Organisation for Economic Co-operation and Development

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ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

Draft Guidance Document for the scientific review of Adverse Outcome Pathways

27 July 2020

This document has been approved by the Extended Advisory Group for Molecular Screening and Toxicogenomics (EAGMST) on 22 July 2020 during a teleconference of the EAGMST.

Post approval modification: on page 15, the Secretariat suggests changing the title of one item of the template for the development of an AOP scientific review report, and replace "Annex 1: Table with reviewers' name" by "Annex 1: Review panel", so that it doesn't necessarily include only the reviewers' names, but also potentially a general statement confirming that there are no COIs of reviewers, based on the analysis of the COI declarations.

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JT03432848

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1. Foreword

1. The Adverse Outcome Pathway (AOP) framework has been developed to facilitate the collection of mechanistic information derived from toxicological science in a structured manner, to assist in establishing causal relationships between molecular and cellular events that lead from exposure to a stressor to adverse effects, and to identify critical data gaps in the understanding of those pathways.

2. AOPs are intended to help regulatory agencies and risk assessors utilise a broader range of mechanistic data concerning the effects of stressors on humans and wildlife in their work. The widespread acceptance of AOPs as a source of information to guide interpretation, generation and application of data from alternative methods depends on the confidence in the quality of the AOP and therefore, on the review process used to evaluate whether the scientific evidence underpinning the AOP is reliable, credible, and balanced and thus that the science used to inform policy is trustworthy.

3. In order to maintain the development of high quality AOPs, it is important to standardise the way in which AOPs are developed and reviewed while retaining an appropriate degree of flexibility to ensure efficiency. The existing Users' Handbook supplement to the Guidance Document for developing and assessing Adverse Outcome Pathways (OECD, 2018) focuses on practical aspects of AOP development and assessment. The objective of the present document is to provide guidance on the quality standards required for the scientific review of an AOP on the AOP-Wiki. It defines the core principles associated with AOP scientific review in order to enable consistent scientific reviews to be conducted, regardless of who is doing the review, and thus will facilitate OECD endorsement.

2. Abbreviations

AOP: Adverse Outcome Pathway

AOP-KB: AOP Knowledge-Base (https://aopkb.oecd.org/)

AOP-Wiki: Collaborative Adverse Outcome Pathway Wiki (https://aopwiki.org/)

EAGMST: Extended Advisory Group for Molecular Screening and Toxicogenomics

FAQs: Frequently Asked Questions

IATA: Integrated Approaches to Testing and Assessment

ITS: Integrated testing strategy

JM: Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology

OECD: Organisation for Economic Co-operation and Development

WNT: Working Group of the National Coordinators of the Test Guidelines Programme

WPHA: Working Party on Hazard Assessment

3. Background: The OECD AOP Development Programme

3.1. Objectives of the AOP Development Programme

4. The objectives of the chemical safety programme of the Organisation for Economic Co-operation and Development (OECD) are to assist countries in developing and implementing policies and instruments that make their systems for managing chemicals as efficient and robust as possible, while protecting human health and the environment.

5. In this context, the OECD launched in 2012 a new programme on the development of Adverse Outcome Pathways (AOP). The AOP concept is expected to guide risk assessors in their work to use existing and emerging information on the effects of chemicals on humans and wildlife, and to target the generation of additional information to the regulatory objective.

6. A variety of potential uses has been described for AOPs. AOPs can, for example, inform the work of the OECD Test Guideline Programme by describing the rationale for the use of particular methods and also by identifying potentially more predictive methods for development. AOPs can be used as a basis for developing an Integrated Approaches to Testing and Assessment (IATA) or an Integrated Testing Strategy (ITS) (OECD, 2016a). The Defined Approaches for skin sensitisation are also based on the corresponding AOP (OECD, 2012, 2016b). They can also be used for further development and application of alternative approaches, such as read-across, as well as in a number of other regulatory contexts, such as priority setting for further testing, hazard identification, classification and labelling, and risk assessment (OECD, 2017).

7. Any stressors that perturb biological pathways and/or functions, including e.g. ionising radiation, are also part of the AOP framework. Although the scientific review principles apply to all stressors, some procedures described in this guidance (e.g. endorsement see para 14) may apply to chemicals stressors only.

3.2. Development of AOPs under the OECD AOP Development Programme

8. The development of an AOP under the OECD AOP Programme consists of three main phases (Figure 3.1). The first phase is the assembly of the knowledge in the AOP-Wiki (Collaborative Adverse Outcome Pathway Wiki, https://aopwiki.org/; a module of the AOP Knowledge-Base AOP-KB; https://aopkb.oecd.org/). The second phase is the review of the AOP, the subject of this Guidance Document. The third phase is the endorsement of the AOP by the responsible OECD Committees.

Figure 3.1. The three phases of the AOP development process

3.2.1. The role of the Extended Advisory Group for Molecular Screening and Toxicogenomics

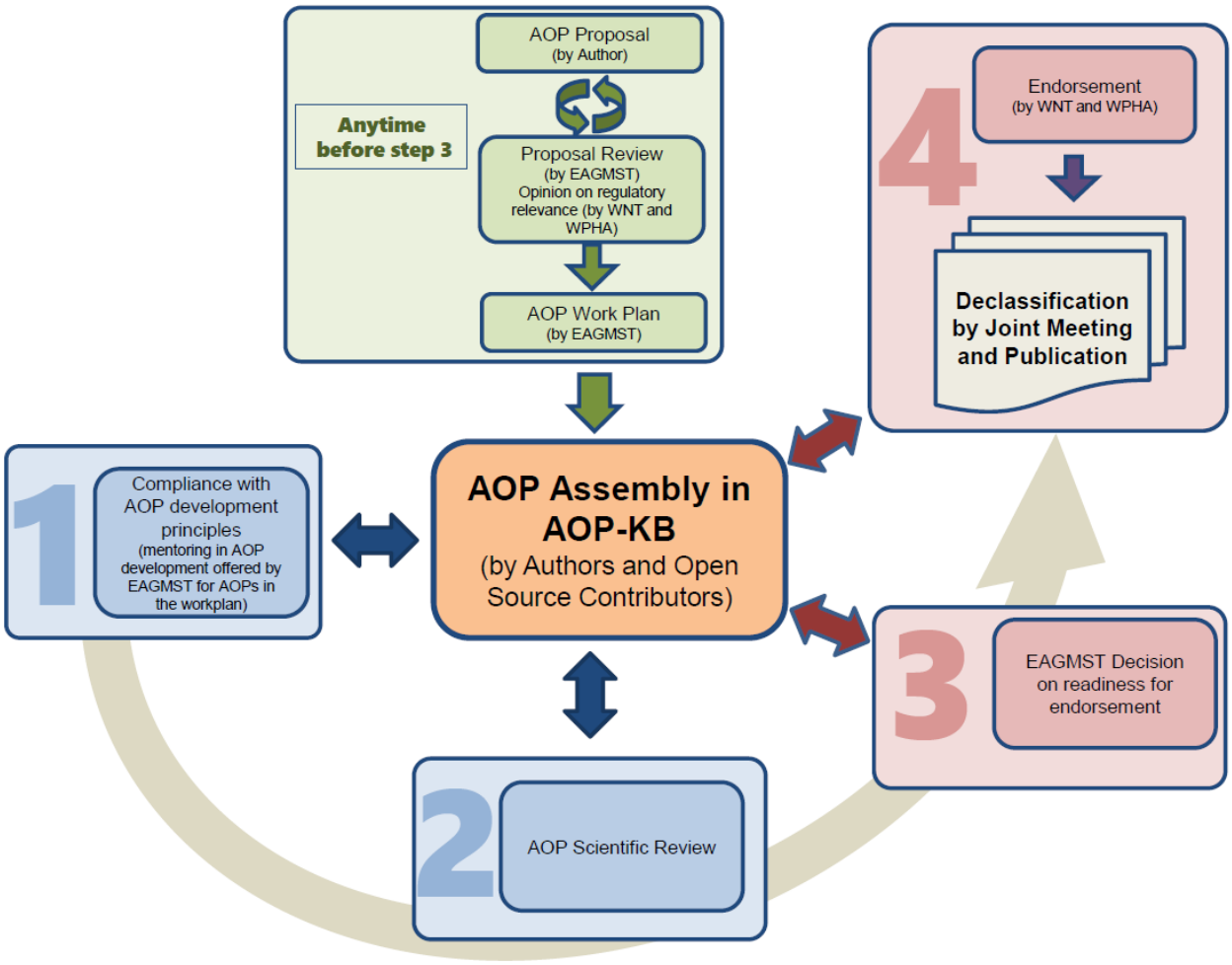
9. The OECD AOP Development Programme is guided by the Extended Advisory Group for Molecular Screening and Toxicogenomics (EAGMST) which is under the oversight of the Working Group of the National Coordinators of the Test Guidelines Programme (WNT) and the Working Party on Hazard Assessment (WPHA).

10. The EAGMST has primary responsibility for (i) examining AOP proposals and deciding on their inclusion in the work plan of the AOP Development Programme, (ii) reviewing the AOPs for their consistency with principles and guidance set out in the User's Handbook (OECD, 2018) and (iii) approving the release of AOPs to WNT and WPHA for endorsement (see section 6), after the completion of the scientific review. In addition, many EAGMST members also play an active role in the development of AOPs.

3.2.2. The various steps and interlinkages between the parties involved in AOP development

11. Figure 3.2. provides an overview of the OECD AOP development process.

Figure 3.2. Detailed description of the AOP development process



12. Assembly phase: Normally, an AOP is assembled by its authors in the AOP-Wiki after submission of a project proposal to the OECD Secretariat. This proposal is reviewed by the EAGMST and submitted to the WNT and WPHA for an opinion on its regulatory relevance before the EAGMST decides on its inclusion in the AOP work plan. The AOP should be assembled by the authors in the AOP-Wiki in compliance with the AOP development principles (OECD, 2018). Coaching in AOP development is offered to the authors by EAGMST for AOPs in the work plan, and a compliance check (Step 1 in Figure 3.2) is performed prior to moving to the next step.

13. Scientific review phase (Step 2 in Figure 3.2): The next step, after the AOP has been assembled in the AOP-Wiki and checked for compliance (see chapter 4), is the scientific review.

14. Endorsement phase (Steps 3 and 4 in Figure 3.2): The endorsement phase is OECD-specific. It is based on the outcome of the scientific review and subsequent revisions by the authors addressing the reviewers' comments. It consists of a three-step endorsement (EAGMST, WNT and WPHA, Joint Meeting) of the work conducted. This process can involve further reviewing of the scientifically reviewed AOP and potential comments to be further addressed by the AOP authors. AOP endorsement is followed by the publication of the AOP on the OECD dedicated Series on AOPs in i-Library.

4. Pre-requisite for the AOP scientific review

Coaching and compliance check

15. Before scientific review, the AOP is checked for compliance with the principles and guidance set out in the Users' Handbook supplement to the Guidance Document for developing and assessing Adverse Outcome Pathways (OECD, 2018). The Users' Handbook is analogous to the "instructions for authors" used in preparing a journal article, but rather than describing the preparation of a technical manuscript, it details how to structure the elements of an AOP in the AOP-Wiki (OECD, 2018).

16. Until 2018, this compliance check was conducted by experts within the EAGMST (so-called "internal review"), after the authors had assembled an AOP in the AOP-Wiki and notified EAGMST that it was ready for review.

17. In 2019, EAGMST introduced a coaching process for the authors of an AOP, starting when an AOP project is accepted onto the work plan. The coach, a member of the EAGMST who is familiar with AOP guidance and development, helps developers to begin and continue on the right track. Once the AOP is mature enough, the coach is in charge of filling in a compliance check form that ensures that the requirements of the Users' Handbook are met before the AOP undergoes scientific review. The coaches may be trained with the latest situation of AOP development process upon request. The coach will not participate in the scientific review as a reviewer to avoid any potential conflict of interest.

Inclusion of a project in the OECD AOP Development Programme work plan

18. Although it is possible for scientists to initiate and assemble an AOP in the AOP-Wiki outside of the OECD AOP development programme, particularly in the case of AOPs covering valuable aspects of biology that do not have immediate regulatory application, contributing via the OECD development programme allows authors to be supported during AOP assembly, provides more visibility and confidence in the AOP developed, and facilitates its potential use by regulators and more broadly by the scientific community. AOPs developed outside the OECD development programme can receive ad-hoc mentoring from the Society for the Advancement of AOPs.

19. Developers of an AOP who wish their project to be included in the OECD AOP Development work plan should fill in a project submission form and submit it via the OECD Secretariat to the EAGMST. The EAGMST decides whether the proposed AOP should be included in the OECD AOP Development work plan, and submits it for consultation to WPHA/WNT to help assess regulatory relevance and raise awareness about AOP developments. WPHA/WNT may also help identify opportunities for

collaboration between groups and consider how AOPs can be better aligned to support regulatory needs of countries and how resources can be focused.

20. In principle, the submission of a project proposal for inclusion of an AOP in the OECD AOP development work plan can be done before any of the three- phases in the development of an AOP (see Figure 3.1); however, in practice, the submission of a project proposal is encouraged before assembly of the AOP into the AOP-Wiki platform, so that authors can benefit from the coaching provided by EAGMST.

5. The AOP Scientific review

21. The scientific review of an AOP, developed in the AOP-Wiki, is initiated after completion of the Users' Handbook compliance check by coaches. It is based on the following principles:

- The scientific review should be independent
  - ✓ Avoid conflicts of interest
- The scientific review should be transparent
  - ✓ Transparent selection of reviewers through diverse recruitment channels – e.g. making use of OECD expert groups with expertise in relevant fields.
  - ✓ Public disclosure on AOP wiki or e.AOP.portal of the names of the reviewers, their declaration of interest, their comments and the responses of the AOP authors to the reviewers' comments
- The collective scientific expertise of the panel should cover the technical, biological and toxicological scope of the AOP
- The scientific review should address a standard set of pre-defined charge questions (see paragraph 32 below)

5.1. Review organiser

22. In the first years of the OECD AOP Programme, scientific reviews were organised by the OECD Secretariat. However, in principle, any organisation or individual can act as a review organiser and conduct an acceptable review by following the principles described in this Guidance Document. As appropriate, the OECD Secretariat, on an ad hoc basis, may consult with the WNT and the WPHA to identify potential review organisers.

23. Prospective review organisers are encouraged to inform the OECD Secretariat of their interest and intention to conduct an external review and in doing so can avail of advice and potential support from EAGMST.

5.2. Conflict of interest

24. Confidence in the AOP evaluation process depends on a high scientific quality of the review and on an independent and transparent process throughout evaluation at any step. The scientific review needs to be free of any conflict of interest in order not to undermine the credibility of a future published AOP.

25. We adopt the definitions of a conflict of interest (COI) proposed by the US National Academies (National Academies, 2003) in the context of committees developing reports. COI is defined as being any financial or other interest that conflicts with the service of an individual because it (1) could significantly impair the individual's objectivity or (2) could create an unfair competitive advantage for any person or organisation.

26. Both financial and other interests are important (ICMJE, 2018). In the context of the AOP review, review organiser and reviewer COIs include, in addition to financial interests, having participated in the development of the AOP under review or of another closely related AOP or being from the same team or laboratory as the AOP developer.

27. The review organiser's responsibility is to ensure the quality and integrity of the review. A review should not be organised by a group/entity with a potential COI (i.e. groups/entities directly impacted financially or otherwise by the outcome of the review), which could result in the review being compromised. Under the request of the review organiser, EAGMST can check the absence of COI of the review organiser prior to the scientific review. Otherwise, absence of COI of the review organiser will be checked by EAGMST after the scientific review, before the AOP is submitted to WNT and WPHA for endorsement.

28. Review managers (see section 5.7) and reviewers have to declare any interests that are relevant to the functions to be performed, in the form of a declaration of interest or a COI questionnaire on potential conflicts. This form serves to document if interests are of a significantly conflicting nature, or may be perceived as such, potentially preventing participation in the review process of the AOP under consideration. If there is a COI, participation in the review is not possible. A proposed declaration of interest form is available in Annex 2.

5.3. Call for reviewers and recruitment of candidate reviewers

29. It is up to the review organiser to launch a call for relevant reviewers and contact a broad network of experts via various appropriate channels. If the credentials and qualifications of the candidate reviewers are not publicly available, a short CV will be requested. Situations where an AOP developer suggests potential reviewers should be avoided.

30. The call for reviewers can be made via various channels depending on the organisation responsible for the scientific review. For example, when the review is organised by the OECD Secretariat, the WNT is invited to nominate relevant experts via the different expert groups of the Test Guideline programme; independent scientific societies with access to subject matter expertise may also be solicited. The WNT and the WPHA will be consulted when a call for reviewers is circulated, in order to be given the possibility to nominate experts and thus broaden the pool of candidates for the review. This can be done in coordination with the OECD Secretariat.

5.4. Selection of reviewers from the pool of candidate reviewers

31. Following the call for reviewers, a balanced panel for the scientific review will be established by the review organiser. The EAGMST recommends panels of 3 to 5 reviewers. This ensures diversity of opinions but also a manageable and efficient process. The number of reviewers may be adapted to provide sufficient expertise to evaluate the entire pathway being reviewed.

32. The selection of the reviewers will be based on both individual and panel criteria. Prior work with AOPs is not required, since the review of the AOP should focus on the scientific aspects presented in it.

- Individual criteria:

    - The reviewers' expertise should be relevant to the AOP under review, not only for the hazard/endpoint (i.e. the AO) but at the various levels of biological organisation of the key events leading to the AO. This can be evaluated, for example, by examining the publications that a candidate reviewer has authored or co-authored and their relevance to the AOP under review;
    - The reviewers should have no conflict of interest.

- Panel criteria

    - Appropriate collective scientific expertise of the panel is needed to ensure that the various parts of the AOP are covered and can be fully evaluated, i.e. addressing the various levels of biological organisation characterised within the AOP for the relevant endpoint;
    - Balanced representation of research and regulatory fields and affiliation (country/region level) is desirable, but should not be achieved at the expense of scientific expertise.

33. Prior to the review, the review organiser must ensure that the reviewers are sufficiently informed of the AOP conventions, by consulting the training material available on-line. Videos, PPTs, kick off review webinars, OECD webinars on AOPs, and/or the online training course could for example be consulted. Training resources are available under the Tox21 workstream, at this link: https://www.afsacollaboration.org/tox21/get-trained/#training-resources. Furthermore, a folder with the training modules can be downloaded at this link: https://drive.google.com/drive/folders/1_BWfP-f2kH7u2uwCoQS43oHjax6zmUYd. Reading the available documentation, especially the Guidance Document on Developing and Assessing Adverse Outcome Pathways (OECD, 2017), the Users' Handbook (OECD, 2018) and the Frequently Asked Questions (FAQs) is also strongly recommended.

5.5. The review process

34. The online version of an AOP on AOP-Wiki can evolve over time. Therefore, the AOP-KB offers the possibility to generate a "snapshot" of the AOP at a certain point in time, in the form of a versioned, date-stamped PDF document. This snapshot is the document of reference for the review.

35. The scientific reviewers' tasks are to:

    - Take note of comments that may have been made on previous versions of the AOP during the compliance check; these are available in the discussion pages of the AOP in the AOP-KB;
    - Review the scientific evidence that has been presented to substantiate the AOP;
    - Respond specifically to the following charge questions (additional questions may be added on a case-by-case basis, for example depending on the outcome of the Users' Handbook compliance check):

        1. Scientific quality:

            - Does the AOP incorporate all appropriate scientific literature and evidence?
            - Does the scientific content of the AOP reflect current scientific knowledge on this specific topic?

        2. Weight of evidence:

            - In your opinion, is the weight-of-evidence judgement/scoring well described and justified based on the evidence presented? If not please explain.
            - Please consider weight-of-evidence for each KER and for the AOP as a whole.

36. Assessment criteria for performing the scientific review are provided in the Users' Handbook (OECD, 2018). Reviewers should avoid recommending changes that, if adopted, would cause the AOP under review to lose compliance with the Users' Handbook or with the Guidance Document.

37. The reviewers send written responses and comments back to the review organiser, who is responsible for review collation and correspondence with the AOP authors.

38. It is recommended that during the review phase and until the submission of the reviewers' comments to the organiser of the review, the AOP authors are not informed of the membership of the review panel and any direct communication between the reviewers and the authors should be avoided. After AOP authors have received the reviewer' comments however, interactions between authors and reviewers can be organised and are encouraged. Bringing together the reviewers and the AOP authors has proven to be helpful because it enables them to discuss, exchange views and share experience about the AOP after the review. It also facilitates the revision of the AOP by their authors, in line with the reviewers' comments.

39. The reviewers' comments are processed by the review organiser according to its organisation's standard process. If no formal process exists, the outcome of the scientific review could take the form of a scientific review report (see example of a template in Annex 1).

5.6. Public information related to the reviewers

40. The names of the reviewers, their affiliation and comments will be made publicly available on the AOP-Wiki after completion of the review. The EAGMST recommends that the reviewers' names be provided as an AOP specific list, but not associated with their individual comments. This option was

chosen as a compromise between having individual comments linked to individual reviewers (which some reviewers may not feel comfortable with as the comments become publicly available) and having a master list of reviewers across all AOPs (which may dilute the visibility of a reviewer's participation). The reviewers should be informed about this before the start of the review.

41. Reviewers are considered as critical contributors AOP development and thus participation in the review of an AOP is regarded as a notable scholarly activity and achievement. Consequently, reviewers are encouraged to cite their contributions to the review of AOPs as part of their professional credentials (e.g., listed on a CV as evidence of scholarly activity and expertise).

5.7. The role of review managers

42. The review organiser may wish to delegate tasks to a review manager (e.g. internal staff, consultant, journal editor) who ensures coordination between the reviewers during the review and as necessary, and between the AOP authors and the reviewers once reviewers have submitted their initial comments. The review manager should have sufficient general knowledge in the field of the AOP under review in order to be able to facilitate the review, but should not personally contribute to the review. The review manager should have no conflict of interests associated with the AOP under review and should ideally be affiliated with an independent organization (e.g., government body or scientific journal). It is acknowledged that the role of the review manager in the coordination of the review is highly valuable.

6. Subsequent AOP endorsement by OECD

43. At the end of the review process, the authors of an AOP in the OECD AOP Development work plan will be invited either by the review organiser or by the OECD Secretariat to revise their AOP in order to move to the next step, i.e. endorsement by OECD and subsequent publication of their AOP on the OECD public website. The AOP revision should take into consideration the comments from the review panel and the AOP authors should provide written responses addressing the comments. Responses to reviewer comments will also be made publicly available on the AOP-Wiki.

44. The comments from the scientific review, responses from the AOP author, and the revised AOP, as appropriate, are collated by the review organiser and submitted to EAGMST. EAGMST will then determine if the AOP has been adequately revised and if it can be released to the WNT and the WPHA for endorsement.

45. The scope of AOP endorsement by the WNT and the WPHA was clarified in 2016, and the WNT and WPHA agreed on a disclaimer, which has subsequently been updated and which is included in the foreword of published AOPs:

> *"This Adverse Outcome Pathway (AOP) has been developed under the auspices of the OECD AOP Development Programme, overseen by the Extended Advisory Group on Molecular Screening and Toxicogenomics (EAGMST), which is an advisory group under the Working Group of the National Coordinators for the Test Guidelines Programme (WNT). The AOP has been reviewed internally by the EAGMST, its scientific review has*

been conducted following the principles established in the Guidance Document for the scientific review of Adverse Outcome Pathways, and it has been endorsed by the WNT and the Working Party on Hazard Assessment (WPHA).

Through endorsement of this AOP, the WNT and the WPHA express confidence in the scientific review process that the AOP has undergone and accept the recommendation of the EAGMST that the AOP be disseminated publicly. Endorsement does not necessarily indicate that the AOP is now considered a tool for direct regulatory application."

46. After WNT and WPHA endorsement, the last step in the AOP development process (as depicted in Figure 3.2), is declassification[1] by the Joint Meeting (JM) followed by publication on the OECD public website in the OECD Series on Adverse Outcome Pathways.

47. AOPs are viewed as living documents. Crowdsourcing is one principle of the AOP Development programme, and AOPs thus may continue to evolve on the AOP-KB after their publication, as new evidences supporting or rejecting AOPs are generated and/or new knowledge is gained. The purpose of publication in the Series on AOPs is to provide a stable version over time, i.e. the version which has been reviewed and revised based on the outcome of the review. An AOP published in the OECD series on AOPs may be considered for update when significant additional information is available in the AOP-Wiki that justifies the update.

[1] Official OECD information shall be either unclassified or classified as: a) For Official Use -- for information which should not be communicated except for official purposes; or b) Confidential -- for information the unauthorised disclosure of which would seriously prejudice the interest of the Organisation or any of its Member countries. When a classified official document under the responsibility of the Joint Meeting is ready for publication, the Joint Meeting is responsible for its declassification, such that it obtains an unclassified status and can be published.

7. References

ICMJE (2018), International Committee of Medical Journal Editors, Author Responsibilities—Conflicts of Interest [Webpage available at http://www.icmje.org/recommendations/browse/roles-and-responsibilities/author-responsibilities--conflicts-of-interest.html]

National Academies, National Academy of Sciences, National Academy of Engineering, Institute of Medicine, National Research Council (2003), "Policy on committee composition and balance and conflicts of interest for committees used in the development of reports". [Available at http://www.nationalacademies.org/coi/]

OECD (2012), "The Adverse Outcome Pathway for Skin Sensitisation Initiated by Covalent Binding to Proteins", *OECD Series on Testing and Assessment*, No. 168, OECD Publishing, Paris.

OECD (2016a), "Guidance Document for the use of Adverse Outcome Pathways in developing Integrated Approaches to Testing and Assessment (IATA)", *OECD Series on Testing and Assessment*, No. 260, OECD Publishing, Paris.

OECD (2016b), "Guidance Document on the Reporting of Defined Approaches and Individual Information Sources to be Used Within Integrated Approaches to Testing and Assessment (IATA) for Skin Sensitisation", *OECD Series on Testing and Assessment*, No. 256, OECD Publishing, Paris.

OECD (2017), "Revised Guidance Document on Developing and Assessing Adverse Outcome Pathways", OECD Series on Testing and Assessment, No. 184, OECD Publishing, Paris.

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Frequently Asked Questions (FAQs): draft document

Annex 1 – Example of a template for the development of an AOP scientific review report

Annex 2: Declaration of interest

Conflict of Interest Questionnaire[2]:

The following questionnaire is intended to ensure that individuals who organize, manage, or participate in the scientific review of an adverse outcome pathway (AOP) are not compromised by any significant conflict of interest. Conflict of interest means any financial or other interest (including intellectual property) that conflicts with the participation of an individual in particular decisions and evaluation of the scientific content of an AOP because that interest could 1) impair the individual's objectivity or 2) create an unfair competitive advantage for any person or organisation.

Examples of financial conflicts of interest include:

- employment relationships: e.g., private, public sector and self-employment,
- consulting relationships: e.g., commercial and professional consulting and service arrangements, scientific and technical advisory board memberships, serving as an expert witness in litigation, and providing services in exchange for honorariums and travel reimbursements,
- financial: e.g., stocks, bonds, and other financial instruments and investments, including partnerships, real estate investments, patents, copyrights, and other intellectual property interests, commercial business ownership and investment interests, and research funding and other forms of research support.

Conflict of interest applies to the individual's personal interests, as well as to the interests of others with whom the individual has substantial common financial interests if these interests are relevant to the functions to be performed (e.g., consider individual's employer, business partners, spouse and other family members, etc). Consider also the interests for whom one is acting in a fiduciary or similar capacity (e.g., officer or director of a corporation, serving as a trustee).

The intent of the following questionnaire is to determine and eliminate certain potentially compromising situations from occurring, protecting the OECD and/or other institutions, individuals (organizer, manager, or reviewer), and the public interest.

A copy of the declaration should be retained that can be disclosed should questions of a conflict arise.

I. Information:
   a. Date:
   b. Given Name:
   c. Surname:
   d. Role in review (organizer, manager, reviewer):
   e. AOP number:
   f. AOP title:

II. Affiliations: please list your organizational affiliations (relevant business relationships and relevant remunerated or volunteer non-business relationships).

[2] This COI questionnaire was developed based on the International Committee of Medical Journal Editors (ICMJE) COI checklist (http://www.icmje.org/conflicts-of-interest/) and the National Academy of Sciences Background Information and Conflict of Interest Declaration form (BI/COI form A).

III. Direct links to the AOP under consideration for scientific review: these questions are about links that existed at any time to the AOP under consideration including the stages of initial conception and planning to the present.
   a. Did you or your institution at any time receive payment or services from a third party (government, commercial, private foundation, etc) for any aspect of the AOP under review (including but not limited to grants, data monitoring board, study design, AOP preparation/drafting, statistical analysis, etc.)? If yes, please list funders.
   b. Did you or your institution at any time directly fund or provide services (whether for free or for payment) for any aspect of the AOP under review (including but not limited to grants, data monitoring board, study design, AOP preparation/drafting, statistical analysis, etc.)? If yes, please explain.
   c. For a) and b) above, please list:
      i. Name of entity
      ii. Type of funding (grant, personal fees, non-financial support, other)
      iii. Provide any relevant comments
   d. If you have nothing to report, please state "Neither I nor any institution with which I am affiliated have received direct financial payment, financial or otherwise for work directly related to the development of the AOP under consideration for scientific review"

IV. Relevant financial activities outside the AOP considered for scientific review: This section asks about financial interests outside of this AOP that could be perceived to influence, or give appearance of potentially influencing the scientific review, organization, or management of the review of the AOP under review. All sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to review of the AOP under consideration (including all monies from sources with relevance to the specific AOP under review). Also list interactions with the AOP's sponsor that are outside the submitted AOP. If unsure, you must disclose the relationship for review. For grants received related to the content of this AOP, you should disclose support from entities that could be impacted financially by publishing the AOP under review or that could reasonably be perceived to be affected financially by publishing the AOP under review.
   a. Indicate whether you have financial relationships (regardless of the amount of compensation) with entities described above. List each entity you have had a relationship with in the last 36 months prior to this review process.
      i. Name of entity
      ii. Type of funding (grant, personal fees, non-financial support, other)
      iii. Provide any relevant comments
   b. If you have no financial activities outside of the AOP being considered for scientific review, please state "I have had no relevant financial relationships in the last 36 months outside the AOP being considered for scientific review"

V. Intellectual property – patents and copyright. Do you or your institution have any patents, whether planned, pending, or issued, that are relevant to this AOP?
   a. If yes, please list and describe.
   b. If no, please state, "I have no patents, planned, pending or issued that are relevant to the AOP to be reviewed"

VI. Public statements and positions or other relevant aspects of your background or present circumstances not addressed that might be reasonably construed by others to affect your judgment in organizing, managing or reviewing the AOP under consideration for scientific

review. Please list any relevant articles, testimony, speeches, assigned tasks or activities that could be perceived to indicate a position on an issue or problem relevant to the AOP under consideration. Please list by date, title, and publication (if relevant) and a brief description of groups or activities of concern. If none, please state "None".

VII. Lobbying activities. You must disclose any activities that are considered lobbying so that they can be considered for their potential relationship to the development and publishing of the AOP under scientific review. Lobbying activities are those that are performed by a person who receives compensation or reimbursement from another person, groups, or entity for the purpose of promoting, opposing, or in any manner influencing or attempting to influence the introduction, defeat, or enactment of legislation before any legislative body, or the practice of promoting, opposing, or in any manner influencing or attempting to influence the enactment, promulgation, modification, or deletion of regulations before any regulatory body (http://www.ncsl.org/research/ethics/50-state-chart-lobby-definitions.aspx). If none, please state "None".

VIII. Relationships not covered. Are there other relationships or activities that AOP users or the public at large could perceive to have influenced, or that give the appearance of potentially influencing your ability to organize, manage the review of, or review the AOP under consideration?

a. If yes, please list and describe
b. If no, please state “No other relationships, considerations, or circumstances exist that present a potential conflict of interest”.

Disclosure statement:

Dr. NAME HERE has the following potential conflicts to disclose related to the LIST AOP TITLE AND NUMBER HERE:

OR

Dr. NAME HERE has nothing to disclose.

I understand that any inaccuracies or omissions, whether intentional or unintentional, could have a serious impact not only on the AOP being reviewed but on the AOP programme and the OECD more generally. I confirm that I have carefully read and understood the above questions and that my responses above are accurate and complete and do not contain any misleading statements or information. If I at any point before completion of the AOP review realise that I have omitted information from this form, I will immediately contact [X] in order to update this form.

_____

Signature of organizer, review manager, or reviewer

_____

Date