May 2019

OECD ADVERSE OUTCOME PATHWAY

Project Submission Form

If you require further information please contact the OECD Secretariat
Return completed forms to our generic account (env.tgcontact@oecd.org), and Nathalie Delrue (Nathalie.delrue@oecd.org)

PROJECT TITLE

Development of intersecting AOPs that address genetic toxicology endpoints

SUBMITTED BY (Country / European Commission / Secretariat)

USA

DATE OF SUBMISSION TO THE SECRETARIAT

June 1, 2019

May 2019

DETAILS OF LEAD COUNTRY/CONSORTIUM

Country/Organisation:	USA
Agency/ministry/Other:	Health and Environmental Sciences Institute (HESI), Genetic Toxicology Technical Committee (GTTC)
Contact person(s):	Stan Parish
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Phone/fax:	
Email:	sparish@hesiglobal.org

PROJECT CATEGORY

☒ Development of an AOP - applicable to a chemical category

Select the development tool to be used
☐ AOP-Wiki ☐ Effectopedia

☐ Guidance document related to AOP development including its evaluation

☐ Knowledge management tool for supporting AOP development including its evaluation

☐ Other, please specify below

If other category, please specify:

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PROJECT DESCRIPTION

Please provide sufficient information to facilitate the review of the project submission by the OECD secretariat and the Extended Advisory Group with respect to its suitability to be included in the workplan of the AOP programme.

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The mission of HESI's GTTC is "to improve the scientific basis of the interpretation of results from genetic toxicology tests for purposes of more accurate hazard identification and assessment of human risk; to develop follow-up strategies for determining the relevance of test results to human health; to provide a framework for integration of testing results into a risk-based assessment of the effects of chemical exposures on human health; to promote the integration and use of new techniques and scientific knowledge in the evaluation of genetic toxicology; and to monitor and promote the development of innovative test and testing strategies."

To accomplish its mission, the GTTC brings together experts from across industry, government and academia to collaborate on projects addressing key problems and issues in genetic toxicology. Recent emphasis on the use of mechanistic information to improve regulatory testing paradigms and risk assessment led to the development of a Mode of Action (MoA) Working Group within the GTTC. Recognizing the value and strengths of the AOP framework, and alignment with MoA development, sub-groups of the MoA Working Group have now been created to build AOPs that describe critical and prevalent MoAs in genetic toxicology testing. It is envisioned that these AOPs will facilitate the design of testing strategies that can help to identify key follow up tests to inform: (a) an MIE underlying a positive conventional genetox test for risk assessment purposes, and (b) potential downstream genetic toxicology effects from early mechanistic changes identified in screening studies. The group has also identified a variety of ways in which AOPs will serve as powerful tools for genetic toxicology hazard and risk assessment. A manuscript describing workshop outcomes of the use of AOPs in genetic toxicology testing has been submitted to *Environmental and Molecular Mutagenesis*.

In addition to defining key strengths of AOPs in this field, the above manuscript lists a variety of important AOPs that would be of value to the genetic toxicology community. Building on the two genetic toxicology AOPs that exist in the AOP-wiki, the following AOPs were identified:

1. Oxidative DNA damage leading to mutations (AOP1) and chromosomal aberrations (AOP2)
2. Topoisomerase inhibition leading to mutations (AOP1) and chromosomal aberrations (AOP2)
3. Aurora kinase inhibition leading to polyploidy (AOP1) and aneuploidy (AOP2)
4. Tubulin binding leading to polyploidy (AOP1) and aneuploidy (AOP2)

The purpose of the present project is to have GTTC experts work with AOP experts (C. Yauk and M. Luijten), and previous authors (F. Marchetti), to develop the four AOPs above. Substantial progress has already been made on several of these projects.

Two of the AOPs are sufficiently developed to share the flow diagrams. These are shown below. All of the AOPs are very well understood mechanistically (high level of biological plausibility) with extensive support from the literature. Given the importance of genetic toxicology effects as endpoints in human health risk assessment, the GTTC views the development of these AOPs by this team of experts as critical to ensuring that the AOP-wiki contains the highest quality, accurate AOPs addressing genetic effects for the broader community.

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Note: For AOP Development projects please indicate the extent of the pathway to be described (i.e. the anchor points), the intermediate events that are likely to be addressed, the state of current development**,** the degree to which this pathway is already understood and described in the literature, and the expectation on the availability of evidence to support the AOP. Proposers should also indicate if and how the AOP is associated to any regulatory toxicological endpoints (e.g. acute or chronic toxicity, toxicity to reproduction etc.) Please provide references, links or attachments for supplementary information.

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PROJECT PLANNING

In this section, please provide an indication of when the project is likely to commence and the expected duration. Please also make reference to any particular milestones or external factors that will influence project planning, and if the project is linked to programmes of particular organisations or consortia.

Timing:

This project was initiated in spring 2018 and is well underway. We expect that the four categories of AOPs described above will be completed within two years. We note that some AOPs (within #1 and #3) are very mature and have been the subject of extensive discussions. These AOPs are expected to be ready for entry into the AOP-wiki by December 2019.

Links with existing and previous work:

We note that a working group of the International Workshops on Genotoxicity Testing (IWGT) has done extensive preliminary work on #3 and #4 above (refs 1-3)..

To build these AOPs, the MoA working group first surveyed published AOPs that could be leveraged for development of additional pathways. The two AOPs below were noted as containing overlapping KE(R)s and these modules will be used within AOPs produced by the GTTC.

AOP: 15

Alkylation of DNA in male pre-meiotic germ cells leading to heritable mutations

(Lead author Carole Yauk)

and

AOP: 106

Chemical binding to tubulin in oocytes leading to aneuploidy offspring

(Lead author Francesco Marchetti)

In addition, the MoA Working Group noted the inclusion of a radiation-centric AOP leading from energy deposition to lung cancer in the AOP workplan (Lead Vinita Chauhan).

The GTTC MoA Working Group now includes the authors of these AOPs, which will facilitate the ability to re-use (including modifying) existing KE(R)s.

Thus, all of the AOPs in development will be able to take advantage of existing KE(R)s used in these AOPs.

Milestones:

#1. This AOP is complete and in review by the expert working group.

- The intended submission date to the OECD for internal review is summer 2019.

#2. This AOP is under development; submission for review by the expert working group is planned for summer 2020.

#3. This AOP is almost complete; the intended submission date for review by the expert working group is fall 2019.

#4. This AOP is under development; submission for review by the expert working group is planned for fall 2020.

References

[1] A.M. Lynch, D. Eastmond, A. Elhajouji, R. Froetschl, M. Kirsch-Volders, F. Marchetti, K. Masumura, F. Pacchierotti, M. Schuler, D. Tweats. Targets and mechanisms of chemically induced aneuploidy. Part I of the report of the 2017 IWGT workgroup on assessing the risk of aneugens for carcinogenesis and hereditary diseases. Mutat. Res. (2019) https://doi.org/10.1016/j.mrgentox.2019.02.006

[2] F. Pacchierotti, K. Masumura, D. Eastmond, A. Elhajouji, R. Froetschl, M. Kirsch-Volders, A.M. Lynch, M. Schuler, D. Tweats, F. Marchetti. Report of the 2017 IWGT workgroup on assessing the risk of aneugens for carcinogenesis and hereditary diseases. Part II: aneuploidy in germ cells.Mutat. Res. (2019) https://doi.org/10.1016/j.mrgentox.2019.02.004 https://doi.org/10.1016/j.mrgentox.2019.02.004

[3] D. Tweats, D.A. Eastmond, A.M. Lynch, A. Elhajouiji, R. Froetschl, M. Kirsch-Volders, F. Marchetti, F., Masumura, F. Pacchierotti, M. Schuler. Role of aneuploidy in the carcinogenic process: Part 3 of the report of the 2017 IWGT workgroup on assessing the risk of aneugens for carcinogenesis and hereditary diseases. Mutat. Res. https://doi.org/10.1016/j.mrgentox.2019.03.005

FLOW DIAGRAM

In this section, please provide a flow diagram of the proposed AOP, including the MIE, KEs at the various stages (molecular interaction, cellular response, organ response) and the AO.

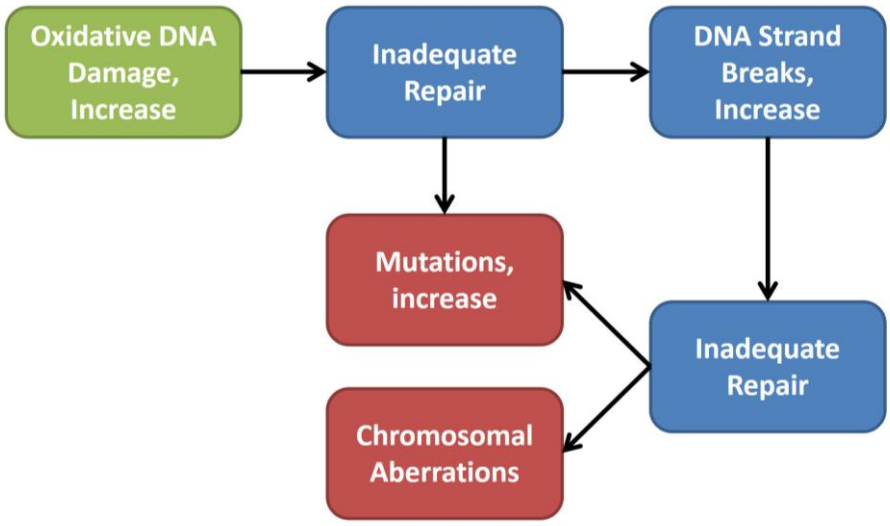

Figure 1. AOP network describing how oxidative DNA damage leads to mutations and chromosomal aberrations. Note that this AOPs leverages existing KE(R)s for DNA repair (to be updated by group and the name revised) and mutations, and accompanying KER. Leads: Carole Yauk and Eunnara Cho (Health Canada). This AOP network outlines work for project #1 above. Note that an existing KE called insufficient/incorrect DNA repair is being renamed (in collaboration with original authors) 'inadequate DNA repair' to more fully capture potential problems associated with this KE.

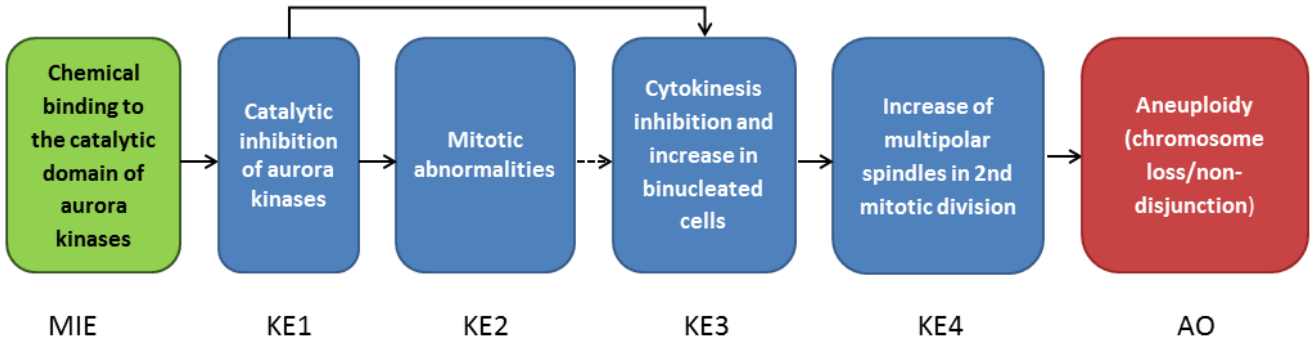

Figure 2: AOP describing how inhibition of aurora B kinase leads to the induction of aneuploidy. Note that catalytic inhibition of aurora B kinase results in both mitotic abnormalities and inhibition of cytokinesis. Lead: Maik Schuler (Pfizer Inc.)

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COORDINATION OF OECD ACTIVITIES

AOP developers who submit a new AOP project proposal are invited to inform their National Coordinator of the Test Guidelines Programme.

National Coordinators' contact details are available at the following URL on the OECD public website:
http://www.oecd.org/env/ehs/testing/national-coordinators-test-guidelines-programme.htm