Meeting Report

Report on the 5th and 6th Mystery of Reactive Oxygen Species Conferences

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1 Introduction

Harmonizing adverse outcome pathways (AOPs) related to reactive oxygen species (ROS) has been a key challenge in advancing the use of AOPs in toxicological testing and research (Tanabe et al., 2023). Numerous key events (KEs) describing ROS dynamics have been developed and incorporated into the AOP-Wiki[1] of the Organisation for Economic Co-operation and Development (OECD). An AOP comprises a molecular initiating event (MIE), a sequence of KEs, and an AO, all interconnected through KE relationships (KERs). The AOP-Wiki provides comprehensive annotations using biological ontologies to support mechanistic clarity and regulatory relevance (Ives et al., 2017). A review of the AOP-Wiki indicates that efforts are required to systematically align (identify, consolidate, and standardize) the core set of KEs and KERs relevant to ROS generation and oxidative stress. To address this need, the international consortium "Mystery of ROS" (MoR) was established in 2021 (Tanabe et al., 2022a). By harmonizing ROS-related KEs, AOPs across diverse biological domains can be linked, enabling integrative toxicological assessment.

As part of recent MoR activities, KE1115 "Increase, Reactive Oxygen Species" was designated as a harmonized KE in August 2025. KE1115 consolidates descriptions originally developed by the MoR consortium and connects 56 AOPs, as of September 2025, serving as part of a hub (Villeneuve et al., 2018), a small set of inter-related and expert-informed KEs that should be shared by diverse AOPs that operate through ROS, reactive nitrogen species (RNS), and impaired antioxidant defense to connect diverse ROS-related pathways. The harmonization process included merging content from KE1940 "Up-regulation of ROS" into KE1115, streamlining ROS-related pathways. This harmonization is critical, as ROS exhibit a dual role: At low levels they function as signaling molecules, while at excessive levels they induce oxidative damage. Establishing KE1115 provides a standardized framework that enables interoperability across AOPs and strengthens their regulatory applicability.

Furthermore, the MoR consortium emphasized distinguishing causal versus resultative ROS events, clarifying the relationship between ROS increase and oxidative stress (KE1392), and addressing temporal aspects such as acute versus chronic exposure. These efforts underscore the importance of measurable biomarkers and quantitative approaches in future AOP development. The overarching goal of the MoR consortium is to facilitate the development of interconnected robust ROS-related AOP networks that can be harnessed to improve toxicological risk assessment and guide regulatory decision-making, ultimately supporting the advancement of quantitative AOPs (qAOPs) and new approach methodologies (NAMs) for chemical safety assessment.

2 Summary of MoR V

MoR V took place on May 17, 2024. The conference consisted of three presentations focusing on the introduction and current status of MoR, error-corrected next-generation sequencing to study mutagenesis induced by chemicals causing ROS, and DNA biomarkers of oxidative stress in the era of the exposome and adductome (Tab. 1), followed by free discussion.

MoR V began with a brief introduction of the MoR consortium and review of current challenges to be solved. Following this, the use of *in vitro* mutation analysis by duplex sequencing and its application within AOP-informed testing strategies (Ge et al., 2014) were discussed, using AOP296 "Oxidative DNA damage leading to mutations and chromosomal aberrations" as case example. In this case study, human TK6 cells were treated in a concentration-dependent study design with 4-nitroquinoline 1-oxide (4NQO) and sampled at different times post-exposure. The high-throughput CometChip assay (+/- formamidopyrimidine DNA glycosylase) was used to measure oxidatively damaged DNA, inadequate DNA repair, and DNA strand breaks, the first three KEs in the AOP. This was integrated with analysis of chromosome damage using the *in vitro* micronucleus assay and mutations using duplex sequencing (Huliganga et al., 2025; Cho et al., 2023; Kennedy et al., 2014). The case study demonstrated the resolution of oxidatively damaged DNA and strand breaks over time, in parallel with the induction of concentration-dependent increases in chromosome damage and mutations at later time points. The work shows the use of these NAMs as a modern, integrated approach to understand chemicals that operate through AOP296.

DNA biomarkers of oxidative stress were then presented with a focus on the emerging concept of oxidative eustress and oxidative distress, which provides a more refined and biologically relevant understanding of oxidative stress. The exposome concept was introduced to consider the health risk caused by environmental ex-

[1] https://aopwiki.org/

Tab. 1: Outline of Mystery of ROS V

	Title	Presenter
1	Introduction and current status of MoR	Dr Shihori Tanabe
2	Error-corrected next generation sequencing to study mutagenesis induced by chemicals causing ROS	Dr Carole Yauk
3	Are DNA biomarkers of oxidative stress still relevant in the era of the exposome and adductome?	Dr Marcus S. Cooke

posure (Wild, 2005), and the value of cellular and urinary DNA adductomics together with nucleic acid adductomics (Balbo et al., 2014; Cooke et al., 2018, 2023) in the analysis of the exposome was highlighted. Oxidative stress is a hallmark of environmental exposure (Peters et al., 2021).

2.1 Threshold of ROS and quantitative AOPs

Oxidative stress is a complex, dynamic biological process, not a single discrete event. While an increase in ROS is often the trigger, the biological relevance of oxidative stress depends on its persistence, severity, sub-cellular location, and impact on cellular functions. No single marker can fully capture this complexity. Using multiple, complementary markers provides a more accurate and mechanistically informative representation of oxidative stress and helps fulfill the causality requirements. When referring to oxidative stress as a KE, it is important to go beyond simply detecting ROS. A spike in ROS might be transient and adaptive. To meaningfully define oxidative stress in an AOP, a composite of measurements is needed such as ROS, RNS, impaired antioxidant defense, and oxidatively damaged macromolecules (DNA, e.g., 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxo-dG)). Given that the DNA of all DNA-containing cells is likely to contain 8-oxo-dG, threshold levels will need to be established for any biomarker of oxidative stress to differentiate between a physiological (oxidative eustress) and pathological (oxidative distress) redox environment (Sies, 2021). Such "reference values" will likely need to consider factors that can influence the level of the biomarker, e.g., age, sex, cell and organ type, etc. These provide temporal and mechanistic resolution that better reflect true biological impact.

The establishment of a threshold of ROS level is a critical issue in developing ROS-related AOPs. In many cases, only when ROS levels exceed a defined threshold can the biological system transition to the next KE. Importantly, these thresholds vary across cell types, tissue, and species, reflecting differences in baseline antioxidant capacity and cellular sensitivity to oxidative stress. Reference ranges will need to be established for the threshold of ROS in each condition. Direct detection using electron spin resonance and spin trapping or nuclear magnetic resonance (NMR) may serve as important quantification methods for increased ROS (Hasegawa et al., 2004; Bayati-Komitaki et al., 2024; Park et al., 2023; Togashi et al., 2016). However, current methods for detecting ROS primarily rely on fluorescent probes or chemiluminescent assays, which provide direct though often non-specific, measurements of ROS activity. In contrast, indirect approaches assess biomarkers of oxidative damage, such as oxidized DNA bases, protein carbonyls, or lipid peroxidation products, which reflect recent or cumulative ROS exposure. Quantitative validation of these endpoints would be valuable for developing qAOPs. To develop qAOPs, cell type- or species-specific KEs with well-characterized dose-response relationships and standardized biomarker readouts are required, which raises additional challenges and requires further research.

2.2 Toxicological role of ROS

It is important to distinguish ROS that play a causal role in directly inducing toxicity from ROS that arise as secondary, resultative effects of other toxic processes. ROS have dual roles: (i) they induce toxicity when present at high, pathophysiological levels, or (ii) they function in intracellular signaling as second messengers at low, physiological levels. The concept of ROS-associated adverse events was introduced in earlier discussions at MoR IV (Tanabe et al., 2022b, 2023). At MoR V, AOP-informed integrated testing strategies were also discussed, and participants noted that the comet assay is one of the methods for assessing the ROS-induced DNA damage KE. Overall, the discussions emphasized the need to clearly define the toxicological role of ROS, whether as causal drivers or downstream markers, to strengthen the mechanistic basis of ROS-related AOPs and enhance their predictive and regulatory utility.

2.3 Outcome of MoR V

The discussion at MoR V highlighted the importance of quantifying ROS levels and defining transition points between KEs to support the development of qAOPs. They underscored the importance of representing the various context-dependent roles of ROS within AOPs to clearly distinguish causal from secondary, resultative events.

3 Summary of MoR VI

MoR VI was held on May 22, 2025. The meeting included three presentations (Tab. 2) followed by an open discussion on the harmonization of ROS-related KEs. The history of the MoR consortium and the future directions for ROS AOP networks was introduced. In addition, progress in harmonizing ROS KEs (KE1940 and KE1115) was reviewed. An AOP network linking excessive ROS to growth inhibition, as well as collaboration and harmonization on a ROS network, were also discussed.

In parallel with these efforts, an AOP network addressing non-cancer outcomes relevant to radiation exposure has been developed. This work was guided by a systematic scoping review to identify, evaluate, and organize evidence (Kozbenko et al., 2024).

Tab. 2: Outline of Mystery of ROS (VI)

	Title	Presenter
1	History of MoR – Future and past of ROS AOP networks	Dr Shihori Tanabe
2	AOP network for chronic ecotoxicity mediated by ROS	Dr You Song
3	AOPs in radiation protection	Dr Vinita Chauhan

Unlike chemical stressors that act through receptor-mediated mechanisms, ionizing radiation interacts stochastically with biological matter, depositing energy along particle tracks that can affect multiple molecular targets and organ systems simultaneously. The resulting pattern of damage is non-selective and multisite, generating primary ionizations and secondary reactive species that can perturb diverse cellular processes in parallel. The established radiation AOP network encompasses four non-cancer outcomes, learning and memory impairment, vascular remodeling, bone loss, and cataract formation, each initiated by the deposition of energy and converging onto oxidative stress as the central macromolecular-level KE (Chauhan et al., 2025). Deposition of energy induces radiolysis of water and production of ROS, leading to redox imbalance and macromolecular damage. When antioxidant and repair mechanisms are overwhelmed, sustained oxidative stress triggers pro-inflammatory signaling and cell-tissue level dysfunction. In the vascular remodeling AOP, oxidative stress promotes endothelial activation and chronic inflammation, which disrupt nitric oxide signaling and vascular integrity (Kozbenko et al., 2024). In the bone loss AOP, redox imbalance shifts osteoblast-osteoclast dynamics toward bone resorption and structural weakening (Sandhu et al., 2024). The learning and memory impairment AOP links persistent oxidative stress and inflammation to neural remodeling and impaired synaptic function (Sleiman et al., 2024), while the cataract AOP connects oxidative modification of lens proteins to opacity formation (Carrothers et al., 2024).

Across these AOPs, oxidative stress emerges as a unifying mechanistic KE, providing a quantitative anchor for integrating molecular perturbations with functional outcomes. The network highlights the need to strengthen KERs, linking oxidative stress to downstream inflammation, remodeling, and organ dysfunction, and to develop qAOPs that capture dose, dose-rate, and radiation quality dependencies. Such qAOPs will enable benchmark dose modeling and probabilistic risk characterization, advancing radiation protection for both terrestrial exposures and spaceflight conditions. Future research directions should include strengthening KERs in the AOP network with limited evidence, using study designs that specifically address the modified Bradford-Hill criteria (Chauhan et al., 2025). A focus of this work should be investigating cellular senescence and mitochondrial dysfunction KEs that may contribute to the AO, and refining broad KEs (e.g., neural remodeling, endothelial dysfunction) for better quantification.

In close synergy with the OECD AOP coaching program and AOP-Wiki administration, multiple KEs describing an increase in ROS have been harmonized into KE1115 "Increase, Reactive Oxygen Species", as of August 2025 (Tanabe et al., 2025). The text in KE1940 "Up-regulation of ROS", developed in the MoR consortium, was transferred and merged into KE1115, thereby establishing KE1115 as the harmonized event for ROS increase across AOPs. The progress in the harmonization of KE1115 was presented.

3.1 Oxidative stress and ROS

In addition to KE1115 "Increases, Reactive Oxygen Species", the potential role of KE1392 "Oxidative stress" was discussed, including how it connects to different downstream KEs. The consortium participants agreed that since oxidative stress, defined as an imbalance between ROS and antioxidants, encompasses several distinct molecular events and ROS can act as second messengers not necessarily leading to DNA damage, "oxidative stress" and "ROS increase" should be separate KEs. Oxidative stress, in principle, means ROS overwhelming antioxidants and could be a "hub" KE in ROS-related AOPs. In the oxidative stress KE, glutathione depletion is described as one of the measurements to detect oxidative stress, which distinguishes it from KE1115. Glutathione depletion is an indirect and inverse measurement of oxidative stress; it is also rather non-specific since enzyme levels can decrease due to protein/amino acid deficiency, independent of ROS. ROS and antioxidants work in parallel, but often in opposite directions, and in balance, and this interplay is essential for determining whether an AO will ultimately occur. More discussion is needed on the defining feature and methods used to describe "oxidative stress" as a KE.

3.2 Oxidative stress, inflammation, and ROS

An important discussion focused on the inter-connections between oxidative stress, inflammation, and tissue injury, where any of the three may induce the other two (Halappanavar et al., 2021). An additional step exists in the transition from oxidative stress to inflammation. The process between oxidative stress and inflammation can be described in KERs. "Oxidative stress" and "Inflammation" can be in different hubs that occur at different levels of biological organization. KEs "Oxidative stress" and "ROS increase" are different KEs within the hub. Accurate measurement is key to distinguishing the hub KEs.

[2] https://aopwiki.org/events/1115

3.3 Acute and chronic ROS exposure

Following MoR VI, discussions on acute versus chronic timeframes of ROS continued, focusing on how to categorize and relate defense mechanisms and antioxidant production. Acute ROS can play a role as second messengers, while chronic ROS induces inflammation and cancer. These time-dependent effects should be described in the KERs between ROS increases and downstream KEs. Decreases in antioxidant defense mechanisms and ROS production can be different KEs; in parallel, oxidative stress causes an imbalance in antioxidants and an increase in ROS. Thus, as discussed above and emphasized again in this discussion, oxidative stress must be defined using multiple markers rather than a single endpoint. However, this needs to be balanced against the simplicity and clarity required for building AOPs, especially when moving toward qAOPs. The group also emphasized that having a single, dose-responsive, measurable KE is a requirement.

The challenges in quantifying oxidative stress need to be overcome for future development of qAOPs. Oxidative stress can lead to various forms of cellular damage, including DNA damage that contributes to cancer (Nymark et al., 2021). Differences in cellular responses to low-concentration H_2O_2 (oxidative eustress) versus relatively high-concentration H_2O_2 (oxidative distress) need to be considered (Sies, 2017). However, oxidative stress-induced DNA damage and subsequent mutations should be treated as separate KEs, since they represent distinct mechanistic processes. A parallel discussion on aryl hydrocarbon receptor (AhR) activation similarly concluded that sustained AhR activation may be defined as a MIE in an AOP for rodent liver tumor promotion. Indeed, sustained activation or persistent biological effects appear to be pivotal steps in many AOPs (Becker et al., 2015). Including the timeframe of events in KERs is a continuous discussion.

4 Future directions

The development of qAOPs remains a central challenge for the MoR consortium. Building on the harmonization of KE1115 "Increase, Reactive Oxygen Species", future efforts will focus on establishing dose-response and response-response relationships, refining recommendations for detection methodologies, and defining transition thresholds between KEs. The consortium recognizes the need for cell-type and species-specific KEs to support quantitative modeling and regulatory application.

Further exploration of temporal dynamics, particularly the distinction between acute and chronic ROS exposure, will be essential for constructing robust qKERs. The integration of oxidative stress markers, such as glutathione depletion, and the delineation of causal versus resultative ROS effects will enhance mechanistic clarity.

Collaborative efforts with OECD AOP-Wiki initiatives will continue to support the refinement and expansion of ROS-related AOP networks. The MoR consortium aims to facilitate the development of NAMs by providing harmonized, measurable, and biologically relevant KEs that can be applied across disciplines.

5 Conclusion

The MoR consortium has emerged as a global platform for advancing the harmonization of ROS-related AOPs. Through six international conferences and ongoing collaborative efforts, the consortium is developing and integrating hub KEs that are an important tool for AOP developers. This hub currently includes KE1115, which now connects 56 AOPs across diverse biological domains. At MoR V, discussions focused on the threshold concept of ROS, recognizing that a minimum ROS level must be exceeded to trigger subsequent KEs. Quantitative validation and the distinction between causal ROS (initiating toxicity) and resultative ROS (secondary events) were emphasized, highlighting the dual role of ROS in toxicity and signaling. MoR VI concentrated on the integration of KE1940 into KE1115 and introduced KE1392 "Oxidative stress" as a potential umbrella KE in an oxidative stress hub. The meeting further examined the transition from oxidative stress to inflammation, the role of biomarkers such as glutathione depletion, and the critical differentiation between acute and chronic ROS exposure.

Following the six conferences, continued discussion has focused on the temporal dynamics of ROS, distinguishing acute signaling roles from chronic pathological efforts. More than 100 participants from over 24 countries have contributed to the MoR initiative, underscoring its interdisciplinary and international reach, the importance of clarifying hub KEs, the need to establish measurable validated biomarkers (e.g., 8-oxo-dG, protein carbonyls), and defining dose-response relationships.

As the field moves towards qAOP development, challenges remain in defining dose-response relationships, establishing measurable thresholds, integrating cell type specificity, refining the definition of oxidative stress, distinguishing causal versus resultative ROS, and developing robust qAOPs that enable regulatory application of ROS-related AOP networks. The MoR consortium is committed to addressing these challenges and facilitating development of NAMs for chemical safety assessment.

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