HESI Genetic Toxicology Technical Committee

Quantitative Interpretation of Genetic Toxicity Dose-response Data for Risk Assessment and Regulatory Decision-making – State of the Science, Applications, and Persistent Challenges

Monday 15 May 2023
9:00 – 15:00

Objectives / Goals

Genetic toxicology is moving from dichotomous hazard identification to quantitative dose-response analyses for potency ranking, risk assessment, and regulatory decision-making. Advancements in quantitative methods is driven by several factors including the availability of tools that facilitate dose-response analyses (e.g., Benchmark Dose software), as well as advances in the application of risk assessment concepts to interpretation of genetic toxicity test results. The workshop will provide an overview of recent developments in quantitative interpretation of genetic toxicity dose-response data; first by outlining basic concepts and best practices for PoD (point of departure) determination, then by outlining approaches to extrapolate below the PoD for risk assessment and regulatory decision-making. The latter half of the workshop will provide examples of applications related to impurities in pharmaceutical products. More specifically, examples that demonstrate how an approach based on quantitative dose-response analyses can be used to determine human exposure limits to potent genotoxicants.

The morning session will provide recommendations regarding suitable benchmark response (BMR)/critical effect size (CES) values for genetic toxicity endpoints; additionally, for the uncertainty factors (UFs) required to extrapolate below the BMD. The latter are required for determination of human exposure limits, sometimes referred to as HBGVs (Health-based Guidance Values), below which the likelihood of adverse health effect can be deemed negligible. Presentations will outline recommendations for UFs to account for interspecies variability, variability across individuals (i.e., intraspecies), and the effect of treatment duration. Presentations will also address the critical need to develop and deploy methods for quantitative interpretation of *in vitro* dose-response data generated using new approach methodologies (NAMs). Ongoing efforts have demonstrated that analyses of NAMs dose-response data, coupled with in vitro to in vivo extrapolation, can be used for potency ranking, chemical screening and prioritization, and risk assessment.

The afternoon session will focus on the application of quantitative methods to genotoxic impurities that cause deleterious changes in genetic material via a variety of mechanisms. These genotoxic impurities are emerging as a common problem in drug development, as well as in certain marketed pharmaceuticals. Although the proactive reduction of these impurities through advanced chemistry and suitable safety assessment is excellent, there are emerging cases where a safety assessment based on quantitative dose-response analyses is needed for regulatory decision making. Speakers will provide an overview of the problem of genotoxic impurities, with a focus on the results of quantitative dose-response assessments based on analyses of genetic toxicity and cancer bioassay data. The application of duplex sequencing, in combination with standard genotoxicity testing strategies, for determination of PoDs and mechanism, will also be discussed. The workshop will close with a critical discussion of regulatory considerations related to quantitative interpretation of genetic toxicity dose-response data.

Workshop Agenda

8:00 – 9:00	**Registration & Breakfast (provided)**
Quantitative Dose-response Analyses: State of the Science	
9:00 – 9:10	**Welcome & Overview of Workshop Goals** *Co-chairs:* Andreas Zeller (Roche, SWITZERLAND), George Johnson (Swansea University, UK), Paul White (Health Canada, CANADA)
9:10 – 9:40	**Quantitative Interpretation of In Vivo Mutagenicity Dose Response Data for Risk Assessment and Regulatory Decision-Making** Paul White (Health Canada, CANADA) & Stefan Pfuhler (Procter and Gamble, USA)
9:40 – 10:10	**The interpretation of in vitro dose-response data for risk assessment and regulatory decision-making** Marc Beal (Health Canada, CANADA)
10:10 – 10:40	**Guided discussion**
10:40 – 11:10	**Coffee Break (provided)**
Application of Quantitative Data Interpretation to Pharmaceutical Impurities	
11:10 – 11:40	**Nitrosamine impurity issues and potential resolutions** George Johnson (Swansea University, UK)
11:40 – 12:10	**In vivo genetic toxicity assessments for nitrosamines** Maik Schuler (Pfizer, USA) or Shaofei Zhang (Pfizer, USA)
12:10 – 12:40	**Dose response analysis of NDMA-induced genotoxicity in MutaMouse and implications for risk assessment** Anthony Lynch (GlaxoSmithKline, UK)
12:40 – 13:40	**Lunch (provided)**
13:40 – 14:10	**Regulatory considerations related to mutagenic impurities in pharmaceuticals** Roland Frotschl (BfArM, GERMANY)
14:10 – 14:50	**Guided Discussion**
14:50 – 15:00	**Concluding remarks**