Piratome sheet #2: Prussian blue

! Key points not to forget

→ The 1st emergency measures are:
- extraction of victims from the hazard area;
- treatment of medical-surgical emergencies, that always takes precedence over the treatment of contamination and/or of irradiation, under all circumstances of exposure to nuclear and radiological agents;
- protection of victims' airways by FFP3 or, failing this, by any other device, even minimalist, with decontamination including unclothing (if possible preceded by spraying with water), followed by a shower.

→ Antidote treatment pertains to internal contamination (neither external contamination nor irradiation) These are chelating agents used to limit radionuclide distribution and, consequently, its short and long-term radiological effects. The chelator's efficacy is determined by the chemical element and is independent of its radioactivity.

→ In the event of internal contamination, there are generally no immediate clinical symptoms, except in cases of particularly high levels of radioactivity. Antidote treatment is initiated on strong presumption of internal contamination, as early as possible and based on measures taken on-site (within 2 hours of contamination) in order to minimize distribution to accumulation organs and without waiting for identification by assay (see Piratome sheet no. 1 for samples to be collected rapidly).

→ Medium or long-term chemical toxicity may exist alongside radiological toxicity for certain radionuclides, depending on their physicochemical form [e.g.: thallium and neurotoxicity] and that should be taken into consideration in therapeutic treatment.

→ In France, Prussian blue does not possess a marketing authorisation (MA). There is thus no national Summary of Product Characteristics for this antidote available for reference.

→ For additional information concerning the risk, assistance with patient treatment and follow-up, we recommend contacting the competent authority in radionuclear safety.

Afssaps / DEMEB / SURBUM / Toxicology Dept / Clinical Toxicology Unit - **Tel. Secr.:** +33 1 55 87 34 75.
143/147, bd Anatole France - F-93285 Saint-Denis cedex - Tel. +33 1 55 87 30 00 - **www.afssaps.sante.fr**

1. List of concerned radionuclides & physicochemical properties of interest for treatment.

In the table presents

. T is the radioactive half-life and $\mathbf{T_{eff}}$ is the effective half-life

. The risk is assessed on a scale of 1 to 5: All radionuclides possess an exemption threshold expressed in total activity (Bq) or in specific activity ($Bq.g^{-1}$). This threshold corresponds to the value beyond which any intent to hold, handle or transport this radionuclide must be declared in writing to the competent authorities. Thus, this value can be used to draw up a risk scale as follows:

Risk no.	Risk	Exemption threshold (Bq)
1	Very high	ET < 10^4
2	High	ET = 10^5
3	Moderate	ET = 10^6
4	Low	ET = 10^7
5	Very low	ET > 10^8

. Concerning accumulation organs: This data is given for the 2 main routes (inhalation and ingestion) and corresponds to the exposed organ with the greatest contribution to the effective dose. Indeed, metabolic and dosimetric models allow the determination of equivalent doses present in the various organs, then, after weighting these doses by the tissue weighting factor, they are added to obtain the effective dose present in the entire body. Moreover, it is possible to specify the organ with the greatest contribution to the effective dose.
It should be noted that organ-weighted doses and the effective dose are determined by the route of ingress into the body (inhalation or ingestion), by the methods of transfer within the body and by the compounds physicochemical form (R: rapid, M: moderate or S: slow), along with the particle size (1 µm or 5 µm) for inhalation.
Thus, the effective dose is determined by the combination of parameters and the organ with the greatest contribution to this effective dose and may differ according to the value of these parameters. When this is the case, for each organ, the physicochemical form of the compound for ingestion, the mode of transfer (R, M or S) and, where applicable, its particle size for inhalation, are specified. When a parameter is not specified, then the organ is the same, whatever this parameter's value.

. The potential efficacy of chelating agents with respect to the elements is ranked, according to levels of scientific efficacy evidence based on data available in the scientific literature, as follows:

- Evidence level I - Chemical chelation: complex stability, affinity constant.
- Evidence level II - Efficacy in animals: elimination kinetics, effective dose.
- Evidence level III - Efficacy in humans: elimination kinetics, effective dose.

These evidence levels are provided for information purposes, without prejudice to the granting of an MA and **must be balanced against the chelating agent's tolerance profile.**
It should be noted that Prussian blue does not possess an MA in France.

Radionuclides	**General characteristics**	**Accumulation organs** (R: rapid; M: moderate and S: slow)	**Levels of scientific evidence of efficacy**
Cesium 137 (^{137}Cs)	Risk 1 β^- and γ emitter T = 30.1 years / Teff = 109 d	Inhalation: Upper respiratory tract (R) Ingestion: colon	**III**
Cesium 134 (^{134}Cs)	Risk 1 β^- and γ emitter T = 2.07 years / Teff = 96 d	Inhalation: Upper respiratory tract (R) Ingestion: Soft tissues	**III**
Indium 111 (^{111}In)	Risk 3 γ emitter T = 2.80 d / Teff = 2.80 d	Inhalation: Upper respiratory tract (R, M) Ingestion: colon	**I**
Indium 115m (^{115m}In)	Risk 2 e^- and γ emitter T = 14.5 h / Teff = 4.5 h	Inhalation: Upper respiratory tract (R, M) Ingestion: colon	**I**

Radionuclides	General characteristics	Accumulation organs (R: rapid; M: moderate and S: slow)	Levels of scientific evidence of efficacy
Rubidium 84 (^{84}Rb)	Risk 3 β^- and γ emitter T = 32.8 d	Inhalation: upper respiratory tract Ingestion: bone	**II**
Rubidium 86 (^{86}Rb)	Risk 2 β^- and γ emitter T = 18.64 d	Inhalation: bone Ingestion: bone	**II**
Rubidium 88 (^{88}Rb)	Risk 2 β^- and γ emitter T = 17.82 min	Inhalation: upper respiratory tract Ingestion: stomach	**II**
Thallium 201 (^{201}Tl)	Risk 3 X and γ emitter T = 3.04 d/ Teff = 2.3 d	Inhalation: Upper respiratory tract (R) Ingestion: kidneys	**III**
Thallium 204 (^{204}Tl)	Risk 1 β^- emitter T = 3.78 years / Teff = 9.9 d	Inhalation: kidneys (R 1 µm), upper respiratory tract (R 5 µm) Ingestion: kidneys	**III**

2 - Specific treatments

Prussian blue (ferric ferrocyanide) - Radiogardase® 500 mg, capsule

Prussian blue does not have any MA in France, though it does have one in Germany and in the United States, under the name Radiogardase®, for the treatment of suspected internal radioactive cesium and/or radioactive or non-radioactive thallium contamination, by increasing their elimination rate.

1. Pharmacological mechanism of action

Prussian blue, a water-insoluble compound, is a chelating agent with a very high affinity for cesium and thallium, by ion exchange. The Prussian blue / cesium and Prussian blue / thallium complexes formed in the digestive tract, in cases of acute intoxication, are poorly absorbable and serve to reduce the bioavailability of caesium and thallium, promoting their excretion in stools. By this same chelating action, Prussian blue is able to block the enterohepatic cycle of cesium and thallium.

2. Administration protocol(s) according to severity

Treatment should be initiated as soon as contamination is suspected. This contamination must be checked as soon as possible. Prussian blue treatment remains effective even when administered a certain time after contamination.

Populations	Recommended posologies	Remarks
Adults and Adolescents > 12 years	3 grams repeated 3 times/day by oral route.	Once radioactivity has decreased considerably, PB can be reduced to 1 to 2 grams, twice daily in order to improve gastrointestinal tolerance.
Children aged 2 to 12 years	1 gram repeated 3 times/day by oral route.	
Newborns and infants	No data available	
Treatment duration is determined by assay results and should be continued based on the elimination kinetics of the concerned element, in consultation with radiological institutes or poison control centres.		

3. Efficacy evaluation parameters for Prussian blue

The efficacy of Prussian blue can be assessed by means of assays performed on excreta, or by anthroporadiometry, more rarely by means of blood assays.
These assays use the radiological properties of the isotopes; the choice of matrix (urine, stools) is governed by the mode of contamination, along with the radionuclide's physicochemical form and metabolism. Thus, in the absence of upstream data, the choice of one or other examination is difficult.
In practice, even though not always the most relevant, **urinary examination is the easiest to perform** (24-hour urine sample), along with whole-body anthroporadiometry (though this test requires that the establishment possess a measurement cell).
The following table specifies the possible technique if only urine is available and indicates whether whole-body anthroporadiometry should be considered or not.

Radionuclides	Urine radiotoxicology	Anthroporadiometry	Remarks
Cesium 134 (^{134}Cs)	γ spectro	Possible	-
Cesium 134 (^{137}Cs)	γ spectro	Possible	-
Indium 111 (^{111}In)	γ spectro	Possible	Short half-life (2.8 d)
Indium 115m (^{115m}In)	γ spectro	Possible	Short half-life (4.49 h)
Rubidium 84 (^{84}Rb)	γ spectro	Possible	Short half-life and Low gamma emissions intensity (<10%)
Rubidium 86 (^{86}Rb)	γ spectro	Difficult	Low gamma emissions intensity (<10%)
Rubidium 88 (^{88}Rb)	γ spectro	Difficult	Short half-life (17.82 min)
Thallium 201 (^{201}Tl)	γ spectro	Possible	Short half-life (3.04 d)
Thallium 204 (^{204}Tl)	β counting	Impossible	Photon energy and intensity too low

4. Contraindications

None.

5. Main adverse effects (due to their frequency or severity)

No severe adverse effects or deaths reported with Prussian blue. On the other hand, constipation, most frequently severe, was reported in ¼ of the victims of the Goaiania accident.
Blackish stool colouring (trivial) is possible due to the colour of Prussian blue.

6. Precautions for use

Prussian blue may interfere with laboratory test results. Cases of asymptomatic hypokalaemia have been reported in victims treated with Prussian blue. Thus, serum electrolytes must be closely monitored during Prussian blue treatment (particularly if there is a history of cardiac arrhythmia or of electrolyte imbalance).

7. Interactions and Incompatibilities

Based on animal data, it has been demonstrated that the co-administration of Prussian blue with other radionuclide elimination-promoting agents, does not interfere with the efficacy of Prussian blue for ^{137}Cs.

8. Use of Prussian blue in specific populations

Pregnancy: due to the life-threatening situation, the use of Prussian blue is possible during pregnancy, whatever the term.
Breast feeding: not relevant in exceptional emergency situations.