



Liposomal formulations of bisphosphonate molecules for the treatment of internal strontium/cobalt contamination

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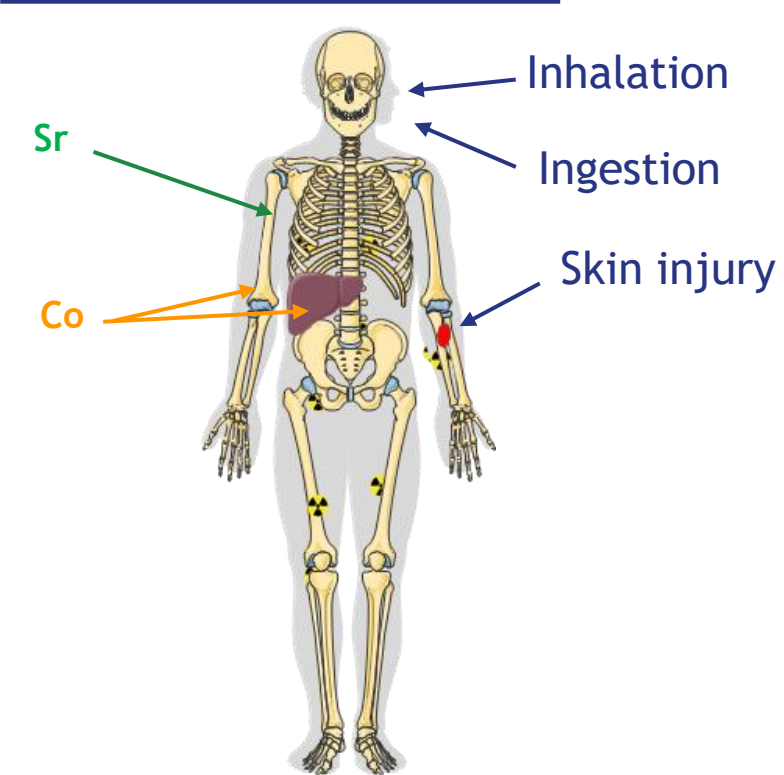
CONTEXT

The situations of exposure

- Nuclear accident
- Decommissioning site, maintenance operation
- Nuclear medicine
- Research activities
- Malevolent act

➡ Civilian population, military responders and nuclear industry workers

The health risks



Internal contamination

Potential chemical and radiological toxicities

STRONTIUM-90

- Alkaline earth metal
- Fission product
- β emitter
- T_{1/2} ~ 29 years

COBALT-60

- Transition metal
- Activation product
- β emitter
- T_{1/2} ~ 5 years

⁹⁰Sr

- Bone tumours (Clarke 1970)
- Haematopoietic disorders (White 1993)

⁶⁰Co

- Respiratory effects (Yoshihisa 2012)
- Skin effects (Adams 2017)
- Potential carcinogenic (Karagas 2022)

The patient care process

Emergency medical treatment recommended (ASN 2008):

⁶⁰Co: DTPA calcium salt (first intention) and cobalt gluconate

⁹⁰Sr: Ammonium chloride or calcium gluconate

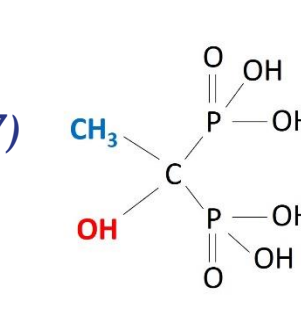
- Modest effectiveness
- Lack of specificity (except for DTPA)

OBJECTIVES

To propose a more effective pharmacological treatment for decorporation with the use of:

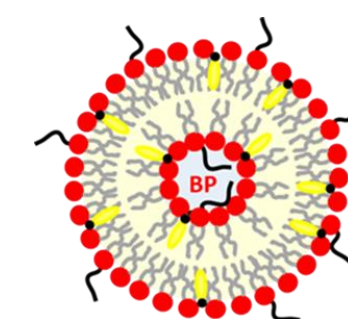
1 A molecule from bisphosphonate series (Landon 2023)

- Bone tropism (Cremers 2011)
- Molecular modeling data favourable (Burgada 2007)
- Confirmed affinity between Co and etidronate (EHBP) (Scheglova 2019)



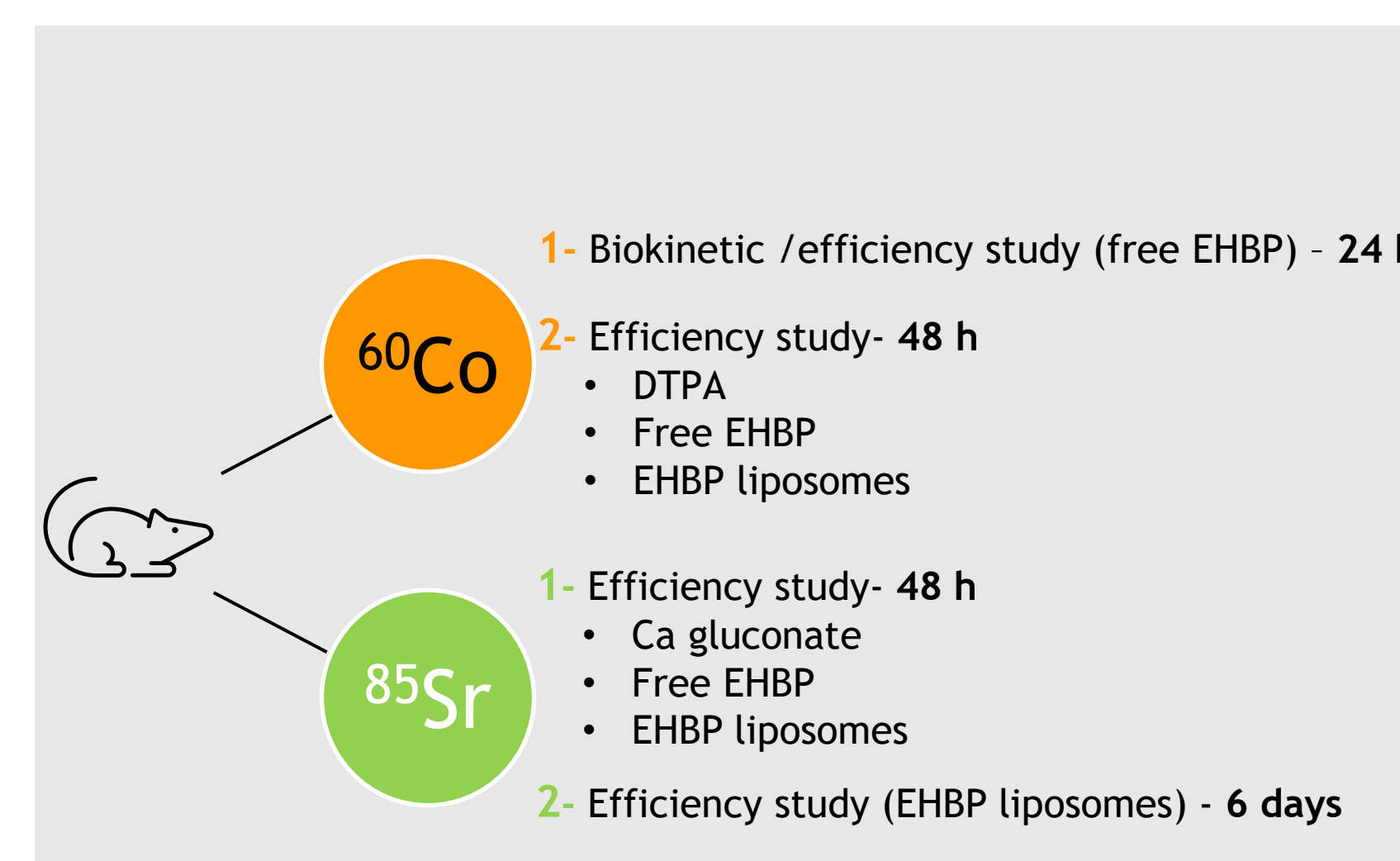
2 Stealth liposomes formulation

- Protect active substances (Niu 2012)
- Prevent chelation of endogenous cations
- Target major retention organs (skeleton, liver)
- Delay their elimination from the body (Allen 1995)



MATERIAL & METHODS

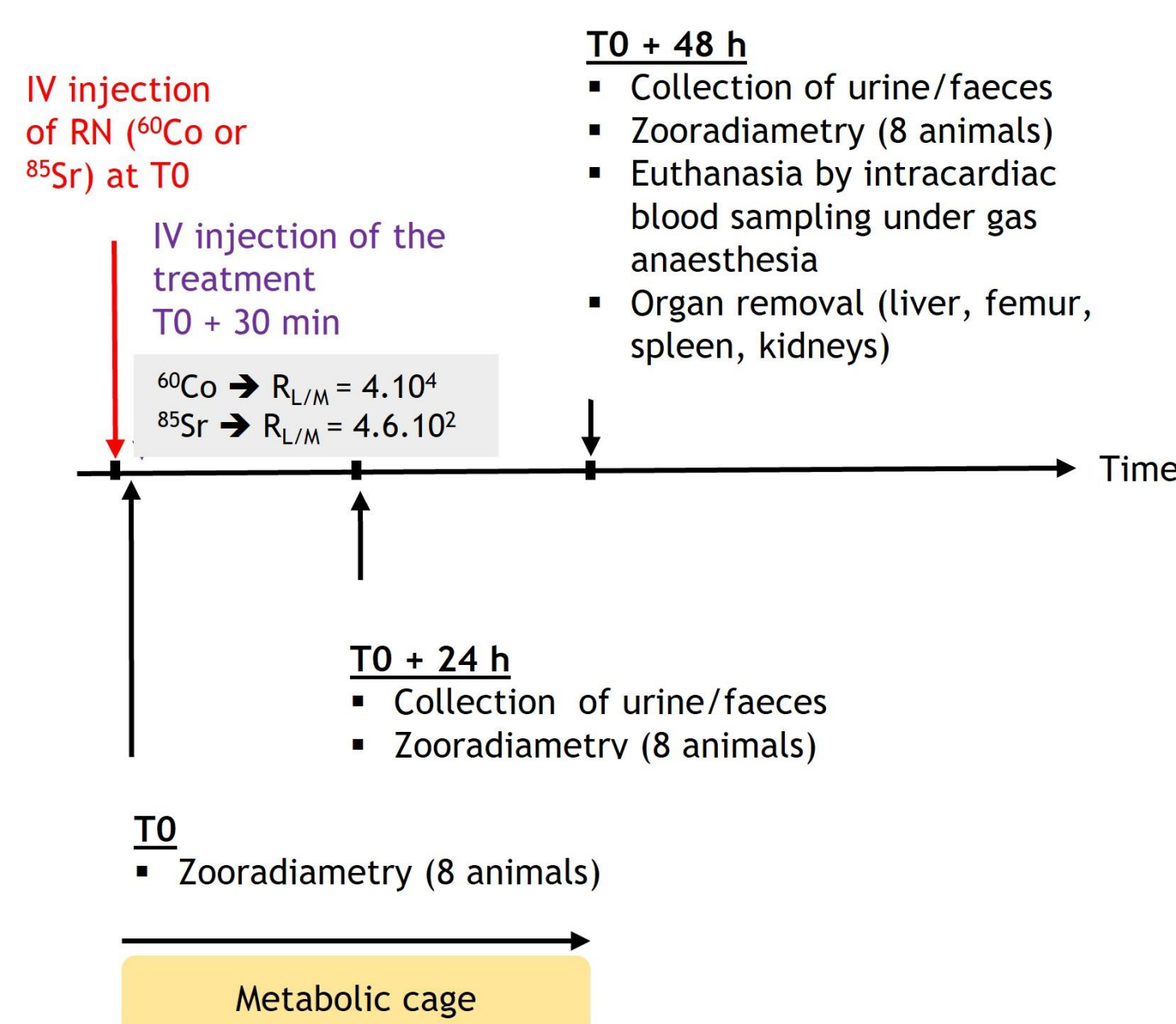
Decorporation experiments



Measurements

- Animal: zooradiometry
- Biological samples: gamma counting

Experimental protocol : catheterized adult male Wistar rats (4 controls, 8 treated)

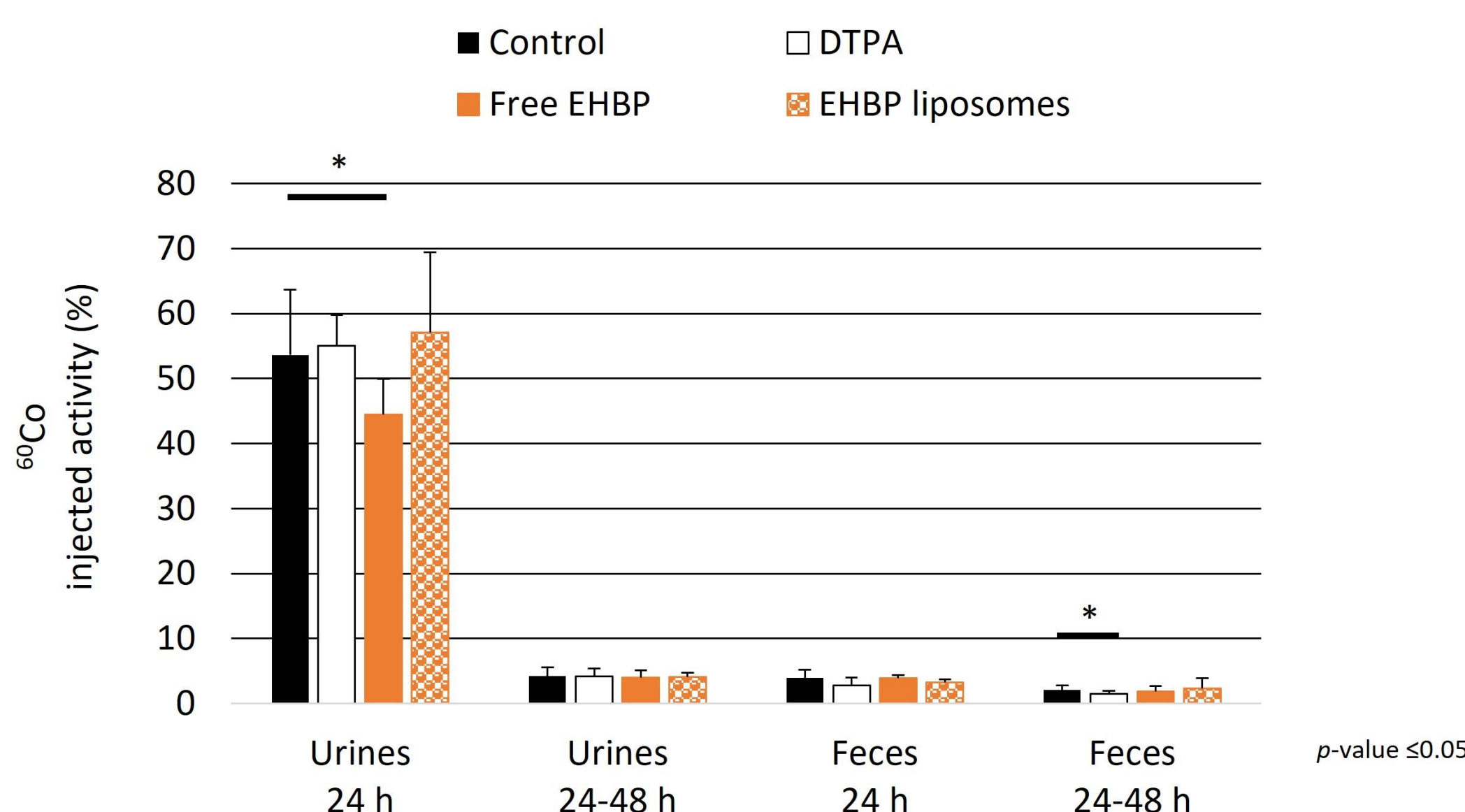


RESULTS & DISCUSSION

Cobalt decorporation experiments

Efficiency study of 48 hours

Total elimination of ⁶⁰Co on day 1 and between day 1 and day 2



Tissue distribution of ⁶⁰Co at day 2 as function of treatments (% of injected activity, mean ± standard deviation)

	Control n=12	DTPA n=8	Free EHBP n=6	EHBP liposomes n=7
Liver	3.9 ± 1.0	3.0 ^a ± 0.7	4.3 ± 1.4	4.0 ± 1.0
Kidneys	0.8 ± 0.1	0.7 ^b ± 0.1	1.1 ± 0.5	0.9 ± 0.1
Skeleton	0.7 ± 0.1	0.5 ^c ± 0.1	0.8 ± 0.2	0.8 ± 0.1
Blood	0.28 ± 0.05	0.17 ^c ± 0.02	0.29 ± 0.09	0.34 ^a ± 0.07
Spleen	0.049 ± 0.010	0.035 ^c ± 0.005	0.045 ± 0.014	0.066 ^b ± 0.016

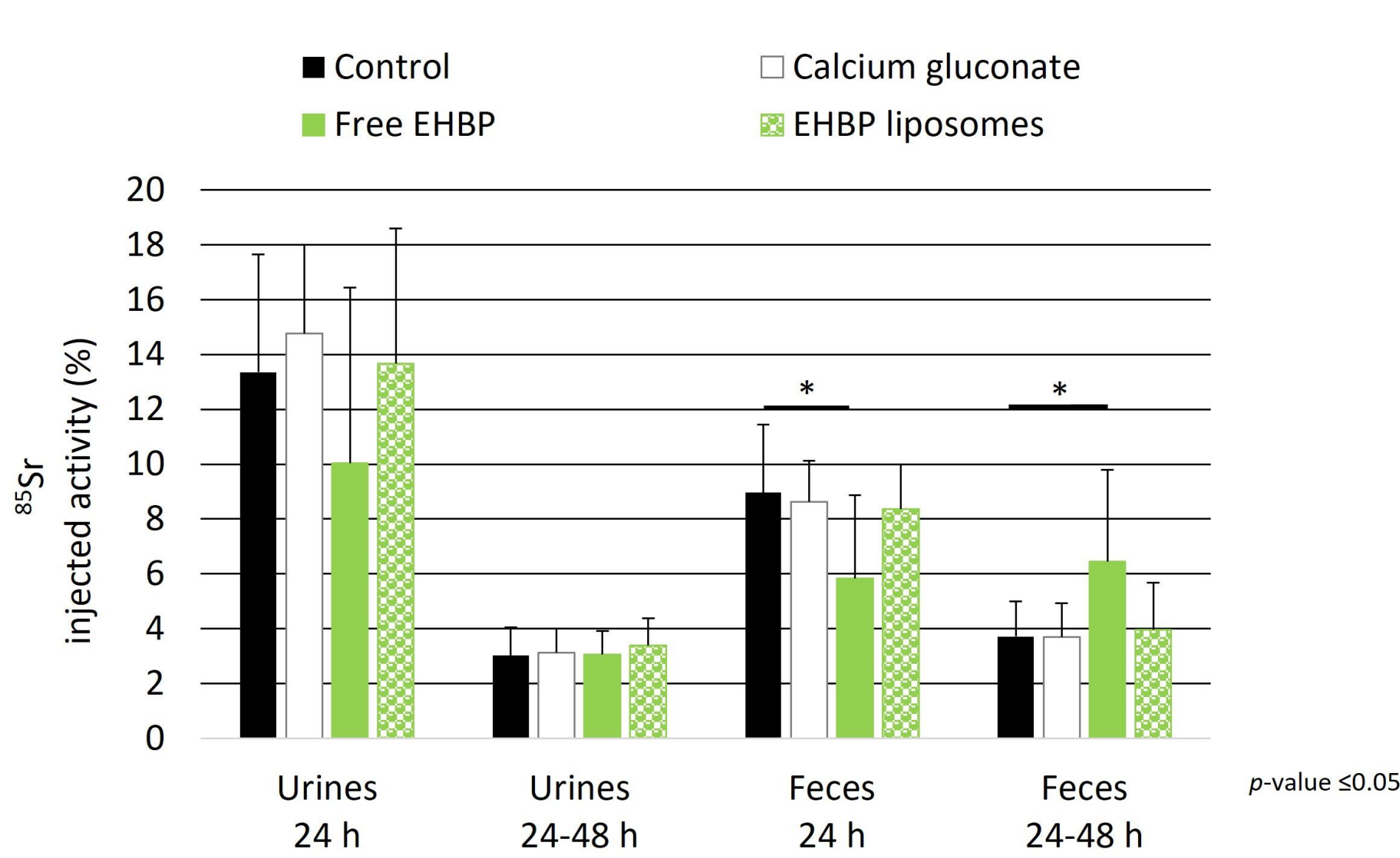
Treatments were administered by IV, at 30 μmol.kg⁻¹, 30 min after IV injection of 9 kBq ⁶⁰Co.
n, number of animals.
Significantly different from the control group: ^a p-value <0.05, ^b p-value <0.01, ^c p-value <0.001.

- ⁶⁰Co is excreted mainly in the urine and rapidly within 24 hours
- The liver is the main storage organ for ⁶⁰Co
- Low decorporation efficacy of reference medical treatment (DTPA)
- EHBP liposomes treatment => delayed action
 - Blood: release of EHBP from liposomes after prolonged circulation
 - Spleen (organ of the reticuloendothelial system): chelation of ⁶⁰Co by EHBP molecules release from liposomes

Strontium decorporation experiments

Efficiency study of 48 hours

Total elimination of ⁸⁵Sr on day 1 and between day 1 and day 2



Tissue distribution of ⁸⁵Sr at day 2 as function of treatments (% of injected activity, mean ± standard deviation)

	Control n=12	Calcium Gluconate n=8	Free EHBP n=8	EHBP liposomes n=8
Skeleton	59.1 ± 7.0	59.3 ± 7.3	64.9 ± 11.4	61.2 ± 9.8
Blood	0.12 ± 0.03	0.12 ± 0.02	0.16 ± 0.07	0.11 ± 0.03
Liver	0.03 ± 0.01	0.03 ± 0.01	0.03 ± 0.01	0.03 ± 0.01
Kidneys	0.02 ± 0.004	0.02 ± 0.004	0.03 ± 0.01	0.02 ± 0.003
Spleen	0.003 ± 0.001	0.003 ± 0.001	0.004 ± 0.002	0.003 ± 0.001

Treatments were administered by IV, at 30 μmol.kg⁻¹, 30 min after IV injection of 56 kBq ⁸⁵Sr.
n, number of animals.

- Elimination ⁸⁵Sr slower (urinary and fecal route)
- Preferential retention organ: skeleton
- Absence of efficacy of calcium gluconate (reference medical treatment)
- Absence of efficacy of EHBP-based treatments (free and liposomal form)

Efficiency study after 6 days

Tissue distribution of ⁸⁵Sr at day 6 as function of treatments (% of injected activity, mean ± standard deviation)

	Control n=4	EHBP liposomes n=8 ^a
Skeleton	46.3 ± 18.3	38.8 ± 10.5
Blood	0.03 ± 0.01	0.03 ± 0.006
Liver	0.007 ± 0.002	0.006 ± 0.001
Kidneys	0.006 ± 0.002	0.005 ± 0.002
Spleen	0.001 ± 0.0003	0.001 ± 0.0001

Treatment was administered by IV at 30 μmol.kg⁻¹ immediately after IV injection of 56 kBq ⁸⁵Sr.
n, number of animals.

^a Except for the spleen (n=7).

Longer-term decorporation study under more optimal conditions (no delay between injections):

- At T0 + 6 days, the skeleton retains most of the ⁸⁵Sr
- Following the use of EHBP liposomes, encouraging 16% reduction in ⁸⁵Sr content in the skeleton (result not significant)

Hypothesis of these results

- Low molar ratio (R_{L/M} = 4.6.10²)
- Strong competition with endogenous Ca²⁺
- Short plasma half-life of Sr (~ 1 h). When injections are delayed by 30 min, the kinetics of Sr and EHBP do not coincide.

CONCLUSIONS & PERSPECTIVES

Conclusions

- EHBP-based treatments did not show an expected efficacy under the conditions of administration (dosage and time) defined in our studies
- The results obtained with the reference treatments (DTPA salts and Ca gluconate) show little or no efficacy
 - ➔ questions about their use in the event of internal contamination

Perspectives

- Use more suitable decorporation conditions ➔ increase the R_{L/M} after EHBP toxicity studies
- Evaluate the effectiveness of decorporation over the longer term (more than 6 days) ➔ small stealth liposomes having a delayed action
- Increase the capabilities of the galenic formulation ➔ development of active stealth liposomes

REFERENCES

- Clarke, W. J., R. F. Palmer, et al. (1970). "Strontium-90: Effects of chronic ingestion on farrowing performance of miniature swine." *Science* 169(3945): 598-600.
- White, R. G., O. G. Raabe, et al. (1993). "Bone sarcoma characteristics and distribution in beagles fed Strontium-90." *Radiation Research* 136(2): 178-189.
- Yoshihisa, Y. and T. Shimizu (2012). "Metal allergy and systemic contact dermatitis: An overview." *Dermatology Research and Practice* 2012, N°749561.
- Adams, T. N., Y. M. Butt, et al. (2017). "Cobalt related interstitial lung disease." *Respiratory Medicine* 129: 91-97.
- Karagas, M. R., A. Wang, et al. (2022). "Carcinogenicity of cobalt, antimony compounds, and weapons-grade tungsten alloy." *The Lancet, Oncology* 23(5): 577-578.
- ASN (2008). *Guide National - Intervention médicale en cas d'événement nucléaire ou radiologique*.170 pages
- Landon, G., Phan, G., Fay, F., Bouvier-Capely, C., Fattal, E. (2023). "Nanotechnologies and controlled release formulations for the administration of bisphosphonates and their potential in radiation protection." *Journal of Drug Delivery Science and Technology* 90: 105154.
- Cremers, S. and S. Papapoulos (2011). "Pharmacology of bisphosphonates." *Bone* 49(1): 42-49.
- Burgada, R., T. Bailly, et al. (2007). "Synthetic strategy of new powerful tris-bisphosphonic ligands for chelation of uranyl, iron, and cobalt cations." *Tetrahedron Letters* 48(13): 2315-2319.
- Scheglova, N. V., T. V. Popova, et al. (2019). "Spectrophotometric study of complexation of cobalt (II) with HEDP in aqueous solutions." *Journal of Molecular Liquids* 286: N°110909.
- Niu, M., Y. Lu, et al. (2012). "Hypoglycemic activity and oral bioavailability of insulin-loaded liposomes containing bile salts in rats: The effect of cholate type, particle size and administered dose." *European Journal of Pharmaceutics and Biopharmaceutics* 81(2): 265-272.
- Allen, T. M., C. B. Hansen, et al. (1995). "Pharmacokinetics of long-circulating liposomes." *Advanced Drug Delivery Reviews* 16(2-3): 267-284.