NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) Adverse Outcome Pathways (AOPs)

Background Material:

- Ankley *et al*. Adverse outcome pathways: a conceptual framework to support ecotoxicology research and risk assessment. 2010. *Env Tox Chem* 29(3):730-741
- Jaworska *et al*. Baysian integrated testing strategy to assess skin sensitization potency: from theory to practice. 2013. *J Appl Tox* 33:1353-1364
- Development of Integrated Testing Strategies to Identify Potential Sensitizers (http://ntp.niehs.nih.gov/go/its)
- Adverse Outcome Pathways, Molecular Screening and Toxicogenomics (http://www.oecd.org/chemicalsafety/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm)

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An Adverse Outcome Pathway (AOP) is an analytical construct that describes a sequential chain of causally linked events at different levels of biological organization that lead to an adverse health or ecotoxicological effect. Utilization of the AOP conceptual model has been embraced by the Organisation for Economic Co-operation and Development (OECD) as well as some U.S. regulatory agencies. OECD serves as the repository for AOPs being developed by member countries, and OECD workgroups will be addressing the issue of AOP validation and utilization. However, there is currently no coordinated effort in the U.S. to develop, evaluate, or utilize AOPs in a regulatory framework.

The adverse outcome pathway for skin sensitization is well characterized and will be the first AOP to be assessed for regulatory utility in the U.S. The skin sensitization AOP includes penetration of the potential sensitizer into the skin and its binding to proteins in the skin, mobilization of immune cells in response to the sensitizer, proliferation of cells in the lymph nodes stimulated by immune cell activity, and skin inflammation upon subsequent exposure to the potential sensitizer. Non-animal alternative test methods exist that measure the potential of test substances to produce each of these effects.

ICCVAM is developing a plan for the evaluation of alternative test methods for skin sensitization and has requested information from the public on this topic and public comment on ICCVAM's proposed activities. NICEATM is collaborating with industry scientists to develop an integrated decision strategy that will allow consideration of all available information, including results from multiple test methods and a test substance's physical or chemical properties, to support hazard classification decisions for skin sensitizers.