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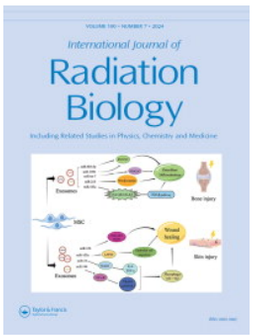

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REVIEW



# Radiation Adverse Outcome pathways (AOPs): examining priority questions from an international horizon-style exercise

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**ABSTRACT**

**Purpose:** The Organisation for Economic Co-operation and Development (OECD) Adverse Outcome Pathway (AOP) Development Programme is being explored in the radiation field, as an overarching framework to identify and prioritize research needs that best support strengthening of radiation risk assessment and risk management strategies. To advance the use of AOPs, an international horizon-style exercise (HSE) was initiated through the Radiation/Chemical AOP Joint Topical Group (JTG) formed by the OECD Nuclear Energy Agency (NEA) High-Level Group on Low Dose Research (HLG-LDR) under the auspices of the Committee on Radiological Protection and Public Health (CRPPH). The intent of the HSE was to identify key research questions for consideration in AOP development that would help to reduce uncertainties in estimating the health risks following exposures to low dose and low dose-rate ionizing radiation. The HSE was conducted in several phases involving the solicitation of relevant questions, a collaborative review of open-ended candidate questions and an elimination exercise that led to the selection of 25 highest priority questions for the stated purpose. These questions were further ranked by over 100 respondents through an international survey. This final set of questions was judged to provide insights into how the OECD's AOP approach can be put into practice to meet the needs of hazard and risk assessors, regulators, and researchers. This paper examines the 25 priority questions in the context of hazard/risk assessment framework for ionizing radiation.

**Conclusion:** By addressing the 25 priority questions, it is anticipated that constructed AOPs will have a high level of specificity, making them valuable tools for simplifying and prioritizing complex biological processes for use in developing revised radiation hazard and risk assessment strategies.

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## Introduction

The Organisation for Economic Cooperation and Development (OECD) launched the Adverse Outcome Pathway (AOP) Development Programme in 2012 following a call to modernize toxicity testing of chemicals intended for industrial uses (NRC 2007; Seidle and Stephens 2009; Krewski et al. 2010). A framework was created within which multiple types of data characterizing toxicants could be combined and synthesized for subsequent use by hazard/risk assessors and risk management authorities. The overall approach provides an understanding of critical events across multiple levels of biological organization anchored to an adverse health or biological outcome of interest to regulatory decision-making (Ankley et al. 2010).

An AOP is defined by an adverse outcome (AO), the induction of which is described by a series of key or necessary events across multiple biological levels of organization.

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This article has been corrected with minor changes. These changes do not impact the academic content of the article.

This progression is considered to arise from an exposure-related molecular initiating event (MIE) along the pathway via cellular, tissue and/or organ and organismal levels, with each step being associated with one or more key events (KEs). Thus, these KEs provide a proposed connectivity from the MIE to an AO. In the process, qualitative, semi-quantitative or quantitative data are used to support the causality of linked KEs, through the development of key event relationships (KERs). The modular structuring of available knowledge is then deposited within the AOP-Wiki (https://aopwiki.org/) where it undergoes open scientific peer-review for assessment of essentiality, plausibility and empirical evidence utilizing the modified Bradford-Hill criteria, to determine the strength of an association between the AO and its presumed causative agent (Becker et al. 2015). The AOP framework also provides traceability and transparency in the creation, approval, review and endorsement process of new AOPs (OECD 2021).

In June 2021, the OECD Nuclear Energy Agency (NEA) Committee on Radiological Protection and Public Health (CRPPH) established the High-Level Group on Low Dose Research (HLG-LDR) Radiation (Rad)/Chemical (Chem) AOP Joint Topical Group (JTG) (Chauhan, Beaton et al. 2022). The JTG aims to promote AOP use and its integration into planning and outcome interpretation of radiation research and subsequently into the hazard/risk assessment process. To meet this goal, a horizon-style exercise (HSE) was initiated in September 2021. The overall objective of this HSE was to generate a shortlist of priority questions that, if addressed through research programs, would help define the strengths and constraints of the AOP framework as applied to low dose/low dose-rate hazard/risk assessment. Thus, the goal of the AOP JTG is that uncertainties in estimating the risk of adverse human health and ecological outcomes from exposures to low dose and low dose-rate ionizing radiation will be reduced.

The process and methodology used in generating the shortlist of 25 priority questions and survey results are described by Burtt et al. (2022). Briefly, survey respondents were presented with a randomized survey and repeatedly shown a list of four of the 25 questions for ranking. Aggregate responses revealed the relative importance of the 25 questions based on counts and a hierarchical Bayesian score. Although no specific questions were clearly identified to be significantly more important and separated from the list of 25 questions, the list can guide the future program of work of the JTG. The 25 questions relate generally to: (1) how the use of AOPs can improve existing approaches to hazard/risk assessment; (2) methods for evidence gathering and review; (3) defining AOP components; (4) AOP networks, radiation phenomena (e.g., non-targeted effects), multigenerational effects, dual property stressors; (5) individualized risk assessments (6) AOP communication, acceptance, and future directions (Figure 1). This is a follow-up paper to Burtt et al. (2022) which discusses the 25 questions in the context for the use of AOPs in a hazard/risk assessment framework for ionizing radiation. The 25 questions are thematically grouped into six main categories as described above and examined in this context.

## How can the use of AOPs improve existing approaches to hazard/risk assessment?

Central among the 25 questions from the HSE is to understand how AOPs have added value to existing approaches used in the interpretation of radiation risk estimates and the associated uncertainties at low doses and dose-rates. Over the last few decades, an abundance of biological data has been generated to explore the mechanisms of radiation-induced effects in both humans and non-human biota. These data complements the wealth of information gathered from

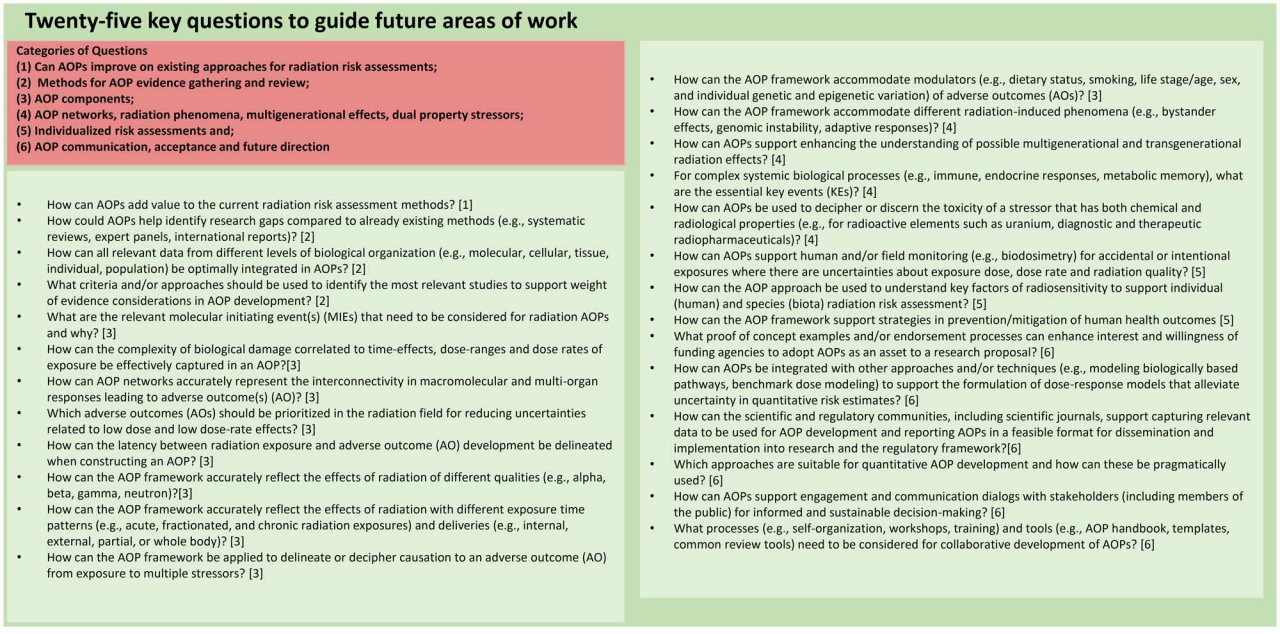


**Figure 1.** Twenty-five key questions categorized to guide future areas of AOPs in radiation research and policy work.

epidemiological and field (monitoring) studies, offering a strengthened foundation for radiation regulatory decision-making. Currently however, there is a general lack of integration of the diverse sets of data into a holistic and mechanistically informed hazard assessment framework. Such integration is crucial to make the fullest use of the most relevant data and scientific knowledge to support radiation hazard/risk assessments (NCRP 2020).

The field of radiation protection also faces the significant challenge of predicting health risks associated with low linear energy transfer (LET) exposures at low doses (less than 100 mGy) and low dose-rates (<0.1 mGy/min or <6 mGy/h) (UNSCEAR 2010; Rühm et al. 2015). At present, estimates of radiation-induced adverse health effects in humans largely rely on epidemiological studies that analyze cancer and non-cancer endpoints in various exposed populations, notably survivors of the Hiroshima and Nagasaki atomic bombs and individuals with known or estimated doses from medical, occupational, and environmental exposures (ICRP 2012; Little et al. 2018; NCRP 2020; Little et al. 2022; Hamada & Zablotska 2023; Hauptmann et al. 2023). Past research has provided valuable data to quantify the relationship between radiation absorbed dose and cancer risk, including the impact of modifying factors like sex or age at exposure. Recent studies have also yielded significant results for cancer (Rühm et al. 2022; Hauptmann et al. 2023; Richardson et al. 2023) and non-cancer effects (Little et al. 2020, 2023; Hamada, 2023) in the low dose range. While the data implies non-linear dose associations for specific cancers, overall, the linear-non-threshold (LNT) model is generally considered not to appreciably overestimate the hazards at low doses (NCRP 2018; Laurier et al. 2023). The influence of mechanisms that are not rooted in gene mutations on the sensitivity to radiation-induced cancer at low doses remains a complex evaluation. Addressing this challenge is essential for reducing uncertainties in selecting specific models for specific types of cancer used in risk assessment (ICRP 2007; UNSCEAR 2021).

Interpreting human cancer data in the low dose range presents challenges due to variation of high baseline cancer rates, confounding factors such as lifestyle, preexisting diseases, age, sex, ethnicity, multiple exposures, uncertainties in exposure and dose reconstruction, as well as a lack of sufficiently large population datasets to achieve statistical power. The quality and quantity of biological studies at low dose exposures also make it more difficult to understand the mechanistic relationship between exposure and effect. Addressing these uncertainties requires more research. The involvement of prior radiation exposures (or other exposure types, e.g., radiation types, chemical stressors) further complicates accurate risk interpolations, limiting the understanding of how specific exposures contribute to cancer outcomes (ICRP 2007, 2012; Cool et al. 2019; Hauptmann et al. 2020). The consideration of non-cancer risks from radiation exposures is an evolving field of research, some of which have been judged as tissue reactions with a dose-response threshold (ICRP 2012; Hamada 2023).

To complement human epidemiological data and address their associated uncertainties, assessment of adverse risk may benefit by incorporating more mechanistically informed knowledge generated from laboratory animal and cellular/molecular radiobiological studies. The adoption and use of AOPs (Ankley et al. 2010) can be instrumental in this effort as it serves to prioritize the most reliable mechanistic data to derive mechanistically informed risk models as well as to support the existing biologically-based, epidemiology-derived models of cancer and non-cancer diseases, notably for cardiovascular diseases (Simonetto et al. 2022). Such models termed, biologically-based dose-response (BBDR) models (Preston 2017) provide an important interface by harnessing the biological information from AOPs for quantitative risk assessment (Stainforth et al. 2021).

AOPs can also serve as one practical solution for managing the vast amounts of data derived from radiobiological research conducted in diverse fields such as environmental, occupational, medical, and space exploration research. These AOPs can be constructed initially using data from epidemiological and field studies and integrating both traditional endpoints and information obtained from newer high throughput technological advancements like broad-content analysis (e.g., omics). By defining AOPs across various biological levels of organization, taking into consideration different stressors and organisms, this integrated approach can effectively organize decades of research into an informative framework for effects of single and multiple stressors that affect different toxicity pathways leading to adverse effects of relevance to risk assessment (e.g., cancer and non-cancer diseases).

With the systematic organization of information, several steps can be undertaken to increase confidence in the data and evidence before utilizing that endpoint to predict an AO for risk assessment purposes. This includes a thorough evaluation of the data quality, conducting validation studies to confirm the reliability and reproducibility of the endpoint measurement methods, and exploring potential confounding factors or uncertainties. Furthermore, consideration of species extrapolation, can enhance the confidence in the predictive value of the endpoint. Collaborative experimental studies can be coordinated across institutions to gather data for integration into reliable quantitative risk models, using the most relevant KEs identified from AOPs. The interconnected data in AOPs, covering various diseases and biological levels, will further provide insights into the applicability of these models across animal species and demographics (e.g., sex, age, species) and stressor initiation parameters (e.g., absorbed dose, dose-rate, period elapsed following exposure to initial dose). This information can then be utilized to:

- reduce (or address) uncertainties associated with current risk estimates;
- identify bioindicator/biomarkers/endpoints/test methods most informative for human and environmental/ecological health (safety) assessments;
- identify endpoints related to KEs/KERs that are influenced by confounding factors (e.g., age, sex);
- identify synergistic/additive/antagonistic effects and biological mechanisms relevant for adversity progression from complex exposure scenarios (e.g., multiple stressors);

- provide opportunity for more mechanistically informed knowledge dissemination to international radiation protection governing bodies.

These aspects are viewed as essential for increasing the robustness of radiation dose criteria (e.g., dose limits, reference levels) for protection purposes. Although examples provided illustrate relevance for human health assessments, the challenges and applications of AOPs presented are equally applicable to environmental health assessments.

## Methods for AOP evidence gathering and review

The credibility of the AOPs developed heavily depends on the process of evidence gathering and synthesis. A robust and systematic approach for gathering evidence is essential to ensure that the information used to construct AOPs is of high quality, unbiased, scientifically sound, and able to assess accurately the certainty. The HSE identified four questions specific to the approach for evidence gathering to support the weight of evidence (Figure 1). The strength of an AOP comes from the evidence evaluation informed from studies that meet the modified Bradford-Hill criteria (Becker et al. 2015). These criteria originally proposed for epidemiological assessments use nine considerations (strength, consistency, specificity, time concordance, incidence-concordance, biological plausibility, biological gradient, dose-concordance, and coherence). Of these, four (biological plausibility, dose-, time-, incidence-concordance) support AOP construction alongside the essentiality of KEs (Becker et al. 2015). This approach differs from how information is presented and assessed in systematic reviews or reports generated by international regulatory organizations. These latter reports serve to distill available knowledge to address a precisely defined research question. AOPs possess a broader scope and offer a graphical view for depicting and conveying the sequence of biological events and interactions that arise from an MIE – such as the deposition of energy – and lead to more complex AOs, such as organ toxicity, as well as identification of causal connections based on the Bradford-Hill criteria. Within an AOP narrative, the empirical substantiation underpinning the AOP is summarized, and information on modulators, the range of applicability across each KER, and even the prototypic stressors that trigger the perturbation of events along the AOP are presented. The comprehensive detailing of empirical evidence, critical for establishing a mechanistic understanding, forms a foundation for constructing and supporting risk assessment models and tools. The AOP approach can therefore be seen as complementary to approaches such as systematic and expert organization reviews.

Although many criteria and/or approaches could be used to identify the most relevant studies for providing evidence for AOP development, systematic tools alongside expert consultations are key to capturing the most relevant data in support of a specific AOP (Figure 2). Working groups formed through a workshop organized by the Multidisciplinary European Low Dose Initiative (MELODI) and the European Radioecology Alliance associations held in 2021, highlighted how bringing experts together on a particular topic area could facilitate the process of identifying potential KEs in an AOP (Chauhan, Hamada et al. 2021; Chauhan, Villeneuve et al. 2021; Azimzadeh et al. 2022; Jaylet et al. 2022; Klokov et al. 2022; Tollefsen et al. 2022). Artificial intelligence (AI) typically using various forms of machine learning (ML) and natural language processing (NLP), may also help distill data to support AOP development (Jaylet et al. 2023). AI can automate literature screening to improve efficiency, potentially playing a role in identifying informative data across different levels of biological organization as seen in tools such as the AOP-helpFinder (Jornod et al. 2022).

For efficient AOP development, an investment in resources and tools used to transparently identify the most informative data, including documenting the collated information alongside the appropriate evaluation through expert consultation is essential (Chauhan, Wilkins et al. 2021). Systematic review tools are available to help increase efficiency of the workflow (Leist et al. 2017; Svingen et al. 2021), and different

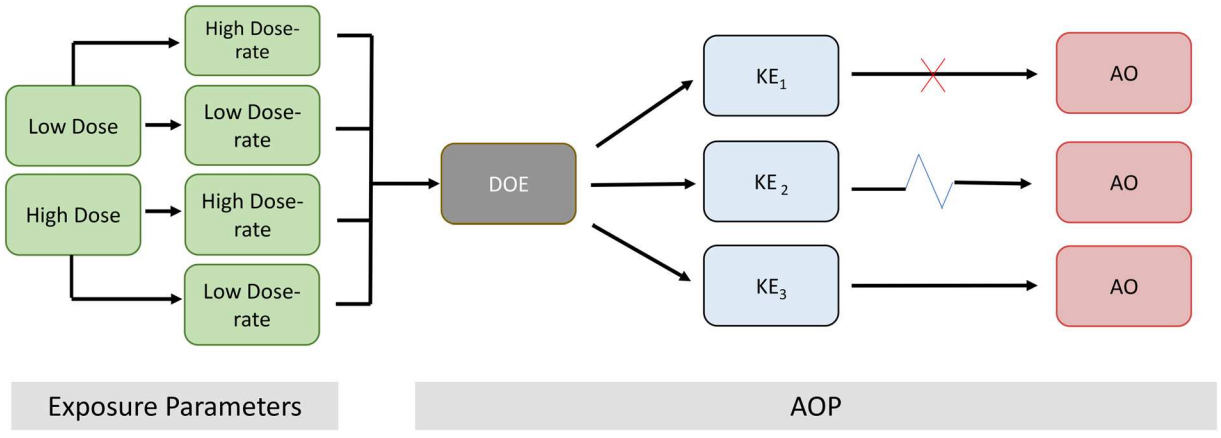


**Figure 2.** Hypothetical example of how radiation exposures conditions (acute or chronic) can lead to a common molecular initiating event of deposition of energy (DOE) to multiple different key events (KEs) depending on the radiation exposure parameters. Not all KEs are sufficient to progress to adverse outcome (AO). Red X represents a no-go to the AO, the blue zig zag represents multiple KEs. For the purposes of this example low dose and low dose-rate refers to <100 mGy/<0.1 mGy/min and high dose and high dose-rate refers to >1Gy/>0.01 Gy/min.

approaches spanning from narrative reviews to more advanced approaches such as scoping reviews and full systematic reviews are currently being explored. A recent scoping review example in the radiation field (Kozbenko et al. 2022) provides steps to retrieve relevant studies in a transparent and documented manner, without being resource intensive. The process involves four levels of screening using automated tools beginning with a prioritization step that narrows down the literature search to select the most relevant peer-reviewed studies, followed by screening based on title and full text using a defined "population, exposure, endpoint and outcome" statement, and data extraction for studies that meet the Bradford-Hill criteria.

Conducting full systematic reviews may be somewhat challenging due to the diversity of data that is used to support AOPs and the broad scope for risk of bias analysis. Although narrative reviews are considered the default, these may come with certain types of biases and lack of transparency in data retrieval. Therefore, other formats such as scoping reviews may serve the purpose and could help identify biases in the evidence gathering and/or interpretation process. Discussions on this topic continue among AOP developers, and in the field of scientific review in general, to develop effective, transparent, and standardized approaches. Development of case studies that use different systematic tools and more automated evidence gathering (e.g., AI-informed approaches), will likely emerge to demonstrate standardized and fit-for-purpose approaches for robust data retrieval for AOP development. By following a rigorous evidence-gathering process, AOPs can be constructed with a high level of specificity. The validity of any AOP can be regularly updated and revised to reflect the advancements in scientific knowledge and understanding. This dynamic nature ensures that regulatory decisions are based on the most reliable and credible information available.

## AOP components

The HSE identified multiple questions on a) the representative MIE for radiation exposure; b) the most essential KEs and how parameters such as time-effects could be deciphered within the AOPs construct and c) the interpretation of more complex biological processes (e.g., inflammation). Together 8 key questions (Figure 1) related to AOP components were seen as essential for better characterizing the necessary steps along the pathway from an MIE to an AO alongside the necessary KEs at the level of cells, tissues, or organs along the AOP.

## MIE

Identifying an MIE for radiation exposures over a range of doses, dose rates and radiation types is considerably less complex than it is for environmental chemicals for which the AOP construct was originally proposed. There are numerous MIE's that have been identified for chemicals with several being quite plausible for any chemical or chemical class. For ionizing radiation, the initial interaction with the cell is stochastic and likely multiple in nature. Therefore, incorporating a physical MIE for radiation AOPs would universally capture the effects of primary ionization events and then also accurately describe the correlated events that occur following exposure to any radiation stressor on targeted and non-targeted cells (Preston 2017).

For the recent NEA-endorsed lung cancer AOP (Sherman et al. 2023), an MIE of "deposition of energy" was selected as it was proposed to accurately reflect the first event that initiates the adverse effect of interest and to be most relevant to radiation stressors (Chauhan, Sherman et al. 2021). Deposition of energy (https://aopwiki.org/events/1686) is measurable and is supported through the decades of historical data for numerous ensuing KEs. The selection of the MIE (and other AOP events for that matter) would largely benefit by following a definition principle of "as wide as possible, but as specific as needed" to ensure flexibility to incorporate other stressors that share one or more events along the AOP continuum, stimulate reuse and reduce redundancy of events and event descriptions. This is amply demonstrated by the coherence between AOPs and toxicity pathways for ionizing radiation and non-ionizing radiation (e.g., UVB) in various species (Song et al. 2020; Cao et al. 2023).

## Relevant KEs, complex biology

Due to the non-linear dose response for many radiation effects and the uncertainty surrounding the magnitude of low-dose effects, concerns have been raised about the oversimplification of AOPs and the associated KEs for defining health effects at low doses. What is needed is a systematic approach for establishing the relevant biology under a range of exposure scenarios for AOs relevant hazard/risk assessment scenarios. For such a requirement, the AOP approach is clearly valuable as it helps identify the essential early KEs in a pathway that are crucial for understanding the biological responses to radiation exposure. The necessity of a KE for a specific AO can be assessed by its essentiality, such as addressing how inhibiting or modulating the KE can affect a downstream event linked to the AO of interest. It is such KEs that can be utilized as parameters in a BBDR model to allow for extrapolation from higher doses at which biological events can be measured to doses relevant for protection standards (NCRP 2020). As an example, for the recent development of a space AOP network for non-cancer health outcomes (AOP# 483 (https://aopwiki.org/aops/483); 478 (https://aopwiki.org/aops/478); 482 (https://aopwiki.org/aops/4820; 470 (https://aopwiki.org/aops/470)), some common macromolecular events were identified across the varied outcomes of vascular effects, cataracts, bone loss and cognitive deficits (Carrothers et al. 2024). The KEs within the AOP network are common for a range of radiation-induced injuries and could be categorized into compensatory mechanisms (e.g., DNA repair, reduction in antioxidant potential), direct damage to macromolecules (e.g., DNA, proteins), peripheral systemic events i.e., inflammation and immune suppression) and overt phenotypic effects (e.g., organ dysfunction, remodeling). As such, these AOPs have already

given knowledge gap insights into mechanistic understanding of non-cancer effects. Translating these to radiation protection practices could be achieved with both additional studies and data in the form of dose and time-concordance assessments. More directed research in these areas could be a future priority.

While biological approaches are challenged when being overly reductionist, the OECD recognizes these hurdles and is working toward approaches to integrate complex processes within AOPs. A recent consortium called the "mystery of reactive oxygen species", contemplated how oxidative stress, an overarching KE within the framework in many diseases, requires refinement and focus on its descriptions to capture mechanistic understanding (Tanabe, Beaton et al. 2022; Tanabe, O'Brien et al. 2022), and thus promote a common understanding of KE ontology. This type of consensus approach is recommended for any types of KEs that are characterized as being too broad and complex (e.g., immune response) to be defined as one KE. Therefore, where consensus on a single KE is difficult to identify, the best approach in developing an AOP is to characterize it through multiple diverse endpoints (e.g., radical formation, antioxidant production, oxidative macromolecular damage) connected within a broader KE (a super or umbrella KE).

### Radiation quality dose/dose-rate effects

A feature of the AOP framework is that it is "stressor agnostic", meaning that an AOP is not limited to a specific type of stressor or exposure thus enabling new and emerging stressors to be categorized by their mechanistic profiles. Under the AOP construct, knowledge of the primary energy deposition events (e.g., during the physical and physicochemical stages of interaction of radiation with biological matter) and the magnitude and nature of biological responses they lead to will be influenced by the dose, the dose-rate, and the radiation type (Azzam et al. 2012; Rühm et al. 2015). Different radiation types may trigger the same linear AOP but have different trajectories to the AO depending on the characteristics of a specific radiation type. Such parameters are "exposure parameters" (Figure 2) and will only directly influence the first critical KE following initiation from deposition of energy. However, once the dose (dose-rate)-response and time-response relationships across KERs become more clearly defined (e.g., the responses/KERs are likely to be strongly dependent on the microenvironment of the impacted tissue), it will be feasible to construct a quantitative AOP, which will then fully account for the exposure parameters.

### Time effects

The HSE also identified a prioritized question on how the AOP approach and framework could account for the induction and latency periods or the time from the exposure to disease initiation/detection and then to (clinical or field) manifestation of health effects (e.g., AO). By focusing on latency, the assumption is that the disease state exists but has not been detected or is at the level of being detected. In radiation protection, acute early effects and early tissue reactions observed within days to a few months following an acute exposure to high doses are reasonably well understood, although some tissue reactions and stochastic effects may have extended latency periods (months to decades). It is feasible that an AOP could be instructive in predicting the frequency of late tissue reaction effects by utilizing KEs such as considering and comparing the time-course of KEs occurring early along the pathway (predictive) to those that occur later, as assessed using time-concordance data.

### Prioritized AOs

The HSE also generated questions on which AOs can be considered as a priority for radiation protection purposes based on health and ecological impacts. Priority setting for AOs from a regulatory perspective can be established from radiation-exposed populations (UNSCEAR 2010). Aside from cancer, Publication 118 of the International Commission on Radiological Protection (ICRP) emphasizes that research should also be directed to the better understanding of radiation-induced "tissue reactions" such as those occurring in the eye, circulatory, respiratory, nervous, and reproductive systems (ICRP 2012). In the coming years, these areas are expected to be the primary focus for radiation-AOP development, with relevance to both humans and wildlife. In support of this view, efforts are underway through the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and ICRP to better understand radiation-induced tissue reactions particularly regarding the responses at low doses. On a separate note, future research will also extend ongoing work in radioecology where AOs such as effects on growth development, survival and reproduction are key apical outcomes relevant to population dynamics.

## AOP networks, radiation-induced phenomena, multigenerational effects, dual property stressors

The HSE identified 4 questions (Figure 1) pertinent to understanding complex biological processes, radiation-induced phenomena, dual-property stressors, and multigenerational/transgenerational effects that need to be addressed to enhance the application of AOPs.

### Complex biological processes

AOP networks offer a structured and simplified way to represent complex biological processes. AOP networks are composed of multiple AOPs that share common KEs and KERs and can also provide a record of a multitude of potential events for the subsequent identification of those being key to low dose (and low dose-rate) perturbations when compared with those triggered at higher doses (and dose-rates). AOP networks identify relationships, dependencies, and interactions among various biological processes that contribute to an AO. An AOP network is also a potential map for multiple stressor effects as stressors may be characterized by

different AOPs and share events along the AOP continuum (Beyer et al. 2014; Salbu et al. 2019; Xie et al. 2022). Thus, the AOP networks provide an attractive means to simplify complex biological processes triggered by multiple stressors leading to one common or more diverse sets of AOs.

### Radiation-induced phenomena

The HSE also led to important questions on how radiation-induced phenomena such as bystander effects, genomic instability, and adaptive responses, collectively termed as non-targeted effects (Hamada et al. 2011; Matsumoto et al. 2011) could be integrated into AOPs. These effects may be considered as "modulators", potentially acting across select KEs/KERs in an AOP. Although these phenomena are important for mechanistic understanding, and there is ample evidence for their existence in laboratory experiments, they have not been implicated in radiation cancer risk (UNSCEAR 2021). At present, there are no clear examples within the AOP-Wiki where radiation AOPs have clearly been used to address these complex 'non-targeted effects'. The absence of such AOPs, however, should not be interpreted as lack of relevance, but rather a reflection that the radiation AOP developer community, albeit still small, has focused on less complex radiation effects where information is more widely documented. Generally, if mechanisms in the context of radiation protection are not clear due to significant inconsistency in experimental findings and lack of experimental reproducibility in data, there will be a limit to their applicability for use in AOPs. In addition, it needs to be established as to how these non-targeted effects might play a role in informing risks for the protection of humans and non-human biota.

### Modulating factors

A notable challenge with any type of biological or epidemiological study is the influence of modifiers on the estimated association between exposure and an AO. To account for modulating factors, the AOP framework described in the AOP handbook (OECD 2018) includes sections that can inform the domain of applicability (e.g., sex, species). Although modulating factors are important attributes that need to be captured in the building of qualitative AOPs, currently no method has been implemented to incorporate these parameters in quantitative response-response relationships for AOPs. However, models such as the sufficient component cause (SCC) model (Flanders et al. 2006) are being explored for environmental toxicants and Bayesian networks (BNs) (Moe et al. 2021, Cao et al. 2023) serve as examples of how relationships between direct and indirect events leading to an AO can be characterized. The SCC model recognizes that, on its own, a stressor does not necessarily result in a disease outcome and that a minimal set of conditions needs to be present (KEs) and these will be variable among individuals. The BNs are graphical models that represent probabilistic relationships among variables, and useful for understanding complex systems of multiple interacting factors. Both SCC and BN model may be translatable to quantitative AOPs, and modifiers could be included amongst the component causes leading to the AO (Rothman and Greenland, 2005; Moe et al. 2021).

### Dual property compounds

Dual-property compounds that have both radiological and chemical effects such as radioactive elements (e.g., uranium, plutonium, thorium), or diagnostic and therapeutic radiopharmaceuticals, can be represented in AOPs based on their overall biological effects, rather than solely on the toxicity induced by their individual physical or chemical properties. This approach is necessary because the perturbation of MIEs, KEs, and the eventual AO is often integrative in nature when dealing with such compounds. While these stressors may have different initiating events, they can either converge or diverge to produce similar or dissimilar KEs and AOs. Therefore, it is important to consider the overall biological impact of a compound considering the combined effects of its chemical and physical properties that accounts for the divergent and similar KEs. For example, as an alpha particle emitter, uranium can induce dense ionization events leading to oxidative stress and bind to macromolecules due to its metal ion properties (Sabolić 2006; Guéguen and Frerejacques 2022). Both of these actions contribute to the overall toxicity of uranium. Therefore, understanding the integrated dose-response relationships for both the chemical and radiation properties is essential when assessing the overall impact of dual-property compounds, which helps advise the health protection approaches. However, if experimental data consistently highlights distinct mechanistic aspects of the individual isotopes of dual-property elements, then these delineations can be represented as new and separate KEs in an AOP and independent risk models derived could be used to assess additive risk.

### Transgenerational/multigenerational effects

AOPs have the potential to enhance an improved understanding of multigenerational and transgenerational radiation effects. Incorporating these effects into AOPs can enhance our understanding of the broader impact of exposures on biological systems and provide insights into the long-term consequences of exposures. In addition to the germ-line transmission of genetic mutations, transgenerational effects such as transmission of changes in phenotype or gene expression may involve epigenetic modifications, such as DNA methylation or histone modifications, that can be passed on to subsequent generations. Incorporation of epigenetic and other transgenerational processes is still in its infancy, but efforts to demonstrate how these effects may be included in an AOP are underway (Thaulow et al. 2020; Song et al. 2021).

Multigenerational effects extend beyond transgenerational effects by spanning multiple generations, often involving exposures and responses that affect more than just the immediate offspring. AOPs can be extended to include a series of KEs that account for the effects observed

in multiple generations. For instance, an AOP representing a multigenerational effect might include KEs related to heritable mutations in the first generation, with subsequent non-genomic transferable effects characterized as KEs in the second generation. Currently the AOP-Wiki has an endorsed AOP (e.g., https://aopwiki.org/aops/15) developed for heritable mutations from genotoxic compounds. Representing both transgenerational and multigenerational effects in AOPs can be more complex due to the need to consider interactions between generations and the potential for cumulative effects, including selection for/against these effects. Additionally, the empirical evidence supporting such effects is still evolving, and this could impact the level of detail and certainty in the AOP representation. The issue of how to account for heritable effects in radiation risk assessments has been discussed in detail by UNSCEAR (2010).

Overall, this section highlights that understanding complex processes and phenomena is an important topic for radiation protection. In many cases, the AOP framework can support these areas; however, as most topics are still developing, consistent evidence and understanding of the critical mechanistic aspects need to evolve further.

### *Individualized risk assessment*

Currently, the estimates of adverse health risks for the stochastic effects of radiation (cancers and heritable effects) that inform judgements, particularly on regulatory dose limits, are nominal (averaged over age, sex and population) (Ban et al. 2022). In parallel, there is increasing interest in the use of more individualized or stratified approaches, particularly in medicine, that can provide more accurate risk information for individuals. ICRP in its Publication 147 provided a method for cancer risk estimation that varies by age and sex (ICRP 2021), based on the data from the last general recommendations (ICRP 2007). This change has occurred over a relatively short time frame because of two key factors: (a) dose measurement has become both more accurate and rapid, and the use of artificial intelligence and deep learning to improve dose estimation is increasingly more common; (b) patients and their physicians have always desired individualized care, however, this was somewhat limited by a lack of mature science on the radiation biology, genetics, and pharmacology which are beginning to provide more stratified or individualized care.

This interest in a more individualized approach to imaging and therapeutic care is shared by the patient/family, the medical community, researchers, and the policy makers to decide how best to prioritize resources. The 'individualized risk assessment approach' includes a stratified one where some patients may be tested for their tumor radiosensitivity prior to treatment and then cared for in a treatment protocol based on these results. Only a limited number of cancers currently provide this approach. It is therefore of interest to consider how AOP approaches could be useful in this context. Although it is recognized that the current state of experimental knowledge limits application of AOPs for individualized hazard/risk assessment purposes, two stimulating questions from the HSE (Figure 1) relate to how AOPs could support strategies for individual dose estimation, avoidance, and understanding key factors in radiation sensitivity.

The AOP framework indeed may offer valuable insights into how stratified/individual dose estimation may be improved. By identifying essential biological events and their progression toward AOs, AOPs can inform on relevant biomarkers at the organism-level. Robust, sensitive, and accurate biomarkers may then enable development of tools, similar to cytogenetic assays that can help derive dose-estimates (biodosimetry) or point of departure that can be used to understand radiation sensitivities. Furthermore, since AOPs identify multiple endpoints for each critical KE, this information can be more informative than a single biomarker. For instance, when examining oxidative stress, an essential KE to radiation-injury, multiple aspects such as radical formation, radical generating enzymes, radical removing enzymes, and macromolecular damage can be considered in the assessment. In terms of radiation sensitivity, the doses at which KEs are triggered will be particularly important to inform on individual sensitivity, although this is envisioned as a long-term goal as it is recognized to come with several challenges related to accurate and consistent dose estimation.

## *AOP communication, acceptance, and future directions*

Several prioritized questions (6 in total) from the HSE (Figure 1) related to how knowledge transfer and communication on AOPs will be critical to their acceptance. A recent article published in Nature has suggested that to speed scientific progress, researchers, regulators and policy makers must learn to communicate to understand each other (Clancy et al. 2023). One recommendation was '…to encourage more science-policy research that seeks fundamental understanding of problems while having immediate use for society…'. Engaging stakeholders and collaborators during AOP development will be critical for acceptance and use of AOPs for radiation hazard/risk assessments. Indeed, international organizations with a role in radiation protection (e.g., ICRP, National Council on Radiation Protection and Measurements (NCRP), UNSCEAR, OECD/NEA) have suggested AOPs as one potential tool to integrate population-based studies with molecular level data (NCRP 2020; Laurier et al. 2021). Additionally, as more radiation AOPs progress in various stages of development, funding agencies may recognize their value and adopt them as a necessary aspect for building sound proposals. To achieve this, active promotion and communication on the potential value of AOPs will be needed (Chauhan, Hamada et al. 2022) by informing funding agencies and bringing attention to the ongoing discussions and advancements from the chemical field and the work underway in the radiation field. Endorsement of an AOP by an international agency such as the NEA would greatly enhance interest in the potential added value of an AOP for knowledge consolidation and directing future research.

To advance some of these areas, the scientific, policy and regulatory communities will need to promote AOP development and reporting of AOPs in a format that is applicable for dissemination and implementation into a research framework. Scientific journals can also broadly support AOP development, by providing a platform to help with author submission and the review of AOPs such as with the development of a standard checklist (Chauhan, Stricklin et al. 2021; Chauhan, Villeneuve et al. 2021) alongside the dissemination and publication of the AOP reports. This would expedite AOP review and provide broader dissemination of the information.

Future directions should focus on integrating AOPs within other approaches to help derive quantitative risk estimates. These approaches may include the use of KERs (e.g., as dose-response functions) into BBDR models and tools used in the toxicity field, such as benchmark dose (BMD) modeling, regression modeling and BNs that have shown utility both for chemical and non-chemical stressors (Moe et al. 2021; Bajard et al. 2023; Cao et al. 2023; Chauhan et al. 2023).

BBDR models have thus far largely been developed for cancer incidence but have been shown to have application to other health outcomes (Kaiser et al. 2021). In future research, the relation between AOPs and BBDR models should be mapped out in greater detail. At least, AOPs can guide the broad conceptual design of BBDR models; for example, by suggesting sub-models for the most relevant disease pathways which might be driven by different stressors or by differential radiosensitivity. With more ambition, mechanistic information in AOPs could be applied as parameters for KEs and/or as dose response functions for KERs to improve the biological plausibility of conventional risk estimates (NCRP 2020).

Insight from AOPs on oncogenic mechanisms may confirm whether low dose radiation causes additional cancer cases (e.g., via initiating driver mutations) or shortens the latency time to cancer by accelerating the growth of preneoplastic lesions (e.g., via reduced clearing of precancerous cells caused by inflammation). For retrospective risk assessment, Greenland (1999) discussed the need to distinguish between initiating and promoting radiation action. Eidemüller et al. (2023) quantified Greenland's conjecture with novel risk measures in a simulation study based on BBDR models for radiation-induced breast cancer. Ultimately, the biological plausibility of the dose responses applied in the BBDR models should be substantiated by trusted KERs originating from adequate AOPs.

BNs can be used to represent AOPs by modeling the relationships between MIE, KEs, and specifically infer the probability of an AO occurring on the basis of conditional dependencies between events. Additionally, a BN may support estimating the likelihood of an AOP and identify the KEs, modifiers and AOs within the pathway (Xie et al. 2018; Song et al. 2020; Cao et al. 2023). Approaches such as BMD modeling could also be used to support quantitative risk predictions from early macromolecular events in an AOP (Yu et al. 2022; Chauhan et al. 2023). Although the workflows of these approaches are well established using chemical datasets, there remains a need to understand the applicability using radiation biology and epidemiology datasets, and confirming the best correlative endpoints for deriving meaningful outcomes.

## Conclusion

The HSE provided a significant number of priority questions. Most of the pertinent questions, which there are twenty-five, can be addressed within the AOP framework. A few of the questions were deemed out of scope to support an understanding of the biology to a pre-defined outcome of interest, anchored to an MIE. The out-of-scope questions where data is currently limited (e.g., protective effects, transgenerational effects) to support aspects of the Bradford-Hill criteria were seen as an area for advancement.

In an environment of increasing complexity, the AOP knowledge base can become a practical tool for better predicting effects on both human health and the environment, potentially better understanding of causality, reduction of uncertainty and improved protection. Currently there are no clear examples of how AOPs have been applied for regulatory purposes in the radiation protection field. This is partly due to a consequence of relatively limited mechanistic data to support a quantitative understanding for an AO and the infancy of application of AOPs to radiation. With enhanced knowledge, the AOP approach aims to integrate experimental radiobiological studies with AOs based on epidemiological and clinical data to inform safety assessment decisions. relevant to human and environmental health. The implementation of an AOP framework with its transparent and stringent reviews provides an accessible and reliable source of information that is designed to be continually updated as science progresses.

It is evident that the AOP framework is not to be used in isolation; it is a tool to be used in combination with other approaches, particularly taking into consideration exposure metrics (quality, intensity etc.) to develop quantitative relationships between events and identify points of departure (e.g., the smallest dose at which a pre-defined change occurs from the control) of KERs and regulatory needs and protective goals. The current work that is progressing through the JTG in relation to outcomes from case studies (Chauhan, Villeneuve et al. 2021; Azimzadeh et al. 2022; Jaylet et al. 2022; Klokov et al. 2022; Tollefsen et al. 2022) is expected to provide some valuable insights for the future development, application, and implication of AOPs in research and regulatory approaches.

As AOP development gains momentum in the radiation research and policy communities, several challenges are expected to arise, especially as case studies are identifying constraints to larger scale implementation in research and regulations. Resolving some of these issues may specifically involve focal areas as described in Table 1. By concentrating on these areas and fostering interdisciplinary collaboration, the radiation field can advance the development and application of AOPs, enabling more accurate hazard/risk assessments, informed decision-making, and enhanced protection against radiation-induced adverse health outcomes for humans and non-human species.

**Table 1.** Focus areas for future advancements of AOPs.

| Focus Area | Description |
|---|---|
| Data Integration and Standardization | Efforts could be directed toward consolidating diverse data sources, including radiobiological studies and epidemiological/clinical data, to build robust AOPs. Standardizing data formats and terminologies (vocabularies) will facilitate effective integration and comparison. |
| Data Sharing and Collaboration | Encouraging open data sharing and collaborative efforts will enhance the collective knowledge base and accelerate AOP development. Platforms for sharing AOP-related data, models, and tools can foster a collaborative research and regulatory community guided by the FAIR (Findable, Accessible, Interoperable and Reusable) principle. |
| Longitudinal Studies and Multigenerational Effects | Long-term studies exploring multigenerational effects of radiation exposure can enrich AOPs, providing insights into transgenerational health risks and their mechanisms of induction. |
| Non-Adverse Effects | Currently the framework is directed to toxic pathways. However, if the framework could include pathways leading to protective effects induced by exposure to low dose radiation, it may be possible to rename "Adverse Outcome Pathways" to "Outcome Pathways". |
| Multi-Omics and Systems Biology | Leveraging advancements in multi-omics and systems biology approaches can provide a more holistic understanding of the molecular mechanisms underpinning radiation-induced adverse outcomes. By integrating multi-omics data can reveal intricate pathways and interactions. |
| High-Throughput Screening | Utilizing the most current methods such as high-throughput screening techniques, computational modeling and other relevant new approach methodologies (NAMs) can expedite the identification of KEs and relevant MIEs, supporting the construction of AOPs. |
| Emerging Technologies | Embracing emerging technologies like artificial intelligence and machine learning can facilitate the identification of novel relationships within complex AOP networks and aid in predictive modeling. |
| Quantitative AOPs | Developing quantitative AOPs is crucial for risk predictions in support of regulatory decision-making. This involves translating biological events into their quantitative relationships, enabling the prediction of adverse outcomes at varying exposure levels. |
| Translational Research | Bridging the gap between basic research and real-world applications is vital. Collaborations between basic researchers, clinicians, and policy makers can facilitate the translation of AOP findings into actionable strategies for radiation protection and health management. |
| Regulatory Integration | Working closely with regulatory agencies to integrate AOPs into radiation protection frameworks is essential. Collaborative efforts can result in policies that are informed by new scientific developments. |
| Education and Communication | Continued efforts to inform the scientific community, regulatory bodies, and the public about the essential role for AOPs is essential. Transparent communication of AOP concepts, methodologies, and their implications will foster broader adoption. |

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