



May 30, 2013

Dr. Kenneth Olden
Director
National Center for Environmental Assessment
USEPA Headquarters
Ariel Rios Building
1200 Pennsylvania Avenue, N. W.
Mail Code: 8601P
Washington, DC 20460

Submitted electronically via e-mail to: irisworkshop@epa.gov

Re: Systematic Review Workshop, Request for Input

Dear Dr. Olden:

The American Chemistry Council (ACC) and its Center for Advancing Risk Assessment and Science Policy (ARASP) support EPA's efforts to organize a workshop and to solicit input regarding approaches for the development and implementation of a robust systematic review process. We support EPA's efforts to improve the IRIS program to ensure that up-to-date scientific knowledge that meets the highest of standards of scientific inquiry is evaluated in accordance with acceptable scientific approaches. We have consistently called on the Agency to make permanent changes to IRIS that improve the design and conduct of IRIS assessments. These improvements include enhancing problem formulation and adoption of consistent and transparent study evaluation methods to determine the quality and reliability of critical studies. We have also encouraged EPA to utilize an improved framework for integrating study results based on a weight of evidence approach which incorporates modern knowledge of mode action to establish cause and effect. Furthermore, we continue to recommend that EPA improve its peer review and accountability practices for addressing both public comments and peer review recommendations.

Below we address EPA's May 1, 2013 request for input on the proposed workshop (<http://www.epa.gov/IRIS/irisworkshops/systematicreview/>) which seeks "to receive input regarding approaches for different steps within a systematic review, such as evaluating individual studies, approaches for synthesizing evidence within a particular discipline, and integrating evidence across different disciplines to draw scientific conclusions and causality determinations." In particular, EPA is seeking input on: (a) specific topics for discussion that are relevant to the goal of the workshop(s), and (b) potential speakers or participants. We recommend that EPA include four main sessions in the workshop, as detailed below.

In addition to the workshop discussion topics noted below, we also offer suggestions for ensuring that workshop speakers have the appropriate expertise to offer meaningful input to the workshop. Specifically, potential speakers should be drawn from those that have published in



the topic areas noted below. In addition to the citations provided in footnotes and the experts cited therein, attached is a more extensive reference list (Extended Reference List) which includes other important and relevant publications and authors. EPA should reach out to the experts cited to invite them to provide input at the planned workshop.

Session 1. Problem Formulation and Hypothesis Development

It is no longer scientifically tenable to simply ask “does X pose a carcinogenic hazard?” Such an approach overemphasizes high dose toxicity studies and perpetuates an overreliance on animal tumorigenicity results that may have little to no relevance to humans exposed at environmentally relevant levels. Instead, the very first step of a systematic review employed by the EPA should include problem formulation that, in part, defines the causal question.¹ IRIS should begin each analysis with a set of proposed hypotheses that incorporate mode of action (MOA), the adverse effect(s) of concern, and the exposure level(s) of concern. The available data can then be arrayed to evaluate the extent to which existing data and knowledge does, or does not, support each hypothesis. A presentation and assessment of the underlying uncertainties should be incorporated into each key step. In this way the results of an IRIS analysis can be summarized and presented in a manner which illustrates to risk assessors and risk managers the extent to which each hypothesis is consistent with all of the data – human epidemiology, animal toxicity studies and modern understanding and data on mechanisms of toxicity. Thus the first session of the IRIS workshop should focus on the following aspects:

1. Problem formulation
2. Hypothesis development
3. Recognition of inherent uncertainties that may exist

Session 2. Evaluation and Judging the Relevance, Reliability and Quality of the Evidence

Once the problem formulation step is complete, the next critical step is to determine the criteria for study inclusion and exclusion. The NRC Report (2011)² recommended that EPA “establish protocols for review of major types of studies, such as epidemiologic and bioassay” and “all critical studies need to be thoroughly evaluated with standardized approaches that are clearly formulated and based on the type of research, for example, observational epidemiologic or animal bioassays.” EPA has yet to fully implement these NAS recommendations. Therefore, ACC requests that the workshop include a specific session, detailed below, which focuses on methods for evaluating studies of various types to determine quality and reliability:

¹ For a more thorough discussion of problem formulation and systematic review see the 2012 Keystone Center report “Improving the Use of Science in Regulatory Decision-Making: Dealing with Conflict of Interest and Bias in Scientific Advisory Panels, and Improving Systematic Scientific Reviews” available at:

<https://www.keystone.org/images/keystone-center/spp-documents/Health/Research%20Integrity%20Roundtable%20Report.pdf>.

² National Research Council. 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde. Available at https://download.nap.edu/catalog.php?record_id=13142

1. Evaluating and judging the quality of animal evidence³
 - a. Specific attention should be given to:
 - i. Guidance for validating test methods (including ICCVAM, JRC, and OECD approaches)
 - ii. Understanding Good Laboratory Practices
 - iii. Klimisch Method⁴
 - iv. ECETOC refinements to Klimisch⁵
 - v. The ToxRTool⁶
2. Evaluating and judging the quality of mechanistic information
3. Evaluating and judging the quality of human evidence⁷

Session 3. Integrating Evidence to Draw Scientific Conclusions and Causality Determinations

One of the most critical activities in developing an IRIS assessment is integrating evidence across different disciplines (human, animal, and mechanistic/MOA) to draw scientific conclusions and causality determinations. The current IRIS weight of evidence (WOE) approach, however, relies more on an evaluative framework highly based on observational data rather than on MOA data. Perpetuation of such an approach undervalues the vast extent of mechanistic research conducted over the last 30 years focused on delineating MOAs, understanding species similarities and differences and the dose-dependent transitions and underlying the pathogenesis of toxicities. MOA, therefore, should be considered as a central organizing principle in WOE evaluation and considered as part of the integration of evidence streams. In this manner, data from laboratory experiments, epidemiological investigations, and cutting-edge mechanistic research from all relevant studies and from all investigators, regardless of affiliation or funding source, can be comprehensively reviewed, given appropriate weight, and integrated in a manner that provides a robust, biologically plausible understanding of MOAs and the potential hazards and risks that environmentally relevant exposures could pose. The extent to which the data do or do not support specific hypothesized MOAs can then be compared in an objective and transparent manner. Therefore, ACC requests that the EPA IRIS workshop include presentations and discussions of frameworks that have been developed which focus on use of MOA in hazard and risk assessment. Specific presentations and discussions should include:

1. Understanding the IPCS Mode of Action Human Relevance Framework⁸

³ See <http://arasp.americanchemistry.com/Data-Quality-Evaluation>

⁴ Klimisch, HJ; Andrae, E and Tillmann, U. 1997. A systematic approach for evaluating the quality of experimental and ecotoxicological data. Regul.Toxicol. Pharmacol. 25:1-5

⁵ See ECETOC, JACC report #55 on Linear Polydimethylsiloxanes which incorporates the modified and expanded the justification phrases for each Klimisch reliability category. Available at: <http://www.ecetoc.org/jacc-reports>.

⁶ See http://ihcp.jrc.ec.europa.eu/our_labs/eurl-ecvam/archive-publications/toxrtool

⁷ See Higgins, JPT; Green, S; eds 2011. Cochrane Handbook for Systematic Reviews of Interventions (Version 5.1.0). The Cochrane Collaboration. Accessed on February 03, 2012 at <http://www.cochrane-handbook.org/>.

⁸ See Boobis, AR; Cohen, SM; Dellarco, V; McGregor, D; Meek, ME; Vickers, C; Willcocks, D; Farland, W. 2006. IPCS framework for analyzing the relevance of a cancer mode of action for humans. Crit. Rev. Toxicol. 36(10):781-792; Boobis, AR; Doe, JE; Heinrich-Hirsch, B; Meek, ME; Munn, S; Ruchirawat, M; Schlatter, J; Seed, J; Vickers,

2. Understanding Hypothesis Based Weight of Evidence⁹
3. Understanding and Applying the Bradford Hill Considerations¹⁰

Session 4. Enhancing Public Comments and Independent Peer Review

The establishment of the Chemical Assessment Advisory Committee (CAAC) is a positive development for the IRIS program. However, procedures should be implemented to make the best use of the CAAC and to foster more robust scientific exchange by the reviewers, including adequate consideration of public comments and analyses submitted by outside experts. The recommendation by the EPA's SAB and Board of Scientific Counselors (BOSC)¹¹ notes the NAS example that uses an independent review monitor to provide critical guidance on addressing comments. Similar to the role of a journal editor, the NAS review monitor helps to ensure that comments from reviewers have been appropriately and sufficiently addressed. Currently, the IRIS process lacks such a step and EPA staff, who are the authors of the draft assessments, have discretion and oversight in determining which peer review and stakeholder comments are incorporated and which are not when revising an IRIS assessment. Specific presentations and discussions during this session of the workshop should include:

1. Development of charge questions for a systematic review.
2. Processes to improve meaningful exchange by public commenters with peer reviewers.
3. Practices to ensure that systematic reviews adequately incorporate peer reviewers' recommendations and public comments.

+++++

C. (2008). IPCS framework for analyzing the relevance of a noncancer mode of action for humans. *Crit. Rev. Toxicol.* 38(2):87-96.

⁹ See Pemberton, M; Bailey, LA; Rhomberg, LR. 2013. Hypothesis-based weight-of-evidence evaluation of methyl methacrylate olfactory effects in humans and derivation of an occupational exposure level. *Regul. Toxicol. Pharmacol.* Apr 11. doi:pii: S0273-2300(13)00053-6. 10.1016/j.yrtph.20; Rhomberg, LR; Goodman, JE; Prueitt, RL. 2013. The Weight of Evidence Does Not Support the Listing of Styrene as "Reasonably Anticipated to be a Human Carcinogen" in NTP's Twelfth Report on Carcinogens. *Hum. Ecol. Risk Assess.* 19(1):4-27; Bailey, LA; Prueitt, RL; Rhomberg, LR. 2012. Hypothesis-Based Weight-of-Evidence evaluation of methanol as a human carcinogen. *Regul. Toxicol. Pharmacol.* 62(2):278-91; Borgert, CJ; Mihaich, EM; Ortego, LS; Bentley, KS; Holmes, CM; Levine, SL; Becker, RA. 2011. Hypothesis-driven weight of evidence framework for evaluating data within the US EPA's Endocrine Disruptor Screening Program. *Regul. Toxicol. Pharmacol.* 61(2):185-191.

¹⁰ See Weed, DL. 2005. Weight of evidence: A review of concepts and methods. *Risk Anal.* 25:1545-1557; and Hill, AB. 1971. *Statistical Evidence and Inference. A Short Textbook of Medical Statistics*, 285-296.

¹¹ Implementation of ORD Strategic Research Plans: A Joint Report of the Science Advisory Board and ORD Board of Scientific Counselors. 2012. Available at:

[http://yosemite.epa.gov/sab/sabproduct.nsf/3822EB089FCCB18D85257A8700800679/\\$File/EPA-SAB-12-012-unsigned.pdf](http://yosemite.epa.gov/sab/sabproduct.nsf/3822EB089FCCB18D85257A8700800679/$File/EPA-SAB-12-012-unsigned.pdf) at page 24.

We appreciate the consideration EPA will give to these suggestions. Please feel free to contact either one of us by email (Rick_Becker@americanchemistry.com or Kimberly_Wise@americanchemistry.com) or phone (202-249-7000) with any questions.

Sincerely,



Richard Becker, Ph.D., DABT
Senior Toxicologist
Regulatory & Technical Affairs



Kimberly, Wise, Ph.D.
Senior Director
Chemical Products & Technology
ARASP

Extended Reference List:

Adami, HO; Berry, SC; Breckenridge, C; Smith, L; Swenberg, J; Trichopoulos, D; Weiss, NS; Pastoor, T. 2011. Toxicology and epidemiology: Improving the science with a framework for combining toxicological and epidemiological evidence to establish causal inference. *Toxicol. Sci.* 122(2):223-234.

Bailey, LA; Prueitt, RL; Rhomberg, LR. 2012. Hypothesis-Based Weight-of-Evidence evaluation of methanol as a human carcinogen. *Regul. Toxicol. Pharmacol.* 62(2):278-91.

Becker, RA; Janus ER; White, RD; Kruszewski, FH; Brackett, RE. 2010. Good Laboratory Practices: Becker et al. *Respond. Environ. Health Perspect.* 118(5): A194–A195.
doi: 10.1289/ehp.0901755R

Boekelheide, K; Campion, SN. 2010. Toxicity testing in the 21st century: Using the new toxicity testing paradigm to create a taxonomy of adverse effects. *Toxicol. Sci.* 114(1):20-24.

Boobis, AR; Cohen, SM; Dellarco, V; McGregor, D; Meek, ME; Vickers, C; Willcocks, D; Farland, W. 2006. IPCS framework for analyzing the relevance of a cancer mode of action for humans. *Crit. Rev. Toxicol.* 36(10):781-792.

Boobis, AR; Doe, JE; Heinrich-Hirsch, B; Meek, ME; Munn, S; Ruchirawat, M; Schlatter, J; Seed, J; Vickers, C. 2008. IPCS framework for analyzing the relevance of a noncancer mode of action for humans. *Crit. Rev. Toxicol.* 38(2):87-96.

Borgert, CJ; Mihaich, EM; Ortego, LS; Bentley, KS; Holmes, CM; Levine, SL; Becker, RA. 2011. Hypothesis-driven weight of evidence framework for evaluating data within the US EPA's Endocrine Disruptor Screening Program. *Regul. Toxicol. Pharmacol.* 61(2):185-191.

European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC). 2009. Framework of the Integration of Human and Animal Data in Chemical Risk Assessment. ECETOC Technical Report No. 104. 130p., January.

European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC). 2011. JACC 055 - Linear Polydimethylsiloxanes CAS No. 63148-62-9 (Second Edition).

European Chemicals Agency (ECHA). 2012. Practical Guide 2: How to Report Weight of Evidence. ECHA-10-B-05-EN. 26p.

European Commission, Directorate-General for Health & Consumers, Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). 2012. Memorandum on the Use of the Scientific Literature for Human Health Risk Assessment Purposes – Weighing of Evidence and Expression of Uncertainty. 46p., March 19.

European Food Safety Authority (EFSA). 2010. Application of systematic review methodology to food and feed safety assessments to support decision making. EFSA J. 8(6):1637.

Goodman, JE; Dodge, DG; Bailey, LA. 2010. A framework for assessing causality and adverse effects in humans with a case study of sulfur dioxide. Regul. Toxicol. Pharmacol. 58:308-322.

Guyatt, GH; Oxman, AD; Vist, GE; Kunz, R; Falck-Ytter, Y; Alonso-Coello, P; Schunemann, H. 2008a. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. BMJ 336(7650):924-926.

Guyatt, GH; Oxman, AD; Kunz, R; Vist, GE; Falck-Ytter, Y; Schunemann, H. 2008b. What is "quality of evidence" and why is it important to clinicians? BMJ 336(7651):995-998.

Guzelian, PS; Victoroff, MS; Halmes, NC; James, RC; Guzelian, CP. 2005. Evidence-based toxicology: A comprehensive framework for causation. Hum. Exp. Toxicol. 24:161-201.

Higgins, JPT; Green, S; eds. 2011. Cochrane Handbook for Systematic Reviews of Interventions (Version 5.1.0). The Cochrane Collaboration. Accessed on February 03, 2012 at <http://www.cochrane-handbook.org/>.

Hill, AB. 1971. Statistical Evidence and Inference. A Short Textbook of Medical Statistics, 285-296.

Julien, E; Boobis, AR; Olin, SS. 2009. The Key Events Dose-Response Framework: A cross-disciplinary mode-of-action based approach to examining dose-response and thresholds. Crit. Rev. Food Sci. Nutr. 49(8):682-689.

Keystone Center, Research Integrity Roundtable. 2012 Improving the Use of Science in Regulatory Decision-Making: Dealing with Conflict of Interest and Bias in Scientific Advisory Panels, and Improving Systematic Scientific Reviews.

Klimisch, HJ; Andreae, M; Tillmann, U. 1997. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regul. Toxicol. Pharmacol.* 25(1):1-5.

Lavelle, KS; Schnatter, AR; Travis, KZ; Swaen, MMH; Pallapies, D; Money, C; Priem, P; Vrijhof, H. 2012. Framework for integrating human and animal data in chemical risk assessment. *Regul. Toxicol. Pharmacol.* 62(2):302-312.

Linkov, I; Loney, D; Cormier, S; Satterstrom, FK; Bridges, T. 2009. Weight-of-evidence evaluation in environmental assessment: Review of qualitative and quantitative approaches. *Sci. Total Environ.* 407(19):5199-5205.

Meek, ME; Bucher, JR; Cohen, SM; Dellarco, V; Hill, RN; Lehman-McKeeman, LD; Longfellow, DG; Pastoor, T; Seed, J; Patton, DE. 2003. A framework for human relevance analysis of information on carcinogenic modes of action. *Crit. Rev. Toxicol.* 33(6):591-653.

Pemberton, M; Bailey, LA; Rhomberg, LR. 2013. Hypothesis-based weight-of-evidence evaluation of methyl methacrylate olfactory effects in humans and derivation of an occupational exposure level. *Regul. Toxicol. Pharmacol.* Apr 11. doi:pii: S0273-2300(13)00053-6. 10.1016/j.yrtph.20

Prueitt, RL; Goodman, JE; Bailey, LA; Rhomberg, LR. 2011. Hypothesis-based weight-of-evidence evaluation of the neurodevelopmental effects of chlorpyrifos. *Crit. Rev. Toxicol.* 41(10):822-903. <http://informahealthcare.com/doi/pdf/10.3109/10408444.2011.616877>.

Rhomberg, LR; Bailey, LA; Goodman, JE. 2010. Hypothesis-based weight of evidence: A tool for evaluating and communicating uncertainties and inconsistencies in the large body of evidence in proposing a carcinogenic mode of action – Naphthalene as an example. *Crit. Rev. Toxicol.* 40:671-696.

Rhomberg, LR; Bailey, LA; Goodman, JE; Hamade, A; Mayfield, D. 2011. Is exposure to formaldehyde in air causally associated with leukemia? – A hypothesis-based weight-of-evidence analysis. *Crit. Rev. Toxicol.* 41(7):555-621.

Rhomberg, LR; Goodman, JE; Prueitt, RL. 2013. The Weight of Evidence Does Not Support the Listing of Styrene as "Reasonably Anticipated to be a Human Carcinogen" in NTP's Twelfth Report on Carcinogens. *Hum. Ecol. Risk Assess.* 19(1):4-27.

Seed, J; Carney, EW; Corley, RA; Crofton, KM; DeSesso, JM; Foster, PM; Kavlock, R; Kimmel, G; Klaunig, J; Meek, ME; Preston, RJ; Slikker, W; Tabacova, S; Williams, GM; Wiltse, J; Zoeller, RT; Fenner-Crisp, P; Patton, DE. 2005. Overview: Using mode of action and life stage information to evaluate the human relevance of animal toxicity data. *Crit. Rev. Toxicol.* 35(8-9):664-672.

Sonich-Mullin, C; Fielder, R; Wiltse, J; Baetcke, K; Dempsey, J; Fenner-Crisp, P; Grant, D; Hartley, M; Knaap, A; Kroese, D; Mangelsdorf, I; Meek, E; Rice, JM; Younes, M. 2001. IPCS conceptual framework for evaluating a mode of action for chemical carcinogenesis. Regul. Toxicol. Pharmacol. 34:146-152.

Swan, G; van Amelsvoort, L. 2009. A weight of evidence approach to causal inference. J. Clin. Epidemiol. 62(3):270-277.

Swan, GM. 2006. A framework for using epidemiological data for risk assessment. Hum. Exp. Toxicol. 25(3):147-155.

Weed, DL. 2005. Weight of evidence: A review of concepts and methods. Risk Anal. 25:1545-1557.