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Sexual dimorphism in ^{137}Cs accumulation after chronic low dose exposure in mice

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The presence of Cesium-137 (^{137}Cs) in the environment after nuclear accidents at Chernobyl and Fukushima Daiichi raises many health issues for the surrounding populations chronically exposed through the food chain. Unlike previous in vivo studies that focused solely on male exposures, this experimental research aims to assess the biodistribution and dosimetry of low-dose ^{137}Cs internal exposure in both male and female C57BL/6 mice. This study uses a previously established model for chronic ingestion of ^{137}Cs, simulating various exposure scenarios. Male and female C57BL/6 mice were exposed to concentrations resembling those ingested daily by residents in contaminated areas (20 kBq/L), as well as 5- and 10-times higher concentrations, for either 6 or 24 weeks. These exposure periods were chosen to assess both short-term and long-term effects of chronic ^{137}Cs exposure, allowing us to observe differences in ^{137}Cs accumulation and elimination in mice. Throughout this period, the animals were closely monitored to determine and quantify the ^{137}Cs content and to calculate absorbed doses. After 6 or 24 weeks exposure to chronic ^{137}Cs in drinking water at 500 kBq/L, ^{137}Cs concentration varied according to the organs and the sex of the animals. Males showed a higher body burden of ^{137}Cs compared to females, with significant differences observed as soon as day 11. As well, the organs showing the highest ^{137}Cs concentrations were skeletal muscle in males and in females, with significant differences between males and females. Regarding excretion, it appears that the elimination of ^{137}Cs through feces was similar in males and females. By contrast, female mice showed a higher rate of ^{137}Cs urine excretion than males, thus explaining the lower body burden in females. The resulting absorbed doses, calculated using dose conversion factors provided by ICRP publication 108, showed that the absorbed dose is 1.85 times less in female mice compared to male mice. 36.1 mGy in females and 66.9 mGy in males after 6 weeks exposure. 182.0 mGy in females and 310.0 mGy in males after 24 weeks exposure. This study demonstrates for the first time, sexual dimorphism in ^{137}Cs biokinetics between males and females. These findings could refine biokinetic models of cesium and absorbed dose estimations in case of internal contamination, especially in post-accidental situations.

Internal contamination by Cesium-137 (^{137}Cs) is a significant concern in radioprotection, particularly following nuclear accidents. ^{137}Cs, an artificial radionuclide coming from uranium and plutonium fission in nuclear reactors can be used as source in radiation therapy. Following nuclear accidents, such as Chernobyl and Fukushima and the lesser-known Goiânia accident in Brazil, significant amounts of ^{137}Cs are released into the environment. Steinhauser et al., finds that Chernobyl released approximately 5.2 million TBq of radioactive material, significantly more than Fukushima's 0.9 million TBq[1]. This radionuclide enters the food chain through contaminated soil and water, ultimately accumulating in plants and animals. Beresford et al. investigated the transfer of ^{137}Cs to wildlife in terrestrial ecosystems, highlighting pathways of uptake and bioaccumulation by organisms[2]. They reports that radionuclide concentrations in wildlife resulted in radiation dose rates ranging from 0.1 to 50 µGy/h, with certain species like small mammals and invertebrates exhibiting higher exposure

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levels, reflecting the variable transfer rates and ecological impacts in the contaminated area[3]. Other studies underscore the potential for human exposure through the consumption of contaminated food sources[4–6]. Moreover, and due to its half-life of approximately 30 years, this is a persistent pollutant in the environment. A 2016–2018 study found 30% of participants had detectable radioactivity, highest with mushroom consumption, especially in winter[7].

The resulting absorbed doses to humans were evaluated in several studies. Cardis et al. (2006) described that about 5 million people continue to live in areas of Belarus, Ukraine and Russia that were contaminated by the accident of Chernobyl. The mean effective dose accumulated up to 2005 among residents in the strict control zones (with ^{137}Cs deposition density of 555 kBq/m^2 or more) is of the order of 50 mSv, while in less contaminated areas it is of the order of 10 mSv[8]. The extensive environmental contamination with long-lasting radionuclides such as cesium-137 and cesium-134, affecting over 5 million people and 150,000 square kilometers of land around Chernobyl[8]. In contrast, Fukushima's coastal location led to substantial marine contamination, while Chernobyl primarily impacted terrestrial ecosystems, with both accidents resulting in long-term environmental consequences. Another example is the Goiânia accident that provides a crucial example of acute localized contamination, wherein approximately 250 people were significantly exposed to ^{137}Cs due to the mishandling of a radiotherapy device containing the isotope and dissemination of ^{137}Cs[9].

Thus, assessing the biokinetic and the dosimetry of internal exposure to ^{137}Cs is crucial for understanding associated health risks, especially long-term effects on human health.

Given the critical need of the dose assessment aspects of radioisotope contamination, various studies have been conducted to assess the distribution, retention, and biological effects of radioisotope contamination in the human body. These studies employ sophisticated modeling techniques and empirical measurements to estimate the internal dose from radioisotope contamination and its subsequent health impacts[10–12].

Experimental studies involving animal models have provided valuable insights into the biological mechanisms underlying ^{137}Cs toxicity. These studies often involve controlled administration of ^{137}Cs- to assess its biodistribution, clearance rates, and resultant pathological changes. Such research is crucial for refining dose–response models and enhancing our understanding of the potential risks associated with chronic low-dose exposure. For instance, studies in adult, postnatal, and in utero rat models have assessed the effects of low-dose ^{137}Cs on circulating biomarkers, suggesting potential implications for human health[13]. Moreover, chronic contamination studies in rats have investigated the cardiovascular effects of ^{137}Cs, revealing significant impacts on cardiovascular biomarkers and functions such as hypotension[14]. Other, research based on $ApoE^{-/-}$ knockout animal models of mice suggests that chronic exposure to low-dose ^{137}Cs may positively impact the stability of atherosclerotic plaques by reducing inflammation[15]. These findings underscore the complexity of ^{137}Cs exposure scenarios and their potential health outcomes.

Despite substantial progress in knowledge, there remains a pressing need for further research, particularly focusing on the differential effects of ^{137}Cs between males and females. The paucity of sex-specific data limits our ability to make stratified risk assessments according to the sex and develop targeted mitigation strategies. However, it is now essential to address these gaps by studying the kinetics of contamination, the gender-specific distribution of 137Cs, and its organ-specific effects, in order to enhance future radiation protection guidelines.

In this study, we present a detailed biokinetic analysis of chronic ingestion of ^{137}Cs, simulating various exposure scenarios across both sexes and multiple organs. This provides a robust framework for future research and radiation protection policy development. In addition, we provide a dosimetric evaluation of absorbed doses resulting from chronic exposure to ^{137}Cs.

Materials and methods

Animal model and experimental design

All experiments and procedures were carried out in accordance with the Guide for the Care and Use of Laboratory Animals as published by the French regulations for animal experiments (Ministry of Agriculture Order No. B92-032-01, 2006) with European Directives (86/609/CEE), and were approved by the local ethical committee of the Institute for Radiological Protection and Nuclear Safety (Permit Numbers: P19-20, P21-03). This study is reported in accordance with ARRIVE guidelines.

Male and Female C57BL/6 J $ApoE^{-/-}$ mice, aged 8 weeks, were obtained from Charles River Laboratory. The mice were housed per group of 3 in standard laboratory conditions with a 12-h light/dark cycle, controlled temperature (22 ± 2 °C), and humidity (55 ± 10%). They were housed for 2 weeks before starting the experimentation for acclimatation.

The C57BL/6 J $ApoE^{-/-}$ mouse model was chosen as part of a coordinated experimental design involving multiple related studies, in order to ensure consistency and reduce overall animal use. Although the present study does not focus on cardiovascular outcomes, this model is concurrently used in a separate investigation on radiation-induced vascular effects. Using the same strain across studies supports comparability of data while adhering to the 3Rs principle (Replacement, Reduction, and Refinement). In addition, this well-characterized and widely available strain facilitates experimental reproducibility.

Humane endpoints and animal welfare

Mice were monitored daily for general health and behavior, and weighed regularly to detect any signs of distress. Early euthanasia was performed if animals exhibited significant distress or deteriorating conditions. To minimize stress and aggressive interactions, mice were housed in enriched groups of three, following supplier recommendations. Restraint during gamma spectrometry was limited to a maximum of one hour, with prior acclimation to reduce stress and avoid the need for anesthesia. Daily visual inspections and weekly body weight measurements were conducted. Criteria for intervention included signs such as social isolation, abnormal posture, or a weight loss exceeding 20%, which would prompt veterinary assessment and possible humane euthanasia.

Instances of fighting were managed by treating wounds and isolating affected animals as needed. Time spent in metabolic cages was limited and scheduled toward the end of the protocol to reduce animal discomfort. Euthanasia procedures involved anesthesia followed by exsanguination and cervical dislocation, performed in a dedicated room to minimize stress. Animals were continuously monitored for distress throughout the process.

Chronic ^{137}Cs exposure

The mice were randomly divided into four groups: ApoE-/- mice receiving either Evian bottle water ad libitum or Evian bottle water ad libitum supplemented with 0, 20, 100 kBq/l or 500 kBq/L of ^{137}Cs (^{137}Cs Cl final concentration 5×10^{-9} M, CERCA-LEA, Pierrelatte, France), during 6 weeks (n = 8 mice per group) and during 24 weeks (n = 15 mice per group).

The concentration in the water was verified at each dilution using a gamma spectrometer.

Water consumption monitoring

To accurately follow water consumption, the water bottles in each cage were weighed weekly. The initial weight of the water bottle after filling it was recorded, and then the bottle was reweighed after one week. The difference in weight was used to calculate the amount of water consumed, which was then divided by the number of mice per cage and the number of days between weightings to determine the average daily consumption per mouse. This process was repeated throughout the duration of the study to monitor the consistency of ^{137}Cs intake and to detect any changes in drinking behavior.

Internal dosimetry

Internal dose assessment was performed after in vivo measurements of the ^{137}Cs activity in the mice at different time points (n = 3 mice per group). This non-invasive method allowed for the quantification of ^{137}Cs in live animals. Mice were monitored at baseline, day 43, 83, 111 and 162 for the 24 weeks contaminations' group and day 1, 4, 11, 15, 20, 29, and 40 for the 6 weeks contamination group. The monitoring device consists of a lead-shielded cell and a germanium detector (model GR4020, Canberra, Olen, Belgium) with a 60-mm-diameter crystal and a 0.6-mm carbon composite window. The device was calibrated with known cylindrical sources of ^{137}Cs to ensure accurate quantification[16]. The activity of ^{137}Cs within each mouse was counted, and the data were processed to calculate the internal dose absorbed by each animal over time[17].

The in vivo measurements provided a measure of mice whole body activity at specific time points. For each monitoring session, the ^{137}Cs activity (in Bq) was determined and then normalized to the body weight of the mouse to obtain the activity concentration, a(t).

The internal dose of the animal (D in mGy) was calculated over the follow-up period (i.e. T = 6 or 24 weeks) as the integral of the dose rate, the dose rate being the product of a dose conversion coefficient (DCF in units of dose rate per activity concentration) and the activity concentration in the animal.

$$D = \int_0^T \dot{D}\,(t)\,dt = \int_0^T DCF * a\,(t)\,dt = DCF \int_0^T a\,(t)\,dt \tag{1}$$

The integral of the activity concentration was calculated by the trapezoidal rule. The last integral term in Eq. (1) has units of Bq*days/kg, i.e. the number of nuclear disintegrations per animal weight during the follow-up.

In the ICRP 108, an adult reference mouse does not exist. The closest animal in size and mass would be the frog with a mass of 31.4 g represented by an ellipsoid with dimensions of $8 \cdot 3 \cdot 2.5$ cm. Since DCF is intended to estimate the absorbed radiation dose due to a uniform internal contamination with a specified radionuclide in an animal, the main parameter to take into account is the mass of the animal used as a reference. In our study, assuming a mean body weight of 30 g for adult mouse, the most suitable DCF for ^{137}Cs appeared to be the one for the frog with a body weight of 3.14×10^{-2} kg and a DCF value for internal exposure of 3.7×10^{-3}(µGy/day)/(Bq/Kg)[18].

External dosimetry

To assess the external dose from environmental radiation within the cages, passive Radiophotoluminescent (RPL) dosimeters were placed in phantoms within the mouse cages. The dosimeters were calibrated according to the manufacturer's specifications and exposed alongside the animals throughout the experimental period. Dosimetric readings were taken at the end of the experiment and analyzed using standard dosimetric software to estimate the radiation dose received by the mice.

Tissue collection

Mice were terminally anesthetized after 6 or 24 weeks of contamination by intraperitoneal injection of ketamine/xylazine (300 µl IP). Blood was collected by cardiac puncture with a heparinized syringe. Mice were then euthanized by cervical dislocation and perfused with PBS through the left ventricular after sectioned the left renal artery to remove blood from other organs. Organs, including skeletal muscle, liver, kidneys, heart, spleen, muscle, lung, aorta, adrenals, brain, olfactory bulb and olfactory epithelium were collected, weighed, and processed for gamma spectrometry. These organs were selected according to their relevance to ^{137}Cs physiology and potential radiological impact.

Gamma spectrometry

Gamma spectrometric analysis was performed using a Wizard 2480 automatic gamma counter (PerkinElmer). Each organ was placed in pre-weighed counting tubes (n = 15 samples from different animals per group for skeletal muscle for 24 weeks contamination, n = 5 or 6 samples from different animals per group for other organs

and for 6 weeks contamination), and the gamma counter was calibrated with ^{137}Cs standards. The specific activity of ^{137}Cs in each organ was measured, with counts corrected for background radiation. The counting efficiency of 0.22 was determined using known activity standards, and the data were expressed as Bq/g of tissue. The detection limit was calculated using the formula:

$$4 \text{ x } (2 \text{ x background x time})^{0.5} / \text{time} \quad (2)$$

Only values above this detection limit were considered and reported. Urine samples were counted for 900 s, muscle samples for 1800s, the brain, heart, liver, spleen, and kidney samples for 3600 s each. To improve the accuracy of measurements in very small organs, the counting duration on the gamma counter was extended to ensure sufficient detection of low radioactivity levels, minimizing statistical errors and enhancing data reliability. For smaller organs and tissues, such as the aorta, olfactory epithelium, olfactory bulb, adrenal glands, and blood, the counting duration was 7200 s.

Metabolic cage housing

To evaluate metabolic changes and precise intake and excretion of ^{137}Cs, mice were placed in individual metabolic cages (Techniplast/France) for 24-h periods after 6 weeks of contamination (n = 8 per group). Food and water intake were monitored, and urine and feces samples were analyzed for ^{137}Cs- activity using a gamma counter.

Data analysis

Statistical comparisons between groups were performed using two-ways ANOVA followed by post-hoc tests to identify significant differences in radiation dose and ^{137}Cs distribution among different exposure groups and time points. For comparisons between males and females, non-parametric Mann–Whitney tests were used to assess sexual dimorphism, while multiple comparison tests corrected by Tukey's test were employed for time and sex analyses. Exact P-values are reported in the text and figures, with significance levels indicated as follows: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. GraphPad Prism, a statistical software used for data analysis and graphing, was utilized for data representation and statistical analysis (GraphPad Software, San Diego, CA, USA, www.graphpad.com).

Sample size determination

The sample size for this study was determined based on statistical, practical, and ethical considerations. We aimed to achieve sufficient statistical power to detect meaningful differences between groups while maintaining feasibility within our resource limits. The choice of a minimum of six animals per group was informed by previous studies in the field and established guidelines for comparable experimental designs. Some groups included larger numbers of animals to accommodate future planned experiments on vascular effects using subsets of the same mice. Potential exclusions due to humane endpoints, such as euthanasia from animal suffering, were also taken into account in the initial sample size planning.

Radiation safety

All handling of radioactive materials was performed exclusively by personnel trained and certified in radiation safety. Procedures strictly followed current regulatory guidelines to ensure the safety of researchers and to minimize environmental contamination.

Results

No difference in water consumption between male and female mice compared to their weight.

Throughout the study, water consumption of the animals was carefully monitored. The data showed no significant differences in the daily water intake per animal among the different contamination groups (0, 20, 100, and 500 kBq/L of ^{137}Cs) in males (Fig. 1A) or females (Fig. 1B). On average, the animals consumed between 3.3 and 5.1 mL of water per day.

Although there was a slight difference in water consumption between male and female mice, this variation was attributed to their differences in body weight (supplemental Fig. 1). When normalized to body weight, the water consumption was found to be consistent between the sexes, (Fig. 2). This suggests that the presence of ^{137}Cs in drinking water has no influence on their water consumption.

Male mice accumulate more ^{137}Cs in whole body than female mice after 6 and 24-weeks internal exposure

The whole-body activity was measured at different time points during 6 and 24-weeks exposure (Fig. 3). The whole-body measurements revealed that activity increases consistently with the concentration of ingested ^{137}Cs, without sexual dimorphism for the lowest concentrations of ^{137}Cs and reaches a plateau around 40 days. However, at the highest contamination level of 500 kBq/L, a significant sex-specific difference in measured activity appeared at 11 days and persisted until 24 weeks. Indeed, male mice contaminated with 500 kBq/L had a mean final measured activity of 577.77 10^3 Bq/kg for male mice vs 322.54 10^3 Bq/kg for female mice after 6-weeks of contamination and 476.49 10^3 Bq/kg for males vs 269.90 10^3 Bq/kg for females after 24 weeks of contamination. Whole body activity values were normalized to the weight of the animals suggesting that the differences cannot be attributed to a higher body weight among males.

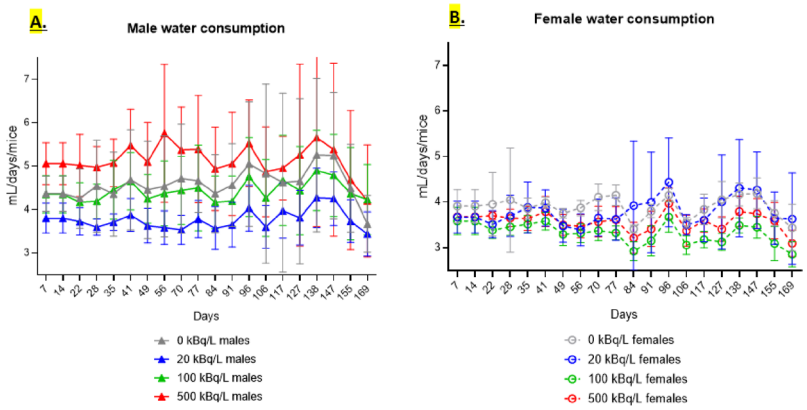

Fig. 1. Water consumption in male and female mice after ^{137}Cs exposure in drinking water with 0. 20. 100. 500 kBq/L during 24 weeks. (**a**) water consumption in male and (**b**) in female mice (n = 15 per group).

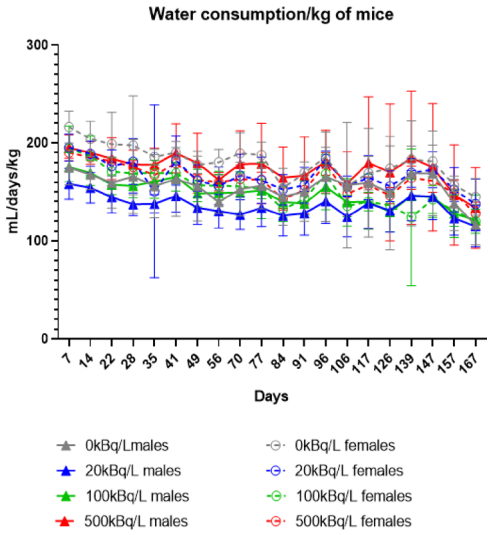

Fig. 2. Water consumption in all groups per Kg of mice over time (n = 15 per group).

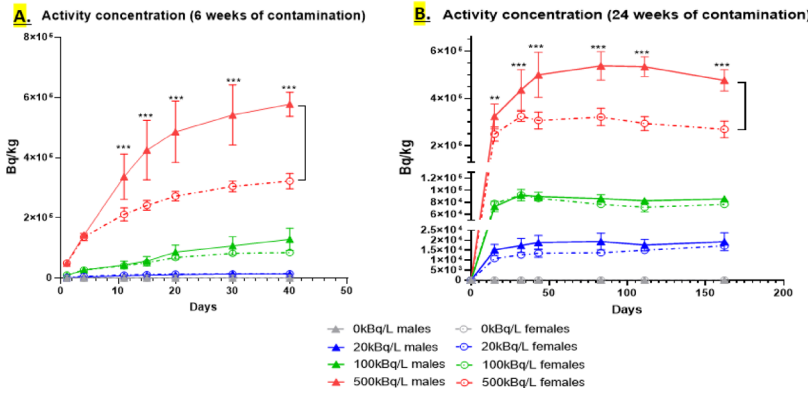

Fig. 3. Whole body activity measured over the time during the 6 weeks **(A)** or 24 weeks **(B)**^{137}Cs contamination experiment in Bequerel per gram of body weight. Two way Anova. Tukey multiple comparaison test ns: $p > 0.05$. *: $p < 0.05$; **: $p < 0.01$; ***:and ***:$p < 0.001$. (**A**) 500 kBq/L: Day 11: $p < 0.0001$; Day 15: $p < 0.0001$; Day 20: $p < 0.0001$; Day 30: $p < 0.0001$; Day 40: $p < 0.0001$. (**B**) 500 kBq/L: Day 15: $p = 0.0080$; Day 32: $p < 0.0001$; Day 43: $p < 0.0001$; Day 83: $p < 0.0001$; Day 111: $p < 0.0001$; Day 162: $p < 0.0001$.

Concentration of contamination	Males (Bq/g)			Females (Bq/g)		
	20 kBq/L	100 kBq/L	500 kBq/L	20 kBq/L	100 kBq/L	500 kBq/L
Skeletal muscle	**56.6** ± 12.9; (n = 15)	**279.9** ± 59.5; (n = 14)	**1281.6** ± 338.2; (n = 13)	**39.1** ± 15.5; (n = 12)	**180.8** ± 60.4; (n = 14)	**805.4** ± 246.7; (n = 14)
Right kidney (flushed)	**20.7** ± 3.5; (n = 6)	**103.0** ± 7.4; (n = 5)	**428.0** ± 128.7; (n = 6)	**21.7** ± 5.8; (n = 5)	**106.4** ± 24.1; (n = 6)	**403.3** ± 119.5; (n = 6)
Left kidney	**21.4** ± 3.8; (n = 6)	**105.0** ± 9.6; (n = 5)	**426.6** ± 142.2; (n = 6)	**18.6** ± 2.9; (n = 6)	**109.5** ± 10.2; (n = 5)	**358.8** ± 113.7; (n = 6)
Left adrenal	*ND*	**71.0**; (n = 1)	**297.5** ± 114.2; (n = 6)	*ND*	**77.1** ± 18.7; (n = 3)	**243.8** ± 64.6; (n = 6)
Heart	**14.0** ± 2.2; (n = 6)	**72.1** ± 5.6; (n = 5)	**289.6** ± 78.5; (n = 6)	**12.4** ± 3.1; (n = 5)	**62.7** ± 6.7; (n = 6)	**232.5** ± 49.6; (n = 6)
Olfactory epithelium	*ND*	**67.9** ± 18.9; (n = 5)	**273.4** ± 116.0; (n = 6)	*OOR*	**42.0** ± 19.8; (n = 6)	**239.3** ± 81.8; (n = 5)
Spleen	**10.8** ± 4.8; (n = 4)	**69.4** ± 37.1; (n = 5)	**272.9** ± 44.4; (n = 6)	**9.5** ± 3.2; (n = 5)	**51.1** ± 16.4; (n = 6)	**187.3** ± 50.3; (n = 5)
Liver	**10.7** ± 1.8; (n = 6)	**52.8** ± 4.1; (n = 5)	**258.2** ± 46.9; (n = 6)	**8.9** ± 2.3; (n = 5)	**39.1** ± 5.3; (n = 6)	**169.3** ± 27.1; (n = 6)
Olfactory bulb	**17.3** ± 7.3; (n = 6)	**57.7** ± 24.5; (n = 5)	**251.9** ± 200.2; (n = 6)	**13.7** ± 2.8; (n = 4)	**52.5** ± 10.6; (n = 5)	**237.5** ± 65.1; (n = 6)
Lung	**12.3** ± 3.7; (n = 5)	**53.9** ± 12.9; (n = 5)	**240.8** ± 36.4; (n = 5)	**6.7** ± 3.6; (n = 5)	**51.1** ± 17.3; (n = 6)	**215.6** ± 35.1; (n = 6)
Right adrenal	*ND*	*ND*	**211.2** ± 77.7; (n = 5)	*ND*	**85.7** ± 18.8; (n = 3)	**235.2** ± 65.1; (n = 5)
Brain	**9.1** ± 1.5; (n = 6)	**42.0** ± 2.3; (n = 5)	**200.6** ± 27.8; (n = 6)	**7.9** ± 2.0; (n = 5)	**36.1** ± 7.3; (n = 6)	**154.2** ± 31.3; (n = 6)
Aorta	*OOR*	**17.4** ± 10.3; (n = 6)	**63.1** ± 39.5; (n = 5)	*ND*	**22.8** ± 6.7; (n = 5)	**65.3** ± 49.1; (n = 6)

Table 1. Table of mean activity per gram of tissue in males and females different organs after 24 weeks ^{137}Cs contamination (OOR: out of range) (n = 15 per group for skeletal muscle. n = 5/6 per group for other organs). Values are expressed in Bq/g with standard deviation. ND indicates 'Not Detected', meaning the measurement is to low for the detection capacity of the instrument. (n = 15 per group for skeletal muscle. n = 5/6 per group for other organs).

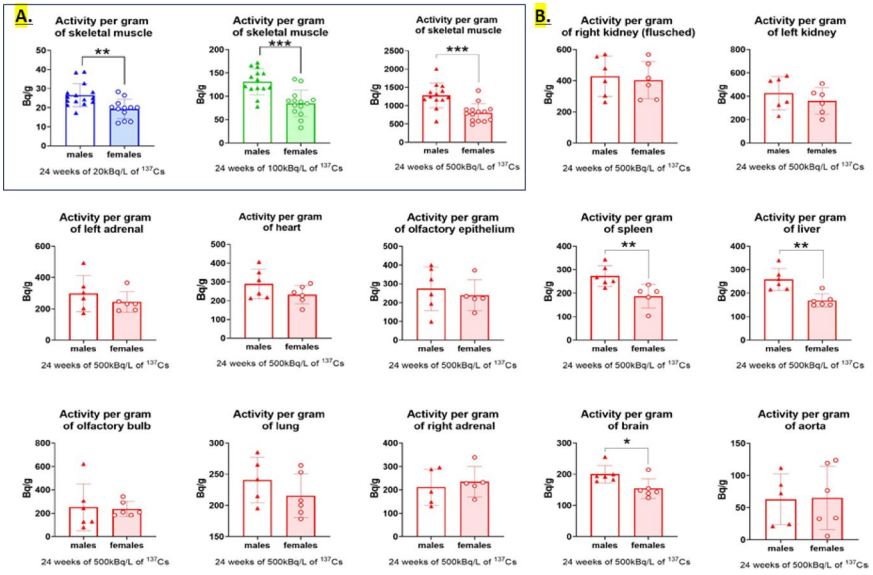

Fig. 4. ^{137}Cs Activity in Bq/g of tissue in skeletal muscle after 24 weeks of exposure at 20. 100 or 500 kBq/L (n = 15 per group) **(A)**. ^{137}Cs Activity in Bq/g of tissue in all other organs after 24 weeks of exposure at 500 kBq/L (n = 5/6 per group for other organs) **(B)**. Mann–Whitney test ns: $p > 0.05$. *: $p < 0.05$; **: $p < 0.01$ and ***:$p < 0.001$. (**A**) 20 kBq/L: p = 0,0026; 100 kBq/L: p = 0.0006; 500 kBq/L: p = 0,0004. (**B**) Spleen : p = 0.0087 ; Liver: p = 0.0087; Brain : p = 0.0411.

Female mice had lower ^{137}Cs activity per gram of tissue in different organs compared to males after 6 and 24-weeks exposure to 500 kBq/L

Biodistribution within different organs conducted after 6 and 24 weeks of contamination confirmed a relationship between ^{137}Cs-concentration in drinking water and activity measured in different tissues. Animals exposed to higher ^{137}Cs concentrations exhibited higher levels of radioactivity in their tissues, indicating increased uptake and accumulation over time (Table 1). Muscle tissue emerged as the primary site of ^{137}Cs accumulation. After 24 weeks, we observed a significant reduction in activity per gram of skeletal muscle in females exposed to 20 or 100 kBq/L compared to males (Fig. 4A), but not in other organs (data not shown). Moreover, in animals exposed to 500 kBq/L of ^{137}Cs, there was a significant reduction in activity per gram of skeletal muscle (805.4 Bq/g vs 1281.6 Bq/g, p = 0.0004), spleen (187.34 Bq/g vs 272.9 Bq/g., p = 0.0087), liver (169.3 Bq/g vs 258.2 Bq/g, p = 0.0087), and brain (154.2 Bq/g vs 200.6 Bq/g, p = 0.04) in females compared to males (Fig. 4B).

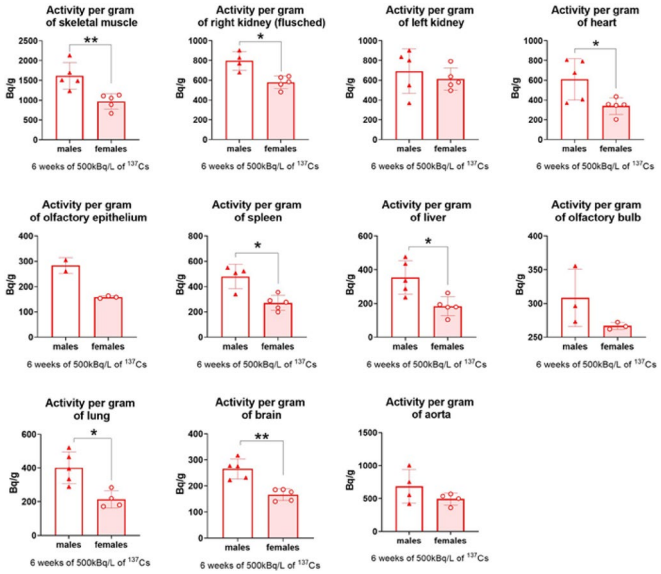

Fig. 5. Activity in Bq/g of tissue in different organs after 6 weeks ^{137}Cs contamination. (n = 6 per group. except for olfactory epithelium and bulb n = 3 per group) Mann–Whitney ns: $p > 0.05$. *: $p < 0.05$; **: $p < 0.01$ and ***:p < 0;001. Skeletal muscle: p = 0.0079 ; Right Kidney: p = 0.0159 ; Heart: p = 0.0317 ; Spleen: p = 0.0317 ; Liver: p = 0.0159 ; Lung: p = 0.0159 ; Brain: p = 0.0079.

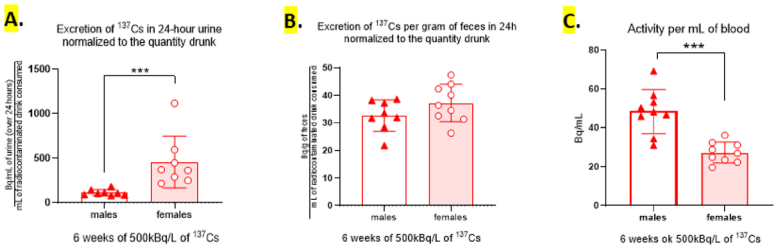

Fig. 6. ^{137}Cs Activity in Bq/mL in 24 h urines (**A**) and feces (**B**) in male and female mice exposed to 500 kbq/L of ^{137}Cs during 6 weeks. Activity in Bq/mL in blood of contaminated male and female mice exposed to 500 kBq/L of ^{137}Cs during 6 weeks (**C**). Mann–Whitney test ns: $p > 0.05$. *: $p < 0.05$; **: $p < 0.01$ and ***:$p < 0.001$. (**A**) P = 0.0002; (**C**) P = 0.0005.

This discrepancy in organ-specific activity levels may help explain the observed differences in whole-body ^{137}Cs accumulation between male and female animals.

To determine if there were modulations in the retention or elimination of ^{137}Cs in different organs over time, we conducted a study measuring ^{137}Cs activity after only 6 weeks of contamination. We did not observe any differences between males and females for animals contaminated with 20 or 100 kBq/L of ^{137}Cs (data not shown). However, Interestingly, the differences in ^{137}Cs accumulation between males and females were more pronounced in a wider range of organs after 6 weeks of contamination as compared to 24 weeks. Female mice, after 6 weeks of contamination, had also lower activity per gram of tissue in the muscle (968.9 Bq/g vq 1611.4 Bq/g, p = 0.0079), liver (183.9 Bq/g vs 354.4 Bq/g, p = 0.0159), and brain (166.7 Bq/g vs 265.4 Bq/g, p = 0.0079) as compared to males. However, after the 6 weeks of contamination, this reduced activity in females was also evident in the heart (338.6 Bq/g vs 610.4 Bq/g, p = 0.0317), lungs (214.2 Bq/g vs 401.5 Bq/g, p = 0.0159), spleen (271 Bq/g vs 480.5 Bq/g, p = 0.0317), and right kidney (578.4 Bq/g vs 795.1 Bq/g, p = 0.0159) (Fig. 5). It is important to note that the right kidney, unlike the left, was pre-cleaned of blood, suggesting potential differences in renal elimination processes.

Female mice eliminate more ^{137} Cs in urines than male mice after 6 weeks exposure to 500 kBq/L

To further investigate the observed differences in ^{137}Cs accumulation between male and female mice, we measured the ^{137}Cs activity in 24-h urine and feces samples of mice after 6 weeks of contamination at 500 kBq/L to evaluate the ^{137}Cs elimination. The activity was normalized to the volume of radiocontaminated water ingested by each mouse in 24 h. The results revealed a significantly higher excretion of ^{137}Cs in the urine of female mice as compared to male mice (458.1 Bq/mL/ml vs 114.5 Bq/mL/mL, p = 0.0002) (Fig. 6A) but not in feces (Fig. 6B).

The activity measured in males' blood was, in contrast to the urine, significantly higher in males than in females' (Fig. 6C). This increased urinary excretion in females supports the hypothesis that females eliminate ^{137}Cs more efficiently than males.

Whole body absorbed doses is higher in male mice compared to female mice after 6 and 24 weeks exposure to 500 kBq/L

The activity measured in the whole body, relative to the mice's weight allowed for the calculation of the total absorbed dose (Fig. 7). After 6 weeks of contamination, animals exposed to 20 kBq/L of ^{137}Cs had a mean absorbed doses ranging from 1.5 for females to 1.7 mGy for males. According to Eq. 1 the dose of 1.5 mGy corresponds to a time integrated activity concentration of 4.05E + 05 Bq*day/kg, which amounts to 1.05E9 nuclear disintegrations over 6 weeks for a typical animal weight of 30 g. The mice exposed to 100 kBq/L received mean absorbed doses ranging from 8.3 for females up to 11.2 mGy for males. At the highest contamination level of 500 kBq/L, a significant sex-specific difference was observed in absorbed dose since days 15. Male mice in this group received a notably higher mean absorbed dose of 66.9 mGy, which was approximately 1.9 times higher than the mean absorbed dose of 36.1 mGy observed in females (Fig. 7A). After 24 weeks of contamination animals exposed to 20 kBq/L of ^{137}Cs had mean absorbed doses ranging from 7.4 for females to 11.3 mGy for males (Fig. 7B). For those exposed to 100 kBq/L, the mean absorbed doses were between 46.8 mGy for females and 44.9 mGy for males but without significant differences. At the highest contamination level of 500 kBq/L, a significant sex-specific difference in absorbed dose was observed from the beginning of the measurement (6 weeks) to the end (24 weeks). Male mice in this group received a mean cumulative absorbed dose of 310.0 mGy, which was approximately 1.6 times higher than the mean absorbed dose of 182.0 mGy observed in females after 24 weeks (Fig. 7 B).

External radiation plays a minimal role in overall radiation exposure

External dosimetry measurements were conducted to assess potential radiation exposure from contaminated water bottles, contaminated mice and bedding materials. These measurements aimed to evaluate the contribution of external irradiation from ^{137}Cs present in the environment surrounding the animals. The results indicated a correlation between external radiation exposure and ^{137}Cs concentration in the water bottles. Higher ^{137}Cs levels in the bottles corresponded to increased external radiation levels detected by the dosimeters placed inside the cages. However, the external radiation exposure constituted less than 7% of the total absorbed dose, indicating that external irradiation was negligible compared to internal contamination after 6 or 24 weeks of contamination (Table 2).

Discussion

This study aims to investigates sex-specific differences in the retention and elimination of ^{137}Cs in mice exposed to chronic contamination through drinking water, simulating long-term low-dose ^{137}Cs exposure in populations affected by post-accident situations like Chernobyl[12]. Some studies have provided valuable insights into chronic ^{137}Cs- exposure in mice at a concentration of 20 kBq/L in drinking water[15,19]. In these investigations ^{137}Cs concentration corresponds to a daily ingestion of approximately 3.2 kBq/kg/day for mice, resulting in a daily exposure of approximately 75 to 90 Bq/day per animal[19]. This level of exposure reflects the estimated human intake of 20 to 2100 Bq/day by populations living in regions contaminated by the Chernobyl accident[4,5,20]. Other studies confirmed ^{137}Cs concentrations in total body or tissues reaching up to 2000 Bq g^{-1}[21,22]. Mice are known to be more radioresistant than humans, allowing us to observe effects of contamination at higher concentrations

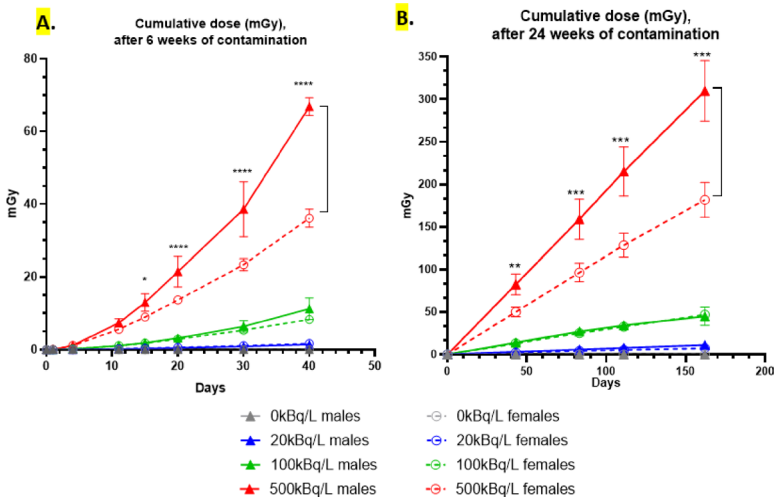

Fig. 7. Whole body Internal absorbed dose over the time during 6 weeks (**A**) or 24 weeks (**B**). Two way Anova. Tukey multiple comparaison test ns: $p > 0.05$. *: $p < 0.05$; **: $p < 0.01$ and ***:$p < 0.001$ 0 kBq/L; 20 kBq/L; 100 kBq/L and 500 kBq/L: $p < 0.0001$.

Absorbed dose	0 kBq/L		20 kBq/L		100 kBq/L		500 kBq/L	
	♂	♀	♂	♀	♂	♀	♂	♀
(A)								
Internal (mGy)	Not detectable	Not detectable	1.5	1.7	11.2	8.3	60.3	36.1
External (mGy)	0.1	0.1	0.6	1.9				
Total (mGy)	0.1	1.6	1.8	11.8	8.9	68.8	38.0	
External/Total (%)	100%	6.3%	5.6%	5.1%	6.7%	2.8%	5.0%	
(B)								
Internal (mGy)	Not detectable	Not detectable	11.3	7.4	44.9	46.8	310.0	182.0
External (mGy)	0.1	0.5	2.1	8.9				
Total (mGy)	0.1	11.8	7.9	47.0	48.9	318.9	190.9	
External/Total (%)	100%	4.2%	6.3%	4.5%	4.3%	2.8%	4.7%	

Table 2. Internal absorbed dose over time & total absorbed dose after 6 weeks (A.) or 24 weeks (B.) of ^{137}Cs contamination.

than would typically affect humans[23]. Our findings revealed that male mice accumulated more ^{137}Cs in the whole body than females at higher contamination levels (500 kBq/L), contrary to what we observed at lower concentrations (20 and 100 kBq/L). This sexual dimorphism suggests that males and females respond differently to high levels of ^{137}Cs in terms of absorption and retention.

To ensure that the observed differences genuinely reflect variations in ^{137}Cs uptake and retention patterns, rather than differences in body size, we normalized the results to the body weight of the animals.

As previously observed in other studies, our research also found that muscle tissue emerged as the primary site of ^{137}Cs accumulation, consistent with its chemical similarity to potassium or observations after Goiâna accident[9], and experimental studies on mice[19]. Cesium is incorporated into the intracellular compartment through active transport, primarily via potassium channels and Na + /K + -ATPase pumps[24] and the body's potassium levels influence the retention of cesium within cellular compartments[25,26]. This preferential accumulation in muscle underscores ^{137}Cs to mimic potassium in biological systems. The skeletal muscle was the only organ where a difference between males and females was observed at contamination levels below 500 kBq/L, only after 24 weeks of contamination. Although skeletal muscle is the primary site of accumulation, it does not appear to be sufficient to manifest a detectable difference between males and females in whole-body accumulation for contamination level of 20 or 100 kBq/L.

The biodistribution data revealed varying levels of ^{137}Cs across different organs, reflecting differential uptake patterns that were certainly influenced by tissue composition and metabolic activity.

Biodistribution analyses highlighted reduced ^{137}Cs activity per gram in various organs of females compared to males. This pattern suggests that females metabolize cesium less and may either eliminate ^{137}Cs more efficiently or retain it less effectively in different tissues, even at the onset of contamination. Furthermore, the organs exhibiting persistent sex-specific differences after 24 weeks of exposure are fewer in number and are those known to have higher potassium storage capacities as reported in the literature[27,28]. However, these are not necessarily the organs with the highest ^{137}Cs accumulation. This suggests that while the biodistribution of ^{137}Cs in primary organs such as muscle mirrors that of potassium, this parallel could not extend to all organs. The discrepancy may also be partly due to an artificially increased accumulation of ^{137}Cs in our measurement in the elimination organs as it passes through, despite the flushing performed to clear the circulation.

More importantly, measurement on flushed or not flushed kidneys highlight a difference in elimination through this organ. Indeed, ^{137}Cs is known to be eliminated 85% via urine, 13% is eliminated via feces and 2% through transpiration without any treatment like Prussian blue[29]. Our measurements of urine excretion revealed a significantly higher excretion rate in females. This supports the hypothesis of enhanced renal elimination of ^{137}Cs in females. This is consistent with their lower level of ^{137}Cs measured in the blood and could explain their lower body burden observed in female mice compared to males exposed to the same concentration of ^{137}Cs. Studies on sexual dimorphism in renal function provide insight into these findings. For instance, Veiras et al. highlighted the differential expression of renal transporters such as Na + -Cl − cotransporter or epithelial sodium channel between sexes, which involves potassium-related ion transporters that exhibited sexual dimorphism, impacting electrolyte handling[30]. As mentioned earlier, ^{137}Cs is known as a potassium analogue due to its chemical similarities, suggesting that differences in ion transporters between sexes could influence ^{137}Cs clearance.

This finding contrasts with the evidence from Goiânia, which did not show significant sex-specific differences in ^{137}Cs metabolism and elimination among the victims. One reason for this discrepancy is certainly the use of Prussian blue as a treatment in Goiânia to decorporate ^{137}Cs. Treatment with Prussian blue can reduce the biological half-life of ^{137}Cs from approximately 70 days to about 30 days, representing a reduction of around 60%[9]. Prussian blue binds to cesium in the gastrointestinal tract and enhances its excretion through feces, rather than urinary excretion. As a result, any potential differences in cesium elimination through urine between males and females were likely masked. While numerous studies have explored the accumulation of ^{137}Cs in humans following radioactive contamination, few have specifically investigated sex-based differences. For instance, Hoshi et al. (1996) reported minimal variation between males and females in the levels of ^{137}Cs accumulation among

children residing in the western districts of the Bryansk Oblast, following the Chernobyl incident. This finding is consistent with the general scarcity of data highlighting significant sex differences in radiocesium retention[21].

Additionally, the activity measured after 6 weeks of contamination with 500 kBq/L of ^{137}Cs in male organs such as kidneys, heart, spleen, lungs and aorta is higher than that measured after 24 weeks of contamination at the same concentration. This could be due to a difference of metabolic activity with age or suggest an adaptive response in the elimination process in reaction to chronic exposure in these organs but not in skeletal muscle, the primary site of accumulation, nor in the olfactory organs or liver, where substances from the blood can accumulate as part of a regulatory process[31–35].

The observed sex-specific differences in ^{137}Cs accumulation and elimination at 500 kBq/L but not at lower concentrations raise intriguing questions about the threshold effects and the role of physiological mechanisms. One plausible explanation is that at higher electrolyte concentrations, differences in renal function and ion transporters become more pronounced, leading to observable disparities in ^{137}Cs metabolism between males and females. In the study of Vieras et al., authors demonstrated that when female rats were given a potassium-rich meal (2% K+), they exhibited a stronger kaliuretic and natriuretic response than males, indicating that females maintain a lower set point for plasma potassium levels. Similar to males, this response was associated with a decrease in the total abundance of the sodium-chloride cotransporter (NCC) and its phosphorylated forms, suggesting that both sexes regulate potassium levels adaptively, but with a lower baseline plasma potassium concentration in females.[30]. This suggests that similar mechanisms might be at play with cesium, where high concentrations could exacerbate inherent sex-specific differences in transporter activity and renal handling, thereby influencing ^{137}Cs- clearance rates and retention. This study underscores the need for personalized approaches that consider individual variability in ^{137}Cs biokinetics and radiation response, with a particular focus on sex-specific differences influenced by hormonal, genetic, and physiological factors[36]. The increased excretion of ^{137}Cs observed in female mice suggests that enhancing renal clearance could be a potential strategy for reducing internal contamination and associated health risks in both sexes. Investigating the molecular mechanisms underlying these differences—such as the role of sex hormones, renal transporters, and genetic factors—could provide insights into therapeutic targets aimed at improving ^{137}Cs clearance and minimizing radiation exposure.

In this study, we focus on the absorbed dose, measured in milligrays (mGy), to quantify the energy deposited in the tissues of mice. It is important to note that the concept of effective dose, which includes tissue weighting factors, is specific to humans and is used to estimate the risk of stochastic effects such as cancer. Therefore, the effective dose is not applicable to animal studies due to differences in physiology and metabolism. A significant increase of the absorbed doses at 500 kBq/L of contamination in male mice compared to female mice could explain some sex-specific differences in biological effects. Indeed, measuring radioactivity in mice, associating the activity measured in becquerels with absorbed dose presents challenges due to the absence of a species-specific Dose Conversion Factor (DCF) for mice. To address this, we employed the DCF for frogs provided in CIPR 108, since frogs have a similar body weight to mice, despite physiological differences. This approach aligns with simplified methods commonly used in radiation dosimetry, where organisms are modeled as basic geometric shapes like ellipsoids or cylinders. Instead of accounting for radionuclide distribution across different organs, the focus is placed on estimating the average whole-body absorbed dose using DCF, which link the absorbed dose to the activity concentration in the organism or its environment. Although this method introduces some limitations, it provides a practical solution when species-specific DCFs are unavailable[37].

Our findings could partly explain threshold effects observed in different studies on radiation exposures and health effects suggesting that biological responses to radiation can vary significantly depending on dose levels and exposure scenarios[38–41]. Also the difference in absorbed doses between males and females at the highest contamination level could suggest that some biological sex-specific effects observed after internal exposure to ^{137}Cs is not only attributable to hormonal variations.

Preliminary results from this study were previously presented at international scientific meetings to promote early dissemination and receive feedback from the research community. Specifically, the study was presented as a poster at the European Radiation Research Society (ERRS) meeting in September 2022 (Catania, Italy), submitted as a poster to the European Radiation Protection Week (ERPW) in October 2022 (Estoril, Portugal), and presented as an oral communication at the annual meeting of the French Society for Radiation Biology (SFBR) in November 2022 (Saint-Raphaël, France).

Conclusions

These findings provide further evidence for sex-specific differences in ^{137}Cs metabolism and elimination, which are critical for understanding variations in radiation dose absorption and the resultant health impacts. The increased urinary excretion of ^{137}Cs-in females explain their lower internal contamination levels and underscores the importance of considering sex differences in studies of radioactive contaminant exposure. We highlight the complex and varied biological responses to internal cesium contamination. These responses necessitate a nuanced understanding of radiation biology that incorporates sex-specific differences in metabolism and elimination pathways. Such an approach will be crucial for developing effective and personalized strategies to mitigate the health risks associated with ^{137}Cs exposure. This research serves as a foundation for future experiments, such as the effect on vascular pathologies extending from 100 to 500 kBq/L, while accounting for sex differences. By addressing these gaps, our findings could significantly contribute to the existing body of knowledge and inform future research directions in radiobiology.

Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Received: 14 April 2025; Accepted: 26 September 2025
Published online: 03 November 2025

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Acknowledgements
The authors thank B.Leguen from EDF. This work was supported by grants from Electricite de France (EDF) to B. Leguen.

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Conceptualization, T.G.E..; Data curation, H.Q., C.B., C.E. E.C and F.B.; Formal analysis, H.Q., C.B., F.B, T.G.E., S.G; V.M, E.C Funding acquisition, T.G.E.; Investigation, H.Q, F.B, C.B, V.M, C.E Methodology, H.Q., C.B, F.B., C.E., D.B, Y.R, F.T, S.G, J.M.B; R.B; E.C Software, H.Q, D.B, J.M.B; R.B, D.B Supervision, T.G.E.; Validation, T.G.E.; Visualization, H.Q. C.E; V.M Writing—original draft, H.Q., Writing—review & editing, T.G.E.,J.M.B and H.Q.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by grants from Electricite de France (EDF) to B. Leguen.

Competing interests
The authors declare no competing interests.

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-22162-4.

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