerged - namely bilateral numbness and loss of exteroceptive and proprioceptive sensations in the toes. She had mild weakness in the proximal muscles of the lower limbs, as indicated by the patient’s difficulty in rising from the squatting position. She also complained of right-sided headache and tachycardia. She was immediately admitted to a University Medical Centre for treatment with oral Prussian blue (potassium ferric hexacyanoferrate) 4g every 8 hours. The blood thallium level at the time of hospitalization was 0.15µmol/L. No other heavy metals were present. The patient tolerated Prussian blue very well, but hypoesthesia developed over the medial aspect of her left calf on the second day of treatment. She was discharged 1 week later, when the urine level of thallium was 0.14µmol/L. In week 9 the patient experienced neurological deterioration, impairment of short-term memory, double incontinence, tremor ataxia and falls. Physical examination showed hypoesthesia of the right trigeminal nerve, general weakness of the extremities, cerebellar ataxia, tremor and dyskinesia. Plantar reflexes were normal and the urine thallium level was 0.33µmol/L. By week fourteen the right facial
numbness fully recovered, by week twenty there was recovery of sphincter control and
regrowth of hair. Urine thallium was undetectable 2 weeks later. The weakness in the lower
limbs, unsteady gait, falls and bruises persisted until 11 months after the initial presentation,
when her condition improved noticeably although residual weakness continued (Pau., 2000).

A 24-year old female was admitted to hospital with a 4-month history of illness. Eight days
after admission a diagnosis of thallium poisoning was made based on rapid diffuse alopecia,
gastro-intestinal disturbance and a worsening neurological state combined with laboratory
results. Whole blood thallium was measured and the first level was 300 µg/L (normal
<10µg/L, toxic >100 µg/L); the corresponding 24-hour urinary thallium value was 4300
µg/L (normal < 10 µg/L, toxic > 200 µg/L), consistent with severe intoxication. Colloidal
soluble Prussian blue (KFe[Fe(CN)6]) was given orally at a dose of 250mg/kg/day in 2-4
divided doses for 14 days. The patient also received mannitol as a cathartic, cisapride for
her persistent constipation (started on the 5th day of treatment) and forced diuresis, which
was achieved with furosemide, glucose, potassium and sodium chloride. The patient’s
clinical course after treatment was uncomplicated with recovery of her vital signs within a
week. Four months after treatment thallium was undetectable in a 24-hour assay. However
after 6 months she still suffered from a lack of concentration and insomnia and never fully
returned to her previous functional level. The source of thallium was never established

<table>
<thead>
<tr>
<th>Days before/after treatment</th>
<th>24 hour-urinary thallium level µg/L</th>
<th>Whole blood thallium level µg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>-8</td>
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</tr>
<tr>
<td>0</td>
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<tr>
<td>14</td>
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</tr>
<tr>
<td>18</td>
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</tr>
<tr>
<td>31</td>
<td>260</td>
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</table>

(Vrij et al., 1995).

A thirty nine year old male with a history of heavy alcohol consumption became ill one
week after returning from holiday in Spain. His symptoms started acutely with generalized
pain and tingling all over his head and body and he was admitted to hospital where he was
greatly distressed and complaining of shooting pains in his legs and back and leg weakness.
It was thought initially that his illness was an alcoholic syndrome. Because of his continued
deterioration despite multivitamin treatment he was transferred initially to the regional
neurology unit and then further to an intensive care unit, 20 days after first becoming ill. On
initial neurological examination he had respiratory distress, evidence of scalp hair loss, gaze
evoked nystagmus in all directions, bilateral lower motor neuron, facial and bulbar
weakness; his arms were minimally weak with normal reflexes but his legs showed a flaccid
paralysis with absent reflexes. Initial biochemical investigations were within normal ranges
(electrolytes, urea, creatinine and liver function tests). The electrophoresis pattern of serum
proteins was normal and a non-specific auto-immune profile did not detect any auto-
antibodies. Screening tests for abnormal urinary porphyrins gave negative results. A
complete blood count was within the reference range, except for a slightly increased mean
corpuscular volume. Cerebrospinal fluid was acellular with a protein count of 1.5g/L.
Nerve conduction studies showed absent sensory and motor responses for the legs but
normal values for the arms. On the basis of the clinical picture at this stage, in particular
with respect to the hair loss, serum and urine were assayed for thallium and it was found to be present at toxic levels (value not stated). The patient deteriorated further and developed visual failure, complete external ophthalmoplegia, and total arreflexic paralysis of all limb and neck muscles. He was given two treatments of plasma exchange and treatment with potassium ferrihexacyanate (colloidal soluble Prussian blue), 5g every 6 hours by nasogastric tube was started (now thirty five days into the illness) and continued for 2 months. At the same time intravenous potassium supplements (100-400mmol/day) were given. Excretion concentrations of thallium in serum and urine are tabulated below. The patient made a slow recovery which was complicated by septicaemia, recurrent supraventricular tachycardias and psychosis. He required 96 days of assisted ventilation and a total of 224 days in hospital. Some 500 days after the initial insult he still had a significant visual handicap, no fine finger function and could only walk a few steps with assistance. The source of the thallium poisoning was never discovered.

<table>
<thead>
<tr>
<th>Hospitalization day</th>
<th>Excretion (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>914.4</td>
</tr>
<tr>
<td>46</td>
<td>54.8</td>
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<td>48</td>
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<td>49</td>
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<td>60</td>
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<table>
<thead>
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<th>Hospitalization day</th>
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</tr>
</thead>
<tbody>
<tr>
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<td>7.8</td>
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<tr>
<td>59</td>
<td>5.4</td>
</tr>
</tbody>
</table>

Day zero = date of admission to hospital
(Chandler et al., 1990)

Villanueva et al (1990) describe 5 cases of thallium poisoning in Spain. Four were members of a single family and the source of thallium was never ascertained. The fifth case was a female adult with a history of depression who intentionally ingested a thallium sulphate rodenticide. The family members (2 adults and two children aged 10 years and 3 years) presented initially with varying symptoms and the two children required admission to
intensive care. Total hair loss of the 10-year old 2 weeks after admission led to the
diagnosis of thallium poisoning. In all of the 5 cases urinary thallium was measured. The
10 year old child’s first measured thallium level was 18.4 mg/L, seven days later it was 5.8
mg/L, at 27 days later it was 0.14 and by approximately 4 months it was 0.004 mg/L. The
child had been treated with Prussian blue at a dose of 250mg/kg by duodenal tube
administration every 6 hours until the urinary excretion of thallium was 0.5 mg/day. Her
symptoms resolved in 20 days. The female adult who intentionally ingested the thallium had
an initial urinary level of 2.4mg/L which decreased to 0.9mg/L in 4 days and to 0.1 mg/L in
5 weeks. She had also been given Prussian blue at a dose of 250mg/kg/day (duration of
treatment not stated) and 6 weeks later recovery was complete. The case reports also outline
the thallium concentrations of the other family members but it is unclear whether or not they
received Prussian blue therapy.

A 20-year-old chemistry student presented with a 3 day history of malaise and polyuria with
paraeesthesia of the fingers and lips. He had been using thallium and blood and urine
analyses showed very high concentrations (5750 µg/L and 60000 µg/L, respectively),
although he denied ingestion. Tests for thallium in hair samples were negative which
excluded chronic ingestion however, despite exhaustive enquiries by the police and college
authorities, the mode of thallium administration remained undetermined. Shortly after
admission he became drowsy and had a convulsion. He developed progressive weakness
over the next 12 hours, with severe pain in the calf muscles. He had peripheral and sensory
impairment, dysarthria, dysphagia, paralytic ileus, tachycardia and ECG changes. He was
started on soluble Prussian blue (5 g in 50 ml of 15% mannitol 4 times daily) and forced
diuresis. On day 6 dialysis and haemofiltration were started and diethyldithiocarbamate was
given. The diethyldithiocarbamate produced a short-lived increase in thallium excretion
(from 17 to 142mg/24 h in urine, and 63 to 81mg/6 h dialysis) but also led to a rise in serum
thallium concentration (from 800 to 1350 µg/L and worsening neurological signs (including
respiratory failure) and it was stopped. He required ventilation for 4 weeks. He developed
almost complete alopecia before hair regrowth started. By 13 weeks he could swallow fluids
and by 20 weeks he had normal upper limb function. But after 12 months he was still in a
wheelchair owing to nerve damage to the lower limbs. Prussian blue and laxatives were the
most effective means of enhancing thallium elimination, even though paralytic ileus caused
long periods of constipation. High concentrations of thallium were present in the faeces up
to day 18, and it was estimated that at least 2000 mg of thallium was excreted via this route
in the first 20 days (see table). This is twice the quantity excreted by all the other methods
in the same period. Forced diuresis was estimated to have eliminated 820 mg of thallium in
46 days with 225 mg eliminated via haemodialysis in 25 days.

<table>
<thead>
<tr>
<th>No. of days from admission</th>
<th>Serum (µg/L)</th>
<th>Urine (µg/L)</th>
<th>Urine (mg)</th>
<th>Faeces (mg)</th>
<th>Dialysate (mg)</th>
<th>Urine Filtrate (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5750</td>
<td>60000</td>
<td>129</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-5</td>
<td>2390</td>
<td>35900</td>
<td>398</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-10</td>
<td>680</td>
<td>7750</td>
<td>230</td>
<td>550</td>
<td>146</td>
<td>3.5</td>
</tr>
<tr>
<td>11-15</td>
<td>225</td>
<td>1520</td>
<td>42</td>
<td>155</td>
<td>64</td>
<td>1.0</td>
</tr>
<tr>
<td>16-20</td>
<td>35</td>
<td>640</td>
<td>12</td>
<td>1280</td>
<td>5.0</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>21-25</td>
<td>15</td>
<td>280</td>
<td>2.6</td>
<td>0.5</td>
<td>5.4</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>
The serum and urine concentrations presented in the table above are daily averages for the periods stated. The quantities excreted are totals for each period. All values are given as elemental thallium, measured by atomic absorption spectrometry (Wainwright et al., 1988).

A group of 14 people ate dinner together and the following morning all complained of abdominal pain, vomiting and diarrhoea and were taken to hospital. Five of the 14 patients died in hospital within the next four days. The remaining nine patients (age range 16-70 years) were seen over the following 4-7 days. One patient was pregnant, one had pre-existing Parkinson’s disease and a third had elephantiasis of the legs. All of them complained of varying degrees of pain in the feet and legs and 6 were unable to walk. Some had headaches, constipation, abdominal pains, chest discomfort, loss of appetite, and loss of sleep. On examination they all had varying degrees of peripheral neuritis with hyperaesthesia, hyperalgesia, mental confusion, tachycardia, muscle and abdominal tenderness. A diagnosis of heavy metal poisoning was made based on the sudden onset of peripheral neuritis in a group of people who had eaten the same food and also because of similar case presentations in the previous year that had proven to be thallium poisoning. Blood and urine samples were sent for heavy metal analysis. Thallium was detected quantitatively in all the samples. The food they ate was suspected of being contaminated with a thallium-containing rodenticide but this could not be confirmed. Prussian blue was started between the 4th and 7th day at a dose of 2g three times a day orally, together with magnesium sulphate solution (30ml three times a day) to avoid constipation. For the first few days some of the patients required parenteral pethidine (100mg every six hours) for severe lower limb pain later changed to oral pentazocine (50mg three times a day). They were also given oral vitamin B complex and amiloride/hydrochlorothiazide daily. Over the next 5 days the leg pains rapidly subsided and analgesics were stopped. Seven of the patients started walking freely without much pain. In the 3rd week all of them gradually started losing scalp hair and there was almost complete alopecia after 4 weeks. Six patients developed Mee's lines on the finger nails along with hyperpigmentation over the knuckles. Four patients were discharged from hospital after the 4th week and the remaining patients after 6 weeks. Prussian blue was continued in all patients at the same dose for a total of 6 weeks and no side effects were noted. On discharge 5 patients had fine tremor of the upper limbs with slight incoordination of movement. After sixteen weeks regrowth of scalp hair was complete. The pregnant woman had a premature delivery in the sixth month of pregnancy at another hospital but no details were available. By sixteen weeks all patients had returned to active life.

<p>| Serum and urine thallium concentrations after two weeks of Prussian blue therapy |
|---------------------------------------------|---------------------|-----------------|---------------------|---------------------|</p>
<table>
<thead>
<tr>
<th>Patient number</th>
<th>Patient age (years)</th>
<th>Serum Thallium (µgm/ml)</th>
<th>Urine Thallium (µgm/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62</td>
<td>16</td>
<td>2200</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>4</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>4</td>
<td>250</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>4</td>
<td>250</td>
</tr>
</tbody>
</table>
A 21-month old girl arrived at a hospital in the UK from Qatar for investigation of ataxia of five days duration. On admission she was semi-conscious and irritable but extensive investigations including routine toxicology screen on blood and urine, could only achieve a diagnosis of encephalopathy. On the 5th day of hospitalization hair loss was noted and a suggestion of thallium poisoning was made by a nurse in charge of the child (the subject of the crime thriller she was reading at the time, Agatha Christie’s *A Pale horse*). The child was treated with oral Prussian blue and potassium chloride (doses not stated) and after 3 weeks of treatment there was marked clinical improvement and no thallium was detected in her urine. The clinical improvement continued and after four months the child was alert, ataxic but able to walk with help. The source of thallium was never determined but was thought to be the cockroach bait that was used in the home (Robb-Smith, 1987).

A 32 year-old woman was admitted to hospital 6 hours after allegedly ingesting 100mg of thallium sulphate. On admission the patient had malaise, nausea, vomiting and a burning retrosternal pain. After gastric lavage Prussian blue was administered 250mg/kg in divided doses) and combined haemoperfusion-haemodialysis (HP-HD) was started 7 hours after the alleged ingestion. HP-HD was instigated because the dose of thallium and whether there were possible co-ingestants were unknown. The patient was treated for 4 hours by HP-HD. Blood samples were taken before and after the charcoal column and after the artificial kidney at 1 hour intervals. Blood flow was 200ml/min. After HP-HD treatment 7 more blood samples were taken, initially at 1-hour intervals later at 2-hour intervals. During HP-HD treatment the patient’s blood pressure remained constant however there were frequent supraventricular extrasystoles. The patient improved and after 4 hours of HP-HD she felt well. Subsequent to her treatment no neurological or dermatological symptoms were noted. The combination of HP-HD in this patient obtained an overall clearance of 150ml/min in blood compared to 47ml/min (mean value) using HD only (De Backer et al., 1982).

A 28-year-old female presented 4 days after ingestion of nearly 1 g of thallium sulphate with lower abdominal pain, nausea, and hyperaesthesia of the limbs. Thallium was detected in the urine (3 mg/L) and gastric aspirate (10.8 mg/L). She was started on intravenous fluids and soluble Prussian blue (5 g four times daily via duodenal tube with 50 mL of 15% mannitol). Over the next two days the abdominal and lower limb pain persisted, with drowsiness and vomiting. On the third day she became hypotensive with bilateral ptosis. Alopecia was also noted. Neurological signs and gastrointestinal symptoms began to improve 4 days later, but hair loss continued. She had severe constipation for the first 6 days despite laxative administration. By 11 days her symptoms improved; Prussian blue was discontinued after 20 days, by which time hair regrowth had started. Thallium concentrations fell dramatically over the first 2 days of admission, with a slower decline thereafter (see table). No faecal samples could be obtained until the 10th day after poisoning (hospital day 6) owing to the severe constipation. At this time 1.6 mg of thallium was detected in the 24 hour faeces and 1.93 mg in the urine. In 28 days of hospitalization approximately 5 mg of thallium was eliminated via the intestinal tract and 35 mg in the urine. Approximately 55 mg was eliminated in the saliva between days 9 and 26 after
poisoning. In total the quantity eliminated was thought to be <5% of the dose ingested. She was discharged asymptomatic at 28 days.

<table>
<thead>
<tr>
<th>No. days after poisoning</th>
<th>Urine (mg/day)</th>
<th>Faeces (mg/day)</th>
<th>Saliva (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>5.68*</td>
<td>Not determined</td>
<td>Not determined</td>
</tr>
<tr>
<td>5-6</td>
<td>4.54</td>
<td>Not determined</td>
<td>Not determined</td>
</tr>
<tr>
<td>7-9</td>
<td>2.26</td>
<td>Not determined</td>
<td>10.15</td>
</tr>
<tr>
<td>10-12</td>
<td>1.93</td>
<td>0.84</td>
<td>4.69</td>
</tr>
<tr>
<td>13-16</td>
<td>1.08</td>
<td>Not determined</td>
<td>2.03</td>
</tr>
<tr>
<td>17-22</td>
<td>0.27</td>
<td>0.41</td>
<td>0.38</td>
</tr>
<tr>
<td>23-26</td>
<td>0.25</td>
<td>0.02</td>
<td>0.18</td>
</tr>
</tbody>
</table>

*Value calculated on 14 hour urine (Richelmi et al., 1980).

Comment: In the above case study the patient’s response to Prussian blue was slow to manifest and this may possibly have been due to her constipation. A very small amount of thallium was excreted in the faeces, and in fact, a very small amount was excreted overall so possibly the patient may have improved anyway regardless of therapy.

The efficacies of different therapies were evaluated in 18 cases of thallium poisoning treated between 1971 and 1979 at the University Hospital of Utrecht, the Netherlands. Patients were treated with gastric lavage if ingestion had occurred within the preceding 48 hours and then given 10 g soluble Prussian blue with 100 ml 15% mannitol via a duodenal tube twice daily. Eight patients were also treated with forced diuresis. Furosemide was given only if necessary to prevent fluid overload. Sixteen patients survived and two patients with cardiovascular insufficiency died. The cases are summarized in the table below.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Amount of thallium ingested (mg) - from patient history</th>
<th>Time between thallium ingestion &amp; admission (days)</th>
<th>Thallium concentration in urine on admission (mg/L)</th>
<th>Treated with forced diuresis</th>
<th>Treated with haemoperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>F</td>
<td>21</td>
<td>500</td>
<td>28</td>
<td>2.1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>B³</td>
<td>F</td>
<td>22</td>
<td>2400</td>
<td>2</td>
<td>47.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C</td>
<td>F</td>
<td>21</td>
<td>350</td>
<td>1</td>
<td>8.8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>D</td>
<td>F</td>
<td>55</td>
<td>1000</td>
<td>4</td>
<td>20.2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>E</td>
<td>M</td>
<td>23</td>
<td>1000</td>
<td>2</td>
<td>71.1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F</td>
<td>M</td>
<td>28</td>
<td>480</td>
<td>½</td>
<td>1.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>G</td>
<td>F</td>
<td>19</td>
<td>unknown</td>
<td>2</td>
<td>2.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>H³</td>
<td>F</td>
<td>24</td>
<td>1000</td>
<td>1</td>
<td>84.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>I</td>
<td>F</td>
<td>32</td>
<td>1000</td>
<td>2 hours</td>
<td>40.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>J</td>
<td>M</td>
<td>45</td>
<td>unknown</td>
<td>?</td>
<td>3.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>K</td>
<td>M</td>
<td>50</td>
<td>750</td>
<td>4</td>
<td>24.6</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>L</td>
<td>M</td>
<td>26</td>
<td>875</td>
<td>1</td>
<td>54.0</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
1) Patient died after 4 days.

2) The patient survived this suicide attempt. Four months later she died within 6 hours after ingestion of an unknown amount of thallium.

3) These patients were admitted with hair loss of the head.

With soluble Prussian blue therapy, the mean half-life of thallium was $3.0 \pm 0.7$ days. When administration of Prussian blue was combined with forced diuresis, the mean half-life of thallium was $2.0 \pm 0.3$ days (van Kesteren et al., 1980).

An early report on the use of Prussian blue therapy in thallium poisoning reviewed 11 patients hospitalized between 1971 and 1973. There were three men (aged 30 to 44 years), six women (aged 24 to 64 years) and two children (both female, aged 2 and 6 years). Three patients received Prussian blue by duodenal tube ($2 \times 10$ g every two days, $2 \times 10$ g or $20$ g daily). The other nine patients received oral Prussian blue ($4 \times 5$ g daily in the adults, $4 \times 1$ g daily in the 6-year-old and $4 \times 1.7$ g daily in the 2-year-old). Four patients treated within 24 hours of ingestion of thallium did not develop any signs of toxicosis. Improvement also occurred in most of the other patients even though treatment was started late (between 9 and 151 days after exposure). Thallium elimination was primarily via the faeces. Although no adverse effects were attributed to the Prussian blue therapy, one patient developed constipation and had constantly high blood thallium concentrations during the first few weeks of treatment (Stevens et al., 1974).

A 26 year old female student, epileptic and treated with phenobarbital and phenytoin, ingested approximately $700$mg of thallium sulphate when she was in a depressed mood. She ingested half of the amount during the evening and the remainder the following morning. She was admitted to hospital twelve hours later and was at this stage asymptomatic. On the third day hyperaesthesia of the legs and feet developed and she had abdominal discomfort. The next day (day 4) she developed a prickly, burning sensation in the feet and pain in the legs and shoulders. No other neurological symptoms could be demonstrated. The pain subsided during the subsequent days and then a slight polyneuropathy was found. Hair loss began on the tenth day and progressed but was not extreme. After two weeks only traces of neurological damage could be demonstrated and this disappeared during the following weeks. No Mees’ lines were seen on the nails. On initial admission to hospital, no thallium was evident after gastric lavage but it was shown to be present pharmacologically. She was treated with Prussian blue $250$mg/kg body weight/day (given in 4 daily doses of $3.75$g) along with $15\%$ mannitol through a duodenal tube. Potassium chloride and activated charcoal were also given on the first two days. A multivitamin preparation was given intramuscularly 3 times a week and a fluid intake of 3-4 litres/day was prescribed. The decrease in urinary thallium concentration during the patient’s hospitalization is shown in the table below. Prussian blue was stopped on the 13th day when the amount of thallium in the urine was below $0.5$ mg/24hours.
A twenty two year-old alcoholic ingested approximately 700 mg of thallous sulphate in a suicide attempt. He was admitted to hospital 6 hours later with no complaints. Gastric lavage showed only a trace of thallium. He was treated with Prussian blue 250mg/kg body weight in 15% mannitol via duodenal tube in 4 doses a day. Fluid intake of 3-4 litres a day was prescribed. After 4 days slight paraesthesia and sensory impairment of the toes could be demonstrated, however this improved and disappeared during the next few days. Hair loss started after 2 weeks but was mild. Thallium excretion in the urine is shown in the table below. Prussian blue treatment was stopped after the 10th day results were known.

### Daily excretion of thallium in urine

<table>
<thead>
<tr>
<th>Hospitalization day</th>
<th>Daily excretion (mg/24 hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>3.3</td>
</tr>
<tr>
<td>3</td>
<td>3.4</td>
</tr>
<tr>
<td>5</td>
<td>1.8</td>
</tr>
<tr>
<td>10</td>
<td>0.2</td>
</tr>
</tbody>
</table>

(Van der Meerwe., 1972-Case study 2)

### Summary of Evaluation

#### 13.1 Indications

Prussian blue is indicated in the treatment of patients with known or suspected internal contamination with radioactive caesium, radioactive thallium and non-radioactive thallium, to increase their rates of elimination. Treatment should be started as soon as possible after exposure.

#### 13.1.1 Thallium

The recommendation for the use of Prussian blue in thallium poisoning is based on evidence derived from animal studies and limited clinical data from human poisoning in the form of case reports and case series.

In animals experimentally poisoned with thallium, Prussian blue has been shown significantly to reduce absorption of thallium, increase its elimination and reduce its concentration in the brain. Moreover, Prussian blue significantly lowered mortality in animals poisoned by this metal.

Uncontrolled case reports / series have generally been associated with a favourable outcome, although there are some cases where patients were slow to respond to treatment and some patients have been left with long-term sequelae. In many of these cases other treatments were given concurrently (e.g. activated charcoal) and it is therefore difficult to clearly determine the contribution of Prussian blue to the overall outcome.
identify the benefits of Prussian blue alone.

Soluble Prussian blue has been shown to more than halve the elimination half-life, when compared to historical controls, in a large series of thallium poisoned patients. Although such extensive clinical documentation is not available for insoluble Prussian blue, the overall evaluation is that insoluble Prussian blue is also effective.

13.1.2 Caesium

The recommendation to use Prussian blue in patients having ingested radioisotopes of caesium is based on its ability significantly to decrease absorption of, and increase the faecal excretion of, caesium in animals exposed to caesium-137. The body half-life was halved in the species tested and reduced content of caesium-134 in various organs was also documented. In healthy volunteers, insoluble Prussian blue more than halved the body half life of this radioisotope of caesium. The limited case studies available are consistent with the effect in healthy volunteers. There appears to be no data on the use of soluble Prussian blue in this situation.

13.2 Advised routes and dose

Prussian blue should only be given orally. The manufacturers of the pharmaceutical preparation recommend the following doses (Heyl data sheets Radiogardase and Antidotum Thallii-Heyl, 2004):

- **Adults**: In early-presenting cases when thallium or caesium may still remain in the gut an initial dose of 3g is suggested. In late-presenting cases when thallium or caesium have already been mostly absorbed, 3 to 20 g per day in divided doses should be given.

The individual dose should be based on the severity of exposure and clinical features.

- **Children 2 to 12 years**: 1 g orally 3 times a day.

The efficacy and dosing for the paediatric population of insoluble Prussian blue has been extrapolated from adult data and supported by paediatric patients who were internally contaminated with cesium-137 and treated with Prussian blue in the Goiânia incident. Paediatric patients aged 2-4 years are expected to have biliary and gastrointestinal function that is comparable with a 4-year old (Heyl, 2004).

- **Children less than 2 years**

The dosing regimen for children less than 2 years old has not been established although it has been used in this age group (Robb-Smith, 1987). Variations exist in the developmental maturity of the gastrointestinal and biliary systems of neonates and infants and the dose-related effects of Prussian blue on an immature gastrointestinal tract are unknown (Heyl, 2004).

**Administration**

The capsules of Prussian blue can be swallowed whole with liquid or if the patient is unable to swallow large numbers of capsules they can be opened and dispersed in bland food or fluid. A suspension of Prussian blue can also be administered via a stomach tube following gastric lavage.

In many patients with thallium poisoning mannitol (100 ml of 15% solution) has also been
given with each dose in an effort to prevent constipation. This may not work and other measure to prevent or treat constipation may need to be undertaken.

**End point of therapy**

The clinical end-point of Prussian blue therapy is generally considered to be when urinary thallium levels fall below 0.5mg/day (however this is clearly only a guide as most of the elimination will be faecal particularly in patients receiving Prussian blue therapy).

### 13.3 Other consequential or supportive therapy

#### 13.3.1 Caesium

Specialist advice should be sought for the management of radiation accidents. This may require a multidisciplinary approach with radiation protection and dosimetry professionals, and medical and nursing staff trained and experienced in managing victims of radiation exposure (Breitenstein, 2003).

It is essential to prevent further incorporation of any radioactive material. Additional measures include the administration of laxatives to enhance gastrointestinal transit, antacids for radionuclides that become colloid or insoluble in the gastrointestinal tract (and therefore less absorbable), nasal and/or lung lavage and decontamination of skin and wounds (Gerber & Thomas, 1992).

In preliminary studies based on animal data, co-administration of Prussian blue with other radioeliminators does not affect the efficacy of Prussian blue (Heyl, 2004; Kostail et al., 1983).

#### 13.3.2 Thallium poisoning

The treatment of thallium poisoning is primarily concerned with the prevention of absorption from the intestinal tract and enhanced elimination from the body.

Gastric lavage should be considered in patients who present early. As patients generally present to healthcare facilities many hours after exposure it is unlikely that lavage would be beneficial however gastric decontamination has been been undertaken as late as 48 hours after thallium ingestion in some previous cases (van Kesteren et al, 1980). Many patients will also have vomited spontaneously by the time they attend hospital so as with gastric lavage, emesis should be considered but may not be of any benefit. Enhanced elimination is often required in severe cases and haemodialysis (Barckow & Jenss, 1976; Pederson et al., 1977), forced diuresis (Nogué et al., 1972; Heath et al., 1983; de Groot & van Heijst, 1988; Malbrain et al., 1997) and charcoal haemoperfusion (de Groot et al., 1985; van Kesteren et al., 1980) have all been used in thallium-poisoned patients.

### 13.4 Controversial issues and areas of use where there is insufficient information to make recommendations

#### 13.4.1 Optimal form of Prussian blue

Uncertainty exists in the historical literature regarding which of the two forms of Prussian blue (soluble or insoluble) is most effective as an antidote for radiocaesium and thallium. Human case study data is limited and this combined with the lack of analogous animal data on Prussian blue use (for both thallium and radiocaesium), means that whether the physicochemical differences between soluble and insoluble Prussian blue have any effect on
outcomes in human poisoning is currently unknown. A relatively recent literature review by Thompson & Callen, (2004) highlights these controversies although they do conclude that there is sufficient evidence to state that insoluble Prussian blue is effective in radiocaesium toxicity but that data are inconclusive for thallium.

From a pragmatic point of view, however, preference should be given to insoluble Prussian blue as this is the only commercially available pharmaceutical preparation.

### 13.4.2 Optimal dosage regimen

The optimal dose of Prussian blue has not been established in clinical studies. The doses recommended by the manufacturer are empirical, reflecting the doses that have been used to treat cases of poisoning with thallium and radioactive caesium. In the case reports of poisoning with radioactive caesium the doses of Prussian blue used were smaller than those used for cases of thallium poisoning, typically 3g compared with 20g. Moreover, in one case series adults given doses of 3g, 6g and 10g per day showed very similar reductions in the half-life of caesium-137 (Lipsztein et al 1991). Since, however, the half-life of caesium-137 was also found to be influenced by patient body weight and body burden of caesium-137 interpretation of the impact of dosing is difficult.

In the case reports of poisoning with radioactive caesium, treatment was with insoluble Prussian blue, whereas for thallium poisoning treatment was often with the soluble form. Whether the form of Prussian blue has an impact on the effective dose for thallium poisoning is unknown.

Food may increase the effectiveness of insoluble Prussian blue by stimulating bile secretion and increasing enterohepatic circulation. The increase in enterohepatic circulation may increase the amount of caesium and thallium in the gastrointestinal lumen and hence increase the amounts available for binding with Prussian blue (Heyl, 2004).

### 13.5 Proposals for further studies

In their review Thompson & Callen (2004) concluded that further research is needed to determine the significance of any differences between the two forms of Prussian blue and whether their physicochemical differences have any effect on outcomes in human poisoning.

Studies of the effect of Prussian blue in exposures to other radioisotopes may be warranted, e.g. in the case of rubidium-86. Although animal experiments suggest that Prussian blue may reduce the whole body retention of rubidium-86, the use of Prussian blue in this situation should be considered controversial.

### 13.6 Adverse effects

Severe adverse effects have not been reported with Prussian blue (Hoffman, 2003). Mild to moderate constipation may occur which can be managed with a high fibre diet or bulk laxatives. In 46 patients involved in the Goiânia incident treated with Prussian blue, 10 developed constipation (Farina & Brandão-Mello, 1991). It is essential to monitor for and treat constipation because elimination of thallium and caesium are dependent on the transit and elimination of Prussian blue from the gut. Faeces will be coloured blue and blue sweat and tears have been reported with prolonged administration, however this effect appears to be benign and transient (Hoffman, 2003). If capsules are opened and mixed with food or fluid, the teeth and mouth may be discoloured blue (Heyl, 2004).
Hypokalaemia is a potential risk as Prussian blue can bind potassium, however no significant variations in serum potassium concentrations have been reported, even when large doses have been given (IAEA, 1988). In 46 patients involved in the Goiânia incident treated with Prussian blue there were only 3 cases of hypokalaemia (2.5 to 2.9 mmol/L) without clinical complications. Oral and intravenous potassium supplements resulted in prompt correction of hypokalaemia (Farina & Brandão-Mello, 1991).

Cyanide toxicity has not been reported from oral dosing with Prussian blue.

13.7 Restrictions for use
None known. Prussian blue has been used in the treatment of thallium poisoning in pregnancy (Hoffman, 2000).

14. Model Information Sheet

14.1 Uses
Prussian blue (soluble or insoluble) is indicated

• for antidotal therapy in acute or chronic thallium poisoning,
• in the case of incorporation of radioisotopes of caesium (caesium-134, caesium-137),

14.2 Dosage and route
Prussian blue is available as Radiogardase®-Cs (Radiogardase® in the United States of America) and Antidotum Thallii-Heyl® distributed by Heyl Chemisch-pharmazeutische Fabrik GmbH, Berlin, Germany. Both products are available in bottles of 30 hard gelatine capsules, each containing 0.5 g of insoluble Prussian blue.

Prussian blue should only be given orally.

Adults and adolescents see comments above
The recommended dose of Prussian blue is 3g orally three times/day

When the dose of radioactivity is substantially decreased the dose may be reduced to 1 or 2g three times/day to improve gastrointestinal tolerance

Paediatric dose (2-12 years)
The recommended dose of Prussian blue is 1g orally 3 times/day

Neonates and infants
Dose has not been established

In patients who cannot tolerate swallowing large numbers of capsules, the capsules may be mixed with bland food or liquids (this may result in blue discoloration of mouth and teeth).

Radiocaesium contamination: Treatment should be initiated as soon as possible after contamination is expected. Treatment should continue for a minimum of 30 days and then the patient should be reassessed for the amount of whole body radioactivity. The duration of
treatment after exposure will be dictated by the level of contamination.

1790

Thallium contamination: Ideally treatment should be initiated as soon as possible after exposure however Prussian blue is still thought to be effective after a delay in starting treatment and should not be withheld.

1794

14.3 Precautions/contraindications

1796

As the antidotal effect of Prussian blue is due to the binding of thallium or caesium in the gut, it is only effective if the motility of the intestines is intact. In patients in coma or needing sedation, with reduced intestinal motility, medications to increase intestinal motility should be considered, although they are not proven effective in this setting.

1809

Prussian blue decreases the duration of radiation exposure but does not treat the complications of radiation exposure. Supportive treatment for radiation toxicity symptoms should be given concomitantly with Prussian blue treatment.

1819

In radiological emergencies the type of elemental exposure may not be known, Prussian blue may not bind to all the radioactive components and these elements may not undergo enterohepatic circulation which is necessary for Prussian blue binding and elimination. Thus patients contaminated with unknown or multiple radioactive elements may require additional treatments.

1838

In severe thallium poisoning additional means for enhancing elimination should be considered; both charcoal haemoperfusion and haemodialysis have been used, although there are limited data to suggest that they have an impact on outcome.

1842

14.4 Pharmaceutical incompatibilities and drug interactions

1816

Prussian blue may bind oral drugs. When given together with oral tetracycline it is anecdotally reported to decrease the bioavailability of tetracycline.

1823

Prussian blue may bind electrolytes in the gastrointestinal tract and asymptomatic hypokalaemia has occasionally been reported with its use.

1829

14.5 Adverse effects

1823

Prussian blue is well tolerated; death or serious adverse effects have not been reported with Prussian blue. Mild to moderate constipation may occur which can be managed with a high fibre diet or bulk laxatives. It is essential to treat constipation as it will decrease elimination of thallium and caesium. Faeces will be coloured blue and blue sweat and tears have been reported with prolonged administration.

1835

14.6 Use in pregnancy and lactation

1830

No contraindications. Prussian blue has been used in pregnant women and since it is not absorbed from the gastro-intestinal tract, effects on the fetus are not expected. The risk of toxicity from untreated radioactive caesium or thallium exposure is expected to be greater than the risk of reproductive toxicity from Prussian blue.

1838

Prussian blue is unlikely to be excreted in breast milk as it is not significantly absorbed from the gastrointestinal tract, however, women with thallium toxicosis or exposure to radiocaesium should not breast feed due the risks to the baby from these elements.
14.7 Storage

The pharmaceutical products of Prussian blue should be stored in the dark at 25 °C; occasional variations of temperature within the range 15 to 30 °C are permitted (Heyl, 2004).

15. References


Bozorgzadéh A (1971) [Decorporation of radiocaesium by various hexacyanoferrates (II)] (German). Strahlentherapie, 142(6): 734-738.


Dvořák P, Günther M, Zorn U & Catsch A (1971) [Metabolic behaviour of colloidal ferrihexacyanoferrate (II)] (German). Naunyn Schmiedebergs Arch Pharmakol, 269(1): 48-56


1945 Forth W (1986) [How useful is administration of colloidal Berlin blue for the decontamination of radio-caesium?] (German). Klin Wochenschr, 64(17): 810-812.


1987 Havlíček F, Kleisner I, Dvořák P & Pospisil J (1967) [Effects of cyanoferrates on the

Heath A, Ahlmén J, Branegård B, Lindstedt S & Wickström I (1983) Thallium poisoning -

Pharmacol, 6(3): 340-344.

www.heytex.com site accessed October 08


Lewin NA, Hoffman RS, Nelson LS (eds). Goldfrank’s Toxicologic Emergencies, 8th

Hoffman RS (2003) Thallium toxicity and the role of Prussian Blue in therapy. Toxicol Rev,


Vienna.

Ioannides KG, Mantzios AS & Pappas CP (1991) Influence of Prussian blue in reducing

IPCS (1990) Poisons Information Monograph 525: Thallium. Available at
http://www.inchem.org/documents/pims/chemical/pim525.htm

Jax W, Grabensee B & Schröder E (1973) [Treatment of thallium poisoning] (German). Med
Welt, 24(17): 691-693.


Kamerbeek HH, Rauws AG, ten Ham M & Van Heijst ANP (1971) Prussian blue in therapy
of thallotoxicosis An experimental and clinical investigation. Acta Med Scand, 189: 321-
324.

Kargačin B & Kostial K (1985) Reduction of $^{85}$Sr, $^{137}$Cs, $^{131}$I and $^{141}$Ce retention in rats by
simultaneous oral administration of calcium alginate, ferrihexacyanoferrate (II), KI and Zn-
DTPA. Health Phys, 49: 859-864.

Keggin JF & Miles FD (1936) Structures and formulae of the prussian blues and related

Kemper FH (1979) [Thallium poisoning] (German). Münch Med Wochenschr, 121(42):


16. Author(s) Name, Address

Initial draft by ANP van Heijst, A von Dijk & J Ruprecht.

Update and revision by Maev McParland, Paul Dargan, London

November 2009

17. Additional Information

Table 1: Results of EMBASE search 4th November 2009

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<td>Thallium</td>
<td>7299</td>
</tr>
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<td>3</td>
<td>Caesium</td>
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<td>Caesium</td>
<td>2718</td>
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<td>Radiocesium</td>
<td>392</td>
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<tr>
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<td>11</td>
<td>1 AND 5</td>
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<td>Rubidium</td>
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<td>Caesium</td>
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<tr>
<td>4</td>
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Results of Cochrane Library Search 4th November 2009

No results found for Prussian blue using all possible MeSH terms.
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<th>Case reports</th>
<th>Animal studies</th>
</tr>
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<tbody>
<tr>
<td>Radiocaesium</td>
<td>No controlled trials</td>
<td>Prussian blue treatment reduced the half-life of caesium in 5 patients accidentally exposed to $^{137}$Cs (Ma et al., 1985)</td>
<td>Administration of a single dose of radiocaesium and concomitant oral dosing of Prussian blue resulted in reduction of caesium-uptake from the gastrointestinal tract (Brenot &amp; Rinaldi, 1967; Dresow et al., 1990, 1993; Giese &amp; Hantzch, 1970; Nielsen et al., 1988b; Nigrović, 1963; Nigrovčić, 1965).</td>
</tr>
<tr>
<td></td>
<td>Volunteer studies: 3 g daily of Prussian blue given before $^{137}$Cs did not reduce caesium absorption. The increase in $^{137}$Cs excretion was small following 0.5 g of Prussian blue three times daily (Madshus &amp; Strömme, 1968). In 6 volunteers it was shown that Prussian blue (4 x 0.5 g or 10 x 0.2 g daily for 2-3 weeks) did not fully block caesium uptake from contaminated food (Volf et al., 1987). Both forms of Prussian blue were equally effective in reducing radiocaesium absorption in 2 male volunteers who ingested meals labelled with a tracer dose of $^{134}$Cs, 10 minutes after ingestion of 1 g of Prussian blue (Dresow et al., 1993).</td>
<td><strong>Goiânia incident</strong> Of 249 people contaminated with $^{137}$Cs, 46 were treated with Prussian blue and this significantly increased the rate of faecal excretion and reduced the whole body burden retention of caesium (IAEA, 1988). In 15 of these patients the body burden of $^{137}$Cs was reduced by an average of 71% within 2 months of the exposure (Melo et al, 1994). Comparing the elimination of $^{137}$Cs from the bodies of 18 adults after varying regimens of Prussian blue therapy, Lipsztein et al (1991) found that overall the half-life of $^{137}$Cs was reduced by 32% and higher dose rates of Prussian blue gave a greater reduction. <strong>Chernobyl incident</strong> Fifteen students were exposed to Administration of a single dose of radiocaesium and concomitant oral dosing of Prussian blue resulted in reduction of caesium-uptake from the gastrointestinal tract (Brenot &amp; Rinaldi, 1967; Dresow et al., 1990, 1993; Giese &amp; Hantzch, 1970; Nielsen et al., 1988b; Nigrović, 1963; Nigrovčić, 1965).</td>
<td>The biological half-life was reduced (Madshus et al., 1966; Nigrović et al., 1966; Havliček et al., 1967; Havliček, 1968; Müller et al., 1974; Richmond, 1968; Strömme, 1968). The reduced whole-body retention of caesium after treatment with Prussian blue was seen in individual organs: muscle, bone, carcass, liver and kidney (Bozorgzadéh, 1971; Bozorgzadéh &amp; Catsch, 1972; Brenot &amp; Rinaldi, 1967; Kostial et al., 1983; Müller et al., 1974; Strömme, 1968).</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Metal</th>
<th>Clinical trial data</th>
<th>Case reports</th>
<th>Animal studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In volunteer studies with 2 male adults, the ingestion of Prussian blue ten minutes before eating a meal containing $^{134}$Cs reduced the caesium absorption more than the simultaneous administration of Prussian blue along with the labelled test meal. Administration of Prussian blue prior to the meal reduced absorption of the radiocaesium to 3-10% of the ingested dose whereas simultaneous ingestion of Prussian blue and the test meal only reduced absorption to 38-63% (Nielsen et al., 1991). In volunteer studies involving self-dosing by the study authors, ingestion of Prussian blue 180 days after ingestion of $^{137}$Cs reduced the biological half-life of caesium from the pre-treatment values of 110 and 115 days to 40 days (Madshus et al., 1966). In five cases where Prussian blue was given several months after caesium ingestion the</td>
<td>$^{134}$Cs and $^{137}$Cs following the Chernobyl accident. In 3 volunteers the biological half-life of caesium ranged from 42 to 71 days. Insoluble Prussian blue was given from day 114 to 145 post-exposure and this was reported to reduce the half-life of caesium and enhance elimination (Tang et al., 1988).</td>
<td>Stather, 1972; Wolsieffer et al., 1969). In piglets soluble and insoluble Prussian blue reduced the uptake of $^{134}$Cs by more than 97% (Nielsen et al., 1988b). Prussian blue reduces the body content of $^{137}$Cs fed chronically to rats (Stather, 1972)</td>
</tr>
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<td>Clinical trial data</td>
<td>Case reports</td>
<td>Animal studies</td>
</tr>
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<tr>
<td></td>
<td>biological half-life of caesium was reduced on average to one third of its original half-life (Madshus &amp; Strömme, 1968; Strömme, 1968).</td>
<td>A 37-year-old male was given oral $^{137}\text{Cs}$ followed by Prussian blue. The biological half-life of caesium was reduced from 140 days to approximately 50 days (Richmond, 1968).</td>
<td></td>
</tr>
<tr>
<td>Non-radiocaesium</td>
<td>No controlled clinical trials</td>
<td>Prussian blue therapy has been reported to reduce the half-life of non-radioactive caesium in two separate case reports (Chan et al, 2009; Thurgar et al, 2009).</td>
<td></td>
</tr>
<tr>
<td>Rubidium</td>
<td>No human data</td>
<td>No Human data</td>
<td>Prussian blue reduced the biological half-time of retention of Rubidium-86 in rats (Stather, 1972)</td>
</tr>
<tr>
<td>Thallium</td>
<td>No volunteer studies. Bhardwaj et al, 2006 (thallium-201) studied the effect of Prussian blue in 2 patients following $^{201}\text{Tl}$ myocardial scintigraphy. In patient-1 whole body radioactivity was reduced by 18 and 30% after 24 and 48 hours.</td>
<td>A total of 30 published reports of thallium poisoning treated with Prussian blue were found, involving 144 cases. These reports varied in terms of amount of detail provided on treatment. In addition there were a number of other variables that makes comparison difficult. These reports were also used to increase the understanding of the effects of Prussian blue on thallium.</td>
<td>Concomitant oral administration of thallium and of Prussian blue in rats resulted in a lower uptake of the metal and lower concentrations found in organs (Dvořák, 1969; Heydlauf, 1969; Rauws, 1974). Reduced retention and increased...</td>
</tr>
<tr>
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<td>Animal studies</td>
</tr>
<tr>
<td>-------</td>
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</tr>
<tr>
<td></td>
<td>hours, respectively, of oral Prussian blue therapy. Patient-2 developed constipation and did not pass any stools after oral Prussian blue for 48 hours. The whole body radiation counts were similar to those when Prussian blue was not given but there was a concentration of radioactivity in the colon suggesting that the radioactivity was unavailable for resorption. Van Kesteren, (1980) retrospectively assessed the efficacy of different therapies used in conjunction with Prussian blue for thallium poisoning in 18 patients. Two patients died, and for the other 16 mean half-life of thallium was 3.0 ± 0.7 days whilst when Prussian blue was combined with forced diuresis this was reduced to 2.0± 0.3 days Kamerbeek et al, (1971) are credited with the first use of Prussian blue in thallium</td>
<td>reports are tabulated below. There are single case reports: (Atsmon, 2000; Chandler 1990; DeBacker, 1982; Fred &amp; Accad, 1997; Hologittas et al, 1980; Malbrain et al; Niehues et al 1995; Pau, 2000; Pedersen et al 1978; Richelmi, 1980; Rob-Smith, 1987; Schwartz et al 1988; Stevens 1978; Villa et al, 2009; Vrij, 1995; Wainwright, 1988; and multiple case reports: (CDC, 2008; Diaz et al 1990; Ghezzi et al, 1979; Kamerbeek et al 1971; Meggs et al 1994; Moore et al 1993; Pai, 1987; Pelcova et al 2009; Rangel-Guerra et al 1990; Stevens, 1974; Van Kesteren, 1980; Villanueva, 1990) The extent and source of thallium exposure is often unknown, diagnosis delayed and hence a delay in starting Prussian blue therapy. Therapy was started within 24 hours in only 14 of the above reports (see case summary table below). In other cases there</td>
<td>excretion of thallium by Prussian blue results in a decrease of the thallium content in liver, kidney, skeleton, blood, heart and muscles (Dvořák, 1969; Günther, 1971; Heydlauf, 1969; Kravzov et al., 1993; Manninen et al., 1976; Rauws, 1974; Rios et al., 1991; Rios &amp; Monroy-Noyola, 1992; Sabbioni et al., 1982). Rios &amp; Monroy-Noyola (1992) demonstrated that Prussian blue increased LD₅₀ of thallium by 31%. Meggs et al (1997) found that Prussian blue decreased the mortality from thallium poisoning in mice In an evaluation of the effect of Prussian blue in thallium-fed rats Lehman &amp; Favari (1985) observed that whilst the control group eliminated only 53% of the administered thallium dose over the study period, the rats that received Prussian blue</td>
</tr>
<tr>
<td><strong>Metal</strong></td>
<td><strong>Clinical trial data</strong></td>
<td><strong>Case reports</strong></td>
<td><strong>Animal studies</strong></td>
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</tr>
<tr>
<td></td>
<td>poisoning, demonstrating an approximately 7-fold increase in faecal elimination with its use. A reduction in thallium half-life was observed in thallium poisoned patients when compared with no therapy at all (De Groot &amp; van Heijst, 1988)</td>
<td>were varying delays: Villa et al, (2009) - 42 days; CDC, (2008) - 8 days; Atsmon, (2000) -10-11 weeks; Pau, (2000) - 6 weeks; Vrij, (1995)&gt; 4 months; Chandler (1990) - 35 days; Villanueva, (1990) &gt; 2 weeks; Wainwright, (1988) approx. 5 days; Pai, (1987) - 4 to 7 days; Rob-Smith, (1987) - 5 days. Dosing patterns for Prussian blue varied from case to case (amount given and duration of treatment) as did use of concomitant therapy. From the limited case studies Prussian blue appears to be well tolerated and reported to be effective in enhancing the excretion of thallium. Constipation is reported in earlier case studies (Wainwright, 1988; Richelmi, 1980), less so in later cases however many have given mannitol along with the Prussian blue.</td>
<td>eliminated 82% of the dose. Kamerbeek, (Kamerbeek, 1971; Kamerbeek et al., 1971) showed that after four days of Prussian blue 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 and a dose dependent relationship was determined. (Günther, 1971) demonstrated that soluble Prussian blue increased excretion of thallium in rats and reduced the LD$_{50}$ however only if started within 24 hours of exposure.</td>
</tr>
<tr>
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<td>Thallium level on presentation</td>
</tr>
<tr>
<td>------------------------</td>
<td>----------</td>
<td>-----------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Villa et al 2009</td>
<td>1</td>
<td>NK</td>
<td>Urine: 5118 µg/g creatinine</td>
</tr>
<tr>
<td>Atsmon et al 2000</td>
<td>1</td>
<td>NK</td>
<td>Renal excretion 7mg/24 hours</td>
</tr>
<tr>
<td>Pau, 2000</td>
<td>1</td>
<td>Urine at 35d: 8.56 µmol/L (NR = 0.003 µmol/L) Blood at 42d: 0.15 µmol/L (NR &lt;0.07 µmol/L)</td>
<td>~42 days</td>
</tr>
<tr>
<td>Vrij et al 1995</td>
<td>1</td>
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<td>Urine (24 hr): 4300 µg/L (NR &lt;10 µg/L) Blood: 300 µg/L (NR &lt;10 µg/L)</td>
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<td>Malbrain et al 1997</td>
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<td>8.75g thallium sulphate</td>
<td>Urine: 69,600 µg/L Blood: 5,240 µg/L</td>
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<tr>
<td>al 1988</td>
<td></td>
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<td>Blood 5750 µg/L</td>
</tr>
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<td>Robb-Smith 1987</td>
<td>1 (21 mth child)</td>
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<td>?</td>
</tr>
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<td>100 mg thallium sulphate</td>
<td>Blood: 415 µg/L</td>
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<td>1 (2 admissions)</td>
<td>NK</td>
<td>Urine: 9000 µg/L 2nd adm.: 3700 µg/L</td>
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<td>Nogue et al</td>
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<td>750 mg thallium</td>
<td>Blood: 950 µg/L</td>
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<td>Thallium level on presentation</td>
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<tr>
<td>1982</td>
<td></td>
<td>sulphate</td>
<td>(approx)</td>
</tr>
<tr>
<td>Pedersen et al 1978</td>
<td>1</td>
<td>2g</td>
<td>?</td>
</tr>
<tr>
<td>CDC 2008</td>
<td>10 (5 children)</td>
<td>NK</td>
<td>Blood: 289 µg/L (median); range 53 - 1408 µg/L Urine (24hr): 3063 µg/L (median); range 542 - 12556 µg/L</td>
</tr>
<tr>
<td>De Groot et al 1985</td>
<td>Case 1</td>
<td>NK</td>
<td>Blood 2800 µg/L</td>
</tr>
<tr>
<td></td>
<td>Case 2</td>
<td>NK</td>
<td>Blood 5800 µg/L</td>
</tr>
<tr>
<td></td>
<td>Case 3</td>
<td>NK</td>
<td>Blood 1900 µg/L</td>
</tr>
<tr>
<td>Diaz et al 1990</td>
<td>Case 1</td>
<td>NK</td>
<td>Urine: 11400 µg/L</td>
</tr>
<tr>
<td></td>
<td>Case 2</td>
<td>NK</td>
<td>Urine: 6300 µg/L</td>
</tr>
<tr>
<td>Author</td>
<td>No cases</td>
<td>Amount thallium</td>
<td>Thallium level on presentation</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>----------</td>
<td>-----------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>Case 3</td>
<td>NK</td>
<td>Urine: 3500 µg/L</td>
<td>7 days</td>
</tr>
<tr>
<td>Case 4</td>
<td>15 mg</td>
<td>Urine: 3090 µg/L</td>
<td>15 days</td>
</tr>
<tr>
<td>Villanueva et al 1990</td>
<td>4 (2 children)</td>
<td>NK</td>
<td>10yr old: 18400 µg/L</td>
</tr>
<tr>
<td>Van der Merwe 1972</td>
<td>1 adult</td>
<td>NK</td>
<td>2400 µg/L</td>
</tr>
<tr>
<td>Case 1</td>
<td>700 mg thallium sulphate</td>
<td>12 hrs</td>
<td>?</td>
</tr>
<tr>
<td>Case 2</td>
<td>700 mg thallium sulphate</td>
<td>&gt;6 hours</td>
<td>?</td>
</tr>
<tr>
<td>Pai 1987</td>
<td>14 Case 1</td>
<td>NK</td>
<td>Urine 2200 µg/mL (sic) Blood 16 µg/mL (sic)</td>
</tr>
<tr>
<td>Case 2</td>
<td></td>
<td>Urine 48 µg/mL</td>
<td></td>
</tr>
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<td>Amount thallium</td>
<td>Thallium level on presentation</td>
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<tr>
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<td>----------</td>
<td>-----------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(sic)</td>
</tr>
<tr>
<td>Case 3</td>
<td></td>
<td></td>
<td>Blood 4 µg/mL (sic)</td>
</tr>
<tr>
<td>Case 4</td>
<td></td>
<td></td>
<td>Urine 250 µg/mL (sic)</td>
</tr>
<tr>
<td>Case 5</td>
<td></td>
<td></td>
<td>Urine 250 µg/mL (sic)</td>
</tr>
<tr>
<td>Case 6</td>
<td></td>
<td></td>
<td>Urine 660 µg/mL (sic)</td>
</tr>
<tr>
<td>Case 7</td>
<td></td>
<td></td>
<td>Blood 6 µg/mL (sic)</td>
</tr>
<tr>
<td>Case 8</td>
<td></td>
<td></td>
<td>(sic)</td>
</tr>
<tr>
<td>Case 9</td>
<td></td>
<td></td>
<td>Blood 4 µg/mL (sic)</td>
</tr>
<tr>
<td>Van Kesteren et al 1980</td>
<td>18 (details below):</td>
<td>Urine concentration (mg/L)</td>
<td>Colloidal soluble</td>
</tr>
<tr>
<td>A</td>
<td>500 mg</td>
<td>2.1</td>
<td>28 days</td>
</tr>
<tr>
<td>B</td>
<td>2.4 g</td>
<td>47.4</td>
<td>2 days</td>
</tr>
<tr>
<td>C</td>
<td>350 mg</td>
<td>8.8</td>
<td>1 day</td>
</tr>
<tr>
<td>D</td>
<td>1 g</td>
<td>20.2</td>
<td>4 days</td>
</tr>
<tr>
<td>E</td>
<td>1 g</td>
<td>71.1</td>
<td>2 days</td>
</tr>
<tr>
<td>Author</td>
<td>No cases</td>
<td>Amount thallium</td>
<td>Thallium level on presentation</td>
</tr>
<tr>
<td>----------</td>
<td>----------</td>
<td>-----------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>F</td>
<td>480 mg</td>
<td>1.0</td>
<td>½ day</td>
</tr>
<tr>
<td>G</td>
<td>unknown</td>
<td>2.0</td>
<td>2 days</td>
</tr>
<tr>
<td>H</td>
<td>1 g</td>
<td>84.0</td>
<td>1 days</td>
</tr>
<tr>
<td>I</td>
<td>1 g</td>
<td>40.0</td>
<td>2 hours</td>
</tr>
<tr>
<td>J</td>
<td>unknown</td>
<td>3.0</td>
<td>?</td>
</tr>
<tr>
<td>K</td>
<td>750 mg</td>
<td>24.6</td>
<td>4 days</td>
</tr>
<tr>
<td>L</td>
<td>875 mg</td>
<td>54.0</td>
<td>1 day</td>
</tr>
<tr>
<td>M</td>
<td>1.5 g</td>
<td>79.8</td>
<td>14 days</td>
</tr>
<tr>
<td>N</td>
<td>1.5 g</td>
<td>80.0</td>
<td>1 day</td>
</tr>
<tr>
<td>O</td>
<td>unknown</td>
<td>8.0</td>
<td>?</td>
</tr>
<tr>
<td>P</td>
<td>unknown</td>
<td>10.0</td>
<td>?</td>
</tr>
<tr>
<td>Q</td>
<td>unknown</td>
<td>2.2</td>
<td>2 days</td>
</tr>
<tr>
<td>R</td>
<td>3 g</td>
<td>50.0</td>
<td>1</td>
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<tr>
<td>Stevens et al 1974</td>
<td>Case 1</td>
<td>NK</td>
<td>Urine 1430 µg/L</td>
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<td>Case 2</td>
<td>1000mg</td>
<td>Not stated</td>
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<td>Case 3</td>
<td>NK</td>
<td>Urine: 7100 µg/L</td>
</tr>
<tr>
<td>Author</td>
<td>No cases</td>
<td>Amount thallium</td>
<td>Thallium level on presentation</td>
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<td>----------</td>
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<td>---------------------------------</td>
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<tr>
<td>Case 4</td>
<td>300 mg</td>
<td>Urine elimination 3220 µg/24 hrs</td>
<td>10 hours</td>
</tr>
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<td>Case 5</td>
<td>NK</td>
<td>Urine elimination 120 µg/24 hrs</td>
<td>94 days</td>
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<td>Case 6</td>
<td>NK</td>
<td>Urine 570 µg/L</td>
<td>28 days</td>
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<td>Case 7</td>
<td>NK</td>
<td>Urine 232 µg/L 2nd admission: urine 230 µg/L</td>
<td>62 days</td>
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<td>Case 8</td>
<td>NK</td>
<td>Not stated</td>
<td>151 days</td>
</tr>
<tr>
<td>Case 9</td>
<td>300 mg</td>
<td>Urine elimination 2310 µg/24 hrs</td>
<td>2 hours</td>
</tr>
<tr>
<td>Case 10 (child 6yrs)</td>
<td>225 mg</td>
<td>Urine elimination 840 µg/24 hrs</td>
<td>9 days</td>
</tr>
<tr>
<td>Case 11 (child 2yrs)</td>
<td>NK</td>
<td>Urine elimination 180 µg/24 hrs</td>
<td>1 day</td>
</tr>
<tr>
<td>Kamerbeek et</td>
<td>Case 1</td>
<td>400 mg</td>
<td>Not stated</td>
</tr>
<tr>
<td>Author</td>
<td>No cases</td>
<td>Amount thallium</td>
<td>Thallium level on presentation</td>
</tr>
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<td>-------------------</td>
<td>----------</td>
<td>-----------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>al 1971</td>
<td></td>
<td></td>
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<tr>
<td>Case 2</td>
<td>400 mg</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>Case 3</td>
<td>2000 mg</td>
<td>Not stated</td>
<td>14 days</td>
</tr>
<tr>
<td>Meggs et al 1994</td>
<td>4</td>
<td>NK</td>
<td>Urine: 10837 µg/L and 9569 µg/L</td>
</tr>
<tr>
<td>Moore et al 1993</td>
<td>2</td>
<td>NK</td>
<td>Blood: 600 µg/L (approx)</td>
</tr>
<tr>
<td>Pelclova et al 2009</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Case 1</td>
<td>NK</td>
<td>Urine: 8.5 µg/L</td>
<td>NK - had probably been poisoned several times over 2 years</td>
</tr>
<tr>
<td>Case 2</td>
<td>NK</td>
<td>Urine: 2800 µg/L Blood: 770 µg/L</td>
<td>4 weeks approx</td>
</tr>
<tr>
<td>Rangel-Guerra et al 1990</td>
<td>50</td>
<td>NK</td>
<td>Ranges: Urine 100 - 28000 µg/L Blood: 100 - 1360 µg/L</td>
</tr>
<tr>
<td>Case 1</td>
<td>NK</td>
<td>Urine: 420 µg/L</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Case 2 (neonate from Case 1)</td>
<td></td>
<td>Urine: 60 µg/L</td>
<td>14 days</td>
</tr>
<tr>
<td>Author</td>
<td>No cases</td>
<td>Amount thallium</td>
<td>Thallium level on presentation</td>
</tr>
<tr>
<td>--------</td>
<td>----------</td>
<td>------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Case 45</td>
<td>NK</td>
<td>Urine: 950 µg/L</td>
<td>2 months</td>
</tr>
</tbody>
</table>