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Development of an AOP-based IATA for genotoxicity

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Genotoxicity assessment of chemicals currently involves a tiered approach starting with an in vitro testing battery covering bacterial and/or mammalian cell gene mutations, and structural and numerical chromosome aberrations followed by in vivo testing in case of a positive result. However, this strategy has several limitations including the high number of misleading positive results triggering unnecessary animal testing, the limited mechanistic information provided, and the insufficient integration of new approach methodologies (NAMs).

One strategy to include NAMs in chemical risk assessment involves the development of 'integrated approaches to testing and assessment (IATAs)'. IATAs integrate existing information and newly generated data from NAMs or traditional toxicity tests to address a specific regulatory question. Genotoxicity is a particularly interesting area for developing IATAs as many innovative non-animal methods have become available over the last years. The selection of NAMs to be included in an IATA should be structured and science-driven, a process in which adverse outcome pathways (AOPs) could play an important role.

This project, performed within the framework of the Horizon Europe Partnership for Assessment of Risks from Chemicals (PARC) and involving many different partners, aims to deliver an AOP-based IATA for genotoxicity to support the transition to animal-free genotoxicity assessment. As a first step, inventories of AOPs and NAMs linked to genotoxicity have been compiled. Nineteen AOPs related to DNA damage were found in the AOP-wiki. These AOPs are in different stages of development and ten of them are already in the OECD work plan. Similarly to Huliganga et al. [1], an AOP network has been drafted based on the four most advanced AOPs. This network will be used as a starting point to design a more extended AOP network with "increase in gene mutations" and "increase in chromosomal aberrations' as adverse outcomes. In addition, in the AOP network, each NAM of the inventory was linked to the key event it can measure.

Based on the AOP network, a first version of the IATA will be drafted. Where needed, knowledge gaps within the network will be filled, including quantification of key event relationships. Finally, the newly developed IATA's applicability will be evaluated in case studies.

Keywords:
Genotoxicity, Adverse Outcome Pathway (AOP), Integrated Approaches to Testing and Assessment, Chemical risk assessment, New Approach Methodologies (NAMs).

Bibliography:
[1] E. Huliganga, F. Marchetti, J. M. O'Brien, V. Chauhan and C. L. Yauk, "A Case Study on Integrating a New Key Event Into an Existing Adverse Outcome Pathway on Oxidative DNA Damage: Challenges and Approaches in a Data-Rich Area.," Frontiers in toxicology, 28 April 2022.