Adverse Outcome Pathways (AOPs)

Background Material:

- Adverse Outcome Pathways: A conceptual framework to support ecotoxicology research and risk assessment. Ankley et al. *Env Tox Chem* 29 (3) 730-741 (2010)
- Website: Adverse Outcome Pathways, Molecular Screening and Toxicogenomics
- The AOP for Skin Sensitisation Initiated by Covalent Binding to Proteins. Part 1: Scientific Evidence. OECD (2012)
- The AOP for Skin Sensitisation Initiated by Covalent Binding to Proteins. Part 2: Use of the AOP to Develop Chemical Categories and Integrated Assessment and Testing Approaches. OECD (2012)
- Bayesian integrated testing strategy to assess skin sensitization potency: from theory to practice. Jaworska J, Dancik, Y, Kern P, Gerberick F, and Natsch A. J Applied Tox (Epub 2013 May 14)
- OECD list of projects on the AOP development program workplan
- ICCVAM's Proposed Activities on Alternative Skin Sensitization Test Methods and Testing Strategies

An Adverse Outcome Pathway (AOP) is a conceptual model that links exposure to a substance to a toxic effect by identifying the sequence of biochemical events required to produce the toxic effect. Utilization of the AOP conceptual model has been embraced by the Organisation for Economic Co-operation and Development (OECD) as well as some US Regulatory Agencies. However, many AOPs are being developed in an ad-hoc manner (based on available knowledge rather than need) and little work has been done to assess the utility of AOPs in a regulatory framework. 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. There is currently no coordinated effort in the US 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. The skin sensitization AOP includes penetration of the potential sensitizer into the skin, 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 has requested public comment as it develops a plan for moving forward with alternative skin sensitization test methods and testing strategies. 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.