MUT/2016/02

COMMITTEE ON MUTAGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COM)

Development of the adverse outcome pathways for "alkylation of DNA in male premeiotic germ cells leading to heritable mutations" and "chemical binding to tubulin in oocytes leading to aneuploid offspring" - for information

As part of the ongoing COM review of germ cell mutagenesis, our attention was brought to recent papers by the group from Health Canada – two adverse outcome pathway (AOP) analyses for topics related to germ cell mutagenesis. These are appended for Members information.

In brief, an AOP is specific to a molecular initiating event (MIE) and not chemical specific. Key events (KE) are identified and should be essential for the toxicological response and measurable. The connection between KE's are termed a KE relationship (KER).

Modified Bradford Hill criteria are used to evaluate the empirical evidence and biological knowledge and this evaluation establishes the KER's. KER's can be described qualitatively, semi qualitatively or quantitatively depending on the knowledge available.

Overall, assessments involve examining the confidence and extent of the evidence, the biological plausibility and how this evidence supports the KES's.

The DNA alkylation AOP focusus on premiotic germ cell DNA alkylation, using ethylnitrosourea (ENU) as a model alkylating agent. Unique features of germ cells that suggest that they should be considered separately from somatic cells. It makes the assumption that the processes of DNA repair and damage are conserved across eukaryotic cells.

The tubulin binding AOP uses colchicine as the prototypical example, and states that the majority of data is generated in rodents. It is noted that some other chemicals that induce this AOP are benzimidazoyl pesticides.

Questions for consideration:

- What are Members views of the value of the AOP approach in general?
- How could COM utilise such an approach?
- Does this information impact on COM's current position on benzimidazoyls (COM/07/S3)?
- Would Members like to make any comments on the development of further AOP's in relation to genetic toxicology?

Secretariat/PHE Toxicology Unit

February 2016

ANNEX:

Yauk CL, Lambert IB, Meek ME, Douglas GR, Marchetti F. (2015) Development of the adverse outcome pathway "alkylation of DNA in male premeiotic germ cells leading to heritable mutations" using the OECD's users' handbook supplement. Environ Mol Mutagen. 56(9):724-50.

Marchetti F, Massarotti A, Yauk CL, Pacchierotti F, Russo A. (2015) The adverse outcome pathway (AOP) for chemical binding to tubulin in oocytes leading to aneuploid offspring. Environ Mol Mutagen. doi: 10.1002/em.21986. [Epub ahead of print]