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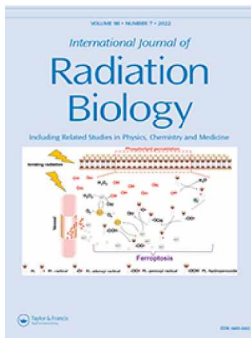
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Establishing a Communication and Engagement Strategy to Facilitate the Adoption of the Adverse Outcome Pathways in Radiation Research and Regulation

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ABSTRACT

Background: Studies on human health and ecological effects of ionizing radiation are rapidly evolving as innovative technologies arise and the body of scientific knowledge grows. Structuring this information could effectively support the development of decision making tools and health risk models to complement current system of radiation protection. To this end, the adverse outcome pathway (AOP) approach is being explored as a means to consolidate the most relevant research to identify causation between exposure to a chemical or non-chemical stressor and disease or adverse effect progression. This tool is particularly important for low dose and low dose rate radiation exposures because of the latency and uncertainties in the biological responses at these exposure levels. To progress this aspect, it is essential to build a community of developers, facilitators, risk assessors (in the private sector and in government), policy-makers, and regulators who understand the strengths and weaknesses of, and how to appropriately utilize AOPs for consolidating our knowledge on the impact of low dose ionizing radiation. Through co-ordination with the Organisation of Economic Co-operation and Development (OECD) Nuclear Energy Agency (NEA) High-Level Group on Low-Dose Research (HLG-LDR) and OECD's AOP Programme, initiatives are under way to demonstrate this approach in radiation research and regulation. Among these, a robust communications strategy and stakeholder engagement will be essential. It will help establish best practices for AOPs in institutional project development and aid in dissemination for more efficient and timely uptake and use of AOPs. In this regard, on June 1, 2021, the Radiation and Chemical (Rad/Chem) AOP Joint Topical Group was formed as part of the initiative from the NEA's HLG-LDR. The topical group will work to develop a communication and engagement strategy to define the target audiences, establish the clear messages and identify the delivery and engagement platforms. **Conclusion:** The incorporation of the best science and better decision-making should motivate the radiation protection community to develop, refine and use AOPs,

recognizing that their incorporation into radiation health risk assessments is critical for public health and environmental protection in the 21st century.

Introduction

Over the past few decades a vast amount of biological data has been generated to understand mechanisms of radiation-induced health effects (for humans and non-human species). These data complement the extensive information that has been gleaned from epidemiological studies and other evaluations that now create a robust framework on which to base decision making. However, at present there is no effective tool for collating and evaluating this extensive body of new evidence and identifying an optimal way of integrating it so that the most relevant scientific knowledge can be deployed to support radiation risk assessments. Additionally, radiation protection is confronted with a challenge to better understand health risks from low dose and low dose rate radiation exposures (<100 mGy and <5 mGy/h for low linear energy transfer radiation) to reduce the uncertainty related to the linear-no-threshold model (LNT) that constitutes one of the main assumptions underlying the international radiation protection system (ICRP 2007; NCRP 2020).

Current risk estimates for radiation-induced adverse health effects in humans rely heavily on epidemiologic studies that evaluate cancer and non-cancer endpoints in a variety of exposed populations, particularly survivors of the Hiroshima and Nagasaki atomic bombs and people with known or estimated doses from medical, occupational, and environmental exposures (UNSCEAR 2006; NCRP 2020). A considerable amount of past research has provided a coherent set of data to quantify the relationship between radiation dose and the risk of cancer and has been used to estimate the impact of modifying factors such as sex or age, and now current research provides significant results in the low dose range (Hauptman et al. 2020; Rühm et al. 2022; Little et al. 2022). Such past epidemiological data have been used as a basis for the development of a robust system of radiation protection (ICRP 2007). Nevertheless, in the low dose range data interpretation is challenging because of confounding factors such as lifestyle, pre-existing disease, age, sex, uncertainties in exposure dose reconstruction, and a lack of

sufficient population datasets to achieve statistical relevance. These uncertainties warrant further research (Laurier et al. 2021). Many of the same challenges are relevant for non-human biota, where ecological risk can be derived for a number of organisms that display high variance in sensitivity across taxa, life stages, size, age, environmental adaptation and nutritional status amongst a background incidence (Real et al. 2020; Sazykina et al. 2018). There is also the barrier of prior exposures that complicate the ability to obtain accurate interpolations of risk, a confounder that limits understanding of how any particular exposure might contribute to a particular disease or adversity (ICRP 2007, 2012; Hauptmann et al. 2020; Boice et al. 2018). In short, to complement human epidemiologic studies and field studies with wildlife, and to begin to address the uncertainties that accompany them, it is essential to move towards a risk assessment approach that both takes full advantage of the epidemiologic data and incorporates radiobiological studies. This important effort to improve risk analysis will be aided by adoption and use of adverse outcome pathways (AOPs) (Ankley et al., 2010). It is anticipated that existing biologically-based, epidemiology-derived models of cancer risk will be accompanied by identifying reliable data that will support building of mechanistically-informed risk models of disease or adversity progression (Kaiser et al. 2021).

Originally developed to support mechanistic-based hazard identification, the movement to use AOPs has been driven by the needs within the chemical field. Efforts are now underway in the radiation field with case examples being developed for human and non-human biota (Chauhan et al. 2019; Helm et al. 2020; Song et al. 2020). Although still in its infancy, initial work to quantitate stressor-response and response-response relationships through development of quantitative AOPs (Conolly et al., 2017; Moe et al., 2021; Song et al., 2020) and pragmatically address combined toxicity and cumulative risk lends promise for use in risk assessment of single and multiple stressors (Beyer et al., 2014).

Over the past decade, the Organisation for Economic Co-operation and Development (OECD) has been working to integrate mechanistic data in the form of AOPs into a framework that can be used to support regulatory decision making of chemical toxicity (NRC 2007; OECD 2016a, 2016b; Wang et al. 2020). The OECD AOP Development Programme has direction, guidelines and criteria for building high quality AOPs (www.aopwiki.org). AOPs are analytical constructs

that define key events in a path to an adverse outcome of interest to regulatory decision making. AOPs are informed by evidence through the causality association of two essential key events relevant to adversity or disease progression. AOPs bring together the most relevant studies to provide justification and confidence for use of data on these key events in hazard assessment (Becker et al. 2015; Knapen et al. 2018; Pittman et al. 2018; Villeneuve et al. 2014; and Pollesch et al. 2019). Acceptance of the approach has evolved over the years, with currently only a few examples of reviewed and endorsed AOPs being used in regulatory decision making (Delrue et al. 2016). However, leveraging these few examples alongside current radiation-specific AOPs could help shift the momentum for use in the radiation field.

As efforts are underway to better understand health hazards and risks from low dose and low dose-rate exposures, the timing is ideal to consider the value of AOPs to inform the radiation research framework as a whole (Preston et al. 2021; NCRP 2015, 2018, 2020). The initial focus would be directed towards addressing where the approach could best be integrated and how engagement of the broader radiation community could be achieved. The next step is to build relevant case studies that could be used for identifying the most relevant experimental data to support construction of quantitative hazard and risk models. In this context, the OECD Nuclear Energy Agency (NEA) Committee on Radiological Protection and Public Health (CRPPH) recently formed a High-Level Group on Low-Dose Research (HLG-LDR) in 2020. The overall objective of HLG-LDR is to support harmonization and co-ordination of efforts on future low dose research. The HLG-LDR will work to ensure that research outcomes are effectively communicated to end-users. It will be a forum to network and form effective collaborations to build more impactful research and allow for information sharing and resources.

To further these objectives three topical groups were formed in the HLG-LDR on June 1, 2021. Of these, one topical group is working to advance the OECD's AOP approach in radiation research with a long-term vision to support regulation. Namely, the Radiation/Chemical (Rad/Chem) AOP Joint Topical Group is interfacing with OECD to adapt and/or adopt the use of AOPs in the field radiation research through global co-ordination (Chauhan et al., 2022). The vision of the group is to promote AOP use for structuring research and facilitating the design of experiment, and engaging the radiation community for uptake and demonstration of the utility of

AOPs in research and regulations. The Rad/Chem AOP Joint Topical Group will be working closely with the HLG-LDR communication topical group, as this alliance could effectively expedite the integration of AOPs into the radiation field.

Perspective on Adverse outcome pathways

Through co-operation, the Rad/Chem AOP Joint Topical Group have been actively promoting the use of AOPs in radiation research and regulation (Preston et al. 2020; NCRP 2020; Chauhan et al. 2016, 2018, 2020, 2021d; Laurier et al. 2021). Although the efforts are being recognized, the increased interest on AOPs has not yet led to a clear approach that can practically improve current practices used in the radiation field. There is general agreement that the AOP approach could be valuable for organizing data to define the knowledge domain, identify knowledge gaps and prioritize research. There is confidence that AOPs can be applied to regulatory decision making, but the full extent of that application has not yet been explored. The conceptual approach is attractive; in an era of information overload simplifying biology and reducing complexity by focusing on the most relevant biological pathways is needed. However, this conceptual need brings forth questions that are not easily answered about the human and environmental health impacts of radiation exposure. For example, how will AOPs reflect modulating events and the latency between radiation exposure and cancer occurrence? Can the information in AOPs be used effectively to understand the health risks from single and multiple stressors? Can reliable data be generated to support the building of quantitative AOPs? How reliable and predictive of disease are KEs in an AOP, given the challenges of individual variability in response? Also, as the AOP approach requires a level of commitment for follow-on work either related to further branching of the AOP into AOP network or the development of appropriate experiments to inform new or additional evidence for existing AOPs, this can often deter from the process of building AOPs. Particularly, as experiments to support an AOP need to be designed to span multiple levels of biological organisation, this can be challenging to develop. There is also limited acceptance on the use of non-animal approaches for informing regulatory decisions, although the use of these techniques is growing and their promise for improving regulatory decision making has long been recognized (Lalone et al. 2017; Leist et al. 2017; Sauer et al. 2020; Locke and Myers 2011). Further challenges related to such hurdles need to be addressed before the AOP approach can be maximized to protect public and environmental

health, particularly as there are currently limited examples of their utility to support wide acceptance.

To effectively address the concerns, co-operation and co-ordination will be needed of those engaged in AOP development and use. The Rad/Chem AOP Joint Topical Group has launched a horizon-style exercise to help identify the perceptions and hesitations of using the AOP approach (Lalone et al. 2017). The exercise has identified and prioritized 25 questions of importance to the radiation community. This work has initiated dialogue among radiation experts and has also identified areas for directed workshops to help address the challenges. Additionally, initiated through a recent Multidisciplinary European Low Dose Initiative (MELODI)/European Radioecology Alliance (ALLIANCE) workshop in April 2021, four AOP case studies are underway that address adverse outcomes of interest to the radiation community (Chauhan et al. 2021e). These case studies will provide a vehicle to assess the OECD's AOP framework, what works and what needs to be adapted including how AOPs can improve existing research efforts. In parallel to these efforts, and to take advantage of the information they provide, a communication and engagement strategy will be developed that will assist in furthering the work of the HLG-LDR.

Communication on the AOP framework is already underway. For the past few years there have been efforts to convey the value of AOPs to radiation scientists and encourage their development and adoption. This initial engagement has led to some consistent institutional followers at workshops and presentations on the topic (Chauhan et al. 2019, 2021d). However, there is a need to translate this interest to actionable uptake by the wider community of radiation scientists, policy-makers, regulators and risk assessors. Radiation scientists will need to be persuaded of the value of the approach in guiding their research priorities and policy-makers and regulators need to be convinced that applying mechanistic data will improve human and ecological risk assessments and advance risk-based decision making. Funding agencies will need to recognize AOPs as an important step in project proposal development. Journals will need to work with OECD to adapt their current publication streams to support AOP development. For this alignment to happen, a communication and engagement strategy is needed to help message the benefits and attract the end-users to establish two-way dialogue to address the hesitations and

challenges on implementing the AOP approach, especially in radiation risk assessment. Cross-disciplinary co-operation would benefit all, potentially expediting the process of integration. A structured plan for outreach and engagement activities is outlined below that identifies the appropriate audience, the key messages and the tools for knowledge.

Targeted audience for communication and engagement

Three key Groups

Identifying and involving key target audiences will be critical to success as they will provide AOP advocates with incentives for effective uptake of the AOP approach. Currently, three audiences seem to be appropriate targets for the Rad/Chem AOP Joint Topical Group; the AOP developers, facilitators and end-users. These professionals each have a distinctive role in the AOP engagement plan. They would work independently as well as collectively in support of efforts to develop AOPs either by reviewing data and identifying gaps or by providing the tools/framework/fora (e.g., researchers and international governing bodies), enable and coordinate their implementation and uptake (e.g., journals, funding agencies), translate the outcomes to policy-based decisions and provide resources for further AOP development and deployment (e.g., regulators, policy-makers). Communication and engagement with all these groups will be important in order to achieve accelerated AOP assimilation in radiation research.

Developers as a key group

The developers consist of scientists and groups that are committed to support the construction of both qualitative and quantitative AOPs and/or designing experiments informed by AOPs. Developers will aid in demonstrating and validating the value of the AOP approach to the end-users. Identifying these target groups will be challenging but as a starting point, this key audience could comprise individuals or groups that are already considering AOPs in their research approach or conducting literature reviews that can inform AOP development. Furthermore, the experience of the chemical research and regulatory community could be leveraged and joint proposals could be developed to support an understanding of multiple stressors. This would also be in-line with the vision of crowd-sourced AOP construction. An important end result of this collaboration would be showing the value of how AOP development

could support multiple regulatory questions, broadening their scope and reducing the burden on one community. This is particularly apt given AOPs can be triggered by radiation or chemical exposures, or a combination of these stressors (Beyer et al., 2014; Salbu et al., 2019). It will also be important to promote interaction between radiobiologists and epidemiologists as together their combined expertise will be instrumental in finding the direction needed to build quantitative AOPs, to help consolidate human and environmental health risk management in the radiation field. In this way, the impact of such an AOP end-product would be high demonstrating the strength and efficiency of collaborative undertakings.

Another target group of developers of potential interest could be senior radiation scientists, who have years of expertise, experience and wealth of knowledge and are in positions of leadership in the radiation science community. These scientists could act as consultants on AOPs (AOP coaches) or be active participants in AOP development and utilization. Additionally, scholars-in-training or next generation graduates/students could also be targeted. Another niche group that could be engaged are those working in the field of systematic review and artificial intelligence/machine learning, as their work aligns well with AOP concept (Bell et al., 2016 and Oki et al., 2016). Their experience in transparently and efficiently acquiring data would greatly benefit AOP development and uptake. These individuals could provide guidance on best practices and provide the validation on methods to facilitate uptake and the building of AOPs.

Facilitators as a key group

Engagement of facilitators will be important as well. Facilitators include journals, funders and professional societies. It is not anticipated that facilitators will directly build AOPs. Their leadership is essential to promote the use of AOPs, help co-ordinate the development of projects that are AOP-informed, and disseminate AOP scholarship in the scientific community. Facilitators provide opportunities for introducing AOPs to key audiences, and can create a platform for discussion about AOPs in an environment that brings together like-minded professionals. Journals in particular could, incentivize more AOP contributions, and support the review of AOPs. Journals could in this way, expedite the endorsement process and reduce the burden of AOP reviews being undertaken through OECD, which can be slow and be a deterrent for AOP building. Journals could also be informed on the benefits of publishing and promoting

AOPs, including more informative papers that are cross-disciplinary in nature that would have greater visibility. For funding agencies, the value of AOPs can be promoted as a tool to identify priority research, reduce duplication of work and improve scientific inputs into public health and ecological decision making. In addition, AOPs frequently align with the goals and objectives of funding agencies.

Decision-makers as a key group

The last group to engage are the end users, including international governing bodies (e.g. International Atomic Energy Agency and International Commission of Radiological Protection), regulators, policy-makers and public health authorities/institutes. These groups will use the information within AOPs to inform the policy development and standards. This group will need clear examples of how AOPs have informed decision making. This is where the experience and examples from the chemical and human- and ecotoxicology community could be leveraged, particularly around examples that have moved towards quantitative AOP development. As more AOPs are developed in the future, it would provide a template to support their promotion to end-users. As discussed above, an important attribute of AOPs is their ability to capture the mechanistic information that is currently not fully captured by current hazard and risk assessment methodologies. Regulatory decision making will be improved if it is based on a more robust, biologically-based model of how adverse conditions develop. AOPs have the potential to incorporate scientific information from these different disciplines (Daniak et al. 2017).

Engaging the Public as a second step

Communication to the public (e.g., toxicology and law students, patients, and citizen scientists) would be the next logical step following engagement of the other groups. Outreach to the public on AOPs could be valuable for increasing transparency about the information used to support regulatory decision making. AOPs could also be a portal for educating the public about the underlying biological bases of radiation's hazards and risks. However, public perceptions about radiation risk suffer from a perception gap that is not easily bridged (Slovic 2012). Accordingly, at this point, it is probably premature to directly engage the public. Before any such efforts are launched, robust communication and engagement should be accomplished in the three key groups mentioned earlier – radiation scientists, facilitators and end-users. After these activities

are underway, it might be useful to undertake a piloted endeavor using radiation-relevant AOPs in the Wiki, organized around those AOPs that are validated and well-progressed in the OECD's endorsement process, with the goal of developing an outreach and communications strategy for communities and other stakeholders.

Key Messages

Developing key messages that are specific to each of these groups (e.g., developers, facilitators and decision-makers) is essential to the communication and engagement strategy. A concrete, directed and detailed messaging strategy will arise as additional information is collected and engagement activities advance. Conceptually, it is clear that messaging should be centered around (1) how the AOP process complements current approaches for assessing radiation related risks 2) how the AOP approach is innovative and supportive of discovery-based science; (3) why AOPs are more consistent with the contemporary understanding of radiation effects and integrative across scientific disciplines; and (4) how AOPs can support more effective protection of public and environmental/ecological health. Table 1 shows these messaging themes and roughly estimates their relative importance within each target group.

Tools and platforms for communication

A range of approaches are available to deliver the key messages to the target audience of interest. A detailed, concrete and directed set of strategies is expected to evolve as engagement increase. Educators and developers may be more receptive to the newer platforms (Twitter, Instagram, LinkedIn, Facebook, Youtube, academia.com, podcasts, popular scientific articles etc.), while others such as experienced scientists, could be reached through the traditional dissemination channels (website, publications, pre-prints, government and non-governmental expert reports). Some social media platforms such as Twitter and Research gate, are particularly effective in delivering targeted messages quickly and have the potential to be impactful for achieving the necessary end goals. These tools will be especially important in increasing the flow of information and allowing for a more interactive engagement. Additionally, the expertise and experience of the OECD AOP programme, including that of the AOP forum (AOP Forum (aopwiki.org)) and active engagement in the AOP Community of Practice Symposium (organized by AOP developers), should be leveraged as for years it has successfully engaged the

chemical research and regulatory communities on AOPs. Focus groups and structured conversations with leaders among both OECD experts and the radiation community can provide insights into the benefits and challenges of different channels of communication. In addition, gathering data about the opinions of those currently engaged in AOP building, such as students, and those currently involved in designing AOPs for decision making may also be valuable to solicit their experience and advice on what messaging will reach the younger target groups. At the same time, the knowledge of senior radiation scientists could be valuable on how new ideas have been successfully disseminated in the radiation research community. Lastly, continued presentations at national and international conferences and at external non-solicited events will be needed to maintain the momentum that has currently been built.

Conclusion and Next Steps

AOPs are being recognized as a valuable tool for integrating knowledge from the molecular level through to individual and population levels (Ankley et al. 2010) and providing a means to structure research to progress understanding of radiation effects. However, it is less clear how the AOP framework can support regulatory decision making in the radiation field. The path from new knowledge to regulation is a long-term process (>10 years), involving steps like scientific review of the literature, proposing recommendations, setting standards and transpiring the information to national legislation. Each of these components will have a separate role in communication and engagement. Therefore, continued dialogue with relevant stakeholders and specific scientific disciplines will be an important step towards this vision. Through the NEA's HLG-LDR, an effective communication and engagement strategy will assist in identifying potential opportunities, obstacles and key strategies to integrate AOPs into radiation research and eventual risk assessment. Next steps will include:

- Developing a web presence;
- Developing infographics with key messaging for target audience using novel and interactive platforms;
- Initiating a focus group with key players from the chemical and ecological fields (e.g., biologists, toxicologists, epidemiologists); and
- Promotion activities (e.g. publications, presentations, workshops)

With these undertakings it is envisioned that the goal of wide acceptance and uptake of the AOP approach for use in priority research identification could be achieved. Over the long term, it is anticipated that ongoing efforts to build AOPs, strengthened by an effective communication strategy, will lead to more informative assessments that can take fuller advantage of mechanistic data. Combined with other approaches, these studies will strengthen the scientific evidence used for protecting public health and ecological resources.

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Disclosure statement

The authors declare no conflict of interest.

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Table 1: Key messaging among target groups (key audience)

Target Groups	Conceptual message			
	Uniqueness of AOPs	AOPs supporting best science	AOPs as knowledge integrators	AOPs as protective of human and ecosystem health
Developers	++	++++	++++	+
Facilitators	++++	++++	++	+
Users	+	+++	+++	++++

+ indicates relative importance of conceptual message in persuading targeted community members about AOPs (+, least important, ++++ most important).

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Figure 1: A summary of key messages, tools and platforms needed to effectively communicate and engage target audience to build and use AOPs. SIT: Scholars-in-training. The figure is created with Biorender.com.

