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







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Radiation adverse outcome pathways (AOPs) are on the horizon: advancing radiation protection through an international Horizon-Style exercise

Julie J. Burt^a , Julie Leblanc^a , Kristi Randhawa^a , Addie Ivanova^a , Murray A. Rudd^b , Ruth Wilkins^c , Edouard I. Azzam^d , Markus Hecker^e , Nele Horemans^f , Hildegard Vandenhove^g , Christelle Adam-Guillermin^h , Olivier Armant^h , Dmitry Klokov^{h,i} , Karine Audouze^j , Jan Christian Kaiser^k , Simone Moertl^l , Katalin Lumniczky^m , Ignacia B. Tanaka IIIⁿ , Yutaka Yamada^o , Nobuyuki Hamada^p , Isaf Al-Nabulsi^q , R. Julian Preston^r , Simon Bouffler^s , Kimberly Applegate^t , Donald Cool^u , Danielle Beaton^d , Knut Erik Tollefsen^{v,w,x} , Jacqueline Garnier-Laplace^{h,y} , Dominique Laurier^h , and Vinita Chauhan^c 

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ABSTRACT

Purpose: The Adverse Outcome Pathway (AOP) framework, a systematic tool that can link available mechanistic data with phenotypic outcomes of relevance to regulatory decision-making, is being explored in areas related to radiation risk assessment. To examine the challenges including the use of AOPs to support the radiation protection community, an international horizon-style exercise was initiated through the Organisation for Economic Co-operation and Development Nuclear Energy Agency High-Level Group on Low Dose Research Radiation/Chemical AOP Joint Topical Group. The objective of the HSE was to facilitate the collection of ideas from a range of experts, to short-list a set of priority research questions that could, if answered, improve the description of the radiation dose-response relationship for low dose/dose-rate exposures, as well as reduce uncertainties in estimating the risk of developing adverse health outcomes following such exposures.

Materials and methods: The HSE was guided by an international steering committee of radiation risk experts. In the first phase, research questions were solicited on areas that can be supported by the AOP framework, or challenges on the use of AOPs in radiation risk assessment. In the second phase, questions received were refined and sorted by the SC using a best-worst scaling method. During a virtual 3-day workshop, the list of questions was further narrowed. In the third phase, an international survey of the broader radiation protection community led to an orderly ranking of the top questions.

Results: Of the 271 questions solicited, 254 were accepted and categorized into 9 themes. These were further refined to the top 25 prioritized questions. Among these, the higher ranked questions will be considered as 'important' to drive future initiatives in the low dose radiation protection community. These included questions on the ability of AOPs to delineate responses across different levels of biological organization, and how AOPs could be applied to address research questions on radiation quality, doses or dose-rates, exposure time patterns and deliveries, and

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uncertainties in low dose/dose-rate effects. A better understanding of these concepts is required to support the use of the AOP framework in radiation risk assessment.

Conclusion: Through dissemination of these results and considerations on next steps, the JTG will address select priority questions to advance the development and use of AOPs in the radiation protection community. The major themes observed will be discussed in the context of their relevance to areas of research that support the system of radiation protection.

1. Introduction

The Adverse Outcome Pathway (AOP) framework has been demonstrated to be an effective means to consolidate and structure multiple lines of evidence, spanning many levels of biological organization. The AOP framework facilitates access to and understanding of complex data for risk assessors and decision-makers involved in setting guidelines for the protection of human health and the environment. Briefly, an AOP is a collaborative tool. It begins with a molecular initiating event (MIE) and is followed by key events (KEs) to a hypothetical toxicity pathway that ends in an adverse outcome (AO) (including cancer and non-cancer outcomes) linked via key event relationships (KERs) (Figure 1) (OECD 2016, 2021). The KERs are empirically supported through evidence using the modified Bradford Hill (B-H) criteria and best represented through the development of AOP networks.

AOPs were initially conceived by experts in the chemical toxicology field (Ankley et al. 2010) and then adopted by the Organisation for Economic Co-operation and Development (OECD) Extended Advisory Group on Molecular Screening and Toxicogenomics (EAGMST). Currently the framework has over 460 deposited AOPs at different stages of development and this number is continually growing to meet the needs of risk assessors. More recent discussions on formalizing the OECD AOP Development Programme within EAGMST is a testament of the framework's success.

This success has instigated dialog on the value of using the AOP framework to compile the decades of mechanistic data generated in the radiation field and linking it to health outcomes documented in epidemiological studies (NCRP 2020). Case examples of AOPs have been initiated (Chauhan, Hamada et al. 2021; Chauhan, Sherman et al. 2021; Azimzadeh et al. 2022; Jaylet et al. 2022; Klokov et al. 2022; Tollefsen et al. 2022), including a vision of how AOPs could broadly support the radiation field (Chauhan, Leblanc et al. 2021; Chauhan, Stricklin et al. 2021; Chauhan, Villeneuve et al. 2021; Chauhan, Wilkins et al. 2021). There is agreement that the AOP approach could help reduce uncertainties in health and environmental risks from low

dose and low dose-rate exposures, which are most relevant to the public. However, there is also hesitation on how the approach can effectively achieve this, considering its simplistic representation of disease progression.

In June 2021, the OECD Nuclear Energy Agency (NEA) High-Level Group on Low Dose Research (HLG-LDR) formed the Radiation and Chemical (Rad/Chem) AOP Joint Topical Group (JTG) to investigate how the successes of the AOP framework in chemical toxicology could be further explored for structuring knowledge and data from radiation research, guiding radiation risk assessment and regulation.

As described by Chauhan, Beaton et al. (2022), concrete tasks were documented to achieve the vision and mission of the Rad/Chem AOP JTG. A horizon-style exercise (HSE) was the first element of the workplan. Horizon scanning is a method for systematically searching for and identifying emerging trends, opportunities, and limitations that might impact the future direction of a defined subject (Sutherland et al. 2011). In this case, the HSE was conducted to gauge the level of awareness, interest, and hesitation or even barriers in implementing the AOP framework in radiation research and regulation. The HSE described here followed the methodology of a similar horizon scan previously completed in the chemical toxicology field (LaLone et al. 2017). However, the goal of the horizon scan by LaLone et al. (2017) was to clarify to AOP developers the basic knowledge on structure and terminology. It also led to recognizing a need for training sessions and workshops to address common misperceptions on AOPs. Several follow-on activities have helped to address these challenges, evolve the framework, and further engage the chemical toxicity community leading to an evident rise in AOP development (Hecker and LaLone 2019). Horizon scans facilitate expanding the input from few contributors to collecting thoughts and ideas from a broad range of international experts (Sutherland and Woodroof 2009; Sutherland et al. 2011).

The overall objective of this HSE was to short-list a set of priority research questions that could, if answered, improve the description of the radiation dose-response relationship for low dose and low dose-rate exposures as well as reduce uncertainties in estimating the risk of developing adverse health outcomes following such exposures.



Figure 1. A hypothetical adverse outcome pathway (AOP), beginning with a molecular initiating event (MIE), followed by measurable and essential key events (KEs) connected by key event relationships (KERs), leading to an adverse outcome (AO) of interest to regulatory decision-making.

Here, we describe the process and methodology used, present the results from the survey, and discuss how the findings can guide the future programme of work of the Rad/Chem AOP JTG. The outcomes and identified future research needs will also provide valuable awareness, insights, and engagement opportunities to the broader radiation protection community (which includes researchers, regulators, and policymakers) dealing with human health and ecological risk assessment from radiation exposure.

2. Materials and methods

2.1. Phase I: Solicitation of candidate research questions

The HSE comprised three main phases (Figure 2). Phase I of the HSE involved first establishing a steering committee (SC) with membership from industry, academia and government consisting of experts and researchers in various scientific fields related to radiation protection research, regulation, and practices (authors of this paper). The role of the SC was to guide and promote the different phases of the HSE, play an active role in sorting, ranking, and refining the questions; and to increase the international impact of the exercise.

To ensure broad participation in the solicitation of candidate research questions and future phases of the HSE, SC members advertised the HSE through the second half of 2021 and into 2022 at numerous events, including Radiation Research Society (RADRES) webinar (RADRES 2021), International Commission on Radiological Protection (ICRP) Digital Workshop (ICRP 2021), International Society of Radiation Epidemiology and Dosimetry (ISoRED) webinar (ISoRED 2021), International Dose Effect Alliance (IDEA) Virtual Workshop (EPRI 2021), the 5th European Radiation Protection Week (ERPW) (EURAMED 2021), and the 6th European Congress on Radiation Protection (IRPA 2022).

To promote additional participation, SC members reached out to their professional networks and encouraged submission of radiation related AOP questions through a dedicated website created for this purpose. The call for questions was further circulated within the broader community of radiation protection professionals via social media posts and select email distribution lists. Both individuals and organizations were encouraged to submit candidate research questions. There were no requirements to self-identify, though the website did give the opportunity for those submitting to provide general information on their professional backgrounds. For individuals, this included years of experience in radiation-related work, primary domain of work, work sector, country of residence, familiarity with AOPs, number of publications in the general field of radiation research, number of publications in the specific field of

AOP research, and engagement in professional organizations. For institutional submissions, background questions included only type of organization and country in which the organization is based.

Submissions could be either ‘a research question of interest that can be supported by the AOP framework’ or ‘a question that may be a challenge or limitation for the AOP framework to support’. Following criteria outlined by Sutherland et al. (2011), the candidate research questions should:

- address ‘important’ knowledge gaps (e.g. significant improvement of understanding of biological effects of radiation exposure, or reduction of uncertainties in risk estimates, with positive impact of the robustness of the system of radiation protection);
- provide a factual answer that does not depend on value judgment;
- cover a spatial and temporal scale that can realistically be addressed by expert groups; and
- not be answerable by ‘yes’, ‘no’, or ‘it depends’.

2.2. Phase II: Refining candidate research questions

Following an initial review of 271 questions, the SC accepted 254 for the inclusion in the next phase of the survey development. In addition to the criteria outlined by Sutherland et al. (2011) as listed in section 2.1, duplicate questions were merged. In the first stage of the refinement process, SC members independently sorted collected questions using a best-worst scaling (BWS) ranking methodology (completed in October 2021) as described in Rudd et al. (2014) and used in sustainable environmental quality research (Fairbrother et al. 2019; Van den Brink et al. 2018). In each ranking task, SC members were repeatedly shown subsets of 4 questions drawn from the full list of 254 relevant questions. This preliminary work helped streamline the deliberations during the second stage, a 3-day virtual workshop held in December 2021. The workshop was limited to SC members only and attended by 28 of the 30 members. It also ensured that the virtual workshop breakout groups could quickly scan ‘important’ (higher ranked) and ‘unimportant’ (lower ranked) questions, focusing their time on questions which needed more deliberation.

The workshop consisted of an opening plenary, 9 breakout groups (3 parallel sessions), and a final plenary. Participants could rephrase or combine candidate questions or propose new questions to address issues not directly covered by submitted candidate questions. During the final plenary, the group discussed and agreed on the ‘top 25’

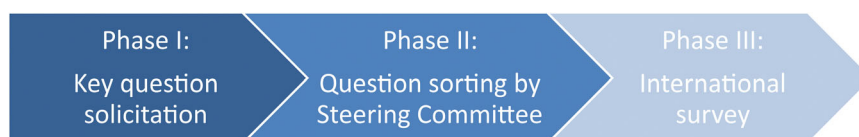


Figure 2. Phases of the horizon-style exercise (HSE).

candidate questions. Some post-workshop discussions were required to finalize the top 25 candidate question list.

2.3. Phase III: International survey

2.3.1. International survey approach

An internet-based survey sent to the broader radiation protection community was used to rank the top 25 priority questions using the BWS approach, as described in section 2.2. The representatives of the SC did not take part in the survey to avoid bringing bias into the replies. After the survey's purpose and measures to ensure confidentiality were outlined, respondents were requested to complete 15 BWS ranking tasks. In each ranking task, respondents were repeatedly shown subsets of 4 questions drawn from the top 25 questions and were asked to select which questions were of relatively greater and of lesser importance. In addition to the ranking choices, respondents were also asked to indicate if they viewed all, some or none of the options shown as 'important'. This option allowed for calibrating the responses, enabling the SC to determine if the research questions that scored low in the overall rank were still 'important'. Ranks for each item were calculated for each respondent in real time, allowing for follow-up open-end responses as to why respondents chose specific questions as top choices and whether they would like to propose any replacement questions for the items that they ranked lowest. Finally, because this was an international survey, the BWS approach eliminated anchoring effects (Furnham and Boo 2011) that can be caused in rating-based survey techniques, allowing for non-biased mixing of international respondents' answers.

2.3.2. International survey instrument

The survey was designed using Sawtooth Software's Lighthouse Studio 9.12.1 (Sawtooth Software 2009), a

professional marketing and research software platform with dedicated and secure hosting services. The international survey was non-interventional, querying respondents only about professional opinions, and did not collect any personal information that would identify respondents or their institutions. It was designed similar to other previous surveys (e.g. Fairbrother et al. 2019; Rudd et al. 2014; Van den Brink et al. 2018), and all confidentiality protection measures were of similar standards. Respondents were assigned randomly to one of 300 versions of the BWS design, each of which consisted of 15 individual ranking tasks. Figure 3 shows an example of a BWS ranking task exercise.

2.3.3. International survey delivery

The HSE used a simple distribution method involving a combination of emails to appropriate scientific organizations and one-on-one contact (i.e. SC members encouraging their networks to distribute the survey among relevant contacts). While this method was not an ideal approach, because it precludes (1) use of an individually oriented 'tailored design' protocol (Dillman et al. 2009), and (2) calculation of survey response rates, for the relatively small radiation protection community, it was the only viable option to ensure as many opinions as possible were received and recorded.

2.3.4. Data analysis

The overall rankings of the top 25 questions were calculated using counts derived from Lighthouse Studio (Sawtooth Software 2009). For each respondent completing the ranking tasks, a fit score (root likelihood x 1000) was calculated, a measure of how consistent participants were in making choices across their ranking tasks. When 4 items are shown in each ranking task, random responses would imply a fit score of 250 (any random set of responses should be able to predict respondents' answers correctly with 25% likelihood, giving a fit score of 250). With a small sample (n up to 150), any fit

Topic A - AOP components

Considering **only the four questions below** for now, which do you consider of greater and lesser **relative importance**?

(Ranking comparison 14 of 24)

Relatively least important	Relatively most important	Candidate question submission
<input type="radio"/>	<input type="radio"/>	Can AOP determine the threshold dose for radiation effects and, if so, is the threshold dose determined for each KE, or is it determined only for AO?
<input type="radio"/>	<input type="radio"/>	Which adverse endpoints are of largest importance within the field of radiation protection?
<input type="radio"/>	<input type="radio"/>	Can an adverse event be predicted by an upstream key event?
<input type="radio"/>	<input type="radio"/>	Is it possible to incorporate the available knowledge on radiation-induced chronic inflammation, immunosenescence, and acceleration of organismal senescence at individual levels into the KE of "inflammation and tissue remodeling"?

Click the 'Next' button to continue...

Figure 3. Example of a best-worst scaling (BWS) ranking task exercise for AOP questions.

score < 300 suggests that a respondent answered ranking tasks randomly and their answers could be deleted.

3. Results

3.1. Phase I: Candidate research question solicitation

A website for candidate research question solicitation was constructed in June 2021 and remained open until early September 2021. A total of 271 candidate questions were submitted by 88 individuals and 13 organizations across over 20 countries (Figure 4(A)). Respondents generally had a high level of professional experience and were from sectors including government (31), academia (32), industry (12), international agencies (5), other (9), as well as some unspecified (13). An overview of the experience, domain, sector, number of publications, and overall familiarity with AOPs of the question solicitation respondents is captured in Figure 4(B).

3.2. Phase II: Refining candidate research questions (i.e. question sorting into themes)

Of the 271 candidate research questions received, 254 were deemed relevant, and sorted by the SC into 9 general themes (Figure 5):

- Themes 1–3 all related to mechanisms of radiation injury, discussed in plenary (99 questions)
- Theme 4: AOP components, discussed in breakout session (37 questions)
- Theme 5: Regulatory significance, discussed in breakout session (24 questions)
- Theme 6: Radiation vs chemicals, discussed in breakout session (22 questions)
- Theme 7: AOP challenges, discussed in breakout session (26 questions)
- Theme 8: Tools, approaches, integration, discussed in breakout session (27 questions)

- Theme 9: Data or weight of evidence, discussed in breakout session (19 questions)

During the breakout groups, participants were tasked with identifying 3 or 4 priority research questions in each theme. This was an effective way of reducing the 254 candidate questions to the 25 priority questions (Figure 6) considered of significance in guiding low dose radiation protection research and regulation.

3.3. Phase III: International survey

3.3.1. International survey sample

The top 25 questions identified in phase II were used in the international survey, where respondents were asked to comparatively rank their importance. A total of 173 individuals visited the survey website (17 January to 23 February 2022), 98 of whom completed and submitted the full survey. Of the 75 incomplete surveys, 19 completed the ranking exercise but dropped out later in the survey. Given the low number of completed surveys, the ranking responses provided by the 19 who completed only the ranking exercise were included. One respondent was deleted due to random answers in the ranking tasks (root likelihood score of 0.270).

3.3.2. International survey ranking results

Upon completion of the ranking section of the survey, every respondent was shown the AOP research questions that they, as an individual, had ranked as top 5 and bottom 5 priorities. Respondents were then asked how accurate they felt the ranking results reflected their true priorities.

Among the 97 survey respondents who fully completed the survey, answers to the accuracy query were:

- 31 excellent ('the list of higher and lower-ranked questions closely reflected my true priorities');

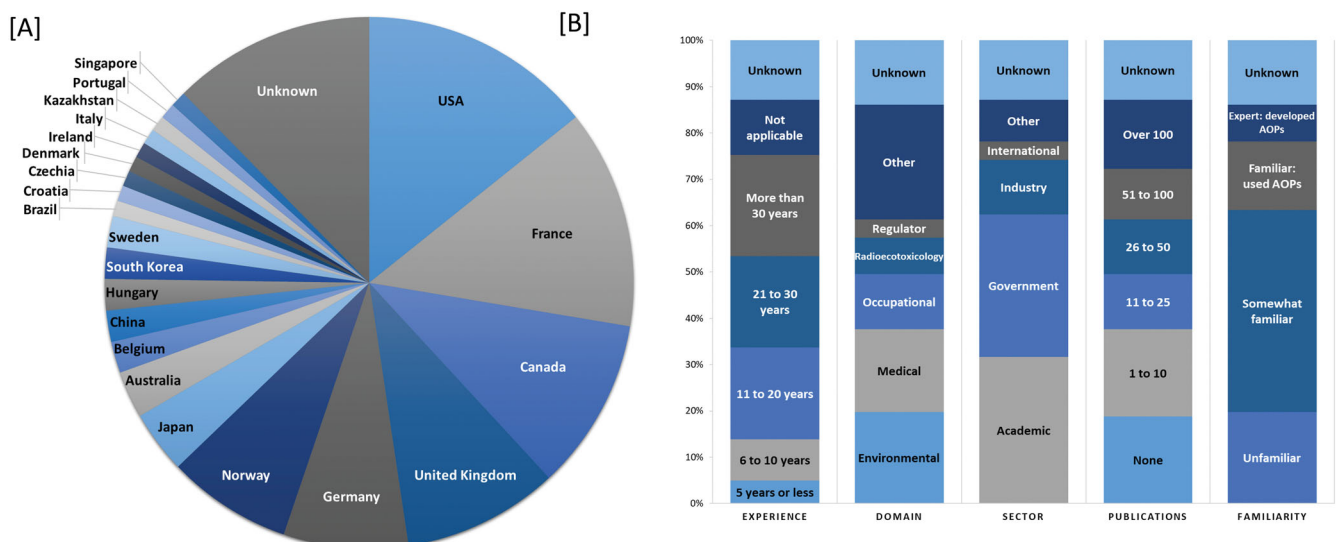


Figure 4. (A) Demographic representation of the 101 participants in Phase I of the project, question solicitation, and (B) Overview of the experience, domain, sector, number of publications, and overall familiarity with AOPs of the question solicitation respondents. N.B. some respondents opted not to provide this information.

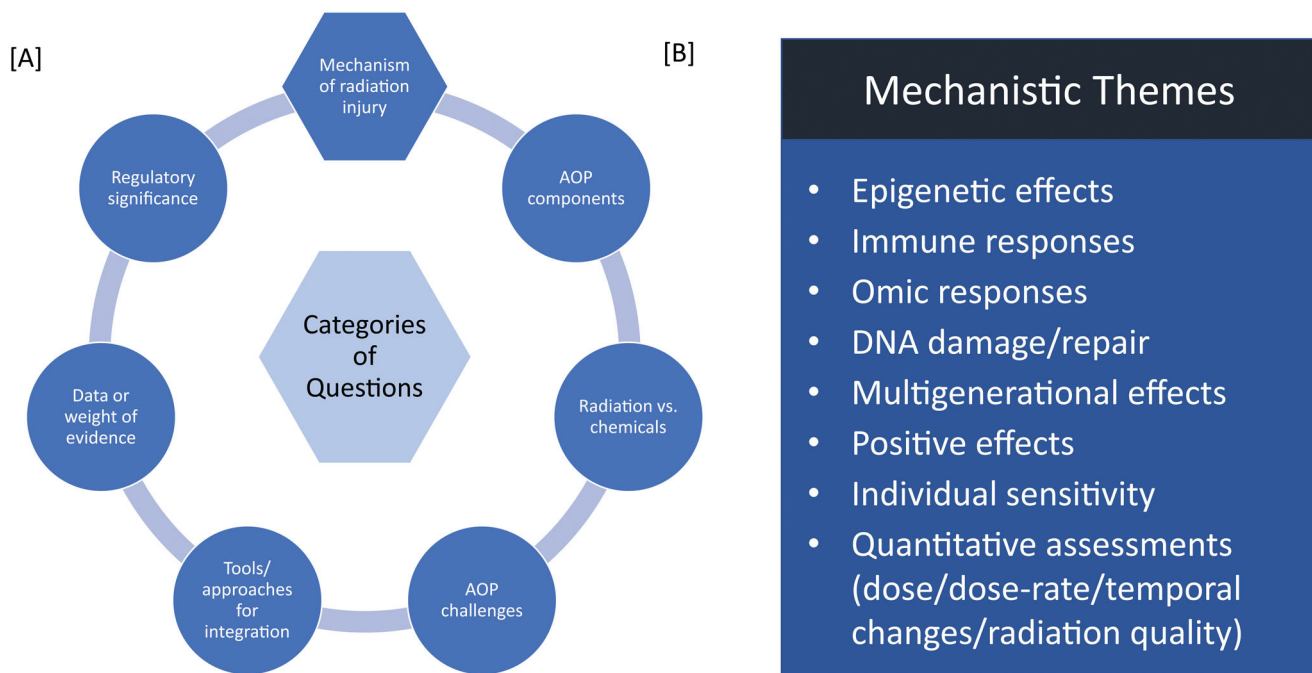


Figure 5. (A) Categories of questions received in Phase II of the HSE and (B) Emerging mechanistic themes from the solicitation process.

- 61 good ('the list reflected most of my priorities with only some minor discrepancies');
- 5 adequate ('the list reflected some of my priorities but there were also obvious discrepancies between this list and my true priorities'); and
- 0 poor ('the list did not at all reflect my true priorities').

A rank-order of the top 25 questions is provided in [Supplemental Table 1](#). The proportion of times that a question was chosen as a top 3 and bottom 3 is provided in addition to the simple counts for which a priority research question was chosen as a top 3 or bottom 3 question. Differences in score values in [Supplemental Table 1](#) indicate conflicts in ranking priority to some degree. For example, the 23rd ranked question, 'How can AOPs support enhancing the understanding of possible multigenerational and transgenerational radiation effects?' despite being ranked in the bottom 3 twenty-four times, still had 10 respondents rate it as being within their 3 most 'important' questions. Higher ranked questions, although lacking discernable separation from others, included questions on the ability of AOPs to delineate different levels of biological organization, and how AOPs could be applied to address regulatory and research questions on radiation quality, doses or dose-rates, exposure time patterns and deliveries, and uncertainties related to low dose and low dose-rate effects.

4. Discussion

To date, the HSE has met its objectives to short-list a set of priority research questions that could, if answered, improve the description of the radiation dose-response relationship for low dose and low dose-rate exposures as well as reduce uncertainties in estimating the risk of developing adverse

health effects following such exposures. The validity of the HSE was highly dependent on the successful collection of diverse views and opinions from a broad and representative stakeholder group throughout the entire length of the exercise. The HSE has engaged the broader international radiation community of researchers, regulators and policymakers, instigated discussions on AOPs and has helped prioritize key questions to guide future work. The process of the HSE has both strengths and limitations as described below.

4.1. Strengths

The greatest strength of the HSE was in the diverse experience of the SC members, which included regulators, epidemiologists, dosimetrists, radiation biologists, chemical toxicologists, among other disciplines. The SC was established through an international call for experts through the NEA Committee on Radiological Protection and Public Health (CRPPH). The composition of the CRPPH (as of July 2022) is approximately 140 delegates from 29 countries, with several strategic partners, including China and invited experts from relevant international organizations and regional associations with expertise in radiation protection research. This wealth in experiences and opinions was pivotal in driving the discussions and identifying the finalized list of questions. Additionally, SC members were instrumental in promoting and increasing awareness of the exercise and supporting the refinement of the questions to accurately represent the current deficiencies and needs. The HSE benefited from the experience of previous key question exercises in other fields. As a result of including experts with previous experience in horizon scans to the SC (Rudd 2014; Fleishman et al. 2011; Rudd and Fleishman 2014; Boxall et al. 2012; Rudd et al. 2014), the HSE collected additional information compared to



Figure 6. Twenty-five key questions to guide future areas of AOP work in the radiation field, including questions that align well with initiatives through the EAGMST.

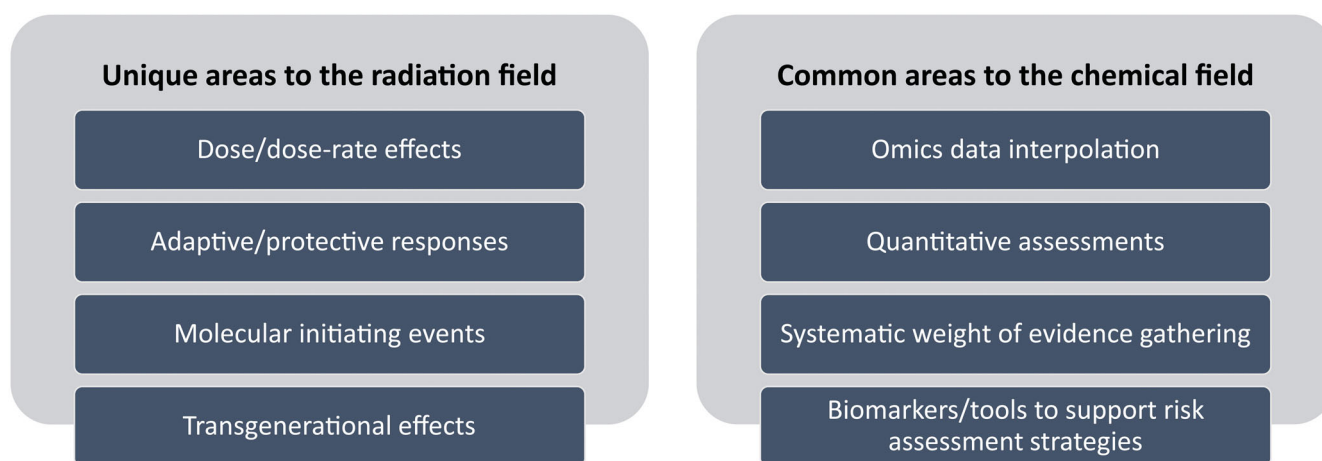


Figure 7. Suggestions on areas to focus efforts and future initiatives.

previous publications. For example, detailed information was collected on the respondents' rationale for choosing specific research questions as their highest and lowest choices and any foreseen constraints to answering those questions (discussed below in the 'specific comments and other considerations' subsection). This additional information will help inform the next steps of the Rad/Chem AOP JTG work plan. Further, the paucity of new proposed questions confirm that the initial two phases of the exercise successfully identified and ranked the relevant candidate questions. Further, nearly 70% of respondents were familiar or somewhat familiar with AOPs, ensuring strong candidate question submissions.

4.2. Limitations

From a methodological perspective, the main challenge in conducting this HSE was the relatively small population of experts from which to solicit candidate questions and recruit international survey respondents. This limitation led to some modifications in candidate question solicitation for the final survey (i.e. very active solicitation efforts by SC members within their own networks). Snowball sampling by asking contacted individuals to further spread survey invites by email or social media is often used for research surveys for which the sample frame is hard to identify or difficult to contact, even if biases arise (Lopez et al. 2019). In this exercise, the number of available experts who contributed to survey submissions was, however, limited, and the network ties between those potentially relevant respondents were very tight, resulting in possible clustering of specific questions. Thus, the use of snowballing and personal outreach was more relevant compared to surveys with many participants where snowball sampling can be promoted within epistemic communities, encouraging high response rates and potentially biasing results. Some of the more relevant international scientific organizations and associations to this exercise included the ICRP, the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), the NEA, and the International Radiation Protection Association (IRPA). The small sample size had another impact on the

results: the ranking of any individual AOP research question was not distinctly discernable from the questions around it. The data obtained allowed for a general distinction to be made between groups of questions, but not for a comprehensive ranking of the questions in order of perceived importance. Nonetheless, despite these few limitations, the exercise did allow for the extraction of meaningful data to support justification of future initiatives.

4.3. Specific comments and other considerations

The international survey permitted respondents to provide additional comments explaining their rationale for the ranking, note any anticipated constraints, and add any open-ended comments or replacement questions. This information was valuable for understanding the various perspectives and misperceptions on the scope of AOPs. The large volume of comments is summarized below, with applicable interests to the radiation and chemical fields outlined in Figure 7.

Several respondents expressed that the value of AOPs must be apparent to justify the effort of their development in terms of defining clear criteria and purpose. AOPs offer an excellent means to organize information from large numbers of epidemiological studies and biological experiments. The systematic approach to gathering the most relevant studies and data for inclusion with clear criteria is fundamental to the success of AOPs. Tangible examples of how AOPs can support radiation risk assessment are needed. Fundamentally, the value of AOPs can best be demonstrated if current aspects in the system of radiation protection can be improved to enhance protection of people and the environment.

It is feasible for the AOP framework to address latency effects related to temporal kinetics induced by various types of radiation, dose ranges, and dose-rates. AOP networks could be a means to facilitate this understanding through the integration of common modes of action across different hazards and exposure scenarios. Furthermore, the stressor-response and response relationship along the AOP continuum will have utility for building quantitative AOPs

(Moe et al. 2021; Song et al. 2020; Perkins et al. 2019). This will allow the framework to be used for risk assessment and create a bridge between radiobiological and epidemiological data. Additionally, quantitative AOPs will need to accurately account for the pattern of energy deposition, micro-environmental and susceptibility effects (e.g. age at exposure, sex), DNA damage repair systems, the role of direct (e.g. DNA damage directly mediated by radiation) and indirect (e.g. DNA damage mediated by radiation-induced ROS formation) damage related to progression of adverse outcome or disease (Tanabe, Beaton et al. 2022; Tanabe, O'Brien et al. 2022). Other aspects that need to be considered are factors that may modulate radiosensitivity and the role of AOPs in multiple stressor assessment (Beyer et al. 2014; Salbu et al. 2019), immune surveillance, persistence of inflammatory responses, and confounding factors (e.g. co-exposures) among others. However, these aspects are not unique to AOPs and are also considerations in the current approaches used in radiation protection.

Several comments emphasized that AOPs must consider the possibility of MIEs other than energy deposition resulting in DNA damage. These comments recognize the importance of defining and characterizing the initial molecular events related to the interaction of different types of radiation with a biomolecule. Although concrete suggestions on the prioritization of AOs (including cancer and non-cancer outcomes) were not identified by survey respondents, it was suggested that data-rich fields and critical gaps could be an area to focus AOP development. It was also suggested that particular focus could be given to the immune response and its role within tumorigenesis as well as a consideration for it to be a potential AO. Additionally, the emerging themes from the question solicitation phase of the HSE suggest a focus area could also be in new approach methods or technologies in the field of omic responses and AOP development (Azimzadeh et al. 2022; Yu et al. 2022). Given the complex nature of radiation effects, the use of artificial intelligence could be employed to delineate the multitude of biological changes, produced by radiation. Several comments were raised at the prospect of the AOP framework to include beneficial outcomes in addition to AOs.

For regulatory purposes, it is critical for stakeholders to benefit from the AOP framework approach. Otherwise, although relevant to basic knowledge of stress responses, the effort will remain an academic pursuit with limited real-world applicability. Much remains to be done to socialize the AOP framework and demonstrate viability of its use in decision-making to government agencies and other stakeholders, particularly where epidemiological studies lack statistical significance. An effective communication strategy will be critical to identify target audiences and appropriate messages for broader use of the tool (Chauhan, Hamada et al. 2022).

4.4. Key constraints of AOPs

In addition to providing specific comments on each of the top priority questions, survey respondents were also able to provide comments on key constraints they felt might impact

AOP development. Three key constraints were repeatedly raised by survey respondents, touching on resources (i.e. availability of experts and funding), multi-disciplinary collaborative teams, and limitations of the AOP framework itself (e.g. discussion on radiation stressors, agreement on nomenclature). Significant resources will be required to educate and train future AOP developers, engage with funders and other stakeholders, allow for confirmation of data reproducibility, as well as reduce difficulties in sharing financial and biological resources across different institutions. AOPs are designed as collaborative projects where knowledge across multiple fields is required, and so a central agency such as the OECD NEA is well positioned to facilitate the level of international collaboration required for future AOP development. It would be beneficial for these collaborative relationships to include communications and social science experts who can help advise on how to best distill the large amount of data and information to achieve a greater understanding of the risks associated with different radiation exposures (Chauhan, Hamada et al. 2022). Any constraint of individual AOPs to address different exposure patterns or tackle multiple stressors (Salbu et al. 2019) could be dealt with by building AOP networks (Moe et al. 2021; Song et al. 2020). However, in-depth knowledge and understanding of available data on the importance of exposure time patterns and deliveries must be systematically organized to identify gaps. Identifying these key constraints and considering them when developing AOPs will help minimize their impact.

4.5. Recommended activities

The HSE outcomes have identified clear hesitations on the use of AOPs. Addressing these challenges may advance application in the radiation field and alleviate some misperceptions on the scope of AOPs. This exercise and previous discussions from workshops on the topic (e.g. those described in section 2.1), highlighted that delineating dose and dose-rate effects could be explored in the context of AOP construction. It is well known that radiation parameters may influence KEs and associated biological processes to ensuing health effects. Another aspect that was considered a priority by the international radiation community was defining causal associations of KEs with protective and adaptive responses. Additionally, further discussions are needed on defining the early initiating events relevant to multiple exposures and radiation types. The initial case AOP of lung cancer uses deposition of energy (Chauhan, Sherman et al. 2021) to DNA damage; however, could other MIEs accurately reflect the first physical interaction of radiation exposure within the body? Multigenerational and transgenerational effects may also need considerations given the recent interest on this topic for international governing bodies. Additionally, efforts should also focus on new technologies, quantitative assessments, systematic weight of evidence gathering and biomarkers as indicators for development of tools and strategies (Kozbenko et al. 2022). A number of these latter topical areas align well with initiatives underway through EAGMST.

To effectively address these questions, practical examples will be needed, including consideration of adaptations to the current OECD AOP Development Programme. It may also be useful to deliberate on whether these types of questions are beyond scope and possibly deter from the broad vision of AOPs as a platform to understand complex data, by simplifying the biology of disease.

Overall, the HSE has derived valuable data that can form the basis of further discussions through joint forums with the chemical community, similar to initiatives undertaken recently through EAGMST (Tanabe, Beaton et al. 2022). Priority questions that align well with EAGMST, such as development of quantitative AOPs and omic-informed AOPs, could also be priority focus areas to advance the use of AOPs in the radiation field (Figure 7).

5. Conclusions

Based on the large volume of data collected during this HSE, there is valuable information to shape the future programme of work of the JTG. This work has helped expand awareness of and highlight the potential application of the AOP framework to the field of radiation, while identifying challenges to be addressed. Moving forward, further discussions are needed on which research questions to prioritize and address first, using active solicitation of advice from the broader radiation protection community. Prioritization could be based on alignment of work undertaken by the broader radiation protection community, including EAGMST, particularly in new approach methodologies (e.g. omics), and assessments of qualitative AOPs. Synergies across these groups could also help to prioritize the AOs of interest and mechanisms to disease states that are critical to capture in an AOP. International coordination and collaborative partnerships and capacity/resource availability may also drive which initiatives move forward. Immediate next steps include potential forums to discuss some of the frequent challenges and concerns related to the MIE and dose/dose-rate effects and applicability to support risk assessment. Ongoing efforts by the JTG, particularly in the context of advancing four AOP case studies (Chauhan, Hamada et al. 2021; Azimzadeh et al. 2022; Tollefsen et al. 2022; Klokov et al. 2022; Jaylet et al. 2022) can serve as a starting point to initiate discussions of challenges, including promotion of the work at international conferences, and hosting dedicated webinars. Through continued conversation and discussions, the broader HLG-LDR are confident that the list of priority research questions identified in this HSE could, if answered, improve the qualitative and quantitative description of the dose-response relationship for low dose and low dose-rate exposures as well as reduce uncertainties of radiation risk estimates.

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