NUCLEAR SCIENCE AND TECHNOLOGY SYMPOSIUM 2019

Cevidra®
CALIXARENE

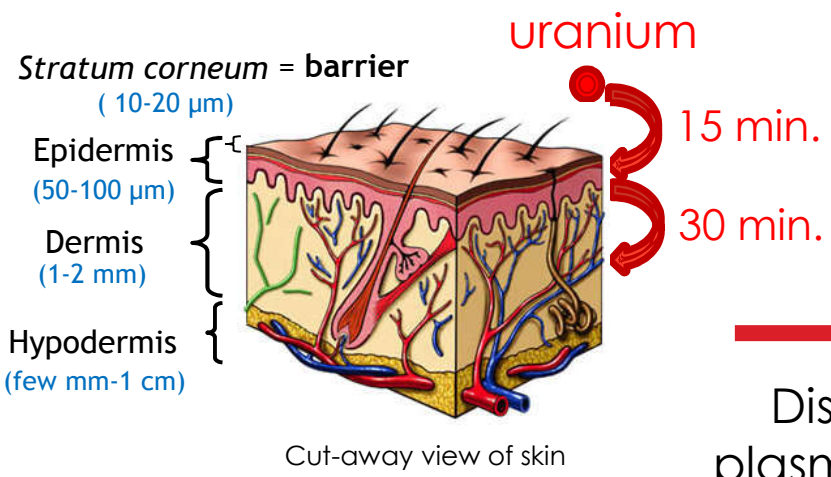
Emergency treatment for external radionuclides contamination

Helsinki, Marina Congress Center

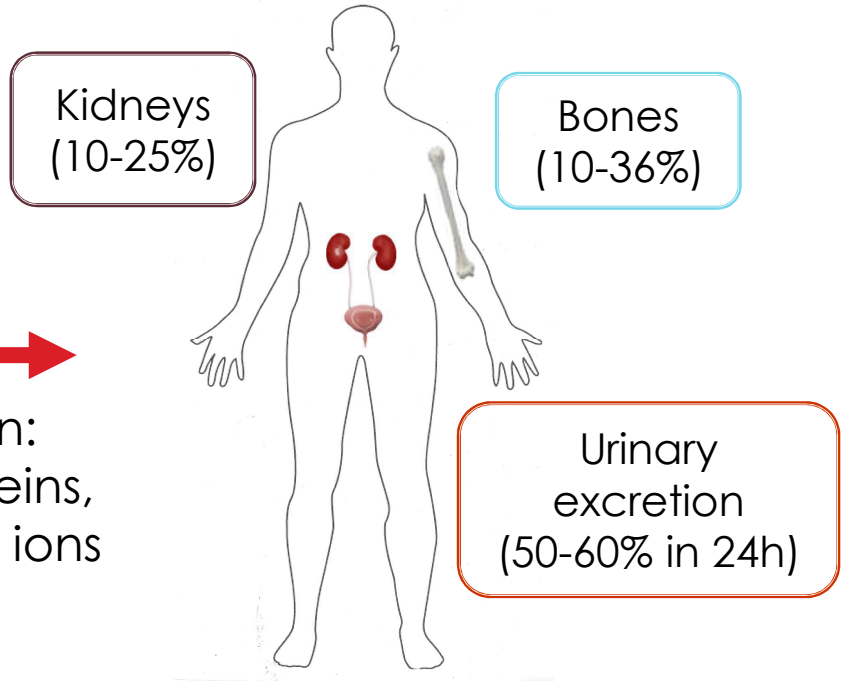
October 30-31, 2019

THE CONTAMINATION

What is an external contamination ?



Distribution:
plasma proteins,
bicarbonate ions



Fast diffusion even through intact skin

De Rey *et al.*, Environ. Res., 1983; 30(2):440-91

Petitot *et al.*, Can. J. Physiol. Pharmacol., 2004; 82(2):133-9

Toxicity on retention organs and skin

Lopez *et al*, Health Physics, 2000; 78(4):434-7

Kathren and Burklin, Health Physics, 2004; 94(2):170-9

Brugge *et al*, Rev. Environ. Health, 2005; 20(3):177-93

THE DECONTAMINATION

Criteria for a good decontamination :

- **Avoid the percutaneous penetration** of radionuclides
- **Decrease the use of treatment for internal contamination**
- **Avoid dissemination / cross contamination**
- **Prevent inhalation/ingestion** of radionuclides from the cutaneous contamination (resuspension etc.)

DEVELOPING THE EMULSION

DEVELOPING THE EMULSION

In the early 1990s and 2000s **Knowledge about calixarene family**

- The calixarenes have strong affinity for actinides due to **complexing function**

  + **geometry**

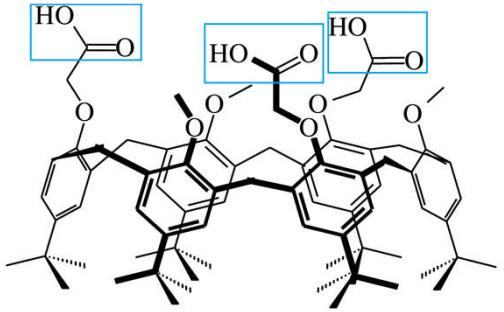


Fig. 1. Chemical structure of 1,3,5-OCH3-2,4,6-OCH2COOH-*p*-*tert*butylcalix[6]arene.

- Use in **radiotoxicology** : analyze/extract actinides from urine, drinking water, etc.
- **In 1990s** calixarene were considered for internal decontamination from uranium. But two **sulfonic** calixarenes showed **hepatotoxicity**.

→ **The use of calixarenes in decontamination treatments was ruled out for a long time.**

DEVELOPING THE EMULSION

2006-2016 **IRSN worked on a treatment for external contamination**

- **No efficient treatment** for uranium internal contamination **without toxicity**
- What about a treatment with calixarenes for external contamination ?

The main challenge was to find a galenic form that :

→ **immobilizes the calixarene** in the topical form

→ **prevents the absorption of the topical form** with the trapped radionuclides

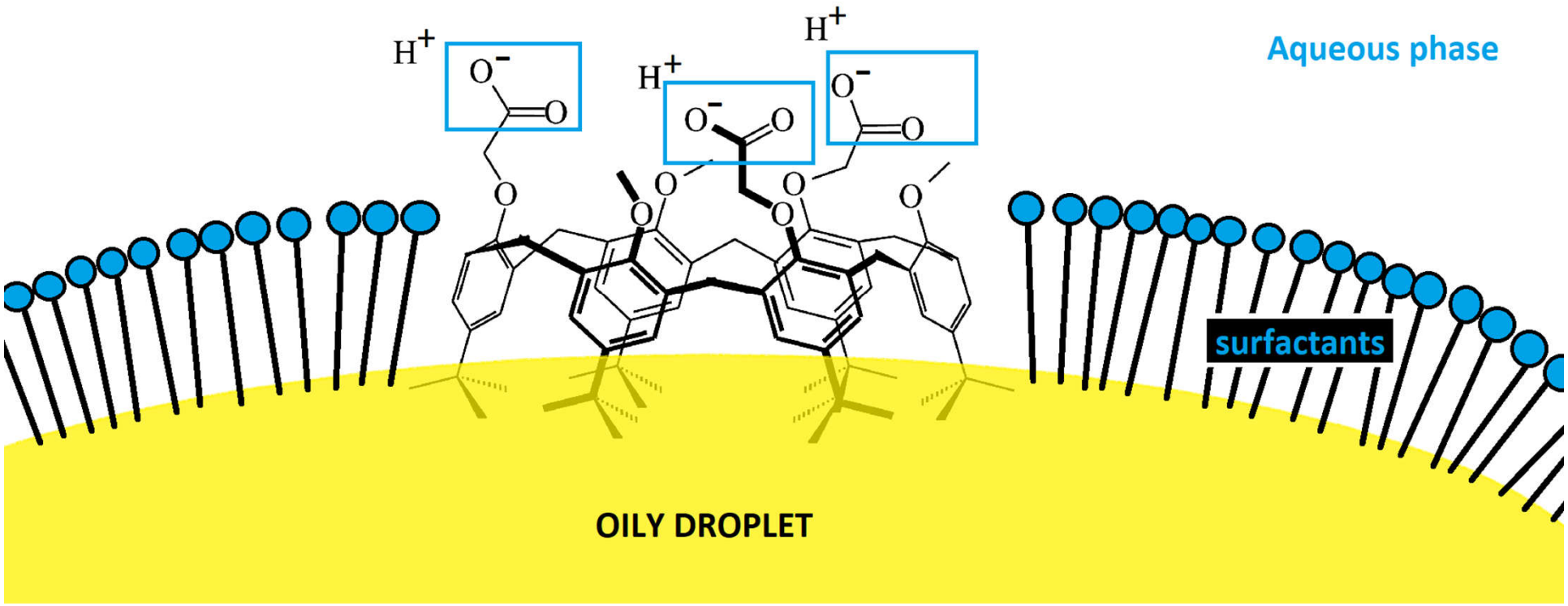
→ and allows the **maximum amount of uranium** to be trapped.

DEVELOPING THE EMULSION

2006-2016 **IRSN worked on a treatment for external contamination**

- The calixarenes used are liposoluble molecules
- Developing an oil-in-water emulsion should locate the calixarene at the surface of the oily droplets

WHAT IS AN OIL-IN-WATER EMULSION ?

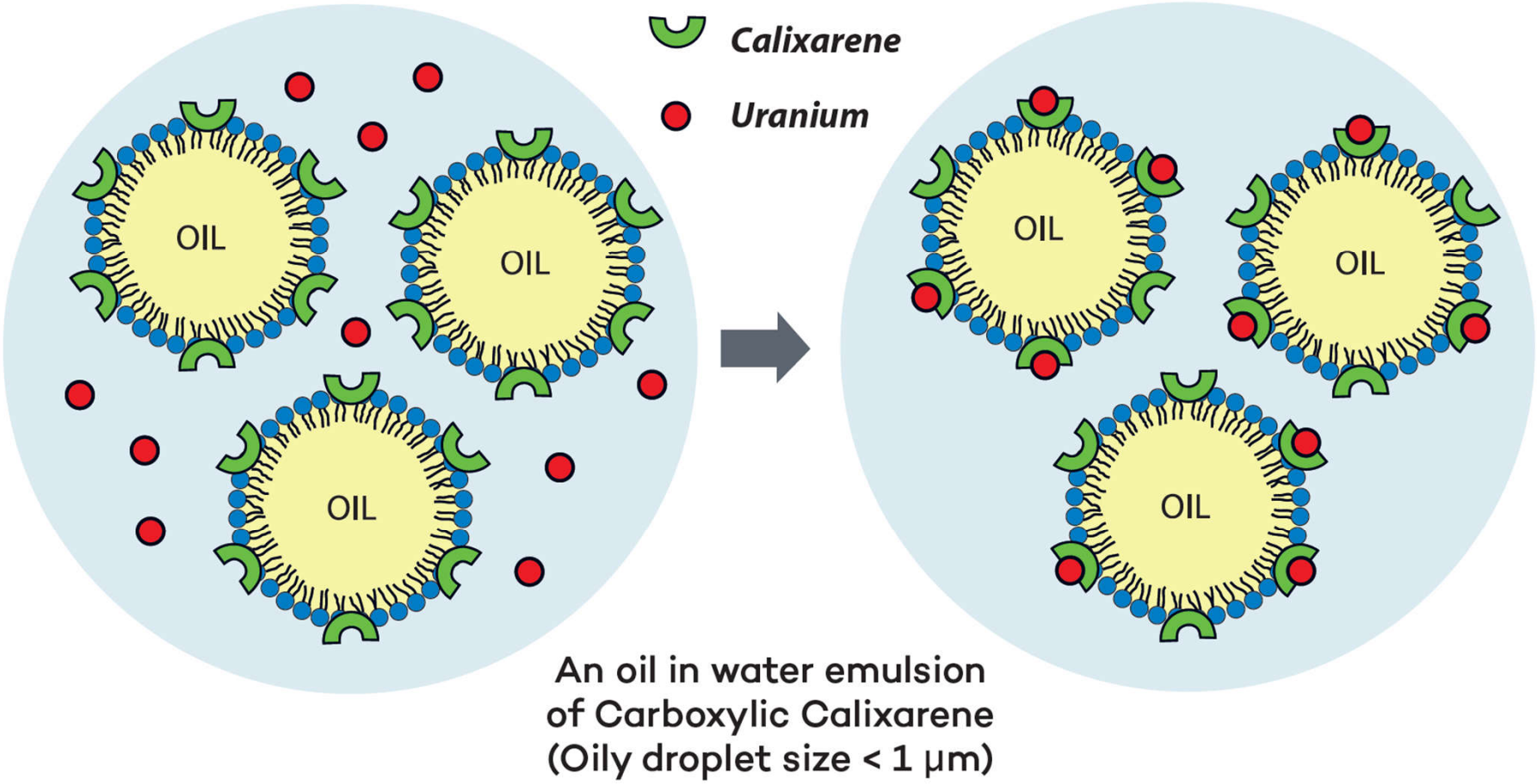


DEVELOPING THE EMULSION

2006-2016 **IRSN worked on a treatment for external contamination**

- The calixarenes used are liposoluble molecules
- Developing an oil-in-water emulsion should locate the calixarene at the surface of the oily droplets
- The droplets' surface makes the calixarene more available to chelate radionuclides → need to **decrease the droplet size** to increase the total surface.

WHAT IS AN OIL-IN-WATER EMULSION ?



An oil in water emulsion
of Carboxylic Calixarene
(Oily droplet size < 1 µm)

DEVELOPING THE EMULSION

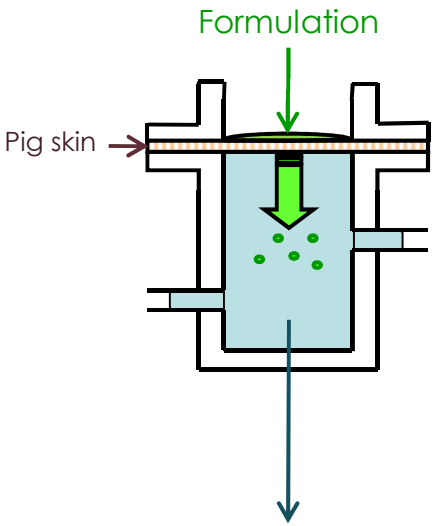
2006-2016 **IRSN worked on a treatment for external contamination**

- The calixarenes used are liposoluble molecules
- Developing an oil-in-water emulsion should locate the calixarene at the surface of the oily droplets
- The droplets' surface makes the calixarene more available to chelate radionuclides → need to **decrease the droplet size** to increase the total surface.
- The droplets (with calixarene) must be too large to be absorbed by the skin. → **do not decrease too much the droplet size**.
- The contamination would not be absorbed anymore

EFFICACY STUDIES

Calixarene formulations

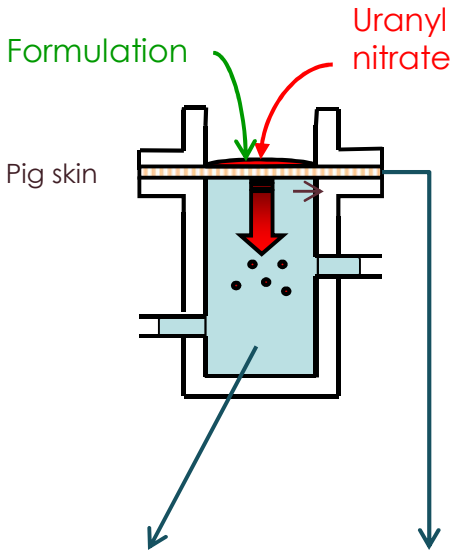
Ex vivo calixarene diffusion studies



Calixarene quantification by HPLC

Franz diffusion cell

Ex vivo decontamination studies



Uranium quantification by ICP-MS

Uranium skin distribution by SIMS

Franz diffusion cell

THE DECONTAMINATION

Criteria for a good decontamination :

- **Avoid the percutaneous penetration** of radionuclides
- **Decrease the use of treatment for internal contamination**
- **Avoid dissemination / cross contamination**
- **Prevent inhalation/ingestion** of radionuclides from the cutaneous contamination (resuspension etc.)

THE DECONTAMINATION

Criteria for a good decontamination :

- **Avoid the percutaneous penetration** of radionuclides ✓
- **Decrease the use of treatment for internal contamination**
- **Avoid dissemination / cross contamination**
- **Prevent inhalation/ingestion** of radionuclides from the cutaneous contamination (resuspension etc.)

THE DECONTAMINATION

Criteria for a good decontamination :

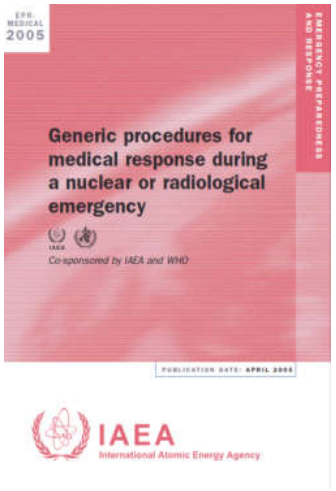
- **Avoid the percutaneous penetration** of radionuclides ✓
- **Decrease the use of treatment for internal contamination** ✓

- **Avoid dissemination / cross contamination**
- **Prevent inhalation/ingestion** of radionuclides from the cutaneous contamination (resuspension etc.)

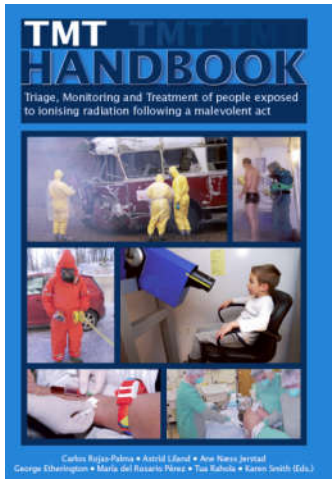
?

GUIDELINES

INTERNATIONAL GUIDELINES



AIEA
(2005)



TMT Handbook
European Union
(2009)

THE ACTUAL GUIDELINES FOR DECONTAMINATION ON HEALTHY SKIN:

1. **Water + mild detergent = soapy water**

   or hydrogen peroxide 3% (H_2O_2)

   or sodium hypochlorite 1% (bleach)

   or potassium permanganate 5% ($KMnO_4$)

2. Anti-inflammatory pomade (in case of fixed contaminations)

THE CEVIDRA CALIXARENE CREAM

THE CALIXARENE CREAM

A CHELATING AND CLEANSING EMULSION

3 major modes of action :

1) **Chelation (really strong bond)** from the carboxylic calixarene for **cationic radionuclides**

2) **Several capabilities of affinity** (hydrogen bonds, hydrophobic interactions, electrostatic interactions)

3) **Cleansing action**, removes the contaminants which are not chelated

Enlarge the spectrum of efficacy towards **non-cationic radionuclides**

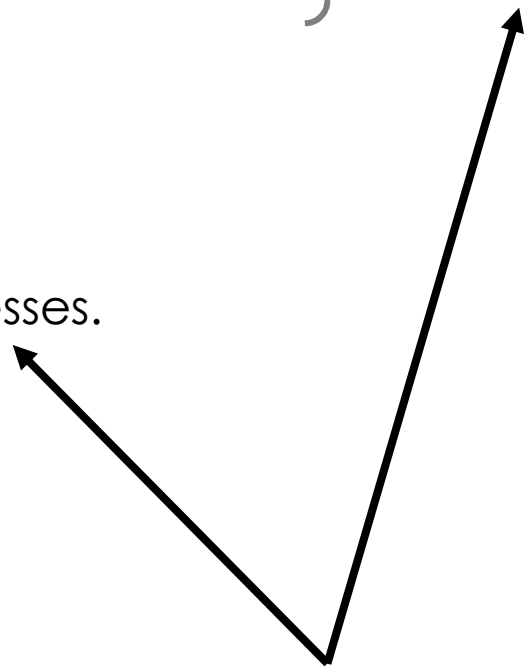
THE CALIXARENE CREAM

APPLICATION OF THE DECONTAMINATING CREAM

- **Moisten** the skin with warm water on a compress

Optional step

- **Apply** with **gentle rubbing motion**.
- **Rinse/wipe** with water or wet compresses.



Avoid contaminated effluent

THE CALIXARENE CREAM

→ The **modes of action** :

- Retain the contamination into the cream
- Reduce the risk of cross contamination.

→ The **viscosity** and the **removal with compresses** :

- Avoid flowing of contamination on non-contaminated areas
- Avoid dissemination
- Reduce the risk of cross contamination.
- Reduce the volume of contaminated waste

THE DECONTAMINATION

Criteria for a good decontamination :

- **Avoid the percutaneous penetration** of radionuclides ✓
- **Decrease the use of treatment for internal contamination** ✓
- **Avoid dissemination / cross contamination**
- **Prevent inhalation/ingestion** of radionuclides from the cutaneous contamination (resuspension etc.)

THE DECONTAMINATION

Criteria for a good decontamination :

- **Avoid the percutaneous penetration** of radionuclides ✓
- **Decrease the use of treatment for internal contamination** ✓
- **Avoid dissemination / cross contamination** ✓
- **Prevent inhalation/ingestion** of radionuclides from the cutaneous contamination (resuspension etc.)

THE DECONTAMINATION

Criteria for a good decontamination :

- **Avoid the percutaneous penetration** of radionuclides ✓
- **Decrease the use of treatment for internal contamination** ✓
- **Avoid dissemination / cross contamination** ✓
- **Prevent inhalation/ingestion** of radionuclides from the cutaneous contamination (resuspension etc.) ✓

THE CALIXARENE CREAM

Current knowledge about external decontamination with carboxylic calixarene

- **Since July 2018, a specific treatment does exist as a medical device**

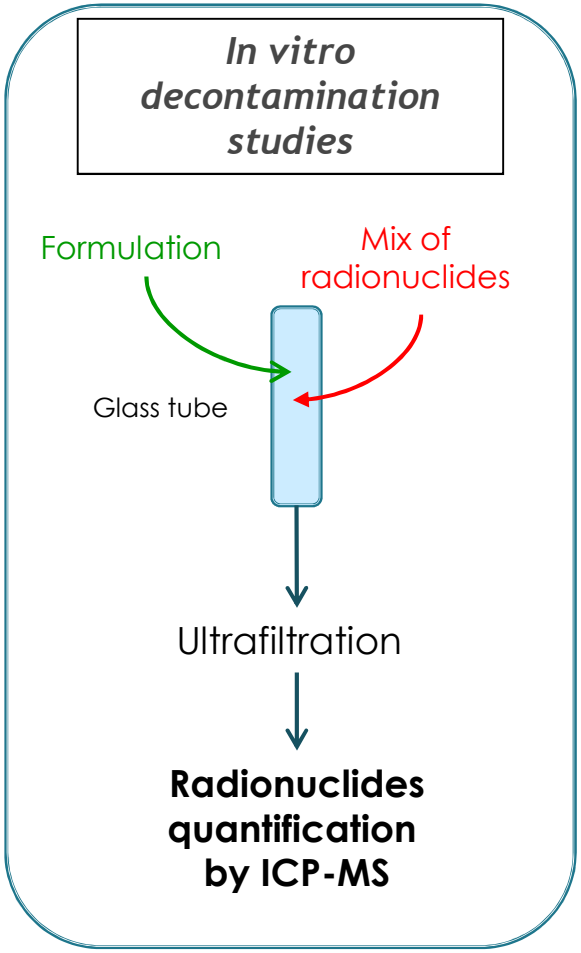
- The **spectrum is large** and the proven efficacy is not limited to actinides (**uranium, plutonium, americium, thorium**) :

  → Chelation on : **cobalt, antimony, silver, zirconium, manganese, cesium, strontium**

  → Cleansing action on : **all other radionuclides**

THE CALIXARENE CREAM

IN VITRO - SCIENTIFIC STUDIES



- **Two recent studies**: IRSN

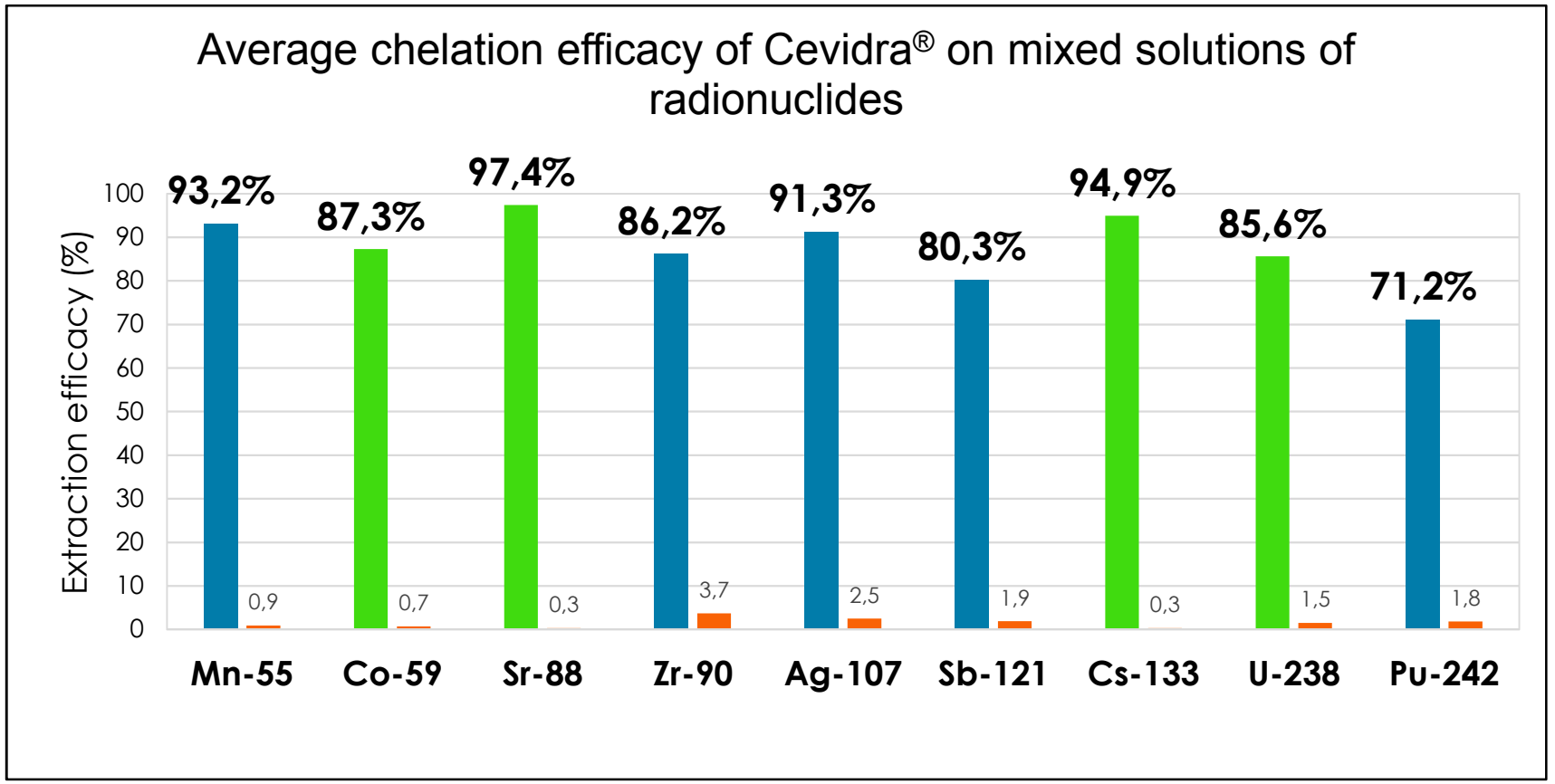
  Mix for study n°1 = **U** + **Cs** + **Sr** + **Co**

  Mix for study n°2 = **Mn** + **Zr** + **Ag**+ **Sb** + **Pu**

- Studies were carried out with stable isotopes when possible. As a reminder, the isotopes of the same element have **identical chemical properties** but **different physical properties** (stable or radioactive in particular).
  - ➢ <u>It does not influence the chelation.</u>

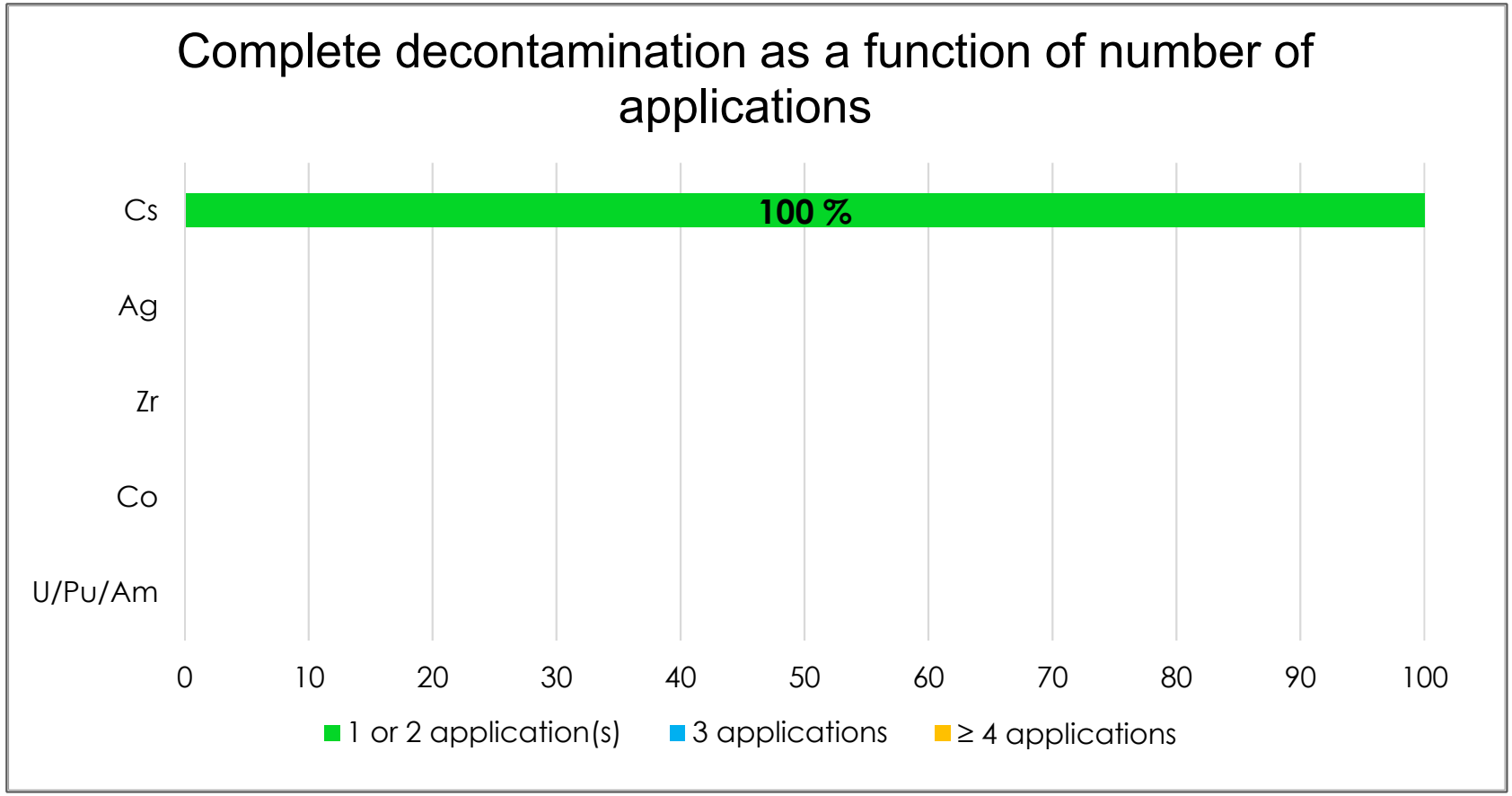
THE CALIXARENE CREAM

IN VITRO - SCIENTIFIC STUDIES



THE CALIXARENE CREAM

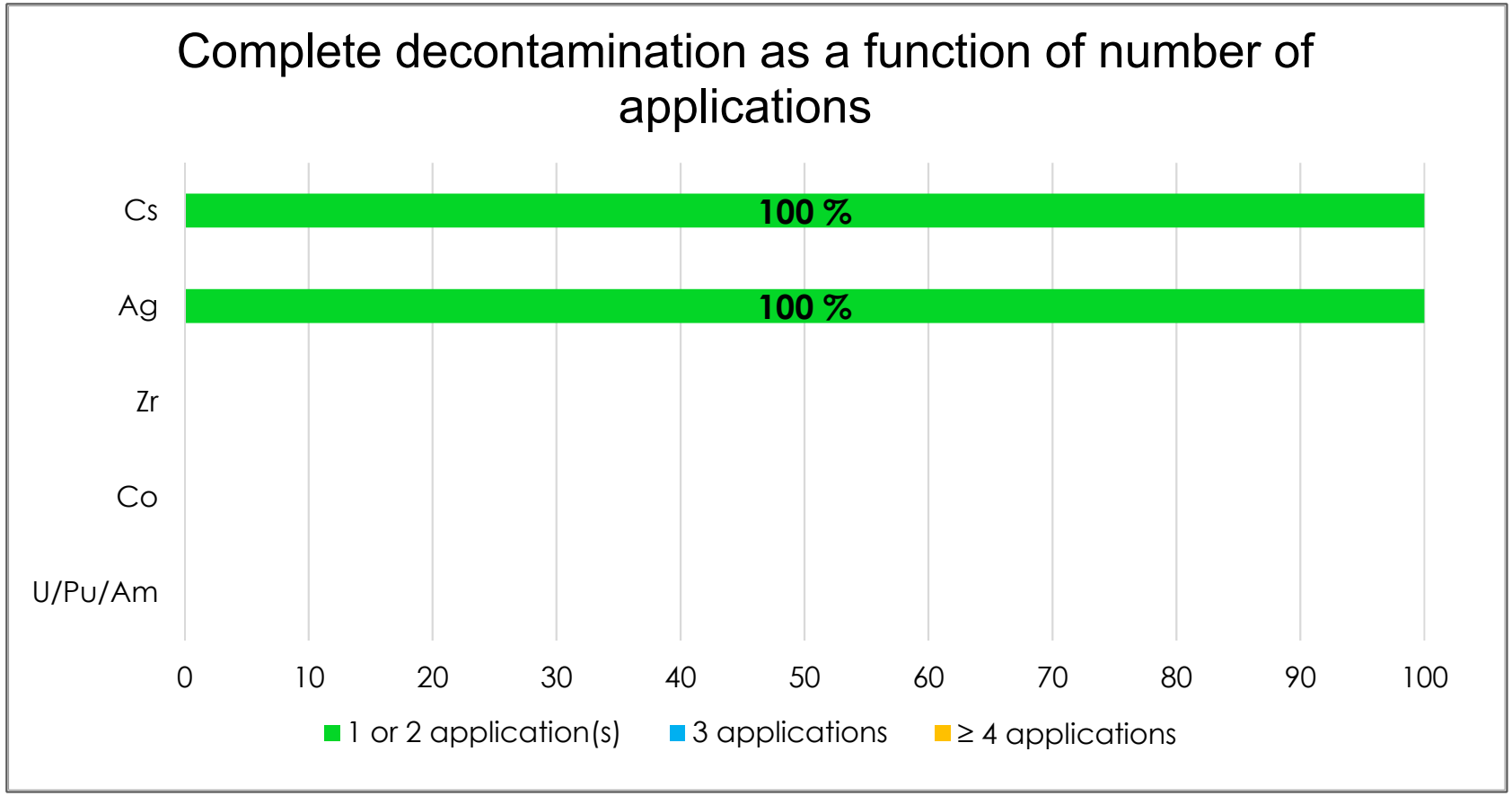
IN VIVO - REAL CASES OF DECONTAMINATION IN NUCLEAR FACILITIES



Analysis of post market data on a 14 months period (from August 2018 to September 2019). 28 areas were treated.

THE CALIXARENE CREAM

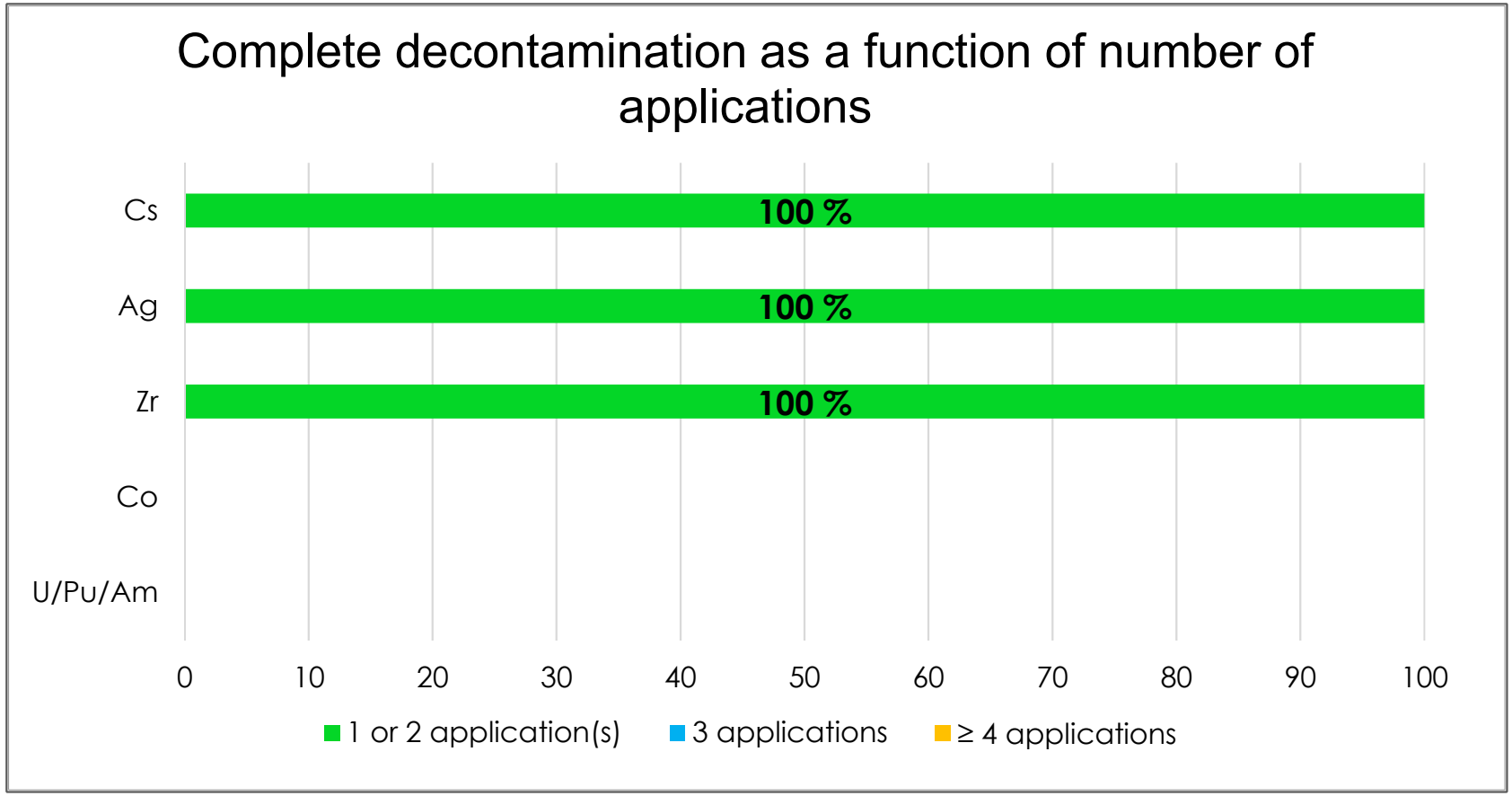
IN VIVO - REAL CASES OF DECONTAMINATION IN NUCLEAR FACILITIES



Analysis of post market data on a 14 months period (from August 2018 to September 2019). 28 areas were treated.

THE CALIXARENE CREAM

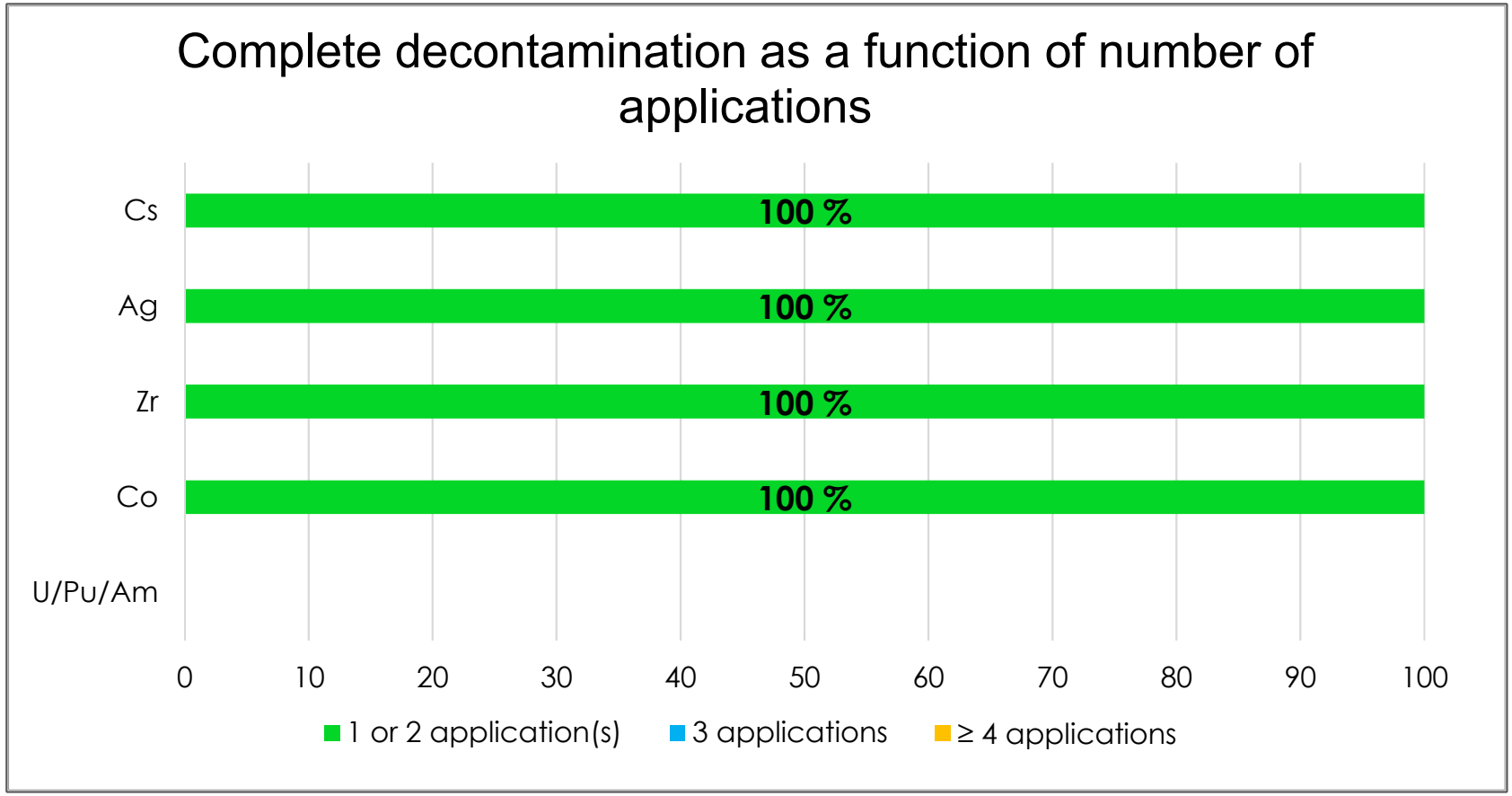
IN VIVO - REAL CASES OF DECONTAMINATION IN NUCLEAR FACILITIES



Analysis of post market data on a 14 months period (from August 2018 to September 2019). 28 areas were treated.

THE CALIXARENE CREAM

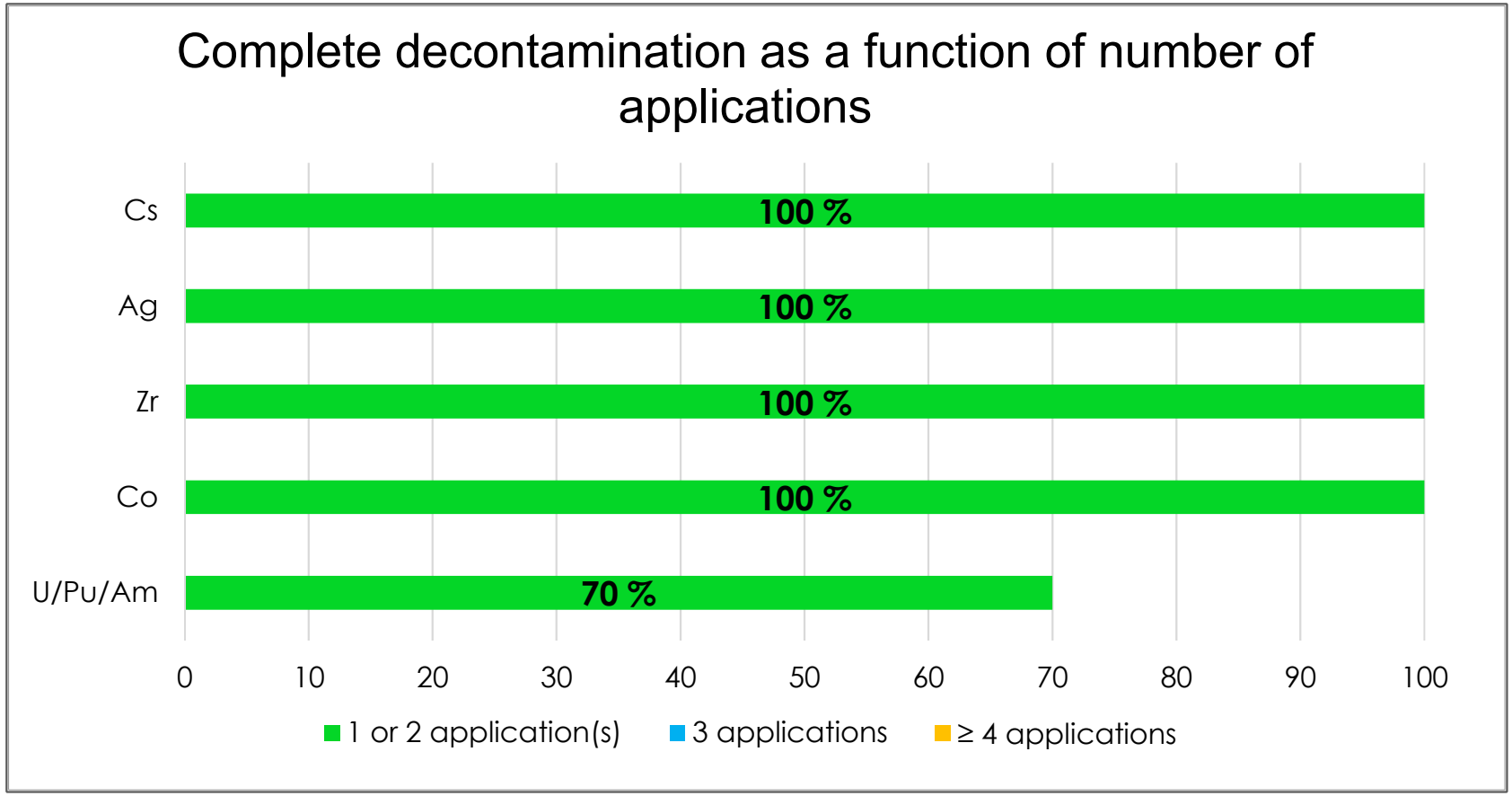
IN VIVO - REAL CASES OF DECONTAMINATION IN NUCLEAR FACILITIES



Analysis of post market data on a 14 months period (from August 2018 to September 2019). 28 areas were treated.

THE CALIXARENE CREAM

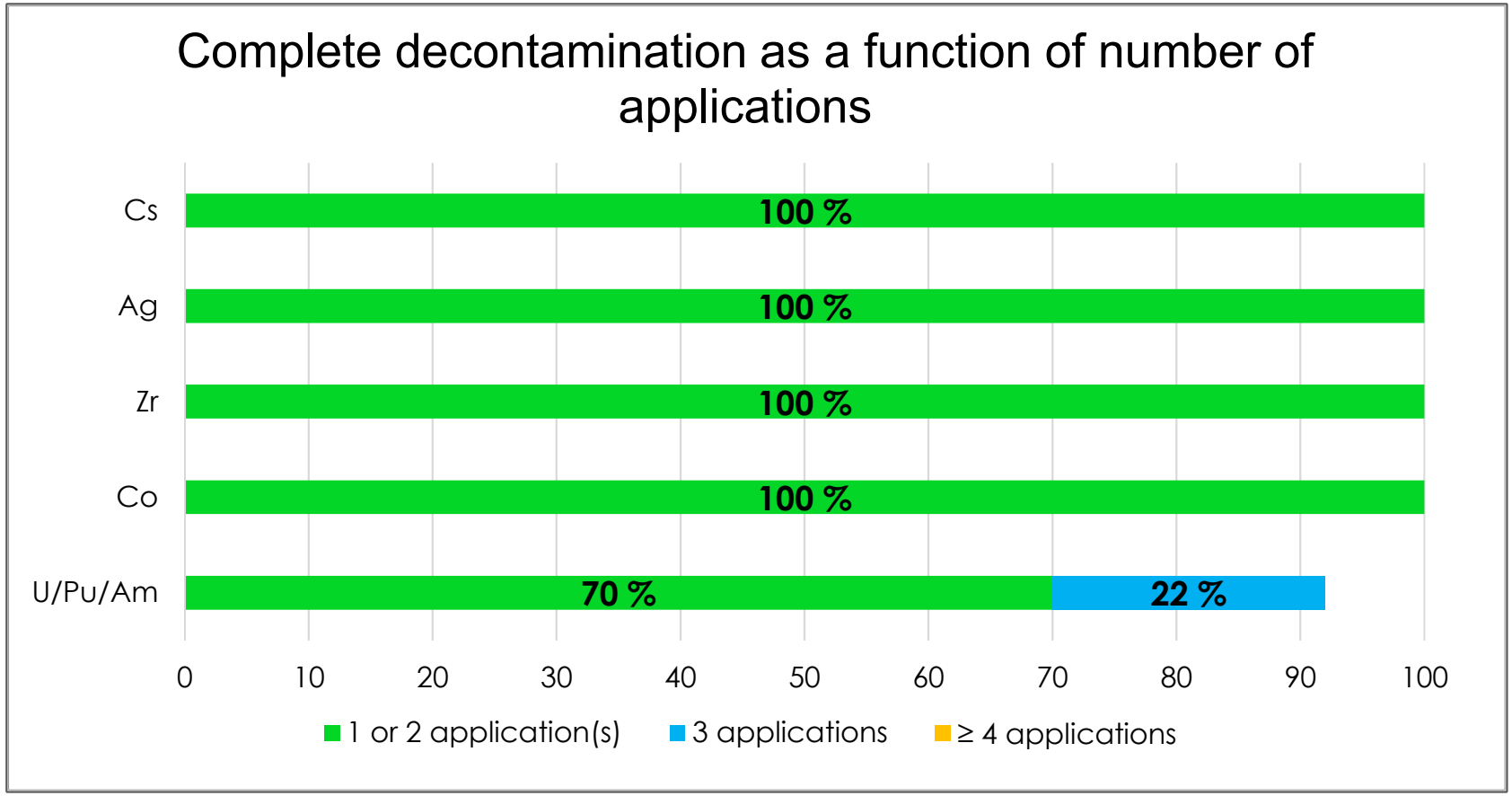
IN VIVO - REAL CASES OF DECONTAMINATION IN NUCLEAR FACILITIES



Analysis of post market data on a 14 months period (from August 2018 to September 2019). 28 areas were treated.

THE CALIXARENE CREAM

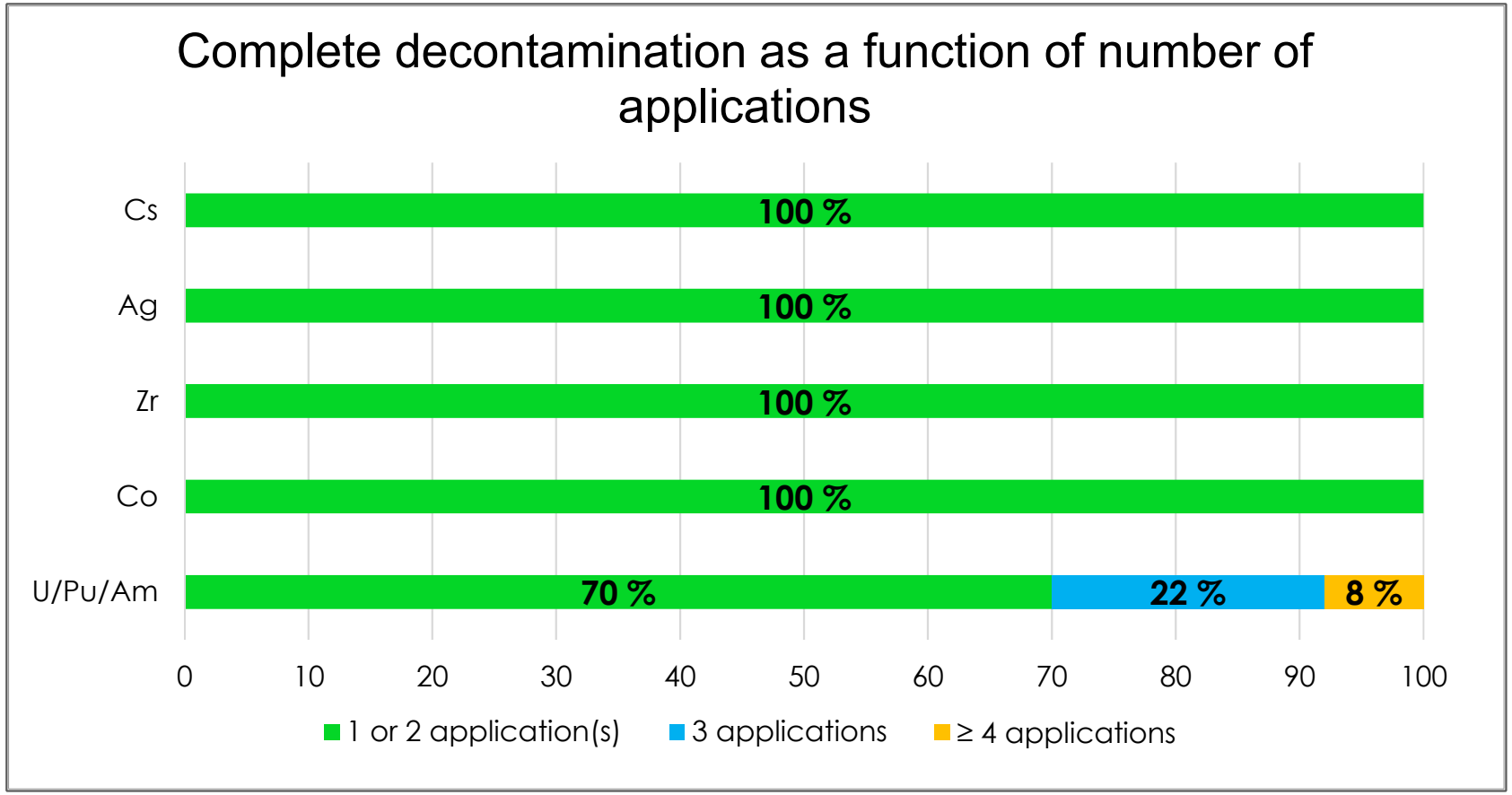
IN VIVO - REAL CASES OF DECONTAMINATION IN NUCLEAR FACILITIES



Analysis of post market data on a 14 months period (from August 2018 to September 2019). 28 areas were treated.

THE CALIXARENE CREAM

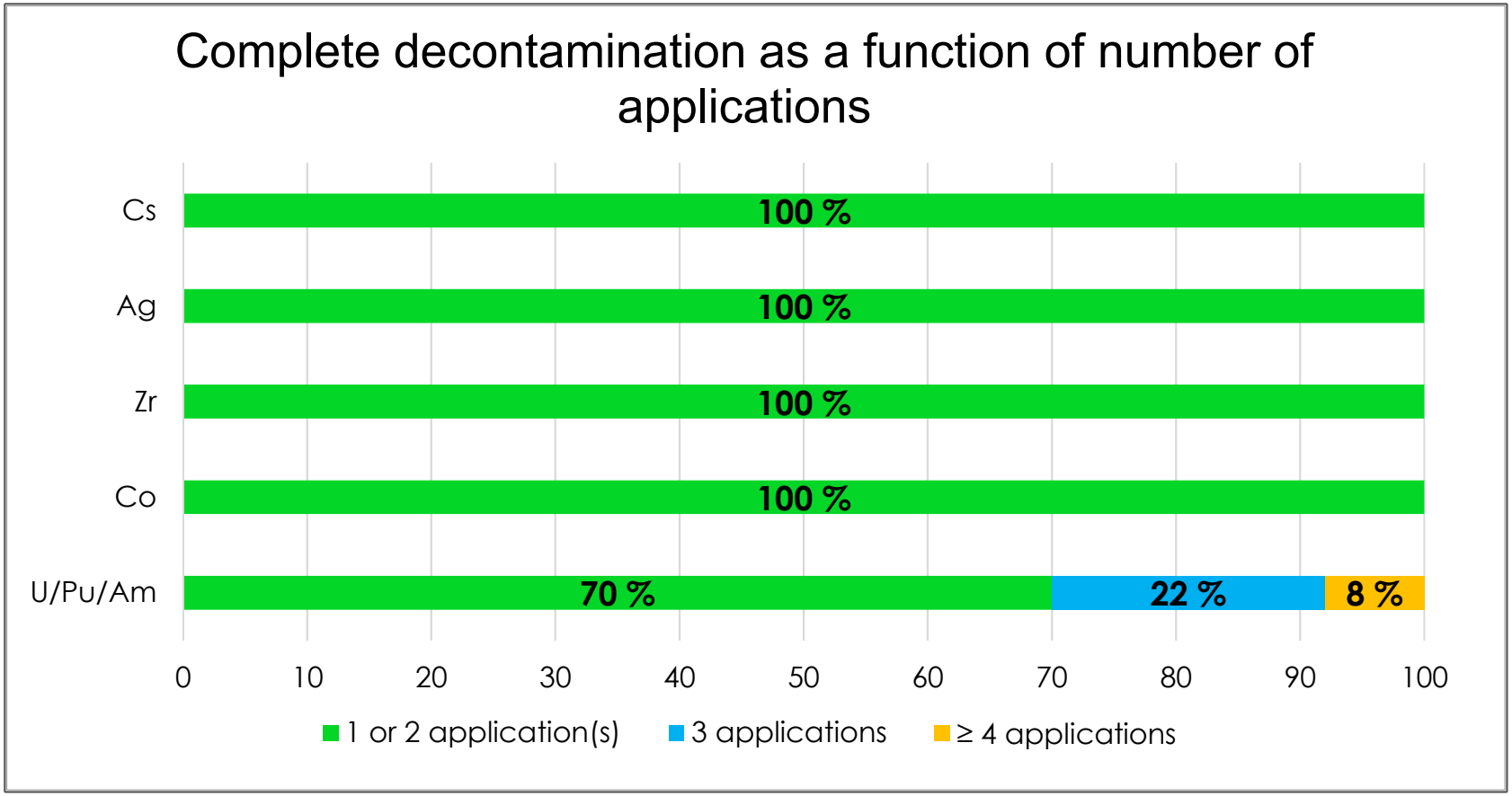
IN VIVO - REAL CASES OF DECONTAMINATION IN NUCLEAR FACILITIES



Analysis of post market data on a 14 months period (from August 2018 to September 2019). 28 areas were treated.

THE CALIXARENE CREAM

IN VIVO - REAL CASES OF DECONTAMINATION IN NUCLEAR FACILITIES



→ The **cream led to a complete decontamination** without associated treatment **in 100% of the cases.**

Analysis of post market data on a 14 months period (from August 2018 to September 2019). 28 areas were treated.

BIBLIOGRAPHY

- Bouvier-Capely, C., Manoury, A., Legrand, A., Bonthonneau, J. P., Cuenot, F. et Rebière, F. (2009). "The use of calix[6]arene molecules for actinides analysis in urine and drinking water: An alternative to current procedures". Journal of Radioanalytical and Nuclear Chemistry, 282(2), 611-615

- Mekki, S., Bouvier-Capely, C., Jalouali, R. et Rebière, F. (2010). " The extraction of thorium by calix[6]arene columns for urine analysis ". Radiation Protection Dosimetry, 144(1-4), 330-334

- Spagnul, A., Bouvier-Capely, C., Phan, G., Rebière, F. et Fattal, E. (2010). "Calixarene-entrapped nanoemulsion for uranium extraction from contaminated solutions". Journal of Pharmaceutical Sciences, 99(3), 1375-1383

- Spagnul, A., Bouvier-Capely, C., Adam, M., Phan, G., Rebière, F. et Fattal, E. (2010). "Quick and efficient extraction of uranium from a contaminated solution by a calixarene nanoemulsion". International Journal of Pharmaceutics, 398(1-2), 179-184

- Spagnul, A., Bouvier-Capely, C., Phan, G., Landon, G., Tessier, C., Suhard, D., Rebière, F., Agarande, M. et Fattal, E. (2011). "Ex vivo decrease in uranium diffusion through intact and excoriated pig ear skin by a calixarene nanoemulsion". European Journal of Pharmaceutics and Biopharmaceutics, 79(2), 258-267

- Phan, G., Semili, N., Bouvier-Capely, C., Landon, G., Mekhloufi, G., Huang, N., Rebière, F., Agarande, M. et Fattal, E. (2013). "Calixarene cleansing formulation for uranium skin contamination". Health Physics, 105(4), 382-389

- Grives, S., Phan, G., Morat, G., Suhard, D., Rebiere, F. et Fattal, E. (2015). "Ex vivo uranium decontamination efficiency on wounded skin and in vitro skin toxicity of a calixarene-loaded nanoemulsion". Journal of Pharmaceutical Sciences, 104(6), 2008-2017

Cevidra® cream has been developed with the support of

THE GENERAL DIRECTORATE FOR ARMAMENT

Liberté • Égalité • Fraternité
RÉPUBLIQUE FRANÇAISE
MINISTÈRE DE LA DÉFENSE ET DES ANCIENS COMBATTANTS

DGA

AND

THE FRENCH INSTITUTE FOR RADIATION PROTECTION AND NUCLEAR SAFETY

IRSN
INSTITUT DE RADIOPROTECTION ET DE SÛRETÉ NUCLÉAIRE

Thank you for your attention !

Contact: **Alexis Finet** – Pharmacist / Radiation Protection Engineer

Laboratoire Cevidra, 45 boulevard Marcel Pagnol
06130 GRASSE – FRANCE

Phone: +33 (0)4.93.70.58.31
Email: afinet@cevidra.com

ANNEXES

REAL CASES IN NUCLEAR FACILITIES

URANIUM / PLUTONIUM / AMERICIUM	Contaminated body area	Initial measure of contamination	Elapsed time before treatment	Final measure and number of applications
Case 1 (U and Pu)	Head	70 c/s (3,2 Bq/cm²)	< 2 h	Fully decontaminated. 0 c/s and 0 Bq/cm² after **1 application**
Case 2 (Pu)	Head	1,6 Bq/cm²	< 2 h	Fully decontaminated. 0 Bq/cm² after **1 application**.
Case 3 (U and/or Pu, no information)	Head	14 c/s alpha 10 c/s beta	< 2 h	Fully decontaminated. 0 c/s after **2 applications**.
Case 4 (U)	Hand	2 Bq/cm²	< 15 min	Incompleted decontamination. Misuse had been confirmed from the user*
Case 5 (U and Pu)	Head + upper limbs	32 Bq/cm²	< 2 h	Fully decontaminated. 0 Bq/cm² after **2 to 5 applications** (depending on the location).
Case 6 (U and/or Pu, no information)	Head	2 Bq/cm²	< 2 h	Fully decontaminated. Already 0 Bq/cm² after **1 application**. 2 applications were performed.
Case 7 (Pu and Am)	Hands and fingers	2 c/s	< 2 h	Fully decontaminated. 0 c/s after **3 applications**.
Case 8 (U and Pu)	Upper limb	0,2 Bq/cm²	< 2 h	Fully decontaminated. 0 Bq/cm² after **1 application**.
Case 9 (Pu)	Head and upper limb	2 c/s	< 1 h	Fully decontaminated. 0 c/s after **2 applications**.

Analysis of post market data on a 14 months period (from August 2018 to September 2019).

COBALT	Contaminated body area	Initial measure of contamination	Elapsed time before treatment	Final measure and number of applications
Case 1	Head	15 c/s	< 1 h	Fully decontaminated. 0 c/s after **1 application**.
Case 2 (Co and Zr)	Head	70 c/s	< 1 h	Fully decontaminated. 0 c/s after **1 application**.
Case 3	Head	220 c/s	< 2 h	Fully decontaminated. 0 c/s after **1 application**.
Case 4	Head	40 c/s	< 1 h	Fully decontaminated. 0 c/s after **1 application**.

ZIRCONIUM	Contaminated body area	Initial measure of contamination	Elapsed time before treatment	Final measure and number of applications
Case 1	Head	70 c/s	< 1 h	Fully decontaminated. 0 c/s after **1 application**.
Case 2	Head	10 c/s	< 1 h	Fully decontaminated. 0 c/s after **1 application**.
Case 3 (Co and Zr)	Head	70 c/s	< 1 h	Fully decontaminated. 0 c/s after **1 application**.

Analysis of post market data on a 14 months period (from August 2018 to September 2019).

REAL CASES IN NUCLEAR FACILITIES

SILVER	Contaminated body area	Initial measure of contamination	Elapsed time before treatment	Final measure and number of applications
Case 1	Head	5 c/s	< 2 h	Fully decontaminated. 0 c/s after **1 application**.
Case 2	Head	10 c/s	< 2 h	Fully decontaminated. 0 c/s after **1 application**.

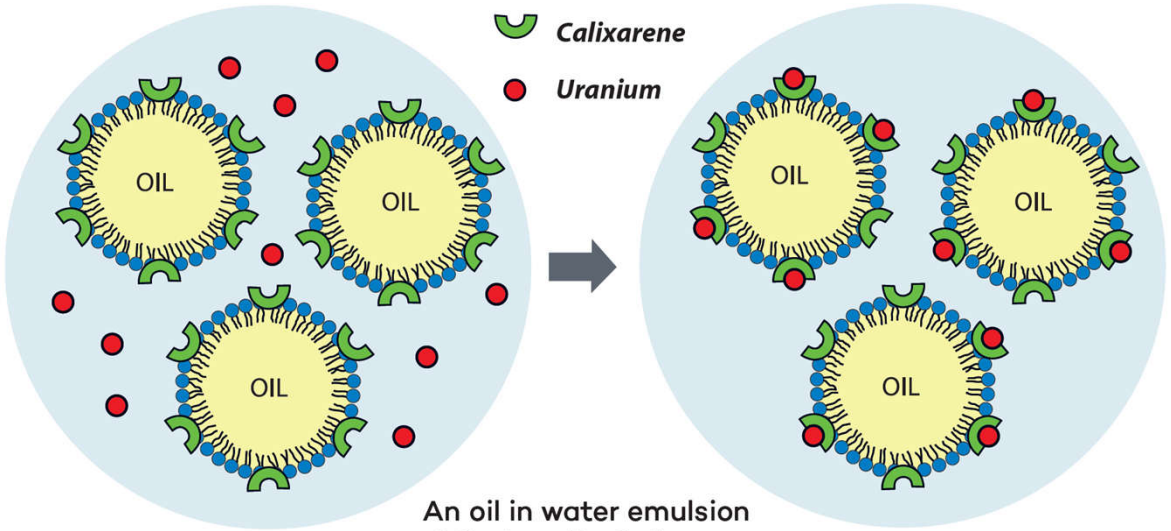
CESIUM	Contaminated body area	Initial measure of contamination	Elapsed time before treatment	Final measure and number of applications
Case 1	Head et upper limb	250 Bq/cm²	< 30 min	Fully decontaminated. 0 Bq/cm² after **2 applications**.

Analysis of post market data on a 14 months period (from August 2018 to September 2019).

WHAT IS THE CEVIDRA CREAM

The **Cevidra®** cream is an oil in water emulsion composed of:

- **carboxylic calixarene** (active substance)
- paraffin oil
- water
- surfactants
- emulsifiers
- preservatives



An oil in water emulsion
of Carboxylic Calixarene
(Oily droplet size < 1 µm)