



HAL
open science

The ICRP, MELODI, and ALLIANCE workshop on effects of ionizing radiation exposure in offspring and next generations: a summary of discussions

Amilie Degenhardt, Shayenthiran Sreetharan, Aidana Amrenova, Christelle Adam-Guillermin, Fieke Dekkers, Sara Dumit, Sandrine Frelon, Nele Horemans, Dominique Laurier, Liudmila Liutsko, et al.

► To cite this version:

Amilie Degenhardt, Shayenthiran Sreetharan, Aidana Amrenova, Christelle Adam-Guillermin, Fieke Dekkers, et al.. The ICRP, MELODI, and ALLIANCE workshop on effects of ionizing radiation exposure in offspring and next generations: a summary of discussions. *International Journal of Radiation Biology*, 2024, Special Issue of the ICRP 2022 Budapest workshop, 20247, pp.1-11. 10.1080/09553002.2024.2306335 . hal-04598255

HAL Id: hal-04598255

<https://hal.science/hal-04598255v1>

Submitted on 3 Jun 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License



The ICRP, MELODI, and ALLIANCE workshop on effects of ionizing radiation exposure in offspring and next generations: a summary of discussions

Ämilie Degenhardt, Shayenthiran Sreetharan, Aidana Amrenova, Christelle Adam-Guillermin, Fieke Dekkers, Sara Dumit, Sandrine Frelon, Nele Horemans, Dominique Laurier, Liudmila Liutsko, Sisko Salomaa, Thierry Schneider, Manoor P. Hande, Richard Wakeford & Kimberly E. Applegate

To cite this article: Ämilie Degenhardt, Shayenthiran Sreetharan, Aidana Amrenova, Christelle Adam-Guillermin, Fieke Dekkers, Sara Dumit, Sandrine Frelon, Nele Horemans, Dominique Laurier, Liudmila Liutsko, Sisko Salomaa, Thierry Schneider, Manoor P. Hande, Richard Wakeford & Kimberly E. Applegate (29 Jan 2024): The ICRP, MELODI, and ALLIANCE workshop on effects of ionizing radiation exposure in offspring and next generations: a summary of discussions, *International Journal of Radiation Biology*, DOI: [10.1080/09553002.2024.2306335](https://doi.org/10.1080/09553002.2024.2306335)

To link to this article: <https://doi.org/10.1080/09553002.2024.2306335>



Published online: 29 Jan 2024.



Submit your article to this journal [↗](#)



Article views: 182



View related articles [↗](#)
















View Crossmark data [↗](#)

MEETING REPORT



The ICRP, MELODI, and ALLIANCE workshop on effects of ionizing radiation exposure in offspring and next generations: a summary of discussions

Ämilie Degenhardt^a, Shayenthiran Sreetharan^b , Aidana Amrenova^c, Christelle Adam-Guillermin^c , Fieke Dekkers^d , Sara Dumit^e , Sandrine Frelon^c , Nele Horemans^f , Dominique Laurier^c , Liudmila Liutsko^g , Sisko Salomaa^h , Thierry Schneiderⁱ , Manoor P. Hande^j , Richard Wakeford^k , and Kimberly E. Applegate^l 

^aDivision of Medical and Occupational Radiation Protection, German Federal Office for Radiation Protection (BfS), Neuherberg, Germany; ^bRadiation Safety, London Health Sciences Centre (LHSC), London, Canada; ^cFrench Institute for Radiological Protection and Nuclear Safety (IRSN), France; ^dNational Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands; ^eLos Alamos National Laboratory, Radiation Protection Division, Los Alamos, NM, USA; ^fBelgian Nuclear Research Centre (SCK CEN), Mol, Belgium; ^gIDIAP JGol/ICS/ISGlobal, Spain; ^hRadiation and Nuclear Safety Authority (STUK), Finland; ⁱNuclear Protection Evaluation Centre (CEPN), Fontenay-aux-Roses, France; ^jYong Loo Lin School of Medicine, National University of Singapore, Singapore; ^kCentre for Occupational and Environmental Health, The University of Manchester, UK; ^lDepartment of Radiology (retired), University of Kentucky College of Medicine, Lexington, KY, USA

ABSTRACT

Purpose: Task Group 121 – Effects of ionizing radiation exposure in offspring and next generations – is a task group under the Committee 1 of the International Commission on Radiological Protection (ICRP), approved by the Main Commission on 18th November 2021. The main goals of Task Group 121 are to (1) review and update the scientific literature of relevance to radiation-related effects in the offspring of parent(s) exposed to ionizing radiation in both human and non-human biota; (2) to assess preconceptional and intrauterine effects of radiation exposure and related morbidity and mortality; and, (3) to provide advice about the level of evidence and how to consider these preconceptional and postconceptional effects in the system of radiological protection for humans and non-human biota.

Methods: The Task Group is reviewing relevant literature since Publication 90 'Biological effects after prenatal irradiation (embryo and fetus)' (2003) and will include radiation-related effects on future generations in humans, animals, and plants. This review will be conducted to account for the health effects on offspring and subsequent generations in the current system of radiological protection. Radiation detriment calculation will also be reviewed. Finally, preliminary recommendations will be made to update the integration of health effects in offspring and next generations in the system of radiological protection.

Results: A Workshop, jointly organized by ICRP Task Group 121 and European Radiation Protection Research Platforms MELODI and ALLIANCE was held in Budapest, Hungary, from 31st May to 2nd June 2022. Participants discussed four important topics: (1) hereditary and epigenetic effects due to exposure of the germ cell line (preconceptional exposure), (2) effects arising from exposure of the embryo and fetus (intrauterine exposure), (3) transgenerational effects on biota, and (4) its potential impact on the system of radiological protection.

Conclusions: Based on the discussions and presentations during the breakout sessions, newer publications, and gaps on the current scientific literature were identified. For instance, there are some ongoing systematic reviews and radiation epidemiology reviews of intrauterine effects. There are newer methods of Monte Carlo simulation for fetal dosimetry, and advances in radiation genetics, epigenetics, and radiobiology studies. While the current impact of hereditary effects on the global detriment was reported as small, the questions surrounding the effects of radiation exposure on offspring and the next generation are crucial, recurring, and with a major focus on exposed populations. This article summarizes the workshop discussions, presentations, and conclusions of each topic and introduces the special issue of the International Journal of Radiation Biology resulting from the discussions of the meeting.

ARTICLE HISTORY

Received 8 August 2023
Revised 19 December 2023
Accepted 10 January 2024

KEYWORDS

Preconceptional exposure; epigenetics; radiation exposure; non-human species; offspring; prenatal exposure

Introduction

The potential for radiation-related deleterious effects in offspring is a recurrent issue for the general public and a concern for parents exposed or potentially exposed to

ionizing radiation from occupational, medical or environmental sources. There are still some gaps in the knowledge (and subsequent uncertainties in risk estimates) about the fundamental mechanisms underlying potential

radiation-related genetic diseases, the contribution of epigenetic processes to adverse outcomes, and the potential contributory role of lifestyle, physiological, and maternal versus paternal factors. This uncertainty is reinforced by several studies with differing experimental set up or models either in the laboratory and/or in the field on various fauna and flora species, and between humans and non-human species.

This topic has not been updated by the ICRP since 2003 for intrauterine exposures (Publication 90, 2003) and since 2001 for hereditary effects by UNSCEAR (UNSCEAR 2001). More recently, NCRP Report No.174 covered this subject in 2013 but not reviewed studies of non-human biota (NCRP 2013). In the current system of radiological protection, congenital malformations due to intrauterine exposures are considered as tissue reactions (formerly called deterministic effects) whereas cancer and hereditary effects are considered stochastic effects. Consequently, in some ways, congenital malformations are considered both as stochastic effects and tissue reactions, depending on the type of exposure (preconceptional or intrauterine). Currently, hereditary effects are considered as a simple add-in risk estimate to the radiation detriment calculation process, representing approximately four percent of the total. So far, there is no specific consideration that the data used for the calculations are derived primarily from animal experiments. A revised assessment of the effects of ionizing radiation on offspring and the next generations is needed to inform future general recommendations of the ICRP on the system of radiological protection. In the second half of 2021, an ICRP task group (TG121) was formed dedicated to this topic.

One of the first major projects of this task group (TG) was to bring together its members and other experts to examine key questions to study, to generate updates of current knowledge and to identify ongoing knowledge gaps. The TG identified MELODI and ALLIANCE as interested organizational partners. The present article summarizes the discussions that took place during the Workshop 'Effects of Ionising Radiation Exposure in Offspring and Next Generations' in May-June 2022 in Budapest in conjunction

with the sixth European Congress of International Radiation Protection Association (IRPA).

Motivation of the workshop and breakout sessions

The MELODI, ALLIANCE and ICRP Workshop 'Effects of Ionising Radiation Exposure in Offspring and Next Generations' took place from 31st May to 2nd June. Invitations were sent out to these three organizations for participation. There were 52 (32 in-person and 20 online) workshop participants. Short presentations at the breakout sessions were planned. Before the workshop, participants were assigned to one of the four breakout groups. In each group, specific questions were prepared in advance to guide discussions.

Group A: Hereditary and epigenetic effects due to exposure of germ cell line (preconceptional exposure) (Sisko Salomaa, chair; Manoor Prakash Hande, co-chair; and Fieke Dekkers, Katalin Lumniczky – rapporteurs);

Group B: Effects arising from exposure of the embryo and fetus (post-conceptional exposure, also termed the prenatal period) (Richard Wakeford, chair; Kimberly Applegate, co-chair; and Liudmila Liutsko, Ämilie Degenhardt, Sara Dumit – rapporteurs);

Group C: Transgenerational effects in biota (Christelle Adam-Guillermin, chair; Nele Horemans, co-chair; and Sandrine Frelon, Shayan Sreetharan – rapporteurs);

Group D: Potential impact on the System of Radiological Protection (Dominique Laurier, chair; Thierry Schneider, co-chair; and Aidana Amrenova, Friedo Zölzer – rapporteurs) (Figure 1).

The Workshop began with a plenary session for all participants with in-depth presentations on the current understanding of genetics, epigenetics, trio studies, and congenital malformations in children of atomic bomb survivors. Transversal topics were presented on both the dosimetry and confounders/complexity of health effects of radiation



Figure 1. The first page of the announcement and invitation sent out and also placed on the ICRP web page.

pre- and post-conception. Most of the discussions were held in the four breakout groups during the 2 first days of the Workshop. On the final day, the breakout groups prepared and presented the summary of their discussions.

The final day of the workshop included a joint session between ICRP TG121 and the IRPA radiation biology session. Presentations included dosimetry issues of epidemiological studies of Chernobyl clean-up workers (Vadim Chumak, Ukraine), and effects of radiation exposure on offspring and next generations in both human and non-human biota. Sisko Salomaa presented a brief review of the key genetic and epigenetic factors for the TG121 consideration (representing Group A) while Richard Wakeford summarized the current radiation epidemiology effects from intrauterine exposures. Stephane Grison discussed 'Multigenerational Effects from Chronic Low-Dose Intrauterine Exposure' in a mouse model (representing Group B). Christelle Adam-Guillermin presented current knowledge of hereditary effects in non-human species (representing Group C) and Dominique Laurier gave an overview of the potential impact and issues for consideration in the system of radiological protection (representing Group D). Several complementary manuscripts from the presentations at the workshop were agreed to be prepared and to be published in this special issue of the International Journal of Radiation Biology.

All TG121 workshop presentations were recorded and are available on the ICRP website.

Group A – Hereditary and epigenetic effects due to exposure of germ cell line (preconceptional exposure)

The activities of Group A started with short topical presentations of the state of the art on recent developments that are relevant to our understanding of the effects of preconceptional exposure. An epidemiological re-analysis of the A-bomb survivor studies showed consistent, but not significant, associations between preconceptional exposures and the increase in the risk of major congenital malformations and perinatal death (Yamada et al. 2021). In another important trio study – exposed parents and their offspring – the findings indicated that multisite *de novo* mutations could be suitable to assess DNA damage from ionizing radiation in humans (Holtgrewe et al. 2018). However, in both the Yamada and Holtgrewe studies, information about dosimetry was limited. In addition, tools such as whole genome sequencing have opened new possibilities for research (Satoh et al. 2020). A critical point addressed was on the uncertainty on the risks associated with preconceptional exposure.

State of the science since the last general recommendations

Based on the state of the art on technologies used in the analysis of mutations following preconceptional exposures, no conclusive evidence has emerged for the effects of preconceptional exposure leading to disease in humans (Holtgrewe. 2018). A re-analysis of A-bomb survivor studies

is indicative of effects on untoward pregnancy outcomes, although most results are not statistically significant (Yamada et al. 2021).

Whereas studies of the A-bomb survivors can contribute to risk estimates, trio studies are not yet at a stage where long-term risk estimations for preconceptional exposures could be evaluated. Trio studies appear to point toward an effect of age of the individual during the exposure rather than dose. It should be noted that in trio studies involving military personnel exposed during atmospheric testing, the effects of low doses incurred 60–70 years ago have been investigated (Rake et al. 2022; Moorhouse et al. 2022). However, they are characterized by having large uncertainties on the estimates of the external and internal exposures. Regarding the health endpoints that are seen as potentially relevant after preconceptional exposure, they have not changed in recent years, but new findings on mechanisms that may contribute have emerged, indicating that epigenetic mechanisms may play an important role on the effects of the radiation exposure during preconceptional phases to the offspring and next generations. However, quantitative estimates for such effects are not yet available.

Epidemiology: open questions, directions for further research and new cohorts

Follow-ups of existing epidemiological cohorts did not start until years after exposure for example in Hiroshima/Nagasaki and Chernobyl, and in the nuclear weapons testing veterans, and therefore contain very limited information about possible sensitive stages in oogenesis or spermatogenesis. Existing epidemiological studies therefore would not be a reliable source of information on sensitive stages in preconceptional exposure. In addition, dosimetry is still a challenge in epidemiological studies, due to the lack of information on background radiation exposure and other parameters to estimate the radiation exposure.

It was remarked that in trio studies, parental age is particularly important (Kaplanis et al. 2022), as can be seen from the following: the doubling *parental age* for mutations in off-spring is 20–40 years; the doubling dose of ionizing radiation is defined as 1 Gy in mice. In a low dose-setting, the effects of ionizing radiation will be far smaller than those that are a result of variations in parental age.

It is hoped that future studies would involve French veteran cohorts as French atmospheric tests went on for longer than those carried out by other countries. Information about sensitive stages, for which data collected soon after exposure would be relevant, for instance data on medical exposures and occupationally exposed persons. Furthermore, cohorts of pediatric patients followed over time may contribute new insights.

Confounding factors could be one reason why transgenerational effects are not seen in humans. The confounding factors which may influence the outcome of preconceptional exposures to radiation were highlighted and include: medical exposure, residential exposure (categorical high/low radon), smoking, alcohol, ethnicity, chemical exposures

(e.g. pesticides and medications), time after radiation exposure (for example, effects not seen in Chernobyl trios study), diet, stress and inflammatory status. Confounding factors that could be particularly important for preconceptional exposure are (i) parental age (most likely maternal for chromosomal aberrations, paternal for germline mutations), (ii) parity, (iii) general gynaecological health (miscarriages), (iv) other parental occupational exposures to radiation and chemical compounds, and (v) social factors and perinatal infections (e.g. in studying leukemia). These confounding factors may modulate the effects of preconceptional radiation exposure and/or alter the interpretation of the outcome. Identifying the relevance of candidate confounding factors requires structured interviews, which may add layers of complexity to the existing research studies. The inclusion of lifestyle and personal choice factors in research may lead for example, to ethical considerations.

Open research questions

Beyond the recent (and ongoing) trio studies (Boice 2020; Chumak et al. 2021; Rake et al. 2022), a study on Mayak workers is under review for this *special issue* series (reference will be updated later). According to review conducted by Boice (2020) from the epidemiological studies carried out to date on the Trinity population, no effect has been seen in the low doses estimates received by the occupational exposed parents. However, there is a large uncertainty in the dosimetry and there may be added cancers, primarily thyroid cancers in the exposed resident population (Boice 2020; NCI 2020). Adverse Outcome Pathway (AOP) approaches may be applicable to preconceptional effects, but the crucial question is: what would be the event initiating epigenetic changes?

Recommendations for future research

There was a consensus that new tools such as those used to study epigenetic changes and whole genome sequencing could be utilized in both human and mouse studies to achieve comparability. However, radiation sensitivity may differ over orders of magnitude between species, so caution should be taken when making comparisons. In addition, new mathematical models can contribute when extrapolating data between species.

The group suggested that collection of data from at least three generations would be pertinent for understanding preconceptional effects, but studies beyond 3 generations may not be feasible in humans. It is important to note that fathers and mothers may contribute in different ways—qualitatively and quantitatively to offspring after preconceptional exposure. Existing human studies were started years after exposure, and therefore do not contain some pertinent information needed to identify sensitive stages in oogenesis and, spermatogenesis.

Dosimetry details are often limited in the literature or ongoing epidemiological studies. Future epidemiological studies need to include the following information: variations

in dose and dose rate (acute/chronic), internal and external exposure and radiation quality, and age at exposure. This can be applied to animal studies as well.

Diseases that occur earlier in life and continue to have an effect could be considered to limit the need for long-term follow-up research (Nakamura et al. 2013). Since hereditary diseases are not very common, the group suggested research on diseases caused by loss of a single allele as an effective method to study the effects of preconceptional exposure.

In cohorts including cancer survivors and their offspring, the occupational and environmental exposure to radiation should be described. Genetic and life-style factors may influence the consequences of preconceptional exposure; therefore, standard information about these factors need to be included in future epidemiological studies.

In general, the members of Group A recommended collecting as much data as is reasonable for future use, which includes biological samples. Similarly, the group suggested considering a range of (possible confounding) outcomes as described above, including those with (currently) uncertain relevance for detriment. While the group agreed on the collection of data for three generations after exposure, they recommend reconsidering the use terminologies such as F1, F2 and F3 terms. TG121 has begun a review of important terminologies from ICRP and other pertinent publications to create a glossary. This glossary would be a part of the final Annals publication and would be integrated into the ICRPaedia glossary.

Group A Conclusions

The three key points identified by group A were i) to date effects associated with preconceptional exposure to radiation in humans remain unclear, 2) epigenetic mechanisms may play an important role on such effects, but there are no available quantitative estimates for them, and 3) fathers and mothers may contribute in different ways to the transgenerational effects after preconceptional exposure.

To conclude, to make progress in our understanding of the effects of preconceptional radiation on offspring and later generations, it is important to look beyond the radiation sciences. This widened scientific perspective would include the study of epigenetic effects, where collaboration with non-radiation genetics researchers is expected to contribute to a better mechanistic understanding. For example, a recent animal study by Wang et al. (2023) identified a mechanism by which paternal DNA damage was inherited through a unique epigenetic pathway. While epidemiological studies provide data on human preconceptional exposures, animal studies continue to add important mechanistic information.

Group B – Effects arising from exposure of the embryo and fetus (post-conceptional exposure)

The activities of Group B started with short topical presentations of new findings on transgenerational effects due to

ionizing radiation exposure during the intrauterine period based on medical, epidemiology, and radiobiology studies.

Fundamental biology of embryonic and fetal development

‘Are we unable to detect human central nervous system effects especially cognitive ones from low dose irradiation?’ That was the kickoff of the discussions in group B. This group acknowledged the lack of human studies on the outcomes of infants and children of pregnant patients who were exposed to diagnostic and therapeutic radiation and yet there are newer imaging methods to do so (e.g. MRI). And in fact, there is also an exponential increase in the amount of radiological imaging since the last ICRP review of fetal effects. Low dose fetal exposures have estimated leukemia risk similar to that for the young child, and at high doses, the cancer risks are known to persist into late adulthood (Sugiyama et al. 2021). The key takeaway for post-conceptual exposures is its critical link to fetal development based on both animal and limited human data (UNSCEAR 2001). In addition, several recent radiation epidemiology publications reported an association between low dose fetal exposures with cancer risk in childhood (Wakeford and Bithell 2021), and with small head size (Hatch et al. 2017; Sugiyama et al. 2021)). There is uncertainty about whether the risk might be higher when the exposure occurs during late gestation.

Development and irradiation: a quick look relevant for Multigenerational and transgenerational effects studies

There are epidemiological observations in which no significant transgenerational effects were seen with preconceptional exposures in F0 humans and animals. On the other hand, post-conceptional exposures in women seemed to be a more sensitive phase. The possible involvement of epigenetic effects, induced genomic instability or neighborhood effects were not considered. In epigenetics and developmental origins of health and disease, the intrauterine developmental periods appear to be more sensitive to environmental injuries. DNA methylation programming occurs during the organogenesis period to differentiate cell function, which means that intrauterine epigenetic DNA methylation switch during this particularly sensitive period, may induce genetic instability and potentially cause late adverse effects. The hypotheses include:

- Low doses of ionizing radiation appear to induce little to no biological effects: but can early intrauterine radiation stress increase the risk of long-term effects through epigenetic mechanisms?
- Impact of endogenous/exogenous factors (pollution, disease, diet, aging, gender, genetic background): can confounding factors influence the effect of ionizing radiation on the fetus and increase the risk of later adverse health effects?

- Epigenetic DNA methylation profile as a potential biomarker: can epigenetic fingerprints be useful as an indicator of hereditary effects and risks of delayed adverse effects?

Radiation exposure during brain development & long-lasting persistent effects

Animal studies investigating the intrauterine radio-sensitivity at different developmental stages showed that in mice the gestational day 7.5 (E7.5) is the most radiosensitive day for microphthalmia and anophthalmia, and the dose threshold for exencephaly was at 1.0 Gy. Doses ≤ 0.5 Gy at E7.5 cause adult sensory and brain defects but do not affect postnatal survival. Irradiation at the onset of neurogenesis (E11) induces cognitive impairments in adult mice (Craenen et al. 2018). However, further studies are needed to identify countermeasures to prevent microcephaly and lifelong cognitive impairments after intrauterine exposure to radiation.

Main discussion in Group B

The Group B discussions produced a fruitful exchange of knowledge, limitations, and uncertainties, and participants raised numerous questions, resulting in a lively debate.

Discussions on the experimental evidence for congenital malformations and the presence or absence of a threshold were a substantial part of the discussion. It is unclear whether the recent contribution of new results and their potential impact has changed what we know currently about the effects of prenatal exposure and the effect on the classification and risk calculation after prenatal exposure. For example, the ‘all-or-none’ was pointed out to be a 50-year-old concept which may need to be reconsidered using biomarkers, epigenetics, organoids, or simulations. Regarding the important features to be considered in such studies, the focus was on understanding the mechanisms of radiation-induced conceptus effects. For example, clinical and/or lifestyle information may be important to control confounding factors, such as parental age, improved dose estimations, and perhaps provide insights into effect modifiers. Likewise, there is a need to better understand which endpoints and/or surrogate markers are likely to be most informative. These features are important to better understand the pathways and processes of systemic, local and multi-organ effects (e.g. central nervous system – central nervous system, cognitive disorders, epigenetics, growth retardation, dose dependence, types of tissue, accelerated aging/other biological processes, etc.) The group noted the need for better stakeholder education and radiological protection training at large (including members of the public, technical audience, etc.).

The discussions also concluded that the potential effect on IQ is not a single-cell effect for instance, and in this particular case, the brain continues to develop after birth. The IQ threshold model was based on studies developed during the decade of the 1950s and it is an oversimplification of the process. The new concept should account for multi-cellular effects and the existence or not, of a threshold. In the

pre-implantation phase, there is also evidence for stochastic induction suggested by recent data, especially related to genomic stability.

Regarding the data available to study the effects of radiation exposure during fetal development, there was a general agreement that threshold doses for malformation observed for animals could not be directly transferred in human models. A recent summary of mice and human data was presented earlier in the workshop and later published to describe why there may be shorter cancer latency after radiation exposure (Nakamura 2023). However, most of the data that has been used is derived from radiobiology studies due to ethical and practical reasons. Another topic of ongoing concern to researchers, parents, the medical community, and the public is the uncertainty of effects related to ionizing radiation at low (defined by the ICRP as <100 mGy) to moderate doses (100–500 mGy). The threshold of 100 mGy was also based on animal research, limited human data, and therefore oversimplified, prudent estimations. Thus, new information and mathematical approaches to relate to old and new data is required. One example is the radiation epidemiology follow-up studies (Chernobyl, Hiroshima and Nagasaki). They would provide information on tissue (congenital malformations) effects after intrauterine exposure and also cancer effects that are still being found many decades after exposure in those populations.

Priorities for research

Group B was challenged to identify gaps in what is known, what is important but not known, and what are the uncertainties surrounding them in post-conceptual exposures.

Regarding the exposure of pregnant women to ionizing radiation, there are fewer studies on occupationally exposed women compared to men which need further review. Although there are more recent publications, especially of women in the medical radiation protection careers, not much has been discussed. More significant data on pregnant women exposed to environmental radiation (e.g. radon), outcomes of the fetus from pregnant women exposed to low dose CT and other imaging procedures, and those women undergoing radiation therapies would be crucial to further conclusions.

Another topic that requires a thorough review and further investigation is the correlations between animal and human models, especially on chromosomal translocations and, for example, neural tube defects induced by radiation.

On medical exposures, the estimated risk of childhood cancers (except for bone tumor risk) are found to be uniform from low dose fetal exposures. Further research to understand the reason is needed. It is important to note that the radiological protection community will need to prepare multi-media materials and learn how to share this information with the medical community and patients/families is also crucial.

Considering the non-cancer effects, their role in epigenetics is still a question that remain unanswered. Applying a holistic model approach considering social trauma and other

confounding factors in epidemiological studies (such as by Sugiyama et al. 2021) could also be taken into account. Are we missing health effects that can also impact well-being, even though they may not be related to mortality?

As with the Group A discussions, dosimetry was considered to be a crucial area that needs improvement in understanding and standardization (regarding the dosimetry standardization, a contribution to this special issue was published by Degenhardt et al. [2023]). The embryonic dose is taken to be the same as the uterine dose in some publications (ICRP 2003) depending on the age of development. Do we have new models or is this assumption still acceptable? What is the impact of fractionated dose rates on the dose-response compared to the A bomb intrauterine cohort?

Lastly, it is important to study the new analytical methods applied in epidemiological studies and the impact of their application in old studies. Would this lead to new findings?

Group B conclusions

The key points and priority research topics identified during the discussions were the following: the need to review and reconsider, for intellectual disability and for the ‘all or none phenomenon’, whether there is a dose threshold or if these effects are better thought as stochastic effect; modeling the impact of fractionation on dose response; the impact of radon and NORM exposures on the embryo/fetus in pregnant women; and the revision of the effects of exposure to ionizing radiation at low doses that were based on animal studies – new mathematical approaches to relate to old and new data are required.

Group C – Transgenerational effects on biota

The activities of Group C started with short topical presentations of recent findings of transgenerational or multigenerational effects caused by ionizing radiation exposure during various life stages.

Is there evidence of ionizing radiation effects in offspring and next generations for non-human biota?

One of the first transgenerational studies was done in the frog *Rana japonica* after in vitro fertilization with F0 irradiated gametes, resulting in a decreased egg laying and female frequency still observed in the F4 generation (Nishioka 1978). Dubrova hypothesized that ionizing radiation could indirectly lead to persistent genetic instability, manifested as transgenerational increases in mutation rates. In line with that assumption, they showed that the F2 offspring of irradiated male mice continued to exhibit an increase in tandem repeat mutation rate despite being a generation removed from the exposure (Dubrova et al. 2000).

Such transgenerational genetic changes have also been observed in natural populations of *Drosophila melanogaster* sampled in 2007 in Chernobyl and later studied under laboratory conditions. The survival rate of offspring

decreased over 160 generations and significantly correlated with gross chromosomal rearrangements (dominant lethal mutation levels). However, no significant change in the frequency of point or gene mutations (recessive sex-linked lethal mutations) was observed (Yushkova and Bashlykova 2021). For multigenerational field exposures, decreased fertility increased mutation rates, and increased levels of DNA/chromosomal damage were also observed in birds (Ellegren et al. 1997; Bonisoli-Alquati et al. 2010) and mice in Chernobyl (Pomerantseva et al. 1997). Such changes were also observed at the mitochondrial level, in Chernobyl frog populations approximately 30 years after the accident, displaying a higher mitochondrial mutation rate and a smaller effective population size (Car et al. 2022).

Regarding laboratory investigations of *D. magna* gamma irradiations (^{137}Cs) over several generations, studies have reported an increase in the severity of effects in the offspring (slowed growth and delayed egg laying) after 3 generations, as well as an increase in DNA alterations (Parisot et al. 2015; Trijau et al. 2018). In addition, the dose rate at which these observations become statistically significant tended to decrease (from 35 mGy.h $^{-1}$ to 70 $\mu\text{Gy.h}^{-1}$) from one irradiated generation to another (Parisot et al. 2015). Multigenerational exposure showed evidence for an increased severity in damage in later generations. Data from a laboratory experiment that demonstrated evidence for changes in DNA methylation following exposure of multiple generations of a plant species (*A. thaliana*) was presented and also discussed (Laanen et al. 2021).

Multigenerational studies and ecological risk assessment in environmental radiation protection

Ecological risk assessment relies on the link between exposure and effects; which requires the development of reference levels. Derived Consideration Reference Levels (DCRLs) are ranges of dose-rates that have been proposed and identified following a review of the literature, to guide environmental radiation protection work in a number of different species. For more information on DCRLs, the reader is referred to ICRP Publication 108 (ICRP 2009). Several values have been recommended for these reference levels, such as 10 $\mu\text{Gy/h}$ for radiation protection of 95% of environmental species (i.e. a generic ecosystem). However, most of the data relies on studies that monitored effects in a single generation. This leads to potential problems of representativeness and extrapolation of the effects observed in one generation to the next (i.e. questions about persistence, aggravation and transmission of effects between generations) and highlights the need to understand the long-term response of populations to radio-contaminants. This new information could challenge the currently prescribed reference values under ecologically realistic exposure conditions.

Main discussion in Group C

Following the short topical presentations, members of Group C engaged in fruitful discussion of this evidence in

non-human biota, and potential challenges when incorporating this evidence into the systems of radiological protection of the environment.

Differences in study designs of multigenerational effects in non-human biota were one aspect of the discussions. This included a discussion of the advantages and disadvantages of information that is gained in laboratory versus field experiments. For example, laboratory studies allow for precise control and manipulation of experimental parameters, which aims to limit the influence of confounding variables. Alternatively, field studies bring more realistic conditions of exposure, multiple inputs or stressors but can make it more difficult to isolate the effects of radiation alone. It is valuable to understand the effects of multiple stressors that better simulate field conditions (Vanhoudt et al. 2012; Salbu et al. 2019).

The choice of study model, and differences between different biota species were also discussed. Several differences between species such as generation time, reproductive strategy and radio-sensitivity would influence responses across generations. Therefore, it is important to exercise caution when extrapolating results across species. Comparisons and understanding variation within the same species or category of species was another important discussion point for study design. The group noted the importance of understanding the diversity of species with a range of radio-sensitivity, in an attempt to cover a broad range of ecosystems and environments. Using the Reference Animals and Plants (RAP) system from ICRP (ICRP 2009) would represent a starting point of categories when assessing radiation protection of the environment and these species. Also, since endpoints for human radiological protection are very different (effects generally considered for individuals rather than populations for non-human biota), and more dependent on confounding factors (such as the lifestyle or other contributing factors), the applicability of data from these non-human species for the purposes of human radiological protection needs to be very carefully considered.

There was also a discussion on the possibility that epigenetics can play a role in species evolution when considering responses over many generations, which has been reported and discussed previously (Esteller 2008; Ashe et al. 2021). There is evidence of organisms adapting to a changing environment (which could include areas with high background radioactivity or radioisotope contaminated areas such as Chernobyl or Fukushima). The study by Laanen et al. (2021) of DNA methylation in *A. thaliana* is one example of the growing literature that demonstrated epigenetic modifications after radiation exposure over multiple generations.

There was consensus toward the conclusion of Group C's discussions that this is an exciting and important area of future research regarding long-term effects of ionizing radiation exposure over multiple generations. It is not easily feasible to perform such investigations in humans (although biobanks could capture information for future study in select medical, occupational, and accident exposed populations); therefore, it is important to investigate if radiation

exposure can lead to long-term adaptation and possibly even evolutionary changes in non-human biota.

Group C conclusions

The group's discussions highlighted non-human biota models as a critical tool for the study of transgenerational and multigenerational effects of ionizing radiation exposure which is not possible in humans. Indeed, it offers numerous possibilities for study designs, models and endpoints, dose range, and new understanding of epigenetics as noted in Group A. The group could not identify a single ideal species, endpoint, or experimental design during these discussions.

For a more detailed and comprehensive review of these concepts, we direct the reader to the publication prepared by members of Group C available in this *special issue* (Sreetharan et al. 2023).

Group D – Potential impact on the system of radiological protection

The Group D discussions focused on various important aspects related to the assessment of hereditary effects in ICRP Publication 103 (ICRP 2007), consideration of hereditary effects in the implementation of the system of radiological protection, and ethical aspects related to radiological protection of offspring and next generations.

How hereditary effects were quantified in ICRP Publication 103

The ICRP Publication 103 (ICRP 2007) and UNSCEAR 2001 report (UNSCEAR 2001) served as an introduction to the quantification of hereditary effects observed in human offspring. It describes the doubling dose method used, provides insights into the justification behind the method, and discusses the data sources and how the parameters have evolved. The concept refers to the amount of radiation dose required to double the number of spontaneous genetic mutations in a given population of cells. It is calculated as a ratio of the average rate of spontaneous and induced mutations at a set of defined gene loci. This doubling dose method has been used from the early 1970s onwards until now, and the conceptual basis to calculate doubling dose has undergone various changes and fluctuations over time.

Addressing hereditary effects in the implementation of the system of radiological protection: preliminary reflections

It was noted that the challenges to estimate the risk of hereditary effects are mainly due to limited scientific knowledge compared to radiation-induced cancer, and most available knowledge comes from animal experiments and not from accidental medical patient, environmental, or occupational human exposures. For example, concerns expressed by parents with young children and pregnant women/families

regarding nuclear installations such as Sellafield, La Hague, legacy sites, and Polynesia emphasized the need for addressing several issues. These concerns include the review process of how the integration of hereditary effects in the calculation of radiation detriment and consideration of the potential long-term impact of radiation on future generations. In conclusion, it necessitates an integrated approach that includes hereditary effects, ethical considerations, long-term surveillance, dialogue with stakeholders, and a focus on resilience and reproductive issues.

Ethical aspects of radiological protection for offspring and next generations

It is important to address the growing recognition of ethical and societal aspects within radiological protection. ICRP has acknowledged the importance of ethics in its publications, with specific works dedicated to ethical foundations and ongoing discussions in a wide variety of areas of radiological protection (ICRP 2018). The Group highlighted the relevance of ethical and societal perspectives in assessing preconceptional and postconceptional radiation exposures, given the heightened global concern for children's health and well-being and the desire to protect future generations. ICRP provided valuable insights into these critical aspects and contributed to advancing the understanding of their impact on the system of radiological protection.

Key points discussed

- Group D identified several areas for future research, highlighting the need to review and update old data, and consider the results of new epigenetic studies. These insights will contribute to the advancement of knowledge in the field of radiological protection and improve risk assessment for post-conceptional exposures.
- The participants acknowledged the limitation of directly transferring threshold doses for malformations observed in animal studies to human models. They emphasized the need for reliable methodologies to correlate animal data with human models and suggested further research in this area.
- Some questions related to the epidemiological evidence and dosimetric assessments raised by Group B were discussed, including: the lack of human epidemiological evidence for somatic cell effects, the importance of controlling for clinical and lifestyle factors that can be confounding variables or play as effect modifiers in epidemiological studies, the need for more detailed dosimetric information and assessments to support epidemiological studies, the relevance of different species as models for human risk assessment in radiation studies, the contribution of new research results published since 2007 to understanding and calculating risks of prenatal radiation exposure, the definition of targets for intervention in stakeholder education and radiological protection community training.

Group D participants identified the following questions where there is a lack of knowledge regarding preconceptional and/or postconceptional exposures:

- What are the non-threshold effects of irradiation during the preimplantation (malformations) stage (as in animal experiments)?
- What role does genetic predisposition play?
- How confident are we about the threshold doses established for malformations (based on animal experiments) and severe mental retardation (based on data from Hiroshima and Nagasaki)?
- What kind of safety margins would be prudent when transferring animal data to humans? Do the earlier recommendations still seem appropriate?
- Can we anticipate any potential influence on dose limits or radiological criteria due to new data?
- Should postconceptional (prenatal) effects, for example cancer, be part of the detriment?
- Should hereditary effects be taken into consideration for derived consideration reference levels?
- What is the paramount role of prudence, inclusivity/empathy and justice in considering both male and female individuals, as well as mother and fetus, and the impact on future generations?

Group D conclusions

The impact on the radiation protection system can only be assessed after recent scientific evidence has been thoroughly reviewed and analyzed. It is currently difficult to foresee the outcome of this review, but the ICRP TG121 is expected to contribute valuable explanations to support future ICRP recommendations. This work will help identify areas that require refinement and assess the potential impact on detriment calculation. While the current impact of hereditary effects on the global detriment is currently small, the questions surrounding the effects of radiation exposure on offspring and the next generation are urgent, recurring, and a major focus for exposed populations. It is crucial to give special attention to the ethical dimensions when considering hereditary effects within the radiological protection system.

Two articles derived from the work of Group D are also included in this *special issue* (Amrenova et al. 2023; Zölzer et al. 2023).

General conclusions

Continued research and analysis of new data from human and non-human species in the fields of epidemiology, genetics, epigenetics, and cell biology as it becomes available will be needed to improve knowledge on possible effects of exposure to ionizing radiation on offspring and future generations in human and non-human biota. New frontiers of research are opening that were not available at the last ICRP review that include epigenetics, artificial intelligence in combination with large data registry research, and the use of organoids in understanding radiation biology mechanisms.

To provide advice about the level of evidence and consideration of these effects in the system of radiological protection for human and non-human biota, a Task Group of Committee 1 of the ICRP was recently established. In close cooperation with stakeholders, Task Group 121 will review published literature and consider both preconceptional and post-conceptional (intrauterine) effects of radiation, addressing genetic and epigenetic effects as well as effects due to the exposure of the embryo and fetus, respectively, and ethical and societal issues for the application of the system of radiological protection. The final results of TG121 will be presented in an ICRP Annals issue.

Acknowledgements

Funding and Acknowledgements: We appreciate the generous support from the IRPA 2022 Congress leadership and organizers, the funding and support from ALLIANCE and ICRP, and especially from MELODI. We are grateful for all the participants who provided excellent comments, suggestions, and references.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

Notes on contributors

Ämilie Degenhardt, Ph.D., is a postdoctoral fellow of the Unit 'External and internal dosimetry, biokinetics' at the Department of Medical and Occupational Radiation Protection of the German Federal Office for Radiation Protection (BfS), Oberschleißheim, Germany. In the RadoNorm project she is the Chairperson of the Early Career Researchers Council. She is also a member-mentee of the ICRP Task Group 121.

Shayenthiran Sreetharan, Ph.D., is the Radiation Safety Specialist for London Health Sciences Center (LHSC) and St. Joseph's Healthcare London (SJHC), responsible for maintaining an effective radiation safety program for regulated x-ray and nuclear workers at three hospital sites in London, Ontario, Canada. He teaches medical radiation sciences topics. He is also a member-mentee of the ICRP Task Group 121.

Aidana Amrenova, Ph.D., is a postdoctoral fellow at the Health and Environment Division of the Institute for Radiological Protection and Nuclear Safety (IRSN) in France. She is also a member-mentee of the ICRP Task Group 121.

Christelle Adam-Guillermin, Ph.D., is a senior scientist and project leader at the French Institute of Radioprotection and Nuclear Safety (IRSN). She is working on (i) the effects of ionizing radiation on non-human biota and (ii) on the side effects of hadron therapy on DNA and mitochondria damages, in contexts of reproductive toxicity and neurotoxicity. She is a member of the High-Level Group on Low-Dose Research (HLG-LDR) Joint Topical Group Rad-Chem and of the ICRP Task Groups 99 (Reference Animal and Plants), 118 (RBE) and 121 (Offspring and next generations).

Fieke Dekkers, Ph.D., is a senior scientist at the National Institute for Public Health and the Environment in the Netherlands. Her research interests include long term health effects of exposure to low doses of

ionizing radiation. She is a member of the Belgian delegation to UNSCEAR.

Sara Dumit, Ph.D., is a Scientist at the Internal Dosimetry Group of the Radiation Protection Division at Los Alamos National Laboratory (LANL), Los Alamos, United States of America. She is also a member-mentee of the ICRP Task Group 121.

Sandrine Frelon, Ph.D., is a researcher at the French Institute of Radioprotection and Nuclear Safety (IRSN), in a laboratory dealing with radioecology and ecotoxicology of radionuclides (LECO). She has expertise in multi-elemental analysis and biochemistry of adverse effects from chronic and acute exposure of organisms.

Nele Horemans, Ph.D., is a plant physiologist and radioecologist studying effects of environmentally relevant radiations exposures on plants with an emphasis on (epi)genetic regulation of long-term effects. She obtained her PhD in 1997 and is since 2008 affiliated with the Belgian Nuclear Research Center (SCK CEN) where she leads the research group Biosphere Impact studies. She teaches radio- and ecotoxicity at Hasselt University Belgium.

Dominique Laurier, Ph.D., is the Deputy Head of the Health Division at the French Institute of Radioprotection and Nuclear Safety (IRSN). He is the Chair of ICRP Committee 1. He's also a member of the French delegation to the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), and the Chair of the Nuclear Energy Agency (NEA) High-Level Group on Low Dose Research (HLG-LDR).

Liudmila Liutsko, Ph.D., MSc. Currently work at the Catalanian Institute of Health (ICS in Spanish) and IDIAP Jordi Gol (affiliated to ICS). Previously 6 years of work as a post-docs and co-PI at ISGlobal (Radiation Programme), Spain. She is also a member-mentee of the ICRP Task Group 121.

Sisko Salomaa, Ph.D., has the title of docent in genetics by Helsinki University. She worked for STUK (Radiation and Nuclear Safety Authority in Finland) for 35 years. She worked most recently as research director and coordinator of national radiation safety research programs, until her retirement in 2022. During 2016–22, she held the position of professor of radiobiology in University of Eastern Finland. She was representative of Finland to UNSCEAR and member of ICRP Committee 1, chairing TG121 during 2021–22.














Thierry Schneider, Ph.D., is the director of the Nuclear Protection Evaluation Center (CEPN) in France. He is the Chair of ICRP Committee 4. He is also the Chair of the OECD-NEA Committee on Radiological Protection and Public Health.

M. Prakash Hande, Ph.D., MPH, Associate Professor at the Department of Physiology, Yong Loo Lin School of Medicine, National University of Singapore (NUS). His research interests are biomarkers of radiation exposure, DNA-repair-telomeres-telomerase in aging and cancer, and experimental cancer therapeutics. Dr Hande teaches cancer biology and aging and conducted integrated study modules on Biomedicine and Society and Radiation and Society. He was a consultant at the Division of Human Health, International Atomic Energy Agency, Vienna, Austria in 2015–2016 while on sabbatical from NUS. Dr Hande was an expert member of the workgroup on 'Biological mechanisms influencing health effects from low-dose radiation exposure' with United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (2017 – 2021). He is a member of ICRP Committee 1 (Radiation Effects), Task Group 118 (RBE) and co-chair of the task group 121 (Offspring and next generations).

Richard Wakeford, Ph.D., is an Honorary Professor in Epidemiology in the Center for Occupational and Environmental Health at The University of Manchester, United Kingdom. Prof. Wakeford is specialized in radiation epidemiology and has served on UNSCEAR, ICRP, NCRP, UK and EU committees throughout his career.

Kimberly E Applegate, MD, MS, is a pediatric radiologist and retired professor from the University of Kentucky College of Medicine who is chair of the ICRP committee on medicine.

ORCID

Shayenthiran Sreetharan  <http://orcid.org/0009-0002-8986-8449>
 Christelle Adam-Guillermin  <http://orcid.org/0000-0002-8833-0762>
 Fieke Dekkers  <http://orcid.org/0000-0002-2206-6049>
 Sara Dumit  <http://orcid.org/0000-0002-2027-7643>
 Sandrine Frelon  <http://orcid.org/0000-0003-1583-1037>
 Nele Horemans  <http://orcid.org/0000-0002-6241-0342>
 Dominique Laurier  <http://orcid.org/0000-0003-1432-4738>
 Liudmila Liutsko  <http://orcid.org/0000-0002-2569-0760>
 Sisko Salomaa  <http://orcid.org/0000-0002-6866-655X>
 Thierry Schneider  <http://orcid.org/0000-0003-0094-5293>
 Manoor P. Hande  <http://orcid.org/0000-0002-4511-6256>
 Richard Wakeford  <http://orcid.org/0000-0002-2934-0987>
 Kimberly E. Applegate  <http://orcid.org/0000-0001-7716-1636>

References

- Amrenova A, Ainsbury E, Baudin C, Giussani A, Lochard J, Rühm W, Scholz-Kreisel P, Trott K, Vaillant L, Wakeford R, et al. 2023. Consideration of hereditary effects in the radiological protection system: evolution and current status. 1–13.
- Ashe A, Colot V, Oldroyd BP. 2021. How does epigenetics influence the course of evolution? *Philos Trans R Soc Lond B Biol Sci.* 376(1826):20200111. doi:10.1098/rstb.2020.0111
- Boice JD. Jr. 2020. The likelihood of adverse pregnancy outcomes and genetic disease (transgenerational effects) from exposure to radioactive fallout from the 1945 Trinity Atomic Bomb Test. *Health Phys.* 119(4):494–503. doi:10.1097/HP.0000000000001170
- Bonisoli-Alquati A, Voris A, Mousseau TA, Møller AP, Saino N, Wyatt MD. 2010. DNA damage in barn swallows (*Hirundo rustica*) from the Chernobyl region detected by use of the comet assay. *Comp Biochem Physiol Part C.* 151(3):271–277. doi:10.1016/j.cbpc.2009.11.006
- Car C, Gilles A, Armant O, Burraco P, Beaugelin-Seiller K, Gashchak S, Camilleri V, Cavalie I, Laloï P, Adam-Guillermin C, et al. 2022. Unusual evolution of tree frog populations in the Chernobyl exclusion zone. *Evol Appl.* 15(2):203–219. doi:10.1111/eva.13282
- Chumak V, Bakhanova E, Kryuchkov V, Golovanov I, Chizhov K, Bazyka D, Gudzenko N, Trotsuk N, Mabuchi K, Hatch M, et al. 2021. Estimation of radiation gonadal doses for the American-Ukrainian trio study of parental irradiation in Chernobyl cleanup workers and evacuees and germline mutations in their offspring. *J Radiol Prot.* 41(4):764–791. doi:10.1088/1361-6498/abf0f4 PMID: 33752181; PMCID: PMC9426296.
- Craenen K, Verslegers M, Buset J, Baatout S, Moons L, Benotmane MA. 2018. A detailed characterization of congenital defects and mortality following moderate X-ray doses during neurulation. *Birth Defects Res.* 110(6):467–482. doi:10.1002/bdr2.1161
- Degenhardt Ä, Dumit S, Giussani A. 2023. Effects of ionising radiation exposure in offspring and next generations: dosimetric aspects and uncertainties. *Int J Radiat Biol.* 2023:1–7. doi:10.1080/09553002.2023.2280017
- Dubrova YE, Plumb M, Gutierrez B, Boulton E, Jeffreys AJ. 2000. Transgenerational mutation by radiation. *Nature.* 405(6782):37–37. doi:10.1038/35011135
- Ellegren H, Lindgren G, Primmer CR, Møller AP. 1997. Fitness loss and germline mutations in barn swallows breeding in Chernobyl. *Nature.* 389(6651):593–596. doi:10.1038/39303
- Esteller M. 2008. Epigenetics in evolution and disease. *The Lancet.* 372: S90–S96. doi:10.1016/S0140-6736(08)61887-5

- Hatch M, Little MP, Brenner AV, Cahoon EK, Tereshchenko V, Chaikovska L, Pasteur I, Likhtarov I, Bouville A, Shpak V, et al. 2017. Neonatal outcomes following exposure in-utero to fallout from Chernobyl. *Eur J Epidemiol.* 32(12):1075–1088. doi:10.1007/s10654-017-0299-y
- Holtgrewe M, Knaus A, Hildebran G, Pantel J-T, de Los Santos MR, Neveling K, Goldmann J, Schubach M, Jager M, Coutelier M, et al. 2018. Multisite de novo mutations in human offspring after paternal exposure to ionising radiation. *Sci Rep.* 8(1):14611. doi:10.1038/s41598-018-33066-x
- ICRP. 2003. Biological Effects after Prenatal Irradiation (Embryo and Fetus). ICRP Publication 90. Ann. ICRP. 33(1–2).
- ICRP. 2007. The 2007 Recommendations of the International Commission on Radiological Protection. ICRP Publication 103. Ann ICRP. 37(2–4).
- ICRP. 2008. Environmental protection: the concept and use of Reference Animals and Plants. ICRP Publication 108. Ann. ICRP. 38(406).
- ICRP. 2009. ICRP Publication 108. Environmental protection: the concept and use of Reference Animals and Plants. St. Louis, Mo.: Elsevier.
- ICRP. 2018. Ethical foundations of the system of radiological protection. ICRP Publication 138. Ann. ICRP. 47(1).
- ICRP. 2021. Task Group 121 – Effects of Ionising Radiation Exposure in Offspring and Next Generations: a task group under committee 1 (https://www.icrp.org/icrp_group.asp?id=189).
- Kaplanis J, Ide B, Sanghvi R, Neville M, Danecsek P, Coorens T, Prigmore E, Short P, Gallone G, McRae J, et al. 2022. Genetic and chemotherapeutic influences on germline hypermutation. *Nature.* 605(7910):503–508. doi:10.1038/s41586-022-04712-2
- Laanen P, Saenen E, Mysara M, Van de Walle J, Van Hees M, Nauts R, Van Nieuwerburgh F, Voorspoels S, Jacobs G, Cuypers A, et al. 2021. Changes in DNA methylation in Arabidopsis thaliana plants exposed over multiple generations to gamma radiation. *Front Plant Sci.* 12:611783. doi:10.3389/fpls.2021.611783
- Moorhouse AJ, Scholze M, Sylvius N, Gillham C, Rake C, Peto J, Anderson R, Dubrova YE. 2022. Jul 5 No evidence of increased mutations in the germline of a group of British nuclear test veterans. *Sci Rep.* 12(1):10830. doi:10.1038/s41598-022-14999-w PMID: 35790751; PMCID: PMC9256629
- Nakamura N, Suyama A, Noda A, Kodama Y. 2013. Radiation effects on human heredity. *Annu Rev Genet.* 47(1):33–50. doi:10.1146/annurev-genet-111212-133501
- Nakamura N. 2023. Radiation-induced increases in cancer mortality result from an earlier onset of the disease in mice and atomic bomb survivors. *Int J Radiat Biol.* 99(8):1139–1147. doi:10.1080/09553002.2023.2158246
- NCRP. 2013. National Council on Radiation Protection and Measurements. Preconception and Prenatal Radiation Exposure: Health Effects and Protective Guidance. NCRP Report No. 174. National Council on Radiation Protection and Measurements, Bethesda, Maryland.
- NCI. 2020. National Cancer Institute. Cancer Risk Projection Study for the Trinity Nuclear Test—Community Summary [accessed 2023 Dec 18]. <https://dceg.cancer.gov/research/how-we-study/exposure-assessment/trinity/community-summary>.
- Nishioka M. 1978. Abnormalities in the descendants of rana japonica produced from irradiated eggs or sperm. Scientific Report of the Laboratory for Amphibian Biology. 3:384–386. doi:10.15027/330
- Parisot F, Bourdineaud J-P, Plaire D, Adam-Guillermin C, Alonzo F. 2015. DNA alterations and effects on growth and reproduction in *Daphnia magna* during chronic exposure to gamma radiation over three successive generations. *Aquat Toxicol.* 163:27–36. doi:10.1016/j.aquatox.2015.03.002
- Pomerantseva MD, Ramaiya LK, Chekhovich AV. 1997. Genetic disorders in house mouse germ cells after the Chernobyl catastrophe. *Mutat Res.* 381(1):97–103. doi:10.1016/S0027-5107(97)00155-3
- Rake C, Gilham C, Scholze M, Bukasa L, Stephens J, Simpson J, Peto J, Anderson R. 2022. British nuclear test veteran family trios for the study of genetic risk. *J Radiol Prot.* 42(2):021528. doi:10.1088/1361-6498/ac6e10
- Salbu B, Teien HC, Lind OC, Tollefsen KE. 2019. Why is the multiple stressor concept of relevance to radioecology? *Int J Radiat Biol.* 95(7):1015–1024. doi:10.1080/09553002.2019.1605463
- Satoh Y, Asakawa J-I, Nishimura M, Kuo T, Shinkai N, Cullings HM, Minakuch Y, Sese J, Toyoda A, Shimada Y, et al. 2020. Characteristics of induced mutations in offspring derived from irradiated mouse spermatogonia and mature oocytes. *Sci Rep.* 10(1):37. doi:10.1038/s41598-019-56881-2
- Sreetharan S, Frelon S, Horemans N, Laloi P, Salomaa S, Adam-Guillermin C. 2023. Ionizing radiation exposure effects across multiple generations: evidence and lessons from non-human biota. *Int J Radiat Biol.* 2023:1–18. doi:10.1080/09553002.2023.2281512
- Sugiyama H, Misumi M, Sakata R, Brenner AV, Utada M, Ozasa K. 2021. Mortality among individuals exposed to atomic bomb radiation: 1950–2012. *Eur J Epidemiol.* 36(4):415–428. doi:10.1007/s10654-020-00713-5
- Trijau M, Asselman J, Armant O, Adam-Guillermin C, De Schampelaere KAC, Alonzo F. 2018. Transgenerational DNA methylation changes in *Daphnia magna* exposed to chronic γ irradiation. *Environ Sci Technol.* 52(7):4331–4339. doi:10.1021/acs.est.7b05695
- UNSCEAR. 2001. United Nations Scientific Committee on the Effects of Atomic Radiation. Hereditary Effects of Radiation, Annex A. United Nations Scientific Committee on the Effects of Atomic Radiation. New York, USA: United Nations,.
- Vanhoudt N, Vandenhove H, Real A, Bradshaw C, Stark K. 2012. A review of multiple stressor studies that include ionising radiation. *Environ Pollut.* 168:177–192. doi:10.1016/j.envpol.2012.04.023
- Wakeford R, Bithell JF. 2021. A review of the types of childhood cancer associated with a medical x-ray examination of the pregnant mother. *Int. J. Radiat. Biol.* 31:1–59.
- Wang S, Meyer DH, Schumacher B. 2023. Inheritance of paternal DNA damage by histone-mediated repair restriction. *Nature.* 613(7943):365–374. doi:10.1038/s41586-022-05544-w
- Yamada M, Furukawa K, Tatsukawa Y, Marumo K, Funamoto S, Sakata R, Ozasa K, Cullings HM, Preston DL, Kurttio P. 2021. Congenital malformations and perinatal deaths among the children of atomic bomb survivors: a reappraisal. *Am J Epidemiol.* 190(11):2323–2333. doi:10.1093/aje/kwab099
- Yushkova E, Bashlykova L. 2021. Transgenerational effects in offspring of chronically irradiated populations of *Drosophila melanogaster* after the Chernobyl accident. *Environ Mol Mutagen.* 62(1):39–51. doi:10.1002/em.22416
- Zölzer F, Schneider T, Ainsbury E, Goto A, Liutsko L, O'Reilly G, Lochard J. 2023. Ethical and societal aspects of radiological protection for offspring and next generations. *Int J Radiat Biol.* 2023:1–11. doi:10.1080/09553002.2023.2281523