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To: Docket Committee Posted: 06/17/2017
Docket ID: EPA-HQ-OPPT-2016-0728

Re: US EPA Document# EPA-740-R1-7003 (June 2017)
Scope of the Risk Evaluation for 1,4-Dioxane
Toxic Substance Control Act

Dear Docket Committee:

I am pleased to submit these Comments on the U.S. Environmental Protection Agency's documentation on the "Scopes of the Risk Evaluations to be Conducted for the First Ten Chemical Substances under the Toxic Substances Control Act." In light of the tight timelines, I agree that it is reasonable to present the proposed scopes at this time, and additionally take comments on a Problem Formulation document that will refine the current scope.

To that end, I would like to draw your attention to the results of a multi-stakeholder project relevant to improving risk assessment methods and practice, that can be a useful resource for your work. The Alliance for Risk Assessment (*ARA*) project "*Beyond 'Science & Decisions' from Problem Formulation to Dose-Response Assessment*" has extended the work begun by the 2009 NRC report "Science and Decisions: Advancing Risk Assessment" by broadening and deepening scientific discussion on two key recommendations: improving problem formulation and selecting appropriate dose-response assessment methodology. The *ARA* effort represents the value of a broad-based coalition among government and nonprofit groups. This specific *ARA* project has been supported by more than 60 organizations, including government agencies, industry groups, scientific societies and specialty groups, non-profit organizations/consortia, and consulting groups.

The "Beyond Science and Decisions" project began with a solicitation of ideas at an open scientific workshop in March 2010, and continued with the appointment of a Science Panel and convening of a series of nine open scientific workshops, led by the Science Panel. The Science Panel provided input on the utility of the case study methods to address specific problem formulations, and identified areas for additional development of the case study and/or method[1].

[1]Inclusion of a method or case study in the framework as an illustration of a useful technique does not imply panel acceptance of the chemical-specific outcome.

A key goal of the workshop series was to develop a risk methods compendium as a resource for regulators and scientists on key considerations for applying selected dose-response techniques for various problem formulations, with suggested techniques and resources. This tool has been published in the peer-reviewed literature[2] and is available through the National Library of Medicine's Enviro-Health Links at https://sis.nlm.nih.gov/enviro/toxweblinks.html (see Associations). The framework is also available on the University of Cincinnati website at http://med.uc.edu/eh/centers/rsc/risk-resources/dose-response-framework/[3]. The work is based on the fundamental premise that the appropriate methodology for dose-response assessment is necessarily based on objectives specific to that application, including varying levels of analysis. Thus, the tool catalogues, through the use of case studies, a number of practical, problem-driven "fit for purpose" approaches illustrating various aspects of risk assessment methods.

The case studies include many different modes of action and numerous dose response methods (see Table 2), as well as addressing issues raised by the "Science and Decisions" report, such as consideration of background/endogenous exposure, sensitive populations, and "risk above the RfD" (i.e., risk for noncancer endpoints).

I would be pleased to provide additional information on the workshop series or individual case studies. Please do not hesitate to contact me if you have any questions.

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[2]Meek, M.E., M. Bolger, J.S. Bus, J. Christopher, R.B. Conolly, R.J. Lewis, G. Paoli, R. Schoeny, L.T. Haber, A.B. Rosenstein, M.L. Dourson. 2013. A Framework for Fit-for-Purpose Dose Response Assessment. Regul. Toxicol. Pharmacol. 66(2):234-40. Doi: 10.1016/j.yrtph.2013.03.012 Open Access/ http://www.sciencedirect.com/science/article/pii/S0273230013000500

[3] We are currently in the process of migrating the framework content from the standalone chemicalriskassessment.org website to the University of Cincinnati website, so the full documentation for the case studies is currently available only by request.

Table 1 – List of Sponsoring Organizations

- Academy of Toxicological Sciences
- Agency for Toxic Substances and Disease Registry
- American Chemistry Council
- American Chemistry Council Center for Advancing Risk Assessment Science and Policy
- Alliance for Site Closure
- American Cleaning Institute
- American Petroleum Institute
- American Water Works Association
- Barnes & Thornburg, LLP
- Center for Food Safety and Applied Nutrition of the US Food and Drug Administration
- Council of Producers & Distributors of Agrotechnology
- Chemical Producers and Distributors Association
- Chemical Specialty Products Association
- Consortium for Environmental Risk Management LLC
- CropLife America
- Dose Response Specialty Group of Society for Risk Analysis
- Electric Power Research Institute
- ENVIRON
- Ethylene Oxide Panel of the American Chemistry Council
- The Hamner Institute for Health Sciences
- Georgia Department of Natural Resources
- Georgia Pacific
- Gradient
- Grocery Manufacturers Assocation
- Hawai'i State Department of Health; Hazard Evaluation and Emergency Response
- Hull & Associates, Inc.
- Human Toxicology Project Consortium
- ICL Industrial Products
- Illinois Environmental Protection Agency
- Indiana Department of Environmental Management
- Industrial Economics, Incorporated
- International Copper Association
- International Society of Regulatory Toxicology and Pharmacology
- The LifeLine Group
- Minnesota Pollution Control Agency
- The Naphthalene Council
- National Center for Toxicological Research
- New Zealand Ministry of Health
- Nickel Producers Environmental Research Association
- Noblis
- NSF International
- Ohio Environmental Protection Agency
- Ontario Ministry of the Environment
- Personal Care Products Council
- Pastor, Behling & Wheeler, LLC
- Regulatory and Safety Evaluation Specialty Section of Society of Toxicology
- Risk Assessment Specialty Section of Society of Toxicology
- SC Johnson & Son
- Society of Chemical Manufacturers Association
- Society for Risk Analysis
- Society of Toxicology
- Styrene Information and Research Council
- Summit Toxicology
- Ted Simon Toxicology
- Texas Association of Business
- Texas Chemical Council
- Texas Commission on Environmental Quality
- Texas Industry Project
- Toxicology Excellence for Risk Assessment
- University of Cincinnati

Emeritus

- The Mickey Leland National Urban Air Toxics Research Center
- The Sapphire Group

Table 2 – List of Case Studies

(Some case studies are listed under more than one general problem formulation. Where the topic or method is not obvious from the title, or there are additional aspects of the method relevant to different problem formulations, additional key words are listed in italics)

Qualitative Screening

- Estimate Risk Above the RfD Using Uncertainty Factor Distributions (noncancer risk): Spalt E., Kroner O. Advisor: Dourson M.
- Sustainable Futures Screening: Becker E., Ranslow P
- Implications of Linear Low-Dose Extrapolation from Benchmark Dose for Noncancer Risk Assessment (noncancer risk): Kroner O., Haber L. Advisor: Dourson M.
- Development of Screening Tools for the Interpretation of Chemical Biomonitoring Data: Richard A. Becker, Sean M. Hays, Steven Robison, Lesa L. Aylward, Christopher R. Kirman *(also addresses background exposure)*

Quantitative Screening

- Deriving Health-Protective Values for Evaluation of Acute Inhalation Exposures for Chemicals with Limited Toxicity Data Using a Tiered Screening Approach (including threshold of concern approach): Grant R.L., Phillips T., Ethridge S.
- Implications of Linear Low-Dose Extrapolation from Benchmark Dose for Noncancer Risk Assessment (noncancer risk): Kroner O., Haber L. Advisor: Dourson M.
- Weight of Evidence Approach for Chemicals with Limited Toxicity Data (silanes and siloxanes) Tiffany Bredfeldt, Jong-Song Lee, Ross Jones, Roberta Grant
- Screening Tools for the Interpretation of Chemical Biomonitoring Data**:** Richard A. Becker, Sean M. Hays, Steven Robison, Lesa L. Aylward, Christopher R. Kirman *(also addresses background exposure)*

In-Depth Assessment

- Criteria Requirements for Data-Driven Carcinogenicity Mode of Action (MOA) Determinations as Exemplified by Chloroform: Chris Borgert
- Use of human data in cancer risk assessment of chemicals as illustrated by the case of 1,3-Butadiene: Albertini R., Sielken Jr. R.L.

- The Quantitative Human Health Risk Assessment for 1,3-Butadiene Based Upon Ovarian Effects in Rodents: Kirman C.R., Grant R.L *(also addresses endogenous processes contributing to MOA)*
- Value of Information: Eric Ruder, Henry Roman
- Application of National Research Council "Silverbook" Methodology for Dose Response Assessment of 2,3,7,8-Tetrachlorodibenzo(p)dioxin. Simon T., Stephens M., Yang Y., Manning R.O., Budinsky R.A. and Rowlands J.C.
- Implications of Linear Low-Dose Extrapolation from Benchmark Dose for Noncancer Risk Assessment (noncancer risk): Kroner O., Haber L. Advisor: Dourson M.
- Evaluating Human Dose-Response of Morbidity and Mortality from Hepatic Disease from Ethanol Exposure: Are the Predicted Risks from Low-Dose Linear Extrapolation to Environmentally Relevant Concentrations Biologically Plausible?: Becker R., Hays S.
- Assessment of Low-Dose Dose-Response Relationships (Non-linear or Linear) for Genotoxicity, Focused on Induction of Mutations & Clastogenic Effects: Moore M., Pottenger L., Zeiger E., and Zhou T.
- The Human Relevant Potency Threshold: Reducing Uncertainty by Human Calibration of Cumulative Risk Assessments: Chris Borgert *(also addresses background exposure assessment)*
- BBDR model for respiratory tract carcinogenicity of inhaled formaldehyde: Allen B., Clewell H., Conolly R., Haney J., Kester J. *(also addresses endogenous processes contributing to MOA)*
- Background/Endogenous Damage, Processes and Adducts: Considerations for Dose-Response & Risk Assessment: Lynn H. Pottenger, Jim S. Bus, with support from Jim A. Swenberg *(also ddresses sensitive populations)*
- Kinetic Variability Based on PON1 Polymorphism - Quantitative Assessment of Sensitivity and Variability in Humans: Modeling the Effects of Low Dose Exposure to Dietary Residues of Chlorpyrifos: Daland Juberg, Paul Price *(also addresses endogenous processes contributing to MOA)*
- Review and application of data fusion methodologies for toxicological dataset analysis to resolve data quality issues in predictive toxicology and contaminated sites risk assessment. Mohapatra A.K., Sadiq R., Zargar A., Islam S., Dyck R.
- Modeling Multi-pronged Mode of Action (MOA) (acrylamide): Hertzberg R. Advisor: Dourson M.

- Consideration of Human Kinetic Variability (trichloroethylene): Lipscomb J.C., Teuschler L.K., Swartout J., Popken D., Cox T., Kedderis G.L.
- Lead – Dose-response relationship for effect on Children's IQ: Clark Carrington *(addresses sensitive populations)*
- Use of Biomonitoring Equivalents and Biomonitoring Data from NHANES - Risk Assessment of Exposure to Trihalomethane Drinking Water Disinfection By-Products. Aylward L.L., Hays S.M., Kirman C.R., Becker RA *(also addresses background exposure)*
- Biologically-Based Uncertainty Factor Distributions (Hattis approach): Comparison of Hattis strawman approach and BMDs/UFs for noncancer endpoints (carbonyl sulfide and tetrachlorobenzene): Greco S.L., Hattis D.H., Lynch M.K.
- Apply AEGL Methodology to Develop Acute Exposure Guideline Levels for Ethylbenzene: Grant R., Erraguntla N., Hinz J., Camacho I.A.
- Risk-Risk Comparison: Comparative Risk for Use of Perchloroethylene (Perc) or N-propyl-bromide (NPB) in Dry Cleaning: Clewell H., Finkel A.
- Framework for Evaluating Alternative Temporal Patterns of Exposure for Risk Characterization: Maier A., Haber L., Haney J., Kaden D.A., Carrier R., Craft E., and Hertzberg R. Advisor: Dourson, M.
- Biologically-Informed Empirical Dose Response Modeling: Using Linked Cause-Effect Functions to Extend the Dose-Response Curve to Lower Doses (Titanium dioxide - TiO2): Allen B., Maier A., Willis A., Haber L.T.
- Use of Categorical Regression – Risk Above the RfD (noncancer risk) : Danzeisen R., Krewski D., Chambers A., Baker S., Hertzberg R., and Haber L.
- Use of biomarkers in the benchmark dose method: Gentry R., Van Landingham C., Hays S., Aylward L.
- Methods for Deriving Inhalation Effect Levels for Comparison to Health-Protective Values: Roberta Grant, Allison Jenkins; Joseph (Kip) Haney
- Endogenous Chemical Risk Assessment: Formaldehyde as a Case Example: Robinan Gentry, Tom Starr, Jim Swenberg
- Hypothesis-Based Weight of Evidence (Naphthalene as an Example): Lorenz Rhomberg, Lisa Bailey

- Interpretation of 24-hour sampling data. Case Study A. Texas Commission on Environmental Quality Approach: Roberta L. Grant; Allison Jenkins; Joseph (Kip) Haney
- Interpretation of 24-hour sampling data. Case Study B. Ontario Ministry of the Environment (MOE) Approach: Denis Jugloff; Julie Schroeder
- A systematic assessment methodology for flame retardants (FRs) based on hazard and exposure- the FR framework: Smadar Admon, Marc Leifer, Joel Tenney, Tami Weiss-Cohen *(alternatives assessment)*