Health and Environmental
Sciences Institute

740 15th Street, NW
Sixth Floor
Washington, DC 20005
USA

1.202.659.3306 office
1.202.659.3859 fax
www.hesiglobal.org

Validation of New Approaches in Genetic Toxicology

The HESI Genetic Toxicology Technical Committee & the Genetic Toxicology Association

Newark, Delaware

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Background & Objectives:

Novel *in vitro* and *in vivo* assays have been developed to improve the reliability of tools employed for identification of genotoxic hazard. Several of the new assays can provide insight into mode-of-action (MoA). As emerging technologies generally used for evaluating human hazard and/or risk, these novel assays require rigorous evaluation and validation before use in a regulatory setting. Validating novel toxicology assays is a continuing labor-intensive challenge. More specifically, many questions arise around choosing reference compounds, and comparing results against the current standard battery used for genotoxicity testing.

During this workshop we will discuss several new *in vitro* and *in vivo* genotoxicity assays that are currently undergoing formal OECD validation. These assays include:

- **ToxTracker assay:** a stem cell-based reporter system that detects the direct induction of DNA damage, as well as indirect genotoxicity due to oxidative stress or protein damage. The assay can discriminate between a clastogenic and aneugenic MoA
- **3D reconstituted skin micronucleus (3D-RSMN) and comet assays (3D-RSC):** these assays assess the induction of chromosomal damage in advanced *in vitro* skin models; they permit a much more relevant exposure, especially for cosmetics and cosmetic ingredients.
- **Ames-MPF assay:** a miniaturized version of the Salmonella reverse mutation assay (i.e., Ames test). It significantly reduces the amount of test compound required for analysis; it also increases throughput.
- **Pig-A assay:** a flow-cytometry based assay that screens a large number of cells for mutations in a gene encoding a GPI anchor protein (i.e., Pig-a).

Each of the listed assays are currently being validated by an international consortium of laboratories. The OECD has published a guidance document (No. 34) on validation and international acceptance of novel methods; however, the exact validation protocol employed varies across assay. Workshop presenters will share their experiences regarding the OECD validation process; the workshop will conclude with an interactive discussion regarding validation goals, procedures and options.

Each presentation will address questions such as:

1. How do you validate a novel assay?
2. What reference data do you utilize when validating a novel assay?
3. When do we consider a novel method sufficiently validated for regulatory application?

Draft Agenda

1:00 – 1:30 pm	Welcome and Overview of Workshop Jan van Benthem, RIVM
1:30 – 2:30 pm	Development and Validation of the ToxTracker Assay Giel Hendriks, Toxys David Kirkland, Kirkland Consulting Marise Roy, Charles River Laboratories
2:30 – 3:00 pm	Development and Validation of the Ames MPF Assay Dimitri Spiliotopoulos, Xenometrix
3:00 – 3:30 pm	Development and Validation of the 3D Skin Micronucleus and Comet Assays Stefan Pfuhler, P&G
3:30 – 4:00 pm	Development and Validation of the Pig-a Assay Steve Dertinger, Litron Laboratories
4:00 – 4:30 pm	Coffee Break
4:30 – 6:00 pm	Breakout Group Discussion Section