UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

July 15, 2019

EPA-SAB-19-003

The Honorable Andrew R. Wheeler
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Subject: Consultation on Updating EPA Guidelines for Carcinogen and Non-Cancer Risk Assessment

Dear Administrator Wheeler:

EPA's Science Advisory Board held a public meeting on June 5 - 6, 2019, and conducted a consultation with EPA staff on updating the Agency's Guidelines for Carcinogen and Non-Cancer Risk Assessment**.** Members of the Science Advisory Board's Chemical Assessment Advisory Committee also participated in the consultation.

The Science Advisory Board Staff Office has developed the consultation as a mechanism to provide individual expert comments for the EPA's consideration early in the implementation of a project or action. A consultation is conducted under the normal requirements of the Federal Advisory Committee Act (FACA), as amended (5 U.S.C., App.), which include advance notice of the public meeting in the Federal Register.

No consensus report is provided to the EPA because no consensus advice is given. Individual written comments were requested from all members of the Science Advisory Board and the Science Advisory Board Chemical Assessment Advisory Committee. The EPA's charge questions for the consultation are provided in Enclosure A. The individual written comments that were received from EPA Science Advisory Board members are provided in Enclosure B, and the individual comments that were received from members of the Science Advisory Board's Chemical Assessment Advisory Committee are provided in Enclosure C.

We thank the EPA for the opportunity to provide advice early in the Agency's process of updating the Guidelines for Carcinogen and Non-Cancer Risk Assessment.

Sincerely,

/S/

Dr. Michael Honeycutt, Chair
EPA Science Advisory Board

/S/

Dr. Hugh A. Barton, Chair
SAB Chemical Assessment Advisory Committee

Enclosures

NOTICE

This report has been written as part of the activities of the EPA Science Advisory Board (SAB), a public advisory group providing extramural scientific information and advice to the Administrator and other officials of the Environmental Protection Agency. The SAB is structured to provide balanced, expert assessment of scientific matters related to problems facing the Agency. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the views and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names of commercial products constitute a recommendation for use. Reports of the SAB are posted on the EPA Web site at http://www.epa.gov/sab.

U.S. Environmental Protection Agency
Science Advisory Board

CHAIR
Dr. Michael Honeycutt, Division Director, Toxicology Division, Texas Commission on Environmental Quality, Austin, TX

MEMBERS
Dr. Rodney Andrews, Director, Center for Applied Energy Research, University of Kentucky, Lexington, KY

Dr. Hugh A. Barton, Independent Consultant, Mystic, CT

Dr. Barbara Beck, Principal, Gradient Corp., Cambridge, MA

Dr. Deborah Hall Bennett, Professor and Interim Chief, Environmental and Occupational Health Division, Department of Public Health Sciences, School of Medicine, University of California, Davis, Davis, CA

Dr. Frederick Bernthal, President Emeritus and Senior Advisor to the Board of Trustees, Universities Research Association, Washington, DC

Dr. Bob Blanz, Chief Technical Officer, Arkansas Department of Environmental Quality, North Little Rock, AR

Dr. Todd Brewer, Senior Manager, Partnership Programs, American Water Works Association, Denver, CO

Dr. Joel G. Burken, Curator's Professor and Chair, Civil, Architectural, and Environmental Engineering, College of Engineering and Computing, Missouri University of Science and Technology, Rolla, MO

Dr. Janice E. Chambers, William L. Giles Distinguished Professor and Director, Center for Environmental Health Sciences, College of Veterinary Medicine, Mississippi State University, Mississippi State, MS

Dr. John R. Christy, Distinguished Professor of Atmospheric Science and Director of Earth System Science Center, University of Alabama in Huntsville, Huntsville, AL

Dr. Samuel Cohen, Professor, Pathology and Microbiology, University of Nebraska Medical Center, Omaha, NE

Dr. Louis Anthony (Tony) Cox, Jr., President, Cox Associates, Denver, CO

Dr. Alison C. Cullen, Associate Dean and Professor, Daniel J. Evans School of Public Policy and Governance, University of Washington, Seattle, WA

Dr. Otto C. Doering III, Professor, Department of Agricultural Economics, Purdue University, W. Lafayette, IN

Dr. Susan P. Felter, Research Fellow, Global Product Stewardship, Procter & Gamble, Mason, OH

Dr. Joseph A. Gardella, SUNY Distinguished Professor and John and Frances Larkin Professor of Chemistry, Department of Chemistry, College of Arts and Sciences, University at Buffalo, Buffalo, NY

Dr. John D. Graham, Dean, School of Public and Environmental Affairs, Indiana University, Bloomington, IN

Dr. John Guckenheimer, Professor Emeritus and Interim Director, Center for Applied Mathematics, Cornell University, Ithaca, NY

Dr. Steven P. Hamburg, Chief Scientist, Environmental Defense Fund, Boston, MA

Dr. Merlin R. Lindstrom, Independent Consultant, Bartlesville, OK

Dr. Robert E. Mace, The Meadows Center for Water and the Environment, Texas State University, San Marcos, TX

Dr. Clyde F. Martin, Horn Professor of Mathematics, Emeritus, Department of Mathematics and Statistics, Texas Tech University, Crofton, MD

Dr. Sue Marty, Senior Toxicology Leader, Toxicology & Environmental Research, The Dow Chemical Company, Midland, MI

Dr. Kristina D. Mena, Associate Professor, Epidemiology, Human Genetics and Environmental Sciences, School of Public Health, University of Texas Health Science Center at Houston, El Paso, TX

Mr. Robert W. Merritt, Independent Consultant, Houston, TX

Dr. Larry Monroe, Independent Consultant, Braselton, GA

Dr. Thomas F. Parkerton, Senior Environmental Scientist, Toxicology & Environmental Science Division, ExxonMobil Biomedical Science, Spring, TX

Dr. Robert Phalen, Professor, Air Pollution Health Effects Laboratory, Department of Medicine, University of California-Irvine, Irvine, CA

Mr. Richard L. Poirot, Independent Consultant, Burlington, VT

Dr. Kenneth M. Portier, Independent Consultant, Athens, GA

Dr. Robert Puls, Owner/Principal, Robert Puls Environmental Consulting, Bluffton, SC

Dr. Kenneth Ramos, Executive Director, Institute of Biosciences and Technology, Texas A&M University, Houston, TX

Dr. Tara L. Sabo-Attwood, Associate Professor and Chair, Department of Environmental and Global Health, College of Public Health and Health Professionals, University of Florida, Gainesville, FL

Dr. Anne Smith, Managing Director, NERA Economic Consulting, Washington, DC

Dr. Richard Smith, Professor, Department of Statistics and Operations Research, University of North Carolina, Chapel Hill, NC

Dr. Jay Turner, Professor and Vice Dean for Education, Department of Energy, Environmental and Chemical Engineering, McKelvey School of Engineering, Washington University, St. Louis, MO

Dr. Brant Ulsh, Principal Health Physicist, M.H. Chew & Associates, Cincinnati, OH

Dr. Donald van der Vaart, Senior Fellow, John Locke Foundation, Raleigh, NC

Dr. Kimberly White, Senior Director, Chemical Products and Technology Division, American Chemistry Council, Washington, DC

Dr. Mark Wiesner, Professor, Department of Civil and Environmental Engineering, Director, Center for the Environmental Implications of NanoTechnology (CEINT), Pratt School of Engineering, Nicholas School of the Environment, Duke University, Durham, NC

Dr. Peter J. Wilcoxen, Laura J. and L. Douglas Meredith Professor for Teaching Excellence, Director, Center for Environmental Policy and Administration, The Maxwell School, Syracuse University, Syracuse, NY

Dr. Richard A. Williams, Independent Consultant, McLean, VA

Dr. S. Stanley Young, Chief Executive Officer, CGStat, Raleigh, NC

Dr. Matthew Zwiernik, Professor, Department of Animal Science, Institute for Integrative Toxicology, Michigan State University, East Lansing, MI

SCIENCE ADVISORY BOARD STAFF

Dr. Thomas Armitage, Designated Federal Officer, U.S. Environmental Protection Agency, Washington, DC

U.S. Environmental Protection Agency
Science Advisory Board
Chemical Assessment Advisory Committee

CHAIR
Dr. Hugh A. Barton, Independent Consultant, Mystic, CT

MEMBERS
Dr. Richard Belzer, Independent Consultant, Mt. Vernon, VA

Dr. Tiffany Bredfeldt, Senior Toxicologist, Texas Commission on Environmental Quality, Austin, TX

Dr. Karen Chou, Associate Professor, Animal Science and Environmental Science and Policy Program, College of Agriculture and Natural Resources, Michigan State University, East Lansing, MI

Dr. Harvey Clewell, Principal Consultant, Ramboll Environment and Health, Research Triangle Park, NC

Dr. David Eastmond, Professor and Chair, Department of Cell Biology and Neuroscience, Toxicology Graduate Program, University of California - Riverside, Riverside, CA

Dr. Joanne English, Independent Consultant, Menlo Park, CA

Dr. David G. Hoel, Distinguished University Professor, Department of Biometry and Epidemiology, Medical University of South Carolina, Charleston, SC

Dr. Jacqueline Hughes-Oliver, Professor, Statistics Department, North Carolina State University, Raleigh, NC

Dr. Michael Jayjock, Exposure/Risk Assessor, Jayjock Associates LLC, Langhorne, PA

Dr. Wayne Landis, Professor and Director, Institute of Environmental Toxicology, Huxley College of the Environment, Western Washington University, Bellingham, WA

Mr. Charles McConnell, Director, Center for Carbon Management, Office of the Chancellor, University of Houston, Houston, TX

Dr. Dennis Paustenbach, President, Paustenbach and Associates, Jackson, WY

Dr Isaac Pessah, Professor, Molecular Biosciences, School of Veterinary Medicine, University of California, Davis, Davis, CA

Dr. Joann Brooks Powell, Assistant Professor, Center for Cancer Research and Therapeutic Development (CCRTD), Clark Atlanta University, Atlanta, GA

Dr. Kenneth Ramos, Executive Director, Institute of Biosciences and Technology, Texas A&M University, Houston, TX

Dr. Thomas Rosol, Professor, Veterinary Biosciences, College of Veterinary Medicine, Ohio State University, Columbus, OH

Dr. Ted Simon, Toxicologist, Ted Simon, LLC, Winston, GA

Dr. Eric Smith, Professor, Statistics, College of Science, Virginia Tech, Blacksburg, VA, United States

Dr. Laura Vandenberg, Associate Professor, Environmental Health Sciences, School of Public Health and Health Sciences, University of Massachusetts - Amherst, Amherst, MA

SCIENCE ADVISORY BOARD STAFF

Dr. Suhair Shallal, Designated Federal Officer, U.S. Environmental Protection Agency, Washington, DC

Enclosure A

The EPA'S Charge Questions

SAB Consultation on Updating EPA Guidelines for Carcinogen and Non-Cancer Risk Assessment

The U.S. EPA is interested in seeking consultation from the members of the SAB regarding upcoming activities related to an update to the 2005 EPA Guidelines for Carcinogen Risk Assessment and guidelines for noncancer risk assessment. In considering areas for future emphasis, as well as with the work currently underway, EPA's Risk Assessment Forum[1] (RAF) is considering various topic areas including use of defaults, inhalation dosimetry and susceptible populations and lifestages.

The U.S. EPA, primarily through the RAF, maintains a series of guidelines, guidance documents and methodologies that describe the way the Agency conducts its human health and ecological risk assessments.[2] Some key examples include:

- Guidelines concerning: exposure assessment, carcinogen risk assessment, mixtures risk assessment, reproductive toxicity risk assessment, developmental toxicity risk assessment, neurotoxicity risk assessment, and ecological risk assessment;
- Supplemental guidance for mixtures risk assessment, and assessing susceptibility from early-life exposure to carcinogens;
- Guidance for benchmark dose modeling, and applying quantitative data to develop data-derived extrapolation factors;
- Frameworks for cumulative risk assessment and for ecological risk assessment; and
- Methods for and reviews of RfD/RfC processes.

A more detailed listing of some of the Agency guidelines, guidance documents, and technical panel reports that address human health risk assessment is attached.

The RAF is currently engaged in various activities,[3] ranging from drafting updates to longstanding guidelines documents to initial investigative steps on complex topic areas. Some current examples include an update to the Guidelines for Exposure Assessment,[4] activities related to the development of cumulative risk assessment guidance,[5] and consideration of new approaches to dose-response assessment that may be used in risk assessments to augment their usefulness for Agency decision making. Activities are also underway to address specific issues, such as additivity in mixtures risk assessment and consideration of several of the default uncertainty factors used in reference value methods.

---

[1] https://www.epa.gov/osa/basic-information-about-risk-assessment-guidelines-development

[2] A list of many of the human health assessment documents can be found at the following URL: https://www.epa.gov/risk/risk-assessment-guidelines#tab-1, and documents on ecological assessment can also be accessed from that webpage.

[3] https://www.epa.gov/osa/risk-assessment-current-projects

[4] https://www.epa.gov/risk/guidelines-human-exposure-assessment

[5] https://www.epa.gov/risk/framework-cumulative-risk-assessment

The EPA is interested in consultation with the SAB with these general perspectives in mind.

1. Are there particular aspects of existing Agency risk assessment guidance related to cancer and non-cancer endpoints that individual SAB members recommend be revised or augmented to incorporate updated scientific information (based on your experience in usage, new information, or scientific advances)?

2. Are there important topic areas that are <u>not</u> fully represented in existing Agency risk assessment guidance related to cancer and non-cancer endpoints that SAB members recommend EPA address in guidance? What current information supports this recommendation?

As evident from the general questions above, EPA is seeking open-ended input and recommendations from SAB members and will consider all the input received to determine next steps for updating EPA guideline documents in a phased approach.

In the course of development and review of this charge to the SAB, the following additional questions were identified by Agency leadership to highlight for SAB members' input.

3. Are any key elements of hazard and dose-response analysis —including analytical limitations, heterogeneity, natural variability, and non-ambient exposures (i.e., endogenous or indoor exposures)—not adequately characterized in guidance?

4. Current guidance discusses how to describe confidence in hazard conclusions (see, for example, the Cancer Guidelines, section 2.5 "Weight of Evidence Narrative" or Guidelines for Developmental Toxicity, Table 3) and discusses presentation of uncertainty in dose response (see for example the Cancer Guidelines, section 3.7 "Dose Response Characterization"). Examples of current practice can also be seen in various recent EPA assessments of specific chemicals or pollutants.

    i. Do SAB members have recommendations for better ways to characterize conclusions and uncertainties in a transparent way?

    ii. Do SAB members have recommendations for better ways to analyze uncertainty, qualitatively or with quantitative analysis?

    iii. What role should statistical analysis play in this characterization?

    iv. Are there methods SAB members recommend for better analyzing and communicating compounded uncertainty, including the use of uncertainty factors, in the hazard identification and dose response process?

5. The current Agency-wide guidance includes a guideline on cancer assessment, several guidelines for specific noncancer endpoints (e.g., reproductive toxicity, developmental toxicity, and mutagenicity), and guidances or reports on aspects of assessment common to

many assessment endpoints (e.g., inhalation dosimetry, body-weight scaling of oral doses, benchmark dose technical guidance, risk characterization).

i. Are there specific areas within these documents on which there have been advances in risk assessment that should be reflected in updated guidelines?

ii. Are there areas of overlap or disagreement between these guidelines?

iii. What issues or guideline documents would SAB members prioritize for update?

6. Given current understanding of how risk assessments are used in decision making, are there considerations or changes to existing guidance with respect to problem formulation, assessment, data integration, and risk characterization that SAB members recommend EPA consider? Do SAB members have specific recommendations as to questions of importance to decision makers that are not being addressed by current risk assessments?

7. The purpose of some risk assessments (to quantify dose-response or reference values protective of the most sensitive receptors) and the purpose of the assessment of risk to inform benefits in an economic analysis (to create a predictive analysis for judging the effectiveness and feasibility of a regulatory action) can be quite different. As a result, the evaluation methods and key decision points can be quite different. For example, risk assessors may choose a benchmark dose at the high end (>95 percentile) of a distribution in order to define a level likely to avoid adverse effects, while economists may prefer risk assessors characterize the entire distribution or, at a minimum, use benchmark doses in the middle of the distribution, to inform benefit analyses.

i. Do SAB members think risk assessments are providing the information needed by risk managers and those estimating the benefits of potential decisions? If not, what do SAB members recommend might make hazard and dose response analyses more useful to decision makers?

ii. Should EPA's guidance direct staff to consider as part of the development of the assessment the questions decision makers need answered in the end use of the assessment?

With these questions guiding, but not limiting, your review, please provide input to help guide the Agency as it initiates an update to the 2005 EPA Guidelines for Carcinogen Risk Assessment and develops guidelines for noncancer risk assessment.

Attachment

Select Agency Guidelines, Guidance Documents, and Technical Panel Reports that Address Human Health Risk Assessment

- U.S. EPA. 2012. Guideline for Microbial Risk Assessment: Pathogenic Microorganisms with Focus on Food and Water. EPA/100/J-12/001, Jul 2012.
- U.S. EPA. 2005. Guidelines for Carcinogen Risk Assessment EPA/630/P-03/001F, Mar 2005.
- U.S. EPA. 1998. Guidelines for Neurotoxicity Risk Assessment EPA/630/R-95/001F, Apr 1998.
- U.S. EPA, 1996. Guidelines for Reproductive Toxicity Risk Assessment EPA/630/R-96/009, Oct 1996.
- U.S. EPA. 1991. Guidelines for Developmental Toxicity Risk Assessment EPA/600/FR-91/001, Dec 1991.
- U.S. EPA. 1986. Guidelines for Mutagenicity Risk Assessment EPA/630/R-98/003, Sep 1986.
- U.S. EPA. 1986. Guidelines for the Health Risk Assessment of Chemical Mixtures EPA/630/R-98/002, Sep 1986.
- U.S. EPA. 2014. Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation. EPA/100/R-14/022F, Sep 2014.
- U.S. EPA. 2014. Framework for Human Health Risk Assessment to Inform Decision Making. EPA/100/R-14/001, Apr 2014.
- U.S. EPA. 2012. Advances in Inhalation Gas Dosimetry for Derivation of a Reference Concentration (RfC) and Use in Risk Assessment. EPA/600/R-12/044, Sep 2012.
- U.S. EPA. 2012. Benchmark Dose Technical Guidance. EPA/100/R-12/001, Jun 2012.
- U.S. EPA. 2011. Recommended Use of Body Weight 3/4 as the Default Method in Derivation of the Oral Reference Dose. EPA/100/R11/0001, Feb 2011.
- U.S. EPA. 2006. A Framework for Assessing Health Risks of Environmental Exposure to Children. EPA/600/R-05/093F, Sep 2006.
- U.S. EPA. 2006. Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment. EPA/600/R-05/043F, Sep 2006.
- U.S. EPA. 2005. Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens EPA/630/R-03/003F, Mar 2005.
- U.S. EPA. 2002. A Review of the Reference Dose and Reference Concentration Processes. EPA/630/P-02/002F, Dec 2002.
- U.S. EPA. 2000. Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures. EPA/630/R-00/002, Aug 2000.
- U.S. EPA. 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. EPA/600/8-90/066F, Oct 1994.
- U.S. EPA. 1988. Recommendations for and Documentation of Biological Values for Use in Risk Assessment. EPA 600/6-87/008, Feb 1988.

Enclosure B

Individual Comments from Members of the EPA Science Advisory Board on Updating EPA Guidelines for Carcinogen and Non-Cancer Risk Assessment

(July - 2019)

Dr. Hugh Barton

SAB Consultation on Updating EPA Guidelines for Carcinogen and Non-Cancer Risk Assessment

The EPA is interested in consultation with the SAB with these general perspectives in mind.

1. Are there particular aspects of existing Agency risk assessment guidance related to cancer and non-cancer endpoints that individual SAB members recommend be revised or augmented to incorporate updated scientific information (based on your experience in usage, new information, or scientific advances)?

The Agency should have harmonized guidance across all endpoints, rather than continuing the arbitrary separation of cancer and noncancer guidances. For various toxicodynamic processes (modes of action, mechanisms of action, adverse outcome pathways all being terms that describe some version of toxicodynamics), the dose-response relationship may appear more linear or more nonlinear, but this does not appear specific to a safety or toxicity endpoint. The analyses need to characterize the dose-response based upon available data and consideration of human population variability, extrapolation from animals to humans, and other extrapolations (e.g., duration, database weaknesses). In the absence of informative data, a standard default approach should be indicated that would apply across all safety or toxicity endpoints or, like the early life adjustment for mutagenic carcinogens there could be defaults that apply informed by toxicodynamic processes.

2. Are there important topic areas that are <u>not</u> fully represented in existing Agency risk assessment guidance related to cancer and non-cancer endpoints that SAB members recommend EPA address in guidance? What current information supports this recommendation?

Cumulative risk evaluation remains an area needing development. As demonstrated for anti-androgens, there can be several targets that can be modulated within relevant pathways leading to a common health outcome. The simplistic perspective of multiple chemicals modulating a single target (e.g., cholinesterase inhibition) may have been a reasonable starting point, but clearly is inadequate.

In the course of development and review of this charge to the SAB, the following additional questions were identified by Agency leadership to highlight for SAB members' input.

3. Are any key elements of hazard and dose-response analysis —including analytical limitations, heterogeneity, natural variability, and non-ambient exposures (i.e., endogenous or indoor exposures)—not adequately characterized in guidance?

4. Current guidance discusses how to describe confidence in hazard conclusions (see, for example, the Cancer Guidelines, section 2.5 "Weight of Evidence Narrative" or Guidelines for Developmental Toxicity, Table 3) and discusses presentation of uncertainty in dose response (see for example the Cancer Guidelines, section 3.7 "Dose

Response Characterization"). Examples of current practice can also be seen in various recent EPA assessments of specific chemicals or pollutants.

iii. Do SAB members have recommendations for better ways to characterize conclusions and uncertainties in a transparent way?

iv. Do SAB members have recommendations for better ways to analyze uncertainty, qualitatively or with quantitative analysis?

v. What role should statistical analysis play in this characterization?

vi. Are there methods SAB members recommend for better analyzing and communicating compounded uncertainty, including the use of uncertainty factors, in the hazard identification and dose response process?

A key to characterizing and communicating uncertainties is to clearly describe best estimates as well as uncertainties around them. Methods commonly applied to analysis of most health endpoints (e.g., RfD, RfC) are designed to create health protective assessments that build in some protections but not others. Much of this thinking has been driven by a widely held but tenuous belief that doses giving no effect (or no adverse effect) are below a biological threshold. This may be true at time, but as published analyses indicate lack of observation of a response is often a reflection of the detection limit of the study design (e.g., associated with the number of animals in each dose level) rather than a biological threshold. Biological thresholds clearly exist and are subject to population variability, but characterizing them is harder than is commonly acknowledged by toxicologists and risk assessors.

If a point of departure is derived for a given response level (e.g., 15% incidence), then adjustments for animal to human and subchronic to chronic produce an estimate of a dose giving a chronic human response at that level (e.g. 15% incidence). Adjustment for sensitive populations, now makes it a response in some portion of the population that could range from essentially a very rare small subpopulation to ~50% (e.g., one sex) to ~100% (i.e., a sensitive life stage that everyone goes through). None of these adjust to reduce the level of risk in the sensitive population; this needs to be re-evaluated.

5. The current Agency-wide guidance includes a guideline on cancer assessment, several guidelines for specific noncancer endpoints (e.g., reproductive toxicity, developmental toxicity, and mutagenicity), and guidances or reports on aspects of assessment common to many assessment endpoints (e.g., inhalation dosimetry, body-weight scaling of oral doses, benchmark dose technical guidance, risk characterization).

   i. Are there specific areas within these documents on which there have been advances in risk assessment that should be reflected in updated guidelines?

   ii. Are there areas of overlap or disagreement between these guidelines?

iii. What issues or guideline documents would SAB members prioritize for update?

See response to Question 2 above.

6. Given current understanding of how risk assessments are used in decision making, are there considerations or changes to existing guidance with respect to problem formulation, assessment, data integration, and risk characterization that SAB members recommend EPA consider? Do SAB members have specific recommendations as to questions of importance to decision makers that are not being addressed by current risk assessments?

Cumulative risk remains an area needing further development as noted earlier.

7. The purpose of some risk assessments (to quantify dose-response or reference values protective of the most sensitive receptors) and the purpose of the assessment of risk to inform benefits in an economic analysis (to create a predictive analysis for judging the effectiveness and feasibility of a regulatory action) can be quite different. As a result, the evaluation methods and key decision points can be quite different. For example, risk assessors may choose a benchmark dose at the high end (>95 percentile) of a distribution in order to define a level likely to avoid adverse effects, while economists may prefer risk assessors characterize the entire distribution or, at a minimum, use benchmark doses in the middle of the distribution, to inform benefit analyses.

    i. Do SAB members think risk assessments are providing the information needed by risk managers and those estimating the benefits of potential decisions? If not, what do SAB members recommend might make hazard and dose response analyses more useful to decision makers?

    ii. Should EPA's guidance direct staff to consider as part of the development of the assessment the questions decision makers need answered in the end use of the assessment?

It is important for the various parts of assessment processes to provide the appropriate kind of information for the end use of the assessment. Having said that, there are enough different end uses and differences in the available data to inform steps in the assessment, that any directive to consider the end uses will need to be pretty broad and general.

Dr. Barbara Beck

Response to SAB Consultation on Updating Guidelines

Response to question 5.i.

The 2005 Cancer Guidelines represented an advance in risk assessment, providing for flexibility in a number of areas, particularly hazard identification and dose-response assessment. Importantly, EPA proposed the use of threshold or non-linear dose-response models (as an alternative to the default linear no-threshold model) when supported by mechanistic considerations. Unfortunately, non-linear models remain the exception, despite evidence for such models for multiple chemicals (*e.g.,* ethyl tert-butyl ether).

Since 2005, mode of action (MOA) understanding for multiple carcinogens provides support for the use of non-linear models for specific chemicals. In particular, enhancement of cell proliferation is recognized as a key to the MOA of multiple carcinogens. Enhancement of cell proliferation increases the likelihood that an unrepaired DNA mutation or a DNA repair error will occur, thus increasing the probability of activation of an oncogene or inactivation of a tumor suppressor gene. These events can lead to tumor induction. Owing to the lack of direct mutagenic activity, enhancement of cell proliferation operates *via* a threshold dose-response.

Enhanced cell proliferation can occur through multiple mechanisms. These mechanisms and associated example chemicals are listed below:

- Induction of cytotoxicity leading to regenerative hyperplasia
    - Dimethylarsinic acid and rat bladder tumors
    - D-limonene and rat renal tubular tumors
    - Pulegone and rat urothelial tumors
- Receptor-mediated induction of cell proliferation
    - TCDD and AhR binding and rat liver tumors
    - Ciprofibrate and PPARα binding and rat liver tumors
- Hormonally-mediated mechanisms
    - DES and cervical/vaginal adenocarcinoma in women
    - Sulfamethazine and thyroid tumors in rats

In response to question 5.i, I recommend that EPA describe these advances in the understanding of cell proliferation being involved in the MOA for multiple chemicals and associated with a threshold dose- response. A list of several supporting articles (all published since 2005) is provided at the end of these comments.

Further, even for chemicals which can interact directly with DNA to induce gene mutations or chromosome aberrations (and for which a linear no-threshold model is typically recommended), threshold dose-response models may be appropriate. For example, methyl methane sulfonate (MMS) is carcinogenic in rats and mice by multiple exposure routes and mutagenic in *in vitro* and *in vivo* test systems. Work by Swenberg and coworkers (2008) using MMS in an *in vitro* cell system demonstrated a linear dose-response for exogenous 7-methyl

guanine adducts, a biomarker of exposure. In contrast, HPRT mutation frequency, a biomarker of effect, showed a threshold dose-response with MMS in the same system. Also in response to question 5.i, I recommend that EPA consider non-linear models even for DNA reactive carcinogens, when supported by chemical-specific, mechanistic considerations, to ensure that cancer risk assessment is based on the most relevant science.

Barbara D. Beck, Ph.D., DABT, ATS

References

Bevan, RJ; Harrison, PTC. 2017. "Threshold and non-threshold chemical carcinogens: A survey of the present regulatory landscape." *Regul. Toxicol. Pharmacol*. 88:291-302.

Calabrese, EJ; Hanekamp, JC; Shamoun, DY. 2019. "The EPA Cancer Risk Assessment Default Model proposal: Moving away from the LNT." *Dose Response*. 16(3):1-4.

Calabrese, EJ. 2019. "The linear No-Threshold (LNT) dose response model: A comprehensive assessment of its historical and scientific foundations." *Chem. Biol. Interact*. 301:6-25.

Cardarelli, JJ; Ulsh, BA. 2018. "It Is time to move beyond the Linear No-Threshold Theory for low-dose radiation protection. *Dose Response*. 16(3).

Cohen, SM. 2017. "The relevance of experimental carcinogenicity studies to human safety." *Curr. Opin. Toxicol.* 3:6-11.

Cohen, SM; Boobis, AR; Dellarco, VL; Doe, JE; Fenner-Crisp, PA; Moretto, A; Pastoor, TP; Schoeny, RS; Seed, JG; Wolf, DC. 2019. "Chemical carcinogenicity revisited 3: Risk assessment of carcinogenic potential based on the current state of knowledge of carcinogenesis in humans." *Regul. Toxicol. Pharmacol*. 103:100-105.

Cohen, SM; Arnold, LL. 2011. "Chemical carcinogenesis." *Toxicol. Sci*. 120(Suppl. 1):S76-S92.

Da Rocha, MS; Dodmane, PR; Arnold, LL; Pennington, KL; Anwar, MM; Adams, BR; Taylor, SV; Wermes, C; Adams, TB; Cohen, SM. 2012. "Mode of action of pulegone on the urinary bladder of F344 rats." *Toxicol. Sci*. 128(1):1-8.

Doe, JE; Boobis, AR; Dellarco, VL; Fenner-Crisp, PA; Moretto, A; Pastoor, TP; Schoeny, RS; Seed, JG; Wolf, DC. 2019. "Chemical carcinogenicity revisited 2: Current knowledge of carcinogenesis shows that categorization as a carcinogen or non-carcinogen is not scientifically credible." *Regul. Toxicol. Pharmacol*. 103:124-129.

Gollapudi, BB; Johnson, GE; Hernandez, LG; Pottenger, LH; Dearfield, KL; Jeffrey, AM; Julien, E; Kim, JH; Lovell, DP; MacGregor, JT; Moore, MM; van Benthem, J; White, PA; Zeiger, E; Thybaud, V. 2013. "Quantitative approaches for assessing dose-response relationships in genetic toxicology studies." *Environ. Mol. Mutagen*. 54(1):8-18.

Greim, H; Albertini, RJ. 2015. "Cellular response to the genotoxic insult: The question of threshold for genotoxic carcinogens." *Toxicol. Res*. 4(1):36-45.

Swenberg, JA; Fryar-Tita, E; Jeong, YC; Boysen, G; Starr, T; Walker, VE; Albertini, RJ. 2008. "Biomarkers in toxicology and risk assessment: Informing critical dose-response relationships." *Chem. Res. Toxicol*. 21(1):253-265.

Wolf, DC; Cohen, SM; Boobis, AR; Dellarco, VL; Fenner-Crisp, PA; Moretto, A; Pastoor, TP; Schoeny, RS; Seed, JG; Doe, JE. 2019. "Chemical carcinogenicity revisited 1: A unified theory of carcinogenicity based on contemporary knowledge." *Regul. Toxicol. Pharmacol*. 103:86-92.

Wood, CE; Hukkanen, RR; Sura, R; Jacobson-Kram, D; Nolte, T; Odin, M; Cohen, SM. 2015. "Scientific and Regulatory Policy Committee (SRPC) review: Interpretation and use of cell proliferation data in cancer risk assessment." *Toxicol. Pathol*. 43(6):760-775.

Dr. Deborah Bennett

1. It appears the most recent update to the risk assessment process is the "framework for human health risk assessment to inform decision making" and I'm considering advances relative to this document. There is a growing scientific basis for the importance of considering chemicals with a similar mode of action, particularly compounds within the same chemical class, in a cumulative approach, and section 2.1..2.2 could be expanded to provide more details in this regard.

California utilizes a very specific approach for adjusting the cancer potency values and other health endpoint values to account for the increased sensitivity to children. Section 2.1.2.1 of the above mentioned document could be expanded to provide more specific guidance, perhaps following a model like California's. The importance of pre-natal exposures and increased sensitivity at this life stage are also critical to include as there is growing evidence regarding the impact of pre-natal exposure on a host of developmental outcomes.

2. No questions

3. Many of the emerging chemicals of concern are found in consumer products, and therefore have both higher level in ambient air, but also exposure through direct exposure pathways. These should be more explicitly included. Also, there have been a number of papers on the direct from air to dermal pathway. This pathway should be considered. More careful consideration of occupational exposure pathways also needs to be included as these populations are sometimes those at greatest risk.

4. In some cases there will be considerable uncertainty regarding the shape of the dose response curve. In cases where there is uncertainty, I think the EPA needs to consider that the prior practice of relying on a linear dose response may indeed be the most prudent one.

5. The most recent guidelines for evaluating neurotoxic compounds appears to have been published in 1998 and thus is quite dated. There has been an explosion of epidemiology studies conducted since this time that have evaluated a wide range of neurologic developmental outcomes and found many to be related to early life or pre-natal exposure. It is imperative for our economy that our children be able to grow up with the greatest potential for achievement and thus methods for accounting for these endpoints in risk assessments should be developed.

6. It seems that these questions were well addressed in the 2014 document "framework for human health risk assessment to inform decision making."

7. It seems that these questions were well addressed in the 2014 document "framework for human health risk assessment to inform decision making."

Dr. Frederick Bernthal

While I will not comment on the main thrust of the draft SAB consultation letter, which predominantly addresses chemical/biological carcinogens, I do wish to register my strong concurrence with the comments of Dr. Brant Ulsh (B-42), who focuses on the risk from radiation exposure. EPA has for at least 40 years clung to the Linear No Threshold (NLT) principal as it applies to radiation exposure, despite much accumulated evidence and human experience which strongly suggests otherwise. Perhaps this is because EPA has long had limited expertise in this area (which generally resides at the Nuclear Regulatory Commission), and has therefore tended to be ultra-conservative, despite the recommendations of more than one expert panel noted in Dr. Ulsh's comments. Or perhaps it is because the picture seems less clear when it comes to chemical/biological carcinogens, so EPA has inappropriately extended its pre-inclinations in that arena to encompass the risks from radiation exposure. In any case, EPA is long overdue in discarding the NLT principle when it comes to radiation exposure.

Dr. Janice E. Chambers

My comments are based on some of the discussion that occurred recently in the ETBE/tBA discussions in the Panel (augmented CAAC) I chaired as well as the quality review from the SAB. Also, my experience for a number of years on the FIFRA SAP has led me to some of my comments. In addition, I believe that the analysis and recommendations for a path forward presented to the SAB at our recent meeting by Dr. Penny Fenner-Crisp, who certainly had many years of experience within EPA in the risk assessment arena, are right on target and should be strongly considered for future guidelines development/updates. I have placed my comments in bold type in the most relevant questions.
Jan Chambers

1. Are there particular aspects of existing Agency risk assessment guidance related to cancer and non-cancer endpoints that individual SAB members recommend be revised or augmented to incorporate updated scientific information (based on your experience in usage, new information, or scientific advances)?

I think that EPA should have a mechanism for incorporating new scientific information into risk assessments when such information is recognized by knowledgeable scientists as superior; this was particularly apparent in the ETBE/tBA analyses of non-cancer kidney damage when newer scientific assessments and criteria with respect to human relevance of kidney damage observed in laboratory animals (1999) was not used by EPA in deference to Agency criteria of 1991. There needs to be clearer scientifically-based guidance for EPA staff to judge the human relevance of animal toxicity data so that the animal data can be viewed with a well-considered scientific perspective. In addition, there needs to be clearer guidance on how to utilize data and develop dose-response models where cancer is observed only at the high dosage in animal studies, especially when that high dosage might exceed the maximum tolerated dose (MTD). Also if the currently accepted or mandated quantitation method is from only a single type of dose-response modeling, then there needs to be the flexibility to use other models that might be better scientific choices for the types of data used; the guidance and policies utilized in the ETBE/tBA assessments seemed very restrictive and did not seem to give the EPA staff the flexibility to use scientific judgement about human relevance or appropriate computational models.

2. Are there important topic areas that are <u>not</u> fully represented in existing Agency risk assessment guidance related to cancer and non-cancer endpoints that SAB members recommend EPA address in guidance? What current information supports this recommendation?

3. Are any key elements of hazard and dose-response analysis —including analytical limitations, heterogeneity, natural variability, and non-ambient exposures (i.e., endogenous or indoor exposures)—not adequately characterized in guidance?

4. Current guidance discusses how to describe confidence in hazard conclusions (see, for example, the Cancer Guidelines, section 2.5 “Weight of Evidence Narrative” or Guidelines for Developmental Toxicity, Table 3) and discusses presentation of

uncertainty in dose response (see for example the Cancer Guidelines, section 3.7 "Dose Response Characterization"). Examples of current practice can also be seen in various recent EPA assessments of specific chemicals or pollutants.

i. Do SAB members have recommendations for better ways to characterize conclusions and uncertainties in a transparent way?

ii. Do SAB members have recommendations for better ways to analyze uncertainty, qualitatively or with quantitative analysis?

iii. What role should statistical analysis play in this characterization?

iv. Are there methods SAB members recommend for better analyzing and communicating compounded uncertainty, including the use of uncertainty factors, in the hazard identification and dose response process?

5. The current Agency-wide guidance includes a guideline on cancer assessment, several guidelines for specific noncancer endpoints (e.g., reproductive toxicity, developmental toxicity, and mutagenicity), and guidances or reports on aspects of assessment common to many assessment endpoints (e.g., inhalation dosimetry, body-weight scaling of oral doses, benchmark dose technical guidance, risk characterization).

   i. Are there specific areas within these documents on which there have been advances in risk assessment that should be reflected in updated guidelines?

   ii. Are there areas of overlap or disagreement between these guidelines?

   iii. What issues or guideline documents would SAB members prioritize for update?

6. Given current understanding of how risk assessments are used in decision making, are there considerations or changes to existing guidance with respect to problem formulation, assessment, data integration, and risk characterization that SAB members recommend EPA consider? Do SAB members have specific recommendations as to questions of importance to decision makers that are not being addressed by current risk assessments?

7. The purpose of some risk assessments (to quantify dose-response or reference values protective of the most sensitive receptors) and the purpose of the assessment of risk to inform benefits in an economic analysis (to create a predictive analysis for judging the effectiveness and feasibility of a regulatory action) can be quite different. As a result, the evaluation methods and key decision points can be quite different. For example, risk assessors may choose a benchmark dose at the high end (>95 percentile) of a distribution in order to define a level likely to avoid adverse effects, while economists may prefer risk assessors characterize the entire distribution or, at a minimum, use benchmark doses in the middle of the distribution, to inform benefit analyses.

i. Do SAB members think risk assessments are providing the information needed by risk managers and those estimating the benefits of potential decisions? If not, what do SAB members recommend might make hazard and dose response analyses more useful to decision makers?

There needs to be some guidance on how the balance of risk and benefit are considered and prioritized in EPA's assessments, and how these risk assessments are communicated to the scientific and regulated communities, and how they are communicated to the public so that the rationales for the approaches used are as transparent as possible. There needs to be guidance on how EPA evaluates the quality of the data sets used in the risk assessments and what criteria are to be employed for data to be included in risk assessments, especially for quantitative evaluations, to make certain that only high quality and reliable data are used. The relationship of the hazard assessment to the exposure assessment also needs to have clear guidance to make certain that an accurate concept of risk to various receptor populations (which will likely differ among themselves in the exposure levels) is calculated. There is also a need to make certain that any epidemiological data that are applied to any risk assessment is high quality and criteria for inclusion of epidemiological data need to clear and reasonable, with quality analytical chemistry data required and confounders properly considered and dealt with.

ii. Should EPA's guidance direct staff to consider as part of the development of the assessment the questions decision makers need answered in the end use of the assessment?

Dr. Samuel Cohen

I welcome the opportunity to offer suggestions regarding the proposed updates for the U.S. EPA Cancer Guidelines. I realize that you are under a tight deadline, but several of the following issues could be addressed as relatively low-hanging fruit:

1. For non-DNA reactive carcinogens, the assessment approach could be made the same for the cancer guidelines as for the non-cancer guidelines. I realize that some prefer the broader term of nongenotoxic, but non-DNA reactive is a better assessment for potential damage to humans. For other genotoxicity assays, such as micronucleus, sister chromatid exchange, and the Comet assay, there is too much variability and frequently the in vitro assays do not translate to the in vivo situation. I will offer some suggestions regarding genotoxicity assessments in another point. For non-DNA reactive carcinogens, utilizing the mode of action framework, the key events are necessary precursors to the development of cancer. For non-genotoxic carcinogens, these always involve a benign, toxicity endpoint, such as cytotoxicity, receptor activation, immunosuppression, etc. Since these are noncancer endpoints, they have a threshold, and usually involve an RfD or RfS approach. Since these are the precursor lesions for the development of cancer, the exact same approach could be applied to the cancer endpoints. Whatever evaluation protects against the non-cancer endpoint would also be protective for cancer. Thus, for non-DNA reactive carcinogens, the default assumption should be for a threshold approach, the same as currently used for non-cancer endpoints.

2. For the approach for non-DNA reactive carcinogens, a clear definition for DNA reactivity needs to be presented. Currently, the best approach for evaluating DNA reactivity is actual demonstration of the formation of DNA adducts. This is not always practicable in a short-term period of time. Thus, a reliance on structure activity relationships and the Ames assay provide a reasonable surrogate evaluation. For other genotoxicity markers, OECD has recently eliminated some of these assays as not being reliable predictors of the in vivo situation, such as unscheduled DNA synthesis (UDS) and the sister chromatid exchange assays. Most importantly, evaluations for genotoxicity need to rely on properly performed assays. Although guideline studies are preferred, some non-guideline studies could be utilized in the evaluation, but only if they meet reasonable standards, such as pH, control for cytotoxicity, osmolality, etc. for many of these in vitro assays, such as micronucleus and chromosomal aberrations, a positive in vitro setting rarely is translated to a positive in vivo. If an in vivo assay is negative, that should trump the in vitro positive findings, a practice which is currently used in many other regulatory agencies around the world. The major difficulty with most of these in vitro assays is the fact that they are performed at approximately 50% cytotoxicity. Cytotoxicity by definition will lead to cell death, which will certainly be associated with DNA damage. This give rise to enormous variability within the in vitro assays and is an unrealistic assessment for in vivo genotoxicity.

3. The quality of studies being utilized for risk assessment purposes needs to be evaluated carefully. The recent lack of reproducibility regarding Bisphenol A as evaluated in the CLARITY studies clearly illustrates the difficulty with many of the reported studies in the literature. As Begley and Ellis pointed out in their seminal paper in Nature in 2011, a major factor in evaluation of these assays needs to be on the blinding of evaluation of the results. This, unfortunately, is rarely done in many studies that are not performed under OECD guidelines.

4. It should be explicitly stated that studies performed at doses in excess of the maximum tolerated dose (MTD) are not to be utilized for cancer risk assessment (they should not be used for any risk assessment, for that matter).

5. Assessment of the results of well-performed two-year bioassays should invoke the Haseman rule which was developed while Dr. Joseph Haseman was at the National Toxicology Program (1983). For common tumors (defined as those with a background incidence greater than 1%), because of multiple comparisons on a statistical basis, the P value should be $p < 0.01$ for pairwise comparisons and trend tests $p < 0.005$. This guideline has been accepted by OECD and accepted in the ICH guidelines for evaluation of pharmaceuticals.

6. Evaluation of historical controls should be incorporated into any assessment of a two-year bioassay. The parameters to be included in such an evaluation need to be explicitly defined, which EPA is in an excellent position to determine.

7. Two-stage models (so called initiation-promotion studies) need to be evaluated carefully, since the treatment with the so called initiator alone gives enormous variation in tumors. Adding to this with the application of a non-DNA reactive chemical complicates interpretation. Historical controls are needed for the variability for a given initiator in a given model at a given laboratory. This has rarely been done in the past and has led to enormous misinterpretation of results. Specific guidelines could be offered for this.

8. Many rodent tumors are not relevant to humans, and requiring investigations about such findings from a two-year bioassay is wasteful of resources and an inappropriate use of animals. I have written on this extensively and include a few of my publications on this subject (see references below). Such tumors include the forestomach tumors in rodents, thyroid follicular tumors in rats, many types of liver carcinogens, several types of rat kidney carcinogens, such as α2u-globulin and chronic progressive nephropathy, mouse lung, rat lung with particulates, stomach neuroendocrine tumors, rat pancreas, F344 splenic mononuclear cell leukemia, rat pituitary, rat mammary gland tumors, rat Leydig cell tumors and a variety of others. I would be happy to provide references for these if you desire. Expert panels could be formed to provide specific guidelines for each of these tumors as has been done by EPA in the past for α2u-globulin and rat thyroid

follicular tumors. At a recent assessment by IRIS, it was suggested that a similar panel could be formed for chronic progressive nephropathy and kidney tumors. There are several of these tumors which have a large amount of epidemiology data to support non-relevance to humans, such as statin-induced liver tumors, proton pump inhibitor-induced stomach neuroendocrine tumors, and a variety of others.

The two-year bioassay has been performed for more than 50 years, and we have learned a great deal about the limitations of this assay as well as the modes of action involved with the number of tumors induced in these assays. The science that has been learned in this period of time needs to be applied in the new cancer guidelines. I would be happy to provide additional details regarding any of the above points.

Samuel M. Cohen, M.D., Ph.D.
Professor, Department of Pathology and Microbiology Havlik-Wall Professor of Oncology
University of Nebraska Medical Center 983135 Nebraska Medical Center, Omaha, NE 68198-3135

References

Cohen, S.M. 2004. Human Carcinogenic Risk Evaluation: An Alternative Approach to the Two-Year Rodent Bioassay. *Toxicological Sciences* 80, 225–229 (2004) DOI: 10.1093/toxsci/kfh159

Cohen, S.M., A.R. Boobis, V.L. Dellarco, J.E. Doe, P.A. Fenner-Crispe, A. Moretto, T.P. Pastoor, R.S. Schoeny, J.G. Seed, and D.C. Wolf. 2019. Chemical carcinogenicity revisited 3: Risk assessment of carcinogenic potential based on the current state of knowledge of carcinogenesis in humans. *Regulatory Toxicology and Pharmacology*, 103 (2019) 100–105.

Dr. Louis Anthony (Tony) Cox, Jr.

I am pleased to submit the following comments in response to the charge questions.

Recent advances in scientific information, including discovery and elucidation of the roles of inflammasomes (especially the NLRP3 inflammasome) and inflammasome-mediated chronic inflammation in exposure-related cancers and other diseases, suggest that the following questions are important for quantitative risk assessment and dose-response modeling of many carcinogens.

1. What are the minimum concentrations and durations of exposure or doses (referring to administered dose, biologically effective dose, or both) needed to activate inflammasomes and cause chronic inflammation in target tissues?

2. How does chronic inflammation affect the parameters of two-stage clonal expansion (TSCE) or multistage clonal expansion (MSCE) models of carcinogenesis?

3. What other factors (e.g., gene polymorphisms, phenotypic variations) affect the answers to these questions, and how much? For example, how wide is the distribution of NLRP3 inflammasome activation thresholds in the population (and in sensitive subpopulations)?

I believe that better understanding chronic inflammation-mediated carcinogenesis is likely to become increasingly important for carcinogen dose-response modeling and risk assessment in the next decade, and that guidance to address carcinogens for which exposure-related chronic inflammation of target tissue is the main mode of action will be very useful.

Dr. Susan Felter

SAB Input on EPA Cancer and Noncancer Risk Assessment Guidelines (RAGs)

Cancer RAGs:

- The EPA (2005) Cancer RAGs currently specify that a default assumption of a linear, no-threshold (LNT) model be applied to nongenotoxic carcinogens when "there is an absence of sufficient information on modes of action." This has created a very high bar as the question of what constitutes 'sufficient information' is not addressed, and has resulted in a significant divergence from the otherwise globally-accepted assumption of a threshold for nongenotoxic carcinogens (e.g., ECHA (2012), WHO (2009)). Updated cancer RAGs should recommend that the weight-of-evidence (WOE) be used to determine the most scientifically appropriate model to apply to quantitative risk assessment, and align with other major global regulatory agencies to adopt a default assumption of a threshold for nongenotoxic carcinogens. This is consistent with the known biological thresholds associated with modes of action (MOAs) for nongenotoxic carcinogens, and is especially important as newer technologies (both *in vivo* and *in vitro*) are being developed that have the potential to demonstrate a clear threshold for biological activity, but yet may be insufficient to define a MOA for tumors that are induced at much higher doses.

- EPA is encouraged to review and consider other international guidance for the classification (hazard identification) of carcinogens, most notably, Annex VI of the European Commission Directive 2001/59/EC (28th A.T.P. of 67/548 EEC): "General Classification and Labelling Requirements for Dangerous Substances and Preparations." This guidance, which is supported by robust scientific literature, provides examples of interpretation of tumors with regard to human relevance, some of which are also considered by the EPA, but others of which currently represent significant differences leading to a lack of international harmonization. For example, the European Commission Directive states that a substance should not be classified as a carcinogen if "the only available tumour data are liver tumours in certain sensitive strains of mice, without any other supplementary evidence" and that "particular attention should be paid to cases where the only available tumour data are the occurrence of neoplasms at sites and in strains where they are well known to occur spontaneously with a high incidence."
  http://ec.europa.eu/environment/archives/dansub/pdfs/annex6_en.pdf

- While EPA's current Cancer RAGs do encourage the inclusion of *context* (e.g., route, exposure conditions) for the hazard identification step in cancer risk assessment, greater emphasis should be placed on this. For example, EPA's assessment for perchlorate (in IRIS) states: "Under U.S. EPAs 1999 Draft Revised Guidelines for Carcinogen Risk Assessment, perchlorate is not likely to pose a risk of thyroid cancer in humans, at least at doses below those necessary to alter thyroid hormone homeostasis, based on the hormonally-mediated mode of action in rodent studies and species differences in thyroid function." This context is

critical to an appropriate evaluation of the cancer risk posed by perchlorate and should be done routinely where data are available.

- An update to EPA's Cancer RAGs should emphasize the importance of evaluating whether the maximum tolerated dose (MTD) has been exceeded in a cancer bioassay. Where the MTD has been exceeded, those data should not be included in either the hazard identification or dose-response assessment for that substance.

- EPA should explicitly acknowledge that a decision to use the LNT model as a default for genotoxic carcinogens is a risk policy decision. Further, the Agency should acknowledge that other (nonlinear) models may be considered on a case-by-case basis, even for genotoxic chemicals, where data are available to support a nonlinear model. Chemicals that test positive in a genotoxicity assay do not necessarily have a mutagenic MOA, and the guidelines need to provide flexibility to incorporate new science in this field.

- EPA should acknowledge that the application of Age Dependent Adjustment Factors (ADAFs) is a policy decision based on the potential for increased susceptibility associated with early life exposure, and this policy should continue to be restricted to assessments for carcinogens with a known mutagenic MOA. Particularly for carcinogens associated with a threshold, there are no data to support a conclusion of increased risk at human-relevant exposures. Recent literature reviews have confirmed the general adequacy of the default 10X uncertainty factor to provide protection for susceptible subpopulations including infants and children.

- For any new/updated RAGs, it is important to maintain flexibility that will allow for integration of new science streams, some of which are just starting to be used in regulatory applications/risk assessments (e.g., toxicogenomics) and some of which may not yet be imagined.

Noncancer RAGs:

- If an update is initiated to Agency guidelines addressing developmental toxicity, it should be acknowledged that since the 1991 guidelines were issued, there has been a significant investment in research to show mechanisms by which maternal toxicity elicited at high doses can result in abnormal fetal development that is secondary to the maternal toxicity and does not represent a developmental toxicity hazard at non-maternally toxic exposure levels [e.g., Danielsson, BR. 2013. Methods Mol Biol., 947: 311-25.]

References:

ECHA (European Chemicals Agency). (2012). Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health. V2.1 November 2012: https://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258

WHO (World Health Organization) (2009). Environmental Health Criteria 240: Principles and Methods for the Risk Assessment of Chemicals in Food. Chapter 5: Dose-Response Assessment and Derivation of Health-Based Guidance Values. World Health Organization. http://www.inchem.org/documents/ehc/ehc/ehc240_chapter5.pdf

Dr. John Guckenheimer

Guidelines for Carcinogen and Non-Cancer Risk Assessment

My remarks reflect my expertise in studying non-linear dynamical systems, both in biological and physical systems.

1. Experimental measurement of the toxic or carcinogenic effects of substances at very low doses in humans is not feasible. The number of replicates required is several times 1/frequency. Still, the health effect of a substance that triggers a cancer with a frequency of 1/10000/year is 30000 cancers/year. Consequently, EPA must extrapolate estimates of dose responses to very low concentrations using the best science available. An unresolved question in these extrapolations is whether the dose-response has a lower threshold or whether an antagonist is toxic/carcinogenic at arbitrarily low doses. If there is no threshold, is the response approximately linear at some concentration. My opinion is that the answer to these questions depends upon the antagonist and should be determined case by case rather than upon a uniform standard.

2. Exposure to toxins/carcinogens is seldom uniform geographically. Since the federal government already invests in gathering disease statistics, I think the EPA should focus upon using this information to guide epidemiological research into the effects of toxins/carcinogens. There are numerous cases of dramatically higher incidence of very rare diseases in locations where substances have been released. Ameliorating high local release and exposure is a goal that is not subject to the same scientific uncertainty as the effects of very low doses.

3. High throughput, automated experimental methods have made tremendous advances in biology during the past two decades. The current risk assessment guidelines make little use of these techniques. The EPA and other federal agencies can engage in experimental programs to improve the scientific basis for risk assessment, for example by extending measurement of dose-response curves in in vitro systems.

4. Nonlinearity is ubiquitous in biological systems. Discrete events such as activation of a gene can trigger an entire cascade of events. Almost by definition, cancers are initiated in this way. At the same time, regulatory processes are observed to be embedded in hierarchies that maintain physiological behavior within acceptable limits. The immune system, systems for DNA repair, and muscular reflexes stimulated by a stumble or touching a hot object are a few examples. The point here is that statistical approaches to extrapolating dose-response curves are problematic. They do not provide strong scientific underpinnings for risk analysis far outside the regimes where we have data. More effort to identify molecular pathways and biological processes associated with responses to foreign substances is needed for better risk assessment.

Dr. Michael Honeycutt

SAB Consultation on Updating EPA Guidelines for Carcinogen and Non-Cancer Risk Assessment

The U.S. EPA is interested in seeking consultation from the members of the SAB regarding upcoming activities related to an update to the 2005 EPA Guidelines for Carcinogen Risk Assessment and guidelines for noncancer risk assessment. In considering areas for future emphasis, as well as with the work currently underway, EPA's Risk Assessment Forum[1] (RAF) is considering various topic areas including use of defaults, inhalation dosimetry and susceptible populations and lifestages.

The U.S. EPA, primarily through the RAF, maintains a series of guidelines, guidance documents and methodologies that describe the way the Agency conducts its human health and ecological risk assessments.[2] Some key examples include:

- Guidelines concerning: exposure assessment, carcinogen risk assessment, mixtures risk assessment, reproductive toxicity risk assessment, developmental toxicity risk assessment, neurotoxicity risk assessment, and ecological risk assessment;
- Supplemental guidance for mixtures risk assessment, and assessing susceptibility from early-life exposure to carcinogens;
- Guidance for benchmark dose modeling, and applying quantitative data to develop data-derived extrapolation factors;
- Frameworks for cumulative risk assessment and for ecological risk assessment; and
- Methods for and reviews of RfD/RfC processes.

A more detailed listing of some of the Agency guidelines, guidance documents, and technical panel reports that address human health risk assessment is attached.

The RAF is currently engaged in various activities,[3] ranging from drafting updates to longstanding guidelines documents to initial investigative steps on complex topic areas. Some current examples include an update to the Guidelines for Exposure Assessment,[4] activities related to the development of cumulative risk assessment guidance,[5] and consideration of new approaches to dose-response assessment that may be used in risk assessments to augment their usefulness for Agency decision making. Activities are also underway to address specific issues, such as additivity in mixtures risk assessment and consideration of several of the default uncertainty factors used in reference value methods.

---

[1] https://www.epa.gov/osa/basic-information-about-risk-assessment-guidelines-development

[2] A list of many of the human health assessment documents can be found at the following URL: https://www.epa.gov/risk/risk-assessment-guidelines#tab-1, and documents on ecological assessment can also be accessed from that webpage.

[3] https://www.epa.gov/osa/risk-assessment-current-projects

[4] https://www.epa.gov/risk/guidelines-human-exposure-assessment

[5] https://www.epa.gov/risk/framework-cumulative-risk-assessment

The EPA is interested in consultation with the SAB with these general perspectives in mind.

1. Are there particular aspects of existing Agency risk assessment guidance related to cancer and non-cancer endpoints that individual SAB members recommend be revised or augmented to incorporate updated scientific information (based on your experience in usage, new information, or scientific advances)?

I would like to see the 2007 Framework for Determining a Mutagenic Mode of Action for Carcinogenicity: Using EPA's 2005 Cancer Guidelines and Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (External Peer Review Draft). U.S. Environmental Protection Agency, September 2007. EPA 120/R-07/002-A finalized.

2. Are there important topic areas that are <u>not</u> fully represented in existing Agency risk assessment guidance related to cancer and non-cancer endpoints that SAB members recommend EPA address in guidance? What current information supports this recommendation?

I would like to see scientifically reasonable dose-response approaches for endogenous compounds used by EPA. Much data are in the published literature on this topic for compounds such as formaldehyde and ethylene oxide (e.g., published papers by Swenberg and Kirman & Hayes).

EPA should consider reasonability of their toxicity factors in the context of measured background concentrations. Ethylene oxide is an excellent, recent example. Background ambient air concentrations of ethylene oxide are higher than 10-4 excess risk using EPA's new unit risk factor. If background concentrations are unacceptably high, perhaps EPA should check to see if they have been unreasonably conservative in some aspect of their assessment.

As evident from the general questions above, EPA is seeking open-ended input and recommendations from SAB members and will consider all the input received to determine next steps for updating EPA guideline documents in a phased approach.

In the course of development and review of this charge to the SAB, the following additional questions were identified by Agency leadership to highlight for SAB members' input.

3. Are any key elements of hazard and dose-response analysis —including analytical limitations, heterogeneity, natural variability, and non-ambient exposures (i.e., endogenous or indoor exposures)—not adequately characterized in guidance?

See answer to #2 above. Also, EPA should focus on making their dose-response models predictive rather than conservative. Again, using ethylene oxide as an example, EPA conducted their cancer dose-response modeling using data from a NIOSH cohort. To verify that USEPA's final selected model assessment (i.e., upper bound on the linear two-piece spline model) properly fit the original data, it was used to predict the expected number of lymphoid cancers based on the same NIOSH individual exposure data as EPA used for modeling. *Whereas 53 lymphoid cancer deaths were observed* in this cohort of 17,530 workers, *EPA's selected dose-response model assessment predicted 141* (95% confidence interval (CI) of 108, 188) lymphoid cancer. Similarly, USEPA's final selected model assessment statistically significantly over-predicts lymphoid cancer deaths in every cumulative exposure quintile and indicates that statistically increased lymphoid cancer mortality should have occurred in every exposure quintile (including the lowest), when in fact this did not occur. However, the *upper bound of the Cox proportional hazard model predicted 59* (95% CI of 45, 78) lymphoid cancer deaths. Similarly, Cox proportional hazard model neither significantly over- or under-estimated lymphoid cancer for any exposure quintile. When using these two models to extrapolate down to environmental levels, they give results that differ by orders of magnitude. The linear two-piece spline model yields a 10-4 risk concentration of ethylene oxide that is well-below ambient background air concentrations, well-below endogenously-produced concentrations, and is, to date, unachievable by medical sterilization facilities. Consequently, model choice matters.

4. Current guidance discusses how to describe confidence in hazard conclusions (see, for example, the Cancer Guidelines, section 2.5 "Weight of Evidence Narrative" or Guidelines for Developmental Toxicity, Table 3) and discusses presentation of uncertainty in dose response (see for example the Cancer Guidelines, section 3.7 "Dose Response Characterization"). Examples of current practice can also be seen in various recent EPA assessments of specific chemicals or pollutants.

    i. Do SAB members have recommendations for better ways to characterize conclusions and uncertainties in a transparent way? Communicate how risk/hazard implications and conclusions would differ in the event that different yet still scientifically reasonable decisions could have been made at upstream decision points as warranted by the data on a case-by-case basis (e.g., low-dose extrapolation approach, UF values, human relevance).

    ii. Do SAB members have recommendations for better ways to analyze uncertainty, qualitatively or with quantitative analysis?

    iii. What role should statistical analysis play in this characterization?

iv. Are there methods SAB members recommend for better analyzing and communicating compounded uncertainty, including the use of uncertainty factors, in the hazard identification and dose response process?

5. The current Agency-wide guidance includes a guideline on cancer assessment, several guidelines for specific noncancer endpoints (e.g., reproductive toxicity, developmental toxicity, and mutagenicity), and guidances or reports on aspects of assessment common to many assessment endpoints (e.g., inhalation dosimetry, body-weight scaling of oral doses, benchmark dose technical guidance, risk characterization).

    i. Are there specific areas within these documents on which there have been advances in risk assessment that should be reflected in updated guidelines?

    ii. Are there areas of overlap or disagreement between these guidelines?

    iii. What issues or guideline documents would SAB members prioritize for update?

The 2007 draft *Framework for Determining a Mutagenic Mode of Action for Carcinogenicity* guidelines still have not been finalized. It seems a low scientific bar is often used for a finding of mutagenic MOA (e.g., genotoxicity in the absence of data on other possible MOAs), in apparent contrast with the draft guidelines.

6. Given current understanding of how risk assessments are used in decision making, are there considerations or changes to existing guidance with respect to problem formulation, assessment, data integration, and risk characterization that SAB members recommend EPA consider? Do SAB members have specific recommendations as to questions of importance to decision makers that are not being addressed by current risk assessments?

7. The purpose of some risk assessments (to quantify dose-response or reference values protective of the most sensitive receptors) and the purpose of the assessment of risk to inform benefits in an economic analysis (to create a predictive analysis for judging the effectiveness and feasibility of a regulatory action) can be quite different. As a result, the evaluation methods and key decision points can be quite different. For example, risk assessors may choose a benchmark dose at the high end (>95 percentile) of a distribution in order to define a level likely to avoid adverse effects, while economists may prefer risk assessors characterize the entire distribution or, at a minimum, use benchmark doses in the middle of the distribution, to inform benefit analyses.

    i. Do SAB members think risk assessments are providing the information needed by risk managers and those estimating the benefits of potential decisions? If not, what do SAB members recommend might make hazard and dose response analyses more useful to decision makers? Risk managers lack bottom line information on how risk/hazard conclusions could differ using alternative but

still reasonable upstream scientific decisions in the dose-response assessment; sometimes excess risk could be as low as zero (e.g., model slope not statistically different than 0) yet the risk manager assigns 100% confidence to the toxicity factor (e.g., if reviewed by SAB).

ii. Should EPA's guidance direct staff to consider as part of the development of the assessment the questions decision makers need answered in the end use of the assessment? This could confuse the areas of risk assessment versus risk management or policy, depending on the question.

With these questions guiding, but not limiting, your review, please provide input to help guide the Agency as it initiates an update to the 2005 EPA Guidelines for Carcinogen Risk Assessment and develops guidelines for noncancer risk assessment.

Dr. Sue Marty

Comments on "Updating EPA Cancer and Non-Cancer Risk Assessment Guidance" for the EPA Chartered SAB

Dr. Sue Marty, The Dow Chemical Company
June 26, 2019

Thank you to the EPA for this opportunity to provide comments on updating the Agency's risk assessment (RA) guidances.

Below are some high-level comments on potential areas of consideration for the EPA as the Agency updates both its cancer and non-cancer RA guidances. EPA has an opportunity to include new science and better approaches to achieve EPA's goals of human and environmental health protection.

To assist EPA in this effort, there are numerous documents that describe proposed changes to the risk assessment process. Of particular import is the National Research Council's Report on *Science and Decisions: Advancing Risk Assessment* (2009). In addition, comments have been previously submitted to the EPA from groups like the American Chemistry Council (e.g., improving the scientific quality of EPA risk assessments through peer review; September 6, 2011 letter from Dr. Richard Becker). EPA could consult these types of document for advice on how best to reform its RA guidance.

The EPA is interested in consultation with the SAB with these general perspectives in mind.

1. Are there particular aspects of existing Agency risk assessment guidance related to cancer and non-cancer endpoints that individual SAB members recommend be revised or augmented to incorporate updated scientific information (based on your experience in usage, new information, or scientific advances)?

A. EPA and its stakeholders would benefit from a uniform and even application of RA guidances across the Agency. EPA's Pesticide Office has good examples where it has applied the 2005 Cancer guidelines; however, other divisions of the Agency are resistant as evidenced by their reticence to characterize non-mutagenic carcinogens in a threshold manner (i.e., data on MOA and key events are always insufficient to support a threshold for a carcinogen). It would be beneficial if a consistent, state-of-the-art risk assessment approach to chemical risks could be practiced consistently across the EPA. When MOA/key events are deemed insufficient, EPA could provide a science plan for satisfying (or ruling out) the proposed MOA.

B. The 2005 Cancer Guidelines should include the most recent thinking on the MOA/Key Event framework and the OECD adverse outcome pathways (AOPs; ideally quantitative

with consideration of tipping points). Many advances in the biology of carcinogenesis have taken place that can greatly improve how chemical carcinogenesis is evaluated (e.g., differentiation of mutagenicity versus clastogenicity where cytotoxicity may be a significant component and impact the dose-response curve). Finally, EPA must address how NAMs, including the 10 IARC cellular responses (also referred to as the Key Characteristics of Cancer or KCC) fit into the overall assessment of the carcinogenic hazard profile and risk. NAMS are generally insufficient to stand-alone for justifying a hazard classification.

- Non-DNA reactive carcinogens can be managed using a threshold approach as protecting against the initial target organ toxicity can avert cancer. Thus, these types of compounds have thresholds and not require linear, no-threshold risk assessments.
- A positive outcome in a genotoxicity battery can lead to a conservative, linear no threshold (LNT) risk assessment for DNA reactive chemicals. However, quantitative risk assessments can be used to characterize risk at relevant human exposure levels with consideration of mutagenic MoA, toxicokinetics, dose-response relationships, experimental mutagenic point of departure (PoD), and appropriate assessment factors. As referenced above, there are numerous tools/frameworks to facilitate regulatory decision making (MOA-HRF; AOPs) that can include a weight of evidence approach to examine causality. Furthermore, protocols are being developed on the use QSAR modeling and non-animal alternative methods (NAMs) as components of a multi-tiered approach for hazard characterization (IATA, Integrated approach to testing and Assessment), including a recent paper on a tiered approach for genetic toxicity (Hasselgren et al., Regul Toxicol Pharmacol. 107:104403, 2019). The EPA may wish to consider whether there are aspects of these new approaches that can be leveraged in EPA programs.

C. EPA's guidance on bioaccumulation is dated and fails to account for biological processes such as metabolism and bioavailability since it is based largely on the K_{ow}.

2. Are there important topic areas that are <u>not</u> fully represented in existing Agency risk assessment guidance related to cancer and non-cancer endpoints that SAB members recommend EPA address in guidance? What current information supports this recommendation?

As evident from the general questions above, EPA is seeking open-ended input and recommendations from SAB members and will consider all the input received to determine next steps for updating EPA guideline documents in a phased approach.

A. New guidance on Integrated Approaches to Testing and Assessment (IATA) are required for both new chemical approvals or data needs for existing chemistries. The pending advent of NAMs as a vital cornerstone for managing both new and existing chemicals is an issue with processing PMNs under Section 5. IATA guidance, which can begin with QSARs and NAMs, must be a tiered framework that includes exposure information examined against conditions of use, and that can be quickly elevated to require more data to satisfying chemical safety assessments when needed.

B. The most recent thinking on exposure, including how to adopt IVIVE information necessary for interpreting in-vitro results arising from NAMs, is vital to the success of risk assessment. With respect to exposure, EPA should follow-up on updating its January 7, 2016 "Guidelines for Human exposure Assessment" including consideration of public comments (e.g., letter from Sarah Brozena of American Chemistry Council to Mr. Michael Broder on March 22, 2016).

- Guidance for working through IATAs should clearly lay out tiered approaches to both exposure and hazard assessment. EPA should provide this guidance for stakeholders and be prepared to apply such exposure-driven tiered approaches within the Program Offices.
- EPA should foster the development and sharing of exposure data for risk assessment. Examples of approaches to do this could include (but are not limited to) development of additional methods to generate exposure data, continued harmonization of exposure scenarios with OECD and other organizations, and development of databases of publicly available exposure data.
- Update the Jan. 2016 draft exposure guidelines to apply to amended TSCA.
- Guidance on other aspects of exposure assessment: a) approaches for conducting aggregate exposure and sentinel exposure assessments and when these should be used, b) identification of deficits in applying existing tools for occupational exposures as part of TSCA and developing new tools that better address EPA's needs (e.g., dermal exposures), c) assessing dermal exposure to mixtures, and d) exposures over the life cycle of a product.
- Expand methods that can be used by stakeholders to generate measured exposure information, such as emission rates from products - e.g., one example of methods to generate exposure data: https://cfpub.epa.gov/si/si_public_record_report.cfm?dirEntryId=340289&Lab=NRMRL

In the course of development and review of this charge to the SAB, the following additional questions were identified by Agency leadership to highlight for SAB members' input.

3. Are any key elements of hazard and dose-response analysis —including analytical limitations, heterogeneity, natural variability, and non-ambient exposures (i.e., endogenous or indoor exposures)—not adequately characterized in guidance?

C. Ideally, EPA should update all its RA guidances (i.e., 2005 Cancer Guidelines and its Developmental, Reproductive, and Neurotoxicity guidances as well as their exposure, probabilistic risk assessment, and uncertainty analyses guidance with respect to Bayesian methods, including toxicity factors in the uncertainty and probabilistic updates, and the pending advent of NAMs as serving a vital cornerstone for managing both new and existing chemicals). It is recognized that this constitutes a large and ambitious effort. The EPA should leverage their extensive existing guidances to the extent possible to form the foundations of their updates

- The "Framework for Human Health Risk Assessment to Inform Decision Making" could be a reasonable platform to begin updating their risk assessment guidance. All of the cited EPA documents supporting this 2014 framework are potential candidates for updates and improvements.
- This updated guidance should be located in one area of EPA's website and not scattered among EPA's program offices.
- EPA laid out many issues with their Risk Assessment approach in a March 2004 Staff paper from the Office of the Science Advisor entitled "An Examination of EPA Risk Assessment Principles and Practices." EPA could revisit this document and explore how well it has done to address criticisms of its risk assessment approach and use this to identify remaining areas for updating their RA guidance.
- EPA's Risk Assessment Guidance for Superfund (RAGS) documents are 20 to almost 30 years old. Input from stakeholder practitioners of environmental risk assessments would be of high value to understanding where improvements can be made to these important documents.
- EPA's 2014 probabilistic RA white paper should be improved and incorporated into the RAGS guidance document, including more examples of how PRA can be applied to exposure pathways (e.g., soil ingestion, fish exposure pathways) as well as being harmonized with EPA's Exposure Factors Handbook.
- Probabilistic guidance and uncertainty analyses guidance must be developed for generating toxicity values. For example, NAS recommendations on PRA and treatment of uncertainty should be included in EPA guidance.
- EPA's December 5th 2003 "Human Health Toxicity Values in Superfund Risk Assessments" defaults to IRIS values as the first tier toxicity values. This illustrates a well-known issue with IRIS values being applied while creating controversy. Hence, IRIS values should not be the only default, first tier source of toxicity values for use by the Agency. For example, LCSA-generated toxicity values that are likely to be derived with more robust, defendable, and transparent methods may be an improvement over the current IRIS values. This Superfund

memo needs to be revised to permit non-IRIS toxicity values that are transparent, science based, site-specific and an improvement over the controversial IRIS values.

- EPA should follow up and put into guidance what they began with the Risk Assessment Forum's December 2002 "A review of the reference dose and reference concentration processes". This report can be updated to include new data and thinking around MOA, Key Events, dose-response modeling, PRA and uncertainty to take advantage of this information.

4. Current guidance discusses how to describe confidence in hazard conclusions (see, for example, the Cancer Guidelines, section 2.5 "Weight of Evidence Narrative" or Guidelines for Developmental Toxicity, Table 3) and discusses presentation of uncertainty in dose response (see for example the Cancer Guidelines, section 3.7 "Dose Response Characterization"). Examples of current practice can also be seen in various recent EPA assessments of specific chemicals or pollutants.

    i. Do SAB members have recommendations for better ways to characterize conclusions and uncertainties in a transparent way?

    ii. Do SAB members have recommendations for better ways to analyze uncertainty, qualitatively or with quantitative analysis?

    iii. What role should statistical analysis play in this characterization?

    iv. Are there methods SAB members recommend for better analyzing and communicating compounded uncertainty, including the use of uncertainty factors, in the hazard identification and dose response process?

5. The current Agency-wide guidance includes a guideline on cancer assessment, several guidelines for specific noncancer endpoints (e.g., reproductive toxicity, developmental toxicity, and mutagenicity), and guidances or reports on aspects of assessment common to many assessment endpoints (e.g., inhalation dosimetry, body-weight scaling of oral doses, benchmark dose technical guidance, risk characterization).

    i. Are there specific areas within these documents on which there have been advances in risk assessment that should be reflected in updated guidelines?

    ii. Are there areas of overlap or disagreement between these guidelines?

    iii. What issues or guideline documents would SAB members prioritize for update?

6. Given current understanding of how risk assessments are used in decision making, are there considerations or changes to existing guidance with respect to problem formulation,

assessment, data integration, and risk characterization that SAB members recommend EPA consider? Do SAB members have specific recommendations as to questions of importance to decision makers that are not being addressed by current risk assessments?

A. Systematic review - All guidance should have the same level of systematic review, evidence integration, and cost-benefit evaluation. Satisfying data quality questions should be a high priority RA requirement addressed in a transparent manner with information that protects patient/study subject confidentiality needs and confidential business information while allowing stakeholders to assess their validity and correct interpretation.

- For example, EPA published their 3rd Edition of their Peer Review Handbook in 2006 but there is little information on how EPA's peer reviews reach conclusions, such as public disclosure of positions taken by EPA scientists on influential risk assessment generated by the EPA. For example, on pages 82-83, in the handbook the following is stated: "*The validity and objectivity of the comments should be evaluated. Analyses may include consultation with other experts and staff within the Office and Agency. Adequate documentation is needed to show that comments are accepted or rejected. The documentation can be brief, but should address the legitimate, valid comments, whether accepted for incorporation in the final work product or not. The peer review record should contain a document describing the Agency's response to the peer review comments. The Agency's response to the peer review report for highly influential scientific assessments should be posted on the Science Inventory."* While it is recognized that some of this internal information being made public could limit honest discussion within the EPA, it would be helpful to understand the uncertainty EPA faces when finalizing decision regarding hazard and risk.

7. The purpose of some risk assessments (to quantify dose-response or reference values protective of the most sensitive receptors) and the purpose of the assessment of risk to inform benefits in an economic analysis (to create a predictive analysis for judging the effectiveness and feasibility of a regulatory action) can be quite different. As a result, the evaluation methods and key decision points can be quite different. For example, risk assessors may choose a benchmark dose at the high end (>95 percentile) of a distribution in order to define a level likely to avoid adverse effects, while economists may prefer risk assessors characterize the entire distribution or, at a minimum, use benchmark doses in the middle of the distribution, to inform benefit analyses.

    i. Do SAB members think risk assessments are providing the information needed by risk managers and those estimating the benefits of potential decisions? If not, what do SAB members recommend might make hazard and dose response analyses more useful to decision makers?

ii. Should EPA's guidance direct staff to consider as part of the development of the assessment the questions decision makers need answered in the end use of the assessment?

With these questions guiding, but not limiting, your review, please provide input to help guide the Agency as it initiates an update to the 2005 EPA Guidelines for Carcinogen Risk Assessment and develops guidelines for noncancer risk assessment.

Dr. Thomas Parkerton

Response to SAB Consultation on Updating Cancer and Non-Cancer Guidelines

Question 6

Given current understanding of how risk assessments are used in decision making, are there considerations or changes to existing guidance with respect to problem formulation, assessment, data integration, and risk characterization that SAB members recommend EPA consider? Do SAB members have specific recommendations as to questions of importance to decision makers that are not being addressed by current risk assessments?

Response

Risk assessments conducted by EPA typically focus on key study selection, the subsequent dose response curve, and potential exposure to the population. Recent risk assessments could be improved through better data integration across information streams including use of the multiple frameworks and software available to aid this process. One of the developments in cancer risk assessment that has not been consistently applied to non-cancer risk assessments is the identification of mode(s) of action (MOA) and adverse outcome pathways (AOPs). Identifying and developing MOAs/AOPs is critical to understanding threshold of effect and relevance in a risk assessment.

There are two sources available to the agency to help develop an AOP (and by extension, a chemical specific MOA. First, the Organisation for Economic Co-operation and Development (OECD) has publicly available tools and guidance on the development and dissemination of AOPs.[11] The agency should consider adopting principles provided in this guidance, including external peer review, and extend them to the development of MOA. Once the AOP/MOA is reviewed and accepted the results should be posted publicly to foster consistent use by risk assessors within and outside EPA.

Second, the Human Toxicology Project Consortium (HTPC) provides training on the development and use of AOPs.[12] The HTPC is a "group of stakeholders currently drawn from the corporate and public interest communities that share the objective of accelerating implementation of a biological pathway-based approach to toxicology as described in the National Research Council's 2007 report on "Toxicity Testing in the 21st Century." The use of a common training course will help to standardize the language in this area and facilitate dialogue in the development and review of proposed AOPs between stakeholders.

[11] https://www.oecd.org/chemicalsafety/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm

[12] https://humantoxicologyproject.org/about-pathways-2/aop-online-course/

The practical application of AOPs/MOAs in risk assessment are critical to understanding the underlying processes that lead to adverse effects. Like other aspects of risk assessment (e.g. problem formulation, hazard assessment, etc), the development and use of an AOP/MOA should be as clear and transparent as possible. The agency should develop an AOP/MOA(s) that details the pathway (i.e. the series of molecular initiating events or MIE) leading directly to the adverse outcome that is the subject of the risk assessment. It should also be noted if multiple potential AOP/MOA are implicated. The agency should clearly note data gaps (e.g. missing MIE in the proposed pathway), what data supports each MIE in the AOP, any contradictory information available, and how confident the assessor is in each MIE and in the AOP overall. If exposure is a critical component to activating a MIE (e.g. threshold), the agency should denote that fact and put it in context of likely exposure (i.e. can this pathway be activated at expected exposures?). Finally, the agency should conduct a quantitative uncertainty analysis, or if there is insufficient data, the agency should discuss overall uncertainty in a qualitative manner. Understanding the uncertainty, especially uncertainty around thresholds and human relevance, is critical to risk managers who are responsible for protecting human health.

Dr. Kenneth Portier

Please provide input to help guide the Agency as it initiates an update to the 2005 EPA Guidelines for Carcinogen Risk Assessment and develops guidelines for noncancer risk assessment. EPA is seeking open-ended input and recommendations from SAB members on the following questions:

1) Are there particular aspects of existing Agency risk assessment guidance related to cancer and non-cancer endpoints that individual SAB members recommend be revised or augmented to incorporate updated scientific information (based on your experience in usage, new information, or scientific advances)?

   - **The information in U.S. EPA. 1988. Recommendations for and Documentation of Biological Values for Use in Risk Assessment [EPA 600/6-87/008, Feb 1988] needs review and updating.** The biological variables quantified in this document, namely lifespan, body weight, inhalation rate, food consumption, and water consumption for the most common test animals are critical for conversion of exposure data to dose, for modeling, and, for eventual extrapolation to humans (e.g., in support of cross-species scaling procedures, section 3.1.3 in U.S. EPA. 2005. Guidelines for Carcinogen Risk Assessment [EPA/630/P-03/001F, Mar 2005]). Numerous Agencies have established and maintained databases of these information collected from control animals across multiple studies and over time, and analysis of these data have been published. The updating of these data should also include a discussion on how these biological variables may vary over time and test animal populations evolve and adapt to test animal rearing environments.

2) Are there important topic areas that are not fully represented in existing Agency risk assessment guidance related to cancer and non-cancer endpoints that SAB members recommend EPA address in guidance? What current information supports this recommendation?

   - **What constitutes the minimal data needed to characterize the physical and chemical characteristics of the substance for which a risk assessment is being attempted?** With the new TSCA legislation, a larger class of substances are subject to risk assessment. These chemicals have greater variability in physical and chemical properties than those typically considered by past risk assessments (i.e. are not pesticides, medicines, toxic minerals). Many of these substances are chemicals for which almost no information is available on even the most basic of chemical properties, such as molecular formula, molecular weight, flash point, boiling point, melting point, density, vapor pressure, solubility in octanal, solubility in water, Log K_{ow} , and Henry's Law Constant. Standard methods for measuring these values and/or models or relationships for predicting these values should be specified.

- **What constitutes minimal exposure data needed to initiate a risk assessment for a substance not previously assessed?** Again, TSCA legislation opens up the type and number of chemicals that will require assessment, many of these chemicals having potential exposures not previously identified and/or measured. Assuming good information on physical and chemical characteristics, what models can be used to predict exposure in occupational and/or public settings. What amount of actual measurement of exposure levels is required to confirm predicted exposure levels?

- **How will reliance on alternative test methods and strategies designed to reduce vertebrate animal testing impact the quality and uncertainties in carcinogenic and non-cancer risk assessments?** New approach methodologies (NAMs), including in vitro methods, in chemico methods, receptor activation assays, and synthetic tissue assays are being used along with QSARS and read-across to inform hazard identification, fate characterization, and exposure assessment. EPA published a list of NAMs in June of 2018 (https://www.epa.gov/sites/production/files/2018-06/documents/alternative_testing_nams_list_june22_2018.pdf). Current carcinogenic and non-cancer risk assessment guidance needs to discuss how NAMs will be used as primary data sources in future assessments. EPA also needs to provide guidance on associated uncertainties related to use of these methods to inform adverse health outcome likelihood

- **Considering the increasing use of NAMs, what constitutes a minimal set of NAM results needed to establish the potential for cancer and/or non-cancer adverse health outcomes in a new and unassessed substance?**

3) Are any key elements of hazard and dose-response analysis —including analytical limitations, heterogeneity, natural variability, and non-ambient exposures (i.e., endogenous or indoor exposures)—not adequately characterized in guidance?

- Quote from the Cancer Guidelines, page 3-15 – "In cases where curve-fitting models are used because the data are not adequate to support a toxicodynamic model, there generally would be no biological basis to choose among alternative curve-fitting models." Statistical methodology is suggesting that a best practice in this situation would be to use model averaging (see Wheeler M.W and A. J Bailer, Model Averaging Software for Dichotomous Dose Response Risk Estimation, Journal of Statistical Software, 26(5), June 2008.) The Benchmark Dose Guidance mentions model averaging as an option, but provides very little guidance on when and how to use. **Better guidance is needed on when to use and the advantages of using model averaging in this situation**.

- From the Cancer Guidelines, page 3-15 – "*For incidence data* on either tumors or a precursor …" "Additional judgments and perhaps alternative analyses are used when the procedure fails to yield reliable results. For example, when a model's fit is poor, the highest dose is often omitted in cases where it is judged that the highest dose reflects

competing toxicity that is more relevant at high doses than at lower doses." From the Cancer Guidelines, page A-3 and A-4 – "*In general, while effects seen at the highest dose tested are assumed to be appropriate for assessment, it is necessary that the experimental conditions be scrutinized."* **There is a need for better communication of current guidance on handling this specific situation when empirically modeling animal dose response data**. Specifically, in recent scientific reviews, panelists disagreed over how to handle doses that exceed 1000 mg/kg BW, the default level for maximum tolerated dose in rodent experiments. The language in the Cancer Guidelines suggests the decision to include or exclude doses above 1000 mg/kg BW depends on an assessment of whether there is competing toxicity at these doses. But the BMD Technical Guidance, page 35 uses more of a statistical argument and recommends "In the absence of a mechanistic understanding of the biological response to a toxic agent, data from exposures that give responses much more extreme than the BMR may not tell us very much about the shape of the response in the region of the BMR. Such exposures, however, may very well have a strong effect on the shape of the fitted model in the region of the BMD, such as when the highest doses demonstrate a maximum response." And, "Dropping dose groups should be carefully undertaken and conducted, and transparently presented. (Also see Section 2.4.) A clear justification for dropping dose groups should always be provided." **Expert advice should be solicited on what responses demonstrate that effects at the highest dose levels are the result of excessive toxicity rather than carcinogenicity, that is, when is it appropriate to include these highest doses in the dose response estimation step in a risk assessment.**

4) Current guidance discusses how to describe confidence in hazard conclusions (see, for example, the Cancer Guidelines, section 2.5 "Weight of Evidence Narrative" or Guidelines for Developmental Toxicity, Table 3) and discusses presentation of uncertainty in dose response (see for example the Cancer Guidelines, section 3.7 "Dose Response Characterization"). Examples of current practice can also be seen in various recent EPA assessments of specific chemicals or pollutants.

    i. Do SAB members have recommendations for better ways to characterize conclusions and uncertainties in a transparent way?

- The weight of evidence descriptors, "suggestive", "likely" or "inadequate", used by EPA are intended "to represent points along a continuum of evidence" for carcinogenic action (Cancer Guidelines, page 2-15). My experience suggests that scientists participating in risk assessment reviews seem to prefer (*that is, the discussion follows naturally*) to first characterize the available data into the dichotomy of "adequate" or "inadequate". If the information is assessed as "adequate", discussions on the carcinogenic potential of the substance under review seek to establish confidence along a continuum from "unlikely" to "certain". **EPA should explore with the scientific community whether this kind of phased "scoring" approach would be easier to accomplish than forcing decision among the current descriptors.** Even without changing the descriptors, the Cancer

Guidelines should acknowledge this natural affinity to approach the choice of evidence descriptors as two separate decisions. [*I acknowledge that this would be a departure from current practice which has its roots more in legislative mandate than in effectively assessing and reporting weight of evidence*.]

- The same argument above can be made for the potential for non-cancer adverse health outcomes. **EPA should explore with the scientific community whether this kind of phased "scoring" approach should also be used for non-cancer health outcome conclusions.**

ii) Do SAB members have recommendations for better ways to analyze uncertainty, qualitatively or with quantitative analysis?

iii) What role should statistical analysis play in this characterization?

- To the extent that weight of evidence discussion is envisioned as a free-form narrative or summary rather than a point-by-point recap of findings, **there is low utility in adding associated probabilistic statements to the summaries**.

iv) Are there methods SAB members recommend for better analyzing and communicating compounded uncertainty, including the use of uncertainty factors, in the hazard identification and dose response process?

- **A clear terminology for all uncertainty factors should be provided and used consistently among all guidance.** In a recent review of some PBPK-PD models for EPA the need for clear terminology was identified. This panel developed a document, copies in **Appendix A** below, in an attempt to clarify these issues.

5) The current Agency-wide guidance includes a guideline on cancer assessment, several guidelines for specific noncancer endpoints (e.g., reproductive toxicity, developmental toxicity, and mutagenicity), and guidance or reports on aspects of assessment common to many assessment endpoints (e.g., inhalation dosimetry, body-weight scaling of oral doses, benchmark dose technical guidance, risk characterization).

i) Are there specific areas within these documents on which there have been advances in risk assessment that should be reflected in updated guidelines?

- NAMs ?

ii) Are there areas of overlap or disagreement between these guidelines?

- I am certain there are areas of overlap among the different guideline documents. I am less certain that this is a bad situation, as long as the overlapping information is consistent among documents. The list of guidance documents appended to this list of questions illustrates how different aspects of the assessment for cancer and non-cancer health outcomes (and economic impacts?) have been addressed at different times and often with quite different peer review. As EPA updates the guidelines for carcinogen and non-cancer risk assessments, some consideration should be given on how the whole body of guidance can better be communicated. **At a minimum, a "readers guide to carcinogen and non-cancer risk assessment guidance at EPA" should be developed and published.**

  iii) What issues or guideline documents would SAB members prioritize for update?

- Based on recent experiences, **I would recommend prioritization of the inhalation dosimetry assessment endpoint guidance, followed by better guidance on estimating dermal exposures**.

6) Given current understanding of how risk assessments are used in decision making, are there considerations or changes to existing guidance with respect to problem formulation, assessment, data integration, and risk characterization that SAB members recommend EPA consider? Do SAB members have specific recommendations as to questions of importance to decision makers that are not being addressed by current risk assessments?

- **Many risk assessment documents could do a much better job of summarizing how available (dose response and exposure) data are processed, analyzed and integrated to arrive at the final risk evidence descriptor and BMR.** In particular, a decision tree diagram and/or a logic model diagram is needed to summarize how processing of information and intermediate decisions are made in a systematic and logical fashion that lead to the final conclusion on risk.

7) The purpose of some risk assessments (to quantify dose-response or reference values protective of the most sensitive receptors) and the purpose of the assessment of risk to inform benefits in an economic analysis (to create a predictive analysis for judging the effectiveness and feasibility of a regulatory action) can be quite different. As a result, the evaluation methods and key decision points can be quite different. For example, risk assessors may choose a benchmark dose at the high end (>95 percentile) of a distribution in order to define a level likely to avoid adverse effects, while economists may prefer risk assessors characterize the entire distribution or, at a minimum, use benchmark doses in the middle of the distribution, to inform benefit analyses.

   i) Do SAB members think risk assessments are providing the information needed by risk managers and those estimating the benefits of potential decisions? If not, what do SAB members recommend might make hazard and dose response analyses more useful to decision makers?

- **Yes – I do think that risk assessments are providing needed information, and we need to encourage more substances to undergo risk assessment rather than less.**

- **EPA guidance on hazard assessment should more clearly indicate when available information/data is "adequate" versus "inadequate" for hazard assessment**. When information is deemed "adequate" for dose response modeling and for estimation of exposure, a more nuanced communication of risk or more appropriately our confidence in the estimate of risk is needed (see comments to question 4(i) above.)

ii) Should EPA's guidance direct staff to consider as part of the development of the assessment the questions decision makers need answered in the end use of the assessment?

- **Yes – I do feel that any risk assessment, for human health, for environmental health, and/or for economic impact, should clearly identify the KEY questions to which decision makers need answers.** A logic model approach makes this need clear since this statement is critical to the logical flow of information and intermediate decisions in the whole risk assessment process. (see for example how the EPA Mid-Atlantic Region makes use of logic models: https://www.epa.gov/risk/mira-logic-model)

Appendix A: EPA Uncertainty Factors.

FQPA 10X Safety Factor provision: FQPA directs that EPA ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residue when setting tolerances. In the case of "threshold effects," FQPA requires "an additional tenfold margin of safety for the pesticide chemical residue, and other sources of exposure shall be applied for infants and children to take into account the potential pre- and post-natal toxicity and completeness of the data with respect to **exposure** and **toxicity** to infants and children....[and that] the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children."

Standard default uncertainty factors include a 10X factor used to account for:

- Experimental animal-to-human differences - interspecies-**UF_A** – (3X, simplified from square root of 10).

- Interhuman variation - intraspecies differences-**UF_H** (3X).

- These UFs are applied to a Point-of-Departure (POD) BEFORE a decision is made with respect to the appropriate magnitude of the FQPA safety factor

Other traditional default uncertainty factors are also applied to a POD prior to the FQPA SF decision to account for:

- Database deficiency factor - an uncertainty factor applied when it is necessary to extrapolate from sub-chronic or other shorter-term data to chronic end points (**UF_S** – 10X) if deriving a chronic RfD.

- Extrapolation from the NOAEL to LOAEL (**UF_L –** 10X) if no appropriate NOAEL can be identified in the toxicology database but there is a reasonable LOAEL.

- Database uncertainty factor (**UF_{Db}** – 3X to 100X) - intended to account for the absence of sufficient toxicological data from which to derive reference values (which are now codified by FQPA, see next paragraph).

Note that the choice of the appropriate magnitude of the FQPA Safety Factor is informed not only by the completeness of information with regard to toxicity, but also by the completeness of the database with regard to exposure. This is in contrast to the standard and traditional uncertainty factors described above which apply only to the robustness of the toxicity database. The choice of the appropriate FQPA safety factor also is informed by whether or not there are residual concerns in the exposure assessment or for increased susceptibility in infants and children. This latter point addresses the requirement to "take into account the potential pre- and post-natal toxicity." If this aspect of derivation of a reference value (*e.g.*, an RfD) in a hazard assessment is not accomplished with the application of any of the standard or traditional uncertainty factors, then some portion of the FQPA safety factor must be retained to cover it.

The term **"additional" FQPA factor**s is sometimes used referring to all FQPA factors - including traditional uncertainty factors listed above and any special FQPA factors – ***all factors other than the inter- and intraspecies uncertainty factors***.

In an attempt to minimize confusion and communicate the FQPA safety factor decision process more transparently, OPP developed a new term: the "Population Adjusted Dose" or "PAD" to present the results of the before and after application of an FQPA safety factor. The "before" is the RfD. The "after" is the PAD. As an example, if the FQPA safety factor is 10X, then the PAD is the RfD divided by 10. If the FQPA safety factor is 3X, then the PAD is the RfD divided by 3. And, if the FQPA safety factor is reduced to 1X, then the RfD and PAD are the same. The PAD applies to infants and children. The RfD applies to the rest of the population.

And lastly, double-counting is not allowed. This means that if one of the other default uncertainty factors (*i.e.*, UF_S, UF_L, UF_{Db}) has been incorporated into the derivation of an RfD, it cannot be used again in determining the final magnitude of the FQPA safety factor when calculating the PAD. Furthermore, if the RfD has been calculated based upon dose-response data for effects observed in a subpopulation representative of infants and children, the final magnitude

of the FQPA safety factor used to derive the PAD cannot include consideration of this aspect ("taking into account the potential pre- and post-natal toxicity" and "residual concern for increased susceptibility"), since this element was already considered when calculating the RfD. Examples of data in the latter example would be those from ≤ PND 21 (pre-weaned) rats in the developmental neurotoxicity test or in the F1 or F2 generation of a multi-generation reproduction and fertility study or in GD 20-21 offspring in the developmental toxicity study.

References:

- DETERMINATION OF THE APPROPRIATE FQPA SAFETY FACTOR(S) IN TOLERANCE ASSESSMENT. EPA OPP, February 28, 2002.

- CONSIDERATION OF THE FQPA SAFETY FACTOR AND OTHER UNCERTAINTY FACTORS IN CUMULATIVE RISK ASSESSMENT OF CHEMICALS SHARING A COMMON MECHANISM OF TOXICITY, EPA OPP, February 28, 2002.

Finally, there is **model uncertainty** – This is less a factor than a discussion about whether we have the "right" model – sometimes applied to choice of dose response model, or, as in our current discussion, the structure of the PBPK/PD model proposed for use in animal-to-human extrapolation, and/or in assessing population variability within exposed humans.

Dr. Brant Ulsh

SAB Consultation on Updating EPA Guidelines
for Carcinogen and Non-Cancer Risk Assessment
Comments from Brant Ulsh, Ph.D., CHP

Several questions were presented to the Science Advisory Board by the USEPA relating to the Agency's risk assessment guidelines. My input largely focuses on two of these questions (identified below) and specifically on assessing the effects of low-dose radiation, upon which I have expertise.

Agency Question: Are there particular aspects of existing Agency risk assessment guidance related to cancer and non-cancer endpoints that individual SAB members recommend be revised or augmented to incorporate updated scientific information (based on your experience in usage, new information, or scientific advances)?

Comment: *Agency practices for assessing risk from radiation doses at or below background is far outside the scientific mainstream and does not appropriately account for uncertainty in dose-response.*

The USEPA Superfund program guidance (USEPA 2014) asserts that Applicable or Relevant and Appropriate Requirements (ARARs) of 15 mrem are not protective, and should be lowered to 12 millirem – a difference of three mrem. According to (USEPA 2014):

> "This new guidance … changes the Superfund recommendation on what is considered a protective dose-based ARAR from 15 to 12 millirem per year (mrem/yr). The new recommendation of 12 mrem/yr regarding what dose-based ARARs are protective is based on using an updated risk assessment to achieve the same 3×10^{-4} cancer risk as the previous recommendation using 15 mrem/yr".

and further,

> "ARARs that are greater than 12 mrem/yr effective dose equivalent (EDE) are generally not considered sufficiently protective for developing cleanup levels under CERCLA at remedial sites".

USEPA's statements above imply that there is some tangible risk of from the three millirem difference between the old (15 mrem/yr) and new (12 mrem/yr) ARAR, and consequently a benefit from a three mrem reduction. There is no evidence that a dose of three mrem - which is on the order of 100 times less than natural background in the US - presents any human health or environmental risk.

The Agency's latest guidance on applying radiation cancer risk models to the US population (USEPA 2011) has a stated purpose of, "This document presents new U.S. Environmental Protection Agency (EPA) estimates of cancer incidence and mortality risks due to low doses of ionizing radiation for the U.S. population, as well as their scientific basis". The guidance also states,

> "…the average individual receives about 1 mGy each year from low-LET natural background radiation, or about 75 mGy, lifetime. **The average cancer incidence and**

mortality risks from natural background radiation are then estimated to be about 0.87% and 0.44%, respectively". (emphasis added)

But calculating cancer risks from radiation doses comparable to or less than background is contrary to the advice of several advisory and professional groups. For example, as summarized in (Cardarelli and Ulsh 2018):

- "Collective effective dose is an instrument for optimisation, for comparing radiological technologies and protection procedures. **Collective effective dose** is not intended as a tool for epidemiological studies, and it **is inappropriate to use it in risk projections**. This is because the assumptions implicit in the calculation of collective effective dose (*e.g.,* when applying the LNT model) conceal large biological and statistical uncertainties. Specifically, **the computation of cancer deaths based on collective effective doses involving trivial exposures to large populations is not reasonable and should be avoided. Such computations based on collective effective dose were never intended, are biologically and statistically very uncertain, presuppose a number of caveats that tend not to be repeated when estimates are quoted out of context, and are an incorrect use of this protection quantity.**" (ICRP 2007)(emphasis added)

- "United Nations Scientific Committee on the Effects of ionizing Radiation (UNSCEAR) has stated, in general, increases in the incidence of health effects in populations cannot be attributed reliably to chronic exposure to radiation at levels that are typical of the global average background levels of radiation … **the Scientific Committee does not recommend multiplying very low doses by large numbers of individuals to estimate numbers of radiation-induced health effects within a population exposed to incremental doses at levels equivalent to or lower than natural background levels**. (UNSCEAR 2012)(emphasis added)

- "As a scientific organization of professionals who specialize in radiation safety, the HPS believes the **EPA's reliance on the LNT model, especially at very low doses and dose rates, is inappropriate and can exaggerate the risk. Of most concern to the HPS is the EPA's extrapolation of the LNT model to calculate collective dose and the use of collective dose as a metric for risk**". (Kirner 2017, Ring et al. 2017)(emphasis added) "**The Health Physics Society advises against estimating health risks to people from exposures to ionizing radiation that are near or less than natural background levels, because statistical uncertainties at these low levels are great**. The average annual equivalent dose from natural background radiation in the United States is about three mSv. A person might accumulate an equivalent dose from natural background radiation of about 50 mSv in the first 17 years of life and about 250 mSv during an average 80-year lifetime. Substantial and convincing scientific data show evidence of health effects following high-dose exposures (many multiples of natural background). However, below levels of about 100 mSv above background from all sources combined, the observed radiation effects in people are not statistically different from zero". (HPS 2016)(emphasis added)

Comment: *The Agency inaccurately claims there is a consensus supporting their application of the LNT model to estimate low-dose radiation risks.*

In spite of the advice from several professional and advisory groups contradicting the Agency's policies on using the LNT model to estimate low-dose radiation risks discussed above, USEPA has inaccurately claimed a "…continuing wide consensus on the use of LNT for regulatory purposes as well as the increasing scientific confirmation of the LNT model" (Edwards 2015). Ignoring this advice, the Agency notes the repeated endorsement of the LNT model by the National Council on Radiation Protection and Measurements (NCRP) and the US National Academy of Sciences (USEPA 2018b). (Puskin 2009) asserted:

> "To assist the Agency in its assessment of the health risks from ionizing radiation, EPA has often helped sponsor reports from these organizations, particularly from the NAS 'BEIR Committees'. The risk models and supporting evidence is then reviewed by EPA's Scientific Advisory Board of outside distinguished scientists before becoming final and being implemented. Thus, EPA's estimates of risk to low dose radiation reflect a broad scientific consensus".

While the Agency claims independent review of its low-dose risk assessment practices by the National Academy of Sciences' BEIR Committees, both (USEPA 2011) and (Puskin 2009) note USEPA sponsorship of these committees, which raises the question of whether or not these reviews are truly independent.

The USEPA has claimed that its application of the LNT, "…is the position adopted by the USEPA after review by the Agency's Scientific Advisory Board, an independent group of distinguished outside scientists" (Edwards 2015) however, the SAB has not considered the topic of estimating low-dose radiation risk in several years, and current leadership of the Office of Radiation and Indoor Air (ORIA) has expressed the view that Agency reliance on the LNT model is set in stone, and they would never support a review of this policy. Accordingly, the Agency has not tasked the Radiation Advisory Committee with any work since it last met on November 10, 2015 (Wong 2019b), and there is no Committee work planned for the remainder of calendar year 2019 (Wong 2019a).

It is noteworthy that almost 25 years ago, the SAB considered the topic of risk from low radiation doses (Matanoski et al. 1995), and concluded:

> "Significant improvements in the detection limits of analytical techniques … could lead to public demands for stricter regulatory limits in radiation exposures (*e.g.,* radon or plutonium in ground water) as long as stated public policy is that there is no threshold for radiation health hazards. In fact, **laws such as the Delaney Clause of the Food and Drug Act, and the Safe Drinking Water Act, require that carcinogen concentrations in food and drinking water be as close to zero as is practically achievable**. Because radiation is a carcinogen, **indiscriminate application of this policy has led to many controversies** such as the limits for radon in drinking water." (emphasis added)
>
> "**The shape of the dose-response relationship will still be an issue, particularly as to whether there is a real or perceived threshold of exposure below which effects are for all intents and purposes non-existent; whether the dose-response relationship is essentially linear at low doses or departs from linearity at higher doses**; whether saturation of response occurs below 100% incidence; and whether dose rate and type of

radiation influence only the magnitude of the response or also the shape of the dose-response relationship". (emphasis added)

While (USEPA 2011) highlights the general opinion that, "in the cover letter to Administrator Jackson, Dr. Deborah Swackhamer, Chair, SAB, and Dr. Bernd Kahn, Chair, RAC, wrote that the 2008 draft was "impressively researched [and] based on carefully considered concepts" and "scientifically defensible and appropriate", it neglects to acknowledge that the RAC advised (Morgan and Lipoti 2008):

> "…**a major issue with the choice of the LNT model is whether it is appropriately applied at low doses…while the RAC endorses USEPA's use of the LNT model**, the Agency is advised to continue to monitor the science of the biological mechanisms underlying cancer induction at low doses of ionizing radiation and of their influence on the biophysical models used to estimate the cancer risk in this dose range. At radiation exposures in the range of natural background, it is difficult to distinguish radiation-induced changes in risk from the baseline. Thus, **as a cautionary note, the RAC recommends that the USEPA discuss potential problems associated with the use of LNT dose response model risk estimates in very low dose settings. Currently at these low doses, statistically significant differences between the cancer rates among 'exposed' (defined study populations) and 'non-exposed' (defined comparison populations) are not observed.** As BEIR VII acknowledges, the epidemiological data below 100 mSv (0.1 Sv) are not sufficient by themselves for risk estimation, and considerable cellular and animal data suggest complexities beyond the application of a simplified DNA damage model which historically has been used as support for an LNT dose-response model". (emphasis added)

This caution offered by the RAC in 2008, which was not acknowledged or addressed in the Agency's responses (Johnson 2008, Jackson 2010), has proven prescient given the developments described above.

In spite of these cautions and caveats, the Agency continues to claim that there is consensus for their application of LNT to estimate risks from low radiation doses and set cleanup standards. In fact there is wide disagreement on application of the LNT model among expert advisory bodies, professional societies, and individual scientists (Cardarelli and Ulsh 2018). As concluded by the USGAO nearly 20 years ago (GAO 2000),

> "U.S. regulatory standards to protect the public from the potential health risks of nuclear radiation lack a conclusively verified scientific basis, according to a consensus of recognized scientists. In the absence of more conclusive data, scientists have assumed that even the smallest radiation exposure carries a risk. This assumption (called the "linear, no-threshold hypothesis" or model) extrapolates better-verified high-level radiation effects to lower, less well-verified levels and is the preferred theoretical basis for the current U.S. radiation standards. However, this assumption is controversial among many scientists".

Furthermore, "EPA has determined that for Superfund remedial sites a 25 mrem/yr effective dose equivalent level should not be used for the purposes of establishing cleanup levels at CERCLA remedial sites" (USEPA 2014). This guidance puts USEPA at odds with the US Department of

Energy (USDOE) and the US Nuclear Regulatory Commission (USNRC), a longstanding conflict noted by the US General Accounting Office (GAO 1994, GAO 2000).

Comment: *The justification for the Agency's exclusive reliance on the LNT model is logically flawed.*

The Agency's guidance to assume linearity unless there is sufficient evidence to reject it inappropriately shifts the burden of proof away from the LNT model and is logically fallacious (Cardarelli and Ulsh 2018, Ulsh 2018), as it requires proof of absence of effect – proving a negative. Even if in fact, there is no risk at low doses (*i.e*. consistent with a threshold dose-response), it is not possible to prove an absolute absence of risk because it can be, and frequently is, argued that there may be a risk but it is too small to be observed. Such flawed reasoning renders the LNT hypothesis unfalsifiable and is therefore inappropriate. The Agency's guidance for estimating low-dose radiation risks (USEPA 2011) states,

> "Underlying the risk models is a large body of epidemiological and radiobiological data. In general, results from both lines of research are consistent with a linear, no-threshold dose (LNT) response model…".

As discussed in (Ulsh 2018):

> "These statements reverse the burden of proof by suggesting the data are "consistent" or "compatible" with the LNT. Due to imprecision at low doses, multiple alternative dose-response models could be consistent with the data at low doses. The appropriate question is, are the data for any alternative dose-response model sufficient to reject the no effect null, or not? If the LDDR data are insufficient to reject the no effect null while the HDDR data are sufficient to reject the null, then this supports a threshold model".

Comment: *The justification for the Agency's exclusive reliance on the LNT model relies on outdated scientific evidence.*

The Agency's cancer risk assessment guidance (USEPA 2005) states,

> "In the absence of sufficiently, scientifically justifiable mode of action information, EPA generally takes public health-protective, default positions regarding the interpretation of toxicologic and epidemiologic data: animal tumor findings are judged to be relevant to humans, and cancer risks are assumed to conform with low dose linearity".

The justification for assuming linearity (USEPA 1994) is based on an appeal to radiobiological concepts [*e.g.* the "single-hit", or "dual radiation action" model (Lea 1962, Kellerer and Rossi 1972)] on the mode of action for radiation carcinogenesis was flawed from the start (Calabrese 2017a) and ignores several decades of modern radiobiological evidence. It rests on the argument that even the smallest exposure to mutagenic agents necessarily increases risk because biological defenses are imperfect - an idea that has been thoroughly refuted (Ulsh 2010). It has been convincingly argued that modern biological evidence does not support the LNT model (Scott and Tharmalingam 2019, Tharmalingam et al. 2019). The modern biological understanding of low dose, low dose-rate biological effects recognizes nonlinear phenomena such as adaptive responses (Feinendegen 2003, Leonard 2005), and was summarized by (Mothersill and Seymour 2006) over a decade ago (about the same time as the Agency's cancer risk assessment guidance was issued):

> "Over the past 20 years there has been increasing evidence that cells and the progeny of cells surviving a very low dose of ionizing radiation [micro-mGy] can exhibit a wide range of non-monotonic effects such as adaptive responses, low dose hypersensitivity and other delayed effects. These effects are inconsistent with the expected dose-response, when based on extrapolation of high dose data and cast doubt on the reliability of extrapolating from high dose data to predict low dose effects".

The original adoption of the linear no-threshold (LNT) model was based on Hermann Muller's mutagenesis data in fruit flies, however Muller made a number of significant errors (Calabrese 2017b), and modern experiments in the same organisms revealed nonlinear (specifically, hormetic) dose-responses (Koana et al. 2007, Ogura et al. 2009). This undercuts the justification for assuming linearity as a default for ionizing radiation.(USEPA 2011) states:

> "Radiation is known to induce mutagenic damage to the cell's DNA. Due to clustering of ionizations produced by low-LET as well as high-LET radiation, this damage is often complex, involving two or more breaks with concomitant base damage all within a few nanometers in the DNA molecule. This argues against a threshold for radiation-induced carcinogenesis and in favor of a linear dose-response relationship at low doses".
>
> "Cellular repair processes are less capable of repairing DSBs and complex damage than the simpler types of damage almost always induced by isolated free radicals. This makes ionizing radiation unique among environmental carcinogens. Even a single track of the radiation is capable of producing complex damage sites, which, if misrepaired, can leave the cell with a mutated gene that can be passed on to the cell's progeny. Depending on the nature of the mutation, this may be one step in the formation of a malignancy. At reasonably low doses the number of DSBs and sites of complex damage is expected to be strictly proportional to dose (UNSCEAR 2000b, NCRP 2001, NAS 2006); this is the primary basis for the linear no-threshold (LNT) theory in which the probability of inducing a cancer by radiation is proportional to dose with no threshold below which there is no risk."
>
> "Since the damage produced by even a single track of ionizing radiation can sometimes be misrepaired, a threshold for cancer induction would appear improbable unless there is a mechanism for eliminating essentially all dividing cells with damaged DNA (*e.g.*, through some kind of immune surveillance)."

This argument was thoroughly refuted (Ulsh 2010) a year before (USEPA 2011) was published. Briefly, the complexity of DNA damage may make it difficult to repair, but repair is only one defense mechanism available to damaged cells. Others include apoptosis, premature terminal differentiation, and removal via immunosurveillance. Cells that are too damaged to be accurately repaired can simply be dealt with via these other defense mechanisms, so the Agency's argument that complexity implies no threshold substantially misinterprets the biological evidence.

In addition to ignoring the cells' defense mechanisms other than repair, the Agency's argument assumes that even the slightest possibility of misrepair (*e.g.* of a cell with complex damage) *necessarily* leads to an increase in risk. This argument is specious. Cellular defense mechanisms act on both anthropogenic radiation induced damage, and on the spontaneous background damage cells carry with them (*e.g.* mainly from oxygen metabolism, but also a very few from

background radiation and other environmental stressors) – including complex damage. For the sake of argument, even if a few of the radiation-damaged cells are misrepaired, the net action of these defenses on the radiation-induced damage *plus background damage* can easily result in lower levels of damaged cells, which would reduce risk if it is proportional to the levels of damage (Ulsh 2010) – which the Agency's argument assumes [*i.e*. (USEPA 2011) states, "It is presumed that the probability of carcinogenesis induced in an organism from an exposure to radiation is proportional to the number of induced mutations remaining after repair is complete]. Repair mechanisms don't have to be "foolproof" (though they actually do have very high fidelity in reality) – they just have to be good enough to result in lower levels of *net* damage post-exposure to negate the Agency's argument. Relying on this discredited argument damages the Agency's credibility. (USEPA 2011) states, "For the most part, estimates of radiogenic risk in this document are calculated using models recommended in the National Academy of Sciences report: Health Risks from Exposure to Low Levels of Ionizing Radiation, BEIR VII Phase 2 (NAS 2006)". However, the conclusions of BEIR VII have been seriously questioned (Siegel et al. 2018), as discussed in (Cardarelli and Ulsh 2018), two major studies the BEIR VII relied upon [the Lifespan Study (LSS) of the Atomic Bomb Survivors, and the 15-Country Study] no longer support the application of the LNT model at low doses.

In the latest update to the LSS cancer mortality study (Ozasa et al. 2012), no significant excess relative risk was observed for doses below 0.20 Gy. The authors also concluded that,

> "…statistically significant upward curvature was observed when the dose range was limited to 0–2 Gy…the curvature over the 0–2 Gy range has become stronger over time".

In the latest update to LSS cancer incidence (Grant et al. 2017), there were no detectable health effects below 100 mGy, and the authors concluded,

> "At this time, uncertainties in the shape of the dose response preclude definitive conclusions to confidently guide radiation protection policies".

The other major study the BEIR VII Committee relied upon, the 15-Country Study (Cardis et al. 2007) has also compromised the conclusions of the BEIR VII report. As discussed in (Cardarelli and Ulsh 2018), the Canadian Nuclear Safety Commission concluded that Atomic Energy of Canada, Ltd nuclear energy workers cohort included in the original 15-Country Study did not have an increased risk of solid cancer mortality. Incomplete dose records are likely the cause for the apparent increased risk of solid cancer mortality (CNSC 2011). Furthermore, (Zablotska et al. 2014) concluded,

> "Significantly increased risks for early AECL workers are most likely due to incomplete transfer of AECL dose records to the National Dose Registry. Analyses of the remainder of the Canadian nuclear workers (93.2%) provided no evidence of increased risk",
>
> "Study findings suggest that the revised Canadian cohort, with the exclusion of early AECL workers, would likely have an important effect on the 15-country pooled risk estimate of radiation-related risks of all cancer excluding leukaemia by substantially reducing the size of the point estimate and its significance.

Therefore, revisions to both major studies the BEIR VII Committee relied heavily upon have undercut the main conclusions of the BEIR VII report, and by extension (USEPA 2011). At the

very least, these developments warrant a re-examination of this topic by the SAB and/or the RAC.

Another major report examining the latest epidemiological evidence has recently been issued by the National Commission on Radiation Protection and Measurements (NCRP 2018), which endorses the continued use of the LNT model. It has been heavily criticized (Ulsh 2018), and others (Scott 2018, Ricci and Tharmalingam 2019) have argued that modern epidemiological evidence does not support the LNT model. The NCRP report, its criticisms, and the implications for the Agency's risk assessment policies are also worthy of consideration by the SAB and/or the RAC.

(USEPA 2011) states, "EPA adopts the estimate of 0.06 Gy^{-1} for prenatal exposures to diagnostic X-rays", based largely on the Oxford Series studies. However, the Agency neglects to discuss the problems with the Oxford studies identified by [(ICRP 2003) - which notably isn't even cited], including: (1) selection biases; (2) information biases; (3) and uncertainties in dose estimates, and other issues discussed in (Ulsh 2015).

Many additional studies not cited elsewhere in these comments have been published since the Agency considered this topic in (USEPA 2011). These should be included in any re-evaluation of the Agency's policies on estimating risks from low radiation doses, and include (but are certainly not limited to): (Calabrese 2015, Calabrese et al. 2016, Sacks et al. 2016, Shamoun 2016, Siegel et al. 2017, Calabrese 2018, Calabrese et al. 2018, Sutou 2018, Abelquist 2019, Brooks 2019, Calabrese 2019b, Calabrese 2019a, Pennington and Siegel 2019, Sacks and Meyerson 2019), and the many references cited therein.

The Agency's assertion that assuming linearity is protective of public health is presented without evidence and is in fact contradicted by the experiences of the Chernobyl and Fukushima accidents. In those situations, public health responses based on the LNT model of radiation risks were retrospectively found to have done more harm than good – which are clear violations of the as low as reasonably achievable (ALARA) principle (Jaworowski 2008, Gonzalez et al. 2013, Siegel et al. 2017, Thomas 2017, Thomas and May 2017, Waddington et al. 2017, Yumashev et al. 2017, Ulsh 2018). The costs of regulating radiation (and chemical) doses near or below background, for which there is no demonstrable adverse effect, could be as high as $2 trillion each year - nearly 11% of the U.S. gross domestic product (Williams 2019). With Administrator Wheeler's recent direction to increase transparency in balancing costs and benefits (Wheeler 2019), the Agency is presented with a prime opportunity to reconsider how this balance is calculated for extremely low radiation doses.

Comment: *The Agency's policies for estimating low-dose radiation risk are inconsistent with those for other carcinogens.*

The Agency's cancer guidelines (USEPA 2005) acknowledge nonlinear approaches for chemicals if sufficient, scientifically justifiable mode of action information is available, but they specifically exclude ionizing radiation from this approach without explanation, and this is not the only example of a disconnect between the approaches for chemicals and radiation. On the one hand, the Agency refuses to objectively evaluate the possibility that the low-dose radiation dose-

response for cancer might be nonlinear, while on the other hand acknowledging the dose-response for mutations in mammalian germ cells is nonlinear:

> "The Agency is aware that for at least one chemical that has been tested for mutations in mammalian germ cells, **there exist departures from linearity at low exposure and exposure rates in a fashion similar to that seen for ionizing radiation that has a low linear energy transfer**… The Agency will consider all relevant models for gene and chromosomal mutations in performing low-dose extrapolations and will choose the most appropriate model. This choice will be consistent both with the experimental data available and with current knowledge of relevant mutational mechanisms". (USEPA 1986)(emphasis added)

As discussed in (Cardarelli and Ulsh 2018), the Agency's treatment of inorganic metals correctly acknowledges that metals are naturally occurring, vary in concentrations across geographic regions, and in some cases are essential, (all properties that have been demonstrated or postulated for ionizing radiation), and these factors should be taken into account in dose-response considerations and setting reference doses (USEPA 2007). However, a similar approach for radiation has been excluded by the Agency by policy fiat, without scientific justification. Ignoring the thousands of studies showing adaptive or hormetic dose-responses [*e.g.* references cited in (Luckey 1980, Luckey 1991)], and thresholds for adverse effects, the Agency has simply declared,

> "…as the purpose of a risk assessment is to identify risk (harm, adverse effect, etc.), **effects that appear to be adaptive, nonadverse, or beneficial may not be mentioned**. (USEPA 2004) (emphasis added)

and also,

> "As a general principle, our practice is not to base risk assessments on adaptive, non-adverse, or beneficial events. (USEPA 2004)

This policy lacks a legitimate scientific justification (Calabrese 2012). Plenty of data have accumulated over the past two to three decades to justify revisiting this issue by the SAB and/or the RAC.

Agency Question: Are there important topic areas that are <u>not</u> fully represented in existing Agency risk assessment guidance related to cancer and non-cancer endpoints that SAB members recommend EPA address in guidance? What current information supports this recommendation?

Comment*: Dose-response models other than linear and linear-quadratic are not evaluated or considered in the Agency's guidelines for low-dose radiation cancer risk estimation (USEPA 1994, USEPA 2005, USEPA 2011).*

The proposed rule, *Strengthening Transparency in Regulatory Science* (USEPA 2018a), acknowledges:

> "there is growing empirical evidence of non-linearity in the concentration-response function for specific pollutants and health effects. The use of default models, without consideration of alternatives or model uncertainty, can obscure the scientific justification for EPA actions"

and further,

> "EPA should give appropriate consideration to high quality studies that explore: A broad class of parametric concentration-response models with a robust set of potential confounding variables; nonparametric models that incorporate fewer assumptions; various threshold models across the exposure range; and spatial heterogeneity. EPA should also incorporate the concept of model uncertainty when needed as a default to optimize low dose risk estimation based on major competing models, including linear, threshold, and U-shaped, J-shaped, and bell-shaped models".

There is no justification for continuing to arbitrarily ignore evidence for the types of models mentioned in the Agency's proposed rule.

Conclusion: There are numerous issues with the USEPA's current risk assessment practices for estimating risks from low doses of radiation. These include: (1) practices for estimating risks from doses near or below background that are contrary to expert advice; (2) inaccurate claims of a scientific consensus supporting current Agency policies; (3) logically fallacious reasoning; (4) reliance on outdated information; (5) inconsistencies between the Agency's practices for estimating low-dose radiation risk and those for other carcinogens; and (6) ignoring evidence for dose-response models other than the LNT model. These issues are significant enough to warrant a comprehensive review by the SAB and/or the RAC.

References

Abelquist EW. To mitigate the LNT model's unintended consequences—A proposed stopping point for As Low As Reasonably Achievable. Health physics in press; 2019.

Brooks AL. The impact of dose rate on the linear no threshold hypothesis. Chemico-biological interactions; 2019.

Calabrese EJ. NEPA, EPA and risk assessment: Has EPA lost its way? Regulatory toxicology and pharmacology : RTP 64: 267-268; 2012.

Calabrese EJ. An abuse of risk assessment: How regulatory agencies improperly adopted LNT for cancer risk assessment. Archives of toxicology 89: 647-648; 2015.

Calabrese EJ. Flaws in the LNT single-hit model for cancer risk: An historical assessment. Environmental research 158: 773-788; 2017a.

Calabrese EJ. The mistaken birth and adoption of LNT: An abridged version. Dose-response : a publication of International Hormesis Society 15: 1-3; 2017b.

Calabrese EJ. The additive to background assumption in cancer risk assessment: A reappraisal. Environmental research 166: 175-204; 2018.

Calabrese EJ. EPA adopts LNT: New historical perspectives. Chemico-biological interactions; 2019a.

Calabrese EJ. The linear no-threshold (LNT) dose response model: A comprehensive assessment of its historical and scientific foundations. Chemico-biological interactions; 2019b.

Calabrese EJ, Hanekamp JC, Shamoun DY. The EPA cancer risk assessment default model proposal: Moving away from the LNT. Dose-Response 16; 2018.

Calabrese EJ, Shamoun DY, Hanekamp JC. The integration of LNT and hormesis for cancer risk assessment optimizes public health protection. Health physics 110: 256-259; 2016.

Cardarelli JJ, Ulsh BA. It is time to move beyond the linear no-threshold theory for low dose radiation protection. Dose-Response 16: 1-24; 2018.

Cardis E, Vrijheid M, Blettner M, Gilbert E, Hakama M, Hill C, Howe G, Kaldor J, Muirhead CR, Schubauer-Berigan M, Yoshimura T, Bermann F, Cowper G, Fix J, Hacker C, Heinmiller B, Marshall M, Thierry-Chef I, Utterback D, Ahn YO, Amoros E, Ashmore P, Auvinen A, Bae JM, Bernar J, Biau A, Combalot E, Deboodt P, Diez Sacristan A, Eklof M, Engels H, Engholm G, Gulis G, Habib RR, Holan K, Hyvonen H, Kerekes A, Kurtinaitis J, Malker H, Martuzzi M, Mastauskas A, Monnet A, Moser M, Pearce MS, Richardson DB, Rodriguez-Artalejo F, Rogel A, Tardy H, Telle-Lamberton M, Turai I, Usel M, Veress K. The 15-Country Collaborative Study of Cancer Risk among radiation workers in the nuclear industry: Estimates of radiation-related cancer risks. Radiat Res 167: 396-416; 2007.

CNSC. Verifying Canadian nuclear energy worker radiation risk: A reanalysis of cancer mortality in Canadian nuclear energy workers (1957–1994) summary report. Ottawa, Canada; INFO-0811; 2011.

Edwards JD. U.S. Environmental Protection Agency's comments on linear no-threshold model and standards for protection against radiation; Notice of docketing and request for comment ID: NRC-215-0057-0010. Washington, D.C.; 2015.

Feinendegen LE. Relative implications of protective responses versus damage induction at low dose and low-dose-rate exposures, using the microdose approach. Radiat Prot Dosim 104: 337-346; 2003.

GAO. Nuclear health and safety: Consensus on acceptable radiation risk to the public is lacking. Washington, D.C.; GAO/RCED-94-190; 1994.

GAO. Radiation standards: Scientific basis inconclusive, and EPA and NRC disagreement continues. Washington, D.C.; GAO/RCED-00-152; 2000.

Gonzalez AJ, Akashi M, Boice JD, Chino M, Homma T, Ishigure N, Kai M, Kusumi S, Lee JK, Menzel HG, Niwa O, Sakai K, Weiss W, Yamashita S, Yonekura Y. Radiological protection issues arising during and after the Fukushima nuclear reactor accident. Journal of radiological protection : official journal of the Society for Radiological Protection 33: 497-571; 2013.

Grant EJ, Brenner A, Sugiyama H, Sakata R, Sadakane A, Utada M, Cahoon EK, Milder CM, Soda M, Cullings HM, Preston DL, Mabuchi K, Ozasa K. Solid cancer incidence among the life span study of atomic bomb survivors: 1958–2009. Radiat Res 187: 513-537; 2017.

HPS. Radiation risk in perspective: Position statement of the Health Physics Society [online]. Available at: http://hps.org/documents/risk_ps010-2.pdf.

ICRP. ICRP Publication 90: Biological effects after prenatal irradiation (embryo and fetus). Ann ICRP 33: 1-200; 2003.

ICRP. ICRP Publication 103: The 2007 recommendations of the International Commission on Radiological Protection. Ann ICRP 37: 1-332; 2007.

Jackson LP. untitled. 2010.

Jaworowski A. The paradigm that failed. Int J Low Radiat 5: 151-155; 2008.

Johnson SL. untitled. 2008.

Kellerer AM, Rossi HH. The theory of dual radiation action. Current topics in radiation research quarterly 8: 85-158; 1972.

Kirner NP. EPA Request for Regulatory Reform Task Force. McLean, VA; 2017.

Koana T, Okada MO, Ogura K, Tsujimura H, Sakai K. Reduction of background mutations by low-dose X irradiation of Drosophila spermatocytes at a low dose rate. Radiat Res 167: 217-221; 2007.

Lea DE. Actions of Radiations on Living Cells. Second ed. Cambridge, England: Cambridge University Press; 1962.

Leonard BE. Adaptive response by single cell radiation hits-implications for nuclear workers. Radiat Prot Dosim 116: 387-391; 2005.

Luckey TD. Hormesis with Ionizing Radiation. Boca Raton, FL: CRC Press; 1980.

Luckey TD. Radiation Hormesis. Boca Raton, FL: CRC Press; 1991.

Matanoski GM, Loehr RC, Waston JEJ, Gonzalez-Mendez R. Future issues in environmental radiation. Washington, DC; 1995.

Morgan MG, Lipoti J. Advisory on Agency Draft White Paper entitled “Modifying EPA Radiation Risk Models Based on BEIR VII”. Washington D.C.; EPA-SAB-08-006; 2008.

Mothersill C, Seymour CB. Radiation-induced bystander effects and the DNA paradigm: An "out of field" perspective. Mutation research 597: 5-10; 2006.

NCRP. Implications of recent epidemiologic studies for the linear-nonthreshold model and radiation protection. Bethesda, MD; NCRP Commentary No. 27; 2018.

Ogura K, Magae J, Kawakami Y, Koana T. Reduction in mutation frequency by very low-dose gamma irradiation of drosophila melanogaster germ cells. Radiat Res 171: 1-8; 2009.

Ozasa K, Shimizu Y, Suyama A, Kasagi F, Soda M, Grant EJ, Sakata R, Sugiyama H, Kodama K. Studies of the mortality of atomic bomb survivors, Report 14, 1950-2003: An overview of cancer and noncancer diseases. Radiat Res 177: 229-243; 2012.

Pennington CW, Siegel JA. The linear no-threshold model of low-dose radiogenic cancer: A failed fiction. Dose-Response 17; 2019.

Puskin JS. Perspective on the use of LNT for radiation protection and risk assessment by the U.S. Environmental Protection Agency. Dose-response : a publication of International Hormesis Society 7: 284-291; 2009.

Ricci PF, Tharmalingam S. Ionizing radiations epidemiology does not support the LNT model. Chemico-biological interactions; 2019.

Ring JP, Tupin EA, Elder D, Hiatt J, Sheetz MA, Kirner NP, Little C. Health Physics Society comments to EPA Regulatory Reform Task Force. Health physics 114; 2017.

Sacks B, Meyerson G. Linear no-threshold (LNT) vs. hormesis: Paradigms, assumptions, and mathematical conventions that bias the conclusions in favor of lnt and against hormesis. Health physics; 2019.

Sacks B, Meyerson G, Siegel JA. Epidemiology without biology: False paradigms, unfounded assumptions, and specious statistics in radiation science (with commentaries by Inge Schmitz-Feuerhake and Christopher Busby and a reply by the authors). Biol Theory 11: 69-101; 2016.

Scott BR. A critique of recent epidemiologic studies of cancer mortality among nuclear workers. Dose-Response 16: 1-9; 2018.

Scott BR, Tharmalingam S. The LNT model for cancer induction is not supported by radiobiological data. Chemico-biological interactions; 2019.

Shamoun DY. Linear No-Threshold model and standards for protection against radiation. Regulatory toxicology and pharmacology : RTP 77: 49-53; 2016.

Siegel JA, Greenspan BS, Maurer AH, Taylor AT, Phillips WT, Van Nostrand D, Sacks B, Silberstein EB. The BEIR VII estimates of low-dose radiation health risks are based on faulty assumptions and data analyses: A call for reassessment. Journal of nuclear medicine : official publication, Society of Nuclear Medicine; 2018.

Siegel JA, Sacks B, Welsh JS. Time to terminate LNT: Radiation regulators should adopt LT. J Radiol Oncol 1: 49-53; 2017.

Sutou S. Low-dose radiation from A-bombs elongated lifespan and reduced cancer mortality relative to un-irradiated individuals. Genes Environ 40; 2018.

Tharmalingam S, Sreetharan S, Brooks AL, Boreham DR. Re-evaluation of the linear no-threshold (LNT) model using new paradigms and modern molecular studies. Chemico-biological interactions; 2019.

Thomas PJ. Quantitative guidance on how best to respond to a big nuclear accident. Proc Safety Environ Prot 112: 4-15; 2017.

Thomas PJ, May J. Coping after a big nuclear accident. Proc Safety Environ Prot 112: 1-3; 2017.

Ulsh BA. Checking the foundation: Recent radiobiology and the linear no-threshold theory. Health physics 99: 747-758; 2010.

Ulsh BA. Are risks from medical imaging still too small to be observed or nonexistent? Dose-response : a publication of International Hormesis Society 13: 1-27; 2015.

Ulsh BA. A critical evaluation of the NCRP Commentary 27 endorsement of the linear no-threshold model of radiation effects. Environmental research 167: 472-487; 2018.

UNSCEAR. Report of the United Nations Scientific Committee on the Effects of Atomic Radiation Fifty-ninth Session (21-25 May 2012). New York, NY: United Nations; Report No. A/67/46; 2012.

USEPA. Guidelines for mutagenicity risk assessment. Washington, D.C.; EPA/630/R-98/003; 1986.

USEPA. Estimating radiogenic cancer risks. 1994.

USEPA. An examination of risk assessment principles and practices. Washington D.C.; EPA/100/B-04/001; 2004.

USEPA. Guidelines for cancer risk assessment. Washington, D.C.; 2005.

USEPA. Framework for metals risk assessment. Washington D.C.; EPA 120/r-07/001; 2007.

USEPA. EPA radiogenic cancer risk models and projections for the U.S. population. Washington D.C.; EPA 402-R-011-001; 2011.

USEPA. Radiation risk assessment at CERCLA sites: Q&A. Washington D.C.; EPA 540-R-012-13; 2014.

USEPA. 40 CFR Part 30 Docket No. EPA-HQ-OA-2018-0259 Strengthening transparency in regulatory science. Federal Register 83: 18768-18774; 2018a.

USEPA. Radiation health effects [online]. Available at: https://www.epa.gov/radiation/radiation-health-effects.

Waddington I, Thomas PJ, Taylor RH, Vaughan GJ. J-value assessment of relocation measures following the nuclear power plant accidents at Chernobyl and Fukushima Daiichii. Proc Safety Environ Prot 112 Part A: 16-49; 2017.

Wheeler AR. Increasing consistency and transparency in considering benefits and costs in the rulemaking process. Washington, D.C.: USEPA; 2019.

Williams RA. Economic benefit-cost implications of the LNT model. Chemico-biological interactions; 2019.

Wong D. Hours per year estimate for new SGE appointment. 2019a.

Wong D. RE: RAC requests. 2019b.

Yumashev D, Johnson P, Thomas PJ. Economically optimal strategies for medium-term recovery after a major nuclear reactor accident. Proc Safety Environ Prot 112: 63-76; 2017.

Zablotska LB, Lane RS, Thompson PA. A reanalysis of cancer mortality in Canadian nuclear workers (1956-1994) based on revised exposure and cohort data. Brit J Cancer 110: 214-223; 2014.

Dr. Kimberly White

General Comments on the Consultation

During the June 2019 Science Advisory Board (SAB) meeting, EPA staff outlined general plans for updating the EPA's 2005 Guidelines for Carcinogen Risk Assessment and creating new non-cancer guidelines. As the Agency considers this effort it should ensure that any modifications to the current cancer guidelines or the creation of new non-cancer guidelines are based on transparent, science-based approaches that reflect current knowledge regarding how chemicals act at the molecular, cellular and organ levels. This could include development of specific approaches for the incorporation of mode of action information into the problem formulation and scoping phase of a risk assessment; how this type of information could be utilized to reduce uncertainty in understanding toxicity; and develop objective approaches for how to incorporate mode of action information for substances that are data rich as well as data poor to improve hazard characterization.

Additionally, an objective peer reviewed framework for integrating available toxicology, epidemiology and mode of action information based on a weight of the scientific evidence approach to establish cause and effect should continue to be a key focus of any guidance. Notably, development and application of consistent and transparent study evaluation methods to determine the quality and reliability of critical studies for use in the risk assessment is important. The Agency should also allow sufficient time for expert input and peer review of any new or modified guidelines. It generally takes multiple years to draft, review and update guidance of this nature to ensure it adequately reflects the current state of scientific discourse and relevant approaches. Effective and timely peer review is essential to ensure the development of scientifically defensible guidelines and applicability of the guidance to inform decision-making. It also allows for the transparent and objective review of the underlying assumptions, methodology, and approaches recommended in the guidelines. The Agency should not unduly truncate this review process.

Responses to the Specific Charge Questions Posed by EPA in the Consultation

1. Are there particular aspects of existing Agency risk assessment guidance related to cancer and non-cancer endpoints that individual SAB members recommend be revised or augmented to incorporate updated scientific information (based on your experience in usage, new information, or scientific advances)?

Response – There is considerable empirical evidence of non-linearity in dose response modeling and the Agency should evaluate its reliance and application of default models that limit the consideration of alternative approaches. Decades of peer reviewed published literature provide multiple examples of observed chemical specific thresholds for both non-cancer and cancer endpoints. It is critically important to have established guidelines that clearly allow and support utilization of non-linear or biologically-based dose–response modelling, when the scientific evidence is available. Additionally, the Agency could also consider evaluating and understanding relevant exposure scenarios earlier in the risk

assessment process to ensure that assessments are focused on environmentally relevant exposures.

2. Are there important topic areas that are not fully represented in existing Agency risk assessment guidance related to cancer and non-cancer endpoints that SAB members recommend EPA address in guidance? What current information supports this recommendation?

Response – The Agency should consider greater focus on approaches and examples of best practices for integrating multiple streams of evidences to draw conclusions regarding causality. This could include recommended approaches and examples for assessing data quality; how the results of a data quality evaluation directly informs the integration of various evidence streams; and how negative and positive evidence associated with the similar endpoints or streams of evidence are addressed and integrated to draw conclusions which reflect the full weight of the scientific evidence. The Agency should also be thoughtful regarding current classification schemes to determine carcinogenicity or the creation of any non-cancer classification schemes to ensure implementation of transparent criteria, confidence and the scientific utility in the classification for informing human health risk assessment.

3. Are any key elements of hazard and dose-response analysis —including analytical limitations, heterogeneity, natural variability, and non-ambient exposures (i.e., endogenous or indoor exposures)—not adequately characterized in guidance?

Response – The Agency should consider inclusion of more specific information regarding the evaluation of endogenous exposure information and how this information should be considered when conducting dose-response modeling and establishing toxicity values. This could include guidance regarding the types of information which should be consider early in the assessment associated with endogenous exposure levels and possible implications for the hazard characterization assessment. The Agency could also consider some additional focus on incorporation and application of dosimetry information to improve understanding and plausibility of potential proposed modes of action.

4. Current guidance discusses how to describe confidence in hazard conclusions (see, for example, the Cancer Guidelines, section 2.5 "Weight of Evidence Narrative" or Guidelines for Developmental Toxicity, Table 3) and discusses presentation of uncertainty in dose response (see for example the Cancer Guidelines, section 3.7 "Dose Response Characterization"). Examples of current practice can also be seen in various recent EPA assessments of specific chemicals or pollutants.

    i. Do SAB members have recommendations for better ways to characterize conclusions and uncertainties in a transparent way?

    ii. Do SAB members have recommendations for better ways to analyze uncertainty, qualitatively or with quantitative analysis?

    iii. What role should statistical analysis play in this characterization?

iv. Are there methods SAB members recommend for better analyzing and communicating compounded uncertainty, including the use of uncertainty factors, in the hazard identification and dose response process?

Response – Any revised or newly generated guidance should clearly outline any uncertainties in the hazard characterization conclusions and the mode of action analysis. Utilizing a transparent data quality framework will assist in providing clear information regarding limitation or uncertainties in the available data and how it was or was not utilized to support conclusions. There are also peer reviewed publications that are applying a quantitative approach to evaluate plausible modes of action which could also assist in transparently outlining uncertainty.

5. The current Agency-wide guidance includes a guideline on cancer assessment, several guidelines for specific noncancer endpoints (e.g., reproductive toxicity, developmental toxicity, and mutagenicity), and guidances or reports on aspects of assessment common to many assessment endpoints (e.g., inhalation dosimetry, body-weight scaling of oral doses, benchmark dose technical guidance, risk characterization).

    i. Are there specific areas within these documents on which there have been advances in risk assessment that should be reflected in updated guidelines?

    ii. Are there areas of overlap or disagreement between these guidelines?

    iii. What issues or guideline documents would SAB members prioritize for update?

Response – In 2014, EPA finalized its' Framework for Human Health Risk Assessment to Inform Decision Making. This document should be reviewed and any suggested revisions to guidelines should incorporate the principles outlined in the document. This includes a focus on adequate and objective problem formulation at the onset of the risk assessment as well as clear recognition regarding the important contribution that understanding a chemical's mode of action has in risk assessment decisions.

6. Given current understanding of how risk assessments are used in decision making, are there considerations or changes to existing guidance with respect to problem formulation, assessment, data integration, and risk characterization that SAB members recommend EPA consider? Do SAB members have specific recommendations as to questions of importance to decision makers that are not being addressed by current risk assessments?

Response – Clear and transparent problem formulation at the beginning of any risk assessment is critically important to ensure that it will adequately inform decision-making. Similarly having a transparent and defined framework for assessing data quality and integrating multiple streams of evidence to draw conclusions is needed. Including some specific case examples of: how to scope a risk assessment; what key questions should be addressed in the risk assessment based on its intended purpose and use for decision-making; and how to evaluate and integrate data would be incredibly useful for risk assessors.

7. The purpose of some risk assessments (to quantify dose-response or reference values protective of the most sensitive receptors) and the purpose of the assessment of risk to inform benefits in an economic analysis (to create a predictive analysis for judging the effectiveness and feasibility of a regulatory action) can be quite different. As a result, the evaluation methods and key decision points can be quite different. For example, risk assessors may choose a benchmark dose at the high end (>95 percentile) of a distribution in order to define a level likely to avoid adverse effects, while economists may prefer risk assessors characterize the entire distribution or, at a minimum, use benchmark doses in the middle of the distribution, to inform benefit analyses.

    i. Do SAB members think risk assessments are providing the information needed by risk managers and those estimating the benefits of potential decisions? If not, what do SAB members recommend might make hazard and dose response analyses more useful to decision makers?

    ii. Should EPA's guidance direct staff to consider as part of the development of the assessment the questions decision makers need answered in the end use of the assessment?

Response – It would improve the utility of EPA's guidance to have a clear understanding of what information would be of the most use to support decision-making. This could be identified and considered at the problem formulation and scoping phase of the risk assessment and provide clear direction and focus for the risk assessment activities and analysis.

Dr. Richard Williams

Comment on Cancer and Non-Cancer Guidelines
From: Richard A Williams Ph.D.

It is time for EPA to eliminate conservativism in risk assessments. By using conservative risk assessments, EPA is not being public health protective. This is explained below.

As the risks we manage today get ever smaller, and more numerous, being able to make judgments about trade-offs becomes vitally important but we can't do it with yesterday's risk tools.

Twenty years ago, in a report to Congress OMB lamented:

"*Unfortunately, risk-assessment practices continue to rely on conservative models and assumptions that effectively intermingle important policy judgments within the scientific assessment of risk.*

EPA for one, is still using conservative risk assessments, doing it consciously and state in their guidance that:

[S]ince EPA is a health and environmental protective agency, EPA's policy is that risk assessments should not knowingly underestimate or grossly overestimate risks.[1]

There are numerous examples of where EPA is conservative, essentially ensuring that risks are not underestimated but clinging to Linear No-Threshold Dose-Response functions (LNT) is a significant one. As Golden, Bus and Calabrese state,

> "The fundamental biological assumptions upon which the LNT model relied at its early adoption at best reflected a primitive understanding of key biological processes controlling mutation and development of cancer. However, breakthrough advancements contributed by modern molecular biology over the last several decades provided experimental tools and evidence challenging the LNT model for use in risk assessment of radiation or chemicals. Those science advancements have revealed that DNA is not simply an inert chemical target such that even single "hit" potentially results in cancer, or that multiple hits additively cumulate over time. Modern biology has now unequivocally demonstrated that biological systems mount a plethora of highly integrated

[1] U.S. Environmental Protection Agency Office of the Science Advisor. "An Examination of EPA Risk Assessment Principles and Practices; Staff Paper, EPA/100/B-04/001," 2004, p. 13.

> defenses to a continuous chorus of endogenous and exogenous attacks (e.g., ROS) on core genetic material and function. These defenses (expressed at subcellular, cellular, organ and whole body levels) are essential to sustaining cell and organism homeostasis. This massive explosion in fundamental understanding of cell and organism function now clearly points to the need to examine the impact of this vast body of knowledge on the scientific legitimacy of maintaining the LNT model as a continuing and scientifically defensible driver of radiation and chemical carcinogen risk assessment."

Further, as Constantini and Borremans state, "The LNT model is biologically unrealistic compared to threshold and hormetic models" and "If LNT were correct, the evolution of life on Earth would not have been possible."[2]

Recently, the National Research Council chastised the EPA within their review of EPA's formaldehyde risk assessment saying that "Problems with clarity and transparency of the methods appear to be a repeating theme over the years." While the committee did not use the term "conservative," it named some of the key factors that would make it so. For example, the NRC noted the absence of causation, use of weak animal data and lack of mechanistic data and finished by stating that EPA had overstated the conclusion that formaldehyde damages the nervous system and is linked to reproductive effects. Flawed risk conclusions like this lead to regulations that cause economic hardship for no reason, i.e., costs with no benefits.
Hormetic dose-response curves offer a different issue. For ionizing radiation and many chemicals such as methyl mercury, there is an optimal hormetic point (although it will have heterogenous characteristics) for individuals where they experience benefits from low doses.[3] Using the LNT, or any method of conservatively establishing risk levels can cause regulators to set exposure levels beneath the optimal hormetic dose - which can reduce or eliminate the protective effects of adaptive doses.

The practice of medicine had always accepted the idea that medicine is good in small doses but harmful if too much is taken. A few aspirin are good, take too many and you die. Take a small dose of the sleeping pill Nembutal, and you get a good night's sleep. Take too many, as Marilyn Monroe did, and you die. The same is true for vaccines. Get a small dose of a weakened version of measles, and you won't get measles. Allowing children to eat small amounts of dirt trains their immune systems to fight off serious bacterial threats.

A similar thing takes place with exercise. Exercise causes the heart to be "preconditioned" to better cope with future stresses, i.e., heart attacks, even long after the exercise. On the other hand, too much exercise over too short a period can be fatal (causes a life-threatening illness called rhabdomyloysis). Fasting, a type of pre-conditioning stress, has been shown in some studies to extend life span. Obviously, the other side of the curve is starvation.

---

[2] Constantini, David and Benny Borremans, "The linear no-threshold model is less realistic than threshold or hormesis-based models: An evolutionary perspective," Chemico-Biological Interactions, 301(1), March 2019 p. 26.
[3] Tan et al Toxicology and Applied Pharm. 362:59-66, 2019.

Nevertheless, an EPA staff paper from the Risk Assessment Task Force states "effects that appear to be adaptive, non-adverse, or beneficial may not be mentioned [in a risk assessment]" (USEPA, 2004). Today, EPA defines risk on their website as "*EPA considers risk to be the chance of harmful effects to human health or to ecological systems."* There is no mention of positive risks. Meanwhile there were 10,000 citations on hormesis in a leading scientific index in 2018.

Generally, animal tests are performed at high doses and extrapolated into the low dose region using an assumed linear relationship. The lowest response allowed is zero, so no hormetic effects can be detected. In addition, hormetic health endpoints may be different from toxic endpoints but this means that researchers most be more careful to identify them so that the net effects of different endpoints can be considered for regulatory purposes.[4]

RECOMMENDATION: ***For both cancer and non-cancer endpoints, EPA should choose a threshold model as a default. However, they should also be careful to not use only high doses in tests such that a biphasic response cannot detected.***

Health thresholds (and hormetic ones) are one type of threshold, but there are also choice thresholds.

Choice Thresholds

Risk/risk trade-offs

Every action to reduce risk in one place increases a countervailing risk, somewhere else. Take a pesticide off the market and another one takes its place with its own risk profile. That substitution may also raise the price of fruits and vegetables if the substitute (pesticide) risk is less effective (with higher exposure to the substitute) or is higher priced, and causes substitution away from fruits and vegetables which will then negatively nutrition related disease. Establish a lower tolerance for mercury in fish and fish consumption will be reduced but, perhaps, more consumption of less healthy proteins. Banning DDT has led to malaria deaths around the world. If managers wish to compare the risks, conservatively estimating the target risk will make it impossible to compare to countervailing risks. In this case, we will never know if we are making the world safer or riskier. This becomes particularly acute as risks we intentionally regulate get smaller and less certain.

The choices that consumers and producer make in response to the regulation of target risks lead to new risks and at some point, there may be a threshold below which overall risk (to the population) can be increased.

[4] Calabrese, Edward J. "Toxicology Rewrites Its History and Rethinks its Future: Giving Equal Focus in Both Harmful and Beneficial Effects," Environmental Toxicology and Chemistry, Vol. 30, No. 12, pp. 2658–2673, 2011

Health/wealth trade-offs

In addition, by estimating risks conservatively, it forces managers to regulate conservatively and this can have adverse consequences for other private (and other government) expenditures on health and safety. When EPA regulates at very high costs to reduce risks, it crowds out private expenditures to reduce risks like buying safer cars, baby gates, and medical checkups.

In either risk/risk or health/wealth trade-offs, setting exposure levels to protect highly exposed or highly sensitive individuals may increase risk to other subgroups.

RECOMMENDATION: ***EPA should eliminate conservative defaults and begin to examine both risk/risk and health/wealth trade-offs and pay attention to risks to different subgroups.***

Economic Benefits Analyses

Benefits analysis (as a part of a benefit-cost analysis) cannot use conservative risk assessments, including upper bound risk points. The benefits part of the risk benefit equation starts with the amount of actual risk to be reduced, that is, what number of people you expect will be made less sick, have fewer accidents or deaths each year. Economists then determine from people's own actions reducing risk in their private lives what that risk reduction is worth to the average person. Exaggerated risk estimates lead to exaggerated benefits which cannot then be compared to costs. In particular, it means that net benefits will be overstated, and makes it impossible to compare regulatory options. EPA has been aware of this problem for at least fifteen years, particularly since 2004 when "Integrated analysis: combining risk and economic assessments while preserving the separation of powers" was published.[5] That paper argued against both upper bound point estimates (like the RfD) and ignoring probabilistic information. EPA's practices do not appear to have changed since then. Economists need either an actual dose-response distribution (not and upper bound) or a "central" estimate of risk to use in benefits assessments.

RECOMMENDATION: EPA's ***science policy statement should be changed in the following way: [S]ince EPA is a health and environmental protective agency, EPA's policy is that risk assessments should not knowingly underestimate or ~~grossly~~ overestimate risks.***

Team Approach

It is not uncommon for risk assessments to be performed with teams from different professions including chemists, biologists, toxicologists, statisticians, pathologists and engineers, depending on the issue. An addition of an economist to these teams can be an effective check for ensuring that risk assessment results can be used for decision analysis tools such as benefit-cost analysis, risk/risk analysis and health/wealth analysis.

[5] Williams, RA and KM Thompson, "Integrated analysis: combining risk and economic assessments while preserving the separation of powers," Risk Analysis, 24(6) December 2004, pp 1614-23.

RECOMMENDATION: ***EPA risk assessment teams should include an economist to ensure that risk estimates can be used for decision analysis***

Enclosure C

Individual Comments from Members of the EPA Science Advisory Board Chemical Assessment Advisory Committee on Updating EPA Guidelines for Carcinogen and Non-Cancer Risk Assessment

(July - 2019)

Dr. Richard Belzer

MEMORANDUM FOR THE CHARTERED SCIENCE ADVISORY BOARD

FROM: **Dr. Richard B. Belzer**
Member, Chemical Assessment Advisory Committee

DATE: **June 26, 2019**

SUBJECT: **Comments on *SAB Consultation on Updating EPA Guidelines for Carcinogen and Non-Cancer Risk Assessment*[1]**

During the public meeting on June 5, 2019, Science Advisory Board (SAB) Chairman Dr. Michael Honeycutt asked members of the SAB's Chemical Assessment Advisory Committee (CAAC) to provide preliminary comments on this document provided by EPA's Risk Assessment Forum (RAF).

The document provides a link to a webpage listing three current RAF projects: (1) the development of additional guidelines for cumulative risk assessment, (2) revision of the 1992 *Guidelines for Human Exposure Assessment*, and (3) certain "projects addressing recommendations presented to the agency in reports issued by the National Research Council." The latter item appears to include the "consideration of new approaches to dose- response assessment that may be used in risk assessments to augment their usefulness for Agency decision making," such as "additivity in mixtures risk assessment and consideration of several of the default uncertainty factors used in reference value methods."[2] My comments address only the additional questions contained in the RAF's proposed SAB consultation, which supplements these three projects. To be clear, these comments are preliminary and intended only to help focus the SAB/CAAC review.

1. **Are there particular aspects of existing Agency risk assessment guidance related to cancer and non-cancer endpoints that individual SAB members recommend be revised or augmented to incorporate updated scientific information (based on your experience in usage, new information, or scientific advances)?**

The historical practice of using different approaches for cancer and non-cancer endpoints reflects longstanding tradition, not scientific merit. For cancer, EPA has relied on models intended to estimate risk. For non-cancer endpoints, EPA has relied on models that seek to identify safe exposure levels. Safety is not a scientific concept, however; it has no meaning outside policy judgment and personal preference. Reference values thus depend much more on policy judgments than science, and they always will. Safety assessment might be valuable for risk *management*, but it does not belong anywhere near the practice of risk *assessment*.

This bifurcation of risk analysis into risk and safety assessment, predicated solely on the cancer endpoint, may have exacerbated EPA's struggle to develop policy-neutral heuristics for processing new scientific information. The Agency has developed a reputation for interpreting new scientific information as at least potentially adverse. Examples are few in which new science

[1] U.S. Environmental Protection Agency Risk Assessment Forum (2019)
[2] U.S. Environmental Protection Agency (2017)

resulted in a lower Agency risk estimate. This has predictably led to unbalanced investments in scientific inquiry. Research that could yield higher risk estimates has a ready market; research showing that precautionary default assumptions are not scientifically supported does not.

The SAB should consider whether it would be more constructive to focus on the development and implementation of transparent, reproducible, and predictable process reforms for managing new information rather than revising (or publishing yet more) risk assessment guidance. Examples of such process reforms might include value-of-information approaches in which key information gaps are identified; research projects that could close these gaps are designed, validated, and implemented; and changes in risk estimates (in either direction) are guaranteed if pre-specified outcomes are observed. EPA needs a process relying on scientifically-grounded risk assessment performance standards that readily adapts to new science without submission to Agency (or stakeholder) risk management priors.

2. **Are there important topic areas that are not fully represented in existing Agency risk assessment guidance related to cancer and non-cancer endpoints that SAB members recommend EPA address in guidance? What current information supports this recommendation?**

All adverse health effects matter, and how much they matter depends on multiple factors. Yet EPA guidance treats all cancers as if they are the same; interprets biological events along any pathway that could theoretically lead to cancer as if it were indistinguishable from cancer; and denies the coexistence of positive and negative effects from the same substance or exposure, whether to the same or different individuals.

This has incentivized the search for ever-lower thresholds for biological effects that can be interpreted as adverse for risk management purposes. While some science might be present in these debates, they are dominated by EPA risk management policy defaults and the personal judgments of Agency risk assessors. EPA statements indicate that the scientific content in its risk assessments is thus constrained:

> EPA risk assessments tend towards protecting public and environmental health by preferring an approach that does not underestimate risk in the face of uncertainty and variability. In other words, EPA seeks to adequately protect public and environmental health by *ensuring that risk is not likely to be underestimated.*[3]

Multiple layers of policy overwhelm the science in risk assessment. So there should be no uncertainty at all concerning why EPA risk assessments are controversial.

Meanwhile, EPA guidance systematically ignores other factors with equal or greater scientific content. These factors include the opportunity costs resulting from a health effect, or implicated by a choice to prevent or treat it.[4] An effect is *adverse* if individuals or households are

[3] U.S. EPA Office of the Science Advisor (2004, p.11 [emphasis in original])

[4] EPA appears to be especially confused concerning the boundary between science and policy here. A decision to tolerate, treat, or prevent a health effect is a policy choice. The opportunity cost associated with a health effect, whether potential or realized, as well as the opportunity cost of treatment or prevention, is science. Opportunity costs are objectively estimable and subject to refutation – the defining characteristic of science. Meanwhile, toxicological hazard extrapolations from high to low doses and across species – the bread and butter of EPA risk assessments – are rarely refutable.

willing to pay to avoid it,[5] and the severity of an effect depends on the amount that they are willing to pay.[6] Estimating such phenomena therefore requires respectful collaboration between biologists and economists, and these estimates must be objective – not health precautionary.[7] EPA risk assessment guidance does not allow for such collaboration, and it is built on health precautionary defaults.

3. Are any key elements of hazard and dose-response analysis — including analytical limitations, heterogeneity, natural variability, and non-ambient exposures (i.e., endogenous or indoor exposures) — not adequately characterized in guidance?

This is a subset of Question 2. How to constructively answer it therefore depends on its purpose. Addressing "analytical limitations, heterogeneity, natural variability, and non-ambient exposures" is desirable if the objective to characterize risk distributions more accurately. But if the purpose is to further push the envelope of policy precaution embedded within Agency risk assessments, its incremental value is dubious.

Risk assessors always want more data and analysis, so before proceeding further it may be helpful to consider several downside risks of expanding the domain of information required for risk assessment:

i. Agency risk assessors may perceive a need for additional information simply because uncertainty exists. But uncertainty never goes away.

ii. Agency risk assessors may seek to minimize false negatives. This inevitably leads to more false positives, however.

iii. EPA has an institutional practice of interpreting new scientific information in ways that are compatible with precautionary risk management preferences. This selectively inhibits scientific advancement, and incentivizing asymmetric research probably is undesirable.

iv. The Agency has a reputation for demanding proof of the absence of risk before agreeing to moderate a proposed (or especially an existing) risk characterization. A value-of-information approach to acquiring relevant information is appropriate, one that can accurately predict how it will be used in risk assessment before resources are spent to acquire it. Stakeholders should not have to guess.

Each of these traditions and behaviors has significant opportunity costs. There has to be a way to decide which uncertainties to resolve and which to tolerate. False positives have

[5] "Benefits are the favorable effects society gains due to a policy or action. Economists define benefits by focusing on changes in individual well-being, referred to as welfare or utility. Willingness to pay (WTP) is the preferred measure of these changes as it theoretically provides a full accounting of individual preferences across trade-offs between income and the favorable effects." U.S. Environmental Protection Agency (2016, p. xi).

[6] "The [third] step [in benefits assessment] is to estimate willingness to pay…of all affected individuals for the quantified benefits in each benefit category, and then to aggregate these to estimate the total social benefits of each policy option." U.S. Environmental Protection Agency (2016, p. 7-6).

[7] "[Risk assessors and economists should…work to produce expected or central estimates of risk, rather than bounding estimates as in safety assessments." U.S. Environmental Protection Agency (2016, Text Box 7.2]

opportunity costs that the minimization of false negatives ignores. Forcing new science through the astigmatic lens of precautionary policy defaults discourages policy-neutral research. Proof of safety is never possible; demanding it as the price for risk assessment realism makes science subordinate to policy and shuts down scientific progress.

It is interesting to note that *economic* science, which EPA risk assessment guidance omits, routinely accounts for uncertainty, variability, and the contributions of confounders whenever data permit.[8] It is the biological and toxicological components of risk assessment that seem to lag behind. This could be attributable to the dominant role played by health-precautionary policy defaults in EPA *risk assessment* guidance, which EPA *economic analysis* guidance rejects.[9] As long as toxicology is the primary relevant scientific discipline and only the worst-case matters, the consideration of "analytical limitations, heterogeneity, natural variability, and non-ambient exposures" is unlikely to add value to risk assessment.

A more appropriate approach to the problem of uncertainty may be to consider the value of additional information that could resolve it, at least in part, and spend the resources required to obtain this information as long as expected acquisition costs are less than the information's expected value for improving the accuracy of risk assessment. For this to work, however, EPA may need to pre-commit to specific changes in risk characterization if research confirms the stipulated alternative hypothesis that motivated the research investment.

4. **Current guidance discusses how to describe confidence in hazard conclusions (see, for example, the Cancer Guidelines, section 2.5 "Weight of Evidence Narrative" or Guidelines for Developmental Toxicity, Table 3) and discusses presentation of uncertainty in dose response (see for example the Cancer Guidelines, section 3.7 "Dose Response Characterization"). Examples of current practice can also be seen in various recent EPA assessments of specific chemicals or pollutants.**

    i. **Do SAB members have recommendations for better ways to characterize conclusions and uncertainties in a transparent way?**

    ii. **Do SAB members have recommendations for better ways to analyze uncertainty, qualitatively or with quantitative analysis?**

    iii. **What role should statistical analysis play in this characterization?**

    iv. **Are there methods SAB members recommend for better analyzing and communicating compounded uncertainty, including the use of uncertainty factors, in the hazard identification and dose response process?**

These questions certainly deserve attention from the SAB and CAAC. These problems are illustrated by Section 2.5 of the cancer guidelines,[10] which appears to establish impossible

[8] *See*, e.g., footnote 6, with emphasis on *all* affected individuals and *every* benefit category.

[9] U.S. Environmental Protection Agency (2016, Text Box 7.2). "Historically, health and ecological risk assessments have been designed not to support benefits analyses per se but rather to support the setting of standards or to rank the severity of different hazards. Traditional measures of risk can be difficult or impossible to incorporate into benefits analyses. For example, traditional measures of risk are often based on endpoints not directly related to health outcomes or ecological services that can be valued using economic methods. These measures are often based on outcomes near the tails of the risk distribution for highly sensitive endpoints, which would lead to biased benefits estimates if extrapolated to the general population."

[10] U.S. Environmental Protection Agency (2005).

expectations. The weight-of-evidence (WoE) narrative in a risk assessment is supposed to "highlight the key issues and decisions that were the basis for the evaluation of the agent's potential hazard" in a way that is "sufficiently clear and transparent to be useful to risk managers and non-expert readers" alike. WoE narratives must include "descriptors" that are "points along a continuum of evidence" "applicable to a wide variety of potential data sets and weights of evidence" with "sufficient flexibility to accommodate new scientific understanding and new testing methods as they are developed and accepted by the scientific community and the public."

This is astoundingly difficult to do just with respect to a single underlying "key issue," which presumably is scientific. But expecting a WoE narrative to do this for *every* "key issue," *and* also to describe "key … decisions" clearly and transparently, transforms an extraordinarily difficult task into an impossible one. It also reveals that risk assessment has strayed outside the domain of science and into a multifaceted policy realm beset with cataracts. And the WoE narrative must do this in "one to two page[s]" even though EPA needed 9-1/2 pages just to outline what's required.

5. **The current Agency-wide guidance includes a guideline on cancer assessment, several guidelines for specific noncancer endpoints (e.g., reproductive toxicity, developmental toxicity, and mutagenicity), and guidances or reports on aspects of assessment common to many assessment endpoints (e.g., inhalation dosimetry, body-weight scaling of oral doses, benchmark dose technical guidance, risk characterization).**

   i. **Are there specific areas within these documents on which there have been advances in risk assessment that should be reflected in updated guidelines?**

   ii. **Are there areas of overlap or disagreement between these guidelines?**

   iii. **What issues or guideline documents would SAB members prioritize for update?**

While SAB and CAAC review of Agency-wide risk assessment guidance is certainly desirable, it is not clear why that review should focus on these particular areas. As the comments to Question 3 suggest, a value-of-information approach is desirable here. Thus, a first-order task is to examine these (and other) aspects of existing guidance to draw inferences concerning where the SAB and CAAC can provide the greatest return on its investment. This, in turn, should be compared to the return on investment of amending Agency guidelines to include risk assessment factors heretofore excluded, such as those noted in the comments to Question 2.

6. **Given current understanding of how risk assessments are used in decision making, are there considerations or changes to existing guidance with respect to problem formulation, assessment, data integration, and risk characterization that SAB members recommend EPA consider? Do SAB members have specific recommendations as to questions of importance to decision makers that are not being addressed by current risk assessments?**

EPA risk assessments are quasi-regulations, thus resulting in extended delays because of unresolvable conflicts and controversies. It is not clear that any investment of SAB and CAAC time and effort to deal with the particular issues in Question 6 will improve throughput or

dampen controversy at the margin. An alternative approach that is modest rather than comprehensive, strictly limited to science, and respectful of its purpose to inform but not predetermine policy choices, stands a better chance of success.

7. **The purpose of some risk assessments (to quantify dose-response or reference values protective of the most sensitive receptors) and the purpose of the assessment of risk to inform benefits in an economic analysis (to create a predictive analysis for judging the effectiveness and feasibility of a regulatory action) can be quite different. As a result, the evaluation methods and key decision points can be quite different. For example, risk assessors may choose a benchmark dose at the high end (>95 percentile) of a distribution in order to define a level likely to avoid adverse effects, while economists may prefer risk assessors characterize the entire distribution or, at a minimum, use benchmark doses in the middle of the distribution, to inform benefit analyses.**

    i. **Do SAB members think risk assessments are providing the information needed by risk managers and those estimating the benefits of potential decisions? If not, what do SAB members recommend might make hazard and dose response analyses more useful to decision makers?**

    ii. **Should EPA's guidance direct staff to consider as part of the development of the assessment the questions decision makers need answered in the end use of the assessment?**

Obtaining a reasonable worst-case estimate of risk or safety (i.e., "quantify[ing] dose-response or reference values protective of the most sensitive receptors") is certainly one purpose that risk assessment can serve. EPA has elsewhere made clear that this is, indeed, the Agency's de facto purpose:

> [S]ince EPA is a health and environmental protective agency, EPA's policy is that risk assessments should not knowingly underestimate or grossly overestimate risks. This policy position prompts risk assessments to take a more "protective" stance given the underlying uncertainty with the risk estimates generated. Another framing policy position is that EPA will examine and report on the upper end of a range of risks or exposures when we are not very certain about where the particular risk lies.[11]

The entirely predictable result is endless warfare. Critics are not necessarily wrong to observe that, paraphrasing the 1827 aphorism of Carl von Clausewitz, risk assessment has become the continuation of policy through other means.[12] A key opportunity cost of this cultural understanding is damage, possibly permanent, to EPA's reputation for scientific integrity. Note that EPA's scientific integrity policy requires that Agency risk assessments be conducted objectively and be presented fairly and accurately.[13]

An alternative cultural understanding, one that predates EPA's, is that the purpose of risk

[11] U.S. EPA Office of the Science Advisor (2004, p. 13).
[12] Clausewitz (1976, p. 642).
[13] U.S. Environmental Protection Agency (2012, p. 3). A similar requirement can be found in EPA's Information Quality Guidelines. *See* U.S. Environmental Protection Agency (2002), requiring influential information disseminated by EPA (including risk assessments) be objective in substance and presentation.

assessment is to estimate risk. In the practice of benefit-cost analysis, which has been mandatory for major federal agency rulemakings since 1981 – two years before the publication of the NRC *Red Book* – all benefits and costs must be objectively estimated and characterized by their expected values unless distributions are available. But benefits and costs cannot be estimated objectively if they rely on risk assessments that are intentionally biased.

This alternative purpose is discreetly captured in EPA's guidance on economic analysis,[14] cited earlier in response to Question 2 concerning "important topic areas that are not fully represented in existing Agency risk assessment guidance." If the purpose of risk assessment is to objectively estimate risk, it is compatible with the purpose of regulatory impact analysis, which is to objectively estimate the consequences of alternative governmental actions.

Beginning the transformation of EPA risk assessments into strictly scientific work products that can be validly used as inputs to Agency Regulatory Impact Analyses may be the most important goal for SAB and CAAC review. After more than four decades of experience, the existing model, with its uncountable efforts to rationalize the subordination of science to policy, seems to have reached a dead end.

REFERENCES

Clausewitz Cv. 1976. On War. Princeton NJ: Princeton University Press.

Office of Management and Budget. 2997. Final Bulletin for Good Guidance Practices. Federal Register 72:3432-3440

U.S. Environmental Protection Agency. 2002. Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency. EPA/260R-02-008. Washington DC: USEPA.

U.S. Environmental Protection Agency. 2005. Guidelines for Carcinogen Risk Assessment. EPA/630/P-03-001F. Washington DC: USEPA.

U.S. Environmental Protection Agency. 2012. Scientific Integrity Policy. Washington DC: USEPA.

U.S. Environmental Protection Agency. 2016. Guidelines for Preparing Economic Analyses. Washington DC: USEPA National Center for Environmental Economics.

U.S. Environmental Protection Agency. 2017. Risk Assessment Current Projects. Available: https://www.epa.gov/osa/risk-assessment-current-projects [accessed June 22, 2019].

U.S. Environmental Protection Agency Risk Assessment Forum. 2019. SAB Consultation on Updating EPA Guidelines for Carcinogen and Non-Cancer Risk Assessment. Washington DC: USEPA Risk Assessment Forum.

U.S. EPA Office of the Science Advisor. 2004. An Examination of EPA Risk Assessment Principles and Practices; Staff Paper EPA/100/B-04/001. Washington DC: USEPA Risk Assessment Task Force.

[14] U.S. Environmental Protection Agency (2016).

Dr. Tiffany Bredfeldt

SAB Consultation on Updating EPA Guidelines for Carcinogen and Non-Cancer Risk Assessment

The U.S. EPA is interested in seeking consultation from the members of the SAB regarding upcoming activities related to an update to the 2005 EPA Guidelines for Carcinogen Risk Assessment and guidelines for noncancer risk assessment. In considering areas for future emphasis, as well as with the work currently underway, EPA's Risk Assessment Forum[1] (RAF) is considering various topic areas including use of defaults, inhalation dosimetry and susceptible populations and lifestages.

The U.S. EPA, primarily through the RAF, maintains a series of guidelines, guidance documents and methodologies that describe the way the Agency conducts its human health and ecological risk assessments.[2] Some key examples include:

- Guidelines concerning: exposure assessment, carcinogen risk assessment, mixtures risk assessment, reproductive toxicity risk assessment, developmental toxicity risk assessment, neurotoxicity risk assessment, and ecological risk assessment;
- Supplemental guidance for mixtures risk assessment, and assessing susceptibility from early-life exposure to carcinogens;
- Guidance for benchmark dose modeling, and applying quantitative data to develop data-derived extrapolation factors;
- Frameworks for cumulative risk assessment and for ecological risk assessment; and
- Methods for and reviews of RfD/RfC processes.

A more detailed listing of some of the Agency guidelines, guidance documents, and technical panel reports that address human health risk assessment is attached.

The RAF is currently engaged in various activities,[3] ranging from drafting updates to longstanding guidelines documents to initial investigative steps on complex topic areas. Some current examples include an update to the Guidelines for Exposure Assessment,[4] activities related to the development of cumulative risk assessment guidance,[5] and consideration of new approaches to dose-response assessment that may be used in risk assessments to augment their usefulness for Agency decision making. Activities are also underway to address specific issues, such as additivity in mixtures risk assessment and consideration of several of the default uncertainty factors used in reference value methods.

The EPA is interested in consultation with the SAB with these general perspectives in mind.

---

[1] https://www.epa.gov/osa/basic-information-about-risk-assessment-guidelines-development

[2] A list of many of the human health assessment documents can be found at the following URL: https://www.epa.gov/risk/risk-assessment-guidelines#tab-1, and documents on ecological assessment can also be accessed from that webpage.

[3] https://www.epa.gov/osa/risk-assessment-current-projects

[4] https://www.epa.gov/risk/guidelines-human-exposure-assessment

[5] https://www.epa.gov/risk/framework-cumulative-risk-assessment

1. Are there particular aspects of existing Agency risk assessment guidance related to cancer and non-cancer endpoints that individual SAB members recommend be revised or augmented to incorporate updated scientific information (based on your experience in usage, new information, or scientific advances)?

   i. The EPAs guidelines have long served to guide members of the scientific community regarding risk assessments. Many of the guidance documents have fallen behind current risk assessment methodologies and current state-of-the science, and in response, EPA is updating these documents. This a task that is highly recommended and commended.

   Some of the earliest steps in risk assessment include problem formulation, scoping, and identifying alternatives. These steps aid risk assessors in more clearly identifying and characterizing goals or scientific principles, or policies and rules that establish context for the subsequent assessment. These steps lay groundwork or scope and limits within a risk assessment, which aids in the selection of methods, tools, and resources required for the successful completion of the assessment.

   While EPA has put an admirable amount of effort into developing better systematic reviews for chemical of concern, it seems problem formulation and scoping require more up-front effort. Recent assessments have suffered from lack of being fit-for purpose or scoping to better focus the goals of the assessment. For example, assessments such as formaldehyde and ethylene oxide have resulted in regulatory values that imply endogenous levels of these chemicals increase risk. When an assessment results in overly conservative conclusions that are not easily supported by scientific evidence, steps need to be added into the assessment process to prevent such conservative, and potentially meaningless conclusions. Default assumptions, linearization of dose-response curves, and the selection of maximal uncertainty factors can compound the levels of conservatism within an assessment that give rise to risk factors or toxicity factors of little value and potentially high cost. It would be useful for EPA to integrate steps into risk assessments that allow for reality checks while the assessment is underway to prevent results that misguide end users and the public. Further, early steps in problem formulation and scoping may limit the use of compounding conservative assumptions to prevent assessments from taking a direction that wastes time and resources.

   ii. The EPA has improved systematic review and transparency of their data collection and chemical specific mode-of-action analysis. However, the dose-response analysis steps within assessments often lack transparency and clear discussion that reveals what approaches were considered and what approaches or methods were later chosen to move forward within an assessment. Take, for example, the application of Bayesian frameworks that are used in tandem with specific curve fitting tools (e.g., most recent arsenic assessment). While the EPA performed an excellent mode-of-action analysis, it was unclear why they selected certain curve fitting functions to evaluate dose-response. Those options were merely presented to the reader with the justification that the curve fitting function would allow for the exploration of non-monotonic dose-response relationships. It would have been helpful for the EPA to discuss available models that would considered for use in the example assessment. Further, the EPA should present

what strengths and weaknesses those models offer and the basis upon which models or other distributional analysis tools were selected and subsequently used.

This sort of addition to all assessments would probably benefit from the production of a stand-alone document whereby EPA presents various methods that the agency uses for distributional analysis for estimation of exposure and models applied for dose-response. It is likely that such a document would benefit from being evergreen and available online so that it could be subject to stakeholder feedback and perhaps a form of expedited updating to accommodate the incorporation of new tools and methods as they are produced in the future.

2. Are there important topic areas that are <u>not</u> fully represented in existing Agency risk assessment guidance related to cancer and non-cancer endpoints that SAB members recommend EPA address in guidance? What current information supports this recommendation?

    i. The EPA has put in a good deal of effort on developing systematic reviews for specific chemicals and has expanded the scientific defensibility of mode-of-action analyses. However, one area that seems rather weak in current assessments is how mode-of-action information is being quantitatively and qualitatively incorporated into assessments. It is possible that quite a bit of this information is spread over EPA documents. Nonetheless, the way these data are being incorporated into assessments and used to inform various assumptions and uncertainty or variability calculations needs to be placed into a comprehensive document that is user friendly and accessible. Alternatively, it is possible to simply add this to the mode-of-action sections within primary guidance documents during the current effort to update them. It seems that making the process of how this information is specifically applied in a holistic and harmonized manner will be the greatest challenge.

As evident from the general questions above, EPA is seeking open-ended input and recommendations from SAB members and will consider all the input received to determine next steps for updating EPA guideline documents in a phased approach.

In the course of development and review of this charge to the SAB, the following additional questions were identified by Agency leadership to highlight for SAB members' input.

3. Are any key elements of hazard and dose-response analysis —including analytical limitations, heterogeneity, natural variability, and non-ambient exposures (i.e., endogenous or indoor exposures)—not adequately characterized in guidance?

    i. Recent assessments have certainly demonstrated the importance of addressing endogenously produced chemicals and background exposures. It does not appear that there is a single approach agreed upon for the calculation of total dose or how knowing that background/endogenous levels of the chemical of concern exist informs problem formulation or uncertainty. While the EPA has acknowledged these issues in various guidance documents, it needs to develop methodologies to deal with these concerns. For reference, please consider the following:

1. C. Wild. (2005) Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol Biomarkers Prev, 14: 1847-1850
2. J.D. Schroeter, J. Campbell, J.S. Kimbell, R.B. Connelly, H.J. Clewell, M.E. Andersen. (2014) Effects of endogenous formaldehyde in nasal tissues on inhaled formaldehyde dosimetry predictions in the rat, monkey, and human nasal passages. Tox Sci, 138: 412-424.
3. W.H. Farland, A.L., N.K. Erraguntla, L.H. Pottenger. (2019) Improving risk assessment approaches for chemicals with both endogenous and exogenous exposures, Regulatory Toxicology and Pharmacology, 103: 210-215.
4. M.E. Andersen, P.R. Gentry, J.A. Swenberg, K.A. Mundt, K.W. White, C. Thompson, J. Bus, J.H. Sherman, H. Greim, H. Bolt, G.M. Marsh, H. Checkoway, D. Coggon, H.J. Clewell. (2019) Considerations for refining the risk assessment process for formaldehyde: Results from an interdisciplinary workshop. Regulatory Toxicology and Pharmacology, 106:210-223

ii. The EPA needs to contemplate the incorporation of "reality check" into risk assessments. Risk assessors often realize that there are layers of conservatism that go into the derivation of a toxicity factor. However, it is necessary to evaluate when the value that has been calculated does not reflect reality in that it has become so conservative through various assumptions and defaults that it predicts false disease incidence or adverse health outcomes. Such overly conservative estimates are not only unscientific, but they also may result in fear and costs that pose a greater risk to welfare.

4. Current guidance discusses how to describe confidence in hazard conclusions (see, for example, the Cancer Guidelines, section 2.5 "Weight of Evidence Narrative" or Guidelines for Developmental Toxicity, Table 3) and discusses presentation of uncertainty in dose response (see for example the Cancer Guidelines, section 3.7 "Dose Response Characterization"). Examples of current practice can also be seen in various recent EPA assessments of specific chemicals or pollutants.

   i. Do SAB members have recommendations for better ways to characterize conclusions and uncertainties in a transparent way?

      1. The EPA is incorporating newer methods to evaluate uncertainty and dose-response. However, some of the newer methodologies and models are applied or selected in ways that are not transparent. The evidence integration using many of these tools is not transparent. It would be helpful for EPA to more clearly describe how these methods are used in some upcoming assessments by producing general guidelines for how they select different dose-response and uncertainty analysis methods or models. Basic guidelines could then be cited in assessments as the basis for how/why certain approaches, as opposed to others, were selected and utilized.

      2. See above discussions (in short, see list below):

         a. Prepare a white paper or guidelines for the incorporation of mode-of-action in a more systematized way into toxicity factor derivations.

b. Prepare guidelines for how different dose-response or exposure-response analyses of epidemiological studies are conducted.

c. Prepare guidance to discuss and guide risk assumptions and uncertainty when considering children.

d. Consider methods for "reality check" to be incorporated into assessments (examples listed below):

i. Do the rates of cancer projected by the toxicity factors reflect rates of cancer in population or grossly overestimate them?

ii. Does the model selected grossly over predict cancer incidence? (i.e., if the model predicts cancer rates that are not observed within the population)

iii. Does the toxicity factor predict that endogenous levels of a chemical or background levels are of risk?

iv. Does the dose/exposure from which extrapolation is occurring have a different mode-of-action than low-dose exposures?

v. Can the model selected for analysis predict the data that was used as input?

ii. Do SAB members have recommendations for better ways to analyze uncertainty, qualitatively or with quantitative analysis?

1. The EPA is using some newer probabilistic approaches to analyze uncertainty and variability. The application of these approaches is timely and appropriate. However, guidelines need to be produced that describe how these new approaches are being selected and applied.

iii. What role should statistical analysis play in this characterization?

2. There are members of the SAB that are better respondents for this question.

iv. Are there methods SAB members recommend for better analyzing and communicating compounded uncertainty, including the use of uncertainty factors, in the hazard identification and dose response process?

3. There are members of the SAB that are better respondents for this question.

5. The current Agency-wide guidance includes a guideline on cancer assessment, several guidelines for specific noncancer endpoints (e.g., reproductive toxicity, developmental toxicity, and mutagenicity), and guidances or reports on aspects of assessment common to many assessment endpoints (e.g., inhalation dosimetry, body-weight scaling of oral doses, benchmark dose technical guidance, risk characterization).

i. Are there specific areas within these documents on which there have been advances in risk assessment that should be reflected in updated guidelines?

1. There have been many studies dedicated to better evaluating the human relevance of certain reproductive and developmental endpoints. Observations from animal model studies need to be evaluated in a mode-of action context to enable application of such studies to be accurate or fit-for-purpose within assessments. More recent research into these endpoints needs to be added back into guidance documents. Please see the following:

    e. A.R. Scialli, G. Daston, C. Chen, P.S. Coder, S.Y. Euling, J. Foreman, A.M. Hoberman, J. Hui, T. Knudsen, S.L. Makris, L. Morford, A.H. Piersma, D. Stanislaus, K.E. Thompson (2018) Rethinking developmental toxicity testing: Evolution or revolution? Birth Defects Research. 110: 840–850.

    f. B.K. Beyer, N. Chernoff, B.R. Danielsson, K. Davis-Bruno, W. Harrouk, R.D. Hood, G. Janer, U.W. Liminga, J.H. Kim, M. Rocca, J. Rogers, and Scialli, A. R. (2011), ILSI/HESI maternal toxicity workshop summary: maternal toxicity and its impact on study design and data interpretation. Birth Defects Research Part B: Developmental and Reproductive Toxicology, 92: 36-51

2. Similarly, there are other endpoints, particularly in cancer evaluations, where data collected in animal studies indicates that the animal model itself is not useful for evaluating risk for humans. The EPA cancer guidelines do acknowledge that not all animal tumor responses are relevant to humans. However, this body of evidence has substantially increased since the previous guidelines were published, and newer information should be added into possibly into an entire section regarding human relevance. The EPA has certainly discussed steps to determine human relevance in more recent documents (https://cfpub.epa.gov/si/si_public_record_Report.cfm?Lab=NHEERL&dirEntryId=198663). These resources should be integrated into updated guidance documents in a more harmonized and comprehensive manner.

ii. Are there areas of overlap or disagreement between these guidelines?

1. From my perspective, these guidelines do not disagree as much as they become out-of-date and have areas that either do not agree or have evolved scientifically.

2. There are areas of overlap within these documents. However, some overlap is necessary to place specific information within context.

iii. What issues or guideline documents would SAB members prioritize for update?

3. There are some documents that appear to need priority updating. The cancer assessment guidelines, developmental and reproductive guidelines would be high priority in my opinion.

6. Given current understanding of how risk assessments are used in decision making, are there considerations or changes to existing guidance with respect to problem formulation, assessment, data integration, and risk characterization that SAB members recommend EPA consider? Do SAB members have specific recommendations as to questions of importance to decision makers that are not being addressed by current risk assessments?

    i. The EPA has improved problem formulation approaches significantly. However, there are elements that appear later in assessments that may better serve assessments by integration into problem formulation and scoping steps. Endogenous and background exposures, for example, have become major points of discussion in formaldehyde and ethylene oxide assessments, yet there does not appear to be a mechanism for incorporating this information in to the early phases of assessments. During stages of systematic review, findings such as these should be integrated into problem formulation to better integrate these findings into the context of the assessment.

    ii. The selection of certain models and how model selection and curve fitting strategies impact the toxicity factor values are rarely discussed within assessments in detail. However, some of the primary sources of uncertainty within assessments is the formulation of models and estimation of parameter values to input into these models. It would improve assessment transparency to include the reasons certain approaches, studies or uncertainty values/analyses were included or excluded in an assessment. These additions enable readers and users to understand how specific decisions within the assessment (e.g., model selection, uncertainty analysis/values, dose-response extrapolation selections etc.) affected outcomes.

7. The purpose of some risk assessments (to quantify dose-response or reference values protective of the most sensitive receptors) and the purpose of the assessment of risk to inform benefits in an economic analysis (to create a predictive analysis for judging the effectiveness and feasibility of a regulatory action) can be quite different. As a result, the evaluation methods and key decision points can be quite different. For example, risk assessors may choose a benchmark dose at the high end (>95 percentile) of a distribution to define a level likely to avoid adverse effects, while economists may prefer risk assessors characterize the entire distribution or, at a minimum, use benchmark doses in the middle of the distribution, to inform benefit analyses.

    i. Do SAB members think risk assessments are providing the information needed by risk managers and those estimating the benefits of potential decisions? If not, what do SAB members recommend might make hazard and dose response analyses more useful to decision makers?

    1. Often risk managers utilize the product of an assessment as a stand-alone regulatory value or toxicity factor. This can lead to misguided use of regulatory values due to the risk managers not being aware of some of the details, uncertainties, and caveats that come with applying a regulatory value without more information. The application of the end-product of an assessment needs to be done within context so that adjustment can be made, or the value (for

example) may not be used by risk managers if it is deemed not fit-for-purpose. A possible solution to this issue would be for assessments to include an analysis of scientifically-defensible, alternative approaches and the strengths and weaknesses of those approaches and outcomes had those approaches been considered.

ii. Should EPA's guidance direct staff to consider as part of the development of the assessment the questions decision makers need answered in the end use of the assessment?

2. It is important for the EPA to include reasons why certain approaches, models, assumptions, defaults, etc. were chosen and applied within a given assessment. However, risk assessors serve a different role than a risk managers or policy makers. So, it would be important for risk management and policy decisions to not inappropriately shape scientific assessments. If this type of information is considered in assessments, it should not detract from the scientific analysis. It could be used to inform problem formulation or assessment scoping in a transparent, clearly communicated manner, which may assist assessments in being more fit-for-purpose.

With these questions guiding, but not limiting, your review, please provide input to help guide the Agency as it initiates an update to the 2005 EPA Guidelines for Carcinogen Risk Assessment and develops guidelines for noncancer risk assessment.

Dr. Karen Chou

SAB Consultation on Updating EPA Guidelines for Carcinogen and Non-Cancer Risk Assessment

1. Are there particular aspects of existing Agency risk assessment guidance related to cancer and non-cancer endpoints that individual SAB members recommend be revised or augmented to incorporate updated scientific information (based on your experience in usage, new information, or scientific advances)?

Recommendation (a): Requiring the identity of the physical form of the chemical in risk assessment documents, whether it is in a nano- or the traditional bulk form.

Rationale: The physical form of the substance assessed/tested, whether it is in traditional "bulk' form or a nanomaterial, needs to be specified. The toxicity of a nanomaterial can be very different from its corresponding bulk material. A few years ago, I had reviewed toxicity assessment documents, in which a given substance was most likely a nanoparticle, but the "form" of the substance was not identified in the document, therefore the test substance in some of the studies used to support the assessment may not be the same as the substance assessed. To identify a chemical for risk/toxicity assessment, CAS number alone is not always enough.

Recommendation (b): Harmonizing the assessment methods for carcinogens, non-carcinogens, developmental/reproductive toxicants, and neurotoxicants.

Rationale: From the biological point of view, the divisions of the above categories are arbitrary, divided by manmade disciplinary areas. The divisions were needed because the studies were conducted and evaluated with different disciplinary knowledge. Nonetheless, they are not isolated biologically from each other. Fundamentally, they share the same body of an organism and are guided by the same principles of chemistry and physics. As the biological science gradually advances into a higher level of maturity, multi-omics approaches have broken down these disciplinary barriers and rigid separation of the threshold and non-threshold dose-response models. For example, quantitative analyses and interpretation of mutation and genotoxicity assays provide evidence that some genotoxic compounds produce a non-linear dose-response curve, exhibiting a likelihood of threshold dose-response relationship. Harmonizing the many risk assessment guidelines is a complex and huge task, and there will be many steps involved, from planning, drafting, to partial implementation. NOW is a good time to start.

2. Are there important topic areas that are not fully represented in existing Agency risk assessment guidance related to cancer and non-cancer endpoints that SAB members recommend EPA address in guidance? What current information supports this recommendation?

<u>Recommendation (c)</u>: Occupational exposure as a risk factor for identifying susceptible subpopulations is not fully addressed in the guidelines.

<u>Rationale</u>: Susceptible subpopulations and the size of susceptible subpopulations are important information for economic analysis and other risk management decisions. In several risk assessment documents, lifestyle is included as an example of risk factors that is used to identify susceptible subpopulations, for example, in Section 1.3.5 of *Guidelines for Carcinogen Risk Assessment*. Occupation is also a part of lifestyle that can significantly influence the amount of exposure, but it's not addressed, at least not in the Guidelines for Carcinogen Risk Assessment.

As evident from the general questions above, EPA is seeking open-ended input and recommendations from SAB members and will consider all the input received to determine next steps for updating EPA guideline documents in a phased approach.

In the course of development and review of this charge to the SAB, the following additional questions were identified by Agency leadership to highlight for SAB members' input.

3. Are any key elements of hazard and dose-response analysis —including analytical limitations, heterogeneity, natural variability, and non-ambient exposures (i.e., endogenous or indoor exposures)—not adequately characterized in guidance?

4. Current guidance discusses how to describe confidence in hazard conclusions (see, for example, the Cancer Guidelines, section 2.5 "Weight of Evidence Narrative" or Guidelines for Developmental Toxicity, Table 3) and discusses presentation of uncertainty in dose response (see for example the Cancer Guidelines, section 3.7 "Dose Response Characterization"). Examples of current practice can also be seen in various recent EPA assessments of specific chemicals or pollutants.

    i. Do SAB members have recommendations for better ways to characterize conclusions and uncertainties in a transparent way?

    ii. Do SAB members have recommendations for better ways to analyze uncertainty, qualitatively or with quantitative analysis?

    iii. What role should statistical analysis play in this characterization?

    iv. Are there methods SAB members recommend for better analyzing and communicating compounded uncertainty, including the use of uncertainty factors, in the hazard identification and dose response process?

5. The current Agency-wide guidance includes a guideline on cancer assessment, several guidelines for specific noncancer endpoints (e.g., reproductive toxicity, developmental toxicity, and mutagenicity), and guidances or reports on aspects of assessment common to many assessment endpoints (e.g., inhalation dosimetry, body-weight scaling of oral doses, benchmark dose technical guidance, risk characterization).

i. Are there specific areas within these documents on which there have been advances in risk assessment that should be reflected in updated guidelines?

Recommendation (d): The use of genome-wide transcriptomic data for carcinogen and noncancer risk assessment and incorporating the transcriptomic data collection and analyses into existing test protocols.

Rationale: In the past few years, genome-wide gene expression analyses have become more robust and affordable. Incorporating the transcriptomics into existing test protocols can enhance the efficient use of animals and resources in combined studies, which would also provide more extensive data for identifying mode of actions and susceptible subpopulations, and potentially minimize uncertainties in the assessments. Transcriptomics, in combination with the biomarkers of toxicity endpoints and other bioinformatics analyses, can be used to identify biological processes involved in the manifestation of toxicity, therefore identify the mode of action. There are many other possible applications of transcriptomics in risk assessment for enhancing the quality and minimizing uncertainties, including identifying key mechanisms that differentiate short-term and longer-term toxicity, differentiate male and female susceptibility, and provide information to define potential mechanisms that contribute to lifestage differences in susceptibility. This recommendation does not necessarily suggest the use of gene expression as an endpoint for dose-response relationship, instead mRNA expression data offers previously unknown insights in the mode of action, therefore may be used to minimize the uncertainty in endpoint selection. They could also enable identifying susceptible subpopulations from non-susceptible subpopulations and assist in the selection of UF values. For example, gene expression information selected based on mode-of-action may be used to assess the difference in susceptibility between males and females. Similar approaches can be used to assess differences in susceptibility among other subpopulations. This recommendation is in concert with the needs and recommendations identified by the RfD/RfC Technical Panel (U.S. EPA, 2002), which aim to "provide more systematic information on toxicokinetics and toxicodynamics (i.e., mechanism or mode of action), including at different life stages; development of protocols for acute and short-term studies that provide more comprehensive data for setting reference values…." and ".. more efficient use of animals and resources in combined studies that would provide more extensive data on life stages, endpoints, and other factors not well characterized in current testing approaches."

One recent review article on this topic (Schmitz-Spanke, 2019) is offered to facilitate the communication: Schmitz-Spanke S. 2019. Toxicogenomics - *What added Value Do These Approaches Provide for Carcinogen Risk Assessment?* Environ Res 173: 157-164.

Recommendation (e): Recognizing that effects of test substance on gut microbiota and other resident microbial flora can have adverse effects on the health of the host.

Rational: Chemicals can modify the population of resident microbial flora, thus minimizing beneficial effects of or causing adverse effects on the microbial functionality on the health the host. Conversely, microbial populations that live with the human body can directly and indirectly affect toxicokinetics of a substance through biotransformation,

such as decarboxylation, dehydroxylation, demethylation, dehalogenation, and conjugate hydrolysis reactions.

ii. Are there areas of overlap or disagreement between these guidelines?

iii. What issues or guideline documents would SAB members prioritize for update?

Recommended priorities:

(1) Recommendation (a): Requiring the identity of the physical form of the chemical in risk assessment documents, whether it is in a nano- or the traditional bulk form.

(2) Recommendation (b): Harmonizing the assessment methods for carcinogens, non-carcinogens, developmental/reproductive toxicants, and neurotoxicants.

(3) Recommendation (d): The use of genome-wide transcriptomic data for carcinogen and noncancer risk assessment and incorporating the transcriptomic data collection and analyses into existing test protocols.

(4) Recommendation (e): Recognizing that effects of test substance on gut microbiota and other resident microbial flora can have adverse effects on the health of the host.

(5) Recommendation (c): Occupational exposure as a risk factor for identifying susceptible subpopulations is not fully addressed in the guidelines.

6. Given current understanding of how risk assessments are used in decision making, are there considerations or changes to existing guidance with respect to problem formulation, assessment, data integration, and risk characterization that SAB members recommend EPA consider? Do SAB members have specific recommendations as to questions of importance to decision makers that are not being addressed by current risk assessments?

7. The purpose of some risk assessments (to quantify dose-response or reference values protective of the most sensitive receptors) and the purpose of the assessment of risk to inform benefits in an economic analysis (to create a predictive analysis for judging the effectiveness and feasibility of a regulatory action) can be quite different. As a result, the evaluation methods and key decision points can be quite different. For example, risk assessors may choose a benchmark dose at the high end (>95 percentile) of a distribution in order to define a level likely to avoid adverse effects, while economists may prefer risk assessors characterize the entire distribution or, at a minimum, use benchmark doses in the middle of the distribution, to inform benefit analyses.

    i. Do SAB members think risk assessments are providing the information needed by risk managers and those estimating the benefits of potential decisions? If not, what do SAB members recommend might make hazard and dose response analyses more useful to decision makers?

    ii. Should EPA's guidance direct staff to consider as part of the development of the assessment the questions decision makers need answered in the end use of the assessment?

With these questions guiding, but not limiting, your review, please provide input to help guide the Agency as it initiates an update to the 2005 EPA Guidelines for Carcinogen Risk Assessment and develops guidelines for noncancer risk assessment

Dr. Harvey Clewell

SAB Consultation on Updating EPA Guidelines for Carcinogen and Non-Cancer Risk Assessment

The EPA is interested in consultation with the SAB with these general perspectives in mind.

1. Are there particular aspects of existing Agency risk assessment guidance related to cancer and non-cancer endpoints that individual SAB members recommend be revised or augmented to incorporate updated scientific information (based on your experience in usage, new information, or scientific advances)?

The inhalation dosimetry guidelines are seriously out of date and include approaches and calculations that have since been shown to be incorrect (EPA/600/R-09/072).

2. Are there important topic areas that are <u>not</u> fully represented in existing Agency risk assessment guidance related to cancer and non-cancer endpoints that SAB members recommend EPA address in guidance? What current information supports this recommendation?

EPA Guidance currently does not adequately deal with situations where a compound is present endogenously, either as an essential nutrient, e.g., manganese (Gentry PR, Van Landingham C, Fuller WG, Sulsky SI, Greene TB, Clewell HJ 3rd, Andersen ME, Roels HA, Taylor MD, Keene AM. 2017. A tissue dose-based comparative exposure assessment of manganese using physiologically based pharmacokinetic modeling-The importance of homeostatic control for an essential metal. Toxicol Appl Pharmacol. 322:27-40.), or as a product of normal metabolism, e.g., acetone (Gentry, P.R., Covington, T.R. Andersen, M.E. and Clewell, H.J. 2003. Application of a physiologically based pharmacokinetic model for reference dose and reference concentration estimation for acetone. J Toxicol Environ Health (Part A) 66:2209-2225.), formaldehyde (NRC, Review of Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde. The National Academies Press, Washington, DC, 2011.).

As evident from the general questions above, EPA is seeking open-ended input and recommendations from SAB members and will consider all the input received to determine next steps for updating EPA guideline documents in a phased approach.

In the course of development and review of this charge to the SAB, the following additional questions were identified by Agency leadership to highlight for SAB members' input.

3. Are any key elements of hazard and dose-response analysis —including analytical limitations, heterogeneity, natural variability, and non-ambient exposures (i.e., endogenous or indoor exposures)—not adequately characterized in guidance?

EPA Guidance currently does not adequately deal with situations where a compound is present endogenously, either as an essential nutrient (e.g., manganese) or as a product of normal metabolism (e.g., formaldehyde, acetone).

4. Current guidance discusses how to describe confidence in hazard conclusions (see, for example, the Cancer Guidelines, section 2.5 "Weight of Evidence Narrative" or Guidelines for Developmental Toxicity, Table 3) and discusses presentation of uncertainty in dose response (see for example the Cancer Guidelines, section 3.7 "Dose Response Characterization"). Examples of current practice can also be seen in various recent EPA assessments of specific chemicals or pollutants.

    i. Do SAB members have recommendations for better ways to characterize conclusions and uncertainties in a transparent way?

    ii. Do SAB members have recommendations for better ways to analyze uncertainty, qualitatively or with quantitative analysis?

    iii. What role should statistical analysis play in this characterization?

    iv. Are there methods SAB members recommend for better analyzing and communicating compounded uncertainty, including the use of uncertainty factors, in the hazard identification and dose response process?

The SAB Review of EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments (May 2010, EPA-SAB-011-014, p. 35-42) provided a number of recommendations that are pertinent to this question. In particular, they recommended a number of publications describing useful approaches for characterizing uncertainty quantitatively.

5. The current Agency-wide guidance includes a guideline on cancer assessment, several guidelines for specific noncancer endpoints (e.g., reproductive toxicity, developmental toxicity, and mutagenicity), and guidances or reports on aspects of assessment common to many assessment endpoints (e.g., inhalation dosimetry, body-weight scaling of oral doses, benchmark dose technical guidance, risk characterization).

    i. Are there specific areas within these documents on which there have been advances in risk assessment that should be reflected in updated guidelines?

    ii. Are there areas of overlap or disagreement between these guidelines?

    iii. What issues or guideline documents would SAB members prioritize for update?

    The EPA Risk Characterization guidelines should be updated to provide guidance consistent with the OMB Memorandum "Updated Principles for Risk Analysis" (OMB 2007, M-07-24) and considering the recommendations in the SAB Review of EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments (May 2010, EPA-SAB-011-014, p. 35-42).

6. Given current understanding of how risk assessments are used in decision making, are there considerations or changes to existing guidance with respect to problem formulation, assessment, data integration, and risk characterization that SAB members recommend EPA consider? Do SAB members have specific recommendations as to questions of importance to decision makers that are not being addressed by current risk assessments?

Data integration has not typically been performed well in EPA risk assessments. In particular, there has been a strong tendency to focus on the hazard identification, selection of critical study, and dose-response analysis. Despite the emphasis of the current cancer guidelines on the use of MoA evaluation to direct the risk assessment approach, recent assessments have failed to incorporate MoA information in any meaningful way. There appears to be an unwillingness to include risk estimates based on alternative MoA-based approaches. In the case of the dioxin cancer assessment, the agency has repeatedly resisted NAS requests to show the results of dose-response assessments based on both the linear default and a more scientifically plausible nonlinear approach. The recent risk assessments for arsenic and formaldehyde also failed to use available data informing the mode of action, and have relied solely on default dose-response approaches. Future guidance needs to be more directive regarding the necessity of characterizing the impact on the risk assessment of the key decisions made, including presentation of the range of risk estimates that would result from different MoA assumptions. Cf question 7 for additional comments regarding risk characterization.

7. The purpose of some risk assessments (to quantify dose-response or reference values protective of the most sensitive receptors) and the purpose of the assessment of risk to inform benefits in an economic analysis (to create a predictive analysis for judging the effectiveness and feasibility of a regulatory action) can be quite different. As a result, the evaluation methods and key decision points can be quite different. For example, risk assessors may choose a benchmark dose at the high end (>95 percentile) of a distribution in order to define a level likely to avoid adverse effects, while economists may prefer risk assessors characterize the entire distribution or, at a minimum, use benchmark doses in the middle of the distribution, to inform benefit analyses.

Conducting a risk assessment for use in benefit analysis requires much more than just using a different percentile in the dose-response analysis. Every step in the assessment, including analytical methods and key decision points, must be addressed from the viewpoint of "most likely" or "most biologically plausible" rather than "most sensitive" or "health protective".

   i. Do SAB members think risk assessments are providing the information needed by risk managers and those estimating the benefits of potential decisions? If not, what do SAB members recommend might make hazard and dose response analyses more useful to decision makers?

      Often, but not in all cases. Most importantly, assessments should include a transparent and comprehensive risk characterization that is consistent with the OMB Memorandum "Updated Principles for Risk Analysis" (OMB 2007, M-07-24). Important characteristics include:

- Characterizations of risks and of changes in the nature or magnitude of risks should be both qualitative and quantitative, consistent with available data. The characterizations should be broad enough to inform the range of policies to reduce
risks.

- Judgments used in developing a risk assessment, such as assumptions, defaults, and uncertainties, should be stated explicitly. The rationale for these judgments and their influence on the risk assessment should be articulated.

ii. Should EPA's guidance direct staff to consider as part of the development of the assessment the questions decision makers need answered in the end use of the assessment?

Yes, the guidance should emphasize the important of a problem formulation and scoping step early in the development of the assessment that summarizes the agency's understanding of the kinds of information needed by the decision makers that will use the assessment and typical scenarios to which the assessment may be applied. These factors should then be considered when defining the scope and content of the assessment.

With these questions guiding, but not limiting, your review, please provide input to help guide the Agency as it initiates an update to the 2005 EPA Guidelines for Carcinogen Risk Assessment and develops guidelines for noncancer risk assessment.

Dr. Joanne English

June 21, 2019

To: Science Advisory Board, U.S. Environmental Protection Agency
From: Joanne Caroline English, Ph.D., DABT Independent Consultant,
Menlo Park, CA, Member, Chemical Assessment Advisory Committee
RE: Actions Related to Updating EPA Guidelines for Carcinogen and Noncancer Assessment

I am an independent consultant and member of the standing Chemical Assessment Advisory Committee of the Science Advisory Board. At the invitation of the SAB, I joined by phone the June 5, 2019 meeting agenda session titled "Consultation on Updating EPA Guidelines for Carcinogen and Non-Cancer Risk Assessment," and was asked to provide comments on charge questions provided in the EPA presentation and associated document titled "SAB Consultation on Updating EPA Guidelines for Carcinogen and Non-Cancer Risk Assessment."

I offer the following responses to the overarching questions posed by EPA. The responses (below) reflect my suggested priorities for new guidance and updating existing guidance. The suggestions reflect progress in the science supporting risk assessment since publication of previous US EPA guidelines, guidance documents, and technical panel reports. These priorities will modernize risk assessment in keeping with scientific advances, and will clarify procedures for risk assessment practitioners who utilize these US EPA documents in developing human health risk assessments.

Q1. Are there particular aspects of existing Agency risk assessment guidance related to cancer and non-cancer endpoints that individual SAB members recommend be revised or augmented to incorporate updated scientific information (based on your experience in usage, new information, or scientific advances)?

Responses to Q1.

- Risk assessment guidance should be updated to provide an expanded dose-response analysis framework for the evaluation of all chemicals, recognizing the existence of biological thresholds and susceptible and variably exposed populations. A mode of action analysis, using in silico, in vitro and in vivo assays as outlined in Cohen et al. (2019) reflects current understanding of the etiology of cancer and provides a more scientific basis for human cancer risk assessment. The guidance document should address what evidence supports a directly mutagenic mode of action (i.e., DNA reactivity and mutagenicity) versus modes of action associated with cancer precursor effects (e.g., enhanced cell proliferation, immunosuppression). Guidance should also specify the data needed to assign a non-mutagenic mode of action.

- Guidance on the derivation of non cancer RfDs needs expansion and refinement. Some areas that would benefit from additional guidance include: when it is or is not appropriate to apply a dosimetric adjustment factor to a point of departure to calculate a human equivalent dose; guidance for assessing risk for different exposure durations, which can ultimately inform the

chronic RfD (Minnesota Department of Health https://www.health.state.mn.us/communities/environment/risk/guidance/ gw/table.html); updated guidance for assessing risks among susceptible and/or variably exposed populations, including at different life stages, as identified in NRC, 2009.

- The use of default uncertainty factors in the derivation of RfDs needs further elaboration. Some examples of areas needing additional information include: criteria for the use of mechanism/mode of action data and adverse-outcome-pathways to inform the selection of uncertainty factors; use of structure-activity relationships, read-across, and/or high-throughput assays for addressing data gaps and informing uncertainty factors; selection of uncertainty factors in the derivation of target organ-system specific RfDs (i.e., for secondary health effects with application to cumulative risk assessments) versus overall RfDs (i.e., primary or critical health effects).

- Further guidance is needed on approaches to grading the confidence in risk conclusions, and documenting such conclusions in the form of a summary statement, as requested in the Panel reviews of recent IRIS toxicological assessments (e.g., benzo(a)pyrene and hexahydro-1,3,5- trinitro-1,3,5-triazine).

Q2. Are there important topic areas that are not fully represented in existing Agency risk assessment guidance related to cancer and non-cancer endpoints that SAB members recommend EPA address in guidance? What current information supports this recommendation?

Response to Q2.

- Agency risk assessment guidance does not currently address literature search strategies, standardized methods for identifying evidence and grading the quality of evidence, and data synthesis and integration. For the IRIS process, NRC (2011) recommended that a description be included of search strategies used to identify studies with the exclusion and inclusion criteria clearly articulated. In Panel reviews of recent IRIS toxicological assessments (e.g., benzo(a)pyrene and hexahydro-1,3,5- trinitro-1,3,5-triazine) the need for more transparency in the study inclusion and exclusion criteria was identified, including approaches used for including or excluding in vitro and mechanistic studies. Methodology and tools for conducting systematic reviews, consistent with the process being implemented by the IRIS program (e.g., Systematic Review Protocol for the Inorganic Arsenic IRIS Assessment, 2019), should be documented for the purpose of guiding risk assessment practitioners, and likewise, guidance should be provided for conditions or risk assessment contexts where systematic review is or is not warranted.

- Agency guidance is currently not available and should be developed on the use read-across methods, including (quantitative) structure-activity relationships (QSAR) and high throughput assays, for filling data gaps for chemical-specific risk assessments, as well as for grouping chemicals for the purpose of chemical class risk assessments. Guidance relating to the extent and type of evidence necessary to support read-across is needed, as well as guidance on how to document read-across justifications, assess data quality, and characterize uncertainty (Ball

et al. 2016). It would also be helpful for the Agency to provide criteria and/or contexts for implementation of existing international guidance (e.g., OECD 2014 Guidance on Grouping of Chemicals, 2nd Edition; (http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2014)4&doclanguage=en) or future EPA read-across guidance.

- Guidelines for immunotoxicity risk assessment for chemicals (as has been developed by the WHO, 2012) was identified as a need by the Panel review of the benzo(a)pyrene toxicological assessment.

References cited

N. Ball, M.T. D. Cronin, J. Shen, et al. 2016. Alternatives to Animal Experimentation 33(2), 149-166. http://dx.doi.org/10.14573/altex.1601251

NRC (National Research Council) 2009. Science and Decisions: Advancing Risk Assessment. Washington, DC: The National Academies Press.https:// doi.org/10.17226/12209.

NRC (National Research Council). 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde.Washington, DC: National Academies Press.

S.M. Cohen, A.R. Boobis, V.L. Dellarco, J.E. Doe, P.A. Fenner-Crisp, A. Moretto, T.P. Pastoor, R.S. Schoeny, J.G. Seed, D.C. Wolf. 2019. Chemical carcinogenicity revisited 3: Risk assessment of carcinogenic potential based on the current state of knowledge of carcinogenesis in humans. Regul Toxicol Pharmacol, 103, 100-105. ISSN 0273-2300,https://doi.org/10.1016/j.yrtph.2019.01.017.
http://www.sciencedirect.com/science/article/pii/S0273230019300170

Dr. David Hoel

I am very late and simply have only a few quick technical comments about EPA's risk assessment process that I would like to see addressed.

1) While testifying a few years ago in the Senate to Barbara Boxer and her environmental sub-committee about EPA's handling of TCA, I suggested that EPA use outside experts during their analysis and report development instead of waiting for comments and criticisms from the SAB. This should be done with sensitive materials such as dioxin, formaldehyde etc.
2) EPA uses the linear-no-threshold (LNT) dose-response model in estimating low-dose cancer risk. There has been some suggestion that this may over estimate cancer risks at very low doses especially for radiation. However, recent data analyses and committee reports dismiss this idea. What EPA has not addressed is that bystander effects at low radiation exposures may actually result in the use of the LNT risk model to underestimate the low-dose cancer risks. (see e.g. Brenner et al. Rad Res 155:402-8: 2001). An example is the linear extrapolation of radon lung cancer effects extrapolated from the uranium miner studies. The data is very linear but actually underestimates the low-dose effects observed in residential epidemiology studies by a factor of 4 (see Brenner and Sacks: Int. J. Rad. Biol. 78:593-604 (2002)).
3) EPA's IRIS reports include mechanisms, toxicology and epidemiology in developing their cancer risk estimates. Being on a review committee for them on dioxin, I asked if the mechanism/biology section in the IRIS reports had ever impacted the quantitative risk estimates. I was told no except possibly for formaldehyde. Hopefully better use of the non-epidemiology data will impact the quantitative cancer risk estimates that are typically based on epidemiology.
4) For non-cancer effects, safety factors are usually employed with limited epidemiology data. I would like to see a good justification of the particular factors that are used e.g. 10, 20 etc. An example was EPA using a small worker study involving asbestos and plural plaques. Because of being a small unrepeated study the estimated acceptable exposure using a series of large safety factors resulted in a lower acceptable exposure level than that calculated for asbestos and lung cancer. There was of course the argument that plural plaques are a marker of exposure and not an actual adverse health effect.

Dr. Michael Jayjock

Unfortunately, I could not attend the June 5 meeting given the invitation of June 3. I assume that the SAB members originally invited were given the materials more than 2 days in advance of this meeting, wherein we, of course, were not. Given my non-attendance at the meeting, my previous personal and professional commitments, the short deadline of June 26, I do not have the time to review and study the background material sufficiently. As such, I do not intend to provide focused and detailed comments to the charge questions. I do have some opinions and comments on the determination and deliberation of exposure limits which I will provide below. Hopefully these will be of some interest and value.

My sense is that the Cancer Guidelines and the current EPA methodologies for non-cancer should be combined since there is really no objective evidence for their separation. From my study of this issue, there is no reasonable way to technically prove the existence of a threshold for non-carcinogens or non-genotoxic carcinogens. Similarly, there is no definitive evidence that genotoxic carcinogens do not have a threshold of effect. Indeed, there is evidence that some fairly potent genotoxic carcinogens have actually displayed a hormesis effect at low dose.

I believe that it is time to admit to the above reality and treat the sentinel adverse health response from a chemical's exposure, whatever it might be, as the end-point to be addressed with a quantitative assessment (QRA) in both cases. EPA's group responsible for crafting the BMDS and CatReg dose-response software has done an outstanding job of providing tools for extracting the most information from the available data. Adding to this, the knowledge gained in rare, but extremely valuable, PBPK models for target tissue can really enhance the ability to do this QRA with information at lower doses We are also posed to add the insight from genomics which may ultimately show and demonstrate objective and quantifiable thresholds for some if not all chemical effects.

My advice is that when one cannot provide a threshold for any effect, a non-threshold should be assumed and an allowable level of putative risk (ca. 1 in 1000) be determined at which an allowable exposure (*i.e.*, exposure limit) can be set. I admit that is likely that this approach would not be politically popular but it would be one that is scientifically honest given our level of uncertainty with any particular chemical.

I and my co-authors put this idea forward some years ago in a paper that I am attaching (see reference below). A more recent publication of the National Academy (also referenced below) has suggested essentially the same approach but with much more elegant statistical and operational detail.

I believe that unless or until we can admit our level of uncertainty in the assessment of both cancer and non-cancer risk at low dose, new work to lower this uncertainty through research will remain on the backburner.

Sincerely,

Mike Jayjock

Michael Jayjock, PhD CIH

References

Jayjock, M., P.G. Lewis, and J. R. Lynch. 2001. Quantitative level of protection offered to workers by ACGIH threshold limit values occupational exposure limits. *American Industrial Hygiene Association Journal*. 62. 4-11. 10.3320/1.2763497.

NRC (2009): Science and Decisions: Advancing Risk Assessment (The Silver Book), Committee on Improving Risk Analysis Approaches Used by the U.S. EPA, National Research Council, ISBN: 0-309-12047-0, 424 pages, 7 x 10, (2009)

Dr. Wayne Landis

Wayne Landis response to SAB Consultation on Updating EPA Guidelines for Carcinogen and Non-Cancer Risk Assessment

Introduction

As a member of the CAAC I have not been a part of this consultation until just before the SAB committee meeting. My background is in environmental toxicology and ecological risk assessment. In my research we routinely incorporate cumulative effects, extrapolation issues, and now incorporate the connection to human well-being. During the discussion regarding the update process I did hear questions regarding the issues with cumulative impacts, the issues regarding the integration of economics and risk, issues regarding p-values and discriminating between false positives and false negatives.

Many of the points I will make have already been covered in the NRC document Science and Decisions (Silver Book) published in 2010 and funded by EPA. I served on a special SAB committee in response to that report on how to improve the integration of science into decision making at EPA. I will refer to that document in several of my replies. Although nine years old this document and the included recommendations provide a good starting point for updating EPA's risk assessment methodology.

The three documents that I concentrated in reviewing are the 2005 Cancer (EPA/630/P-03/001F) document, the 2012 Benchmark Dose Technical Guidance (EPA/100/R-12/001), and the 2014 Framework for Human Health Risk Assessment to Inform Decision Making (EPA/100/R-14/001).

There are unanswered questions. There are many articles written on these topics by authors from USEPA and from around the world. I will leave it to others to fill in those blanks and instead concentrated on the items I am most familiar with.

Definition of risk

The term risk is used to mean many things. In my analysis of the adverse outcome pathway literature "risk" is often used to be synonymously with hazard. In other literature "risk" is mistaken for mere probability. In the field of risk assessment, the term has a very specific meaning.

A publication by NAS, *Gene Drives on the Horizon* (2016) defines risk as:

"Risk is the probability of an effect on a specific endpoint or set of endpoints due to a specific stressor or set of stressors.

In this probabilistic definition, the stressor is any agent or actor with the potential to alter a component of the ecosystem. The effect refers to potential beneficial and harmful outcomes. And, an endpoint is a societal, human health, or environmental value that is to be managed or protected. Endpoints reflect decisions that need to be made, and are sometimes determined by regulatory requirements (NAS 2016 pages 112-113)."

Such a definition requires that probability distributions are calculated, that the various types of uncertainties described and that consultation with the users be conducted. To the extent the framework and tools used to calculate risk do not meet these requirements then it is not a risk assessment-but is more properly described as a hazard evaluation. The following sections in this chapter also describe how this definition applies to the evaluation of probability, cultural values, public engagement and uncertainty.

The description of risk in this document is compatible with that used in the Silver Book and can be applied to a wide range of endpoints regarding human health and well-being, ecological endpoints, to cumulative effects and to a comparable range of chemical and non-chemical stressors.

Distributions and experimental design

Often there is an assumption that the distribution of exposures, toxicity, error terms or confidence intervals are Gaussian (normal). Such an assumption also introduces uncertainty. In the 2012 Benchmark Dose guidance there are many examples of graphs supposedly depicting exposure-response relationships that instead of plotting the data, depict the response as a mean with a 95 percent confidence interval. I much prefer the raw data to be presented or the use of a box and whisker plot. It is then straightforward to evaluate the variability in the dataset.

The examples in the Benchmark Dose guidance document appear to be experimental designs with doses set to be analyzed using ANOVA with multiple comparisons for a probit to estimate the EC50 (see Figure 1). However, the portion of the exposure-response curve that we are interested in is that at the low dose and low or no response portion. Why not increase the number of doses at those lower values to ensure that this portion of the response is characterized with the lowest uncertainty. Indeed, if a regression model is being used to describe the exposure-response relationship then there should be more doses as a trade-off with and few or no replications. I understand that designing toxicity experiments to enhance the power of the regression will require a restructuring of testing guidance.

Also note that the confidence interval describes the 95 percent range of the regression line, not the range of the possible outcomes. Credible intervals may be of more interest but will require a move away from frequentist approaches—as USEPA has already begun to do.

Cumulative impacts

A long-time issue in the evaluation of toxicity is that the focus on single chemical effects is inherently not realistic. People are exposed to a variety of chemical and other stressors that can affect a toxicological response and risk should be able to be placed in a realistic context.

Chapter 7, Implementing Cumulative Risk Assessment of the Silver Book has a number of approaches that can be used to estimate risk. I am very familiar with the relative-risk model (RRM) as described on page 222. The key to the RRM is that it uses ranks (categories) that allow the combination of various stressors to be analyzed to a variety of endpoints. Since the publication of the Silver Book there have been a number of important developments. The current relative risk model uses Bayesian networks (not to be confused with Bayesian statistics) to inherently deal with uncertainty, variability, and expert judgement to calculate a probability distribution that can be categorized to represent specific (for example, low risk) outcomes. It is possible to simultaneously derive ecological and human health endpoints (Harris et al. 2017). J. Carriger of USEPA National

Risk Management Research Laboratory (Cincinnati) is at the forefront of using Bayesian networks to inform management decisions.

Adverse outcome pathways
In some ways it was refreshing not to read about adverse outcome pathways (AOPs). However, AOPs are part of a major effort to EPA and other agencies across the world to describe toxicological pathways. Although the papers often describe how AOPs are important to risk assessment I can only see them as another part of hazard assessment. To date I cannot find AOPs to be adequately quantitative or probabilistic to be applicable to risk assessment. However, AOPs may be important in building conceptual models to describe cumulative effects. Hooper et al (2013) has demonstrated how AOPs can be used to describe the interactions between chemical sensitivity and climate.

Geographic information systems
The use of geographic information systems (GIS) is now commonplace in the estimation of human health and environmental risk. For the clean-up and long-term management of contaminated sites under RCRA and CERCLA a spatially explicit mapping of risk through a landscape is very useful. In the HHRA framework document I found only one mention of GIS and that was in relationship to computer science. There are many examples of the utility of GIS tools in estimating risk in a spatially explicit manner. Since my risk assessment publications since the late 1990s have all had spatially explicit components (Landis and Wiegers 1997 to Graham et al 2018) I may have a particular point of view. But a simple review of the literature will point to many other examples from across the world.

The responses to specific questions follow.

1. Are there particular aspects of existing Agency risk assessment guidance related to cancer and non-cancer endpoints that individual SAB members recommend be revised or augmented to incorporate updated scientific information (based on your experience in usage, new information, or scientific advances)?

As noted in the first section, the questions of mixtures of chemicals and confounding factors needs to be clearly addressed. In addition, even with the development of the BMD approach there is still a lot to be accomplished in the statistical understanding of exposure-response. Shao et al (2018) now have a web-based resource for using a Bayesian approach to BMD estimation but it is not clear how widely this has been used in the agency. Bayesian curve-fitting has now been around since the 2000s and Fox (2010a, 22010b) provide some excellent examples. Chiu et al 2018 and Yang et al (2018) provides some additional examples, including the combining of mixtures to estimate toxicity.

2. Are there important topic areas that are not fully represented in existing Agency risk assessment guidance related to cancer and non-cancer endpoints that SAB members recommend EPA address in guidance? What current information supports this recommendation?

The statistical guidance is dated and there are much better ways of presenting the analysis of exposure-response. I would prefer that data be plotted on the graphs, that a Bayesian regression

approach be taken to estimate the relationship and that credibility intervals take the place of confidence intervals.

The fundamentals of exposure-response and the use of R is now an undergraduate level program at my and other institutions.

As these tools become more widely available it will also be time to revisit the fundamental assumptions of routine toxicity testing. To improve the characterization of an exposure-response cure it will be necessary to increase the number of doses that are experimental units. In cases where categorical data are being taken, as in histopathological studies, tools such as similarity analysis can be applied (Fox and Landis 2016).

The guidance also does not adequately cover the topic of causality. There have been a number of advances in the field especially in the study of artificial intelligence. Pearl and McKenzie's The Book of Why: The New Science of Cause and Effect (2018) is a great introduction. The ladder of causality model is a good start. I suggest that such an approach will incorporate and then supersede the weight of evidence approach. The key point is that so much of the weight of evidence approach can be made into a quantitative description.

3. Are any key elements of hazard and dose-response analysis —including analytical limitations, heterogeneity, natural variability, and non-ambient exposures (i.e., endogenous or indoor exposures)—not adequately characterized in guidance?

4. Current guidance discusses how to describe confidence in hazard conclusions (see, for example, the Cancer Guidelines, section 2.5 "Weight of Evidence Narrative).e" or Guidelines for Developmental Toxicity, Table 3) and discusses presentation of uncertainty in dose response (see for example the Cancer Guidelines, section 3.7 "Dose Response Characterization"). Examples of current practice can also be seen in various recent EPA assessments of specific chemicals or pollutants.

This question and the items below are all parts of the same issue of dealing with uncertainty. I use Regan et al (2002) as my fundamental taxonomy. Although developed for the environmental sciences I have found it particularly useful no matter the subject of a risk assessment.

Whenever possible I opt for a quantitative analysis. A qualitative analysis opens the door to linguistic uncertainty, such as how safe is safe, and significant versus statistically significant.

I have also had difficulty finding where the role of sensitivity analysis is described in EPA guidance. A proper sensitivity analysis can point to variables where the uncertainty is not going to drive the final calculation. I have made sensitivity analysis an integral part of all of our risk assessments. Sensitivity analysis is critical in understanding the risk assessment.

   i. Do SAB members have recommendations for better ways to characterize conclusions and uncertainties in a transparent way?

Risk communication is its own field of study. I would start with the basics and there are a number of experts in the field at the many schools of public health.

ii. Do SAB members have recommendations for better ways to analyze uncertainty, qualitatively or with quantitative analysis?

Same question as below.

iii. What role should statistical analysis play in this characterization?

A major role. Not just frequentist approaches, there are many other tools that are available. A major issue in the field of risk assessment and many others, is the misinterpretation of p values, confidence intervals are related subjects. The documents that I reviewed had no guidance on these issues. I suggest that Greenland et al (2016) is a good start but there are many similar papers.

iv. Are there methods SAB members recommend for better analyzing and communicating compounded uncertainty, including the use of uncertainty factors, in the hazard identification and dose response process?

The use of uncertainty factors is fraught with numerous issues, so many that I recommend that they not be used. The Silver Book has an excellent section describing these issues. It is one of my frustrations with my prior service on SAB committees that so few reforms followed the recommendations from this document or the EPA SAB subcommittee that reviewed the interactions between science and decision making.

5. The current Agency-wide guidance includes a guideline on cancer assessment, several guidelines for specific noncancer endpoints (e.g., reproductive toxicity, developmental toxicity, and mutagenicity), and guidances or reports on aspects of assessment common to many assessment endpoints (e.g., inhalation dosimetry, body-weight scaling of oral doses, benchmark dose technical guidance, risk characterization).

   i. Are there specific areas within these documents on which there have been advances in risk assessment that should be reflected in updated guidelines?

   ii. Are there areas of overlap or disagreement between these guidelines?

   iii. What issues or guideline documents would SAB members prioritize for update?

The 2014 Framework for Human Health Risk Assessment to Inform Decision Making seems not much more than the 1998 Guidance for Environmental Risk Assessment rewritten for human health. It is dated and references work primarily of the US government and their researchers. There is a lot of valuable work being conducted across the world and in non-governmental laboratories. There is a lack of description regarding how to make risk assessment quantitative and how to communicate effectively. If the framework is not solid, I do not see how the supporting materials can be effectively described.

6. Given current understanding of how risk assessments are used in decision making, are there considerations or changes to existing guidance with respect to problem formulation, assessment, data integration, and risk characterization that SAB members recommend EPA consider? Do SAB members have specific recommendations as to questions of importance to decision makers that are not being addressed by current risk assessments?

7. The purpose of some risk assessments (to quantify dose-response or reference values protective of the most sensitive receptors) and the purpose of the assessment of risk to inform benefits in an economic analysis (to create a predictive analysis for judging the effectiveness and feasibility of a regulatory action) can be quite different. As a result, the evaluation methods and key decision points can be quite different. For example, risk assessors may choose a benchmark dose at the high end (>95 percentile) of a distribution in order to define a level likely to avoid adverse effects, while economists may prefer risk assessors characterize the entire distribution or, at a minimum, use benchmark doses in the middle of the distribution, to inform benefit analyses.

Items 6 and 7 are related questions. The first part of a risk assessment should be to ask specific questions regarding the problem. I do not understand how an organization with the high-quality scientists available to it would ever stop at a benchmark dose analysis when the entire distribution is now easily calculated. If you are using a percentile then you already have the distribution.

i. Do SAB members think risk assessments are providing the information needed by risk managers and those estimating the benefits of potential decisions? If not, what do SAB members recommend might make hazard and dose response analyses more useful to decision makers?

That is a question better answered by the decision makers—but given the question exists I suspect that the answer is no. hazard and dose-response analyses are not generally used by decision makers. However, the results are and there should be care given in how risk communication occurs.

ii. Should EPA's guidance direct staff to consider as part of the development of the assessment the questions decision makers need answered in the end use of the assessment?

The first question in any risk assessment is how decision makers are going to use the document. That is something that the 2014 guidance document does get correct. I have found that many decision makers are not always clear about the questions that they need to have answered. Most decision makers do not have the necessary expertise to evaluate statistics or dose-response curves. It is up to the risk assessor to describe the materials in such a manner to enable the decision maker to move forward and to be able to defend that decision.

In the early development of risk assessment as in the Red Book there was concern that communication with decision makers and risk managers would taint (bias) the risk assessment. One of the major accomplishments of the 1992 Ecological Risk Assessment Framework and the 1998 Guidance is that communication with the decision makers was made a critical part of the risk assessment. It is frustrating to have answered the wrong question.

References

Chiu, W.A., Axelrad, D.A., Dalaijamts, C., Dockins, C., Shao, K., Shapiro, A.J. and Paoli, G., 2018. Beyond the RfD: Broad Application of a Probabilistic Approach to Improve Chemical Dose–Response Assessments for Noncancer Effects. Environmental Health Perspectives, 126:067009.

Fox, D.R., 2010. A Bayesian approach for determining the no effect concentration and hazardous concentration in ecotoxicology. Ecotoxicology and environmental safety, 73:123-131.

Fox, D. R. 2010. B-Tox: A Bayesian Facelift for Ecotoxicology**.** Proceedings JSM 2010 (Session 640: Models in Risk Analysis) Vancouver CA.

Graham SE, Chariton AA, Landis WG. 2019. Using Bayesian networks to predict risk to estuary water quality and patterns of benthic environmental DNA in Queensland. *Integr Environ Assess Manag*. 15:93-111

Greenland, S., Senn, S.J., Rothman, K.J., Carlin, J.B., Poole, C., Goodman, S.N. and Altman, D.G., 2016. Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations. European Journal of Epidemiology, 31:337-350.

Harris, M.J., Stinson, J. and Landis, W.G., 2017. A Bayesian Approach to Integrated Ecological and Human Health Risk Assessment for the South River, Virginia Mercury-Contaminated Site. Risk Analysis, 37:1341-1357.

Landis, W. G. and J. A. Wiegers. 1997. Design considerations and a suggested approach for regional and comparative ecological risk assessment. *Human and Ecological Risk Assessment*. 3:287-297.

Shao, K. and Shapiro, A.J., 2018. A web-based system for Bayesian benchmark dose estimation. Environmental health perspectives, 126:017002.

Pearl, J. and Mackenzie, D., 2018. The book of why: the new science of cause and effect. Basic Books.

Regan H, Mark Colyvan, Mark A. Burgman. 2002. A Taxonomy and Treatment of Uncertainty for Ecology and Conservation Biology. Ecological Applications, 12: pp. 618-628

Yang, G., Li, J., Wang, Y., Chen, C., Zhao, H. and Shao, K., 2018. Quantitative ecotoxicity analysis for pesticide mixtures using benchmark dose methodology. Ecotoxicology and Environmental Safety, 159:94-101.

Dr. Dennis Paustenbach

I have reviewed the various contributions of members of the SAB which are presented in the letter which you distributed. I believe they represent all the various points of view that EPA staff and management should consider.

Like many others, I had hoped that toxicology, cancer research, low dose modeling, and our understanding of mechanism of action (per chemical and per disease) would have matured significantly over the past 15 years. In some ways it has but, generally, it has been inadequate to definitively tell us how to do a better job at characterizing the risks at the very low doses of various chemicals to which most persons are exposed routinely in their daily lives.

All I would say is that I do believe it is time for EPA to focus more on those carcinogens that are clearly genotoxic rather than those that appear to act through non-genotoxic mechanisms (often due to high dose effects). It is clear to me, although not everyone would agree, that the linearized multi-stage model is unable to account for the dozens of compensatory mechanism that clearly exist at low doses which render virtually all chemicals to be harmless at those levels. Dozens of papers of the past 15-20 years that have attempted to study such doses in whole animal studies seem to clearly show this to be true. These are discussed by a number of persons who submitted comments.

I am also aware of the dozens of in-vitro assays that can identify some effects which are different than background at very low doses but, of course, these assays don't have the benefit of the myriad of compensatory mechanisms that are present in whole animal models.

It is noteworthy, and I wish I would have submitted lengthy comments on this matter, that research in the area of genomics is giving us insight regarding the appropriateness, or lack thereof, of our classic rodent bioassays. Most of us believe that the rats and mice commonly used in the cancer bioassays are bred to be particularly susceptible to a number of cancers. Originally, this was thought to be prudent since the goal was to be sure that a chemical which might have carcinogenic potential would be identified. Over the years, in my view, it has become clear that humans are not as susceptible to developing tumors at low doses as these animals (simply by looking at cancer trends per organ in various epi studies).

It would be helpful if EPA would acknowledge the conservatism or bias that occurs when we use cancer susceptible strains in the bioassay. It is hoped that work by the Jackson Lab and others with respect to developing strains of mice (and hopefully rats) that are more representative of humans will soon be available. Soon, using our insights on gene characterization, toxicologists and geneticists will be able to recommend new animal models which will be more accurate predictors of the human response. Recent papers by the Jackson Lab and NIEHS suggest that we are not far away from being able to suggest changes in the basic bioassay. I suggest that this be discussed in this new guidance document. When the better outbred mice or rat is available and known to be more representative of humans, I suggest we recommend its use.

Thus, to the extent that EPA can better describe the limitations of the predicting cancer risks at low doses, and identify equally valid approaches for estimating those risks (and there are surely several), that would be beneficial to society. It is, I believe, our job to share with the public that we really are not certain of the risks for most chemicals in our diets, the water, and in the air but we

can with confidence tell them whether we think the risks are trivial. When we are not sure that they are trivial, we should share with them the wide range of risks that are plausible rather than identify a single point estimate.

Respectfully,

Dennis J Paustenbach, PhD, DABT, FATS, CIH

Dr. Ted Simon

Memorandum

To: Michael Honeycutt, Ph.D., Thomas Armitage, Ph.D.

From: Ted W. Simon, Ph.D., DABT

Date: June 10, 2019

Re: SAB Consultation on Updating EPA Guidelines for Carcinogen and Non-Cancer Risk Assessment

The purpose of this memo is to provide my comments on the seven items in the subject document provided to me by Dr. Armitage by email on June 7, 2019. Please feel free to share this memo as needed.

Item 1: Are there particular aspects of existing Agency risk assessment guidance related to cancer and non-cancer endpoints that individual SAB members recommend be revised or augmented to incorporate updated scientific information (based on your experience in usage, new information, or scientific advances)?

Comment: In my opinion, the most important item to consider for guidance related to both cancer and non-cancer endpoints is mode-of-action (MOA). Mode-of-action (MOA) provides the central organizing principle for understanding the biological underpinnings of toxicity. In US government guidance documents, MOA was first mentioned in the National Research Council's 1993 document Issues in Risk Assessment. [1] This publication considered three issues: the use of the maximally-tolerated dose (MTD) in animal bioassays for cancer; the two-stage initiation/promotion model of carcinogenesis as a regulatory tool; and a paradigm for ecological risk assessment. Mode-of-action was mentioned with regard to the use of the MTD in animal bioassays. The report concluded that bioassays employing the MTD would need additional studies to determine "mode-of-action, pharmacokinetics and applicability of results to the human experience." [1]

Mode-of-action (MOA) provides the central organizing principle for understanding the biological underpinnings of toxicity. In US government guidance documents, MOA was first mentioned in the National Research Council's 1993 document *Issues in Risk Assessment*. [1] This publication considered three issues: the use of the maximally-tolerated dose (MTD) in animal bioassays for cancer; the two-stage initiation/promotion model of carcinogenesis as a regulatory tool; and a paradigm for ecological risk assessment. Mode-of-action was mentioned with regard to the use of the MTD in animal bioassays. The report concluded that bioassays employing the MTD would need additional studies to determine "mode-of-action, pharmacokinetics and applicability of results to the human experience." [1]

How much detail is needed to specify a mode-of-action for a particular type of cancer—whether in humans or in animals? EPA indicates that data richness is

generally a prerequisite for determining MOA and defines the term as follows:

> *The term "mode-of-action" is defined as a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation. A "key event" is an empirically observable precursor step that is itself a necessary element of the mode-of-action or is a biologically based marker for such an element. Mode-of-action is contrasted with "mechanism of action," which implies a more detailed understanding and description of events, often at the molecular level, than is meant by mode-of-action. The toxicokinetic processes that lead to formation or distribution of the active agent to the target tissue are considered in estimating dose but are not part of the mode-of-action as the term is used here. There are many examples of possible modes of carcinogenic action, such as mutagenicity, mitogenesis, inhibition of cell death, cytotoxicity with reparative cell proliferation, and immune suppression.* [2]

EPA's 2005 *Guidelines for Carcinogen Risk Assessment,* from which the above passage was taken, indicates that consideration of mode-of-action should be the centerpiece of any cancer risk assessment. While data richness is highly desirable, even sparse data can be considered in a MOA analysis and, perhaps more important, cancer occurs through finite number of pathogenic mechanisms. These mechanisms necessarily limit the number of MOAs that may be operative for a given tumor type. [3–7]

In the absence of mode-of-action information, EPA'S regulatory policy for cancer assumed that the dose-response was linear in the low dose region. Implicit in the assumption that the dose-response of a chemical is linear all the way down to zero dose is the outlandish notion that a single molecule of a substance may produce adverse effects—a health-protective assumption but also both biologically incorrect and frankly ridiculous.

Even considering only DNA-reactive chemicals as mutagenic is incorrect. This assumption of mutagenicity is an artefact from the 1970s when regulatory scientists adopted the linear no-threshold hypothesis before the fact of DNA repair mechanisms became common knowledge. [8–17]

DNA-reactivity does not necessarily lead to mutations or to cancer. Dr. Ken Olden, former head of EPA's National Center for Environmental Assessment (NCEA), wrote a perspective in the journal *Cancer Prevention Research* commenting on a paper by Johnson et al. in which rats were given both aflatoxin-b1, a potent liver carcinogen in many species that acts via DNA reactivity, with and without an oleanane triterpenoid that activates cellular anti-oxidant pathways. The rats were treated for 28 days and followed for 104 weeks or until death. The triterpenoid reduces both levels of DNA adducts and the size and number of pre-cancerous foci. Dr. Olden emphasized the value of chemoprevention. Dr. David Eaton noted in another commentary in the same issue of the journal that not only did the rats receiving the triterpenoid have lower adduct burdens but also had control levels of pre-cancerous foci. Dr. Eaton notes in

the abstract:

> *... extensive AFB–DNA adduct formation was seen in all animals at early time points, including those treated with CDDO-Im, albeit at lower levels ($30% of the untreated animals), suggesting a strong divergence in the association between early DNA-damaging events, and tumor formation later in life. The authors suggest that this provides compelling experimental support for the concept of carcinogenic "thresholds" for mutagenic chemicals, because the treatment reduced persistent, mutagenic adducts (AFB–FAPyr adducts) only by 70%, but nearly completely eliminated tumors after approximately 2 years and preneoplastic lesions 6 weeks after the last dose of AFB.* {Eaton and Schaupp, 2014, #53705}

In my opinion, the best starting point for updating the 2005 cancer guidelines is provided by three papers that appeared in the journal Regulatory Toxicology and Pharmacology early in 2019. The first of these presented a unified theory of carcinogenesis: cancer results from DNA coding errors that arise either by direct interaction of a chemical with DNA to cause a mutation or indirectly by sustained stem cell proliferation with random mutations. Further, those chemicals that acted indirectly could induce proliferation via activation of biological pathways or by cytotoxicity and proliferation to replace damaged cells. [18]

The second paper indicated that the three categories of mode-of-action by which chemicals can induce cancer— 1) direct interaction with DNA or DNA replication including DNA repair and epigenetics; 2) receptor-mediated induction of cell division; and 3) non-specific induction of cell division due to cytotoxicity —have undermined the idea of separating chemicals into carcinogens and non-carcinogens. Hence, considering carcinogenicity as a separate process from toxicities already described by known modes of action provides no additional public health protection.[6]

The third paper pointed out the folly of the time-consuming, costly and animal-intensive two-year bioassays in assuming that such testing can predict human carcinogens. Instead, the authors propose a decision-tree based on the premise that cancer is the consequence of DNA coding errors that arise either directly from mutagenic events or indirectly from sustained cell proliferation. The first type of investigation would be in silico, i.e. QSAR; the second would be in vitro testing and, then, comparison with the threshold of toxicological concern (TTC); the last step would be targeted testing to identify chemicals that might be associated with key characteristics such as immunosuppression, cell proliferation or estrogenicity. [3]

Item 2: Are there important topic areas that are <u>not</u> fully represented in existing Agency risk assessment guidance related to cancer and non-cancer endpoints that SAB members recommend EPA address in guidance? What current information supports this recommendation?

Comment: In my opinion, what is most lacking in current Agency guidance on

hazard characterization is the recognition of the importance of understanding the biology of the disease endpoint. Prior to the identification of the hallmarks of cancer, Cancer was viewed in a monolithic way – as a single disease. In two important publications, the hallmarks were identified and described; various types of cancer could be investigated in terms of how they fostered development of the hallmarks.

The hallmarks include sustaining a blood supply, cell acquiring a limitless ability to replicate, insensitivity to controls on growth, the ability to escape programmed cell death and other features. These acquired hallmarks provide malignant cells with a Darwinian selective advantage over normal cells; in short, cancer cells can scavenge resources, are essentially immortal, and in a very real sense, parasitize the host. The six original hallmarks of cancer are:

. Self-sufficiency in growth signals;
. Evasion of apoptosis;
. Insenstivity to anti-growth signals;
. Sustained angiogenesis;
. Tissue invasion and metastasis; and,
. Limitless replicative potential. [19]

The four next generation hallmarks/enabling characteristics added in 2011 are:

. Dysregulation of cellular energetics;
. Avoidance of immune destruction;
. Genomic instability and mutation; and,
. Tumor-promoting inflammation. [20]

These hallmarks are acquired capabilities of cells that are necessary for tumor growth and progression. The hallmarks are intended to serve as a general set of clinical targets for development of new drugs and treatment protocols. The authors also mention epigenetic changes but in 2010 did not have sufficient information on the relationship of epigenetics and cancer to add another hallmark.

The "war on cancer" was conceived and carried out during the mid-twentieth century when the biology of cancer was relatively unknown. [21, 22] In the twenty-first century, the pathogenesis, key events and causal factors leading to cancer are much better understood – in large part, due to the emphasis on mode-of-action in regulatory toxicology. [23–31]

In the June 7, 2019 issue of *Science*, an article by David Tuveson and Hans Clevers titled "Cancer modeling meets human organoid technology" appeared. The article discussed 3D cultures of human organoids growth from pleuripotent stem cells. Organoids can also be grown from needle biopsies of liver and pancreatic cancer, and from circulating tumor cells in prostate cancer patients.[32] The prospect of understanding the hallmarks and their progression at the level of individual cells will hopefully put to rest the notion that cancer is a single disease entity.

A.B. Hill's 1965 considerations for causality included biological plausibility. Crafting any new hazard characterization guidance that leaves room for inclusion of the growing knowledge of the biology of disease would be, in my opinion, an improvement over current guidance.

Item 3: Are any key elements of hazard and dose-response analysis —including analytical limitations, heterogeneity, natural variability, and non-ambient exposures (i.e., endogenous or indoor exposures)—not adequately characterized in guidance?

Comment: Human heterogeneity takes many forms. In 2010, I published a paper in Human and Experimental Toxicology titled "Just who is at risk? The ethics of environmental regulation." I wrote:

> *Lifestyle, freedom of choice and regulation. Factors based on lifestyle choices can predispose certain individuals to cancer. How can a regulatory agency reconcile the freedom of choice in western societies, including the freedoms to use tobacco products, to drink unhealthy amounts of alcohol, to eat an unhealthy diet, to eschew physical exercise or to text while driving an automobile, with the need for regulatory protection? Is it fair to use society's resources to reduce cancer risk from environmental chemicals in a three-pack a day smoker who will likely contract cancer anyway? Is it fair that government regulators attempt to regulate and possibly reduce cancer risks from environmental exposures when the same sovereign governments treat much higher cancer risk estimates due to workplace exposures as acceptable?*
>
> *Some of us may be unlucky to have inherited genetic factors that predispose us to disease – there are those in the population who, through no fault of their own, are more susceptible to the effects of chemicals in the environment. For these unlucky few, development of a standard that protects less than 100% of the population is democratic tyranny – the foisting of the wishes of the majority upon the unlucky minority, who happen to possess greater genetic susceptibility.* [33]

Agency staff need to have this discussion to determine what constitutes background exposure and background disease risk and how to address these in guidance.

One area of consideration of background that has rapidly matured and needs to be included is the distinction between exogenous and endogenous exposures. An adequate problem formulation for EPA's 2009 formaldehyde assessment would have included the consideration of endogenously produced formaldehyde as an ongoing background exposure. As a species, Homo sapiens cannot escape the effects, deleterious or beneficial, or endogenously produced chemicals. Reactive oxygen species from endogenous sources modify about 20,000 bases of DNA within a single cell each day. [34] Christopher Wild of IARC brought forward the concept of the exposome and indicated that exposures should include not only chemicals entering the body from air, water, food, medicines, or other sources, but also internally generated toxicants produced by the gut flora, inflammation, oxidative stress, lipid

peroxidation, and other natural biological processes. [35, 36]

Ethylene oxide is classified by IARC as carcinogenic to humans is produced endogenously in the liver from endogenously produce ethylene in circulating blood and from the microbiome. [37, 38] Alkylating agents such as methylnitrosourea (MNU) and methylmethane sulfonate (MMS) react with DNA by methylating guanine or thymine bases and induce mutations. S-adenosylmethionine (SAM) is produced
within the body from the amino acid methionine and sometimes taken as an over-the-counter dietary supplement for osteoarthritis and depression. SAM is the major source of endogenous DNA methylation and may contribute to the background mutation rate. [39] Acetaldehyde is a metabolic product of ethyl alcohol and also endogenously produced as a by-product of cellular metabolism. Experiments in cell cultures using with carbon-13-labeled acetaldehyde indicate that at low exogenous exposures, adduct formation from endogenous adducts dominates; this situation reverses at high exposure, however. [40] Formaldehyde reacts with DNA in a similar fashion to acetaldehyde and distinguishing exogenous from endogenous DNA adducts requires the use of formaldehyde labeled with both carbon-13 and deuterium or heavy hydrogen. [35]

Obviously, the presence of endogenous exposures that contribute to cancer risk raises the problem of determining attributable risk. [41] A bottom-up approach for inclusion of including endogenous exposures as a lower bound when calculating a slope factor is one way of dealing with this, should regulatory agencies persist in using the LNT for TRV derivation for cancer endpoints. [42, 43] Another approach is the derivation of endogenous equivalent values using the correlation between external exposure and an internal biomarker. This approach proved to be a pragmatic way to provide context for estimating and managing risks from ethylene oxide exposures. [44]

Item 4: Current guidance discusses how to describe confidence in hazard conclusions (see, for example, the Cancer Guidelines, section 2.5 “Weight of Evidence Narrative” or Guidelines for Developmental Toxicity, Table 3) and discusses presentation of uncertainty in dose response (see for example the Cancer Guidelines, section 3.7 “Dose Response Characterization”). Examples of current practice can also be seen in various recent EPA assessments of specific chemicals or pollutants.

i. Do SAB members have recommendations for better ways to characterize conclusions and uncertainties in a transparent way?

Comment: Beck et al. (2016) provide a range of useful ways for presenting uncertainty in hazard characterization to different audiences. [45]

ii. Do SAB members have recommendations for better ways to analyze uncertainty, qualitatively or with quantitative analysis?

Comment: Risk may be considered as an event, inherent in a situation in which an

item of value to humans is at stake and its continued existence is uncertain. [46] Risk may also be considered as a consequence, inherent in the uncertain outcome of something valued by humans. Uncertainty arises from the same sources and three basic types of uncertainty exist:

- Aleatory uncertainty, that stemming from the risk analyst's inability to specify how known variability in the outcome or factors on which the outcome is based will manifest;
- Epistemic uncertainty, that stemming from the lack of knowledge of the factors that contribute to the outcome; and,
- Ontological uncertainty, that stemming from inappropriate beliefs or misconceptions regarding the causal factors for the outcome.

iii. What role should statistical analysis play in this characterization?

Comment: Problem formulation should determine the role of statistical analysis. , statistics is hardly an end in itself; rather, statistics provides a set of tools for making inferences from data. These inferences naturally lead to predictions. Bayesian methods involve leveraging what one knows already along with some data collected regarding a question or problem to make inferences about the cause of the problem. This situation is exactly the one found in risk analysis. Bayesian methods allow one to model the problem with a range of assumptions and different data sets and form inferences from this collection of models with differing inputs and assumptions,

The National Academy of Science published a document in 2019 titled Reproducibility and Replicability in Science. [47]The NAS defined reproducibility, replicability and generalizability. The last of these is the extent to which the results of a study could be applied in other contexts or populations that differ from those used in the study. A Bayesian perspective goes hand in hand with the idea of generalizability. The ability to generalize from the results obtained from the sample in hand to the larger world – in a word, predictive power – is the underlying premise of the science of risk analysis. In the 20th century, statistical research has tended to focus on methods using p-values. This trend was viewed as unfortunate by the American Statistical Association due to the belief by ASA's board of directors that the focus on p-values contributed to the reproducibility crisis in science. [48] [49]

iv. Are there methods SAB members recommend for better analyzing and communicating compounded uncertainty, including the use of uncertainty factors, in the hazard identification and dose response process?

Comment: Bayesian methods for combining uncertainties should be considered. Methods for this have already been published. [50]The 2014 WHO *Guidance Document on Evaluating and Expressing Uncertainty in Hazard Characterization* was written by Dr. Weihsueh Chiu, formerly of USEPA and provides data-derived values for extrapolation/uncertainty factors. This document provides methods for adjusting for incidence of an effect within a population and the coverage, which is the confidence that an RfD value will protect a target population from an effect of a

given magnitude and incidence. At present, the coverage of RfD values is assumed to be 100%. The value of the WHO approach would provide a more rigorous approach than a simple assumption. More experience with this method, however, is needed before EPA can recommend the use of uncertainty characterizations that include quantitative population incidence. [51]

Item 5: The current Agency-wide guidance includes a guideline on cancer assessment, several guidelines for specific noncancer endpoints (e.g., reproductive toxicity, developmental toxicity, and mutagenicity), and guidances or reports on aspects of assessment common to many assessment endpoints (e.g., inhalation dosimetry, body-weight scaling of oral doses, benchmark dose technical guidance, risk characterization).

i. Are there specific areas within these documents on which there have been advances in risk assessment that should be reflected in updated guidelines?

Comment: Consistent with my comments on item 1, the advice of the 2005 Cancer Guidelines about mode of action need to be given more than lip service in cancer assessment. The three papers mentioned in the comment on Item 1 provide a methodology that would make the odious concept of the linear cancer slope factor obsolete.

ii. Are there areas of overlap or disagreement between these guidelines?

Comment: The consideration of basic biology in risk assessment is increasing due to efforts such as ToxCast, Tox21 and Adverse Outcome Pathways. As this knowledge develops, areas of overlap may become apparent. For example, alteration of histone deacetylase, an enzyme that "opens up" chromosomes to enable gene expression, produces developmental toxicity. The drug valproic acid is an example. The role of histone deacetylase in other endpoints may become apparent with time and this effect might become a molecular initiating event in AOPs leading to a variety of health effects.

iii. What issues or guideline documents would SAB members prioritize for update?

Comment: The two guidance documents that most need updating are the 2002 *Review of the Reference Dose and Reference Concentration* and the 2005 *Guidelines for Carcinogen Risk Assessment*. The former needs to incorporate Bayesian methods for RfD development and ORD personnel should begin an examination of the methods for population incidence and RfD coverage in the 2014 WHO guidance. The cancer guidelines need to be revamped with the three 2019 papers mentioned in my comment on Item 1 as the starting point

Item 6: Given current understanding of how risk assessments are used in decision making, are there considerations or changes to existing guidance with respect to problem formulation, assessment, data integration, and risk characterization that SAB members recommend EPA consider? Do SAB members have specific recommendations as to questions of importance to

decision makers that are not being addressed by current risk assessments?

Comment: The problem formulation could be improved by the use of relatively simple value-of-information methods to help EPA determine resource allocation for various aspects of the assessment. Data integration has improved considerably with the increased use of systematic review. Hazard characterization is the more apt term and is what is meant by "risk characterization." My comments about Item 1 provide a description of the improvements that could be made in hazard characterization.

Item 7: The purpose of some risk assessments (to quantify dose-response or reference values protective of the most sensitive receptors) and the purpose of the assessment of risk to inform benefits in an economic analysis (to create a predictive analysis for judging the effectiveness and feasibility of a regulatory action) can be quite different. As a result, the evaluation methods and key decision points can be quite different. For example, risk assessors may choose a benchmark dose at the high end (>95 percentile) of a distribution in order to define a level likely to avoid adverse effects, while economists may prefer risk assessors characterize the entire distribution or, at a minimum, use benchmark doses in the middle of the distribution, to inform benefit analyses.

i. Do SAB members think risk assessments are providing the information needed by risk managers and those estimating the benefits of potential decisions? If not, what do SAB members recommend might make hazard and dose response analyses more useful to decision makers?

Comment: As conducted by EPA at present, hazard characterizations generally provide a single number that is viewed as a brightline. The use of Bayesian methods and adopting data-derived distributions for uncertainty factors will enable a "what-if" approach that would likely be helpful for cost-benefit analysis. Tabel 9 in the paper by Beck et al. (2016) shows a graphic tool that I believe is available as an Excel file that would help visualize the effects of this type of approach. [45]

ii. Should EPA's guidance direct staff to consider as part of the development of the assessment the questions decision makers need answered in the end use of the assessment?

Comment: Absolutely. A risk assessment is a decision tool. Consideration of the decisions that the assessment will support will help craft a better assessment. Please see Chapter 3 in Science and Decisions: Advancing Risk Assessment. [52]

References:

1. National Research Council (NRC). (1993) Issues in Risk Assessment.
2. USEPA. (2005) Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001F.
3. Cohen SM, Boobis AR, Dellarco VL et al. (2019) Chemical carcinogenicity revisited 3: Risk assessment of carcinogenic potential based on the current state of knowledge of carcinogenesis in humans. 10.1016/j.yrtph.2019.01.017

4. Wolf DC, Cohen SM, Boobis AR et al. (2019) Chemical carcinogenicity revisited 1: A unified theory of carcinogenicity based on contemporary knowledge. 10.1016/j.yrtph.2019.01.021
5. Clewell RA, Thompson CM, Clewell HJ. (2019) Dose-dependence of chemical carcinogenicity: Biological mechanisms for thresholds and implications for risk assessment. 10.1016/j.cbi.2019.01.025
6. Doe JE, Boobis AR, Dellarco V et al. (2019) Chemical carcinogenicity revisited 2: Current knowledge of carcinogenesis shows that categorization as a carcinogen or non-carcinogen is not scientifically credible. 10.1016/j.yrtph.2019.01.024
7. Vineis P, Schatzkin A, Potter JD. (2010) Models of carcinogenesis: an overview. 10.1093/carcin/bgq087 10.1093/carcin/bgq087
8. Williams RA. (2019) Economic benefit-cost implications of the LNT model. 10.1016/j.cbi.2019.01.028
9. Ricci PF, Tharmalingam S. (2019) Ionizing radiations epidemiology does not support the LNT model. 10.1016/j.cbi.2018.11.014
10. Clewell RA, Andersen ME. (2016) Approaches for characterizing threshold dose-response relationships for DNA-damage pathways involved in carcinogenicity in vivo and micronuclei formation in vitro. 10.1093/mutage/gev078
11. Kobets T, Williams GM. (2019) Review of the evidence for thresholds for DNA-Reactive and epigenetic experimental chemical carcinogens. 10.1016/j.cbi.2018.11.011
12. Brooks AL. (2019) The impact of dose rate on the linear no threshold hypothesis. 10.1016/j.cbi.2018.12.007
13. Tharmalingam S, Sreetharan S, Brooks AL, Boreham DR. (2019) Re-evaluation of the linear no-threshold (LNT) model using new paradigms and modern molecular studies. 10.1016/j.cbi.2018.11.013
14. Scott BR, Tharmalingam S. (2019) The LNT model for cancer induction is not supported by radiobiological data. 10.1016/j.cbi.2019.01.013
15. Costantini D, Borremans B. (2019) The linear no-threshold model is less realistic than threshold or hormesis- based models: An evolutionary perspective. 10.1016/j.cbi.2018.10.007
16. Calabrese EJ. (2019) The linear No-Threshold (LNT) dose response model: A comprehensive assessment of its historical and scientific foundations. 10.1016/j.cbi.2018.11.020
17. Golden R, Bus J, Calabrese E. (2019) An examination of the linear no-threshold hypothesis of cancer risk assessment: Introduction to a series of reviews documenting the lack of biological plausibility of LNT. 10.1016/j.cbi.2019.01.038
18. Wolf DC, Cohen SM, Boobis AR et al. (2019) Chemical carcinogenicity revisited 1: A unified theory of carcinogenicity based on contemporary knowledge. 10.1016/j.yrtph.2019.01.021
19. Hanahan D, Weinberg RA. (2000) The hallmarks of cancer.
20. Hanahan D, Weinberg RA. (2011) Hallmarks of cancer: the next generation. 10.1016/j.cell.2011.02.013 10.1016/j.cell.2011.02.013
21. Mukherjee S. The Emperor of All Maladies : A Biography of Cancer. New York: Scribner; 2011
22. Whelan EM. (1978) The U.S. government versus carcinogens.
23. Cacchione S, Biroccio A, Rizzo A. (2019) Emerging roles of telomeric chromatin alterations in cancer. 10.1186/s13046-019-1030-5
24. Domblides C, Lartigue L, Faustin B. (2019) Control of the Antitumor Immune

Response by Cancer Metabolism. 10.3390/cells8020104
25. Stecca B, Rovida E. (2019) Impact of ERK5 on the Hallmarks of Cancer. 10.3390/ijms20061426
26. Camuzi D, de Amorim ÍSS, Ribeiro Pinto LF, Oliveira Trivilin L, Mencalha AL, Soares Lima SC. (2019) Regulation Is in the Air: The Relationship between Hypoxia and Epigenetics in Cancer. 10.3390/cells8040300
27. Passi A, Vigetti D, Buraschi S, Iozzo RV. (2019) Dissecting the role of hyaluronan synthases in the tumor microenvironment. 10.1111/febs.14847
28. Wang J, Zhang X, Chen W, Hu X, Li J, Liu C. (2019) Regulatory roles of long noncoding RNAs implicated in cancer hallmarks. 10.1002/ijc.32277
29. Cloer EW, Goldfarb D, Schrank TP, Weissman BE, Major MB. (2019) NRF2 Activation in Cancer: From DNA to Protein. 10.1158/0008-5472.CAN-18-2723
30. Archetti M, Pienta KJ. (2019) Cooperation among cancer cells: applying game theory to cancer. 10.1038/s41568-018-0083-7
31. Abdollahzadeh R, Daraei A, Mansoori Y, Sepahvand M, Amoli MM, Tavakkoly-Bazzaz J. (2019) Competing endogenous RNA (ceRNA) cross talk and language in ceRNA regulatory networks: A new look at hallmarks of breast cancer. 10.1002/jcp.27941
32. Tuveson D, Clevers H. (2019) Cancer modeling meets human organoid technology. 10.1126/science.aaw6985
33. Simon T. (2010) Just who is at risk? The ethics of environmental regulation. 10.1177/0960327110379252 10.1177/0960327110379252
34. Sablina AA, Budanov AV, Ilyinskaya GV, Agapova LS, Kravchenko JE, Chumakov PM. (2005) The antioxidant function of the p53 tumor suppressor. 10.1038/nm1320 10.1038/nm1320
35. Nakamura J, Mutlu E, Sharma V et al. (2014) The endogenous exposome. 10.1016/j.dnarep.2014.03.031
36. Wild CP. (2009) Environmental exposure measurement in cancer epidemiology. 10.1093/mutage/gen061 10.1093/mutage/gen061
37. Törnqvist M, Gustafsson B, Kautiainen A, Harms-Ringdahl M, Granath F, Ehrenberg L. (1989) Unsaturated lipids and intestinal bacteria as sources of endogenous production of ethene and ethylene oxide. 10.1093/carcin/10.1.39
38. Filser JG, Denk B, Törnqvist M, Kessler W, Ehrenberg L. (1992) Pharmacokinetics of ethylene in man; body burden with ethylene oxide and hydroxyethylation of hemoglobin due to endogenous and environmental ethylene.
39. Rydberg B, Lindahl T. (1982) Nonenzymatic methylation of DNA by the intracellular methyl group donor S- adenosyl-L-methionine is a potentially mutagenic reaction.
40. Moeller BC, Recio L, Green A et al. (2013) Biomarkers of exposure and effect in human lymphoblastoid TK6 cells following [13C2]-acetaldehyde exposure. 10.1093/toxsci/kft029
41. Farland WH, Lynch A, Erraguntla NK, Pottenger LH. (2019) Improving risk assessment approaches for chemicals with both endogenous and exogenous exposures. 10.1016/j.yrtph.2019.01.029
42. Starr TB, Swenberg JA. (2013) A novel bottom-up approach to bounding low-dose human cancer risks from chemical exposures. 10.1016/j.yrtph.2013.01.004
43. Starr TB, Swenberg JA. (2016) The bottom-up approach to bounding potential low-dose cancer risks from formaldehyde: An update. 10.1016/j.yrtph.2016.01.021
44. Kirman CR, Hays SM. (2017) Derivation of endogenous equivalent values to support risk assessment and risk management decisions for an endogenous carcinogen: Ethylene oxide. 10.1016/j.yrtph.2017.10.032

45. Beck NB, Becker RA, Erraguntla N et al. (2016) Approaches for describing and communicating overall uncertainty in toxicity characterizations: U.S. Environmental Protection Agency's Integrated Risk Information System (IRIS) as a case study. 10.1016/j.envint.2015.12.031
46. Aven T, Renn O, Rosa EA. (2011) On the ontological status of the concept of risk.
47. National Academies of Sciences E, and Medicine. Reproducibility and Replicability in Science. Washington, DC: The National Academies Press; 2019
48. Amrhein V, Greenland S, McShane B. (2019) Scientists rise up against statistical significance. 10.1038/d41586-019-00857-9
49. Wasserstein RL, Lazar NA. (2016) The ASA's Statement on p-Values: Context, Process, and Purpose. 10.1080/00031305.2016.1154108
50. Simon TW, Zhu Y, Dourson ML, Beck NB. (2016) Bayesian methods for uncertainty factor application for derivation of reference values. 10.1016/j.yrtph.2016.05.018
51. WHO-IPCS. (2014) Guidance Document on Evaluating and Expressing Uncertainty in Hazard Characterization.
52. National Research Council. (2009) Science and Decisions: Advancing Risk Assessment.

Dr. Eric Smith

SAB Consultation on Updating EPA Guidelines for Carcinogen and Non-Cancer Risk Assessment

The U.S. EPA is interested in seeking consultation from the members of the SAB regarding upcoming activities related to an update to the 2005 EPA Guidelines for Carcinogen Risk Assessment and guidelines for noncancer risk assessment. In considering areas for future emphasis, as well as with the work currently underway, EPA's Risk Assessment Forum[1] (RAF) is considering various topic areas including use of defaults, inhalation dosimetry and susceptible populations and lifestages.

The U.S. EPA, primarily through the RAF, maintains a series of guidelines, guidance documents and methodologies that describe the way the Agency conducts its human health and ecological risk assessments.[2] Some key examples include:

- Guidelines concerning: exposure assessment, carcinogen risk assessment, mixtures risk assessment, reproductive toxicity risk assessment, developmental toxicity risk assessment, neurotoxicity risk assessment, and ecological risk assessment;
- Supplemental guidance for mixtures risk assessment, and assessing susceptibility from early-life exposure to carcinogens;
- Guidance for benchmark dose modeling, and applying quantitative data to develop data-derived extrapolation factors;
- Frameworks for cumulative risk assessment and for ecological risk assessment; and
- Methods for and reviews of RfD/RfC processes.

A more detailed listing of some of the Agency guidelines, guidance documents, and technical panel reports that address human health risk assessment is attached.

The RAF is currently engaged in various activities,[3] ranging from drafting updates to longstanding guidelines documents to initial investigative steps on complex topic areas. Some current examples include an update to the Guidelines for Exposure Assessment,[4] activities related to the development of cumulative risk assessment guidance,[5] and consideration of new approaches to dose-response assessment that may be used in risk assessments to augment their usefulness for Agency decision making. Activities are also underway to address specific issues, such as additivity in mixtures risk assessment and consideration of several of the default uncertainty factors used in reference value methods.

The EPA is interested in consultation with the SAB with these general perspectives in mind.

---

[1] https://www.epa.gov/osa/basic-information-about-risk-assessment-guidelines-development

[2] A list of many of the human health assessment documents can be found at the following URL: https://www.epa.gov/risk/risk-assessment-guidelines#tab-1, and documents on ecological assessment can also be accessed from that webpage.

[3] https://www.epa.gov/osa/risk-assessment-current-projects

[4] https://www.epa.gov/risk/guidelines-human-exposure-assessment

[5] https://www.epa.gov/risk/framework-cumulative-risk-assessment

1. Are there particular aspects of existing Agency risk assessment guidance related to cancer and non-cancer endpoints that individual SAB members recommend be revised or augmented to incorporate updated scientific information (based on your experience in usage, new information, or scientific advances)?

2. Are there important topic areas that are not fully represented in existing Agency risk assessment guidance related to cancer and non-cancer endpoints that SAB members recommend EPA address in guidance? What current information supports this recommendation?

The 2005 document provides guidelines for developing and using risk assessments and provide information to the public on assessment methodologies. The document needs updating as there are new methodologies and there has been considerable research done since the 2005 update. For example, the statistical methods section (2-9 to 2-11) is somewhat brief and for example, does not include Bayesian methods which are quite useful in risk assessment.

As evident from the general questions above, EPA is seeking open-ended input and recommendations from SAB members and will consider all the input received to determine next steps for updating EPA guideline documents in a phased approach.

In the course of development and review of this charge to the SAB, the following additional questions were identified by Agency leadership to highlight for SAB members' input.

3. Are any key elements of hazard and dose-response analysis —including analytical limitations, heterogeneity, natural variability, and non-ambient exposures (i.e., endogenous or indoor exposures)—not adequately characterized in guidance?

4. Current guidance discusses how to describe confidence in hazard conclusions (see, for example, the Cancer Guidelines, section 2.5 "Weight of Evidence Narrative" or Guidelines for Developmental Toxicity, Table 3) and discusses presentation of uncertainty in dose response (see for example the Cancer Guidelines, section 3.7 "Dose Response Characterization"). Examples of current practice can also be seen in various recent EPA assessments of specific chemicals or pollutants.

    i. Do SAB members have recommendations for better ways to characterize conclusions and uncertainties in a transparent way?

    I would assume that the analysis of uncertainties would be part of a risk assessment document. If there is a section on transparency/reproducibility then the evaluation of uncertainty should also be a component of the section. One should be able to reproduce numerical calculations associated with uncertainty and have a clear understanding of qualitative uncertainties

    ii. Do SAB members have recommendations for better ways to analyze uncertainty, qualitatively or with quantitative analysis?

Uncertainty should be a critical component of the assessment and was a component of the 2005 document. There are of course various approaches to evaluating uncertainty and these should be standardized to some extent in documentation. While the analysis of uncertainty and its importance may be complex, it is still possible to summarize results in a categorical manner (e.g. high, medium, low confidence) as is currently being done. This approach has also been suggested, for example in the preamble to the IARC document on carcinogens (https://monographs.iarc.fr/wp-content/uploads/2019/01/Preamble-2019.pdf**). See also: Using 21st Century Science to Improve Risk-Related Evaluations, (https://www.nap.edu/download/24635). One might try to achieve a probabilistic analysis however the interpretation is often smoothed a bit which is what the categorizations are attempting.**

iii. What role should statistical analysis play in this characterization?

I am not sure I understand this question as uncertainty is a cornerstone of statistical analysis. Decision trees, Bayesian belief networks, Bayesian analysis, meta-analysis, etc., are all useful in dealing with uncertainty. When statistical methods are used the analysis of certain types of uncertainty are part of the modeling process. With computer simulation models, there is also a considerable amount of research on uncertainty and best practices for modeling. See also https://monographs.iarc.fr/wp-content/uploads/2019/01/Preamble-2019.pdf page 24.

iv. Are there methods SAB members recommend for better analyzing and communicating compounded uncertainty, including the use of uncertainty factors, in the hazard identification and dose response process?

This might be a useful paper as they provide a visualization of the process: Dankovic DA, Naumann BD, Maier A, Dourson ML, Levy LS. The Scientific Basis of Uncertainty Factors Used in Setting Occupational Exposure Limits. *J Occup Environ Hyg*. 2015;12 Suppl 1(sup1):S55–S68. doi:10.1080/15459624.2015.1060325
The following articles might be useful

Doyle, E. E. H., Johnston, D. M. and Smith, R. (2019) 'Communicating model uncertainty for natural hazards: a systematic review', International Journal of Disaster Risk Reduction Volume 33, February 2019, Pages 449-476. https://www.sciencedirect.com/science/article/pii/S221242091830663

Van der Sluijs, J.P., Risbey, J.S., Kloproggem, P., Ravetz, J.R., Funtowicz, S.O., Quintana, S.C., Pereira A.G., De Marchi, B., Petersen, A.C., Janssen, P.H.M., Hoppe, R. and Huijs, S.W.F. (2003). The RIVM/ MNP Guidance for Uncertainty Assessment and Communication. Detailed Guidance. Utrecht University, http://www.mnp.nl/leidraad/.

5. The current Agency-wide guidance includes a guideline on cancer assessment, several guidelines for specific noncancer endpoints (e.g., reproductive toxicity, developmental toxicity, and mutagenicity), and guidances or reports on aspects of assessment common to many assessment endpoints (e.g., inhalation dosimetry, body-weight scaling of oral doses, benchmark dose technical guidance, risk characterization).

    i. Are there specific areas within these documents on which there have been advances in risk assessment that should be reflected in updated guidelines?
    ii. Are there areas of overlap or disagreement between these guidelines?
    iii. What issues or guideline documents would SAB members prioritize for update?

6. Given current understanding of how risk assessments are used in decision making, are there considerations or changes to existing guidance with respect to problem formulation, assessment, data integration, and risk characterization that SAB members recommend EPA consider? Do SAB members have specific recommendations as to questions of importance to decision makers that are not being addressed by current risk assessments?

    Data and modeling transparency and reproducibility are clearly important. It would be valuable, to the extent possible, to make data and models used in the analysis of risk to be available. It is also important that data used in analysis from other organizations be made available as part of the risk assessment. Transparency initially seems like an easy step however I believe there are some complications. For example, we often start with raw data and preprocess the data before analysis. This might include outlier evaluation and removal, transformations, etc. Just providing data may not be adequate. Ideally one would like to have enough information to reproduce the analysis. This would imply providing any code and metadata that was used. Even with this information there can be difficulties. For example, it is possible that code that produces a result on one computer may produce a different result on another, due to differences in compilers, random number generators and machines.

7. The purpose of some risk assessments (to quantify dose-response or reference values protective of the most sensitive receptors) and the purpose of the assessment of risk to inform benefits in an economic analysis (to create a predictive analysis for judging the effectiveness and feasibility of a regulatory action) can be quite different. As a result, the evaluation methods and key decision points can be quite different. For example, risk assessors may choose a benchmark dose at the high end (>95 percentile) of a distribution in order to define a level likely to avoid adverse effects, while economists may prefer risk assessors characterize the entire distribution or, at a minimum, use benchmark doses in the middle of the distribution, to inform benefit analyses.

If economic analysis is to be done as part of the assessment then it also seems reasonable to expect and analysis of the uncertainty in the economic assessment and transparency in the analysis process. Perhaps an element of the uncertainty analysis could be the sensitivity of the analysis to the choice of the benchmark dose.

i. Do SAB members think risk assessments are providing the information needed by risk managers and those estimating the benefits of potential decisions? If not, what do SAB members recommend might make hazard and dose response analyses more useful to decision makers?

ii. Should EPA's guidance direct staff to consider as part of the development of the assessment the questions decision makers need answered in the end use of the assessment?

With these questions guiding, but not limiting, your review, please provide input to help guide the Agency as it initiates an update to the 2005 EPA Guidelines for Carcinogen Risk Assessment and develops guidelines for noncancer risk assessment.

William J. Warren-Hicks, Andy Hart, 2017. Application of Uncertainty Analysis to Ecological Risks of Pesticides ISBN 9781138114814 - CAT# K35382 CRC Press

Meagan J. Harris, Jonah Stinson, Wayne G. Landis, 2017. A Bayesian Approach to Integrated Ecological and Human Health Risk Assessment for the South River, Virginia Mercury-Contaminated Site. Risk Analysis Volume37, Issue7, 1341-1357