Perspectives on the Application of Mechanistic Information in Chemical Hazard and Dose-Response Assessments

The National Center for Environmental Assessment, under the Office of Research and Development's Human Health Risk Assessment Multi-Year Plan, initiated a multidisciplinary project to critically review methods for applying mechanistic information in human health risk assessment and to explore strategies for progress in this area. Motivations included the significant ability of mechanistic data to inform chemical hazard and dose-response assessments. The project examined approaches for interpreting observed effects in laboratory animals and their human relevance based on hypothesized modes of action. In addition, a critical aspect of the project was to explore issues pertinent to toxicity-pathway based risk assessment. This is consistent with an emphasis in EPA's strategy for toxicity testing (EPA, 2009) on the identification of toxicity pathways relevant to human health and disease, the exploration of chemical alteration of these multiple pathways, and the use of such data to predict human risk. The focus was on the use of available toxicodynamic and not toxicokinetic information, reflecting interest in the mechanistic actions of the active agent(s).

The project results were reported in several peer-reviewed publications. An initial review identified considerable potential for progress in the application of mechanistic data in human health risk assessment (Guyton et al., 2008). The opportunities identified included: 1) improvements in the evaluation of scientific hypotheses regarding modes of action, to address the necessity and sufficiency of a mode of action hypothesized as the sole causative factor; 2) an expanded consideration of background diseases, exposures and processes, to inform variability in susceptibility; 3) consideration that a chemical may disrupt multiple pathways, mechanisms, and modes of action (including applications of systems-level information); 4) extrapolation across outcomes and exposures using mechanistic information; and 5) quantitative considerations.

These issues were explored in subsequent case studies, workshops and publications. A Bayesian analysis determined that the hypothesis of low-dose linearity could not be statistically precluded in a case study of 2-amino-3,8-dimethylimidazo[4,5-f] quinoxaline (Chen and Guyton, 2008). A case study on the hypothesized peroxisome proliferator-activated receptor (PPAR)-α activation mode of action (Guyton et al., 2009) highlighted recommended improvements in how to discern associated from causative events in a proposed mode of action, and in how to conceptualize and address multiple mode of action hypotheses in human health risk assessments. A workshop entitled "State-of-the-Science Workshop: Issues and Approaches in Low Dose–Response Extrapolation for Environmental Health Risk Assessment" was held April 23–24, 2007 in Baltimore, Maryland. Participants discussed the exploration of population-level considerations (susceptibility), the harmonization of cancer and non-cancer approaches, and the development of modeling approaches integrating animal and human data as priorities for advancement of low-dose extrapolation methods for risk assessment (White et al., 2008). A separate workshop entitled "Moving Upstream: A Workshop on Evaluating Adverse Upstream Endpoints for Improved Decision Making and Risk Assessment" was convened May 16 – 17, 2007 in Berkeley, California. This workshop and the resulting publication (Woodruff et al., 2008) explored possibilities for advancing the understanding and estimation of human population risk using data on pathway perturbations known to be associated with the development of adverse outcomes, particularly, thyroid hormone disruption, antiandrogen effects and immune system

disruption. Another workshop, part of the October 2007 annual meeting of the Environmental Mutagen Society in Atlanta, Georgia was entitled "Predicting Chemical Carcinogenicity: Moving beyond Batteries". The workshop and resulting publication reviewed advancements in the understanding of carcinogenic mechanisms and explored potential improvements in the prediction and assessment of chemical carcinogenicity by considering multiple mechanisms and applying toxicogenomic approaches (Guyton et al., 2009).

This work illustrates opportunities for improving human health risk assessment through enhancing current practice, continuing risk assessment research to advance progress, and implementing novel approaches to address current and emerging scientific ideas and data. Specifically, this includes addressing existing and emerging risk assessment issues identified in this project and in recent reports from the National Research Council (2009; 2008; 2007), particularly: (1) the need to substantially increase the number of environmental chemicals for which there are human health risk assessments; (2) a vision in which population risk is based on upstream perturbations of biological systems; (3) the need to expand the scope of cumulative risk assessment beyond chemicals with the same mode of action to include chemicals affecting similar endpoints; (4) a need to address community-level stressors, socio-economic, life-style, nutritional, shift work, and other factors in a cumulative manner in risk assessments; and (5) a call for going beyond "safety" assessment to quantify population risk as a function of dose for non-cancer effects. This project identifies specific applications for using mechanistic data that will contribute towards these goals. For instance, mechanistic data can aid in identifying sources of human vulnerability, as well as informing the likelihood of other outcomes influenced by the same mechanisms, pathways, and biological processes. In particular, the use of established human "upstream" biomarkers to couple the risk or susceptibility to diseases and disorders with chemically-induced perturbations may be especially fruitful in addressing the issues of cumulative assessment across exposures as well as overall population risk. In addition, as knowledge of the molecular pathways involved in human diseases or disorders becomes more quantitative and predictive, additional molecular biomarkers linked to risk or susceptibility, and high-throughput assays for these biomarkers, are likely to be developed. Such information will also allow the mechanistic-based drivers of both individual and population responses at low doses to be better elucidated. In all, these recommendations will aid the Agency in improving the scientific quality of its human health risk assessments of environmental chemicals while enhancing their relevance to public health issues.

Related NCEA projects include a prior effort (EPA, 2008) evaluating the utility of biologically based dose-response modeling for estimating risks of formaldehyde-induced cancer, a subsequent analysis concluding that biologically based dose-response models are not likely to reduce quantitative uncertainty (Crump et al., 2010), and a case study of dibutyl phthalate exploring approaches for applying toxicogenomic data in risk assessment (EPA, 2009).

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