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## Commentary

### **In Vivo Animal Studies Help Achieve International Consensus on Standards and Guidelines for Health Risk Estimates for Chronic Exposure to Low Levels of Tritium in Drinking Water**

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Existing and future nuclear fusion technologies involve the production and use of large quantities of tritium, a highly volatile, but low toxicity beta-emitting isotope of hydrogen. Tritium has received international attention because of public and scientific concerns over its release to the environment and the potential health impact of its internalization. This article provides a brief summary of the current state of knowledge of both the biological and regulatory aspects of tritium exposure; it also explores the gaps in this knowledge and provides recommendations on the best ways forward for improving our understanding of the health effects of low-level exposure to it. Linking health effects specifically to tritium exposure is challenging in epidemiological studies due to high uncertainty in tritium dosimetry and often suboptimal cohort sizes. We therefore argued that limits for tritium in drinking water should be based on evidence

derived from controlled *in vivo* animal tritium toxicity studies that use realistically low levels of tritium. This article presents one such mouse study, undertaken within an international collaboration, and discusses the implications of its main findings, such as the similarity of the biokinetics of tritiated water (HTO) and organically bound tritium (OBT) and the higher biological effectiveness of OBT. This discussion is consistent with the position expressed in this article that *in vivo* animal tritium toxicity studies carried out within large, multi-partner collaborations allow evaluation of a great variety of health-related endpoints and essential to the development of international consensus on the regulation of tritium levels in the environment. Environ. Mol. Mutagen. 59:586–594, 2018. © 2018 The Authors Environmental and Molecular Mutagenesis published by Wiley Periodicals, Inc. on behalf of Environmental Mutagen Society

**Key words:** toxicity; radiobiology; low dose; tritium; ionizing radiation; radioprotection

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## INTRODUCTION

Internationally, including within the European Union, it is accepted that both nuclear fission and, in the future, fusion technologies will play a significant role in the ongoing provision of low-carbon energy (OECD, 2013; European Commission, 2014; Edenhofer et al., 2014; UN, 2015b; Editorial, 2016). It is also widely accepted that many nations will need nuclear power to achieve the climate change goals they agreed to at the Paris Conference of Parties to the United Nations Framework Convention on Climate Change, in December 2015 (UN, 2015a).

Some existing and all future nuclear fusion technologies, however, involve the production or use of large quantities of tritium, a highly volatile, but low toxicity  $\beta$ -emitting isotope of hydrogen ( $^3\text{H}$ ). Although this radionuclide is not considered highly toxic, tritium has received international attention because of public concerns over its release, mostly in water, to the environment and any resulting potential health impacts (AGIR, 2007; CNSC, 2008; ASN, 2010; Stack, 2016). Because of the prevailing public perception of nuclear (but not natural and medical) radiation as “a mysterious, unequivocally hazardous and deadly force that needs to be avoided at any cost” (Jordan, 2016), public tolerance of radiation releases is poor.

Currently, environmental release of tritium is regulated both by discharge limits and application of the ALARA principle (As Low As Reasonably Achievable), which takes social and economic factors into consideration. Together, these ensure that environmental tritium levels and public exposure are minimized. Because the current radiation protection system is risk-based, these release limits and the application of ALARA should, it is generally agreed, be based on a secure scientific understanding of tritium's environmental behavior and true toxicity.

## TRITIUM REGULATION AND DOSIMETRY: ISSUES

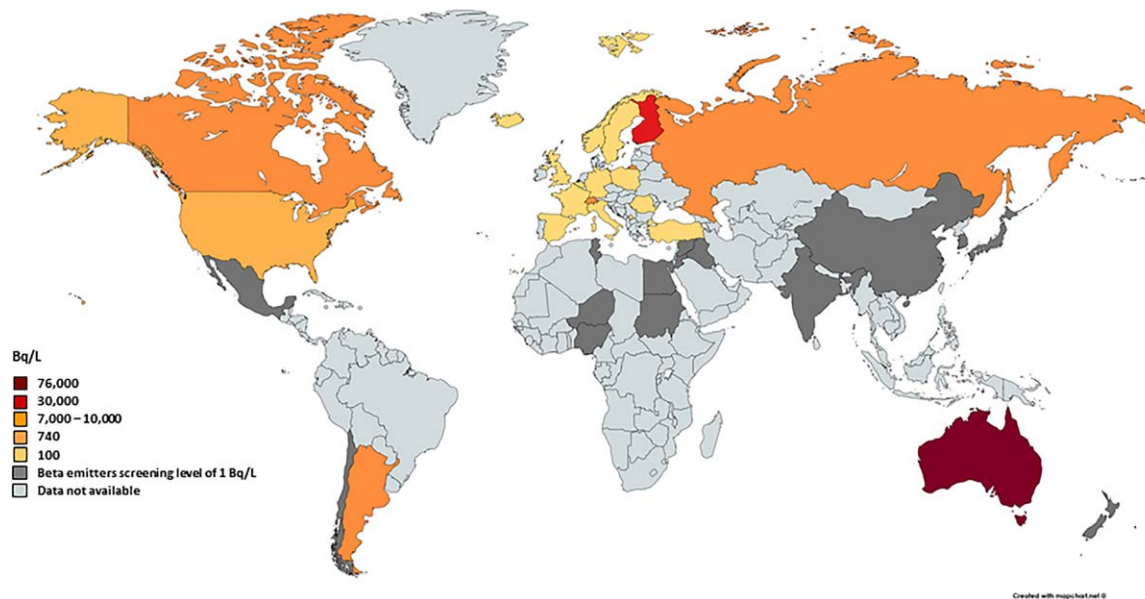
Dose limits and associated standards, including the drinking water standards for radionuclides adopted by most nations, are largely based on the recommendations of the International Commission on Radiological Protection (ICRP) and of the World Health Organization (WHO). These recommend an annual dose limit of 0.1 mSv from tritium (CNSC, 2008; WHO, 2011). By comparison, the average annual dose to the public from natural tritium is estimated at 0.01  $\mu\text{Sv}$  and the total effective dose due to natural radiation at 2.4 mSv/year (UNSCEAR, 2008, 2016). According to ICRP dosimetry models, this corresponds to a tritium level in drinking water of 7.61 kBq/L. Consequently, WHO has recommended a rounded-up guidance level of 10 kBq/L (WHO, 2011). These guidelines are not mandated limits, but are provided for the development of national drinking water standards. Countries remain free to set their own limits—

although, in most cases, these accord with those recommended by the ICRP and the WHO. For tritium, however, national drinking water standards vary by several orders of magnitude (CNSC, 2008; WHO, 2011; Brooks et al., 2013; IWA, 2017) (Fig. 1). This disparity is due in part to minor variations in how tritium activity is calculated by national bodies (CNSC, 2008). It also reflects differences in the application of ALARA, unique national priorities, and dosimetric uncertainties. These uncertainties result from the diverse speciation of tritium in the environment, due to its potential for incorporation into all types of organic molecules. Given the very low levels of tritium in global drinking water supplies, this wide variation in the limits presents few compliance problems (CNSC, 2008). Nonetheless, it is difficult to rationalize, induces controversy, reduces public confidence, and increases public concern. An obvious question must be asked: Is there any scientific toxicological evidence to justify any specific limit?

As indicated above, the root cause of many problems with tritium dosimetry is the complex speciation of this radioactive isotope of hydrogen. Tritium ( $^3\text{H}$ ) gas readily oxidizes to form tritiated water molecules ( $^1\text{H}^3\text{H}^{16}\text{O}$ ) and can subsequently enter biological pathways, becoming part of the organic molecules inside tissues and cells. Consequently, most tritium in the environment exists as either tritiated water (HTO) or as organically bound tritium (OBT). In the special case of heavy water reactors, tritiated heavy water ( $^2\text{H}^3\text{H}^{16}\text{O}$ ) is produced by neutron capture by deuterium ( $^2\text{H}$ ). For dosimetry purposes, it is assumed that tritium behaves the same in light and heavy water.

As a low-energy beta ( $\beta$ )-emitter, tritium poses a health risk only if internalized. The biokinetics of HTO, but not OBT, have been well characterized. Due to the very short average track length of tritium  $\beta$ -particles in water/tissues (mean  $<1 \mu\text{m}$ ), it must enter the nucleus/cell to damage DNA and/or produce other biological effects. Consequently, it is expected that forms of OBT fixed in the proximity of nuclear chromatin may cause more damage to the genome than HTO, which may either fail to enter a cell or transit through it quickly. Overall, it is clear that the toxicity of different tritium species will differ according to their location and retention time. Thus, a radiation weighting factor ( $w_R$ ) of 1 for  $\beta$ -particles of all energies (currently assigned for calculating the committed dose from chronic internal tritium exposure) may not always be appropriate (ICRP, 2007). Indeed, our own research has indicated that OBT, in the form of ingested amino acids, has greater biological activity than ingested HTO, as discussed below.

Relative biological effectiveness (RBE), a parameter in the derivation of  $w_R$ , is measured experimentally as the ratio of the doses of the reference radiation to the doses of the  $\beta$ -radiation producing equal biological effects.



**Fig. 1.** World map of international limits and guidelines for tritium in drinking water. WHO recommended guidance level is 10 kBq/L. Some countries, like EU countries, have a screening level for investigation and a guidance value which is the sanitary limit, while others only have a parametric value for  $\beta$ -emitting radionuclides. Constructed using data from (CNSC, 2008; IWA, 2017; WHO, 2011; Brooks et al., 2013).

Photon radiation types, most commonly gamma ( $\gamma$ )- and X-radiation, are used as references (ICRP, 2007). Importantly, this empirical value may depend on absorbed dose, the endpoint being measured, the type of reference radiation, and the experimental model. The wide range of these variables and uncertainties has led to varying assessments of the RBE for tritium and makes them difficult to interpret, as pointed out by (Little and Lambert, 2008). RBE estimates in their study ranged from 1.2 to 2.5 for carcinogenesis endpoints, from 0.43 to 2.65 for chromosomal aberrations, and from 0.43 to 3.5 for all endpoints and models considered.

In response to public and professional concerns, many study groups and regulatory organizations, including the Canadian Nuclear Safety Commission (CNSC) and the French Nuclear Safety Authority (ASN), have acknowledged that a higher  $w_R$  may be applied, at least for the purpose of sensitivity analysis in radiological impact assessment of tritium releases (AGIR, 2007; Lebaron-Jacobs et al., 2007; CNSC, 2008, 2010; ASN, 2010). Application of modified weighting factors, however, does not conform to the ICRP dosimetry paradigm, which recommends weighting factors for radiation types, and not for specific radionuclides. Using a higher value of  $w_R$  for very low energy  $\beta$ -emitters would impact the dosimetry of tritium, but also a wide range of other radionuclides, for example,  $^{241}\text{Pu}$ .

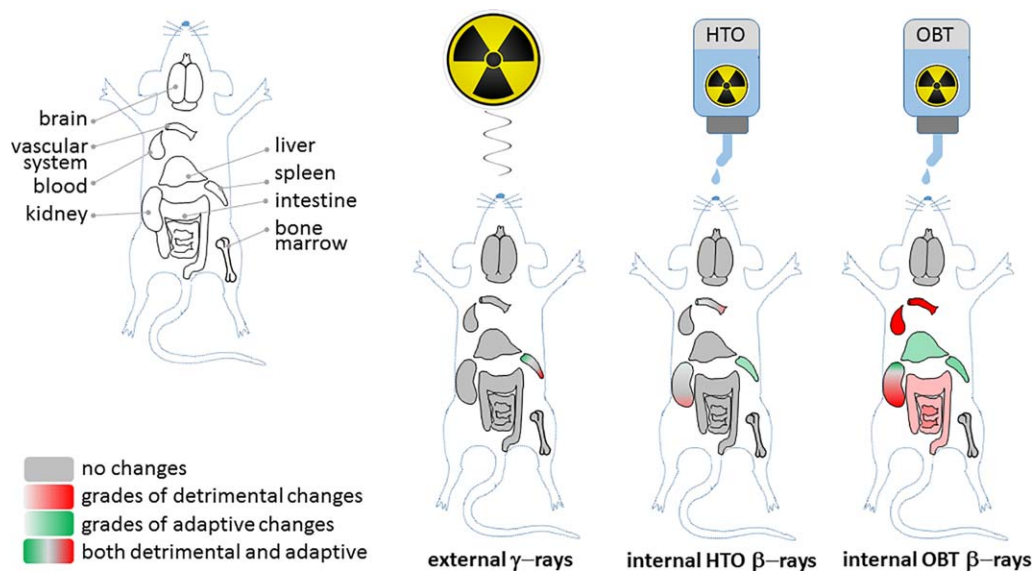
A science-based international consensus on regulatory limits for tritium in drinking water is necessary. Given the limitations of epidemiological studies, this consensus

should, in our opinion, be primarily supported by results of thoroughly planned toxicological studies in laboratory animals. Past *in vivo* and *in vitro* studies using acutely delivered tritium at high doses characterized the levels of tritium required to produce acute lethality, carcinogenicity, and teratogenic, reproductive and cytogenetic effects (Cronkite et al., 1973; Cahill et al., 1975; Brooks et al., 1976; Carsten et al., 1978). These doses were several orders of magnitude higher (GBq) than the average effective dose for the public. Studies of biological effects of low tritium levels ( $<1$  MBq/L) are extremely rare.

### TRITIUM TOXICITY STUDIES

A previous review of studies examining the RBE of tritium (Little and Lambert, 2008) showed that several issues remain unresolved. These include: (1) the use of inappropriately high doses and dose rates, which are irrelevant to occupational and public exposure doses, (2) the use of X-rays as reference radiation with an undefined spectrum of energy, and (3) the use of unmatched dose rates for tritium and a reference radiation.

To address these gaps, as well as the regulatory uncertainties described above, a collaboration was established between the Canadian Nuclear Laboratories (CNL, Canada), formerly known as the Atomic Energy of Canada Limited (AECL, Canada) and the Institut de Radioprotection et de Sûreté Nucléaire (IRSN, France), to conduct a large scale *in vivo* mouse study to examine both the



**Fig. 2.** Summary of mouse tissue responses to chronic external low level  $\gamma$ - or internal  $\beta$ -radiation exposures. In the joint CNL-IRSN study, a variety of molecular and cellular endpoints representing different biological processes, including DNA damage and repair, inflammation, and oxidative stress were evaluated. These were examined in the indicated organs/systems of laboratory mice. The tissue responses are shown schematically in

biokinetics of tritium and the biological effects of chronic internal exposure to low doses of it.

The study was designed based on the recommendations of the UK Health Protection Agency (now Public Health England) to use chronic exposures, very low dose rates, and equivalent dose rates of  $\gamma$ -radiation (AGIR, 2007). We took advantage of a globally unique facility at CNL, which allows low level chronic life-long radiation exposure studies on a large scale (thousands of mice), with both external and internal radiation emitters. Both cancer and non-cancer related endpoints were explored in this study. The wide range of measurements and variety of endpoints required the study to be divided into multiple tasks. More than 5,300 mice were used, as follows:

- Tasks 1 and 2: biokinetics of  $^3\text{H}$  (7 groups of  $n = 6$ , 11 time-points, 462 mice in total)
- Task 3: non-cancer toxicity markers (9 groups of  $n = 12$ , 2 time-points, 216 mice in total)
- Task 4: genotoxicity markers (9 groups of  $n = 12$ , 2 time-points, 216 mice in total)
- Task 5: genotoxicity, with the pkZ1 model (7 groups of  $n = 12$ , 2 time-points, 168 mice in total)
- Task 6: life span and tumorigenesis (12 groups of  $n = 300$  and 1 control group of  $n = 660$ , 4,260 mice in total).

Briefly, mice (C57Bl/6J males) were treated for either 1 or 8 months of continuous exposure to either HTO or OBT (a blend of three common tritiated amino acids: glycine, proline and alanine) in drinking water (0.01, 1, and 20 MBq/L dose levels) and to chronic  $^{60}\text{Co}$   $\gamma$ -irradiation

the diagram. This shows typical results for all endpoints and all doses (0.01 MBq/L, 1 MBq/L or 20 MBq/L) of either HTO or OBT in drinking water, or to equivalent doses and dose rates of  $^{60}\text{Co}$   $\gamma$ -radiation. Detailed information is provided in the Table I and will be disseminated in technical papers.

delivered at the same dose rates (1.4 and 31  $\mu\text{Gy/h}$ ). Although a great variety of various OBT molecule classes exist (Kim et al., 2013), amino acids were chosen because they are an important component of cellular metabolism and are not preferentially fixed within the DNA compartment, as tritiated thymidine is. The lowest dose of 0.01 MBq/L (0.014  $\mu\text{Gy/h}$ ) is consistent with the WHO guidance level for tritium in drinking water. This dose rate could not be matched by  $\gamma$ -radiation since it is less than one tenth than of the natural background radiation (range 0.11–1.25  $\mu\text{Gy/h}$ ) (UNSCEAR, 2008). It is also 100–1000 $\times$  higher than typical tritium levels in drinking water (CNSC, 2008). Levels of 1 and 20 MBq/L are found only at nuclear weapon test sites, where thermonuclear explosions have contaminated surface waters. Although the results of this study are being or will be published in a series of peer-reviewed experimental reports elsewhere (Bannister et al., 2016; Priest et al., 2017; Roch-Lefevre et al., in press), we present here a high-level summary of the findings. We feel that this generalization is important to support the opinion expressed in this article that animal studies are key sources of information to address regulatory inconsistencies related to tritium. Overall, the results indicate that (Fig. 2, Table I):

- The biokinetics of HTO and the form of OBT we used are similar (Priest et al., 2017), in contrast to the existing ICRP model (ICRP, 1989);
- HTO produced a larger dose-dependent biological response than equivalent doses of  $\gamma$ -radiation, and OBT exposures a still larger response ( $\gamma < \text{HTO} < \text{OBT}$ );

**TABLE I. Summary of Biological Changes Induced in Tissues of Mice Exposed to Tritium or Gamma Radiation**

	Biological Response			
	$\gamma$ -radiation*	HTO*	OBT*	
<b>Kidney</b>				
RedOx Status				
TBARS	–	–	↗	
gene expression	–	–	↘	
Metabolism				
gene expression (cholesterol, xenobiotic, vitamin D)	–	↗	↗	
gene expression (iron)	na	–	–	
Apoptosis				
caspase 3 activity	–	↗	↘	
gene expression	–	–	↗	
TUNEL histopathology	na	–	–	
DNA repair				
gene expression	–	–	↗↗	
Inflammation				
gene expression	–	–	↗↗	
cytokine levels	na	–	↗	
Nephrotoxicity				
Urine clinical chemistry (Urea, creat, Glc...)	na	–	–	
biomarkers (OPN, clusterin)	na	↗	↗	
gene expression	–	–	↗↗	
HES histopathology	na	–	–	
Macroscopic observation				
tissue weight	–	–	–	
<b>Central Nervous System</b>				
RedOx status				
gene expression	–	↘	↘	
Cholinergic system				
gene expression	–	↘	–	
Metabolism (cholesterol, xenobiotic, vitamin D)				
gene expression	na	–	↘	
Macroscopic observation				
tissue weight	–	–	–	
<b>Vascular System</b>				
RedOx status				
gene expression	–	↘	↘	
Endothelial dysfunction				
gene expression	–	↘	↘	
Inflammation				
gene expression	↘	↘	↗	
VCAM histopathology	na	–	↘	
ICAM histopathology	na	–	–	
<b>Liver</b>				
RedOx Status				
gene expression	–	–	↘	
Metabolism				
gene expression (cholesterol, xenobiotic, vitamin D)	–	–	–	
gene expression (iron)	na	–	↘	

TABLE I. (continued).

Apoptosis				
gene expression	—	—	—	
Hepatotoxicity				
gene expression	—	—	↘	■
HES histopathology	na	—	—	
Inflammation				
gene expression	—	—	—	
Macroscopic observation				
tissue weight	—	—	—	
<b>Blood</b>				
Hematopoiesis				
red and white blood cells count	—	—	—	
iron markers levels	—	—	↘	■
red blood cells volume	na	—	↘	
cytokine levels (EPO, Flt3-l)	na	—	—	
Chromosome damage				
chromosome aberrations (lymphocytes mFISH)	—	—	↗	■
<b>Spleen</b>				
Hematopoiesis				
gene expression (iron metabolism)	—	—	↘	
gene expression (red blood cells trapping)	—	—	—	
DNA damage				
γH2AX level	↘ ■	↘ ■	↘ ■	
DNA repair				
γH2AX kinetics after exogenous damage	—	—	—	
gene expression	↘ ■	—	—	
RedOx status				
gene expression	↗↘ ■	↗ ■	↗↗ ■	
DNA inversion				
pKZ1 inversions**	—	—	na	
Macroscopic observation				
tissue weight	—	—	—	
<b>Intestine</b>				
Apoptosis				
gene expression	na	↗	↗	
TUNEL in situ	na	—	—	
Cell migration / differentiation				
gene expression	na	—	—	
Cell division / proliferation				
gene expression	na	—	—	
Iron metabolism				
gene expression	—	—	↘	■
Tissue toxicity				
HES histopathology	na	—	—	
<b>Bone Marrow</b>				
Chromosome damage				
micronucleated erythroblasts	—	—	—	

\* data are summarized for three <sup>3</sup>H dose levels (0.01 MBq/L, 1 MBq/L and 20 MBq/L and two γ-radiation dose rates (1.4 and 31 μGy/h); \*\* pKZ1 mouse model on C57Bl6 background was used

—, no change; ↘ or ↗ slight down- or up-regulation; ↘↘↘ or ↗↗↗ strong down- or up-regulation; ■ likely detrimental effect; ■ likely adaptive response; ■ both detriment and adaptation are possible; na, not assessed

EPO, erythropoietin; HES, hematoxylin eosin saffron; ICAM, Intracellular adhesion molecule; mFISH, mouse fluorescence in situ hybridization; OPN, osteopontin; ROS, reactive oxygen species; TBARS, thiobarbituric acid reactive substances; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling; VCAM, vascular cell adhesion molecule

- Neither HTO nor OBT produced detectable biological effects at the WHO guidance level of 0.01 MBq/L;
- Some molecular and cellular responses to tritium seemed to be protective, while others were most likely detrimental; however, no pathological outcomes were observed macroscopically at any dose used;
- Responses to tritium were tissue-specific.

Many of these observations appear to provide important new information that must be considered in assessing the risk of tritium intake for radiological protection. For example, the similarity of biokinetics of HTO and OBT may support the need for adjustments to dosimetry for tritium exposure in humans. Neither the lack of effects at 0.01 MBq/L, suggesting a threshold rather than linear dose response, nor the simultaneous greater biological effectiveness of OBT at higher levels ( $\geq 1$  MBq/L) seem to support current practices in radiation protection. Lastly, since the main health effect considered in radiological protection is cancer, it is necessary to explore in greater detail the links between the physiological/gene toxicity markers and the biological outcomes used in radiological protection. Follow-up studies using additional mouse models and treatments and different toxicological and biological endpoints appear necessary.

## REMAINING QUESTIONS AND OUTLOOK

The study has produced interesting results that contribute to our understanding of the effects of low doses of tritium on processes that may impact cancer and non-cancer diseases. Experimental animal studies in the low-dose exposure domain are clearly the type of scientific research most likely to be relevant to the radioprotection of workers and populations and to provide answers to the questions raised by society. The doses employed by this study delivered total chronic doses of less than  $\sim 200$  mGy and clearly fall within the low dose exposure domain (Table II) (Roch-Lefèvre et al., in press).

This project required collaboration because of the wide range of endpoints to be studied and the need for chronic irradiation. The partnership between AECL/CNL and IRSN brought together the necessary groups specializing in genetics, epigenetics, immunology, toxicology and cancer biology, and their combined expertise facilitated our discovery of the complex interplay of different pathways and networks that are available to produce systemic outcomes. The study showed that for internal-emitter-exposure, like that from tritium, the dose received by the tissues is highly dependent on its speciation, distribution, and elimination. Microdosimetry or subcellular dosimetry and biochemistry experiments are needed to clarify in more detail why OBT produces a greater biological response than equivalent organ doses produced by HTO. For example, how much of the tritium, administered as tritiated amino acids, is incorporated into cell proteins?

**TABLE II. Estimated Dose Rates and Total Cumulative Doses Resulting from the 1 and 8-Month Exposures of Mice with 20 MBq/L of Tritium in Drinking Water or With External Gamma-Radiation**

Treatment group	Dose rate ( $\mu\text{Gy/h}$ )	Cumulative dose for 1 month (mGy)	Cumulative dose for 8 months (mGy)
Control	0	0	0
HTO 20 MBq/L	32.7	18.3	166
OBT 20 MBq/L	41.6	21.7	181.3
Gamma 31 $\mu\text{Gy/h}$	31.0	20.8	167

The regulation of tritium exposure can be improved by generating additional accurate scientific knowledge of systemic biological responses to it (such as cancer and other aging-associated diseases). Unfortunately, human epidemiological studies examining the health effects of tritium in workers or the general public are of limited help in deriving specific risk estimates, due to their low statistical power and the lack of tritium-specific absorbed doses to tissues (Little and Wakeford, 2008; ASN, 2010; UNSCEAR, 2016). Given the complexity of the interacting systemic responses, studies using *in vitro* methods are unlikely to be predictive of health outcomes. It is likely that the challenges presented by the toxicology of tritium will be solved most effectively by thoroughly planned large-scale collaborative *in vivo* research studies utilizing the large spectrum of available biological methodologies. Due to the scale and associated high costs of such mouse studies (e.g., the study examining cancer incidence and lifespan in CBA mice, still underway at CNL, involves  $>3,300$  mice and will finally take 6 years), funding by multiple national and international stakeholders is likely to be required. Unlike Europe's MELODI platform (Editorial, 2012), there are no funding programs specifically dedicated to low-dose radiation research in North America. By an open letter to the White House Office of Science and Technology Policy (Abbott, 2015) and a corresponding bill introduced in Congress (Conover, 2015), U.S. researchers have attempted to revive the low-dose radiation research program previously funded by the U.S. Department of Energy (DOE), but debates and progress in this area have remained dormant since June 2015 (U.S. Congress, 2015). This research program on the biological effects of low-dose radiation funded by Government of Canada (co-funded by the CNSC and the CANDU Owners Group) and maintained at CNL is accordingly unique and represents a great opportunity to bridge research performed in Europe with that in non-European countries.

As an essential part of our low-carbon energy future, both fission and future fusion face many acceptability challenges related to either radiological protection standards or public risk perception. Research to address these

requires support from all stakeholders, including government agencies, the nuclear industry, and academia. It is our contention that an open discussion of the topic in major science publishing media, such as this one, will facilitate sufficient interest to initiate action and allow the international radiological protection system to continue to evolve based on sound scientific evidence.

## AUTHOR CONTRIBUTIONS

YG, JRJ, and DK proposed the concept of the manuscript. NDP, ID, JRJ, DK, and YG designed the experimental study. HW applied for Research ethics approval and provided veterinary care and oversight. YG, LB, CD, TE, EG, SG, CI, AL, PL, SRL, and DK performed the experiments and collected data. All authors contributed to data analyses and interpretation. DK and YG wrote the manuscript with important intellectual input from ID, NDP and SRL. All authors read and provided input in finalizing the manuscript.

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## REFERENCES

Abbott A. 2015. Researchers pin down risks of low-dose radiation. *Nature* 523:17–18.

AGIR, (Advisory, Group, on, Ionising, Radiation). 2007. Report of the Independent Advisory Group on Ionising Radiation; Review of Risks from Tritium Radiation: HPA-RCE report series RCE-4.

ASN, (Autorité, de, Sûreté, Nucléaire). 2010. Livre blanc du Tritium & rejets de Tritium par les INB Autorité de Sûreté Nucléaire.

Bannister L, Serran M, Bertrand L, Klovov D, Wyatt H, Blimkie M, Gueguen Y, Priest N, Jourdain JR, Sykes P. 2016. Environmentally relevant chronic low-dose tritium and gamma exposures do

not increase somatic intrachromosomal recombination in pKZ1 mouse spleen. *Radiat Res* 186:539–548.

Brooks AL, Carsten AL, Mead DK, Retherford JC, Crain CR. 1976. The effect of continuous intake of tritiated water (HTO) on the liver chromosomes of mice. *Radiat Res* 68:480–489.

Brooks AL, Couch LA, Chad SA. 2013. Commentary: What is the health risk of 740 Bq L<sup>-1</sup> of tritium? A perspective. *Health Phys* 104:108–114.

Cahill DF, Wright JF, Godbold JH, Ward JM, Laskey JW, Tompkins EA. 1975. Neoplastic and life-span effects of chronic exposure to tritium. II. Rats exposed in utero. *J Natl Cancer Inst* 55:1165–1169.

Carsten AL, Commerford SL, Cronkite EP. 1978. The genetic and late somatic effects of chronic tritium ingestion in mice. *Curr Top Radiat Res Q* 12:212–224.

CNSC, (Canadian, Nuclear, Safety, Commission). 2008. Standards and Guidelines for Tritium in Drinking Water CNSC(INFO-0766).

CNSC, (Canadian, Nuclear, Safety, Commission). 2010. Health Effects, Dosimetry and Radiological Protection of Tritium INFO-799.

Conover E. 2015. U.S. lawmakers looking to intensify DOE's low-dose radiation research. *Science Insider* doi: 10.1126/science.aaa6325.

Cronkite EP, Robertson JS, Feinendegen LE. 1973. Somatic and teratogenic effects of tritium. Tritium. In: Moghissi AA and Carter MW. USA: Messenger Graphics Publication. pp. 198–210.

EC, (European, Commission). 2014. Towards an Integrated Roadmap: Research and Innovation Challenges and Needs of the EU Energy System EU Strategic Energy Technology Plan (JRC93056).

Edenhofer O, Pichs-Madruga R, Sokona Y, Farahani E, Kadner S, Seyboth K, Adler A, Baum I, Brunner S, Eickemeier P, et al., eds. 2014. IPCC, Climate Change 2014: Mitigation of Climate Change. Contribution of Working Group III to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change. Cambridge, United Kingdom and New York, NY, USA: Cambridge University Press.

Editorial. 2016. Energetic concerns: Rewarding existing nuclear power plants for the value of their low-carbon power makes sense, but the nuclear industry has a lot of work to do if it is to survive and thrive in the twenty-first century. *Nature* 536:125.

Editorial. 2012. The low-level nuclear threat. *Nature* 482:5.

ICRP, (International, Commission, on, Radiological, Protection). 2007. The 2007 Recommendations of the International Commission on Radiological Protection, Ottawa, Ontario, Canada

ICRP, (International, Commission, on, Radiological, Protection). 1989. Age-Dependent Doses to Members of the Public from Intakes of Radionuclides. Oxford: Pergamon Press, (Publication 56, Part 1).

IWA, (International, Water, Association). Compendium of Water Quality Guidelines. Available at: [http://www.iwa-network.org/filemanager/uploads/WQ\\_Compendium/Database/Selected\\_guidelines/](http://www.iwa-network.org/filemanager/uploads/WQ_Compendium/Database/Selected_guidelines/) [accessed 2017].

Jordan BR. 2016. The Hiroshima/Nagasaki survivor studies: Discrepancies between results and general perception. *Genetics* 203:1505–1512.

Kim SB, Baglan N, Davis PA. 2013. Current understanding of organically bound tritium (OBT) in the environment. *J Environ Radioact* 126:83–91.

Lebaron-Jacobs L, Müller W-U, Olko P, Risica S, Smeesters P, Wakeford R. 2007. Emerging issues on Tritium and Low Energy Beta Emitters Proceedings of a EU scientific seminar held in Luxembourg (European Commission): Radiation Protection No 152.

Little MP, Lambert BE. 2008. Systematic review of experimental studies on the relative biological effectiveness of tritium. *Radiat Environ Biophys* 47:71–93.

Little MP, Wakeford R. 2008. Systematic review of epidemiological studies of exposure to tritium. *J Radiol Protect* 28:9–32.

- OECD, (Organisation, for, Economic, Co-operation, and, Development). 2013. G20 Leaders' Declaration. St Petersburg Summit Paragraphs (90, 97).
- Priest ND, Blimkie MS, Wyatt H, Bugden M, Bannister LA, Gueguen Y, Jourdain JR, Klovov D. 2017. Tritium ( $^3\text{H}$ ) retention in mice: Administered as HTO, DTO or as  $^3\text{H}$ -labeled amino-acids. *Health Phys* 112:439–444.
- Roch-Lefèvre S, Grégoire E, Martin-Bodiot C, Flegat M, Fréneau A, Blimkie M, Bannister L, Wyatt H, Barquinero JF, Roy L, Bendadjaoud M, Priest ND, Jourdain JR, Klovov D. (in press). Cytogenetic damage analysis in mice chronically exposed to low-dose internal tritium beta-particle radiation. *Oncotarget*.
- Stack L. 2016. New York State to Investigate Radioactive Groundwater at Indian Point. Available at: [https://www.nytimes.com/2016/02/07/nyregion/new-york-state-to-investigate-radioactive-groundwater-at-indian-point.html?\\_r=0](https://www.nytimes.com/2016/02/07/nyregion/new-york-state-to-investigate-radioactive-groundwater-at-indian-point.html?_r=0).
- U.S. Congress. 2015. H.R.35 - Low-Dose Radiation Research Act of 2015.
- UN (United Nations). 2015a. Paris Agreement, Conference of Parties to the UNFCCC United Nations (FCCC/CP/2015/10/Add.1).
- UN (United Nations). 2015b. Transforming our world: The 2030 agenda for sustainable development.
- UNSCEAR. 2016. Sources, Effects And Risks Of Ionizing Radiation. United Nations Scientific Committee on the Effects of Atomic Radiation. Report to the General Assembly, with Scientific Annexes. Annex C, Biological effects of selected internal emitters—tritium. united nations publication.
- UNSCEAR. 2008. Sources, Effects And Risks Of Ionizing Radiation. United Nations Scientific Committee on the Effects of Atomic Radiation. Report to the General Assembly, with Scientific Annexes. Vol. 1. New York, NY: United Nations Publication.
- WHO (World, Health, Organization). 2011. Guidelines for Drinking-Water Quality. Fourth edition. Geneva: World Health Organization.

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