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United States Senate
COMMITTEE ON ENVIRONMENT AND PUBLIC WORKS
WASHINGTON, DC 20510–6175

August 4, 2017

Dr. Michael L. Dourson
University of Cincinnati, College of Medicine
160 Panzeca Way
Cincinnati, OH 45267-0056

Dear Dr. Dourson:

The Senate Environment and Public Works Committee has received your nomination to serve as the Assistant Administrator of the Office of Chemical Safety and Pollution Prevention at the Environmental Protection Agency (EPA). Your record is extensive, particularly your work with the Toxicology Excellence for Risk Assessment (TERA) that you founded[1]. So the Committee can more fully assess your record, I request that you provide the following supplemental materials and responses to questions prior to the Committee's hearing on your nomination.

1) Please provide copies of the 2014, 2015 and 2016 annual reports for TERA, as the last publicly available report on the TERA website is from 2013[2].

2) TERA's website states that "TERA provides significant pro bono support to local and state governments, NGOS and others to help them address important human health and risk issues[3]." For each of the past ten years, please list a) the name of each entity to whom TERA provided such support and the duration of such efforts, b) the purpose of such support, and c) copies of any documents, presentations or other work products that were provided to the entity as part of such support.

3) TERA's website states that "We are transparent about who our funders are and what role they had, if any, in commenting on the TERA scientific opinions or results." Specific information necessary to determine TERA's transparency about this funding is neither included in the materials that were provided to the Committee nor available in either the publicly available annual reports for TERA or on the TERA website(s)[4]. For each of the past ten years, please provide a list that names each entity that provided grant, contract or other financial support to TERA (or directly to you), the amount and type of such funding, the purpose(s) for which it was provided and a specific description (name of

[1] For purposes of this letter, references to TERA include its successor entity, the Risk Science Center
[2] http://www.tera.org/about/AnnualReports.html
[3] http://www.tera.org/about/mission_history.html
[4] https://med.uc.edu/eh/centers/rsc/about-us/funding

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research publication, expert testimony, or white paper, etc.) of any outcome developed or provided as a result of such funding.

4) TERA's website states that "TERA can provide a variety of litigation support services from review and analysis of data, to written opinions, to expert witness testimony" and that this work has included "testimony as expert witness on U.S. EPA's chromium risk assessment for Defendant in groundwater contamination case." For each of the past ten years, please identify each case in which TERA or any of its employees provided 'litigation support' and the party to which such support was provided, and the amount and type of compensation received. In responding, please include the caption of the case, the court in which the case was heard and the case number, and include copies of all materials produced as part of its litigation support services, including expert witness testimony, analysis of data and written opinions provided by TERA or any of its employees, as well as transcripts of depositions of TERA or any of its employees.

5) TERA's website states that "TERA's work organizing peer input, peer consultation and peer review is intended to meet the needs of public and private sponsors who have developed risk assessment documentation." For each of the past ten years, please provide a) a list naming and describing the purpose of each peer input, peer consultation or peer review activity conducted by TERA, b) the entity(ies) that provided the funding for the peer activity and the amount of such funding, and c) a list of the individuals who participated in the peer activity, along with who chaired the project and which individuals were paid for their participation by TERA or the funding party.

6) The CV you provided to the Committee lists dozens of invited presentations you delivered. Please provide copies of the slides, speech or other briefing materials for the presentations given on the following dates: June 14, 2017, March 21, 2017, March 14, 2017, March 14, 2016, June 24, 2015, April 20, 2015, January 21, 2015, November 18, 2010, November 4, 2010, December 3, 2004, September 29, 2003, September 26, 2003, July 25, 2002, and April 30, 1996.

7) The Public Financial Disclosure Report that was provided to the Committee indicates that you served as a member of the North American Flame Retardant Alliance (NAFRA) until June 2017, and lists that entity as a non-profit. According to its website[5], that entity "was formed in March 2011 to serve as the lead advocacy organization in North America for flame retardant producers and users." Does NAFRA receive any funding from any entity that is not itself a manufacturer, user, distributor of or trade association for flame retardant chemicals? If so, for each of the past two years, please list each such entity and the amount of funding it provided to NAFRA.

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[5] https://flameretardants.americanchemistry.com/About-North-American-Flame-Retardant-Alliance-NAFRA-/

8) The Public Financial Disclosure Report that was provided to the Committee indicates that you serve as the President of the Toxicology Education Foundation, and lists that entity as a non-profit. For each of the past two years, please provide a) a list naming each corporate entity or industry trade association that provided funding to the Foundation, along with the amount of the funding and b) the total amount of funding provided to the Foundation.

9) The Public Financial Disclosure Report that was provided to the Committee indicates that you served as the Secretary of the Toxicology Forum until June 2017, and lists that entity as a non-profit. That entity's website does not list any non-corporate sponsors.[6] Does the Toxicology Forum receive any funding from any entity that is not a corporation or trade association representing corporations? If so, for each of the past two years, please list each such entity and the amount of funding it provided to the Toxicology Forum.

10) Your Ethics Agreement states that "I will not participate personally and substantially in any particular matter in which I know that I have a financial interest directly and predictably affected by the matter, or in which I know that a person whose interests are imputed to me has a financial interest directly and predictably affected by the matter, unless I first obtain a written waiver, pursuant to 18 U.S.C. § 208(b)(1), or qualify for a regulatory exemption, pursuant to 18 U.S.C. § 208(b)(2)." Please provide a list of persons and particular matters (including a list of specific chemical substances, pesticides, regulations, regulatory decisions, risk evaluations, assessments or determinations, or topics) about which you plan to consult with the Designated Agency Ethics Official in order to determine whether you will recuse yourself or require a written exemption or waiver prior to your participation.

11) Your Ethics Agreement states that "Upon confirmation, I will resign from my positions with the following entities: University of Cincinnati, and the Toxicology Education Foundation. I resigned from my position with the North American Flame Retardant Alliance, and the Toxicology Forum in June 2017. For a period of one year after my resignation from each of these entities, I will not participate personally and substantially in any particular matter involving specific parties in which I know that entity is a party or represents a party, unless I am first authorized to participate, pursuant to 5 C.F.R. § 2635.502(d)." Please provide a list of particular matters involving specific parties (including a list of specific chemical substances, pesticides, regulations, regulatory decisions, risk evaluations, assessments or determinations, or topics) about which you plan to consult with the Designated Agency Ethics Official in order to determine whether you will recuse yourself or require advance authorization prior to your participation.

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[6] http://dialogue.toxforum.org/page/become-a-sponsor

12) Your Ethics Agreement also states that you will sign the Trump Ethics Pledge[7]. The Trump Ethics Pledge states "I will not for a period of 2 years from the date of my appointment participate in any particular matter involving specific parties that is directly and substantially related to my former employer or former clients, including regulations and contracts." The Pledge additionally notes that (d) "Directly and substantially related to my former employer or former clients" shall mean matters in which the appointee's former employer or a former client is a party or represents a party" and (i) "Former client" is any person for whom the appointee served personally as agent, attorney, or consultant within the 2 years prior to the date of his or her appointment, but excluding instances where the service provided was limited to a speech or similar appearance. It does not include clients of the appointee's former employer to whom the appointee did not personally provide services." Please provide a list of particular matters involving specific parties (including a list of specific chemical substances, pesticides, regulations, regulatory decisions, risk evaluations, assessments or determinations, or topics) that you plan to recuse yourself from participating in for 2 years. If you plan to request waivers from the Trump Ethics Pledge for any such matter, please also list those.

Thank you very much for your consideration of this important matter. If you have any questions or concerns, please contact [redacted] my staff at 202-224-8832 or [redacted] I look forward to meeting with you.

With best personal regards, I am,

Sincerely yours,

Tom Carper
Ranking Member

[7] https://www.whitehouse.gov/the-press-office/2017/01/28/executive-order-ethics-commitments-executive-branch-appointees

UNIVERSITY OF Cincinnati

Risk Science Center
Department of Environmental Health
University of Cincinnati College of Medicine
PO Box 670056
Cincinnati, Ohio 45267-0056

160 Panzeca Way
Kettering Lab Building, Suite G-24
http://med.uc.edu/eh/centers/tera

Dear Senator Carper

September 6th, 2017

I appreciate your interest in Toxicology Excellence for Risk Assessment (TERA). As you may know, TERA is a nonprofit 501c3 organization with a mission to support the protection of public health by developing, reviewing and communicating risk assessment values and analyses; improving risk methods through research; and, educating risk assessors, managers, and the public on risk assessment issues. TERA was founded on the belief that an independent non-profit organization can provide a unique function to protect human health by conducting scientific research and development on risk issues in a transparent and collaborative fashion. One-third of TERA's effort has been for industry; 2/3rds of its effort has been for government.

In 21 years as an independent and science neutral group, TERA published numerous reports, manuscripts, presentations and education courses, created 5 freely accessible websites, and garnered the sponsorship of over 50 government groups and as many industry and nonprofit organizations. We were often the go-to group for government-industry collaborations such as the perchlorate research program in the late 1990s, the West Virginia PFOA contamination in the early 2000's, and EPA's Voluntary Children's Chemical Evaluation Program in the mid 2000's. TERA also conducted the independent peer review of the 9-government report on the world trade center disaster and the recent Elk River spill in West Virginia. TERA has received many accolades and hundreds of scientists and managers from both government and industry can attest to its independent and science-neutral approach. Even staff of NRDC has commented privately that TERA websites were visited often since they contained so much valuable information.

Please find attached responses to you questions, including a disk of related information. I would be more than happy to answer additional questions from you or your hard-working staff, either before or after the tentatively scheduled committee meeting later this month.

Cheers!



Michael L. Dourson, Ph.D., DABT, FATS, FSRA
Professor of Environmental Health

An affirmative action/equal opportunity institution

Michael L. Dourson, Ph.D., DABT, FATS, FSRA

Responses to Thomas Carper letter to Michael Dourson dated August 4, 2017

Question 1) Please provide copies of the 2014, 2015 and 2016 annual reports for TERA, as the last publicly available report on the TERA website is from 2013.

> Response: Annual reports for 2014 and 2015 are now available on the TERA website as well as a financial summary for 2015. These two annual reports with financial summaries are also attached.

Question 2) TERA's website states that "TERA provides significant pro bono support to local and state governments, NGOS and others to help them address important human health and risk issues." For each of the past ten years, please list a) the name of each entity to whom TERA provided such support and the duration of such efforts, b) the purpose of such support, and c) copies of any documents, presentations or other work products that were provided to the entity as part of such support.

> Response: Please see the list of hours for pro bono, nonprofit, and profit tasks for the years 1995 to 2015. These hours were devoted to either:
>
> - Participation in scientific societies---e.g., see attached resume under appointments starting on page 27,
> - State Hazard Evaluation and Lending Program (State HELP) program---e.g., see reports at www.allianceforrisk.org, which is currently being reconfigured and found at www.archive.org,
> - Corporate science development---e.g., work on projects not otherwise funded, such as the 2004 publication by Strawson et al. on perchlorate, and
> - Miscellaneous answering of phone calls and other generally quick email responses to the public.
>
> Detailed records of this activity were maintained by individual TERA staff for general reporting purposes and corporate records of such efforts were not retained. Several scientific publications resulted from such efforts, as generally described in the acknowledgement section of the publication and available on one or more of our websites.

Question 3) TERA's website states that "We are transparent about who our funders are and what role they had, if any, in commenting on the TERA scientific opinions or results." Specific information necessary to determine TERA's transparency about this funding is neither included in the materials that were provided to the Committee nor available in either the publicly available annual reports for TERA or on the TERA website(s). For each of the past ten years, please provide a list that names each entity that provided grant, contract or other financial support to TERA (or directly to you), the amount and type of such funding, the purpose(s) for which it was provided and a specific description (name of 1 research publication, expert testimony, or white paper, etc.) of any outcome developed or provided as a result of such funding.

Response: TERA's work is independent and science-neutral. In some cases, TERA allowed scientific comments from its sponsors on draft work products. These comments, if any, were considered during the internal quality assurance review prior to finalizing any report. In all cases, the final report reflected the opinions of the TERA scientists, and not necessarily those of the sponsor. All of the TERA reports included explanations for our scientific opinions, particularly for controversial or uncertain scientific decisions when we perceived our opinions or results were at odds with what sponsors may have desired. TERA's approach to accepting and conducting its work is discussed at http://www.tera.org/about/mission_history.html.

TERA maintains a document retention policy of 7 years for files; with the exception of those involved with litigation efforts, which are retained indefinitely. Therefore, details of sponsors other than summary information prior to 2010 are not generally available (note, however, that some reports from projects may be found on the TERA web page). A summary of the extent of either government or industry work can be found at: http://www.tera.org/about/FundingSources.html. Beginning in 2010, this summary information also included a list of those sponsors that represented a 2% or greater part of TERA's efforts for that year.

A list of sponsors and projects from January 2010 through June 2015[1] are attached. From July 2015 to now, TERA's work has been minimal as the corporation winds down. For information regarding the sponsors during this wind-down phase, please contact Dr. Patricia McGinnis, the acting President for Toxicology Excellence for Risk Assessment (TERA) at: mcginnis@tera.org.

Not all of TERA's work resulted in publications or other immediately available public information. For example, many of the tasks done for both government and industry sponsors resulted in reports delivered to the sponsor that were subsequently used by or submitted to a government organization. The immediately available public information is posted or noted on TERA's website. Presentations made on TERA's work may not have always been retained in the corporation's files, particularly presentations and those made at scientific society meetings beyond the 7-year retention policy.

The specific type of compensation is not listed in the attachments, but TERA was primarily paid through contracts, with some government grants, and private gift letters. As noted above, if the work exceeded 2% of TERA's overall effort in any one year, the sponsor is listed on the on-line financial summaries.

Question 4) TERA's website states that "TERA can provide a variety of litigation support services from review and analysis of data, to written opinions, to expert witness testimony" and that this work has included "testimony as expert witness on U.S. EPA's

[1] In July 2015, I and most of the TERA staff joined the University of Cincinnati, College of Medicine

chromium risk assessment for Defendant in groundwater contamination case." For each of the past ten years, please identify each case in which TERA or any of its employees provided 'litigation support' and the party to which such support was provided, and the amount and type of compensation received. In responding, please include the caption of the case, the court in which the case was heard and the case number, and include copies of all materials produced as part of its litigation support services, including expert witness testimony, analysis of data and written opinions provided by TERA or any of its employees, as well as transcripts of depositions of TERA or any of its employees.

Response: Please see the table below. Requests for details of the materials and opinions should be directed to the given contact, as I am uncertain of the existing status of the litigation. Compensation is not listed, but if the work exceeded 2% of TERA's effort in anyone year from 2010 to 2015, it was listed on the financial summaries referred to above.

Case	Issue	Contact
No. CIV MSC 05-01725; IN THE SUPERIOR COURT OF THE STATE OF CALIFORNIA IN AND FOR THE COUNTY OF CONTRA COSTA; RON BLOCK, et al., Plaintiff; DANIEL HELIX, et al., Defendant.	Contaminated site regarding comparison of levels of contaminant exposure and health benchmarks. TCE and other solvents were involved.	Richard Bowles; 925 935 3300 Bowles and Verna LLP 2121 N. California Blvd., Suite 875 P.O. Box 8180 Walnut Creek, CA 94596-8180 Representing the plaintiff.
Case No. BC435759 SUPERIOR COURT OF THE STATE OF CALIFORNIA COUNTY OF LOS ANGELES, CENTRAL CIVIL WEST; COUNCIL FOR EDUCATION AND RESEARCH ON TOXICS, a California corporation, acting as a private attorney general in the public interest, Plaintiff; STARBUCKS CORPORATION, et al., Defendants	Review of toxicology information for acrylamide in coffee and potential mixtures risk assessment for various constituents.	ROBIN STAFFORD (BAR NO. 200950) RStafford@mofo.com MORRISON & FOERSTER LLP 425 Market Street San Francisco, CA 94105-2482 Telephone: 415.268.7000 Representing the defendants
Case: BC 337618 SUPERIOR COURT OF THE STATE OF CALIFORNIA COUNTY OF LOS ANGELES,	Review of toxicology information for acrylamide in french fries and snacks and development of a No	Gary Roberts 601 South Figueroa Street Suite 1500 Los Angeles, California 90017

Environmental World Watch Inc., Plaintiff McDonald's Corporation, Defendants	Significant Risk Level. Three publications resulted; one of them funded by the sponsor. The other two publications were TERA funded.	213-892-5005 Representing the defendants

Question 5) TERA's website states that "TERA's work organizing peer input, peer consultation and peer review is intended to meet the needs of public and private sponsors who have developed risk assessment documentation." For each of the past ten years, please provide a) a list naming and describing the purpose of each peer input, peer consultation or peer review activity conducted by TERA, b) the entity(ies) that provided the funding for the peer activity and the amount of such funding, and c) a list of the individuals who participated in the peer activity, along with who chaired the project and which individuals were paid for their participation by TERA or the funding party.

Response: This information is available for all major peer reviews or peer consultations on TERA website at: http://www.tera.org/Peer/index.html. Less intense peer reviews are done for government, industry and NGOs on a routine basis and are described in response to question 3 above. Compensation is not listed, but if the work exceeded 2% of TERA's effort in anyone year from 2010 to 2015, it was listed on the financial summaries referred to above.

Question 6) The CV you provided to the Committee lists dozens of invited presentations you delivered. Please provide copies of the slides, speech or other briefing materials for the presentations given on the following dates: June 14, 2017, March 21, 2017, March 14, 2017, March 14, 2016, June 24, 2015, April 20, 2015, January 21, 2015, November 18, 2010, November 4, 2010, December 3, 2004, September 29, 2003, September 26, 2003, July 25, 2002, and April 30, 1996.

Response: The titles of my presentations and groups to which I spoke are shown below. The presentations are attached, except the last one, which cannot be located.

"Health risk assessment for perchlorate: New direction in EPA's modeling approach for establishing standards" **American Water Works Association.** Annual Conference. Philadelphia, PA. June 14, 2017.

Managing the non-cancer risks a hazardous waste sites: Trichloroethylene (TCE) as a case study" **Association for Environmental Health and Sciences (AEHS) Foundation**. San Diego, California March 21, 2017.

"The concept of hormesis and application in risk assessment" **Society of Toxicology**, Baltimore, Maryland, March 14, 2017.

"Yes, 'Thresholdable' Carcinogens Are Still Delaney Carcinogens" Roundtable Session: Is a "Thresholdable" Carcinogen Still a Delaney Carcinogen? **Society of Toxicology**, New Orleans, Louisiana, March 14, 2016.

"Defining the range of the reference dose: imprecision versus uncertainty" **The TCE Revolution and its Permanent Impact on Environmental Due Diligence,** EDR Insight, National Teleconference/Webinar. June 24, 2015.

"Assessment and management of Elk River, West Virginia drinking water contamination incident, 2014" **British Toxicology Society Annual Congress**, Birmingham, UK, April 20, 2015.

"Practical Guidance on the Development of a Non-cancer Hazard Range for Effective Risk Assessment and Risk Management of Contaminated Sites: A Case Study with Trichloroethylene and Other Chemicals" **Tri-Service Environmental Risk Assessment Work Group,** Naval Medical Center, Portsmouth, VA. Jan. 21, 2015

"Draft Toxicological Review of Hexavalent Chromium" **Environmental Protection Agency's** IRIS listening session. Washington, D.C. November 18, 2010.

"Perspectives of Air Pollutants: Health Effects Research Update Session: Risk Assessment…*in the 21st Century*" **Clean Air Forum**. Houston, TX. Nov. 4, 2010.

"Mercury Regulation: Fishing For The Facts About Risk"
States and Nation Policy Summit. **American Legislative Exchange Council**. Washington D.C. December 3, 2004.

"History of *TERA* Coordinated Public/Private Partnership on Perchlorate Research" Perchlorate State-of-the-Science Symposium. **University of Nebraska, Center for Environmental Toxicology**. Omaha, Nebraska. September 29, 2003.

"Perchlorate Reference Dose (RfD)" **California Environmental Protection Agency**. September 26, 2003.

"Modeling Of Population Variability" Midwestern States Risk Assessment Symposium. **Indiana Department of Environmental Management.** Indianapolis, IN. July 25, 2002.

"Dose Response Class Exercise: Aroclor" In: Risk assessment. **University of Cincinnati, College of Medicine**. April 30, 1996. [presentation could not be located]

Question 7) The Public Financial Disclosure Report that was provided to the Committee indicates that you served as a member of the North American Flame Retardant Alliance (NAFRA) until June 2017, and lists that entity as a non-profit. According to its website, that entity "was formed in March 2011 to serve as the lead advocacy organization in North America for flame retardant producers and users." Does NAFRA receive any

funding from any entity that is not itself a manufacturer, user, distributor of or trade association for flame retardant chemicals? If so, for each of the past two years, please list each such entity and the amount of funding it provided to NAFRA.

Response: I was a member of the NAFRA Science Advisory Committee and as such was not privy to this information. Please feel free to contact Dr. Kimberly White at Kimberly_White@americanchemistry.com.

Question 8) The Public Financial Disclosure Report that was provided to the Committee indicates that you serve as the President of the Toxicology Education Foundation, and lists that entity as a non-profit. For each of the past two years, please provide a) a list naming each corporate entity or industry trade association that provided funding to the Foundation, along with the amount of the funding and b) the total amount of funding provided to the Foundation.

Response: The following contributions were received:

- Avon, 6/9/16, $300
- Avon, 12/16/16, $1000
- Experimur, 1/13/17, $2500

Question 9) The Public Financial Disclosure Report that was provided to the Committee indicates that you served as the Secretary of the Toxicology Forum until June 2017, and lists that entity as a non-profit. That entity's website does not list any non-corporate sponsors. Does the Toxicology Forum receive any funding from any entity that is not a corporation or trade association representing corporations? If so, for each of the past two years, please list each such entity and the amount of funding it provided to the Toxicology Forum.

Response: Please find attached a funding list from the Toxicology Forum.

Question 10) Your Ethics Agreement states that "I will not participate personally and substantially in any particular matter in which I know that I have a financial interest directly and predictably affected by the matter, or in which I know that a person whose interests are imputed to me has a financial interest directly and predictably affected by the matter, unless I first obtain a written waiver, pursuant to 18 U.S.C. § 208(b)(1), or qualify for a regulatory exemption, pursuant to 18 U.S.C. § 208(b)(2)." Please provide a list of persons and particular matters (including a list of specific chemical substances, pesticides, regulations, regulatory decisions, risk evaluations, assessments or determinations, or topics) about which you plan to consult with the Designated Agency Ethics Official in order to determine whether you will recuse yourself or require a written exemption or waiver prior to participation.

Response: In connection with the nomination process, I have consulted with the Office of Government Ethics and the EPA's designated agency ethics official to identify potential conflicts of interest. Any potential conflicts of interest will be resolved in accordance with the terms of an ethics agreement that I have entered

into with the Agency's designated agency ethics official and that has been provided to this Committee.

The entities from which I expect to be recused under 18 U.S.C. § 208 are:

- Dourson, Dourson and Fowler (until such time that the financial interest is transferred)
- Martha C. Dourson, LLC

Question 11) Your Ethics Agreement states that "Upon confirmation, I will resign from my positions with the following entities: University of Cincinnati, and the Toxicology Education Foundation. I resigned from my position with the North American Flame Retardant Alliance, and the Toxicology Forum in June 2017. For a period of one year after my resignation from each of these entities, I will not participate personally and substantially in any particular matter involving specific parties in which I know that entity is a party or represents a party, unless I am first authorized to participate, pursuant to 5 C.F.R. § 2635.502(d)." Please provide a list of particular matters involving specific parties (including a list of specific chemical substances, pesticides, regulations, regulatory decisions, risk evaluations, assessments or determinations, or topics) about which you plan to consult with the Designated Agency Ethics Official in order to determine whether you will recuse yourself or require advance authorization prior to your participation.

Response: In connection with the nomination process, I have consulted with the Office of Government Ethics and the EPA's agency ethics officials to identify potential impartiality concerns. Any such concerns will be resolved in accordance with the terms of an ethics agreement that I have entered into with the Agency's designated agency ethics official and that has been provided to this Committee.

Pursuant to 5 C.F.R. § 2635.502, I expect to be recused from participation in any specific party particular matter in which any of the following is or represents a party:

- University of Cincinnati
- Toxicology Education Foundation
- North American Flame Retardant Alliance
- Toxicology Forum
- CreateSpace Independent Publishing Platform
- Dourson, Dourson, and Fowler (for one year following the financial transfer)
- Any client of my spouse's firm, Martha C. Dourson, LLC

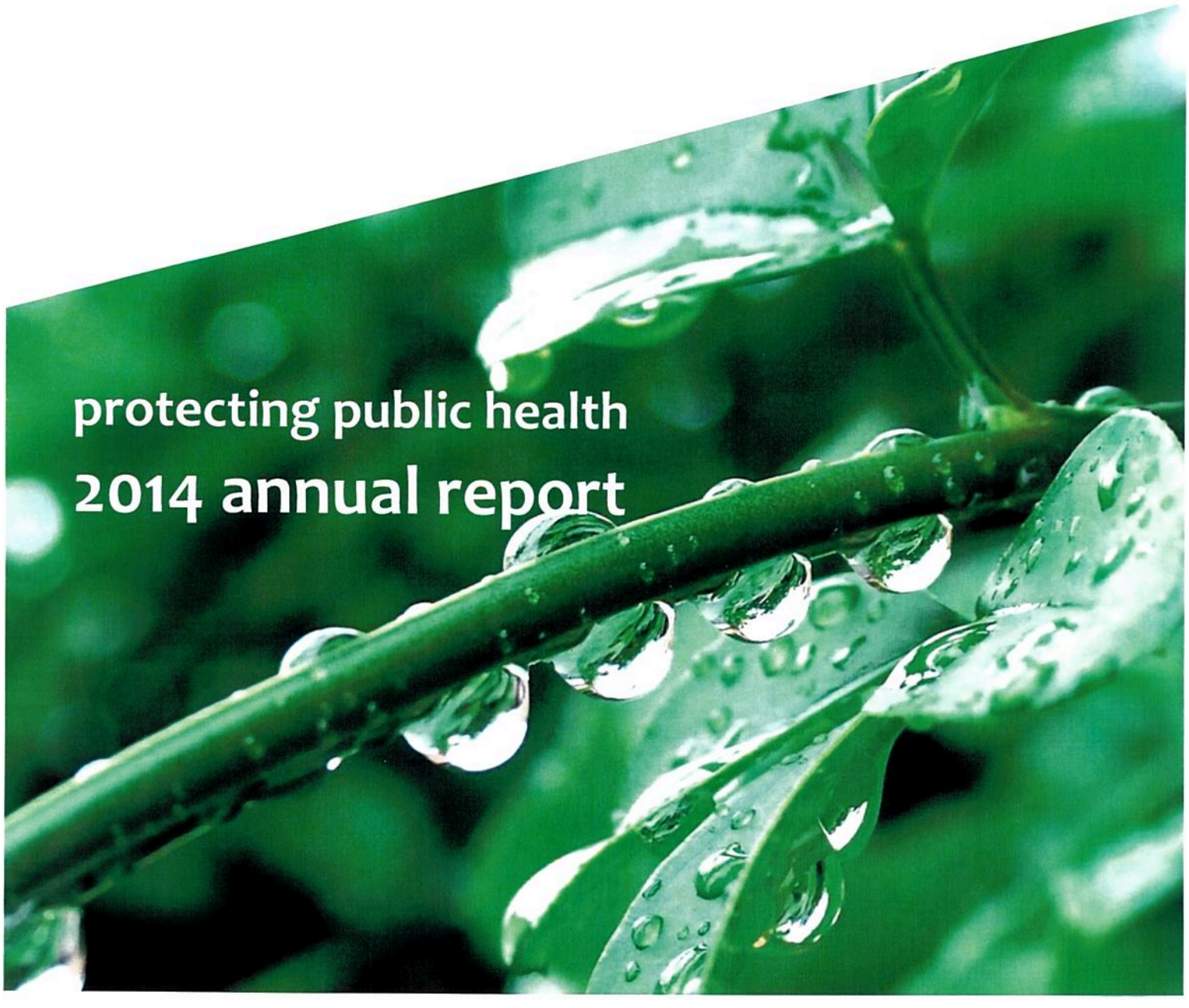
Question 12) Your Ethics Agreement also states that you will sign the Trump Ethics Pledge. The Trump Ethics Pledge states that "I will not for a period of 2 years from the

date of my appointment participate in any particular matter involving specific parties that is directly and substantially related to my former employer or former clients, including regulations and contracts." The Pledge additionally notes that (d) "Directly and substantially related to my former employer and former clients" shall mean matters in which the appointee's former employer or former client is a party or represents a party" and (i) "Former client" is any person for whom the appointee served personally as agent, attorney, or consultant within the 2 years prior to the date of his or her appointment, but excluding instances in which the service provided was limited to a speech or similar appearance. It does not include clients of the appointee's former employer to whom the appointee did not personally provide services." Please provide a list of particular matters involving specific parties (including a list of specific chemical substances, pesticides, regulations, regulatory decisions, risk evaluations, assessments or determinations, or topics) that you plan to recuse yourself from participating in for 2 years. If you plan to request waivers from the Trump Ethics Pledge for any such matter, please also list those.

Response: In connection with the nomination process, I have consulted with the Office of Government Ethics and the EPA's agency ethics officials and been advised that my former employer for the past 2 years has been the University of Cincinnati, which is a local university. As set forth in Section 2(j) of Executive Order 13,770, the term "former employer" does not include any State or local government. I am advised that, for the purposes of the Ethics Pledge, the Office of Government Ethics has determined that this exclusion "does extend to a state or local college or university."[2] Therefore, my only former client/former employer is the University of Cincinnati, which is addressed in my ethics agreement that has been provided to this Committee. I do not intend to seek any waiver from the Trump Ethics Pledge.

[2] *See* Office of Government Ethics (OGE), "Ethics Pledge: Revolving Door Ban – All Appointees Entering Government," DO-09-011 (March 26, 2009). OGE affirmed in its "Guidance on Executive Order 13770," LA-17-03 (March 20, 2107) that the terms used in Pledge paragraph 2 are applicable to Executive Order 13770, sec. 1, par. 6.

Toxicology Excellence For Risk Assessment (TERA)



protecting public health

2014 annual report

Independent

NonProfit



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Mission/Vision/Core Values

Mission



Vision

TERA was founded on the belief that an independent **non-profit** organization can provide a unique function **to protect** human health by conducting scientific research **and development** on risk issues in a transparent and **collaborative** fashion, and communicating these results **widely.**

Core Values

TERA is an independent non-profit and as such we embrace our core principles and values in all our activities. These core principles guide day-to-day TERA operations - from our consideration of new projects and sponsors, to our scientific evaluations and communication of results.

- Honesty and integrity
- Independence
- Transparency
- Collaboration

Board of Directors

DATE INDICATES YEAR OF CURRENT ENDING TERM

Michael Dourson, PhD (perpetual)[2]
President
Toxicology Excellence for Risk Assessment

Gail Charnley Elliott, PhD (2015)
HealthRisk Strategies

Mike Fremont, PhD (2014)
Rivers Unlimited

Jennifer L.S. Knaack, PhD (2015)
Department of Pharmaceutical Sciences
College of Pharmacy & Health Sciences
Mercer University

Laurie Kraus, PhD (2016)

James Rock, PhD (2016)

Gregery S. Romshe, CMA (2015)
VICE CHAIR and FINANCE COMMITTEE CHAIR
The Procter & Gamble Company

Jon L. Seymour, PhD (2014)
AUDIT COMMITTEE MEMBER

Martin L. Stephens, PhD (2016)
Johns Hopkins Center for Alternatives to Animal Testing

Philip E. Tobin, PA-C, MPAS (2016)
NOMINATING COMMITTEE MEMBER
Department of Physician Assistant Studies

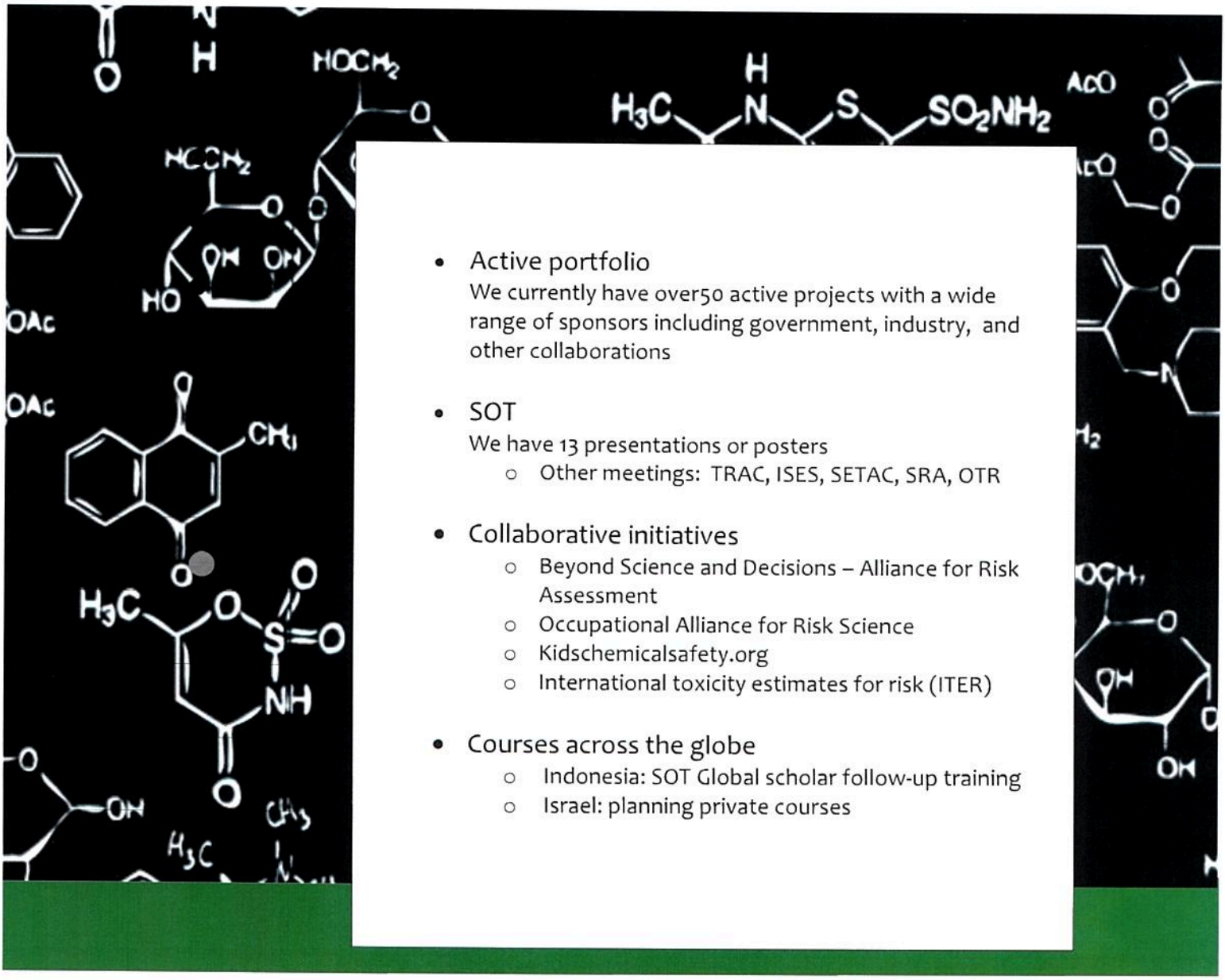
James D. Wilson, PhD (2016)
CHAIR

Chase D. Wright, CPA (2016)
AUDIT COMMITTEE CHAIR

[1] Directors serve 3 year term; date indicates ending year of current term, [2] Michael is an *ad hoc* member of the Board of Directors as the President of *TERA*.

SCIENCE

an overview



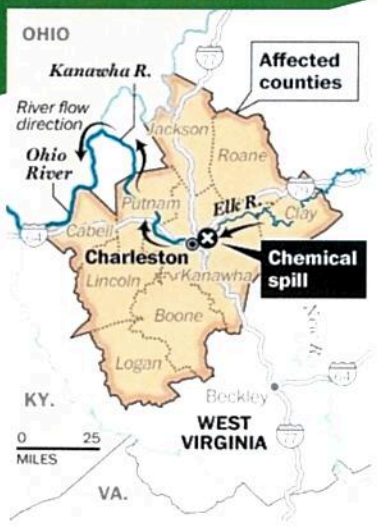
- Active portfolio
  We currently have over50 active projects with a wide range of sponsors including government, industry, and other collaborations

- SOT
  We have 13 presentations or posters
  - Other meetings: TRAC, ISES, SETAC, SRA, OTR

- Collaborative initiatives
  - Beyond Science and Decisions – Alliance for Risk Assessment
  - Occupational Alliance for Risk Science
  - Kidschemicalsafety.org
  - International toxicity estimates for risk (ITER)

- Courses across the globe
  - Indonesia: SOT Global scholar follow-up training
  - Israel: planning private courses

a busy year...



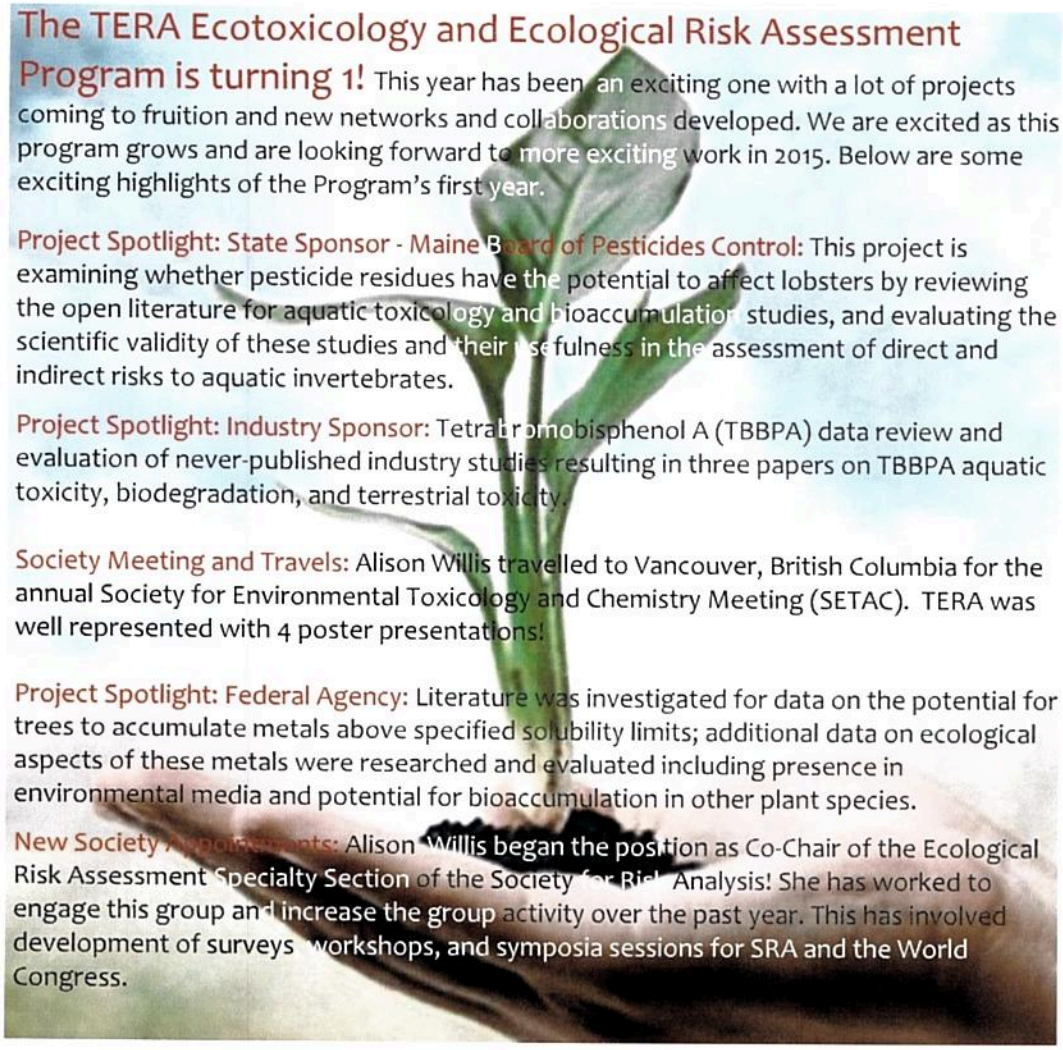
WV TAP Peer Review of the MCHM Screening Level

Last winter the people of Charleston West Virginia complained of a licorice odor from their water. A coal-cleaning chemical, MCHM, had spilled from a storage tank into the Elk River and contaminated the community's water supply. With very limited health effects data, the Centers for Disease Control and Prevention (CDC) provided the state with a screening value of 1 ppm for 4-methyl-1-cyclohexanemethanol (MCHM). One month after the spill, measurements were below the detection limit yet some people could still smell the chemical's characteristic licorice odor, leading the Governor of West Virginia to fund an independent group - the West Virginia Testing Assessment Project (WV TAP) - to conduct research to address the inconsistent results and convene an independent panel to evaluate the health protection of the CDC screening level.

TERA was asked to organize and convene an independent peer review panel to review the available data and determine whether the screening value that the CDC provided the State was protective of public health. The TERA panel of five experts (Shai Ezra, Mekorot, Israel National Water Company Ltd.; James Jacobus, Minnesota Department of Health; Stephen Roberts, University of Florida; Paul Rumsby, National Centre for Environmental Toxicology at WRc plc, UK; and Michael Dourson, TERA) met in Charleston to review the toxicological literature and screening values. The Panel derived a short-term health advisory of 120 ppb for MCHM based on a NOEL of 100 mg/kg-day from a 4 week study (Eastman, 1990). This study and effect level were the same as that used by CDC for its advisory. However, the panel differed from CDC in several regards, including adjusting the experimental dose for the five days per week dosing regimen and accounting for the public's exposure via other routes.

See http://www.tera.org/Peer/index.html for a copy of the panel's report.

Ecotoxicology



The TERA Ecotoxicology and Ecological Risk Assessment Program is turning 1!

This year has been an exciting one with a lot of projects coming to fruition and new networks and collaborations developed. We are excited as this program grows and are looking forward to more exciting work in 2015. Below are some exciting highlights of the Program's first year.

Project Spotlight: State Sponsor - Maine Board of Pesticides Control: This project is examining whether pesticide residues have the potential to affect lobsters by reviewing the open literature for aquatic toxicology and bioaccumulation studies, and evaluating the scientific validity of these studies and their usefulness in the assessment of direct and indirect risks to aquatic invertebrates.

Project Spotlight: Industry Sponsor: Tetrabromobisphenol A (TBBPA) data review and evaluation of never-published industry studies resulting in three papers on TBBPA aquatic toxicity, biodegradation, and terrestrial toxicity.

Society Meeting and Travels: Alison Willis travelled to Vancouver, British Columbia for the annual Society for Environmental Toxicology and Chemistry Meeting (SETAC). TERA was well represented with 4 poster presentations!

Project Spotlight: Federal Agency: Literature was investigated for data on the potential for trees to accumulate metals above specified solubility limits; additional data on ecological aspects of these metals were researched and evaluated including presence in environmental media and potential for bioaccumulation in other plant species.

New Society Appointments: Alison Willis began the position as Co-Chair of the Ecological Risk Assessment Specialty Section of the Society for Risk Analysis! She has worked to engage this group and increase the group activity over the past year. This has involved development of surveys, workshops, and symposia sessions for SRA and the World Congress.

We are pleased to announce our expanded suite of ecological and environmental science services, complementing our strong historical reputation in health risk assessment and industrial hygiene. Our staff now includes scientists with broad experience in ecotoxicology, environmental fate, and ecological risk and hazard assessment of chemical ingredients, products and by-products.

Building partnerships



Alliance for Risk Assessment (ARA)

The Alliance for Risk Assessment (ARA) is a collaboration of diverse organizations representing government, academic, industry, environmental and consulting perspectives, teaming to protect public health. Working together, the ARA pools resources, information, and expertise to address chemical risk assessment issues that individual organizations cannot resolve on their own. State risk assessors have formed coalitions within the ARA to develop guidance methods, to peer review risk assessments, and to find funding for risk projects.
> ALLIANCEFORRISK.ORG

Risk Information Exchange (RISKIE) RiskIE contains over 4700 in-progress human health risk assessment projects from 35 organizations in 13 countries around the world. RiskIE offers a view into the risk science work of other organizations, in an effort to bridge communication gaps among risk assessors of government, industry, academic, and environmental organizations. State risk assessors can use RiskIE to find soon to be released risk values, find potential partners on an upcoming assessment, or publicize their own risk work.
> ALLIANCEFORRISK.ORG/RISKIE.HTM

State Environmental Agency Collaboration for Harmonization (SEARCH) SEARCH is a free online interactive tool designed to help create a collaborative network among state agencies to aid in efficiently sharing information and resources, and to work toward the harmonization of risk values used by state agencies. SEARCH is intended to help state risk agencies communicate, share information, and collaborate.

> ALLIANCEFORRISK.ORG/SEARCH/INDEX.HTML

Guidance for Contaminated Sites A coalition of organizations was formed to develop guidance on how to interpret the non-cancer endpoint when it is used for deciding clean-up standards or acceptable exposure levels when closing sites, using trichloroethylene as a case study. The group sought to clarify the issues surrounding the potential developmental cardiac malformations for use in understanding clean-up standards and short term exposure levels. A webinar will be held this fall to discuss lessons learned and to develop a path forward. State risk assessors working in remediation, or site closure may find the guidance developed by this effort particularly useful.
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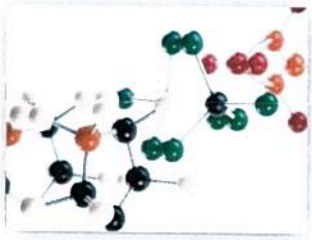


Beyond Science & Decisions

From Problem Formulation to Dose-Response Assessment

May 21 and 22, 2014 at the Texas Commission on Environmental Quality in Austin, Texas

The workshop series, Beyond Science and Decisions: From Problem Formulation to Dose-Response continues and expands upon the discussion initiated by the National Academy of Science report: *Science and Decisions: Advancement of Risk Assessment* (NRC, 2009). The workshops utilize a multi-stakeholder format to support the development of a practical and solution-oriented compendium of risk assessment methods. Conducted under the aegis of the Alliance for Risk Assessment (*ARA*), the workshop series explores both currently available and evolving methodologies, through the development and application of case studies. The workshop series is based on the fundamental premise that the appropriate methodologies for dose-response assessment need to be based on objectives specific to the intended application; this will include varying levels of analysis.

The workshop series continues to advance the framework of *ARA* (2012) on problem formulation and dose-response analysis (beta version available at http://chemicalriskassessment.org/methods/).

The purpose of this workshop report is to document and communicate the workshop results to the workshop participants and interested others. The report contains summaries of the Science Panel discussions with the authors of invited presentations, as well as the Science Panel review of case studies presented at the workshop.

Keeping up with Evolving Risk Methods – the ARA Dose Response Framework

The ARA Dose Response Framework is a library of risk methods, with tools to help you find the method you are looking for, and case studies to illustrate real work applications.

Search by key term, or browse by problem formulation, the Framework offers an overview of how the method works, when it's applicable, and a discussion of limitations.

The ARA Dose Response Framework 2.0 is available in beta at www.chemicalriskassessment.org.

Multi-stakeholder Experts Working Together to Advance Risk Assessment: Recent Reports and Publications

Multi-stakeholder Workshop on Lessons Learned, Challenges, and Opportunities: The U.S. Endocrine Disruptor Screening Program

Workshop report is available now online on the ALTEX website at :http://www.altex.ch/Online-first.95.html and in PubMed PMID:24114257

Workshop on Mode of Action for Nuclear Receptor Mediated Liver Cancer

The report is available at http://www.tera.org/peer/nuclearreceptor/.

Peer Consultation Workshop on the Relationship between PAC Profile and Toxicity of Petroleum Substances

Assessing the mammalian toxicity of high-boiling point petroleum substances, Reg. Tox and Pharm (Volume 67, Issue 2, Supplement - pp. S1-S94 (1 November 2013).



+Balanced, scientifically
accurate chemical health information.



Kids + Chemical Safety

A new feature was added to the website, called "Mom's Perspective." This blog features stories about the adventures of raising children in an environment surrounded by chemicals. We will report on a variety of interesting subjects and mom related facts. For example: Did you know it takes approximately 9 hours for the "stem" of a leaf to pass thru the GI tract of a 3 year old?

Dr. Michael Dourson participated in a live radio interview on behalf of Kids+Chemical Safety. He spoke about the benefits and risks of fluoride in drinking water (based on an essay posted on KidsChemicalSafety.org) and well as general toxicology understanding that all chemicals may be toxic. It was part of the Health, Wealth & Wisdom daily radio show on 1470 AM, WMGG (in the Tamp Bay, FL area).

A visual presentation, along with the radio interview, can be found on our website, along with three articles on fluoride.

OARS WEEL

New OARS-WEEL Values Available

Occupational Alliance for Risk Science initiative (OARS) is an initiative to facilitate sharing of information with workers and occupational health and safety professionals.

Five new WEEL values have been developed and finalized since the transfer of WEELs to OARS. WEEL documentation is now available for

- trans-1-Chloro-3,3,3-trifluoropropylene (HCFO-1233zd(E))
- Menthol
- 2,4-Dinitroanisole (DNAN),
- cis-1,1,1,4,4,4-Hexafluoro-2-butene (HFO-1336mzz-Z)
- 3-Nitro-1,2,4-triazol-5-One (NTO)

Revision of additional WEELs is currently in progress. All current AIHA and TERA WEEL values are available in a tabular format at www.tera.org/OARS/WEEL.html.

iter

What's new with The International Toxicity Estimates for Risk (**ITER**)

ITER is growing in content and usage, and is proud to announce major enhancements to benefit the international risk community:

- New interface to help you find the information you need.
- Over 90 Concise International Chemical Assessment Documents (CICADs) from the World Health organization (WHO) have been added to ITER
- With the help of Summit Toxicology, ITER now includes Biomonitoring Equivalents (BEs) for over 40 chemicals. BEs present an entirely new type of content for ITER users, and can be used to help interpret NHANES data.

News

New Senior Toxicologist at TERA

Dr. Patricia McGinnis has joined TERA as a Senior Toxicologist. Pat has worked in the field or risk assessment and toxicology for over 28 years. We're excited to have her onboard!

Invited speaker at Food Packaging Summit

Dr. Michael Dourson was invited to speak on "Advances in Assessing Food Additive Safety" at the SPI Food, Drug and Cosmetic Packaging Materials Committee, Food Packaging Summit in New Orleans, Louisiana on November 10-12, 2014.

SRA Travel Award Winner

Alison Willis won a Society for Risk Analysis Student/New Researcher Travel Award to this year's Annual Meeting in Denver, Colorado. She will be presenting a poster on data from her recent Master's Project thesis and publication.

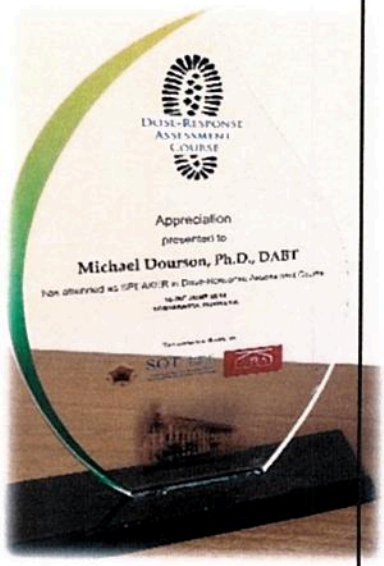
New Toxicologist Formerly of the USEPA

Dr. Jeanelle Martinez has more than 15 years of experience in toxicology and risk assessment. Her expertise includes analysis of health risks for chemical warfare agents and pesticides. Welcome, Jeanelle!

Mouse Lung Tumor Mode of Action (MOA) Workshop

TERAPresident, Michael Dourson recently chaired a science panel workshop that assessed the modes of acon (MOA) of lung tumors in mice from exposures to styrene, ethylbenzene, and naphthalene. The workshop was organized by the Styr ene Information & Research Center (SIRC) and focused on the MOA involving chemically- similar aromatic hydrocarbons and included discussion of available data, including recent studies in knockout and humanized mice. SIRC organized thi s workshop with the purpose of seeking opinions from independent risk and mode of acon experts on a hypothesized mode of acon for mouse lung tumors. TERA prepared the panel's report, which is available at hp://www.tera.org/Peer/SIRC/

training



Making progress in developing countries

TERA, in conjunction with Dr. Noegrohati and the Pharmaceutical Chemistry Department (Faculty of Pharmacy, Gadjah Mada University, Yogjakarta, Indonesia), conducted its first ever, 5-day intensive training in Indonesia, tailored to the needs of the local region and including local teachers. This course was partly sponsored by the Society of Toxicology (SOT) Global Senior Scholar Exchange Program (GSSEP), the Faculty of Pharmacy and the Graduate School of Gadjah Mada University, and the Indonesia Ministry of Agriculture, and was endorsed by the Society for Risk Analysis. The course was taught by Drs. Michael Dourson and Bernard Gadagbui, with local presentations by Dr. Sri Noegrohati (Gadjah Mada University) and Yayah Rodiana (M.Sc., Ministry of the Environment, Jakarta, Indonesia).

Dr. Dourson also gave a lecture on the importance of toxicology and risk assessment to students at the Faculty of Pharmacy, Gadjah Mada University.

The crowning event of this training was the formation and inauguration of the Indonesian Society for Toxicological Sciences (ISTS) on June 20, 2014.

Dose-Response Boot Camp TERA has partnered with the University of Cincinnati, College of Medicine (UC) to offer existing TERA courses and develop new courses. TERA's well-known Dose-Response Assessment Boot Camp has evolved into two new courses: a basic dose-response course for those new to formal risk assessment methods and an advanced dose-response framework and modeling course. The Boot Camp Basics course will include a new component on introduction to toxicology for risk assessors, while also covering the fundamental approaches used in developing most current human health risk assessment with an introduction to complex concepts and modeling. The Boot Camp Advanced Framework and Modeling course will introduce the student to the application of advanced concepts and models, including mode of action evaluation techniques, use of dosimetry and PBPK models, benchmark dose modeling, structure activity evaluation tools and methods, and other tools that are an essential part of the advanced risk assessment practice.

2014 Publications



Andersen, ME; Preston, RJ; Maier, A; **Willis, A; Patterson, J.** 2014. Dose-Response Approaches for Nuclear Receptor-Mediated Modes of Action for Liver Carcinogenicity: Results of a Workshop. Crit Rev Toxicol. 44(1):50-63 (doi:10.3109/10408444.2013.835785).

> Downloads of this and other papers coming out of the nuclear receptor workshop published in *Critical Reviews in Toxicology* are being made available for a limited time free of charge. Please go to http://www.tera.org/Peer/NuclearReceptor/index.html to download a copy. **The paper on the CAR MOA by Elcombe and Lake, et al. was selected as a top 10 risk assessment paper published in 2013 by the Risk Assessment Specialty Section of SOT.**

Budinsky, RA; Schrenk, D; Simon, T; Van den Berg, M; **Reichard, JF**; Silkworth, JB; Aylward, LL; Brix, A; Gasiewicz, T; Kaminski, N; Perdew, G; Starr, TB; Walker, NJ; Rowlands, JC. 2014. Mode of action and dose-response framework analysis for receptor-mediated toxicity: The aryl hydrocarbon receptor as a case study. Crit Rev Toxicol 44(1):83-119 (PMID: 24245878).

Chen, J; Hu, Z; Phatak, M; **Reichard, J;** Freudenberg, JM; Sivaganesan, S; Medvedovic, M. 2013. Genome-wide signatures of transcription factor activity: connecting transcription factors, disease, and small molecules. PLoS Comput Biol. 9(9):PMC3764016.

Dourson, M; Reichard, J; Nance, P; Burleigh-Flayer, H; **Parker, A; Vincent, M**; McConnell, EE. 2014. Mode of Action Analysis for Liver Tumors from Oral 1,4-Dioxane Exposures and Evidence-Based Dose Response Assessment. Regul Toxicol Pharmacol (in press).

Dourson, M; Becker, RA; **Haber, LT;** Pottenger, LH; Bredfeldt, T; Fenner-Crisp, P. 2013. Advancing Human Health Risk Assessment: Integrating Recent Advisory Committee Recommendations. Crit Rev Toxicol. 43(6):467-92 (doi: 10.3109/10408444.2013.807223).

Dourson, M; **Gadagbui**, B; Griffin, S.; Garabrant, D.H.. Haws, L.C.; Kirman, C.; and Tohyama, C. 2013. The importance of problem formulations in risk assessment: A case study involving dioxin-contaminated soil. Reg Toxicol Pharmcol. 66(2):208-216.

Effio, DG; **Kroner, O**; Maier, A; Hayes, W; **Willis, A; Strawson J.** 2013. A Look at State-Level Risk Assessment in the United States: Making Decisions in the Absence of Federal Risk Values. Risk Analysis. 33(1):54-67.

Hasegawa, R; Hirata-Koizumi, M; **Dourson, ML; Parker, A**; Ono, A; Hirose, A. 2013. Safety assessment of boron by application of new uncertainty factors and their subdivision. Regul Toxicol Pharmacol 65(1):108-114 (doi: 10.1016/j.yrtph.2012.10.013).

Hertzberg, RC; Pan, Y; Li, R; **Haber, LT**; Lyles, RH; Herr, DW; Moser, VC; Simmons, JE. 2013. A four step approach to evaluate mixtures for consistency with dose addition. Toxicology. (doi: S0300-483X(12)00368-X. 10.1016/j.tox.2012.10.016).

Juberg, DR; Borghoff, SJ; Becker, RA; Casey, W; Hartung, T; Holsapple, MP; Marty, SM; Mihaich, EM; Van Der Kraak, G; Wade, MG; Willett, CE; Andersen, ME; Borgert, CJ; Coady, KK; **Dourson, ML**; Fowle, JR; Gray, LE; Lamb, JC; Ortego, LS; Schug, TT; Toole, CM; Zorrilla, LM; **Kroner, OL; Patterson, J**; Rinckel, LA; Jones, BR. 2014. *t4Workshop Report, Lessons Learned, Challenges, and Opportunities: The U.S. Endocrine Disruptor Screening Program. ALTEX.*. ALTEX, 31:63-78, January http://www.tera.org/Peer/EDSP/altex_2014_1_063_078_T4Juberg.pdf

Maier, A; **Vincent, MJ**; Hack, E; **Nance, P**; Ball, W. 2014. Derivation of an Occupational Exposure Limit for Inorganic Borates Using a Weight of Evidence Approach. Regul Toxicol Pharmacol. 68(3):424-437. doi: 10.1016/j.yrtph.2014.02.001

Meek, ME;., Bolger, M; Bus, JS; Christopher, J; Conolly, RB; Lewis, RJ; Paoli, G; Schoeny, R; **Haber, LT;** Rosenstein, AB; **Dourson, ML**. 2013. A Framework for Fit-for-Purpose Dose Response Assessment. Regul Toxicol Pharmacol 66(2):234-40 (doi: 10.1016/j.yrtph.2013.03.012). **Available open access.**

Moser, VC; Padilla, S; Simmons, JE; **Haber, LT;** Hertzberg, RC. 2012. Impact of Chemical Proportions on the Acute Neurotoxicity of a Mixture of Seven Carbamates in Preweanling and Adult Rats. Toxicol Sci 129(1):126-34 (doi: 10.1093/toxsci/kfs190).

Patterson, J; Maier, A;, **Kohrman-Vincent, M; Dourson, ML**. 2013. Peer consultation on relationship between PAC profile and toxicity of petroleum substances. Regul Toxicol Pharmacol 67: S86–S93. **Available open access.**

Parsons, BL; Manjanatha, MG; Myers, MB; McKim, KL; Shelton, SD; Wang, Y; Gollapudi, BB; Moore, NP; **Haber, LT;** Moore, MM. 2013. Temporal changes in K-ras mutant fraction in lung tissue of big blue B6C3F, mice exposed to ethylene oxide. Toxicol Sci 136(1):26-38 (doi: 10.1093/toxsci/kft190).

Sweeney, LM; **Parker, A; Haber, LT**; Tran, CL; Kuempel, ED. 2013. Application of Markov chain Monte Carlo analysis to biomathematical modeling of respirable dust in US and UK coal miners. Regul Toxicol Pharmacol 66:47–58.

Book Chapters

Haber, LT; Strawson, JE; Maier, A; Baskerville-Abraham, IM; **Parker, A; Dourson, ML**. 2013. "Noncancer Risk Assessment: Principles and Practice in Environmental and Occupational

Settings." In: Bingham, E., and B. Cohrssen, eds. *Patty's Toxicology, 6th Edition, Volume 5*. John Wiley and Sons Inc.

York, RG; Parker, RM; **Haber, LT**. 2014. "Test Methods for Assessing Female Reproductive and Developmental Toxicology." In: Hayes, A.W., ed. Principles and Methods of Toxicology, 6th Edition, In press.

In *Encyclopedia of Toxicology*: **Gadagbui, B; Vincent, M; Willis, A.,** Methyl isothiocyanate; **Haber, L; Willis, A; Nance, P**. Mode of Action; Abdollahi, M., Karami-Mohajeri, S., **Gadagbui, B**. Oral/Dermal Reference Dose (RfD)/Inhalation Reference Concentration.

TERA Reports

Report of a Workshop to Assess the Modes of Action of Lung Tumors in Mice from Exposures to Styrene Ethylbenzene, and Naphthalene. Prepared by TERA for the Workshop Panel. http://www.tera.org/Peer/SIRC/index.htm

Workshop Report, Lessons Learned, Challenges, and Opportunities: The U.S. Endocrine Disruptor Screening Program. http://www.tera.org/Peer/EDSP/. Also published in ALTEX (See Juberg et al., above).

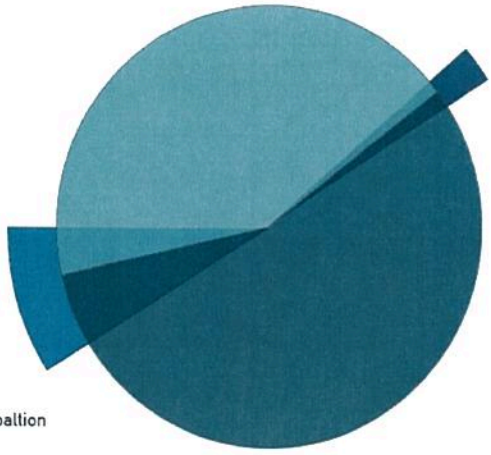
Report of Workshop for the Industry Sponsored Asthma Science Forum. http://www.cleaninginstitute.org/assets/1/Page/AsthmaScienceForumReport.pdf



Funding

Proportion of Work by Project Sponsor

2014 TERA Project Time by Sponsor



43%

For Profit
Projects/Sponsors

+ American Cleaning Institute
+ Amgen
+ Eli Lily
+ Genentech
+ Morrison & Foerster
+ Quinn

2%

Training
Projects/Sponsors

+ Dose Response Boot Camp
+ FDA Training Course

9%

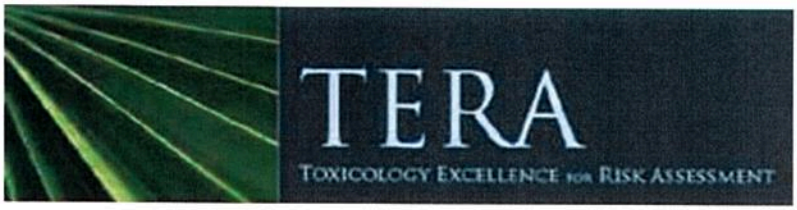
Collaborations
Projects/Sponsors

+ Alliance for Risk Assessment TCE Coaltion
+ Beyond Science & Decisions
+ Kidschemicalsafety.org
+ Occupational Alliance for Risk Assessment

57%

Government/ Nonprofit
Projects/Sponsors

+ Consumer Product Safety Commission
+ ERM: Alaska Sulfolane
+ Health Canada
+ West Virginia Spill - MCHM



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Toxicology Excellence For Risk Assessment (TERA)



contents

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Mission/Vision/Core Values

Toxicology Excellence for Risk Assessment (TERA) is a non-profit and tax-exempt organization designed for scientific and educational purposes.

Mission

To support the protection of public health by developing, reviewing and communicating risk assessment values and analyses; improving risk methods through research; and, educating risk assessors, managers, and the public on risk assessment issues.

Vision

TERA was founded on the belief that an independent non-profit organization can provide a unique function to protect human health by conducting scientific research and development on risk issues in a transparent and collaborative fashion, and communicating these results widely.

Core Values

TERA is an independent non-profit and as such we embrace our core principles and values in all our activities. These core principles guide day-to-day TERA operations - from our consideration of new projects and sponsors, to our scientific evaluations and communication of results.

- Honesty and integrity
- Independence
- Transparency
- Collaboration

Board of Directors

DATE INDICATES YEAR OF CURRENT ENDING TERM

Michael Dourson, PhD
President Toxicology Excellence for Risk Assessment
(1/1/2015 – 8/1/2015)

Patricia McGinnis, PhD (2017)
Interim President Toxicology Excellence for Risk Assessment

Gail Charnley Elliott, PhD (2015)
HealthRisk Strategies

Mike Fremont, PhD (2014)
Rivers Unlimited

Jennifer L.S. Knaack, PhD (2015)
Department of Pharmaceutical Sciences College of Pharmacy & Health Sciences Mercer University

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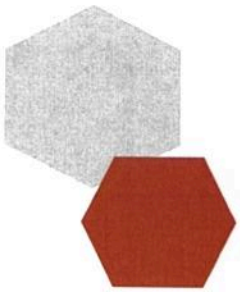




News from TERA's President and Board of Directors

TERA Joins the University of Cincinnati

Toxicology Excellence for Risk Assessment joined the Department of Environmental Health, at the University of Cincinnati's (UC), College of Medicine on July 6, 2015. TERA will be known as the Toxicology Excellence for Risk Assessment Center (or TERA Center).

TERA was organized in 1995 as a nonprofit with a mission to support the protection of public health through the best use of toxicity data. Now as a Center with the Department of Environmental Health at the University of Cincinnati's College of Medicine, we continue to accomplish this mission through independent evaluation of toxicity data and by interpreting and communicating risk assessment information through assessments and websites, organizing peer reviews and consultations, improving risk methods through research, and educating risk managers, assessors, and the public on risk assessment issues. TERA has a strong history of enhancing the use of chemical-specific data to increase the rigor and transparency of evaluations aimed at the prevention of potential human health risks.

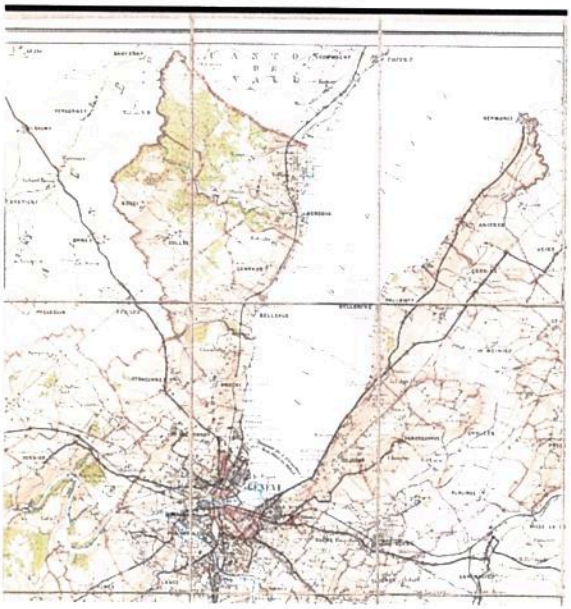
The TERA Center will maintain this rigor and transparency, but will also mesh its work with the research findings of UC investigators in order to develop the next generation of risk assessment methods based on Toxicology 21 principles.

SUPPORTING MISSIONS

TERA Center: To support the protection of public health by developing, reviewing and communicating risk assessment values and analyses; improving risk methods through research; and educating risk assessors, managers, and the public on risk assessment issues.

UC-DEH: To improve the quality of life by identifying the mechanisms of disease and injury due to environmental exposures and genetic factors, and by developing effective methods of preventions and interventions.

Global impact



Geneva

9/14/2015 – 9/25/2015

Dr. Michael Dourson served on the 2015 Joint Meeting of the Pesticide Review panel to determine the appropriate acceptable daily intakes and exposures for up to 20 pesticides.

The meeting was highly interactive and impactful.

A report is available at the World Health Organization website.

Philippines

8/25/2015-8/31/2015

Dr. Michael Dourson served as a US delegate to the Asian Pacific Economic Conference held in Cebu, Philippines, where he gave several lectures on metal toxicity, and led a small study group on methyl mercury contamination of fish.

This organization meets periodically to share technology among member states.



A busy year...

TERA brings RISK ASSESSMENT PERSPECTIVE *to* Nutrition Science

In a novel approach

to addressing the effect of consumption of a macronutrient, TERA has conducted an evaluation of the relationship between the intake of trans fatty acids (TFAs), particularly industrially-produced TFAs (iTFAs), and changes in plasma low density lipoprotein cholesterol (LDL-C), particularly in the low intake region.

A key issue was evaluating the shape of the dose-response curve in the low-dose region. TERA took a two-pronged approach to address the issue. First, the mode of action (MOA) for the impact of TFA on plasma LDL-C was evaluated. Second, TERA conducted a meta-regression of the controlled clinical trial data on iTFAs, using (MCMC) modeling, in collaboration with Bruce Allen for the modeling, and DeAnn Liska of Biofortis for the nutritional perspective.

This approach was unique in nutritional literature, in rigorously considering a variety of flexible curves, including both linear and nonlinear models. The MOA analysis concluded that, although there are several data gaps precluding a rigorous application of the evolved Hill Criteria for evaluation of MOA, the feedback loops and homeostatic controls responsible for maintaining homeostasis of cholesterol and triglyceride levels result in a less than linear relationship between TFA and LDL-C. Consistent with the MOA evaluation, the meta-regression found that an S-shaped curve fit by the Hill model is clearly better than linear model, and linear model is not acceptable.

This novel analysis has generated much interest in the nutrition and risk assessment communities. It has been presented at several venues, including the ToxForum, and SOT-FDA Joint Colloquium; publications are in preparation.

This work was sponsored by the ILSI North America PHO Task Force.

Ozone NAAQS Science and Policy Workshop Report Now Available

Working with the Texas Commission on Environmental Quality (TCEQ) and others, TERA organized a public workshop in April 2015 to provide an independent evaluation and synthesis of key considerations for EPA's November 2014 proposal to lower the primary National Ambient Air Quality Standard (NAAQS) for ozone. A diverse group of well-known and respected science and policy experts engaged in robust discussions on key issues, so that TCEQ and other attendees could gain a better understanding of the issues and implications. This multi-disciplinary group of science and policy experts deliberated on the nexus between scientific findings and implications for public health. The focus was on science related to the level (concentration) of the primary NAAQS and an independent evaluation and synthesis of key policy and other considerations for approaching the difficult and important ozone NAAQS decision.

Presentations, background materials and a summary report are available at http://www.tera.org/Peer/ozone/index.html.

Framework for Addressing Less-than-Chronic and Intermittent Exposures

How does one identify an exposure limit (toxicity reference value, or TRV) for an intermittent exposure (e.g., one day/month for 40 years)? Should one use an acute or a chronic limit for this sort of scenario? How does one decide?

Intermittent exposures such as these are common in many sectors, including manufacturing, waste site cleanup, food safety, and consumer product exposures. Led by Lynne Haber and in collaboration with Bette Meek and Health Canada scientists, the TERA team developed a framework for addressing such scenarios. The framework presents an integrated, tiered approach that assists the user in identifying when existing TRVs can be applied directly, and the adaptations needed to assess the acceptability of short-duration or intermittent exposure scenarios. A manuscript based on the framework is nearing publication, and Dr. Haber shared the framework in a Risk Assessment Specialty Section webinar.



See http://www.toxicology.org/groups/ss/RASS/downloads.asp.

TERA Scientists Assist With Harmonization Effort in Pharmaceutical Industry

Like other industries, the pharmaceutical industry has to manage chemical safety issues—both for workers and consumers. The TERA Center has been working with toxicologists and risk assessment scientists from pharmaceutical industries, consulting groups and academia to discuss current practices for exposure limits, evaluate inconsistencies across guidance documents, identify key areas for harmonization, and document best practices for risk assessment of pharmaceuticals.

"Harmonization doesn't necessarily mean standardization," says Andrew Maier, PhD, an associate professor in the Department of Environmental Health and TERA Center co-director. "It's more a matter of understanding the basis for safety so that we enable savvy users of the risk assessment materials.

Maier and Alison Pecquet were key organizers and facilitators for an October 2014 workshop that was convened in New Brunswick, New Jersey, to identify and address further opportunities for advancing harmonization and best practices in deriving and applying acceptable daily exposures (ADE) in pharmaceutical manufacturing operations. The workshop effort was spurred from a benchmarking assessment to compare current methods in risk assessment for pharmaceuticals.

> "During our benchmarking work, we found that the international guidance documents and methods being used were clearly not harmonized in a number of areas," Pecquet says. "The workshop, which involved most of the top global pharmaceutical companies, was an effort to discuss some of the ways that we could harmonize efforts across agencies so that all of these health-based limits for pharmaceuticals are based on consistent methodologies."

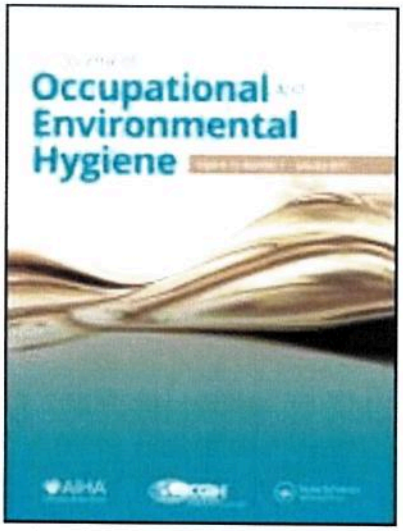
Following the workshop, an article summarizing key workshop findings was published in the September 2015 issue of Contract Pharma, a trade magazine.

The article concluded that a "harmonized set of recognized scientific principles is needed to inform individual efforts in calculating, interpreting, and implementing pharmaceutical risk assessments."

"We are currently working on a series of 10 articles associated with each workshop topic that will appear in a Special Issue of Regulatory Toxicology and Pharmacology in early 2016," Pecquet says. "Our goal is for these reports to shed light on inconsistencies and data needs, lead to further research of the knowledge gaps and contribute to informing decision making among risk assessors in the pharmaceutical industry by providing a 'guide to best practices.'"

"Ultimately, we aim to have one publication that summarizes key issues in this area to help users harmonize and use best practices, all in one place."

SPECIAL ISSUE: State of the Science of Occupational Exposure Limit (OEL) Methods and Guidance



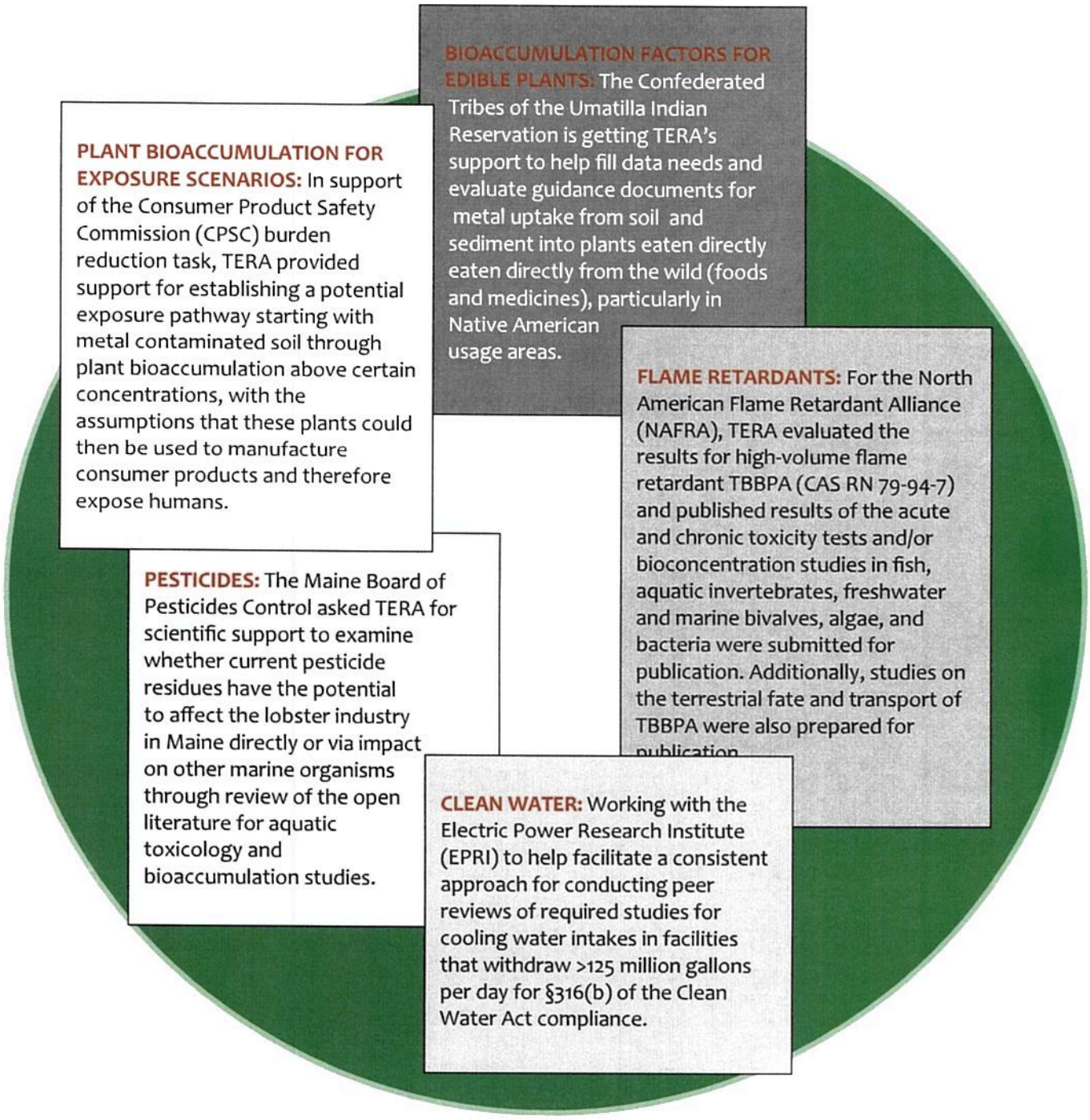
The National Institute for Occupational Safety and Health (NIOSH) conducted an effort to identify and characterize leading issues pertaining to OELs and their development through research, which culminated in a collection of articles focused on each key issue. Those articles and the key issues they explore comprise a Special Issue of the *Journal of Occupational and Environmental Hygiene*. The goal of this effort is to describe the issues related to education and communication of science principles and to understand how they can be incorporated into (and thereby impact) the practices of OEL development and interpretation. Focusing specifically on the state-of-the-science in the fields of exposure science, occupational hygiene, risk assessment, and toxicology this effort sought to provide a clear description of how advances in these research areas can contribute to the practice of OEL setting—by reviewing the methods used for most OELs that are currently available as well as new methods that are actively being incorporated in the OEL process. An essential topic included within the set of complementary and interrelated articles dedicated to this pursuit is the consideration and interpretation of OELs in the context of evolving risk management practices. The articles are intended to serve as a current critical review of occupational risk assessment methods that will enable occupational hygiene professionals to have a clear understanding of the science methods incorporated in the OELs they develop or use.

The ten articles in the supplement resulted from collaborations among scientists at NIOSH, Toxicology Excellence for Risk Assessment (TERA) Center (Dr. Andrew Maier, Dr. Lynne Haber, Dr. Michael Dourson, Dr. Bernard Gadagbui), and other organizations.

While the list of topics for OELs covered in this supplement is in no way exhaustive, it does represent some of the most relevant, promising, and readily applicable scientific advances that can be integrated into risk assessment and management of occupational hazards. The purpose of this collection of article is to inform the practitioner, stimulate the researcher, and provide a basis for more protective and scientifically sound guidance and policy.

TERA's Eco Risk Assessment portfolio is growing!

Ms. Alison Pecquet, M.Sc. and Dr. Charles Pittinger, TERA Fellow, along with additional TERA staff and external collaborators are working to provide support for environmental risk-related services.



BIOACCUMULATION FACTORS FOR EDIBLE PLANTS: The Confederated Tribes of the Umatilla Indian Reservation is getting TERA's support to help fill data needs and evaluate guidance documents for metal uptake from soil and sediment into plants eaten directly eaten directly from the wild (foods and medicines), particularly in Native American usage areas.

PLANT BIOACCUMULATION FOR EXPOSURE SCENARIOS: In support of the Consumer Product Safety Commission (CPSC) burden reduction task, TERA provided support for establishing a potential exposure pathway starting with metal contaminated soil through plant bioaccumulation above certain concentrations, with the assumptions that these plants could then be used to manufacture consumer products and therefore expose humans.

FLAME RETARDANTS: For the North American Flame Retardant Alliance (NAFRA), TERA evaluated the results for high-volume flame retardant TBBPA (CAS RN 79-94-7) and published results of the acute and chronic toxicity tests and/or bioconcentration studies in fish, aquatic invertebrates, freshwater and marine bivalves, algae, and bacteria were submitted for publication. Additionally, studies on the terrestrial fate and transport of TBBPA were also prepared for publication.

PESTICIDES: The Maine Board of Pesticides Control asked TERA for scientific support to examine whether current pesticide residues have the potential to affect the lobster industry in Maine directly or via impact on other marine organisms through review of the open literature for aquatic toxicology and bioaccumulation studies.

CLEAN WATER: Working with the Electric Power Research Institute (EPRI) to help facilitate a consistent approach for conducting peer reviews of required studies for cooling water intakes in facilities that withdraw >125 million gallons per day for §316(b) of the Clean Water Act compliance.

Partnerships



A collaborative effort to organize the world's risk data

Through the Alliance for Risk Assessment, a group of organizations have come together to build the world's premiere database of human health risk values. Building from TERA's *International Toxicity Estimates for Risk (ITER)*, this effort has been dubbed *ITER+* and seeks to first expand the database offerings to include the European Union's Derived No Effect Levels (DNELS), and then additional values to be determined. *ITER* is currently available via the National Library of Medicine, and includes risk values from EPA, ATSDR, IARC, IPCS, and more. The *ITER+* Advisory Committee is responsible for prioritizing the addition of risk values from new sources.

Situation: Exposure analysis requires the use of reference values to qualitatively understand exposure data. Currently, these values are developed by a number of researchers and/or authoritative bodies and reside in a variety of locations. Searching for these values can be time-intensive, values identified can be of varying scientific quality, and often additional expertise is needed to conduct a screening level exposure assessment.

Proposal: Build upon the existing data housed within the International Toxicity Estimates for Risk Assessment (*ITER*) database to include additional values needed for exposure and risk assessment. *ITER* includes peer-reviewed human-health risk values and is searchable using the Toxicology Data Network (TOXNET) on the National Library of Medicine's website (**http://toxnet.nlm.nih.gov/newtoxnet/iter.htm**).

The Alliance for Risk Assessment is organizing a collaborative public/private partnership for the systematic addition of credible values to *ITER+*. The new additions will include the health basis of the value and any assessment or uncertainty factors needed for the lack of key data. These additions will be for chemical ingredients that are known to be used or are found in consumer products. As the initial start for a systematically-phased project, REACH data for derived no effect levels (DNEL) for about 600 chemicals will be added, followed by derived minimal effect levels (DMEL), and the values for the 100 most commonly found

chemical ingredients in consumer products. This focus could encourage analysts to use *ITER+* as their initial 'go to library' site prior to undertaking a full literature search.

Value: Centralizing authoritative reference values from global organizations in a curated database will streamline the risk assessment process, and foster the consideration of exposure for consumer products by removing one of the current barriers to the use of screening level exposure analysis.

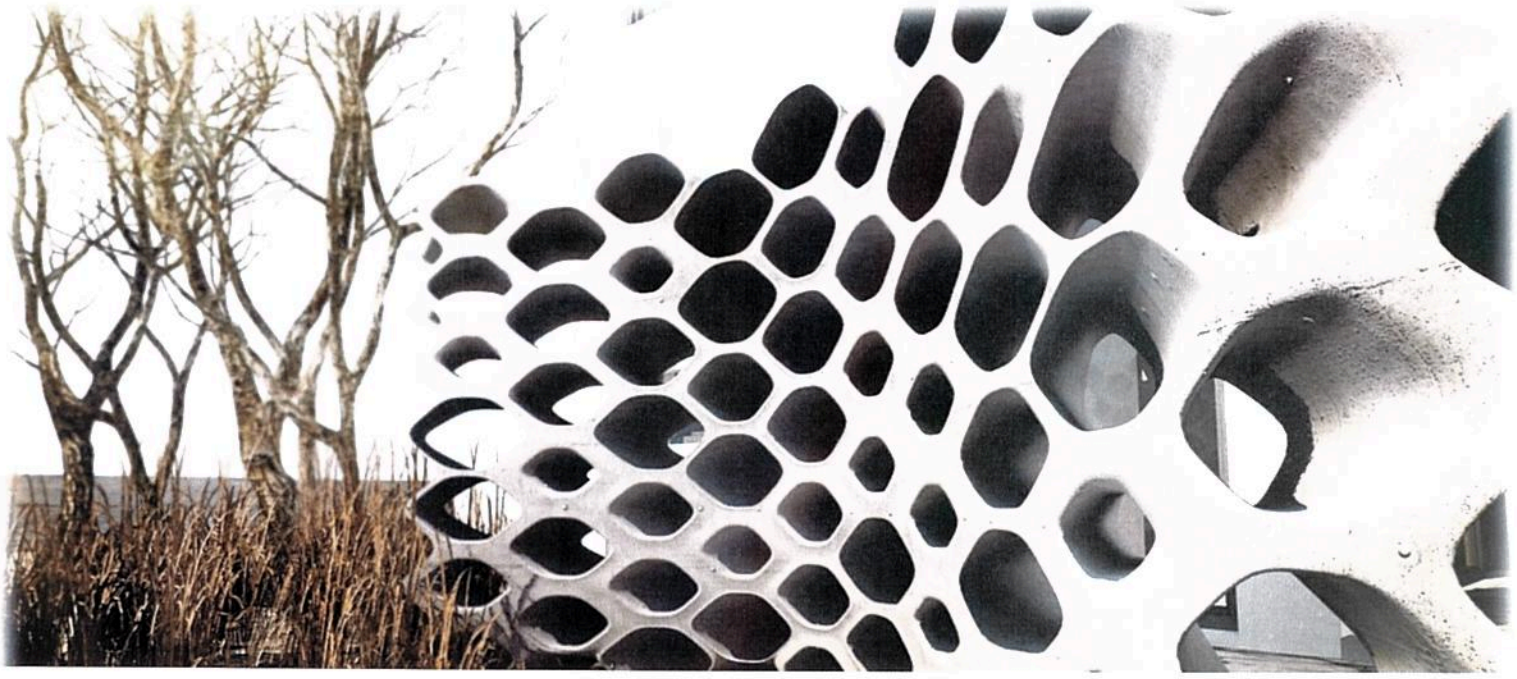
The Alliance welcomes additional partners interested in helping to build ITER+, whether through financial or in-kind support. Additional information can be found at www.allianceforrisk.org.



BIG DATA

Turning Big Data to Knowledge (BD2K): A discussion of the NIH BD2K initiative and how it might advance the practice of Toxicology and Risk Assessment: The fields of toxicology, pharmacology and risk assessment are undergoing a revolution in the use of pathway-based approaches to evaluate the biological effects of chemicals. These fields would benefit from accessible tools that make big data convenient and intuitive to integrate, analyze, query and visualize. The aim of this ancillary meeting is to reach out to toxicological scientists and introduce them to the NIH big data programs. A panel of researchers provided short overviews of the BD2K and LINCS initiative and thoughts on how big data can be leveraged for protection of people and the environment.

This discussion was held March 23, 2015 Society of Toxicology (SOT) Outreach Meeting in San Diego, California.



Beyond Science & Decisions: *From Problem Formation to Dose-Response Assessment*

9

Workshops
the Workshop series has now completed 9 workshops, bringing scientists of various affiliations and expertise together.

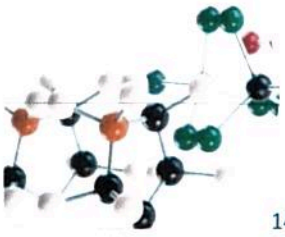
60+

Over 60 organizations
government, industry scientific societies and nonprofits— have contributed to the Workshop's mission to advance the science of risk assessment.

40+

Case Studies
the Workshop series has now reviewed over 40 case studies focusing on a range of risk topics.

Preparation for 2016 Workshop 10 is in underway.



ARA Coalition

1,4-Dioxane Reanalysis of a Regenerative Hyperplasia Mode of Action

EPA's IRIS 2012 external reviewers of the 1,4-dioxane assessment suggested that the histopathology slides from the NCI 1978 dioxane cancer bioassay in mice be reviewed to ascertain whether non cancer pathology was evident. If evident, this finding would support the conclusion that the cancer MOA is regenerative hyperplasia. TERA scientists worked with Dr. Gene McConnell and staff of the NTP to reevaluate these mouse liver slides and found extensive non cancer pathology, thus supporting the regenerative hyperplasia MOA.

This evaluation also suggested the need to re-evaluate the mouse liver slides from a series of Japanese studies on 1,4-dioxane. Five US states and TERA scientists requested the full unpublished reports (including the relevant micrographs) from the study authors. These reports have been reviewed and a draft analysis was prepared.

As described in our draft analysis, the additional information and translations are also supportive of a regenerative hyperplasia MOA but with one exception, specifically, the reported findings from the histopathology and clinical chemistry of the mouse liver in the Japanese studies are contradictory. This may be due in part to the investigators changing the criteria for liver histopathology scoring during the course of reporting their results.

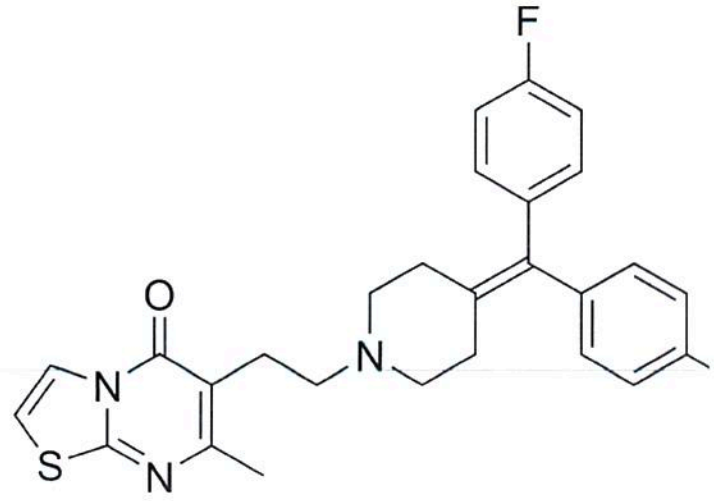
The State of Kentucky petitioned the Alliance for Risk Assessment (ARA) Steering Committee to obtain additional histopathology documentation from the Japanese studies to inform 1,4-dioxane's cancer Mode of Action (MOA). The intent of this project is to use this additional information, together with the earlier re-evaluations, in order to reach a conclusion regarding the hypothesized MOA for 1,4-dioxane's liver tumor formation (and potentially other tumors). The coalition includes 5 groups and others are welcomed to participate. An evaluation of the data is being done by 3 pathologists and will be used in the final publication.

More information, including a project timeline, can be found on the project website at http://allianceforrisk.org/14-dioxane-analysis/

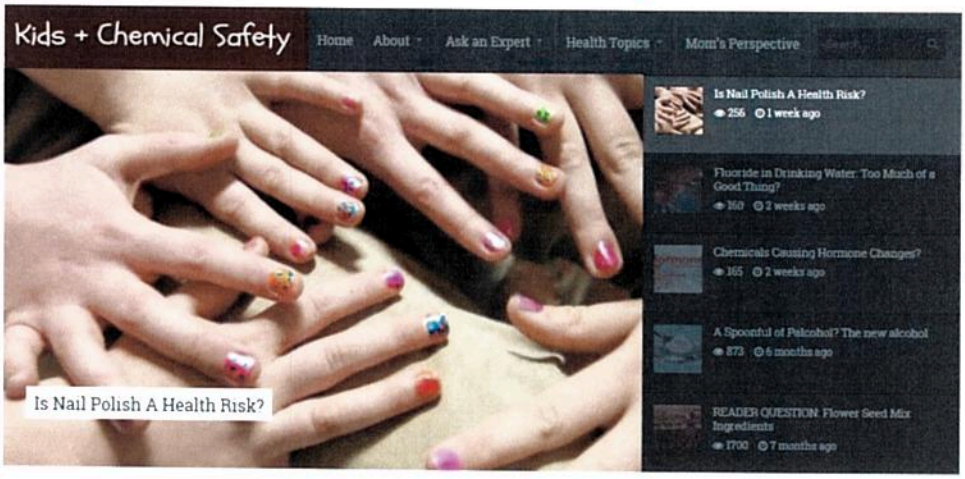
What is *ITER*ate?

*ITER*ate is a new program from TERA to review chemical risk values from published peer-reviewed journals for loading onto the International Toxicity Estimates for Risk (*ITER*) (www.tera.org/iter; http://toxnet.nlm.nih.gov/) Through *ITER*ate, TERA convenes a small group of toxicology and risk assessment experts to evaluate the Enter *ITER*ate. This process will help fill data gaps for missing values or outdated assessments. TCDD example: This controversial chemical has no risk guidance from EPA. The *ITER* database contains data from ATSDR for noncancer endpoints only. The *ITER*ate process was utilized to upload an independently derived cancer value for TCDD. Now, states needing to act to protect human health regarding TCDD have access to this newly derived value.

How to Participate Experts in risk assessment are invited to volunteer for review panels. Authors of risk value papers are invited to submit to *ITERate*.



Kids + Chemical Safety



+ Balanced, scientifically accurate chemical health information.

Latest Updates:



Is Nail Polish A Health Risk?

Moms are not the only ones that think about the health and well-being of their children. Today's "Mom's Perspective" is a "Grandfather's Perspective." My granddaughter, who is with child, dropped by the other day and asked what I was reading? It was an article on nail polish that contained a



Fluoride in Drinking Water: Too Much of a Good Thing?



A new resource addressing the needs of parents and families by providing balanced and scientifically accurate health information on chemical hazards and safe use of chemicals around children.

Partnerships:

Superfund Research Program, Harvard University

Drug and Poison Information Center (DPIC)

Training

Workshops, Courses, and Webinars. Off-the-shelf or Customized

Dose-Response Assessment Boot Camp continues to be our most popular course. Our original 5-day course which is an intensive hands-on training in hazard characterization and dose-response assessment.

Boot Camp Basics begins with an introduction to toxicology for risk assessors. It addresses the fundamental approaches used in hazard characterization and dose-response assessment, as well as introducing complex concepts and modeling.

Boot Camp Advanced Framework and Modeling provides applications of advanced concepts and models, including mode of a provides applications of advanced concepts and models, including mode of action evaluation techniques, use of dosimetry and PBPK models, benchmark dose modeling, structure activity evaluation tools and methods, systems biology and other tools essential to the advanced risk assessment practice.

Practitioner's Guide to Development & Reproductive Toxicology (DART) A 4 hour webinar intended for health scientists and product stewardship professionals, addressing key issues for understanding and interpreting reproductive and developmental toxicity assays, as well as how such data are interpreted in a risk assessment context.

Non-Cancer and Cancer Risk Assessment A 6 hour course providing key concepts of non-cancer and cancer risk assessment followed by a detailed discussion of the methods for hazard characterization and dose-response.

Dosimetric Adjustments in Dose-Response Assessment A 4 hour course designed to provide basic training in dosimetric adjustments for oral and inhalation exposures in dose-response assessment.

Use of Chemical Specific Adjustment Factors A 6 hour course teaching participants methods for refining interspecies and intraspecies uncertainty factors based on toxicokinetic or toxicodynamic data, using chemical-specific adjustment factors (CSAFs)/ data-derived extrapolation factors (DDEFs).

Benchmark Dose Modeling An 8 hour course designed to give an overview of benchmark modeling software for cancer and non-cancer dose-response assessment. This course also provides hands-on experience in using the EPA BMDS software.

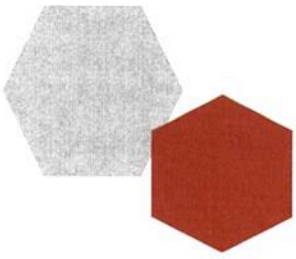
Children's Risk Issues A 1.5 day course discussing the major issues relating to risk assessment for children, such as toxicokinetic differences between adults and children, consideration of windows of susceptibility, and adequacy of the database uncertainty factor.

Mixtures A 2 day course helping scientists to understand and apply methods for risk assessment for multiple exposures or multiple routes ("mixtures risk assessment" or "combined exposures" or "cumulative and aggregate exposure"). Topics include additivity approaches, consideration of interactions, and strategies for addressing complex exposures scenarios.

Occupational Exposures Limit (OEL) Course A 4 day course similar to the Dose-Response Assessment Boot Camp, but focuses on the development of occupational exposure limits (OELs). The training covers the development of OELs, appropriate safety factors, exposure assessment, and hands-on activities to engage all participants.

Globally Harmonized System (GHS) Training A training tailored to corporate needs and circumstances. TERA provides firms with written certification as proof of meeting OSHA requirements. We are familiar with GHS as it relates to the Environmental, Health and Safety (EHS) needs and interests of private corporations and public agencies alike.

Emergency Management and Response Training A 3 day course touching on key toxicology and risk assessment concepts, with an in-depth focus on tools for preventing and responding to chemical emergencies including CAMEO, ALOHA, and MARPLOT. This course is offered onsite to members of your ERM team. CEU credits are available from the University of Cincinnati.





Risk Assessment Lecture Series



TERA is sponsoring a new monthly Risk Assessment Lecture Series within the Department of Environmental Health, University of Cincinnati. The lecture series will be on a range of "risk assessment" topics from a variety of risk assessment experts from various organizations and fields of study.

Dr. Charles Menzie, Global Executive Director for the Society of Environmental Toxicology and Chemistry (SETAC) and a principal with Exponent Inc., a science and engineering consulting company, was the inaugural speaker Friday, November 20th. He presented on *"Using Causal Analysis for Evaluating Environmental and Health Issues."* Since then, topics covered have ranged from issues on hazard & dose response assessment, TOXCAST/TOX21, epidemiology-based risk assessment, and asthma. Speakers have volunteered from various organizations and agencies, such as National Institute of Occupational Safety and Health (NIOSH), U.S. Environmental Protection Agency (EPA), University of Cincinnati, and many others.

The Seminar series is held every third Friday of the month. Anyone outside of the Cincinnati area can participate via webinar. Details on the seminars and how to register can be found on the website at http://eh.uc.edu/tera/seminars/

Posters & Presentations

Sunday, 12:00 PM - 1:00 PM, Marriott Marquis Miramar Room: Alliance for Risk Assessment - "Beyond Science and Decisions"	
"Beyond Science and Decisions" Update and new developments	**L. Haber and M. Dourson**, Toxicology Excellence for Risk Assessment, Cincinnati, OH
Monday, 9:30 AM to 12:30 PM, CC Exhibit Hall: Poster Session: Risk Assessment I (J. Patterson, Chair)	
MCHM Spill in the Elk River – Toxicology and Risk Assessment. (#219)	**J. Patterson**[1], **M. L. Dourson**[1], J. Rosen[1], and A. Whelton[2] [1]Toxicology Excellence for Risk Assessment, Cincinnati, OH [2]Corona Environmental Consulting, Boston, MA and [3]Purdue University, West Lafayette, IN
Mode of Action and Meta Regression Analysis of the Effect of Trans Fatty Acids (TFAs) on LDL-Cholesterol (#224)	**L. T. Haber**[1], **J. F. Reichard**[1], **M. J. Vincent**[1], B. C. Allen[2], Liska, D.J.[3] and **M. L. Dourson**[1] [1]Toxicology Excellence for Risk Assessment, Cincinnati, OH and [2]BCA Associates, Chapel Hill, NC, [3]Biofortis
Monday, 12:15 PM -1:30 PM, Marriott Marquis, Del Mar Room: Turning Big Data to Knowledge (BD2K) Session	
Data Science and 21st Century Toxicology (12:15 PM)	**J. Reichard**, Toxicology Excellence for Risk Assessment, Cincinnati, OH
Monday, 1:00 PM to 4:30 PM, CC Exhibit Hall: Poster Session: Genetic Toxicology I	
Evaluation of cII Mutations in Lungs of Male Big Blue Mice Exposed to Vanadium Pentoxide by Inhalation for Up to 8 Weeks (#521)	M. G. Manjanatha[1], S. D. Shelton[1], **L. T. Haber**[2], B. Gollapudi[3], and M. M. Moore[4] [1]Genetic and Molecular Toxicology, FDA/NCTR, Jefferson, AR, [2]Toxicology Excellence for Risk Assessment, Cincinnati, OH, [3]Center for Toxicology and Mechanistic Biology, Exponent Inc., Midland, MI, and [4]ENVIRON International Corporation, Little Rock, AR
Quantification of Kras Codon 12 Mutations in Lung DNA of B6C3F1 Mice following Inhalation of Aerosolized Particulate Vanadium Pentoxide (#522)	M. Banda[1], K. L. McKim[1], **L. T. Haber**[2], J. A. MacGregor[1], B. Gollapudi[3], and B. L. Parsons[1] [1]Division of Genetic and Molecular Toxicology, National Center for Toxicological Research, US FDA, Jefferson, AR [2]Toxicology Excellence for Risk Assessment, Cincinnati, OH, [3]Toxicology Consulting Services, Arnold, MD, and [4]Exponent, Chicago, IL
Monday, 3:15-4:15, Room 24A: Chemical Risk Assessment Best Practices Session	
Risk assessment databases: dissemination & communication of findings & risk values	**M. Dourson, P. Nance, O. Kroner**, Toxicology Excellence for Risk Assessment, Cincinnati, OH
Tuesday, 9:00 AM to 11:45 AM, CC Ballroom 6E: Workshop Session: Understanding and Communicating Uncertainty in Hazard Assessment and Dose Response	
Unpacking Toxicity Assessments to Understand and Improve Confidence (#873, 9:34AM)	R. L. Grant[1], S. L. Santos[1], **M. L. Dourson**[2], S. Shirley[3], N. R. Emaguntla[4], R. J. Lewis[5], and N. B. Beck[1] [1]Regulatory and Technical Affairs, American Chemistry Council, Washington, DC, [2]Texas Commission on Environmental Quality, Austin, TX, [3]FOCUS GROUP Risk Communication and Environmental Management Consultants, Medford, MA, [4]Toxicology Excellence for Risk Assessment (TERA), Cincinnati, OH and [5]ExxonMobil Biomedical Sciences, Inc, Annandale, NJ
Presenting Uncertainty in the Context of Biological Monitoring and Exposure Information (#874, 10:03AM)	W. H. Farland[1], N. B. Beck[2], J. S. LaKind[3], **P. Nance**[4], and T. Simon[5] [1]Environmental and Radiological Health Sciences, Colorado State University, Fort Collins, CO [2]Regulatory and Technical Affairs, American Chemistry Council, Washington, DC, [3]LaKind Associates, Catonsville, MD, [4]Toxicology Excellence for Risk Assessment, Cincinnati, OH, and [5]Ted Simon, LLC, Winston, GA
Tuesday, 4:30 PM – 6:30 PM, Hard Rock Hotel, Satisfaction Room, OTR Planning Meeting	
Occupational Toxicology Roundtable (OTR) Planning Meeting	**R. Sandhu**[1], **P. Nance**[1], A. Adler[2], R. Sussman[3] [1]Toxicology Excellence for Risk Assessment, Cincinnati, OH, [2]Safebridge Consultants, Inc., New York/California
Wednesday, 1:00 PM to 4:30 PM, CC Exhibit Hall: Poster Session: Bioinformatics	
Big Data to Knowledge (BD2K) – A Graphical Approach for Data Coordination and Integration (#2199)	**J. F. Reichard**[1], M. Medvedovic[2], and S. Sivaganesan[2] [1]Toxicology Excellence for Risk Assessment (TERA), Cincinnati, OH and [2]Department of Environmental Health, University of Cincinnati, Cincinnati, OH
Thursday 8:30 AM –12:00 PM, Sails Pavilion: Late-Breaking Poster Session 4: Developmental Basis of Adult Disease and Developmental Toxicology	
Developmental Toxicity of Ethanol as a Topical Antiseptic in an Occupational Setting: A Review (#2675)	R. York[1], **B. Gadagbui**[2], A. Maier[3], A. Quiñones Rivera[4] [1]RG York and Associates, Manlius, NY, [2]Toxicology Excellence For Risk Assessment, Cincinnati, OH, University Cincinnati College of Medicine, Cincinnati, OH, [3]GOJO Industries, Inc., Akron, OH

Presented at the 2015 SOT Annual Meeting

Presented at the 2015 SRA Annual Meeting

Session	Day	Paper#	Room	Author(s)	Title
WK4S/11S	**Sunday 8:30-5:30PM**	**Workshop**		**Haber; Musso**	**Fundamentals of the Risk Assessment Paradigm, From Hazard Characterization to Risk Communication, with an Emphasis on Contaminated Sites**
M3-A	Monday	M3-A	A	Haber, Chair	D3: Doing Dose- Response Differently
	Monday	M3-A.1	A	Haber; Reichard; Vincent; Allen; Liska; Dourson	Mode of action and meta-regression analysis of the effect of trans fatty acids (TFAs) on LDL-cholesterol
P	**Monday**	**P.27**		**Lange; Tao; Rhomberg; Goodman; Dourson; Honeycutt**	**Dose response curves derived from clinical ozone exposures can inform public policy**
P	Monday	P.118		Willis; Ovesen; Reichard; Sandhu; Maier	Using pharmacokinetic data to replace default adjustment factors in assessing risk from non-clinical exposures to pharmaceuticals
P	**Monday**	**P.189**		**Kroner; Haber; Dourson**	**The Dose-Response Framework: An online compendium of risk methods organized by problem formulation**
P	Monday	P. 207		Nance, Dourson	Alliance for Risk Assessment Project: 1,4-Dioxane Reanalysis in Support of a Regenerative Hyperplasia Mode of Action (MOA)
T3-A	**Tuesday**	**T3-A.3**	**A**	**Willis; Ovesen; Reichard; Sandhu; Maier**	**How does setting an Acceptable Daily Exposure (ADE) for pharmaceutical risk assessment differ from the U.S. EPA Reference Dose (RfD) approach?**
W1-A	Wednesday	W1-A.2	A	Deveau; Maier; Meek; Krewski	Incorporation of chemical-specific data in dose–response assessments for occupational and environmental exposure limits
W4-D	**Wednesday**	**W4-D.3**	**DE**	**Patterson; Kroner; Lee; Willis**	**A Tiered Approach to Investigate Metal Contamination in Unfinished Natural Materials Used in Children's Products**
WK15T	Thursday 8:30AM-12:00PM	Workshop		Haber	Developments in Risk Assessment: State of the Science for Evaluating Toxicity Data for Human Health Risk Assessment

Special Issue Articles

- State-of-the-Science: The Evolution of Occupational Exposure Limit Derivation and Application
- Historical Context and Recent Advances in Exposure-Response Estimation for Deriving Occupational Exposure Limits
- Advances in Inhalation Dosimetry Models and Methods for Occupational Risk Assessment and Exposure Limit Derivation
- Systems Biology and Biomarkers of Early Effects for Occupational Exposure Limit Setting
- The Scientific Basis of Uncertainty Factors Used in Setting Occupational Exposure Limits
- Considerations for using Genetic and Epigenetic Information in Occupational Health Risk Assessment and Standard Setting
- Setting Occupational Exposure Limits for Chemical Allergens—Understanding the Challenges
- Exposure Estimation and Interpretation of Occupational Risk: Enhanced Information for the Occupational Risk Manager
- Aggregate Exposure and Cumulative Risk Assessment—Integrating Occupational and Non-occupational Risk Factors
- The Global Landscape of Occupational Exposure Limits—Implementation of Harmonization Principles to Guide Limit Selection

Publications

Allen, B.C., **M.K. Vincent**, D. Liska, and **L.T. Haber**. Meta-regression analysis of the effect of *trans* fatty acids on LDL-C. Accepted with minor revisions.

Banda, M., K.L. McKim, **L.T. Haber**, J.A. MacGregor, B.B. Gollapudi, and B.L. Parsons 2015. Quantification of *Kras* mutant fraction in the lung DNA of mice exposed to aerosolized particulate vanadium pentoxide by inhalation. Mutat Res Genet Toxicol Environ Mutagen. 789-790:53-60

Beck, N., R. Becker, N. Erraguntla, W. Farland, R. Grant, G. Gray, C. Kirman; J. LaKind, J. Lewis, **P. Nance**; L. Pottenger, S. Santos, T. Simon, **M. Dourson**. 2016. Approaches for Communicating Overall Uncertainty in Toxicity Characterizations: U.S. Environmental Protection Agency's Integrated Risk Information System (IRIS) as a Case Study. Environment International, 89-90:110-128.

Cope RB, Kacew S, **Dourson M.** 2015. A reproductive, developmental and neurobehavioral study following oral exposure of tetrabromobisphenol A on Sprague-Dawley rats. Toxicology. 2015 Mar 2;329:49-59.

Dotson GS, Hudson NL, **Maier A**. 2015. A decision support framework for characterizing and managing dermal exposures to chemicals during Emergency Management and Operations. J Emerg Manag. 13(4):359-80.

Dourson ML, Chinkin L , MacIntosh D, Finn JA, Brown KW, Reid SB, **Martinez JM**. 2016. A Case Study of Potential Human Health Impacts from Petroleum Coke Transfer Facilities. Journal of the Air & Waste Management Association. (*Submitted*)

Greenberg M, Goldstein BD, Anderson E, **Dourson M**, Landis W, North DW. 2015. Whither Risk Assessment: New Challenges and Opportunities a Third of a Century After the Red Book. Risk Anal. 35 (11):1959-1968.

Haber, L.T., R. Sandhu, A. Li-Muller, A. Mohapatra, S. Petrovic, and M.E. Meek. 2015. Framework for Human Health Risk Assessment of Noncancer Effects Resulting from Short-Duration and Intermittent Exposures to Chemicals. Accepted with minor revisions.

Maier, A; Ovesen, J; Allen, C; York, R; Gadagbui, B; Kirman, C; Poet, T; and Quiñones-Rivera, A. 2015. Safety Assessment for Ethanol-Based Topical Antiseptic Use by Health Care Workers: Evaluation of Developmental Toxicity Potential. Regul Toxicol Pharmacol. 73(1):248-64.

Maier A, Vincent MJ, Parker A, Gadagbui BK, Jayjock M. 2015. A tiered asthma hazard characterization and exposure assessment approach for evaluation of consumer product ingredients. Regul Toxicol Pharmacol. doi: 10.1016/j.yrtph.2015.09.028. [Epub ahead of print]

Manjanatha, M.G., S. D. Shelton, **L. Haber**, B. Gollapudi, J.A. MacGregor, and M.M. Moore. 2015. Evaluation of *cII* mutations in lung of male Big Blue mice exposed by inhalation to vanadium pentoxide for up to 8 weeks. Mutat Res Genet Toxicol Environ Mutagen. 789-790:46-52.

Manjanatha, M.G., S. D. Shelton, Y. Chen, B.L. Parsons, M.B. Myers, B.B. Gollapudi, N.P. Moore, **L.T. Haber**, B.C. Allen, and M.M. Moore. Ethylene oxide is a weak mutagen at the *cII* locus as evaluated in the lung of male Big Blue mice exposed for up to 12 weeks by inhalation. Accepted with revisions.

McAvoy, D., **Pittinger, C. Willis, A.** 2015. Biotransformation of Tetrabromobisphenol A (TBBPA) in Freshwater Sediments, Agricultural Soils, and Anaerobic Digester Sludge. *Ecotoxicol Environ Safety.* [Epub ahead of print]

Pittinger, C.A., **Pecquet (Willis), A.M.** 2016. Aquatic Toxicity and Bioconcentration of Tetrabromobisphenol A in Aqueous and Spiked Sediment Exposures to Fish, Algae, and Invertebrates. *[Submitted]*

Rothenbacher, K., **Pecquet (Willis) A.M.** 2016. Effects of the brominated flame retardant tetrabromobisphenol-A (TBBPA) on soil microorganisms, earthworms, and seedling emergence. *[Submitted].*

Reichard, J. and L.T. Haber. 2016. Mode of action evaluation for the effect of *trans* fatty acids on LDL-C. Accepted with minor revisions.

Sweeney, L.M., L. MacCalman, **L.T. Haber**, E.D. Kuempel, C.L. Tran. 2015. Bayesian Evaluation of a Physiologically-Based Pharmacokinetic (PBPK) Model of Long-Term Kinetics of Metal Nanoparticles in Rats. Reg. Toxicol. Pharmacol. 73:151-163

Waters M, McKernan L, **Maier A**, Jayjock M, Schaeffer V, Brosseau L. 2015. Exposure Estimation and Interpretation of Occupational Risk: Enhanced Information for the Occupational Risk Manager. J Occup Environ Hyg. 12 Suppl 1:S99-S111.

Weideman P., Bercu J.P., Callis C., Dolan D.G., Faria E., Flueckiger A., Gould J., Hayes E.P., Jolly R., Lovsin Barle E., Luo W., Molnar L.R., Morinello E., Naumann B.D., Olson M., Pfister T., **Sandhu R.**, Sargent E.V., Seaman C., Sehner C., Shipp B.K., Stanard B., Streeter A.J., Sussman R., Walsh A., **Willis A.M., Maier A,** 2015. Deriving Health-Based Exposure Limits in the Pharmaceutical Industry. Contract Pharma, September, 74-80.

Book Chapters

Nance, P., O. Kroner, L. Haber and M. Dourson. 2015. Assessing Risks to Human Health. In Reference Module in Biomedical Sciences (Online). In-Press.

Nance, P., O. Kroner, L. Haber and M. Dourson. 2015. Assessing Risks to Human Health. In Reference *Comprehensive Toxicology, Third Edition, In-Press*

Special Issue in Journal of Occupational and Environmental Hygiene: State of the Science of Occupational Exposure Limit Methods and Guidance, available at http://www.tandfonline.com/toc/uoeh20/12/sup1

DeBord, D.G., L. Burgoon, S.W. Edwards, **L.T. Haber**, M.H, Kanitz, E.D. Kuempel, R.S. Thomas, B. Yucesoy. 2015. Systems Biology and Biomarkers of Early Effects for Occupational Exposure Limit Setting. J Occup Environ Hyg. 12 Suppl 1:S41-54.

Dankovic DA, Naumann BD, **Maier A, Dourson ML,** Levy LS. 2015. The Scientific Basis of Uncertainty Factors Used in Setting Occupational Exposure Limits. J Occup Environ Hyg. 2015 Nov 25;12 Suppl 1:55-68

Deveau M, Chen CP, Johanson G, Krewski D, **Maier A**, Niven KJ, Ripple S, Schulte PA, Silk J, Urbanus JH, Zalk DM, Niemeier RW. 2015. The Global Landscape of Occupational Exposure Limits-Implementation of Harmonization Principles to Guide Limit Selection. J Occup Environ Hyg. 2015;12 Suppl 1:S127-44.

Dotson GS, **Maier A**, Siegel PD, Anderson SE, Green BJ, Stefaniak AB, Codispoti CD, Kimber I. 2015. Setting Occupational Exposure Limits for Chemical Allergens-Understanding the Challenges. J Occup Environ Hyg. 12 Suppl 1:S82-98.

Lentz, T; Dotson, S; Williams, P; **Maier, A; Gadagbui, B**; Pandalai, S P; Lamba, A; Hearl, F; Mumtaz, M. 2015. Aggregate Exposure and Cumulative Risk Assessment – Integrating Occupational and Non-occupational Risk Factors. J Occup. Environ. Hyg. 12 Suppl 1:S112-26

Maier A, Lentz TJ, MacMahon KL, McKernan LT, Whittaker C, Schulte PA. 2015. State-of-the-Science: The Evolution of Occupational Exposure Limit Derivation and Application. J Occup Environ Hyg. 2015;12 Suppl 1:S4-6

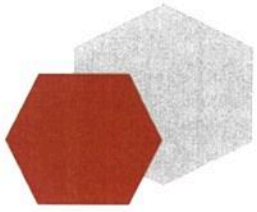
Sargent EV, Flueckiger A, Lovsin Barle E, Luo W, Molnar L, **Sandhu R,** Weideman P. 2016. The Regulatory Framework for Preventing Cross-Contamination of Pharmaceutical Products: History and Considerations for the Future. *In preparation for Regulatory Toxicology and Pharmacology.*

Olson M, Faria E, Hayes EP, Jolley R, Lovsin Barle E, Molnar L, Naumann BD, **Pecquet AM,** Shipp B, Sussman R, Weideman P. 2016. A Harmonization Effort for Acceptable Exposure Methodology Applied to Pharmaceutical Cleaning Validation -- Communication with External Stakeholders. *In preparation for Regulatory Toxicology and Pharmacology.*

Hayes EP, Faria E, Jolly R, Lovsin Barle E, Molnar L, Naumann B, Olson M, **Pecquet AM,** Shipp B, Sussman R, Weideman P. 2016. A Harmonization Effort for Acceptable Exposure Methodology Applied to Pharmaceutical Cleaning Validation -- Operational Aspects. *In preparation for Regulatory Toxicology and Pharmacology.*

Faria EC, Bercu J, Dolan DG, Morinello E, **Pecquet AM,** Seaman C, Sehner C, Weideman, P. 2016. Using Default Methodologies to Derive an Acceptable Daily Exposure (ADE). *In preparation for Regulatory Toxicology and Pharmacology.*

Reichard JF, Maier MA, Naumann BD, **Pecquet AM,** Pfister T, **Sandhu R,** Sargent EV, Streeter AJ, Weideman P. 2016. Pharmacokinetic and Pharmacodynamic Considerations when Deriving Health-Based Exposure Limits for Pharmaceuticals. *In preparation for Regulatory Toxicology and Pharmacology.*



2015 TERA Project Time by Sponsor

6% Collaborators

Coalition of Project Sponsors

- Alliance for Risk Assessment
- Beyond Science and Decisions: From Problem Formation to Dose Response
- Kids Chemical Safety Webpage
- OARS: WEEL

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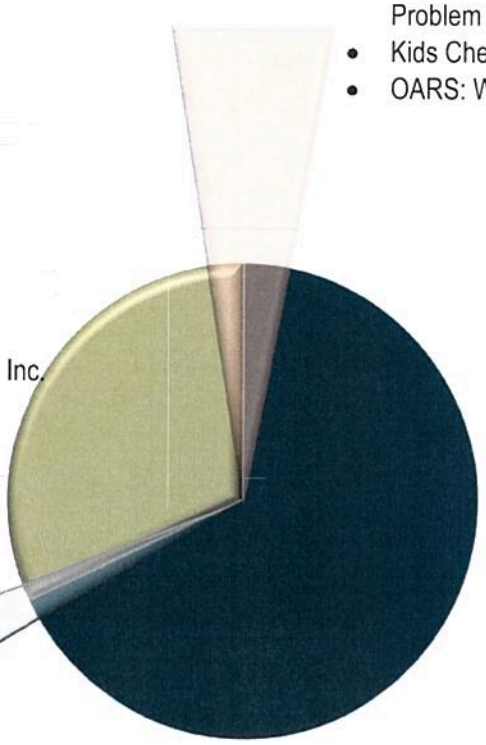

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2017

EMPLOYMENT

2017-	Professor. Risk Science Center (aka TERA Center). Department of Environmental Health, University of Cincinnati, College of Medicine, Cincinnati, Ohio
2015-16	Professor and Director. Toxicology Excellence for Risk Assessment Center, Department of Environmental Health, University of Cincinnati, College of Medicine, Cincinnati, Ohio
1995-15	Director/President. Toxicology Excellence for Risk Assessment, Cincinnati, Ohio
1991-94	Chief. Systemic Toxicants Assessment Branch, Environmental Criteria & Assessment Office (ECAO), U.S. Environmental Protection Agency (EPA), Cincinnati, Ohio
1990-91	Associate Director. ECAO, Cincinnati, Ohio
1989-90	Chief. Pesticides and Toxics Team, EPA, Washington, D.C.
1986-89	Chief. Methods Evaluation and Development Staff, ECAO, Cincinnati, Ohio
1985	Leader. Acceptable Daily Intake (ADI) Group, ECAO, Cincinnati, Ohio
1980-84	Staff Toxicologist. ECAO, Cincinnati, Ohio

EDUCATION

1988-89	Executive Potential Program. U.S. Office of Personnel Management
1986-87	Zenger Miller Supervision Course
1985-2015	Diplomate of the American Board of Toxicology
1975-80	University of Cincinnati, College of Medicine, Ph.D. degree in toxicology
1970-74	Wittenberg University, B.A. degree in biology

TEACHING

I have lectured in courses at the graduate level in several universities and institutes; have lectured high school students on the general principles of toxicology over several years; and have talked with grade school students on several occasions about careers in science and my experiences in Africa. I participated as a member of the Ph.D. thesis committee of Dr. Natalia Foronda of the Ministry of Health, New Zealand.

RESEARCH: INVITED PRESENTATIONS (Selected)

"Current status of Benchmark Dose Modeling for 3-Monochloropropane-1,2-diol (3-MCPD)"
German Fat Scientists Association and the German Federation for Food Law and Food Science. Berlin, Germany, June 20, 2017.

"Health risk assessment for perchlorate: New direction in EPA's modeling approach for establishing standards"
American Water Works Association. Annual Conference. Philadelphia, PA. June 14, 2017.

"Hazard identification"
"Dose response assessment"
"Exposure assessment"
"Risk characterization"
Ateneo School of Medicine and Public Health. Makati City, Philippines. June 1-2, 2017.

"Risk Assessor Certification"
Taiwan Chapter of the Society for Risk Analysis. Taichung City, Taiwan. May 24, 2017.

"Overview of risk assessment"
"Hazard identification II: Cancer"
"Dose response assessment II: Cancer"
"Introduction to dose response assessment modeling"
"Use of PBPK modeling in risk assessment"
"Risk characterization"
The Regional Training Program on Risk Assessment, Bibliotheca Alexandrina, Alexandria, Egypt, April 24-27, 2017.

"Managing the non-cancer risks a hazardous waste sites: Trichloroethylene (TCE) as a case study"
Association for Environmental Health and Sciences (AEHS) Foundation. San Diego, California March 21, 2017.

"The concept of hormesis and application in risk assessment"
Society of Toxicology, Baltimore, Maryland, March 14, 2017.

"The concept of hormesis and application in risk assessment"
Society for Risk Analysis. San Diego, California, December 12, 2016

"Mechanics of Risk Assessment"
In workshop on Risk Analysis. **Institute for Humane Studies and the Mercatus Center at George Mason University**. Portland, Oregon, June 18th, 2016.

"Yes, 'Thresholdable' Carcinogens Are Still Delaney Carcinogens"

Roundtable Session: Is a "Thresholdable" Carcinogen Still a Delaney Carcinogen?
Society of Toxicology, New Orleans, Louisiana, March 14, 2016.

"Distinguishing between Mode and Mechanism of Action, and Some Key Events for MOA"
Colloquium: Role of Mode of Action in Dose-Response Assessment for Carcinogens.
Food and Drug Administration and the Society of Toxicology, College Park, Maryland, February 25, 2016.

"Harmonizing OELs: Commonalities and Differences"
Keynote talk at the annual meeting of the **Occupational Toxicology Roundtable**. New Brunswick, New Jersey, October 4, 2015

"Risk assessment and hazard identification for metals"
"Human health case study: mercury exposure and essential metals"
"Human health criteria and standards"
Asian Pacific Economic Conference Workshop on Metals Risk Assessment, Cebu, Philippines on 28-29th August 2015.

"Hepatotoxicity"
"Cardiac Toxicity"
"Hazard Identification/Dose Response"
"Exposure Assessment/Characterization"
International Workshop On Comprehensive Toxicology, Bengaluru, India, July 27-31, 2015.

"Defining the range of the reference dose: imprecision versus uncertainty"
The TCE Revolution and its Permanent Impact on Environmental Due Diligence, EDR Insight, National Teleconference/Webinar. June 24, 2015.

"Assessment and management of Elk River, West Virginia drinking water contamination incident, 2014"
British Toxicology Society Annual Congress, Birmingham, UK, April 20, 2015.

"Hazard & Dose Response Assessment: Roadmaps & Methods for Using 21st Century Data"
Ohio State University, Columbus, Ohio, February 23, 2015.

"Practical Guidance on the Development of a Non-cancer Hazard Range for Effective Risk Assessment and Risk Management of Contaminated Sites: A Case Study with Trichloroethylene and Other Chemicals"
Tri-Service Environmental Risk Assessment Work Group, Naval Medical Center, Portsmouth, VA. Jan. 21, 2015.

"Advances in Assessing Food Additive Safety"
SPI Food, Drug and Cosmetic Packaging Materials Committee. Food Packaging Summit. New Orleans, LA. Nov. 10-12, 2014.

"Mode of Action and Dose-Response Evaluation of the Effect of Partially Hydrogenated Oils on LDL-Cholesterol"
SOT-FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety. Colloquium One. College Park, MD, Live Webcast. Nov. 7, 2014.

"Risk Assessment Roadmaps & Methods for Using 21st Century Data"
International Institute of Synthetic Rubber Producers, Inc. Houston, Texas. Nov. 6, 2014.

"Advances in Assessing Ingredient Safety"
Workshop on GRAS Determinations. International Society of Regulatory Toxicology and Pharmacology. Washington, DC. Oct. 14, 2014.

"Case study #3: Partially Hydrogenated Oils (PHOs)"
The Role and Use of Nutritional Studies I Evaluating the Safety of a Food or Ingredient. ILSI North American Special Workshop. Washington, DC. July 22, 2014.

"Dose Response Assessment Boot Camp---Lecture series"
Toxicology Excellence for Risk Assessment (TERA) at Gadjah Mada University, Yogyakarta, Indonesia. June 13-21, 2014.

"Opportunities and Challenges Posed By the Use of 'omics' data in Risk Assessment of Mixtures"
Toxicology Risk Assessment Conference (TRAC). Cincinnati, Ohio. April 8, 2014.

"Alliance for Risk Assessment (*ARA*), EDSP, TCE, Science and Decisions"
Monsanto. St. Louis, MO. April 10, 2013.

"Risk Assessment Roadmaps & Methods for Using 21st Century Data"
Weight of Evidence Workshop. **International Life Sciences Institute (ILSI)** North America Technical Committee on Food & Chemical Safety. Miami, Florida. January 23-24, 2013.

"Advancing human health risk assessment: Charting a Course through committee recommendations"
Society for Risk Analysis Annual Meeting. San Francisco, CA. Dec. 9-12, 2012.

"How Individual Variability is Currently Factored into Risk Assessment/Regulation/Decision Making"
Emerging Science for Environmental Health Decisions. **The National Academies of Science**, Board on Life Sciences, Board on Environmental Studies and Toxicology. Washington, D.C. April 18-19, 2012.

"A Hitchhikers Guide to the Galaxy of Practical Risk Assessment"
Resource sharing, partnering, and cooperative science policy resolution. US EPA and Region V States **Vapor Intrusion Video Conference Roundtable.** Columbus, OH. April 12, 2012.

"Problem formulation to dose response: Advance via the *ARA* Beyond Science and Decisions workshops"
New England Chapter of the Society for Risk Analysis. Boston, MA. January 24, 2012.

"Risk Analysis on the Coast"
Society for Risk Analysis Annual Meeting. Charleston, SC. Dec. 4-7, 2011.

"Current Environmental Risk Assessment: Getting ready for Century 21"
Association of Government Toxicologists. Washington, D.C. March 29, 2011.

"Risk Assessment"
Global Chemistry. Baltimore, MD. March 22, 2011.

"Peer Review and Consultation Program"
American Chemistry Council. Washington, D.C. Feb. 16, 2011.

"Fishbowl"
Risk 21: Realizing the Future of Risk Assessment Workshop. **International Life Sciences Institute**. Washington, DC. Jan. 11, 2011.

"Draft Toxicological Review of Hexavalent Chromium"
Environmental Protection Agency's IRIS listening session. Washington, D.C. November 18, 2010.

"Perspectives of Air Pollutants: Health Effects Research Update Session: Risk Assessment…*in the 21st Century*." **Clean Air Forum.** Houston, TX. Nov. 4, 2010.

"A Risk Assessment and Regulatory Agency Perspective on Mixtures Affecting Susceptible Populations"
Society of Toxicology Annual Meeting. Salt Lake City, Utah. March 6-12, 2010.

"Risk Analysis: The Evolution of a Science"
Society for Risk Analysis Annual Meeting. Baltimore, MD. Dec. 5-10, 2009.

"Environmental Risk in the 21st Century"
International Society of Regulatory Toxicology and Pharmacology. Washington, D.C. Dec. 9, 2009.

"Emerging issues and regulatory challenges and the science of risk assessment"
Keynote talk at the **Midwestern States Environmental Consultants Association** biannual meeting. Indianapolis, Indiana. November 3, 2009.

"Making a Successful Transition from Government to Non-Profit Sectors"
Society of Toxicology. Baltimore, MD. March 15-20, 2009.

"Exposure, and Risk Data: Ensuring the Best Science"
Society of Toxicology. Baltimore, MD. March 15-20, 2009.

"Scientific Peer Review: An Overview with Reference to the International Toxicity Estimates for Risk *(ITER)* Database"
Society of Toxicology. . Baltimore, MD. March 15-20, 2009.

"A Risk Assessment and Regulatory Agency Perspective on Mixtures Affecting Susceptible Populations"
Society of Toxicology. Baltimore, MD. March 15-20, 2009.

"Toxicology Excellence for Risk Assessment"
Environmental Council Of States and Department of Defense Sustainability Workgroup. Washington, D.C. June 20-21, 2007.

"Predicting risk above EPA's Reference Dose (RfD)"
Toxicology and risk assessment conference. **Multiple federal agency sponsors**. Cincinnati, Ohio. April 25, 2007.

"Using human data to protect public health"
Toxicology and risk assessment conference. **Multiple federal agency sponsors**. Cincinnati, Ohio. April 24, 2007.

"A Historical Perspective on Risk Assessment and Areas for Advancement"
Twenty-Eighth Annual Meeting of the **American College of Toxicology**. Nov. 11-14, 2007.

"Air toxics: Risk based analysis"
Symposium on air emission from large industrial sources. Endicott House, **Multiple sponsors**. August 16-17, 2006.

"What Should We Really Be Worried About?"
Seafood & Health '05: Issues, Questions and Answers. Session V. Assessing the Real Risks. **Department of Commerce**. Washington, D.C. December 2005.

"Future Use of Default Assumptions and Uncertainty Factors"
Michigan State University, Center for Integrative Toxicology. April 8, 2005.

"Mercury Regulation: Fishing For The Facts About Risk"
States and Nation Policy Summit. **American Legislative Exchange Council**. Washington D.C. December 3, 2004.

"Acceptable Daily Intakes (ADIs) and their Application in the Regulatory Process"
Meeting of the Technical Committee on Food Toxicology and Safety Assessment of the **International Life Sciences Institute**. North America. Washington, DC. Nov. 30, 2004.

"Human dose-response assessment of copper"
Science Symposium Update on Science Supporting the EU Voluntary Risk Assessment, **International Copper Association**. Rome. May 17, 2004.

"Integration of Toxicity and Molecular Mechanistic Data for Nonlinear Dose-Response Assessment. Application to Systems Biology and Risk Assessment"
2003 Annual Meeting, **Society for Risk Assessment**. Baltimore, Maryland. December 10, 2003.

"History of *TERA* Coordinated Public/Private Partnership on Perchlorate Research"
Perchlorate State-of-the-Science Symposium. **University of Nebraska, Center for Environmental Toxicology**. Omaha, Nebraska. September 29, 2003.

"Perchlorate Reference Dose (RfD)"
California Environmental Protection Agency. September 26, 2003.

"Small Non-Profits in a Big Risk World: Greasing the Wheels of Change"
Featured Meeting Speaker, The **Northern California Chapter of the Society for Risk Analysis**. September 25, 2003.

"Risk Assessment"
In: ATSDR and RIVM Expert Panel Meeting on Chemical Risk Assessment and Children's Health. **ATSDR** and **RIVM**, Brussels. June 26, 2003.

"Differential Sensitivity Of Children And Adults To Chemical Toxicity"
Midwestern States Risk Assessment Symposium. **Indiana Department of Environmental Management.** Indianapolis, IN. July 25, 2002.

"Modeling Of Population Variability"
Midwestern States Risk Assessment Symposium. **Indiana Department of Environmental Management.** Indianapolis, IN. July 25, 2002.

"Data Derived Replacement Of Default Uncertainty Factor"

Workshop on modeling of population variability. **Society of Toxicology.** Nashville, TN. March 19, 2002.

"Stone-Age Toxicity: From Factors of 10 to Compound-Specific Adjustments"
University of Cincinnati Medical Center, Dept. of Environmental Health Seminar. Nov. 2002.

"Does The Use Of Data-Derived Uncertainty Factors Allow Risk Assessors To Describe Uncertainty More Accurately?"
Fifth Annual Workshop on Evaluation of Default Uncertainty Factors in Health Risk Assessment, **New Jersey Medical School**. June 1, 2001.

"Risk Assessment"
HESI Agricultural Chemical Safety Assessment Subcommittee Steering Committee Meeting. **International Life Sciences Institute**. Washington, D.C, April 18, 2001.

"Risk Characterization Framework For Non-Lethal Weapons"
Symposium on comparative risk. **Society for Risk Analysis.** Seattle, WA. December 5, 2001.

"Noncancer Risk Assessment: A 20-Year Perspective"
Ohio Society for Risk Analysis. Noncancer Workshop. Cincinnati. June 13, 2000.

"Approaches to assessing dose response assessment relations"
Chulabhorn Research Institute. Training course on environmental and health risk assessment and risk management of toxic chemicals, Lak si, Bangkok, Thailand. November 21, 2000.

"Guidelines for Application of Data-Derived Uncertainty Factor in Risk Assessment"
Fourth Annual Workshop of Evaluation of Uncertainty Factors in Health Risk Assessment, **New Jersey Medical School.** May 3-4. 2000.

"Determining USEPA Reference Doses (RfDs) for Essential Minerals"
University of Ulster. Nutrition & Toxicology Excellence for Risk Assessment Workshop Series. Northern Ireland. June 18, 1999.

"The Challenges Of Using Common Mechanism Of Toxicity In Chemical Regulation"
Roundtable session. **Society of Toxicology**. New Orleans, LA. March 17, 1999.

"Extrapolating Data From Adults To Set ULs For Children"
Workshop on upper levels of nutrients. **National Academy of Sciences**. January 21, 1999.

Incidence and severity in relation to magnitude of intake: mixed effects, categorical regression"
International Life Sciences Institute. Workshop on the significance of excursions of intake above the ADI. Milan, Italy. April 23, 1998.

"Should there be an international accreditation of toxicologists? Accreditation in the USA"
International Congress of Toxicology. Paris, France. July 8, 1998.

"Quality Issues relating to scientific information"
US. EPA Data Quality and Gaps Workshop. **U.S. Environmental Protection Agency.** Washington, D.C. October 19, 1998.

"Noncancer Risk Assessment: Impact of Research on the Underlying Science"
International Society for the Study of Xenobiotics. Hilton Head, South Carolina. October 26-30, 1997.

"Alternatives to the NOAEL Approach (BMD, probabilistic approach)"

Federal Institute for Health Protection of Consumers and Veterinary Medicine. Workshop on Use of Uncertainty Factors in the Risk Assessment Process - New Directions. Berlin, Germany. May 5-7, 1997.

"Risk Assessment And The Role Of Risk Assessment Guidelines"
Workshop: EPA's neurotoxicity risk assessment guidelines. **Society of Toxicology**. Cincinnati, Ohio. March 11, 1997.

"Noncancer Risk Assessment: Impact Of Research On The Underlying Science"
Symposium V: Cancer and noncancer risk assessment. **International Society for the Study of Xenobiotics**. October 28, 1997.

"Overview: Classical Risk Assessment"
Risk Assessment in Establishing Upper Reference Levels of Nutrients Workshop. **Food & Nutrition Board, Inst. of Medicine,** Washington, DC. July 15-16, 1996.

"ADI, BMD, CEL...The Alphabet Soup of Methods for Dose Response Assessment"
In: Conference on Advances in Toxicology and Applications to Risk Assessment. **ATSDR, U.S. Army, Air Force, Navy and EPA**, Dayton, Ohio. April 25, 1996.

"Overview of EPA's Reference Dose Methodology"
In: Toxicology Peer Review Board Meeting of the **U.S. Army** Center for Health Promotion and Preventive Medicine. Aberdeen Proving Ground, Maryland. January 18,1996.

"Non-Cancer Risk Assessment: Three Practical Methods From A Decade Of Research"
In: New Techniques in Risk Assessment. **International Business Communication**. Orlando, Florida. February 15, 1996.

"Evolution of Science-based Uncertainty Factors in Noncancer Risk Assessment"
The 2nd Annual Workshop on the Evaluation of EPA 10X Safety Factors in Health Risk Assessment. **New Jersey Medical School**. Nutley, NJ. December 6, 1996.

"Noncancer Hazard Identification and Dose Response Assessment, Part 2"
In: Risk assessment. **University of Cincinnati, College of Medicine**. April 18, 1996.

"Dose Response Class Exercise: Aroclor"
In: Risk assessment. **University of Cincinnati, College of Medicine**. April 30, 1996.

"Introduction to Risk Assessment"
In: Risk assessment. **University of Cincinnati, College of Medicine**. March 26, 1996.

"Systemic Toxicants, Cross Route Extrapolation, Complex Mixtures"
In: Risk assessment. **University of Cincinnati, College of Medicine**. May 23, 1995.

"On Reference Dose and Its Underlying Toxicity Data Base"
Health Canada. Threshold of Regulation Workshop. Ottawa, Canada. March 28, 1995.

"Presentation of Ongoing Work on Characterization of Distributions of Data which Serve as the Basis for Uncertainty Factor" **Health Canada**. Planning Meeting on Uncertainty Factors. Ottawa, Canada. March 18, 1995.

"Advances in Research Used as an Adjunct to Toxicity Testing: EPA Perspective"
In: Regulatory Update: EPA Regulation and Test Requirements. **American College of Toxicology.** Annual Meeting. Vienna, Virginia. November 12, 1995.

"Alternatives To The RfD: What Are We Getting And How Much Effort Does It Cost?" Interagency Risk Assessment Committee. **State of New Jersey.** April 25, 1994.

"Panel Discussion"
In: Issues in reproductive and developmental risk assessment-boron toxicity as a test case. Annual Winter **Toxicology Forum**. February 22, 1994.

"Regulatory Considerations of the U.S. EPA"
In: Biological effects of low level exposures (BELLE) and potential implications for regulatory decision-making. **American College of Toxicology.** Annual Meeting. October 26, 1994.

"Noncancer Improvements Discussion Panel"
In: Health effects & risk assessment associated with noncarcinogenic, radioactive and mixed waste. **Air & Waste Management Association.** 87th Annual Meeting. June 23, 1994.

"Evaluating Subpopulations: Fish Consumption Advisory Methodology"
In: EPA Workshop on challenges in Risk Characterization. **U.S. Environmental Protection Agency,** Cincinnati. September 8, 1994.

"Inherent Imprecision of RfD"
In: EPA Regional Risk Assessors' Meeting. **U.S. Environmental Protection Agency**, Boston, MA. April 27th, 1994.

"New Methods: Benchmark Dose"
In: EPA Regional Risk Assessors' Meeting. **U.S. Environmental Protection Agency**, Boston, MA. April 26th, 1994.

"Components of Risk Assessment"
In: Risk assessment. **University of Cincinnati, College of Medicine**. March 29, 1994 (This same lecture was also given an additional two times at the Cincinnati State Technical and Community College on September 27th and November 15th).

"How Toxicity Data Are Used in the Process of Hazard Identification and Dose-Response Assessment"
In: Basic Risk Assessment: Current Developments. Continuing Education Course. **Society of Toxicology**. New Orleans, LA. March 14, 1993.

"Modifying Uncertainty Factors for Noncancer Endpoints"
In: Advanced Topics in Risk Assessment. Continuing Education Course. **Society of Toxicology**. New Orleans, LA. March 14, 1993.

"Noncancer Risk Assessment"
In: Course entitled "Introduction to Risk Assessment." **University of Kentucky.** Lexington, Kentucky. July 28, 1993.

"Noncancer Risk Assessment Science"
In: Risk Assessment and the Environment Series. Harvard Center for Risk Analysis. **Harvard School of Public Health.** Boston, MA. February 16, 1993.

"Statistical Research Planning of the Environmental Criteria and Assessment Office"
In: Workshop on Office of Research and Development Statistical Needs. **U.S. Environmental Protection Agency**, Research Triangle Park, North Carolina. May 12, 1993.

"EPA's Integrated Risk Information System"

International Programme on Chemical Safety, World Health Organization. Geneva, Switzerland. June 17, 1993.

"Noncancer Dose-response and Risk Characterization"
In: Course on Environmental Health Risk Assessment. **Nofer Institute of Occupational Health**, Lodz, Poland. March 31, 1993.

"Most Important Problems Encountered in Quantitative Risk Assessment at the National or International Level"
In: Meeting on Consultation on Guiding Principles and Methodology for Quantitative Risk Assessment in Setting Exposure Limits. **International Programme on Chemical Safety, World Health Organization**, Langen, Germany. January 19, 1993.

"Risk above the Reference Dose (RfD) Benchmark Dose (BMD)"
In: Conference on the Risk Assessment Paradigm after Ten Years. **U.S. Army, Air Force, Navy and EPA**, Dayton, Ohio. April 7, 1993.

"Benchmark Dose Approach to Risk Assessment"
In: **Federal-State Toxicology and Risk Analysis (FSTRAC)** Fall Meeting. Washington D.C. December 1-3, 1993.

"Overview of Alternatives to Benchmark Dose"
In: Workshop on Benchmark Dose Methodology. Public workshop sponsored by **U.S. Environmental Protection Agency, American Industrial Health Council, and International Life Sciences Institute**. Fairfax, Virginia. September 28-30, 1993.

"Development of RfDs and the IRIS Process"
In: Cincinnati Forum on Dose Response Issues of Risk Assessment for Trivalent and Hexavalent Chromium Salts. **Public workshop sponsored by U.S. Environmental Protection Agency**. Cincinnati, Ohio. August 19, 1993.

"The Use of Threshold Limit Values for Determining Community Standards: Current Issues"
In: Tutorial Session on Threshold Limit Values and Biological Exposure Indices. 11th International System Safety Conference. **Ohio Chapters of both the System Safety Society and the Society for Risk Analysis**. Cincinnati, Ohio. July 29, 1993.

"The IRIS Process"
In: Cincinnati Forum on Boron Containing Chemicals: Risk Factors and Characterizations. **Public workshop sponsored by U.S. Environmental Protection Agency**. Cincinnati, Ohio. February 11, 1993.

"Introduction to Risk Assessment"
In: Tutorial Session on Environmental and Occupational Risk Assessment and Risk Communication. 11th International System Safety Conference. **Ohio Chapter of the System Safety Society**. Cincinnati, Ohio. July 29, 1993.

"The U.S. EPA's Use of Uncertainty Factors"
In: Workshop on Safety Assessment for Non-Cancer Endpoints: The Benchmark Dose and Other Possible Approaches. **California EPA, U.S. EPA and U.S. Agency for Toxic Substances and Disease Registry**, Tiburon, California, May 12, 1992.

"Risk Assessment: Who needs it?"
All-Ohio Safety and Health Congress and Exhibit. Cincinnati, Ohio. April 1, 1992.

"Bridging the Chasm: Breakthroughs Needed in Noncancer Risk Assessment"

In: Kettering Seminar Series. **University of Cincinnati, College of Medicine.** Cincinnati, Ohio. January 22, 1992.

"Role of Risk Analysis and Risk Management in the U.S"
In: 3rd U.S.-Japan Governmental Conference on Drinking Water Quality Management. **Governments of the United States and of Japan**, Cincinnati, Ohio. September 22, 1992.

"The Reference Dose"
In: Conference on Trace Elements in Health and Disease. **International Society for Trace Element Research in Humans** and **Nordic Trace Element Society**, Stockholm, Sweden. May 27, 1992.

"Novel Approaches to the Estimation of Noncancer Health Risk"
International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland. January 16, 1992.

"The Reference Doses for Chromium"
In: Workshop on Risk Assessment of Essential Elements. Public workshop sponsored by **U.S. Environmental Protection Agency, Agency for Toxic Substances and Disease Registry, and International Life Sciences Institute**, Herdon, Virginia. March 12, 1992.

"The Reference Dose"
In: Workshop on Risk Assessment of Essential Elements. Public workshop sponsored by **U.S. Environmental Protection Agency, Agency for Toxic Substances and Disease Registry, and International Life Sciences Institute**. Herdon, Virginia. March 10, 1992.

"Novel Approaches to the Estimation of Noncancer Health Risk: Probabilistic RfDs, Benchmark Dose, and Severity Modeling"
In: Workshop on Risk Assessment for Noncarcinogens. **Health and Welfare Canada**, Tunney's Pasture, Ottawa. April 29, 1991.

"Novel Approaches to Noncancer Health Risk Assessment"
In: EPA Regional Risk Assessors' Meeting. **U.S. Environmental Protection Agency**, Denver, Colorado. June 25, 1991.

"Risk Communication-A Challenge for the 1990's and Beyond"
System Safety Society. Cincinnati, Ohio. August 5, 1991.

"Quantitative Risk Assessment: The Reference Dose (RfD) and Research to Improve this Model Including the Use of Average Uncertainty Factors"
In: Symposium on Neurotoxicity Risk Assessment: State of the Art. **Society of Toxicology.** Dallas, Texas. March 1, 1991.

"Novel Approaches for Quantitative Assessment of Risks for Noncancer Effects"
Boston Risk Assessment Group and **New England Chapter of the Society for Risk Analysis.** Boston, Massachusetts. February 12, 1991.

"Impact of Risk Related Concerns on the EPA Programs"
In: Advanced Research Workshop on Nitrate Contamination: Exposure, Consequences and Control. **North Atlantic Treaty Organization (NATO)**, Lincoln, Nebraska. September 14, 1990.

"How Are Environmental Criteria Developed?"

In: A course entitled "Environmental and Occupational Health Risk Assessment and Risk Management." Developed for **City of Cincinnati Council** and other local decision-makers. Cincinnati, Ohio. May 3, 1990.

"Non-carcinogenic Risk Assessment"
In: Risk Assessment Workshop. **Federal-State Toxicology and Regulatory Alliance Committee**. Washington D.C. April 19, 1990.

"Risk above the RfD and Benchmark Dose Procedures"
In: Workshop to Discuss Noncancer Risk Assessment Methods/Data Needs to Support the New Clean Air Act Amendments. **U.S. Environmental Protection Agency**, Research Triangle Park, North Carolina. July 23, 1990.

"Reference Dose (RfD)"
In: Workshop to Discuss Noncancer Risk Assessment Methods/Data Needs to Support the New Clean Air Act Amendments. **U.S. Environmental Protection Agency**, Research Triangle Park, North Carolina. July 23, 1990.

"Guidelines Used to Assess Toxicological Hazards: Quantification Issues"
In: Symposium on Access and Use of Information Resources in Assessing Health Risks from Chemical Exposure. **Oak Ridge National Lab** and **U.S. Environmental Protection Agency**, Knoxville, Tennessee. June 28, 1990.

"How Statutes and Executive Orders Affect the Use of Scientific Information"
In: Regulation Development in EPA Course. **U.S. Environmental Protection Agency**, Washington, D.C. June 20, 1990.

"Risk Assessment and Its Uses: Directions of New Research"
National Institute of Occupational Safety and Health (NIOSH), Cincinnati, Ohio. June 20, 1989.

"Health Risk Assessment: Chronic Reference Dose"
In: Washington Conference on Risk Assessment. **Center for Energy and Environmental Management.** Washington, D.C. September 26, 1989.

"EPA's Approach to Developing Acceptable Air Quality Criteria"
In: 4th Annual Conference**. HAZTECH International.** Cincinnati, Ohio. September 13, 1989.

"The Underlying Basis of Risk Management Decisions"
In: 4th Annual Conference**. HAZTECH International.** Cincinnati, Ohio. September 12, 1989.

"Derivation of Risk Values by EPA"
Hazardous Materials Management Conference and Exhibition/Central. Rosemont, Illinois. March 15, 1989.

"The Reference Dose"
American Industrial Hygiene Association, Annual Toxicology Symposium. Williamsburg, Virginia. August 16, 1988.

"Reference Dose: Description and Use in Health Risk Assessments"
In: 54th Annual Meeting. **American Mosquito Control Association.** Denver, Colorado. February 2, 1988.

"Use of Uncertainty Factors for Reference Dose"

In: Workshop on the Use of the EPA Tools in State Risk Assessment. **National Governors' Association**. Copper Mountain, Colorado. May 4-6, 1988.

"Development of Oral Reference Doses"
In: Workshop on EPA's Integrated Risk Information System: Access, Use, and Interpretation. **U.S. Environmental Protection Agency**, Lexington, Massachusetts. July 22, 1987.

"The Systemic Toxicity of Air Pollutants: New Directions in Health Risk Assessment"
In: Session 100: Balanced Approach to Risk Assessment. Annual Meeting. **Air Pollution Control Association.** New York, New York. June 22, 1987.

"Safety Factors in Non-Carcinogenic Risk"
In: Workshop on Reducing Uncertainty in Risk Assessment. **Michigan State University.** East Lansing, Michigan. May 18, 1987.

"New Development in the Derivation and Application of Acceptable Daily Intake Values"
In: Workshop on Approaches to Ecological and Human Health Risk Analysis for Disposal of Contaminated Sediments and Human Consumption of Contaminated Seafood. **U.S. Environmental Protection Agency** and **U.S. Department of the Army**, Seattle, Washington, December 16, 1985.

"Human Health Assessment"
In: Workshop of Water Quality-Based Toxics Control. **U.S. Environmental Protection Agency**, Philadelphia, Pennsylvania. November 14, 1985.

"Systemic Health Hazard Assessment"
In: Workshop on Human Health Criteria. **U.S. Environmental Protection Agency**, Philadelphia, Pennsylvania. October 3, 1985.

"Novel Methods for the Estimation of Acceptable Daily Intake"
In: Course entitled "Risk Assessment 101." **U.S. Environmental Protection Agency**, Washington, D.C. February 19, 1985.

"Use of Risk Assessment to Set Safe Levels"
In: Conference on Emerging Issues in Environmental Analysis and Planning: Implication for Professional Education. **University of Cincinnati**, **U.S. Army Corps of Engineers** and the **U.S. Environmental Protection Agency.** Cincinnati, Ohio. April 12, 1985.

"Environmental Risk Assessment"
In: Course on Applied Toxicology. **University of Cincinnati, College of Medicine.** Cincinnati, Ohio. April 6, 1984.

"Toxicity Risk Assessment"
U.S. Environmental Protection Agency, Atlanta, Georgia. July 7, 1984.

"The Regulatory History and Experimental Support of Uncertainty (Safety) Factors"
In: Workshop on Toxic Air Pollution: A Regulatory Challenge. **State and Territorial Air Pollution Control Officials**. Washington, D.C. October 10-12, 1984.

"Traditional Means of Assessing the Safety of Non-carcinogens"
In: Symposium on Federal Regulation of Carcinogens. **American Chemical Society.** Washington, D.C. August 30, 1983.

"The U.S. Environmental Protection Agency Perspective of Qualitative Risk Assessment"

In: Course on Applied Toxicology. **University of Cincinnati, College of Medicine.** Cincinnati, Ohio. March 30, 1983.

"EPA Criteria Documents"
In: Fifth Annual Course in the Principles and Practices of Genetic Toxicology. Division of Environmental Toxicology. **University of Texas Medical Branch.** Galveston, Texas. 1980.

"Quantitative Considerations in Urethane Induced Neoplasia"
In: Toxicology Division Seminars Series. **University of Cincinnati, College of Medicine.** Cincinnati, Ohio. October 25, 1979.

"Some Quantitative Aspects of Chemical Carcinogenesis II"
In: Toxicology Division Seminar Series. **University of Cincinnati, College of Medicine.** Cincinnati, Ohio. February 2, 1979.

"Some Quantitative Aspects of Chemical Carcinogenesis I"
In: Toxicology Division Seminar Series. **University of Cincinnati, College of Medicine.** Cincinnati, Ohio. March 7, 1978.

"Computer Simulation Studies on Kehoe's Lead Data"
In: Toxicology Division Seminar Series. **University of Cincinnati, College of Medicine.** Cincinnati, Ohio. May 14, 1977.

"A New Approach to Minimum Toxic Dose"
In: Toxicology Division Seminar Series. **University of Cincinnati, College of Medicine.** Cincinnati, Ohio. February 25, 1976.

I also have given over 50 formal, but uninvited, presentations (e.g., abstracts at the scientific annual meetings).

RESEARCH: RISK ASSESSMENT PUBLICATIONS (Selected)

Michael L. Dourson, Jeri Higginbotham, Jeff Crum, Heather Burleigh-Flayer, Patricia Nance, Norman D. Forsberg, Mark Lafranconi, John Reichard. 2017. Update: Mode of action (MOA) for liver tumors induced by oral exposure to 1,4-dioxane. Regulatory Toxicology and Pharmacology 88:45-55.

Richard A. Becker, Vicki Dellarco, Jennifer Seed, Joel M. Kronenberg, Bette Meek, Jennifer Foreman, Christine Palermo, Chris Kirman, Igor Linkov, Rita Schoeny, *Michael Dourson*, Lynn H. Pottenger, and Mary K. Manibusan. 2017. Quantitative weight of evidence to assess confidence in potential modes of action. Regulatory Toxicology and Pharmacology, 86:205–220.

Michael Dourson and Raymond G York. 2016. Advances in Assessing Ingredient Safety. Regulatory Toxicology and Pharmacology. 79:S112-S118.

Michael Dourson, Bernard Gadagbui, Rod Thompson, Edward Pfau, and John Lowe. 2016. Managing Risks of Noncancer Health Effects at Hazardous Waste Sites: A Case Study Using the Reference Concentration (RfC) of Trichloroethylene (TCE). Regulatory Toxicology and Pharmacology 80:125-133.

Ted W. Simon, Yiliang Zhu, *Michael L. Dourson*, Nancy B. Beck. 2016. Bayesian methods for uncertainty factor application for derivation of reference values. Regulatory Toxicology and Pharmacology 80:9-24.

Dourson, Michael, Chinkin, Lyle, MacIntosh, D.L., Finn, Jennifer, Brown, Kathleen, Reid, Stephen, Martinez, Jeanelle. 2016. A Case Study of Potential Human Health Impacts from Petroleum Coke Transfer Facilities. Journal of the Air & Waste Management Association May. DOI: 10.1080/10962247.2016.1180328.

Nancy B. Beck, Richard A. Becker, Neeraja Erraguntla, William H. Farland, Roberta L. Grant, George Gray, Christopher Kirman, Judy S. LaKind, R. Jeffrey Lewis, Patricia Nance, Lynn H. Pottenger, Susan L. Santos, Stephanie Shirley, Ted Simon, *Michael L. Dourson*. 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. Environment International 89–90 (2016) 110–128. **(regulatory and safety evaluation paper of the year, Society of Toxicology, Regulatory and Safety Evaluation Specialty Section)**

Greenberg M, Goldstein BD, Anderson E, *Dourson M*, Landis W, North DW. 2015. Whither Risk Assessment: New Challenges and Opportunities a Third of a Century After the Red Book. Risk Analysis, 35(11): 1959-1968.

Nance, P., O. Kroner, L. Haber and *M. Dourson*. 2015. Assessing Risks to Human Health. In Reference Module in Biomedical Sciences (Online). In-Press.

Dankovic DA, Naumann BD, Maier A, *Dourson ML*, Levy LS. 2015. The Scientific Basis of Uncertainty Factors Used in Setting Occupational Exposure Limits. J Occup Environ Hyg. 2015 Nov 25:12 Suppl 1:55-68

Cope, Rhian B., Sam Kacew, *Michael Dourson*. 2015. A reproductive, developmental and neurobehavioral study following oral exposure of tetrabromobisphenol A on Sprague-Dawley rats. Toxicology 329 (2015) 49–59.

Dourson, M., Reichard, J., Nance, P., Burleigh-Flayer, H., Parker, A., Vincent, M., McConnell, E.E. 2014. Mode of action analysis for liver tumors from oral 1,4-dioxane exposures and evidence-based dose response assessment. Regul.Toxicol. Pharm. 68(3): 387-401.

Cope, R., Nance, P., *Dourson*, ML. 2014. "Chapter 4. Human Health Risk Assessment of Inhaled Materials." IN: Salem, H., Katz, S., eds. Inhalation Toxicology, 3rd Edition, CRC Press.

Juberg, D.R., Borghoff, S.J., Becker, R.A., Casey, W., Hartung, T., Holsapple, M.P., Marty, S.M., Mihaich, E.M., Van Der Kraak, G., Wade, M.G., Willett, C.E., Anderson, M.E., Borgert, C.J., Cody, K.K., *Dourson, M.L.*, Fowle, J.R., Gray, L.E. Lamb, J.C., Ortego, L.S., Schug, T.T., Toole, C.M., Zorrilla, L.M., Kroner, O.L., Patterson, J., Rinckel, L.A., Jones, B.R. 2014. Workshop Report, Lessons Learned, Challenges, and Opportunities: The US. Endocrine Disruptor Screening Program. ALTEX, ALTES. ALTES, 31:63-78, January. Workshop Report is now available via open access publication in ALTEX.

Rosen, JS; Whelton, AJ; McGuire, MJ; Clancy, JL; Bartrand, T; Eaton, A; Patterson, J; *Dourson*, M, Nance, P; Adams, C. 2014. The crude MCHM chemical spill in Charleston, W.Va. Journal AWWA. Vol. 106:65-74.

Patterson J., Maier A, Kohrman-Vincent M, and *ML Dourson*. 2013. Peer consultation on relationship between PAC profile and toxicity of petroleum substances. Reg. Tox and Pharm, Volume 67: S86–S93.

Dourson, M, Becker, R.A., Haber, L.T., Pottenter, L.H.,Bredfeldt, T., Fenner-Crisp, P. 2013. Advancing Human Health Risk Assessment: Integrating Recent Advisory Committee Recommendations. Crit. Rev. Toxicol. 43(6): 467-92 (doi: 10.3109/10408444.2013.807223).

Dourson, M., Gadagbui, B., Griffin, S., Garabrant, D.H., Haws, L.C., Kirman, C. and Tohyama, C. 2013. The importance of problem formulations in risk assessment: A case study involving dioxin-contaminated soil. Reg. Toxicol.Pharmcol. 66(2): 208-216.

Hasegawa R, Hirata-Koizumi M, *Dourson ML*, Parker A, Ono A, Hirose A. 2013. Safety assessment of boron by application of new uncertainty factors and their subdivision. Regul. Toxicol. Pharmacol. 65:1, 108-114.

Haber LT, JE Strawson, A Maier, IM Baskerville-Abraham, A Parker, *ML Dourson*. 2013. "Noncancer Risk Assessment: Principles and Practice in Environmental and Occupational Settings." In: Bingham, E., and B. Cohrssen, eds. *Patty's Toxicology, 6th Edition, Volume 5*. John Wiley and Sons Inc.

Meek, M.E., Bolger, M., Bus, J.S., Christopher, J., Conolly, R.B., Lewis, R.J., Paoli, G., Schoeny, R., Haber, L.T., Rosenstein A.B., *Dourson, M.L.* 2013. A Framework for Fit-for-Purpose Dose Response Assessment. Regul. Toxicol. Pharmacol. 66(2): 234-40 (doi: 10.1016/j.yrtph 2013.03.012.

Maier, A., Kohrman-Vincent, M., Hertzberg, R., *Dourson, M.*, Haber, L.T and Allen, B. 2012. Critical review of dose-response options for F344 rat mammary tumors for acrylamide – Additional insights based on mode of action. Food Chem. Toxicol. 50:5, 1763-1775.

Nance P, Patterson J, Willis A, Foronda N, *Dourson M*. 2012. Human Health Risks from Mercury Exposure from Broken Compact Fluorescent Lamps. Reg. Tox. Pharm: 62(3): 542–552.

Patterson J, Maier A, Kohrman-Vincent M, *Dourson ML*. 2012. Peer consultation on relationship between PAC profile and toxicity of petroleum substances. Regul. Toxicol. Pharmacol: pii: S0273-2300(12)00224-3.

Rider CV, *Dourson M*, Hertzberg RC, Mumtaz MM, Price PS, Simmons JE. 2012. Incorporating nonchemical stressors into cumulative risk assessments. Toxicol Sci: 127(1):10-7.

Rhomberg LR, JE Goodman, LT Haber, *M Dourson*, ME Andersen, JE Klaunig, B Meek, PS Price, RO McClellan, SM Cohen. 2011. Linear low-dose extrapolation for noncancer health effects is the exception, not the rule. Critical Reviews in Toxicology: 41(1): 1-19.

Dourson, M and Haber, L. 2010. Linear Low-Dose Extrapolation. In: Cancer Risk Assessment. Ching-Hung Hsu and Todd Stedeford, ed. John Wiley &Sons.

Dourson, M.L., M.J. Kohrman-Vincent, B.C. Allen and W.S. Cain. 2010. Dose Response Assessment from Effects of Acute Exposure to Methyl Isothiocyanate (MITC). Reg. Toxicol. Pharmacol: 58(2): 181-188. Available on line.

Dourson, M. 2010. U-Shaped Dose-response Curves: Implications for Risk Characterization of Essential Elements and Other Chemicals. J. of Tox. and Env. Health, Part A, 73 (2), 181-186.

Cain, W., *M. L. Dourson*, M.J. Kohrman-Vincent and B.C. Allen. 2010. Human Chemosensory Perception of Methyl Isothiocyanage: Odor and Chemesthesi. Reg. Toxicol. And Pharmacol: 58(2): 173-180. Available online.

Chambers A, Krewski D, Birkett N, Plunkett L, Hertzberg R, Danzeisen R, Aggett PJ, Starr TB, Baker S, *Dourson M*, Jones P, Keen CL, Meek B, Schoeny R, Slob W. 2010. An exposure-response curve for copper excess and deficiency. J Toxicol Environ Health B Crit Rev. 2010 Oct;13(7-8): 546-78.

Gadagbui, B; Maier, *M; Dourson*, M; Parker, A; Willis, A; Christopher, JP; Hicks, L; Ramasany, S; Roberts, SM. 2010. Derived Reference Doses (RfDs) for the Environmental Degradates of the Herbicides Alachlor and Acetochlor: Results of an Independent Expert Panel Deliberation. Regulatory Toxicology and Pharmacology 57:220-234.

Hasegawa R, HK Mutsuko, *ML Dourson*, A Parker, LM Sweeney, A Nishikawa, M Yoshida, A Ono, A Hirose. 2010. Proposal of new uncertainty factor application to derive tolerable daily intake. Regul. Toxicol. Pharmacol. 58(2): 237-242.

Nance, P., Kroner, O., Haber, L. and *Dourson, M.* 2010. Assessing Risks to Human Health. In: The Occupational Environment: Its Evaluation, Control and Management. 3rd Ed., AIHA Press, D. Anna, ed.

Zhao, Q.J., Haber, L. Kohrman-Vincent, M., Nance, P., *Dourson, M.* 2010. Quantitative modeling in noncancer risk assessment. In: Quantitative Modeling in Toxicology, John Wiley, K. Krishnan and M.E. Anderson, ed.

Dourson, M., Hertzberg, R., Allen, B., Haber, L., Parker, A., Kroner, O., Maier, A. and Kohrman, M. 2008. Evidence-Based Dose Response Assessment for Thyroid Tumorigenesis from Acrylamide. Regulatory Toxicology and Pharmacology 52 (2008) 264–289.

Wullenweber, A; Kroner, O; Kohrman, M; Maier, A; *Dourson, M*; Rak, A; Wexler, P; Tomljanovic, C. 2008. Resources for global risk assessment: The International Toxicity Estimates for Risk (*ITER*) and Risk Information Exchange (RiskIE) databases, Toxicol. Appl. Pharmacol. 233: 45–53.

Hays, SM; Aylward, LL; LaKind, JS; Bartels, MJ; Barton, HA; Boogaard, PJ; Brunk, C; DiZio, S; *Dourson, M*; Goldstein, DA; Lipscomb, J; Kilpatrick, ME; Krewski, D; Krishnan, K; Nordberg, M; Okino, M; Tan, YM; Viau, C; Yager, JW. 2008. Guidelines for the derivation of Biomonitoring Equivalents: report from the Biomonitoring Equivalents Expert Workshop. Regul Toxicol Pharmacol. 51(3 Suppl):S4-15.

Dourson, M.L. and Parker, A. 2007. Past and Future Use of Default Assumptions and Uncertainty Factors: Default Assumptions, Misunderstandings, and New Concepts. Hum Ecol Risk Assess. 13(1):82-88.

Hasegawa R, Hirata-Koizumi M, *Dourson M*, Parker A, Hirose A, Nakai S, Kamata E, Ema M. 2007. Pediatric susceptibility to 18 industrial chemicals: A comparative analysis of newborn with

young animals. Regul Toxicol Pharmacol. 47(3):296-307. **(Risk assessment paper of the year, Society of Toxicology, Risk Assessment Specialty Section)**

Stedeford T, Zhor J, *Dourson ML*, Banasik M, Hsu CH. 2007. The Application of Non-Default Uncertainty Factors in the U.S. EPA's Integrated Risk Information System (IRIS). Part I: UF(L), UF(S), and "Other Uncertainty Factors". J Environ Sci Health C Environ Carcinog Ecotoxicol Rev. 25(3):245-79.

Stern, B.R., M. Solioz, D. Krewski, P. Aggett, T-C Aw, S. Baker, K. Crump, *M. Dourson*, L. Haber, R. Hertzberg, C.L. Keen, B. Meek, L. Rudenko, R. Schoeny, W. Slout, T. Starr. 2007. Copper and Human Health: Biochemistry, Genetics and Strategies for Modeling Dose-Response Relationships. J. Toxicol. and Environ. Health, Part B. 10(3):157-222.

Dourson, M and D. Drinan. 2006. Sensitive Populations and Risk Assessment. In: *Toxicokinetics in Risk Assessment.* Taylor and Francis Publishers. J.C. Lipscomb and E.V. Ohanian, Eds. Informa health care, New York. Pp. 251-210.

Gadagbui, B.K., L.T. Haber and *M.L. Dourson*. 2006. Chemical Risk Assessment as Used in Setting Regulatory Levels or Standards. Chap. 3.3.1 in Transforming Sustainability Strategy into Action: The Chemical Industry, edited by Beth Beloff, Marianne Lines, and Dicksen Tanzil. Hoboken , NJ : John Wiley & Sons, Inc.

Schoeny, R., L. Haber, and *M. Dourson*. 2006. Data considerations for regulation of water contaminants. Toxicology. 221 (2-3): 217-224.

Zhao, Qiyu , *M. Dourson* and B. Gadagbui. 2006. A Review of the Reference Dose (RfD) for Chlorpyrifos. Reg. Toxicol. Pharmacol. 44:111-124.

Dolan, D., B. Naumann, E. Sargent, A. Maier, *M. Dourson*. 2005. Application of the threshold of toxicological concern concept to pharmaceutical manufacturing operations. Reg. Toxicol. Pharmacol. 43:1-9.

Fields, C., *M.L. Dourson*, And J. Borak. 2005. Iodine-deficient vegetarians: A hypothetical perchlorate-susceptible population? Reg. Tox. Pharmacol. 42(1):37-46.

Lakind, Judy, Robert Brent, *Michael Dourson*, Sam Kacew, Gideon Koren, Babasaheb Sonawane, Anita Tarzian, Kathleen Uhl. 2005. Human Milk Biomonitoring Data: Interpretation and Risk Assessment Issues. Journal of Toxicology and Environmental Health, vol. 68, no. 20.

Zhao, Q., B. Gadagbui and *M. Dourson*. 2005. Lower birth weight as a critical effect of Chlorpyrifos: A comparison of human and animal data. Reg. Toxicol. Pharmacol. 42:55-63.

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Stara, J. F., *M. L. Dourson* and C. T. DeRosa. 1981. Water Quality Criteria: methodology and applications. In: Conference Proceedings in Environmental Risk Assessment: How New Regulations Will Affect the Utility Industry, Electric Power Research Institute, Palo Alto, California.

Dourson, M. L. and C. S. Baxter. 1981. Reduced incidence and growth rate of urethane induced lung adenomas in aging adult strain A mice. Toxicology, 20:165-172.

Manson, J. M., *M. L. Dourson* and C. C. Smith, 1977. Effects of Cytosine Arabinoside on *in vivo* and *in vitro* Mouse Limb Development. In Vitro, 13(7):434.

I have also co-authored well over 100 documents for the EPA, TERA and others that address either risk assessments for specific chemicals, or risk assessment methods, and have additional published manuscripts that are not listed here. I have also written three stories on integrating science and Biblical text: *Messiah's Star, The Beginning*, and *The Linen Cloths*.

RESEARCH: COMMENTARIES (Selected)

Thomas G. Osimitz, *Michael L. Dourson*, A. Wallace Hayes, and Sam Kacew. 2014. Crystallographic Analysis and Mimicking of Estradiol Binding: Interpretation and Speculation. Environmental Health Perspectives. Volume 122 (number 4), April 2014, page A 91.

Gail Charnley, Thomas Cluderay, *Michael Dourson*, George Gray, Tom Roberts. The Perchlorate Debate: Is the Chemical Worth Regulating. 2011. The Environmental Forum. Nov/Dec. Vol. 28(6), page 46-53.

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Strawson, J., *M. Dourson*, Q. Zhao. 2005. The NAS Perchlorate Review: Is the RfD Acceptable? 2005. Env. Health Perspect 113(11):A729-30; Nov. Author reply A730-2.

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Dourson, M.L. 1996. Editorial: Uncertainty Factors in Noncancer Risk Assessment. Reg. Tox. and Pharmacol. 24, Article No. 0115. p. 107.

Dourson, M.L. 1995. How Regulatory Agencies View Biological Effects of Low Level Exposures. BELLE Newsletter. 4(1):7.

Dourson, M.L. and W. Jordan, 1989. How "Safe" Is the Groundwater that Americans Drink? Ground Water Monitoring Review, Fall Issue. 9:73-74.

Dourson, M. L., R. C. Hertzberg and J. F. Stara. 1986. Letters to the Editor. Fundamental and Applied Toxicology. 6:182-184.

O'Flaherty, E. J. and *M. L. Dourson*, 1983. A Reply to Letter to the Editor "Cells of Origin of Lung Tumors in Mice. Journal of the National Cancer Institute. 70(6):991-992.

SERVICE: SCIENTIFIC SESSIONS CHAIRED OR PLANNED (Selected)

Chair: Well Over 100 Risk Assessment Peer Review Meetings
Since 1986, and to the present, I have chaired well over 100 scientific peer review meetings for risk assessment documents. Documents have covered a number of topics including risk assessment methods and assessments including cancer and non-cancer toxicity. These meetings have been sponsored by a number of organizations through either Toxicology Excellence for Risk Assessment's (*TERA*) program of the International Toxicity Estimates for Risk (*ITER*) database (for examples, please see www.tera.org/peer), by EPA through its IRIS database (see www.epa.gov/iris), or by groups such as Versar. These reviews have discussed well over 400 chemicals or risk issues.

Chair: Tox21: Current Progress, Next Steps and Exploring the Concept of a New Center of Excellence
Society of Toxicology. Baltimore, Maryland. March 12, 2017.

Co-chair: Low-Dose Non-Monotonic Responses
Society of Toxicology. Baltimore, Maryland. March 14, 2017.

Chair: Endocrine Disruption: Research, Analysis, Regulation, & Communication
Society of Toxicology. New Orleans, Louisiana, March 14, 2016.

Chair: Derived No-Effect Levels+ Big Data Toxicology Meeting
Society of Toxicology. New Orleans, Louisiana. March 13, 2016.

Moderator: Can/Should peer-reviewed publications be used to formulate regulatory policy?
Society of Toxicology. San Diego, California. March 23, 2015.

Chair: Beyond Science and Decisions: From Problem Formulation to Dose Response
Alliance for Risk Assessment. Cincinnati, Ohio. May 9-11, 2015.

Facilitator: Integration of Scientific Evidence to Inform Ozone Effects on Human Health
Texas Commission on Environmental Quality. Austin. Texas. April 8, 2015.

Chair: TTC Threshold Levels & TTC Decision Tree
EFSA/WHO workshop on Threshold of Toxicological Concern (TTC). Brussels, Belgium. December 3-5, 2014.

Chair: Chemical Assessment Advisory Committee for Ammonia
U.S. Environmental Protection Agency (EPA). Washington, D.C. July 14-16, 2014.

Chair: Beyond Science and Decisions: From Problem Formulation to Dose Response
Alliance for Risk Assessment. Austin, Texas. May 20-22, 2014.

Chair: Expert Panel Review of Screening Levels for Exposure to Chemicals From the January 2014 Elk River Spill
West Virginia Testing Assessment Project. Charleston, West Virginia. March 31, 2014.

Chair: Workshop to Assess the Modes of Action of Lung Tumors in Mice From Exposures to Styrene Ethylbenzene, and Naphthalene
Styrene Information & Research Center. Cincinnati, Ohio. September 17, 2013.

Chair: Melding Exposure and Toxicology Science I the 21st Century: Moving from Hazard to a Risk Based Paradigm
The Toxicology Forum. Aspen, Colorado. July 7-11, 2013.

Co-chair: Advancing Risk Assessment Approaches…*in the 21st Century*
The Toxicology Forum. Washington, DC. January 30-Feb. 2, 2012.

Rapporteur: Weight of Evidence Workshop, Session #1: From Review to Inference
Center for Advancing Risk Assessment Science and Policy (ARASP). Washington, DC. December 4, 2012.

Chair: Soil Exposure: What Have We Learned and How Do We Improve Problem Formulations for Risk Assessment
The Toxicology Forum. Aspen, Colorado. July 10-14, 2011.

Co-Chair: Determination of the Contribution of Individual Stressors in Cumulative Risk Assessments
Society of Toxicology Annual Meeting. Salt Lake City, Utah. March 6-12, 2010.

Chair: Fetal and Early-Life Perchlorate Exposures and Outcomes
Symposium. Perchlorate Exposures, Iodine Modulation of Effect, and Epidemiologic Associations: Implications for Risk Assessment. An Ancillary Program of the Annual Meeting of the Society of Toxicology. Seattle, Washington. March 2008.

Chair: Perchloroethylene (PERC): Approaches To Evaluating Uncertainty In Health Risk Assessment
Toxicology Forum. Washington D.C. January 30-February 1, 2007.

Chair: Mechanism/Mode Of Action Analyses
Risk Assessment Methodology Technical Committee, Weight of Evidence Workshop. Health and Environmental Sciences Institute. Baltimore, Maryland. December 7-8, 2006.

Session Planner and Chair: Issues In Trichloroethylene Risk Assessment
Midwest States Risk Assessment Symposium. Indianapolis, Indiana. August 23, 2006.

Session Planner and Chair: Panel Discussion On Trichloroethylene Toxicity
Midwest States Risk Assessment Symposium. Indianapolis, Indiana. August 25, 2004.

Chair: Screening Level Assessment Of Exposure And Characterization Of Risk For Humans
Risk Methodologies External Peer Review Panel Meeting, The Soap and Detergent Association. Washington, D.C., January 14, 2004.

Chair: A Review of the Reference Dose (RfD) and Reference Concentration (RfC) Processes
External Peer Review for U.S. EPA via Versar. Washington, D.C., June 19, 2002.

Session Planner and Co-Chair: Modeling of Population Variability
Society of Toxicology. Nashville, TN., Tuesday, March 19, 2002.

Co-Chaired Methyl Mercury: Risk Assessment, Policy and Research Needs
Children's Health and the Environment 2000. 19th International Neurotoxicology Conference. Colorado Springs, Colorado, September 26, 2000.

Session Planner and Co-Chair: Effective Risk Communication: Avoiding the Pitfalls
Continuing Education Course at the Society of Toxicology Annual Meeting, Seattle, Washington, March 1, 1998.

Lead: Panel Discussion on Information Resources for Toxicology and Environmental Health
Society of Toxicology, NCAC. George Washington University. Washington, DC, June 18, 1996.

Moderator: Workshop on Toxicity Assessment
At Harmonization of State/Federal Approaches at the Environmental Risk Symposium. Michigan State University. May 20-21, 1996.

Chair: Session on Risk Assessment
Chromium Symposium. Multiple Sponsors. Arlington, Virginia, April 23-24, 1996.

Session Planner and Co-Chair: Risk Assessment of Essential Trace Elements (ETES)
Society of Toxicology Annual Meeting. Anaheim, California, March 13, 1996.

Session Planner and Chair: Risk Characterization
In: New Techniques in Risk Assessment. International Business Communication. Orlando, Florida, February 16, 1996.

Session Planner and Chair: EPA's Integrated Risk Information System: Future Directions
In: New Techniques in Risk Assessment. International Business Communication. Orlando, Florida, February 14, 1996.

Session Planner and Co-Chair: Role of Toxicology in Tomorrow's Risk Assessment Practices
Sponsored by the Society for Risk Analysis and the International Congress of Toxicology. Seattle, July 2-6, 1995.

Session Planner and Chair: Techniques for Quantifying Uncertainty in Risk Assessment
Society of Toxicology Annual Meeting, March 19, 1995.

Session Planner and Co-Chair: Statistical and Dose Response Models in Risk Assessment
Society of Toxicology Annual Meeting, March 18, 1995.

Member of the Planning Committee: Workshop on Benchmark Dose Methodology
Sponsored by the EPA, the American Industrial Health Council and the International Life Sciences Institute, Fairfax, Virginia, September 28-30, 1993.

Session Planner and Co-Chair: Basics of Risk Assessment
In: Conference on the Risk Assessment Paradigm after Ten Years: Policy and Practice Then, Now, and in the Future. Sponsored by the U.S. Army, Air Force, Navy and EPA, Dayton, Ohio, April 5, 1993.

Session Planner and Co-Chair: Basic Risk Assessment: Current Developments
Continuing Education Course at the Society of Toxicology Annual Meeting. New Orleans, Louisiana, March 14, 1993.

Member of the Planning Committee: Risk Assessment of Essential Elements
Sponsored by U.S. ATSDR, EPA and the International Life Sciences Institute. Herndon, Virginia, March 10-12, 1992.

Session Planner and Co-Chair: Improvements in Quantitative Noncancer Risk Assessment
Society of Toxicology. Seattle, Washington. February 27, 1992.

Session Planner and Co-Chair: Neurotoxicity Risk Assessment: State of the Art
Society of Toxicology. Dallas, Texas. March 1, 1991.

Session Planner and Co-Chair: Improvements in Quantitative Noncancer Risk Assessment
Society of Toxicology. San Francisco, California. February 27, 1985.

SERVICE: APPOINTMENTS OR ELECTIONS (Selected)

2017 to… **Associate Editor**
Toxicological Sciences

2011-17 **Member**
Science Advisory Board of the U.S. Environmental Protection Agency (EPA)

2009 to… **Fellow**
Society for Risk Analysis

2007 to… **Advisor**
African Society of Toxicological Sciences

2007 to… **Fellow**

Academy of Toxicological Sciences

1999 to… **Member and Vice Chair (2003)**
Health Advisory Board. NSF International

1995 to… **Member**
Editorial Board of the Journal "Regulatory Toxicology and Pharmacology"

1994 to… **Member**
Editorial Board of the Journal "Human and Experimental Toxicology"

2016 to 2017 **Secretary**
Board of Directors, Toxicology Forum

2014 to 2017 **Vice President Elect, Vice President, President**
Society of Toxicology's Specialty Section for Regulatory and Safety Evaluation

2012 to 2017 **President and Member**
Board of Directors, Toxicology Education Foundation

2012 to 2017 **Member**
Science Advisory Council. North American Flame Retardant Association

2016 **Member**
Joint Meeting of the Food and Agriculture Organization of the United Nations (FAO) Panel of Experts on Pesticide Residues in Food and the Environment and the World Health Organization (WHO) Core Assessment Group on Pesticide Residues (JMPR)

2015 **Discussant**
Increasing the manganese reference value despite the growing environmental and health concerns, International Manganese Institute, University of Ottawa, October 14, 2015

2015 **Member**
Joint Meeting of the Food and Agriculture Organization of the United Nations (FAO) Panel of Experts on Pesticide Residues in Food and the Environment and the World Health Organization (WHO) Core Assessment Group on Pesticide Residues (JMPR)

2014 **Member**
World Health Organization & European Food Safety Commission Expert Panel. Workshop on Review of the Threshold of Toxicological Concern (TTC) Approach. Brussels, Belgium. December 2-4, 2014.

2011-2014 **Member, Co-Chair, Chair**
Membership Committee of the Society of Toxicology

2010-2015 **Chair**
Audit Committee of the Society for Risk Analysis

2010 **Faculty**

Resource person to the Risk Assessment Summer School (RASS) in Calabar, Nigeria, sponsored by the International Union of Toxicology, May 26 to 30

2009-2011 **Vice President Elect, Vice President, President**
Society of Toxicology's Specialty Section on Mixtures

2008-2014 **Member and President**
Council of Mt. Zion Lutheran Church

2008 **Participant, Essential Metals Workshop**
Institute of Population Health, University of Ottawa

2008 **Member**
Green Chemistry Initiative Science Advisory Panel, California Environmental Protection Agency, Department of Toxic Substances Control. San Francisco, CA

2007 **Lecturer**
Shanghai Municipal Center for Disease Control and Prevention (Shanghai CDC), National Continuing Education Training Workshop on Chemical Risk Assessment and Its Development. Shanghai, P.R. China

2006 to 2007 **Member**
The ECOS and DoD Sustainability Workgroup. Department of Defense, Washington, D.C.

2006 **Panelist**
Joint meeting of the dental products panel of the medical devices advisory committee of the CDRH and the peripheral and central nervous system drugs advisory committee of the CDER, Food and Drug Administration, September 6-7

2005 **Rapporteur**
Workshop on Poisons Centres and the Use of Human Data in Consumer Product Risk Assessment, Work Health Organization (WHO). Berlin, Germany. May 9-10, 2005

2004 **Panelist**
Technical workshop on human milk surveillance and biomonitoring for environmental chemicals in the United States. Milton Hershey Medical Center, Penn State, Pennsylvania, September 24 to 26

2003 to 2006 **Member and Chair**
World Wide Web Advisory Committee. Society of Toxicology

2003 **Panel Member**
Mid-Cycle Peer Review for NHEERL's Neurotoxicology Division, U.S. EPA, RTP, NC

2001 to 2005 **Secretary**
Society for Risk Analysis.

2001 **Panel Member**
Peer Review for NHEERL's Neurotoxicology Division, U.S. EPA, RTP, NC

2000 to 2001 **Temporary Advisor**

World Health Organization for Consultation on Uncertainty and Variability: BGVV, Berlin Germany. 9-11 May

2000 to 2001 **Advisor and Rapporteur**
Food Safety in Europe: Risk assessment of chemicals in food and diet. ILSI: Barcelona, Spain

1999 **Member**
Panel for the harmonization of cancer and non-cancer risk assessment. Society of Toxicology. November 1-3

1999 to 2002 **Member**
Oversight Group for the EPA Cooperative Agreement. George Washington University

1999 to 2002 **Vice President Elect, Vice President, President and Councilor**
Society of Toxicology's Specialty Section on Risk Assessment

1998 to 2004 **Executive Director and Treasurer**
Concordia Lutheran Church, Cincinnati, Ohio

1996 to 1998 **Member**
FDA Science Board Subcommittee on Toxicology

1995 **Co-Guest Editor**
EPA Uncertainty Factor Workshop. Human and Ecological Risk Assessment, 1(5):512-662

1995 to 1999 **Member, Treasurer, Vice President, and President (1998)**
Board of Directors of the American Board of Toxicology

1995 to 1996 **President (first elected)**
Dose-Response Specialty Group, Society for Risk Analysis

1995 to 2006 **Scoutmaster, Assistant Scoutmaster**
Troop 133 of Concordia Lutheran Church, Cincinnati, Ohio

1994 to 2007 **Member**
Editorial Board of the Journal Human and Ecological Risk Assessment

1994 to 1995 **Director, Property Board**
Concordia Lutheran Church, Cincinnati, Ohio

1994 to 1995 **Cubmaster**
Pack 133 of Concordia Lutheran Church, Cincinnati, Ohio

1991 to 1994 **President-Elect, President and Councilor**
The Ohio Valley Chapter of the Society of Risk Analysis

1993 **Member**
Committee on Lutheran Mission Ministry Strategy for Greater Cincinnati

1993 **Expert Witness**
OSHA for Informal Public Hearing on the Proposed Rule on Occupational Exposure to Glycol Ethers, Washington, D.C., July 21

1993 **Temporary Advisor and Joint Rapporteur**
World Health Organization for Consultation on Guiding Principles and Methodology for Quantitative Risk Assessment in Setting Exposures Limits: III, Geneva, Switzerland, June 14-18

1993 **Faculty**
As part of an EPA-sponsored delegation to teach a course on Environmental Management-Risk Assessment Training, Lodz, Poland, March 29-April 2

1993 **Temporary Advisor**
World Health Organization for Consultation on Guiding Principles and Methodology for Quantitative Risk Assessment in Setting Exposures Limits: II, Langen, Germany, January 19-22

1992 **Temporary Advisor and Co-Vice Chair**
World Health Organization for Consultation on Guiding Principles and Methodology for Quantitative Risk Assessment in Setting Exposures Limits: I, Geneva, Switzerland, January 14-17

1990 to 1993 **Vice President and President**
Academy of Kettering Fellows. University of Cincinnati, College of Medicine

1988 to 1992 **Councilor**
The Ohio Valley Chapter of the Society of Toxicology

1988 to 1990 **Vice President (interim), President (first elected) and Councilor**
Society of Toxicology's Specialty Section on Risk Assessment

1987 to 1992 **Chair**
EPA Risk Assessment Forum's technical panel to develop Risk Assessment Guidelines for Non-Cancer Health Effects

1986 to 1993 **Treasurer, Vice President and President**
Lutheran Church of the Cross, Cincinnati, Ohio

1986 to 1994 **Chair and Co-Chair**
Reference Dose (RfD) Work Group of the EPA (with a 1 year break in service)

1986 to 1995 **Charter Member**
Risk Assessment Forum of the EPA

AWARDS (Selected)

2017 **Outstanding Regulatory and Safety Evaluation Paper**. Given for the outstanding published paper in regulatory and safety evaluation during 2016. Regulatory and Safety Evaluation Specialty Section (RSESS). Society of Toxicology. Award was based on a group effort.

2013 **Risk Communication Award.** KidsChemicalSafety.org was honored with the Alliance for Chemical Safety. The risk communication award recognizes a

company, organization or individual who has shown outstanding leadership in communicating about chemical risks. Award was based on a group effort.

2013 **Best Charity Award.** Toxic Chemical Safety awarded for recognition as one of the 'BEST' charities in America. Presented upon rigorous independent review for being able to certify, document and demonstrate on an annual basis that met the highest standards of public accountability, program effectiveness, and cost effectiveness.

2009 **International Achievement Award.** In recognition of his outstanding contributions nationally and internationally to the advancement of regulatory science, policy, and methodologies in risk assessment and risk management and for his distinguished and creative participation in regulatory organizations and in decisions of ultimate public health significance worldwide. International Society of Regulatory Toxicology and Pharmacology.

2008 **Outstanding Risk Assessment Paper**. Given for the outstanding published paper in 2007 demonstrating an application of risk assessment. Risk Assessment Specialty Section, Society of Toxicology. Award was based on a group effort.

2008 **The Independent Charities Seal of Excellence.** Given to the members of Independent Charities of America and Local Independent Charities of America that have, upon rigorous independent review, been able to certify, document, and demonstrate on an annual basis that they meet the highest standards of public accountability, program effectiveness, and cost effectiveness. These standards include those required by the US Government for inclusion in the Combined Federal Campaign, probably the most exclusive fund drive in the world. Of the 1,000,000 charities operating in the United States today, it is estimated that fewer than 50,000, or 5 percent, meet or exceed these standards, and, of those, fewer than 2,000 have been awarded this Seal. Award was based on a group effort.

2007 **Service to the Voluntary Children's Chemical Evaluation Program (VCCEP)**. Given for service as chair and participant on external review panels. Toxicology Excellence for Risk Assessment, Cincinnati, Ohio.

2003 **Arnold J. Lehman Award.** An award in recognition of major contributions to risk assessment and the regulation of chemical agents, including pharmaceuticals. Society of Toxicology.

2002 **Environmental Stewardship Award.** An award issued in gratitude for serving on the C8 Assessment of Toxicity Team as a toxicologist in the development of toxicity factors and screening levels. West Virginia, Department of Environmental Protection. Award was based on a group effort.

2000 **Key Risk Award.** Environmental Studies Topic. Links2Go. *TERA*'s International Toxicity Estimates for Risk (*ITER*) database won this award by being 7th most accessed environmental web site in the world. Award was based on a group effort.

1998 **Outstanding Risk Assessment Paper**. Given for the outstanding published paper in risk assessment during 1997. Risk Assessment Specialty Section. Society of Toxicology. Award was based on a group effort.

1995 **In Appreciation.** An award for outstanding service and scientific contribution to the Environmental Protection Agency and to United States Government.

1994 **Special Achievement.** An award for noteworthy contribution as a member of the Risk Characterization Team towards an EPA-wide workshop on risk characterization.

1992 **Bronze Medal.** An award for outstanding service in the review of EPA's 503 Sludge Regulations. Award was based on a group effort.

1992 **OHEA Peer Award for Scientific Achievement.** An annual peer award for scientific achievement in EPA's Office of Health and Environmental Assessment

1992 **RfD/RfC Work Group Appreciation Award.** For sustained superior leadership of and scientific contributions to EPA's Reference Dose/Reference Concentration Work Group.

1991 **Bronze Medal.** An award for outstanding service in the development of EPA's Integrated Risk Information System (IRIS). Award was based on a group effort.

1990 **Special Achievement.** An EPA award for ensuring ORD's successful involvement in regulatory support issues with EPA's Office of Pesticides and Toxic Substances.

1988 **Special Achievement.** An EPA award for resolution of generic issues associated with the minimum data base needed to estimate Reference Doses (RfDs).

1987 **Special Achievement.** An award for further development of the EPA's -- Integrated Risk Information System (IRIS).

1986 **Bronze Medal.** An EPA award "for outstanding service in the organization and review of Risk Reference Doses (Acceptable Daily Intakes) and the science from which they are derived." Award was based on a group effort.

1984 **Tribute of Appreciation.** An EPA award for the "Development of Risk Assessment Guidelines."

1982 **Coach of the Year (soccer).** Greater Cincinnati League (Catholic Boys High School)

1980 **Bronze Medal.** An EPA award recognizing "Outstanding dedication, completion of tasks and contributions to environmental protection in the development of Water Quality Criteria." Award was based on a group effort.

AFFILIATIONS

I am a member of the American Association for the Advancement of Science **(AAAS)**, the Society for Risk Analysis **(SRA)**, and the Society of Toxicology **(SOT).** I am a Diplomate of the American Board of Toxicology (October 1985) and was recertified in 1990, 1995, 2000, 2005, 2010, and 2015. I am an elected Fellow of the Academy of Toxicological Sciences and the Society for Risk Analysis.

REFERENCES

References will be readily supplied upon request.

Summary of billed hours of Toxicology Excellence for Risk Assessment (TERA) for the years 1995 to 2015, and donated time.*

Year	Non Profit	% of Billed	Profit	% of Billed	Donated Time	% of Billed
1995	917	67%	457	33%	166	12%
1996	1,248	38%	2,073	62%	701	21%
1997	2,173	53%	1,949	47%	769	19%
1998	4,841	61%	3,106	39%	1,133	14%
1999	5,631	66%	2,925	34%	879	10%
2000	4,949	58%	3,583	42%	1,501	18%
2001	5,197	47%	5,964	53%	1,391	12%
2002	11,407	72%	4,527	28%	2,104	13%
2003	10,534	79%	2,870	21%	2,335	17%
2004	12,238	82%	2,629	18%	2,109	14%
2005	11,477	82%	2,538	18%	1,962	14%
2006	9,932	73%	3,741	27%	1,807	13%
2007	10,727	72%	4,225	28%	2,112	14%
2008	9,588	67%	4,812	33%	1,578	11%
2009	10,806	69%	4,966	31%	1,767	11%
2010	10,548	66%	5,434	34%	1,849	12%
2011	9,569	67%	4,713	33%	1,650	12%
2012	9,250	60%	6,166	40%	1,126	9%
2013	11,183	63%	6,585	37%	1,577	9%
2014	8,071	57%	6,006	43%	1,541	11%
2015	9,669	68%	4,550	32%	1,403	10%

* These hours do not include marketing, general science or administrative times.

Sponsor	Project Description	Project Type
Acrylonitrile Group	Proposal to review acrylonitrile IRIS external draft and prepare public comments for	Private Sector
AECOM	TERA organized an independent expert panel to review a draft work plan for a	Private Sector
Albermarle	Review EPA design for environment text on flame retardants.	Private Sector
American Chemistry Council	This project is an enhancement of the ARA Dose Response Framework that was	Collaboration
American Chemistry Council	For Beyond Science & Decisions, continuation of case study 17. Low dose linear	Collaboration
American Chemistry Council	Develop a kids risk webpage, in part.	Collaboration
American Chemistry Council	Build on previous work to develop RfD, including critical evaluation of issues,	Private Sector
American Chemistry Council	TERA will review DINP toxicity data and provide expert opinion on relevance of chronic	Private Sector
American Chemistry Council	Conduct mode of action assessment for liver tumors in mice exposed to diethanolamine.	Private Sector
American Chemistry Council	Assessment Science and Policy's (ARASP) Weight of Evidence Workshop.	Private Sector
American Chemistry Council	Reviewed studies to determine critical effect(s); prepared manuscript; submitted,	Private Sector
American Chemistry Council	Analyze the current display of the uncertainty and variability in the IRIS summaries.	Private Sector
American Chemistry Council	Co-writing a paper on Bayesian approach to developing RfDs	Private Sector
American Chemistry Council	ITER (International Toxicity Estimates for Risk) Peer Review Program for TCDD.	Private Sector
American Chemistry Council	Presentation of recent ecological TBBPA data at SETAC in 2014.	Private Sector
American Chemistry Council	Provide assistance in developing and presenting a continuing education course at AIHce	Private Sector
American Chemistry Council	Gift letter funding the mutagenic mode of action adverse outcome case study.	Private Sector
American Chemistry Council	Conduct BMD analysis of key studies and review data for other studies worthy of	Private Sector
American Chemistry Council	Revise rat PBPK model of propyl series compounds, prepare report and poster, present	Private Sector
American Cleaning Institute	Develop proposal for conducting safety assessment case studies for selected cleaning	Private Sector
American Cleaning Institute	Organize workshop on scientific issues regarding asthma and cleaning products.	Private Sector
American Petroleum Institute	Prepare a manuscript for submission to a peer-reviewed journal that describes the	Private Sector
American Petroleum Institute	The proposed work includes (1) further developing the draft framework, (2) expanding	Private Sector
Amgen Reagents	Developing risk values (permissible daily exposures; PDEs) to calculate toxicology-based limits for drug substances and/or reagents designated by the sponsor. A PDE is the dose that would not result in an appreciable effect to human health from relevant drug substance routes of administration. The PDE is derived by analyzing all potential toxic effects such as acute, chronic, reproductive, and carcinogenicity and choosing the most	Private Sector
Aquilent	Organize and conduct subject matter expert workshop on term and definitions of toxic	Government
Aquilent	Develop content for additional chemicals in CHEMM.	Government
AWWA - American Water Works Association	Brief assessment of the validity of conclusions some commenters have attributed to the	Private Sector
Battelle Memorial Institute	ORNL Health Advisory Guidance. Respond to EPA comments on revisions to draft	Government
Battelle Memorial Institute	Scoping assessment of vinyl acetate PBPK models for possible use in US EPA IRIS	Government
Battelle Memorial Institute	Scoping assessment of PBPK models for possible use in US EPA IRIS assessment of	Government

Battelle Memorial Institute	Develop brodifacoum model based on warfarin model; develop bromadiolone model if	Government
Battelle Memorial Institute	PBPK modeling support for US EPA IRIS assesesment of PCBs.	Government
Battelle Memorial Institute	"Quick Response Statistical Report" EPA Contract No. EP-C-09-006. QA of Hissink et	Government
Bowles and Verna LLP	Contaminated site necessitates review and possible court testimony on the plaintiffs' side regarding comparison of levels of contaminant exposure and health benchmarks. TCE	Non-Profit
British Society of Toxicology	Attend the BSOT annual meeting and make a presentation.	Non-Profit
California Chamber of Commerce	Review the CalEPA Env Health Screening Tool and provide comments at a "meeting of	Non-Profit
Cardno Chemrisk	Provide a peer review on evaluation of the weight of evidence for endocrine disruption	Private Sector
CEFIC	Investigate mode of action for ethylene oxide-induced lung tumors in male mice. Project	Collaboration
Charles A. Pittinger, LLC	Draft ecological manuscripts for TBBPA.	Private Sector
Chevron	An emergency response course for the EHS team, and perhaps individuals from other	Private Sector
Chevron Phillips Chemical LP	Preparation of a Test Plan document, with robust summaries, for chemicals as identified	Private Sector
Chevron Phillips Chemical LP	2-day Emergency Medical Response training course offered to Chevron.	Private Sector
City of Cincinnati	Evaluate the health risks associated with outdoor wood fired boilers.	Government
Combined Federal Campaign	Develop a kids risk webpage, in part.	Collaboration
Coca Cola	Develop a benchmark dose (BMD) for 5-HMF.	Private Sector
Concurrent Technologies Corporation	Provide senior-level peer review and comment on several individual susbtance report	Government
Corona Environmental Consulting, LLC	One day meeting in West Virginia to review available tox data and scientific support for	Government
Dow AgroSciences	Develop a manuscript based on the previously developed issue paper with a critical	Private Sector
Dow Chemical	Prepare and assist in preparation of manuscripts from the nuclear receptor workshop.	Collaboration
Dow Chemical	Chair session on soil exposure at the July 2011 Tox Forum meeting.	Private Sector
Dow Chemical	BMD course (related to Boot Camp) and DR 1 and 2.	Private Sector
Dow Corning	Review and revise industrial hygiene guides and occupational exposure limits (OELS).	Private Sector
Dow Corning	Application of uncertainty factor for the development of the IHG. Submission of literature	Private Sector
Drinker, Biddle & Reath LLP	Identify, gather, review and assemble available data on chemicals as defined in the ELSIE document Safety Database Search and Compilation Protocol.	Non-Profit
Eastern Research Group	Review EPA's text entitled: Application of Quantitative Data to Develop Data-Derived	Government
Electric Power Research Institute	Case study review for Workshop 9: Adverse outcome pathway (AOP) for arsenic	Collaboration
Eli Lilly	Development of OEL documents for pharmaceutical compounds.	Private Sector
EnRisks	Develop course training package, descriptions and outlines of all courses and review	Government
EnSIGHT	Determine cancer slope factors for DINP using California proposition 65 logic and EPA	Private Sector
ERM Alaska, Inc.	Alaska DEC has tasked TERA with conducting an independent, expert peer review of the	Government
Ethyleneamines Product Stewardship Discussion Group	BMD modeling support for aminoethylethanolamine, evaluate relevance of endpoints and	Private Sector
ExxonMobil Biomedical Sciences, Inc	Critical review of available information on decalin (decahydronaphthalene) to confirm if	Private Sector
Genentech	Assist in developing risk assessment procedures.	Private Sector
Georgia Pacific	Met with sponsor to discuss options for IRIS reinvention.	Private Sector

GMA	Development of a periodic newsletter.	Private Sector
Gradient	ITERate (International Toxicity Estimates for Risk) Peer Review Program: Manganese	Private Sector
Gradient	Comment on and contribute to manuscript on issues and assumptions behind arguments	Private Sector
Halogenated Solvents Industry Alliance	Provide comments on EPA IRIS assessment for TCE to EPA's Scientific Advisory Board.	Private Sector
Hamp, Mathews & Associates, Inc.	Procure and translate Japanese studies on 1,4-dioxane; develop analysis and publish a	Collaboration
HAP Task Force	Route-to-route extrapolation of NOAELs and LOAELs from existing and new studies	Private Sector
Health Canada	Letter review of phthlataes.	Government
Health Canada	Peer review of risk assessment documents on PFOS and PFOA with emphasis on dose	Government
Health Canada	Letter peer consultation on flame retardant dechlorane plus.	Government
Health Canada	Review a 4-5 page special issue paper on boron dealing with PBPK, BE and uncertainty.	Government
Health Canada	Letter Consultation on 3 flame retardants.	Government
Health Canada	Assessment AEEA and Ethyl.	Government
Health Canada	CoCAM 5. Three assessment peer reviews.	Government
Health Canada	Review of petroleum substances.	Government
Health Canada	TERA organized and conducted an independent peer consultation of the draft screening	Government
Health Canada	Review documents provided by HC: draft Screening Assessment reports and outlines	Government
Health Canada	Coordinate and manage an independent peer consultation of the draft screening level	Government
Health Canada	Develop a guidance document for using biomonitoring studies to estimate exposures for	Government
Health Canada	Position paper and internal Health Canada peer consultations on risk assessment for	Government
Health Canada	Custom 3-day Boot Camp course.	Government
Health Canada	Peer review of Batch 12 substances N,N-diphenyl -guanidine; carbon black; cristobalite;	Government
Health Canada	Letter peer consultation on flame retardants tricresyl phosphate (TCP).	Government
Health Canada	Letter peer consultation on 2 flame retardants, bis(2-ethylhexyl)	Government
Health Canada	TERA will select a minimum of 5 Canadian Public Health Summaries, based on	Government
Health Canada	TERA organized and conducted a letter peer consultation on two draft guidance	Government
Health Canada	Assessment of Non-Cancer Effects due to Short-Term Exposure and Short-Duration	Government
Health Canada	Update and complete the human health screening risk assessment report for acetone.	Government
Health Canada	(1) prepare "toolbox" of risk assessment methods; (2) framework and discussion of	Government
Health Canada	Organize and conduct independent scientific peer consultation on two draft Health	Government
Health Canada	Organize and conduct an independent scientific peer consultation on the draft Health	Government
Health Canada	Coordinate and manage an independent external scientific and technical peer review of	Government
Health Canada	Review of screening assessment for triclosan.	Government
Health Canada	Review exposure scenarios for azo dyes.	Government
Health Canada	Conduct peer consultation of the revised hydrogen sulfide assessment document. TERA	Government
Health Canada	Peer consultation of the revised State of the Science report on 1,1-biphenyl.	Government

Health Canada	Organize and conduct letter peer consultations on petroleum stream products.	Government
Health Canada	Letter peer consultation on 4 azobenzidine assessments.	Government
Health Canada	Organize and conduct independent scientific opinion on the Health Canada documents	Government
Health Canada	Organize and conduct letter reviews on Petroleum Stream Products.	Government
Health Canada	Organize and conduct a second letter peer consultation on petroleum stream products.	Government
Health Canada	Organize and conduct independent scientific peer consultation on the Health Canada	Government
Health Canada	Organize and conduct independent scientific peer consultation on the Health Canada	Government
Health Canada	TERA will review rat-human dosimetric models and evaluate for diesel exhaust exposure	Government
Health Canada	Participate in 2-day workshop on current state-of-knowledge in the health risk	Government
Health Canada	Quantitative Uncertainty and Variability Analysis of Perfluorinated Chemicals (PFCs)	Government
ICF Incorporated, LLC	The goal of this project is to finalize the content for about 50 potential mass casualty	Government
ICL-IP America Inc.	Case study review for Workshop 9 – flame retardant framework - for addressing risk and	Collaboration
ILSI North America	Dose-response evaluation of relationship between Trans-fat intake and LDL-cholesterol.	Non-Profit
Institute of Environmental Science & Research Limited	Review of NZ risk methods document.	Government
Institute of Environmental Science & Research Limited	Carry out a review of the Hobsonville Health Risk Assessment undertaken by Golders	Government
Institute of Environmental Science & Research Limited	Written peer review for health assessment titled Health risk assessment of diluted	Government
Institute of Environmental Science & Research Limited	Task 1: Technical Information Resources: TERA would provide ESR with a list of	Government
Institute of Environmental Science & Research Limited	Technical review and detailed comments relating to the review of the report entitled "A	Government
Institute of Environmental Science & Research Limited	Technical review and detailed comments relating to the review of the report entitled "A	Government
JT International S.A.	Provide two presentations (40-60 mins) on "Principles for the risk assessment of	Private Sector
LifeLine Group	For Health Canada, TERA organized and managed an expert scientific letter review of a	Government
LifeLine Group	For Health Canada, Development of assessment materials to be used for evaluating	Government
LifeLine Group	For Health Canada, development of a proposed approach for identifying polymers that	Government
Lockheed Martin	Review and comment on new CatReg software interface.	Government
Longenecker & Associates	Providing services for Dept. of Energy (DOE), Office of River Protection (ORP). Tank	Government
McKenna Long and Aldridge	Prepare comments on the trichloroethylene IRIS document on issues related to cancer	Government
Merck & Co.	Develop and deliver an OEL presentation.	Private Sector
Merck & Co.	Provide support for development of dose-response analyses for tumorigenic effects	Private Sector
Methanol Institute	Conduct a letter peer review of a methanol cancer bioassay published as Soffritti et al.	Private Sector
Morrison & Foerster	Rview of information regarding acrylamide in coffee.	Private Sector
Multiple sponsors	TERA hosted and organized a workshop on the Endocrine Disruptor Screening Program	Collaboration
Multiple sponsors	Workshop III of Beyond Science and Decisions- to continue the discussion toward a	Collaboration
Nease Corporation	Prepare response to proposed HPV program test rule.	Private Sector
Neptune	Develop white paper on aggregate and cummulative risk for OPPT.	Government
New Zealand Ministry of Health	Provide review of document regarding recommended cleanup of broken mercury	Government

New Zealand Ministry of Health	Develop publication based on the screening level health assessment on exposure to	Government
Nickel producers research association	Review and comment on draft manuscript on reference value for nickel in ambient air:	Private Sector
Nickel producers research association	Conduct a meta-analysis and meta-regression of respiratory cancer risk following	Private Sector
Nickel producers research association	Monitor progress of research related to evaluation of nickel MOA; provide advice to	Private Sector
Nickel producers research association	Review and rate proposals related to nickel MOA; monitor progress of funded work;	Private Sector
Noblis Inc.	Facilitate the development of a WEEL.	Government
Noblis Inc.	(1) Evaluate of toxicity of emerging contaminants to provide Sponsor with a scientific	Government
NSF International	Run CatReg model for one set of data with chronic progressive nephropathy (CPN) as	Non-Profit
NSF International	Add new data to ITER from NSF International.	Non-Profit
NSF International	Evaulate the MOA and safety studies on DMAA; contribute to the writing of a paper on	Non-Profit
NSF International	Review of polymer toxicity information.	Non-Profit
Ohio State University	Present lecture on environmental risk assessment at Ohio State University.	Government
Ontario Ministry of the Environment	Review Ontario MOE approaches to setting air standards. Conduct research into how	Government
Pfizer Global Research and Development	Provide support for development of dose-response analyses for tumorigenic effects	Private Sector
PPG Industries	Changed dioxane publication to open access.	Private Sector
PPG Industries	Conduct Japanese study translation and anaylsis in part.	Private Sector
Proctor & Gamble	Determination of whether the current TTC limits are protective for	Private Sector
PSA Inc.	Manage registration and workshops for 2011 TRAC conference.	Government
PSA Inc.	Provide assistance with online and onsite registration, catering details and workshop	Government
Quinn Emanuel Urquhart & Sullivan, LLP	Review information on petroleum coke and related materials to assist in understanding	Private Sector
Sapphire Group	Respond to reviewer comments, edit acrylamide manuscript, review proofs.	Private Sector
Shell Inc.	Communicate toxicology related to siting a plant in Pittsburgh.	Private Sector
Silicones Environmental Health and Safety Council	Gather and consolidate SEHSC data in order to develop a summary of all relevant data	Non-Profit
Society for Risk Analysis	Compile information on local contacts at universities for student award for DRSG.	Non-Profit
Society of Toxicology	Host SOT 2013 Global Senior Scholar Exchange program. The program aims to	Non-Profit
State of Maine	Examine whether current pesticide residues have the potential to affect the lobster	Government
State of New Mexico	Provide a comprehensive technical and regulatory support to New Mexico Environment	Government
State of Oregon	Review of in vitro study conducted by private party to determine likely bioavailability of	Government
State of Texas	Organize and hold a workshop on technical and scientific issues related to ozone	Government
State of Texas	Organize and conduct scientific peer review of chemicle-specific development support	Government
State of Texas	Add new data from TCEQ to ITER in the ITER column.	Government
State of Texas	Enter Hexavalent Chromium toxicity factors from the chromium development support	Government
State of Texas	Organize an external technical letter review of the TCEQ draft Development Support	Government
State of Texas	Enter Nickel Toxicity Factors from Nickel Development Support Document on the ITER	Government
State of Texas	Conduct a letter peer review of TCEQ's revised ESL (effects screening level) guidelines,	Government

State of Texas	Letter peer review with follow up teleconference of section 4.2 Carcinogenic Potential of	Government
State of Texas	Letter peer review of section 4.3 Carcinogenic Potential od the DSD for isoprene.	Government
Steptoe	Review CalEPA chloropicrin cancer risk assessment.	Private Sector
Strategic Regulatory Consulting	Review draft MSDS forms provided by SRC for format and content. Editing of forms as	Private Sector
Styrene Information and Research Center	Technical support for public workshop on mouse lung tumor mode of action issues (for	Private Sector
Sudbury Integrated Nickel Operations, a Glencore company	Review and comment on Quebec 24-hour nickel standard.	Private Sector
Summit Toxicology	Work with Sean Hays of Summit Toxicology to add biomonitoring equivalents data to	Government
ToxServices	Conduct literature search, retrieve papers, and write toxicokinetics chapters for the	Government
ToxStrategies	Organize and conduct a letter peer review of a rat 90-day study, conducted as part of a	Private Sector
ToxStrategies	Organize and conduct a letter peer review of a mouse genomics study, conducted as	Private Sector
ToxStrategies	ITERate review of chromium VI.	Private Sector
U.S. Air Force	Conduct focused science reviews of up to 6 chemical risk assessments that assess	Government
U.S. Air Force	Conduct a 4-day boot camp course on-site at WPAFB.	Government
U.S. Army	Form an expert panel and conduct a technical review of two occupational exposure levels	Government
U.S. Army Corps of Engineers	2a. Prepare slides in support of Task 1 (problem formulation) -- draft and final --	Government
U.S. Borax	Develop manuscript on the previous work we did in developing an independent OEL for	Private Sector
U.S. Consumer Product Safety Commission	Develop and deliver a course on mixtures risk assessment issues.	Government
U.S. Consumer Product Safety Commission	Review and compile data relating to human exposure to selected flame retardants.	Government
U.S. Consumer Product Safety Commission	Cconduct literature searches regarding the concentrations of specified elements	Government
U.S. Consumer Product Safety Commission	Conduct research regarding the production and use of specified phthalates. Results of	Government
U.S. Consumer Product Safety Commission	Conduct research regarding the production and use of specified plastics with regards to	Government
U.S. Consumer Product Safety Commission	Review epidemiology and toxicology literature on common molds.	Government
U.S. Consumer Product Safety Commission	Review literature and prepare hazard characterization (tk and toxicity sections) and	Government
U.S. Consumer Product Safety Commission	Conduct a broad, high-level , letter peer review of the CPSC Chronic Hazard Advisory	Government
U.S. Consumer Product Safety Commission	Organize exposure data on flame retardants into database for use in exposure	Government
U.S. Consumer Product Safety Commission	Conduct research regarding the production of engineered wood products and research	Government
U.S. Consumer Product Safety Commission	Conduct a letter peer review of a CPSC draft report on Nanomaterial Toxicity and	Government
U.S. Environmental Protection Agency	Review Technical Qualifications Document provided by NHEERL. Review evaluation	Government
U.S. Environmental Protection Agency	TRAC Conference - TERA to manage social, registration, oversee catering at hotel and	Government
U.S. Food and Drug Administraton	Organize and conduct a 3 day boot camp course.	Government
U.S. National Institute of Occupational Safety and Health	Create and publish TRAC2016 website, work with TRAC committee and provide onsite	Government
U.S. National Institute of Occupational Safety and Health	Create and publish TRAC2014 website, work with TRAC committee and provide onsite	Government
U.S. National Institute of Occupational Safety and Health	Give presentation to NIOSH staff on the use of basic research in developing risk	Government
U.S. National Library of Medicine	Peer consultation workshop for NLM CHEMM to agree on terminology and definitions.	Government
U.S. National Library of Medicine	Continued lease, maintenance and update of ITER database for use on TOXNET.	Government

Underwriters Lab- Environment	QA of ingredient reviews and guide to preparing a toxicological assessment.	Non-Profit
Vanadium Producers & Reclaimers Association	Evaluation of K-Ras and cII mutations in the lungs of Big Blue mice exposed to	Private Sector
Versar	Review of Consumer Products Safety Commission on metal levels in toys.	Government
Versar	IRIS external peer review of hexachloroethane.	Government
Versar	Review CPSC assessment on cadmium in children's metal jewelry.	Government
Vinyl acetate council	Phase I in potential evaluation of vinyl acetate MOA. Conduct validation, cytotoxicity	Collaboration
Waste Management	Support the development of a collaborative effort on 1,4-dioxane risk assessment.	Collaboration
Water Environment Research Foundation	Identify and assemble data on health and ecological endpoints to support an EPA risk	Non-Profit



TERA

Toxicology Excellence for Risk Assessment

a nonprofit corporation dedicated to the best use of toxicity data for risk values

Understanding the Science of Mercury's "Safe" Dose

Michael Dourson

and

Patricia Nance

Toxicology Excellence for Risk Assessment (*TERA*)

June 2004



TERA
Toxicology Excellence for Risk Assessment
a nonprofit corporation dedicated to the best use of toxicity data for risk values

The "Safe" Dose Method As Defined by EPA:

An Reference Dose (RfD) is…

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The estimation of these "Safe" doses involves several judgments



such as...

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"Safe" Doses for Mercury Compared

see www.tera.org/iter

Organization Name	ICF	ATSDR	RIVM	EPA	WHO
"Safe" Dose (µg/kg-day)	0.3 to 1	0.3	0.1	0.1	0.23
Year	**1998**	**1999**	**2000**	**2001**	**2003**
Study	Seychelles	Seychelles	Seychelles	Seychelles, Faroes, New Zealand	Seychelles, Faroes
NOAEL/BMD (µg/kg-day)	0.9 to 3	1.3	1.3	0.9 to 1.5	1.5
Uncertainty Factors	3	4.5	10	10	6.4

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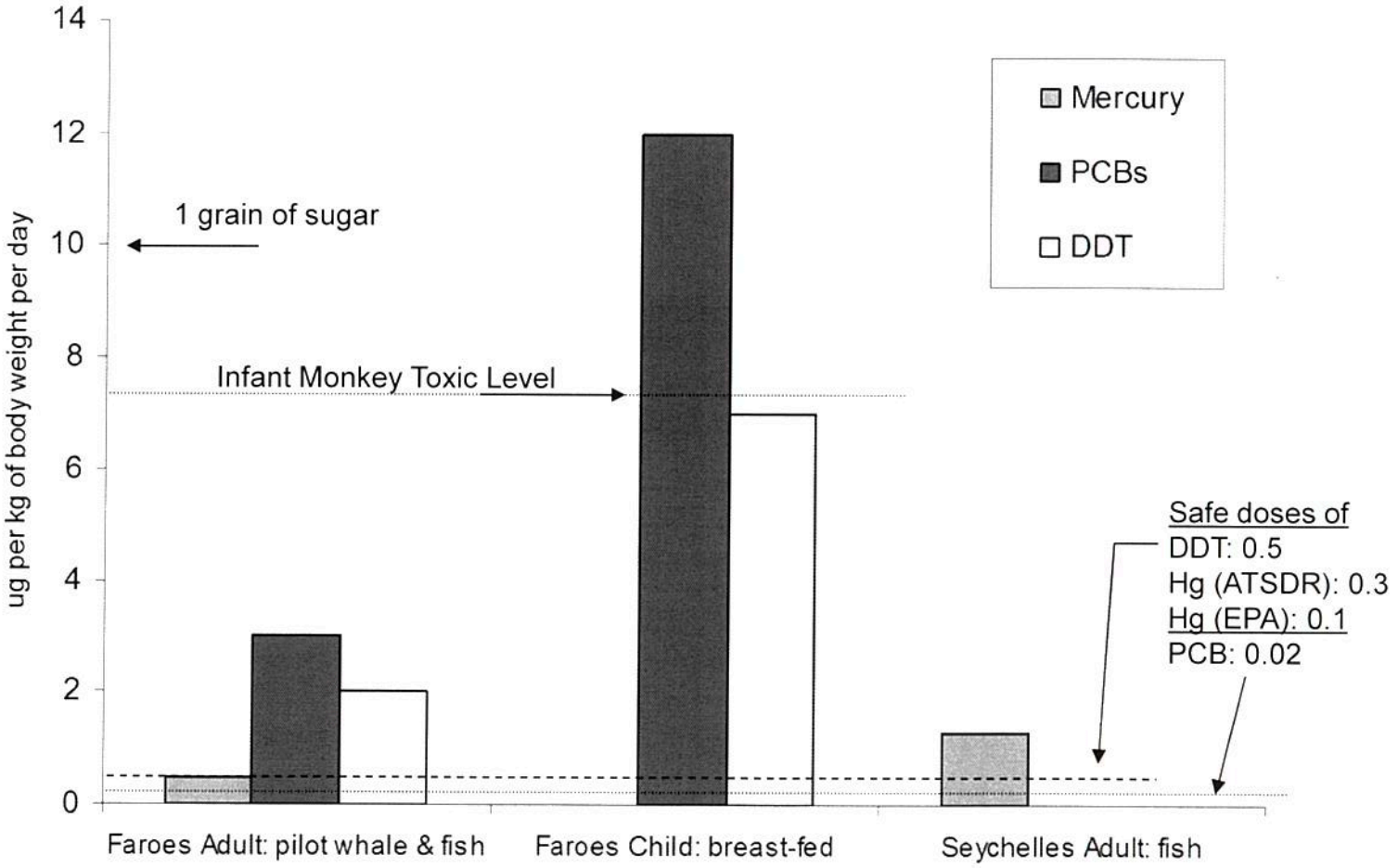
Contaminant Intakes in Faroe & Seychelle Islands

(adapted from Dourson et. al., 2001)



The Faroe islands studies are very good at understanding a mixed exposure. The Seychelle islands studies are very good at understanding exposures to primarily methyl mercury.

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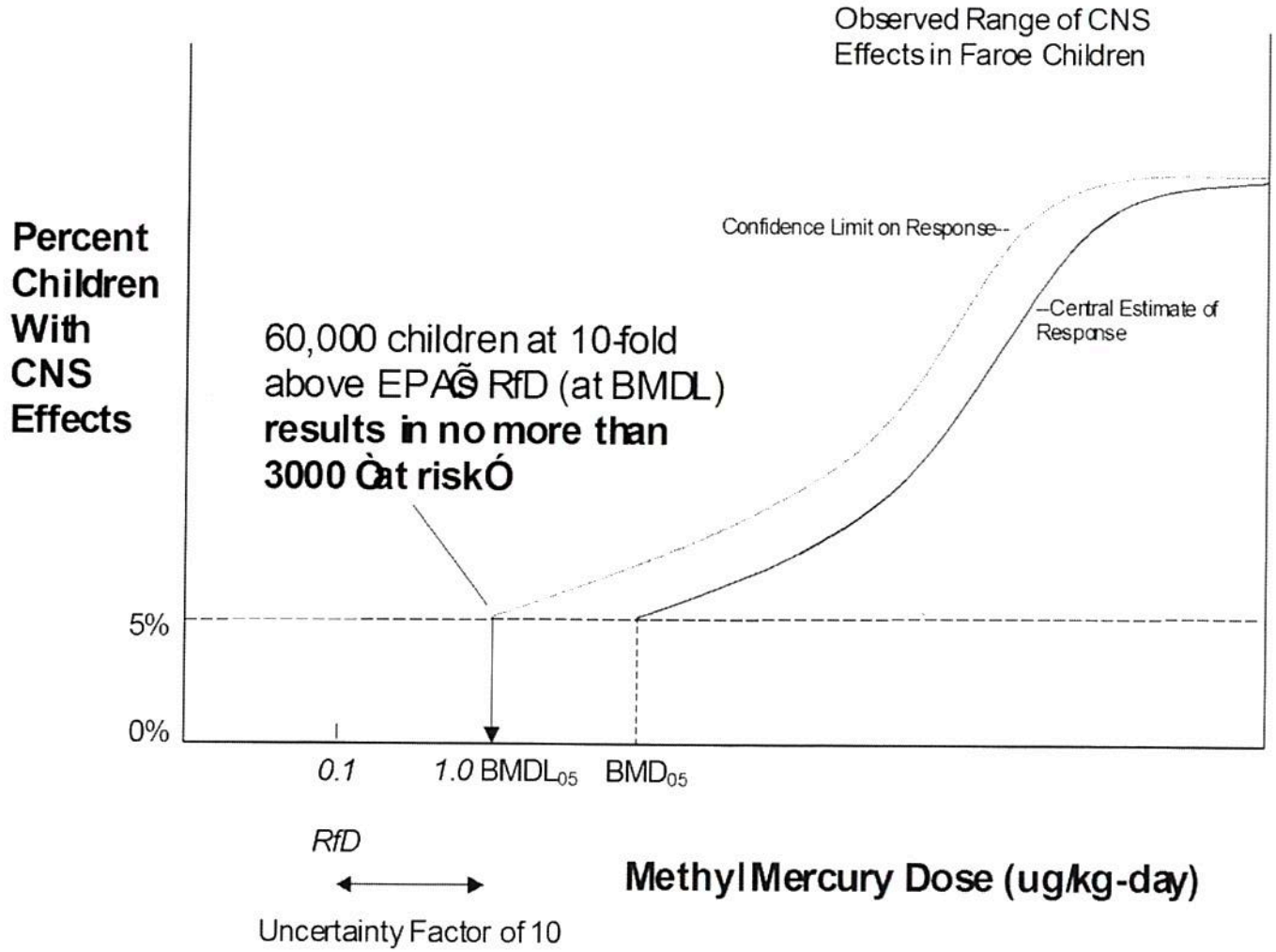

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What Might a Fish Advisory Look Like for Mercury?

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  = Safe Hg Dose x Body Weight ÷ Fish Level

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The Fish Advisories Compared

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Extra slides



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  - developing & communicating risk values
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Partial History of Mercury's "Safe" Dose

Date	Action Taken on Mercury	Michael Dourson's Involvement
1980	EPA Develops RfD of 3 E-4 mg/kg-day	Internal EPA reviewer
1986	EPA Places RfD of 3 E-4 mg/kg-day on IRIS	EPA workgroup chair
1995	EPA Places new RfD of 1 E-4 mg/kg-day on IRIS	Co-author, EPA chair
1998	*ITER* Peer Review for ICF Kaiser RfD of 3 to 10 E-4 mg/kg-day	Chair of independent peer review meeting
2000	*TERA* reviews RfD for the State of Maine & notes heavy PCB contamination of milk	Pro bono reviewer
2000	*TERA* reviews EPA's Draft RfD for the National Food Producers Association	Paid Reviewer
2001	*TERA* publishes on research needs for the mercury RfD, sponsored in part by the EPRI	Co-author
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Understanding the Science of Mercury's "Safe" Dose

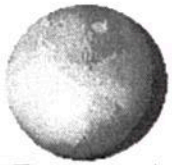
Michael Dourson

and

Patricia Nance

Toxicology Excellence for Risk Assessment (*TERA*)

June 2004



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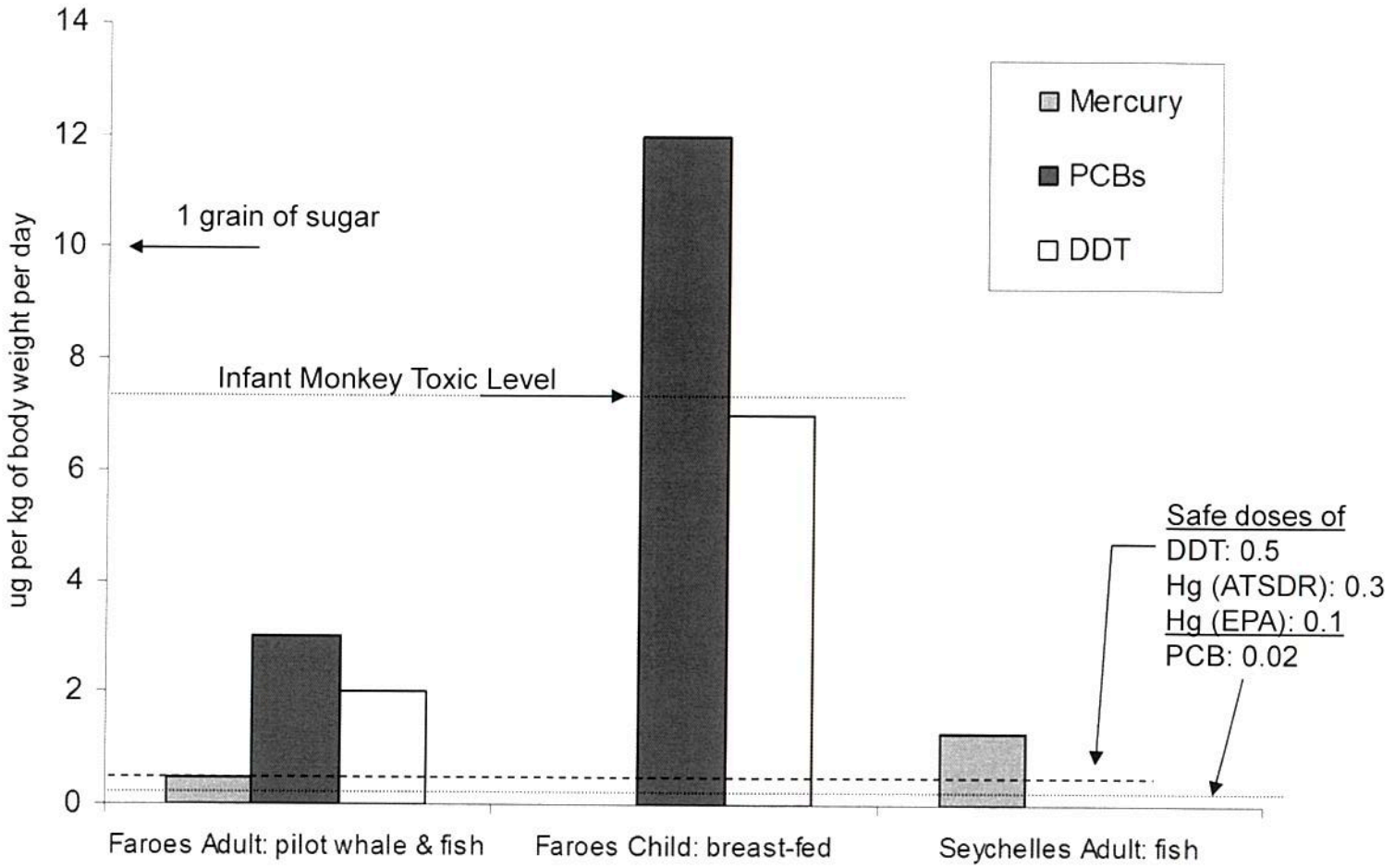

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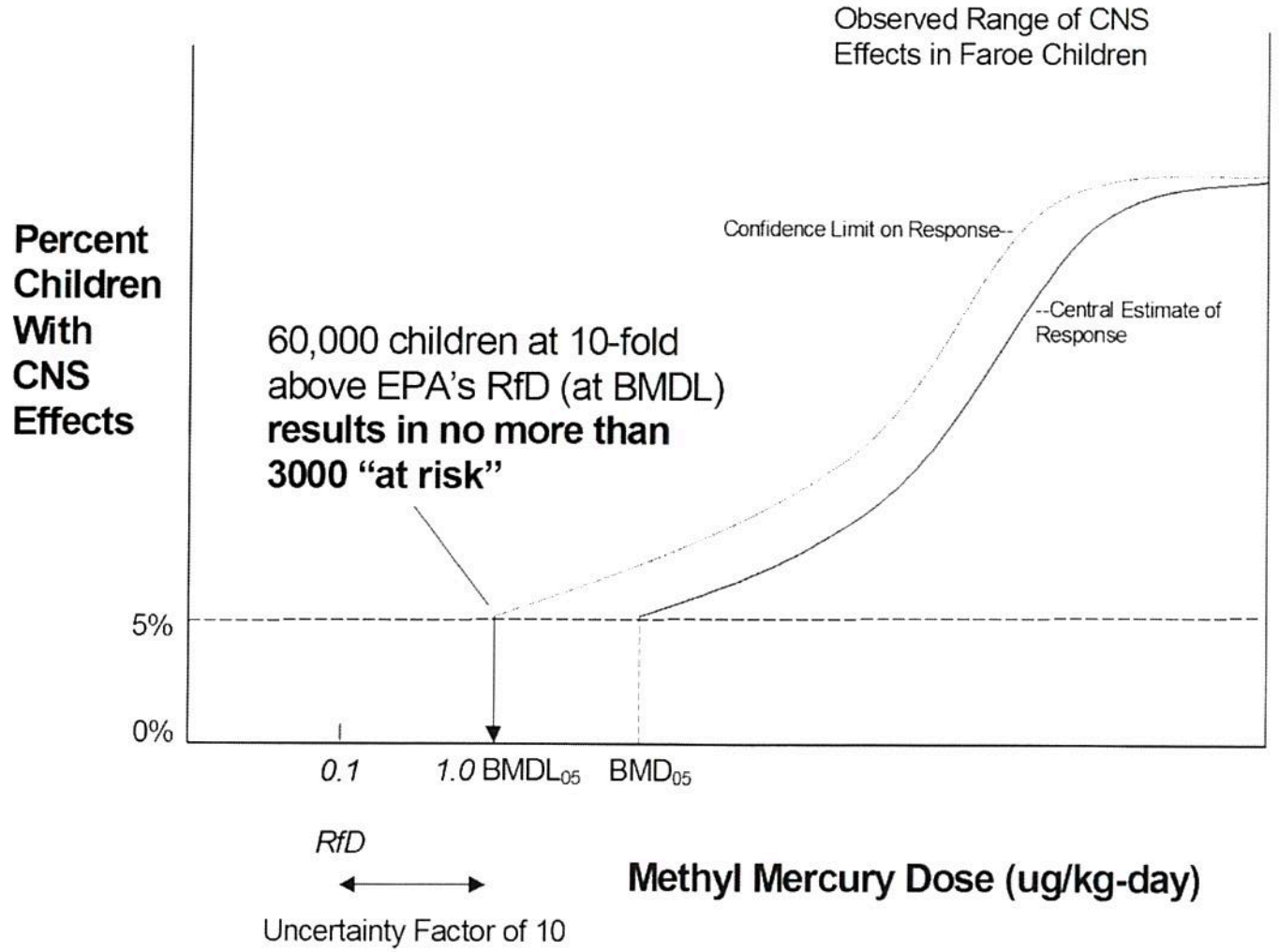

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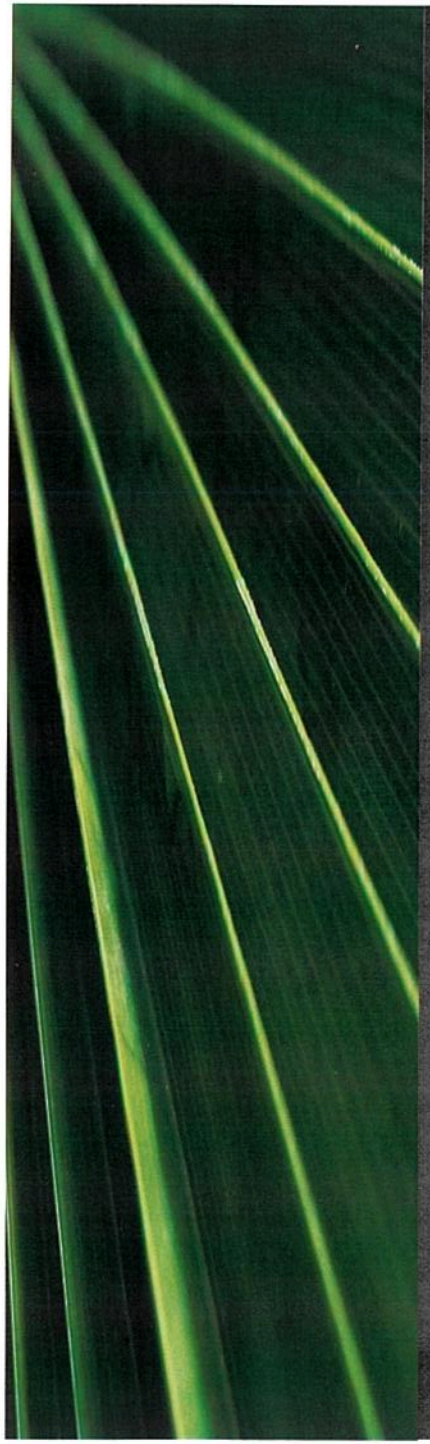


Toxicology Excellence for Risk Assessment

Independent Peer Consultation Hexavalent Chromium Mode of Action Research Plan

Michael Dourson
Toxicology Excellence for Risk Assessment (*TERA*)

Presentation to U.S. EPA's Public Listening
Session on Hexavalent Chromium
November 18, 2010

Independent • Non-Profit • Science
for Public Health Protection

Summary

- An independent science panel conducted a consultation of a proposed chromium VI Mode of Action (MOA) plan.
- Panel gave suggested improvements, but commented that research like this is the future of risk assessment.
- Suggested studies are being completed.
- Panel will peer review study results.

...Peer consultation is credible based on adherence to COI procedures & use of known experts.

...Targeted research is public health protective and consistent with EPA (2005) Guidelines.

Independence
is essential for a credible review

Administrative ground rules to protect independence of the process

- Measures to avoid influence of interested or involved parties on the outcome of the expert consultation/review.
- TERA **independently** selects panel, runs meeting, and prepares report
- Sponsors, authors, and other interested parties do not have direct communication with the panel.

Cr(VI) Review: The Research Plan

Research plan that describes a 6-phase research program to delineate the MOA for Cr VI following oral exposure including

- 90-day drinking water study
- Genomics evaluation via microarray analysis
- PBPK modeling
- In vivo mutation analysis
- In vitro high content imaging analysis
- Integrating MOA analysis into risk assessment

The Charge to Reviewers

- The charge is a critical element of each peer review that serves as an outline for the meeting discussion.

- Purpose of the charge is to identify the **key** scientific issues and guide the panel to thoroughly consider each one; leading to independent panel conclusions.

- Developed by *TERA* with input from the authors and sponsors.

Cr VI Review: The Charge

The 3-page panel charge addressed the research plan:

- –Mode of Action (MOA) Hypothesis
- –General Review of the Study Design
- –Questions on Specific Studies

The full charge is available in the final peer review report, which is available at http://www.tera.org/Peer/Chromium/Chromium.htm

Meeting report is also available at the website above and will be submitted to the public comment docket .

Cr VI Review: Required Expertise

Based on its review of the research plan, TERA determined that the following types of expertise were required for the panel:

- Risk assessment, particularly use of MOA data in risk assessment,
- PBPK modeling,
- Chromium MOA research design and conduct
- Expertise in specialized analysis such as HCA, MRI, genomics etc
- Statistics

- All panelists were screened against COI concerns with sponsors, authors and principal investigators

Cr VI Review: The Panel

- Michael Dourson, Toxicology Excell. for Risk Assess.
- Jeffery Fisher, University of Georgia
- David Gaylor, Gaylor and Associates
- Kirk Kitchin, Environmental Protection Agency
- Bette Meek, Health Canada/University of Ottawa
- Xianglin Shi, University of Kentucky
- Patrick Winter, Washington University

Cr VI Review: The Results – Mode of Action

The panel agreed that dose response and temporal relationships should be examined simultaneously for the following key events:

–cellular uptake of chromium,
–oxidative stress,
–DNA adducts,
–DNA inter- and intra-strand crosslinks,
–mutation,
–cytotoxicity, and
–cell proliferation.

Furthermore, since oxidative stress might be a primary key event, the panel recommended that the research must include more measurements of this endpoint.

Cr VI Review: The Results – Mode of Action (2)

The panel recommended measurement of DNA interaction, such as DNA chromium adducts and DNA inter- or intra-strand crosslinks.

Some panel members also recommended measuring circulating inflammatory markers…

…although it was noted that the microarray study would identify inflammatory changes in the target tissue if those changes were regulated transcriptionally.

Cr VI Review: The Results- Study Design

The panel recommended adding 5 animals/dose, for a total of n=10, for at least the histopathology study to improve the study sensitivity to identify an effect...

...The panel noted that the proposed number of animals was probably adequate for defining the shape of the dose-response curve for continuous data, but was marginal for pairwise comparisons of quantal data.

The increased number of experimental animals may also allow some of the suggested testing for oxidative stress endpoints.

Cr VI Review: The Results- Study Design (2)

The panel agreed with the authors to run the 90-day study using 6 dose groups (including the control)...

... but recommended two unspecified low doses plus the top three doses in the NTP bioassay.

The panel agreed with the authors that the MOA would not likely be different between males and females and, as such, concurred that using only females in the research was sufficient.

Cr VI Review: Next Steps

TERA will organize and conduct peer reviews of 12 MOA studies in a transparent and independent fashion.

Study/Paper	Ready for Review
Mouse 90 day	November, 2010
Mouse genomics, Mouse DNA Adducts	January, 2011
Rat DNA Cr Adducts, Mouse & Rat PK PK Data, Human PK	March, 2011
Rat 90 day, Rat Genomics In vivo Mutation, Mode of Action High Content Imaging	April, 2011

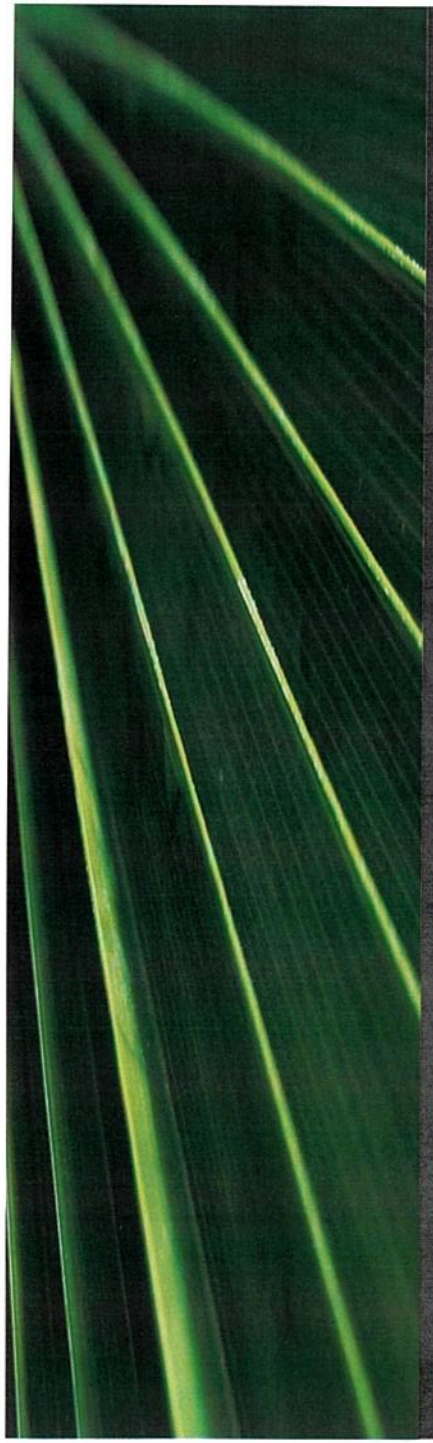
Cr VI Review: Next Steps

- The panel for each review will be composed of 3 to 5 appropriate experts and screened for COI issues...

  ...We anticipate having to add reviewers in areas of toxicokinetics, modeling, genomics, genotoxicity, and high content imaging.

- TERA will create a single core set of charge questions. Separate reports will be prepared for each review, and will include the combined reviewer written comments for each question.

- EPA's and others' thoughts on areas to be covered in these charge questions would be welcome.



Toxicology Excellence for Risk Assessment

Toxicology Excellence for Risk Assessment (*TERA*)

The final peer review report of the Chromium MOA research plan is located at http://www.tera.org/Peer/Chromium/Chromium.htm

Questions? Contact
Joan Strawson
Phone: 919-528-9788
Email: strawson@tera.org

Independent • Non-Profit • Science
for Public Health Protection

Extra Slides

Toxicology Excellence for Risk Assessment (TERA)

Statement of Purpose & Mission
Founded in 1995

Toxicology Excellence for Risk Assessment (*TERA*) is a non-profit, 501(c)(3) corporation organized for scientific and educational purposes.

The mission of *TERA* is to support the protection of public health by developing, reviewing and communicating risk assessment values and analyses, improving risk methods through research, and educating risk assessors and managers and the public on risk assessment issues.

www.tera.org

TERA

Staff of board certified toxicologists with extensive experience in risk assessment, toxicology, and peer review.

- Prepare high quality risk assessments and organize expert peer reviews
- Improve the underlying methods for risk assessment through research and publication
- Distribute peer reviewed risk values through the International Toxicity Estimates for Risk (*ITER*) database - www.tera.org/iter
- Train others on state-of-the-science risk methods.

Mix of work is 65% government & NGO, and 35% industry & Industry related



What is Peer Review?

- For risk assessment products, it involves an in-depth assessment of the assumptions, calculations, alternate interpretations, methodology, and conclusions.
- Peer review panels seek to reach consensus or common agreement regarding the adequacy of the product reviewed.



TERA's Independent Peer Review Process

1. Scientific screen of the documents to insure they are ready for review, and to identify critical scientific issues and questions for development of the charge and needed expertise for panel.
2. Develop the scientific charge to the panel.
3. Identify appropriate expert candidates and select panel members. Identify conflicts of interest and biases.
4. Schedule meeting and logistical arrangements.
5. Prepare meeting report of discussions, conclusions, and recommendations.
6. Distribute the results to the public.

Panel Selection Procedures

- Identification of scientific expertise necessary to address key issues in charge.
- Search for appropriate candidates, evaluate credentials
- Contact most promising for interest and availability. Query them on conflicts of interest and biases.
- Select a panel that is balanced with regard to necessary disciplines and has a diversity of perspectives.

Conflict of Interest (COI)

An independent panel is essential for a credible scientific review

TERA follows National Academy of Sciences (NAS) procedures for panel selection and conflict of interest.

- NAS defines a conflict of interest as *"any financial or other interest which conflicts with the service of the individual because it (1) could significantly impair the individual's objectivity or (2) could create an unfair competitive advantage for any person or organization. ...The term 'conflict of interest' means something more than individual bias. There must be an interest, ordinarily financial, that could be directly affected by the work of the committee."*

Bias

- *"Questions of lack of objectivity and bias ordinarily relate to views stated or positions taken that are largely intellectually motivated or that arise from the close identification or association of an individual with a particular point of view or the positions or perspectives of a particular group."* [NAS]
- Biases are not necessarily disqualifying, but a balance of potentially biasing backgrounds or professional or organization perspectives is needed.
- Some potential sources of bias may be so substantial that they would prevent an individual from considering others perspectives or relevant evidence contrary to their strongly held position.

Meeting Structure

1. Introductory Remarks, Ground Rules and Conflict of Interest discussion

2. Short presentation by authors

3. Panel asks clarifying questions of authors

4. Chair facilitates in-depth discussion of each charge question by panel. Authors available to answer panel questions.

Michael L. Dourson, PhD, DABT, FATS
Toxicology Excellence for Risk Assessment (TERA)

Dr. Dourson was selected for this panel for his expertise in dose-response assessment & mode of action analysis, and familiarity with U.S. EPA's carcinogen risk assessment guidelines. In addition, Dr. Dourson has extensive experience effectively chairing panels.

Disclosure: Dr. Dourson is the President of *TERA*, which is under contract with ToxStrategies to independently organize and conduct this peer review. See further discussion on website. In 1995, Dr. Dourson testified in a legal case about the risk assessment approach used by U.S. EPA to develop the maximum contaminant level (MCL) for chromium. *TERA* has concluded that this is not a conflict of interest or a bias because Dr. Dourson's testimony was limited to explaining how existing U.S. EPA standards were derived, and he did not provide his professional opinion on the toxicity of chromium at concentrations under discussion.

Jeffery Fisher, PhD, FATS, University of Georgia

Dr Fisher was selected for this panel for his expertise in the development of physiologically based pharmacokinetic models and his experience in serving on panels of expert scientists in review of risk assessments. *Disclosure*: None.

David Gaylor, PhD, FATS, Gaylor and Associates

Dr Gaylor was selected for this panel for his expertise in biostatistics, dose-response assessment, and for his experience in serving on panels of expert scientists in review of risk assessments.

Disclosure: Dr. Gaylor indicated that he is a past employee of General Electric, Co. and General Dynamics, Co. In addition, he has consulted in the past with 3M Corporation (2002-May 2009). All three companies are currently members of Aerospace Industry Association, which is the Sponsor of the review. *TERA* concluded that there is no conflict of interest or bias because none of the past work involved chromium and Dr. Gaylor has no current, ongoing financial relationship with these companies.

Kirk Kitchin, PhD, DABT, U.S. EPA

Dr. Kitchin was selected for this panel for his expertise in metals carcinogenicity, cancer mode of action research, and use of genomics in risk assessment.

Disclosure: None.

Bette Meek, M.Sc., University of Ottawa

Ms. Meek was selected for this panel for her expertise in genotoxicity, dose-response assessment, and mode of action analysis in a regulatory context. In addition, Ms. Meek has experience in serving on panels of expert scientists in review of toxicity assessments.

Disclosure: None.

Xianglin Shi, PhD, University of Kentucky

Dr. Shi was selected for this panel due to his expertise in chromium mode of action research, particularly for his understanding of the role of oxidative stress and DNA damage in chromium toxicity. Dr. Shi also has expertise in genomics, proteomics, transcriptional analysis, and imaging.

Disclosure: None.

Patrick Winter, PhD, Washington University

Dr Winter was selected for this panel for his expertise in molecular imaging.

Disclosure: None.

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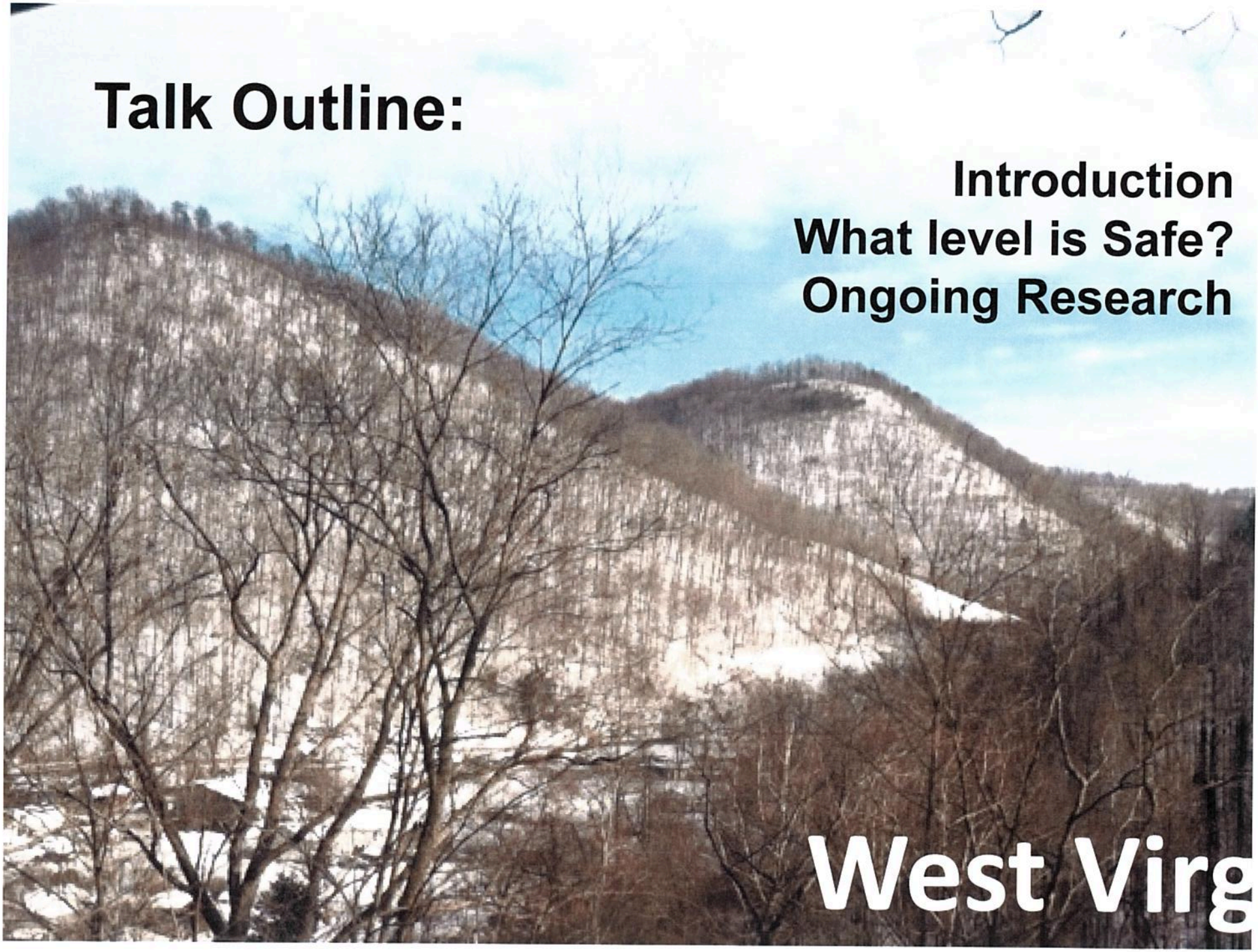
TOXICOLOGY EXCELLENCE FOR RISK ASSESSMENT

WV TAP
WEST VIRGINIA TESTING ASSESSMENT PROJECT

Short Term Health Advisories for Elk River Crude MCHM Spill

Michael Dourson
Toxicology Excellence for Risk Assessment

British Society of Toxicology
April 20, 2015
St. Johns Hotel, Solihull, England


Talk Outline:
Introduction
What level is Safe?
Ongoing Research
West Virg



Freedom Industries, Inc.

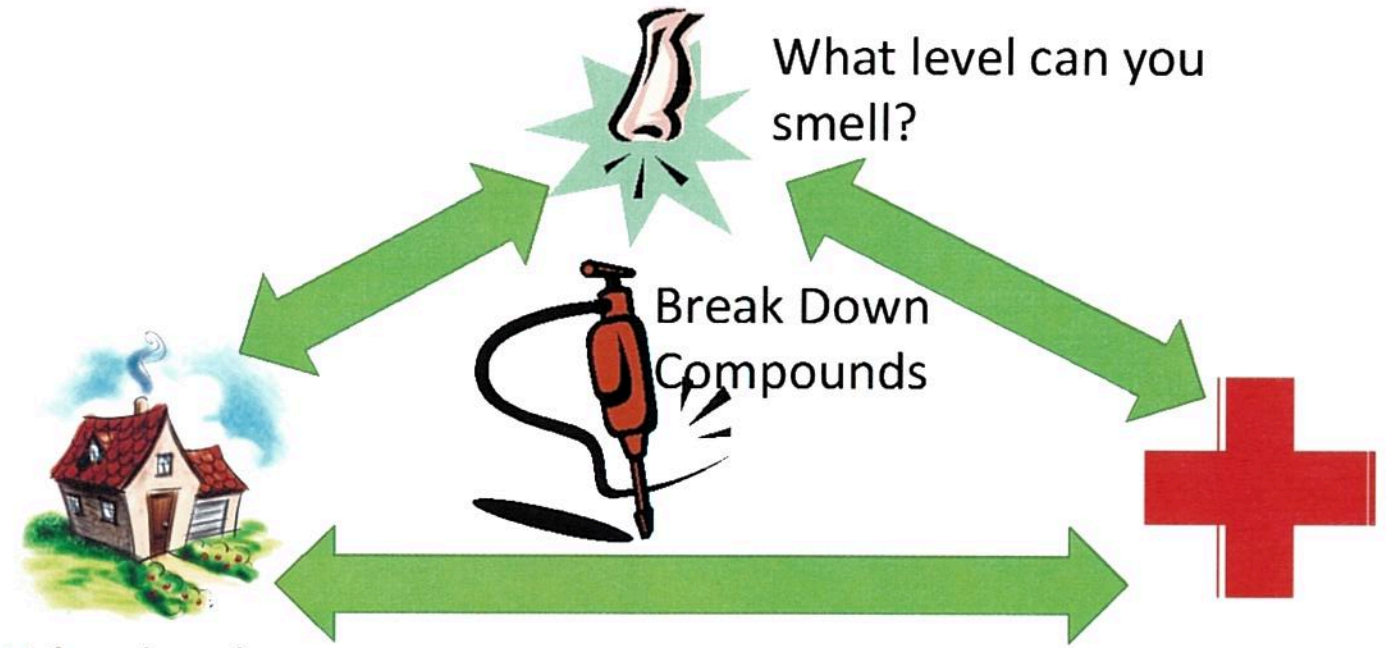
Spill occurred from tank 396 and later discovered also from 397

Window of Detection and Action



- About 1 mile from intake.
- Travel time estimated to be 1.1 – 1.8 hours
- Spill may have started a few days before it was detected.
- First detection, human olfactory sensors.
- Freedom Inc. knew about the spill and was trying to clean it up when it was discovered by state DEP

The Structure and Rationale of WVTAP



What Level is Safe?

TASK: Independently evaluate the safe levels of MCHM and PPH for all members of the population for all intended uses

- Comprehensive literature review of relevant toxicological literature (Adams, 2014)
- Health Effects Expert Panel on March 31, 2014 in Charleston, West Virginia: evaluate available toxicity data and health advisories

What Was Spilled?

- **Crude MCHM (Eastman) 88.5%**
  - Used in coal processing
  - The Crude MCHM is a mixture containing:
    - **4-Methyl-1-cyclohexanemethanol (MCHM) @ 68-89% (w/w);**
    - 4-(Methoxymethyl) cyclohexane methanol (**MMCHM**) @ 4-22% (w/w) ;
    - Methyl 4-methylcyclohexane-1-carboxylate (**MMCHC**) @ 5% (w/w);
    - 1,4-Dimethyl cyclohexanedicarbonate (**DMCHDC**) @ 1-2% (w/w);
    - 1,4-Cyclohexanedimethanol (**CHDM**); and
    - Methanol (**MeOH**) @ 1-2% (w/w).

Specific Charge Questions to Panel

1. Given data now available, what would be appropriate screening levels for MCHM and PPH in drinking water?
2. What additional data, analyses, or studies might reduce uncertainty and provide greater confidence?
3. How should the presence of multiple chemicals in the release to the Elk River be considered?
4. Are the screening values protective for all potential routes of exposures (i.e., ingestion, dermal and inhalation)?
5. Other issues?

WV TAP Expert Panel

(affiliations listed for identification purposes only)

Expertise in toxicology, risk assessment, deriving risk values for water contaminants, and water quality and distribution systems.

- **Dr. Michael Dourson, chair,** Toxicology Excellence for Risk Assessment, Cincinnati, OH, USA
- **Dr. Shai Ezra,** Mekorot, Israel National Water Company Ltd, Tel Aviv, Israel
- **Dr. James Jacobus**, Minnesota Department of Health, Saint Paul, MN,USA
- **Dr. Stephen Roberts**, University of Florida, Gainesville, FL. USA
- **Dr. Paul Rumsby**, National Centre for Environmental Toxicology at WRc plc, Swindon, UK

Available Data on MCHM – very limited

- Crude MCHM, acute gavage in rats, 250 - 1000 mg/kg-day; Possible hematuria (Eastman 1998, 1999)
- Pure MCHM, gavage in rats Eastman (1990)
  - 0, 25, 100, and 400 mg/kg/day, 5 days a week, for 4 weeks
  - 400 mg/kg/day – anemia (F), kidney and liver effects
  - NOEL 100 mg/kg/day
  - Proprietary, OECD and GLP
  - **Study used by CDC**

Critical Effect of MCHM?

Absolute kidney weights for male rats heavier at 25 mg/kg.
Relative kidney weights statistically heavier for all treated males.

No differences were seen in female rats.

Relative and absolute changes might be adverse. However:

- Higher doses did not show statistically significant increase in absolute kidney weights;
- Kidney weights, both relative and absolute, did not show a dose-related trend; and
- Low dose effects did not have matching clinical changes or histopathology, which when compared with organ weight changes, are more definitive.

CDC Advisory MCHM

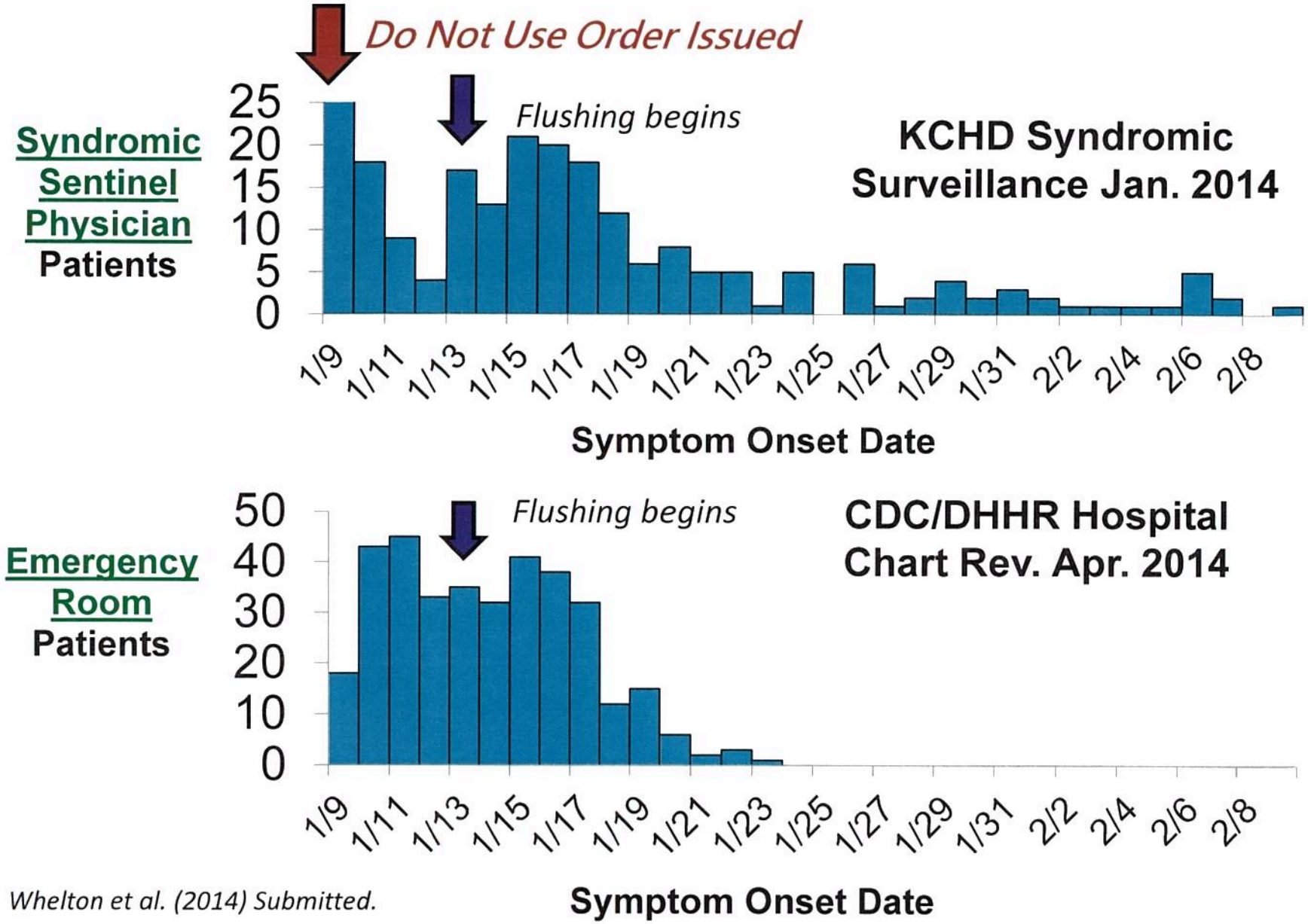
- January 9, 2014, January 20, 2014
- Methodology: EPA DW advisory methods (Donohue and Lipscomb, 2002)

DW Advisory Level ≤ (NOEL × BW) / (UF × Intake)

- NOEL: 100 mg/kg-day (Eastman, 1990)
- Consumption:
  - BW of a child: 10 kg
  - Intake: 1 liter/day, water intake for child.
- Uncertainty Factors (UF): 1000 (UFA, UFH, UFDB)
- **1 ppm or 1000 ppb screening level**

CDC (2014) "Information about MCHM - 2014 West Virginia Chemical Release" http://www.bt.cdc.gov/chemical/MCHM/westvirginia2014/mchm.asp . January 20

Plumbing System Flushing: REAL-TIME Syndromic Surveillance Would Have Revealed Illnesses were being Caused



Whelton et al. (2014) Submitted.

WV TAP Expert Panel

- CDC used traditional methods and reasonable assumptions to develop their screening levels

- The Panel considered additional exposure routes:
  - Direct ingestion of water, including formula-fed infants
  - Inhalation from showering and cooking
  - Skin exposure to water uses in the house
  - Incidental exposures, including brushing teeth, watering plants.

- The Panel determined formula-fed infants to be the most highly exposed population/life stage

Panel Advisory for MCHM

- Methodology – not constrained, used full experience
- NOEL: 100 mg/kg-day (Eastman, 1990)
  - Adjusted to 71 mkd for 5 day/week dosing
- Consumption: 0.285 liters/kg bw (95th percentile)
  - Formula fed infant - most exposed life stage
- Allow for other possible sources and routes of exposure (i.e., dermal, inhalation): factor of 0.5
- Uncertainty Factors (UF): 1000 (UFA, UFH, UFDB)

Panel Calculated Level for MCHM

DW Advisory Level = (NOEL × BW) / (UF × Intake)

→ DW Advisory Level ≤ [(NOEL) / (UF × Intake/BW)] · Exposure factor

where:

DW Advisory Level is the drinking water advisory level (µg/L or ppb)

NOEL = No Observed Effect Level in the experiment = 71 mg/kg/day

UF = uncertainty factors (unitless)

- for differences between humans and animals (10x)
- to account for more sensitive humans (10x)
- to account for in the toxicity database data (10x)

Intake / BW = water consumed daily by a bottle-infant (0.285 L/kg·d)

Exposure factor = to account for other sources of exposure (0.5)

4-week DW Advisory Level = (NOEL) / (UF × Intake/BW) · Exposure factor

= [(72 mg/kg/d)] / [(10×10×10) = 0.0072 (rounded to 0.07)

0.07 mg/kg-day / (0.285 L/kg·day)] · 0.5 = 0.123 mg/L (rounded to 120 µg/L)

PPH and DiPPH

- CDC
  - PPH: 1200 ppb
  - DiPPH: Limited data suggest similar or lower toxicity, the PPH screening value would also be protective for DiPPH.
- Expert Panel
  - PPH: 880 ppb
  - DiPPH:260 ppb

  See expert panel report for details - http://www.tera.org/Peer/WV/WV%20Expert%20Report%2012%20May%202014.pdf

What about the Mixture?

- Toxicity data on specific chemical mixtures are rarely available.
- Toxicity of mixtures in spill could be approximated by a simple additive approach (MCHM, PPH, DiPPH, etc) following US EPA's mixtures guidelines (US EPA 1986 and 2000)
- For example, it is reasonable to assume that the toxicity of the mixture (Crude MCHM) would be similar to the pure MCHM.

Research Needs

1. Determine MCHM potential to cause skin irritation.
2. Conduct toxicology studies for MCHM in pregnant animals.
3. Organize all available data on exposures and health effects (from immediately following the spill) to facilitate the estimation of initial conditions.
4. Pending results of #2 and #3, consider the need for long term health effects study.
5. Determine chemical fate and transport within the treatment plant and water distribution system.

US National Toxicology Program
Research Progress

February 2015 Update for 5-Day *In Vivo* Micronucleus Assay

- The results for all three chemicals were negative; none increased the frequency of micronucleated red blood cells in male rats after oral administration for five days.

December 2014 Update for **Prenatal Developmental Toxicity**

- 150 to 900 mg/kg-day of MCHM was gavaged to pregnant Harlan Sprague Dawley rats from gestational day 6 to 20.
- The results indicate increased post-implantation pregnancy loss occurred at doses that induced maternal toxicity.

Summary

- The WV TAP Expert Panel reviewed the CDC and WV screening values and reached conclusions that are not incompatible with the CDC values.

- Panel used more refined methods, including an adjustment to account for dermal and inhalation exposure.

- MCHM concentrations below 120 ppb are safe for ALL members of the community for ALL intended uses for up to 1 month of exposure.

Acknowledgements

- WV TAP Technical Team
  - Jeffrey Rosen, Program Manager
  - Andrew Whelton, University of South Alabama
  - Craig Adams, Utah State University

- Funding and support from:
  - West Virginia Bureau for Public Health (WVBPH)
  - West Virginia Department of Health and Human Resources (WVDHHR).

More Information and References

Expert Panel Report

- http://www.tera.org/Peer/WV/WV%20Expert%20Report%2012%20May%202014.pdf

WVTAP Web Site

- http://www.dhsem.wv.gov/wvtap/test-results/Pages/default.aspx

Questions?

WVTAP Literature Review

Adams, C., Whelton, A., Rosen, J. (2014) "Health Effects for Chemicals in 2014 West Virginia Chemical Release: Crude MCHM Compounds, PPH and DiPPH,"

Public report by West Virginia Testing Assessment Project (WV TAP) to the State of West Virginia.

Very limited data for MCHM

Additional Question by WV for the Expert Panel

- **Was the additional safety factor applied by the State of West Virginia protective of public health, based on available data?**

  - CDC initial screening value of 1 ppm (1,000 ppb) 4-MCHM
  - WV screening level later set at 10 ppb

Was the additional safety factor applied by the State of West Virginia was protective of public health, based on available data?

--CDC initial screening value of 1 ppm **(1,000 ppb)**

--WV screening level later set at **10 ppb**

- Panel derived short-term advisory of **120 ppb**
- Protect all portions of the population (inc. infants, children, pregnant women)
- Protect for exposures from direct ingestion, inhalation from showering and household water use, dermal exposure.
- Appropriate for apply to exposure situations of 1 day up to 3 months.

What Was Spilled?

- **DOW PPH Basic 7.3%**
  - It is reported that the source of the Freedom Industries' PPH was DOW PPH Basic
  - DOW Basic contains:
    - Dipropylene glycol phenyl ether (**DiPPH**) concentration at between 40% and 85%;
    - Propylene glycol phenyl ether (**PPH**); and
    - Other compounds.

Key Studies for PPH

- Oral toxicological data on PPH include:
  - A 90-day drinking water study (and 28-day range finding study) in rats (OECD 408 – BASF AG 1997a) study used by PANEL
  - A two-generation study drinking water study in rats (OECD 416 – BASF 2000)
  - A prenatal developmental toxicity studies using gavage with rats (OECD 414 – BASF AG 2000) and rabbits (OECD 414 – BASF AG 1995 and OECD 2006c) study used by CDC
  - In vitro and in vivo genetic toxicity tests

WV TAP Panel Screening Level for PPH

DW Advisory Level ≤ (NOEL × BW) / (UF × Intake)

→ DW Advisory Level ≤ [(NOEL) / (UF × Intake/BW)] · Exposure factor

where:

DW Advisory Level is the drinking water advisory level (µg/L or ppb)

NOEL = No Observed Effect Level in the experimental species = 146 mg/kg/day (from 90-day DW study)

UF = uncertainty factors (unitless)

for differences between humans and animals (10x)

to account for more sensitive humans (10x)

to account for in the toxicity database data (3x)

Intake / BW = water consumed daily by a bottle-infant (0.285 L/kg·d)

Exposure factor = factor to account for other sources of exposure other than ingestion (i.e., inhalation, dermal) (0.5)

90-day DW Advisory Level = (NOEL) / (UF × Intake/BW) · Exposure factor

= [(146 mg/kg/d)] / [(10×10×3) = 0.49 (rounded to 0.5 for a short term RfD)

0.5 mg/kg-day / (0.285 L/kg·day)] · 0.5 = 877 (rounded to 880 µg/L or ppb)

CDC	PANEL
No Observed Adverse Effect Level (NOAEL) = 40 mg/kg-day teratology study in rats, maternal toxicity	NOAEL = 146 mg/kg-day ((ECHA, 2014), 90-day DW study in rats
Uncertainty Factor = 10H, 10A, 10D	Uncertainty Factor = 10H, 10A, 3D (missing second repeat dose tox study)
Intake = 1 liter water/day (child) Body Weight = 10 kg (child)	0.285 liters/kg bw (95th percentile) Formula fed infant most exposed life stage
Ingestion of water only	RSC = 0.5 to allow for other possible sources and routes of exposure (i.e., dermal, inhalation)
PPH Screening Level = 1200 ppb	PPH Short-Term Health Advisory = 880 ppb

10H = 10x human variability; 10A = 10x animal to human extrapolation; 10D = 10x data base sufficiency

WV TAP Panel Screening Level for DiPPH

DW Advisory Level ≤ (NOEL × BW) / (UF × Intake)

→ DW Advisory Level ≤ [(NOEL) / (UF × Intake/BW)] · Exposure factor

where:

DW Advisory Level is the drinking water advisory level (µg/L or ppb)

NOEL = No Observed Effect Level in the experimental species = 146 mg/kg/day (from 90-day DW study)

UF = uncertainty factors (unitless)

for differences between humans and animals (10x)

to account for more sensitive humans (10x)

to account for in the toxicity database data (10x)

Intake / BW = water consumed daily by a bottle-infant (0.285 L/kg·d)

Exposure factor = factor to account for other sources of exposure other than ingestion (i.e., inhalation, dermal) (0.5)

90-day DW Advisory Level = (NOEL) / (UF × Intake/BW) · Exposure factor

= [(146 mg/kg/d)] / [(10×10×10) × (0.285 L/kg·d)] · 0.5 ≤ 256 or 260 µg/L (ppb)

Note short term Reference Dose not calculated since toxicity is based on PPH.



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Environmental Risk Assessment…
…in the 21st Century

Michael L. Dourson, Ph.D., DABT, ATS



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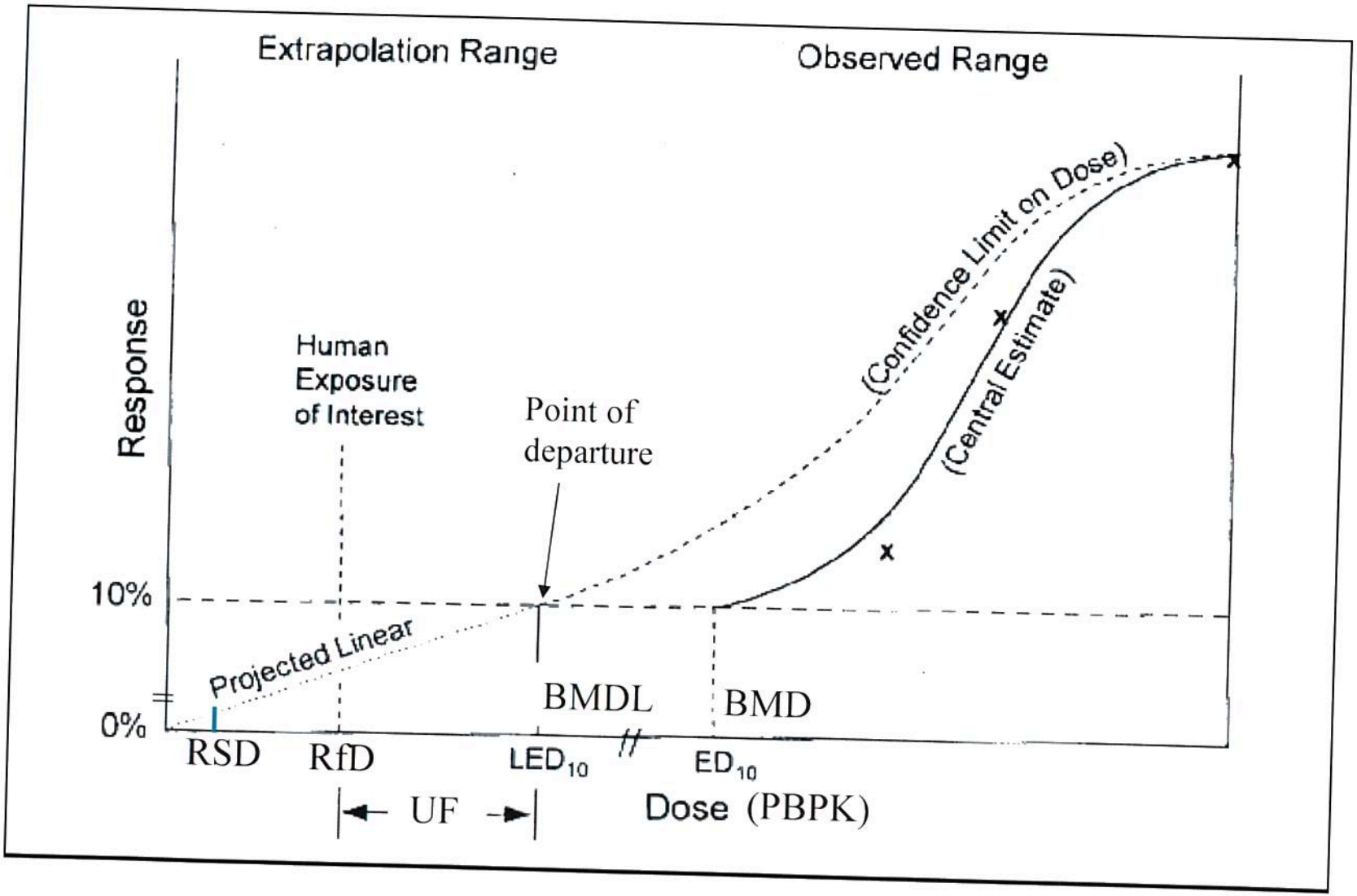
Seminar Overview

- Know traditional risk methods…cold
  - Think like a clinician
  - Challenge non-experts
- Use contemporary methods often
  - BMD, categorical regression, CSAF, PBPK
- Create future by collaboration and research
  - Hang together, or hang separately (paraphrased B. Franklin)
  - Focus on collaboration among agencies

Do You Know the Traditional Methods?

Adapted from EPA, 1999



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Do You Know the Traditional Methods?

- If we had a array of effects that were all linked into one syndrome of toxicity, what would be the point of departure for a dose response assessment?
- If we had only 8 fingers, what would be the uncertainty factor covering experimental animal to human and within-human variation?

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Traditional: Critical Effect

- Risk assessment is… preventive medicine. Thus, involve clinicians in judgment of critical effect, or at least think like one…
  - …but do not let them do the dose response assessment!
  - 25 years in the clinic does not prepare one to estimate an RfD, even if the critical effect appears to lie within your area of expertise.
- Critical effect is…

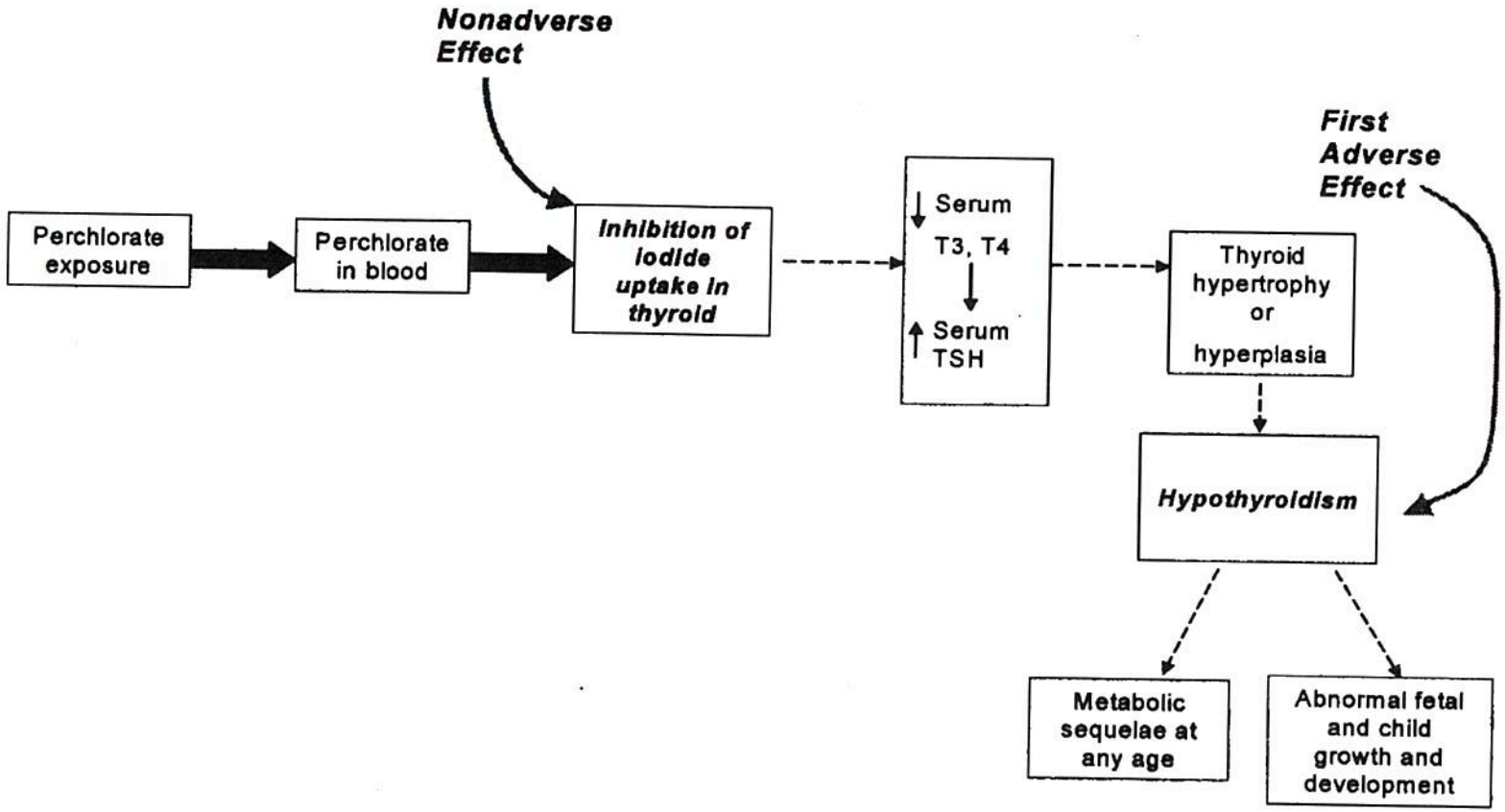

FIGURE 5-2 Committee's suggested mode-of-action model for perchlorate toxicity in humans indicating first adverse effect in the continuum.

NAS, 2005. Health implications of perchlorate ingestion.



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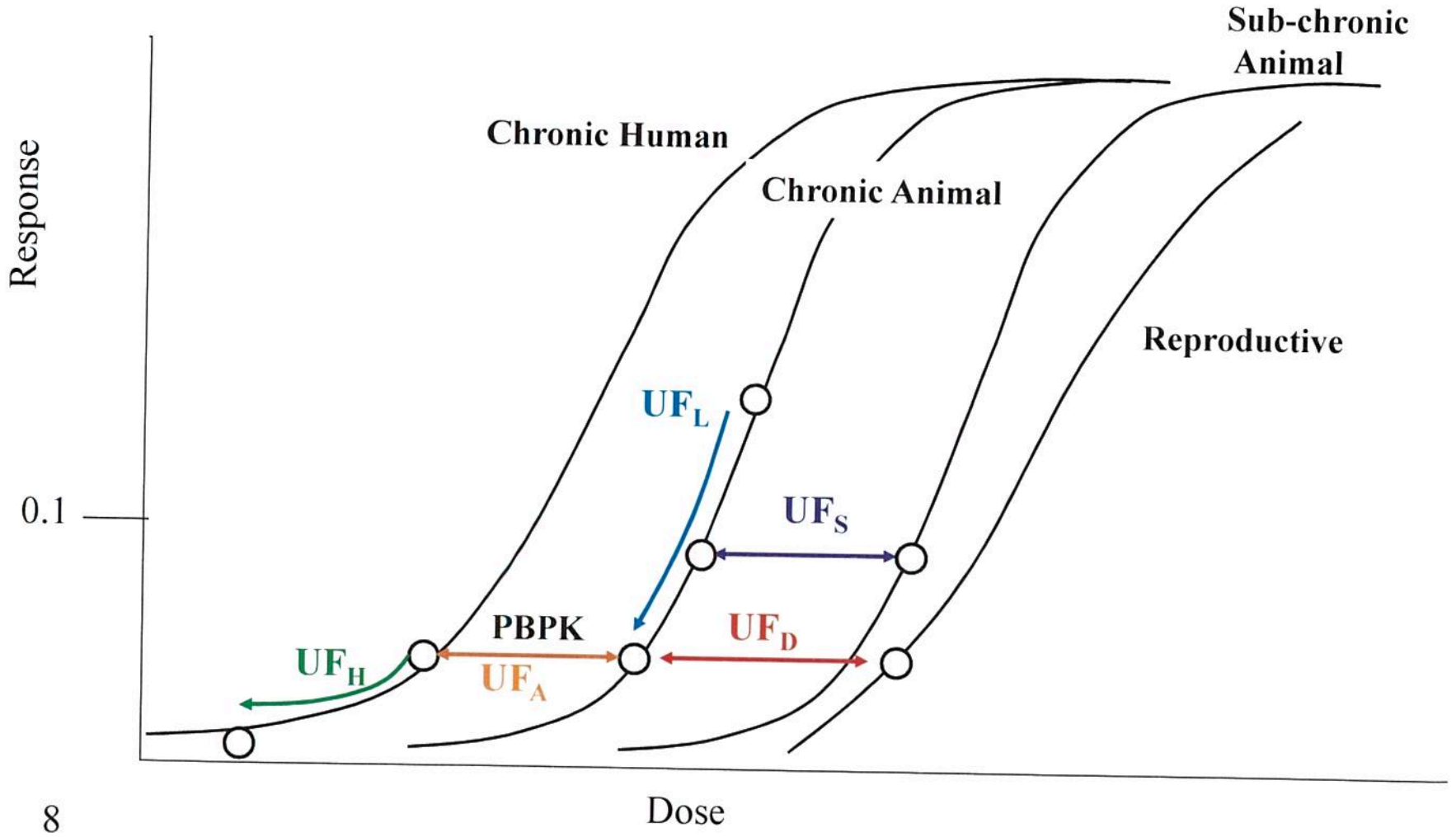
Traditional: Uncertainty Factors

- Uncertainty factors for within human, experimental animal to human, LOAEL to NOAEL, subchronic to chronic and lack certain data.

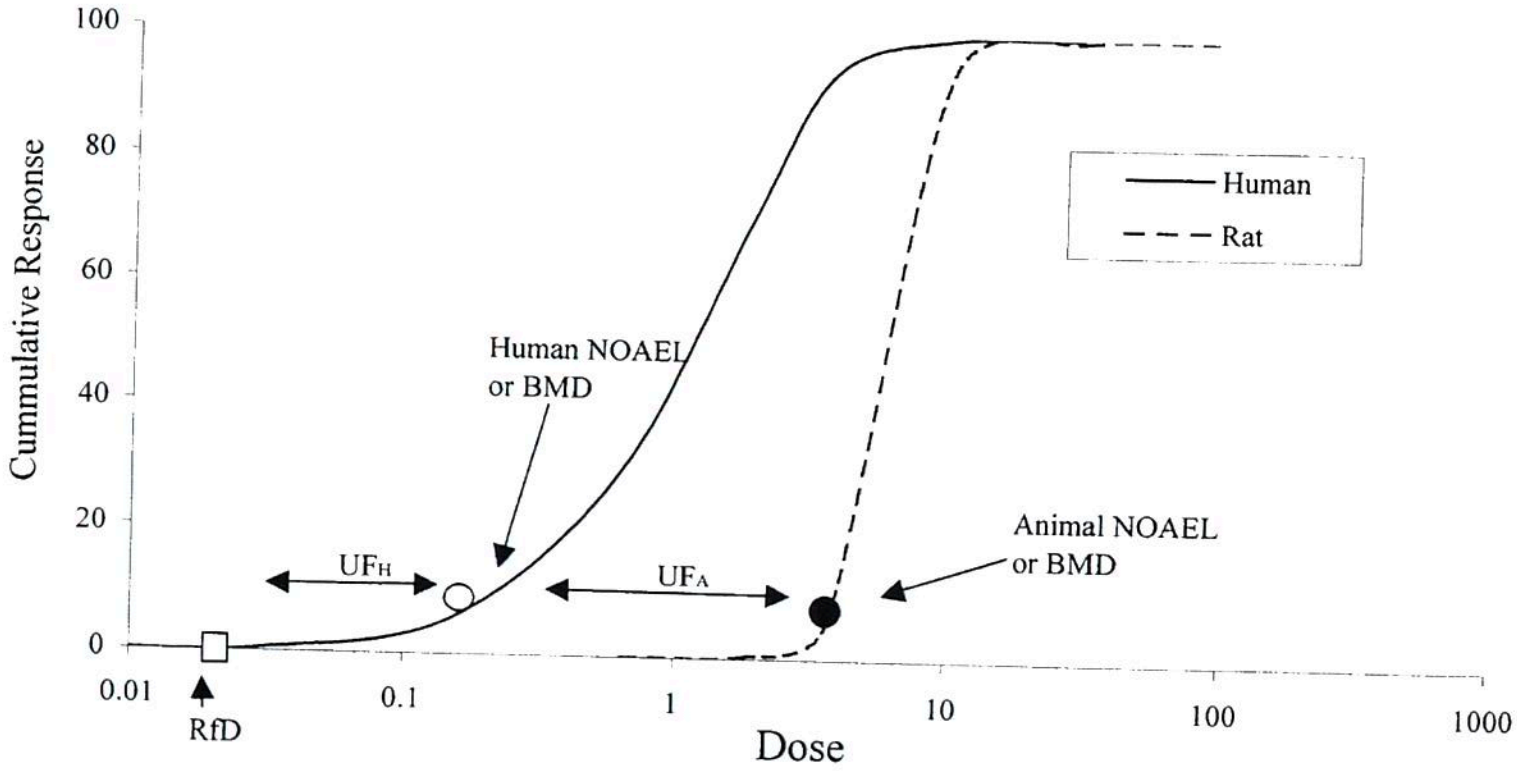
- Misconceptions:
  - Studies with small "n" are not useful.
  - An uncertainty factor of 10-fold with human data is often not enough.

Areas of Uncertainty to Consider in Noncancer Dose Response Assessment



Factor of 10 Enough?

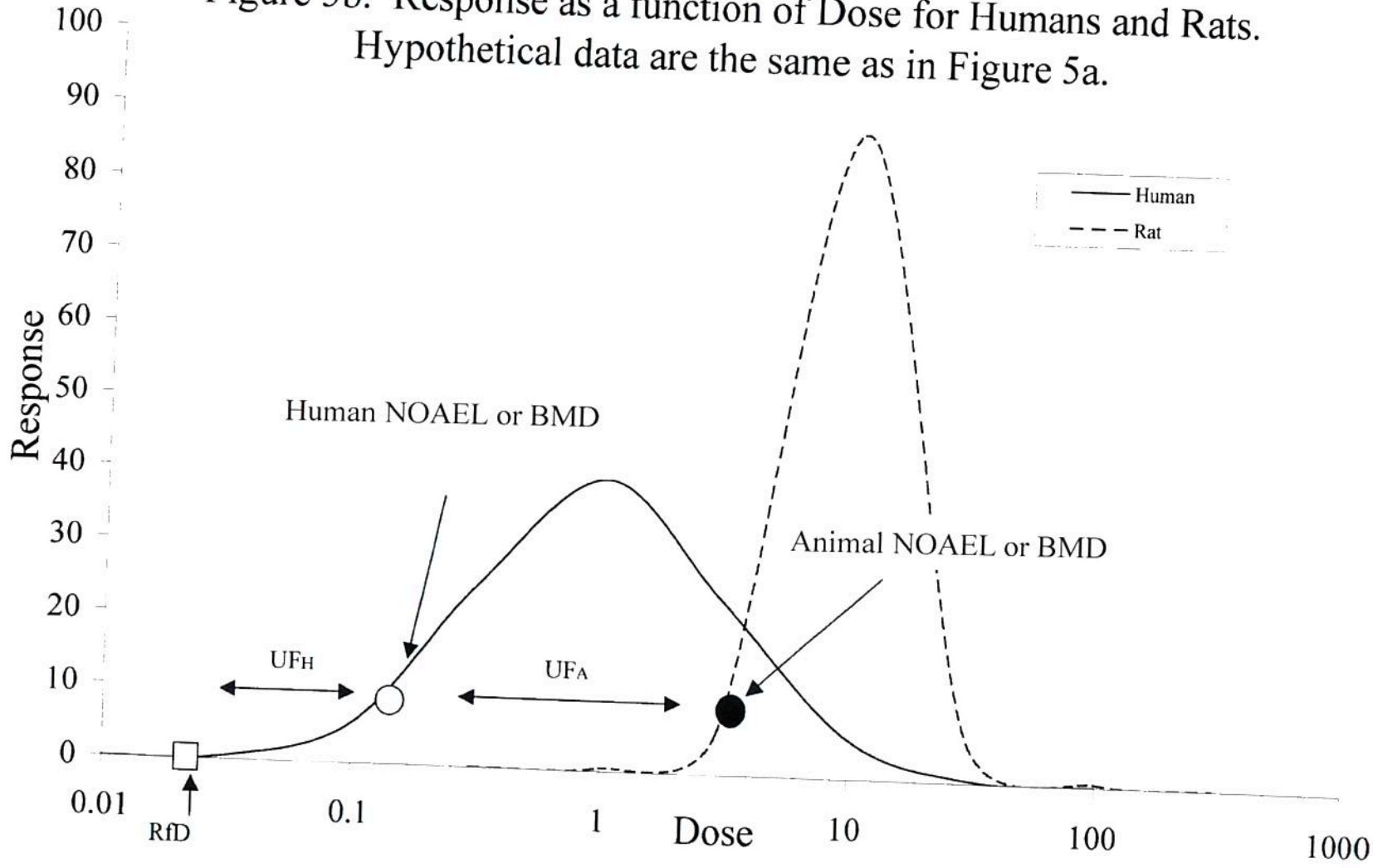
Figure 5a. Cumulative Response as a function of Dose for Humans and Rats. Data are hypothetical, but approximate real situations.



Dourson, M.L., G. Charnley and R. Scheuplein, 2002

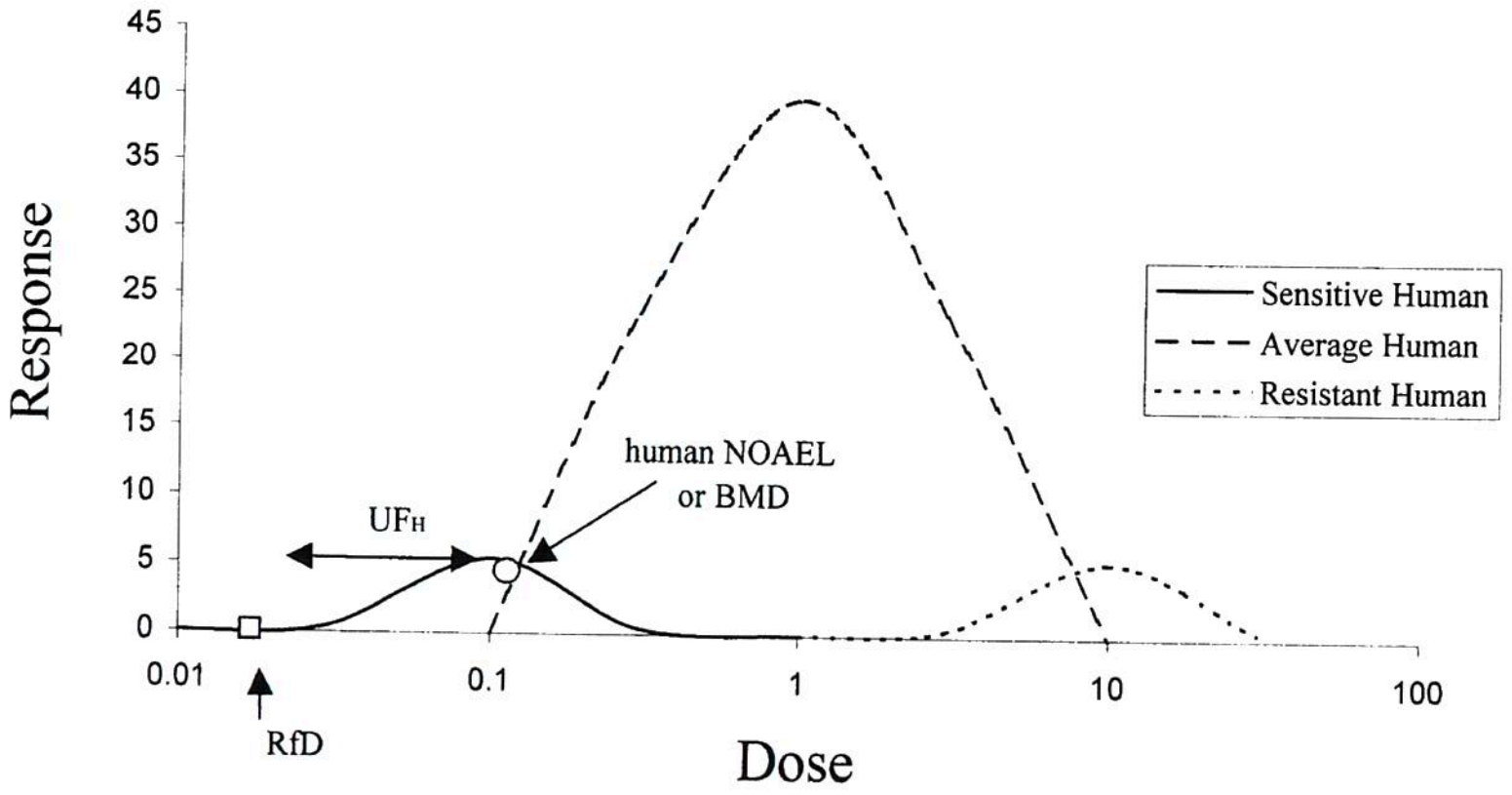
Factor of 10 Enough?

Figure 5b. Response as a function of Dose for Humans and Rats.
Hypothetical data are the same as in Figure 5a.



Factor of 10 Enough?

Figure 6a. Response as a function of dose for humans of different sensitivities. Hypothetical data for humans are the same as in Figure 5b.



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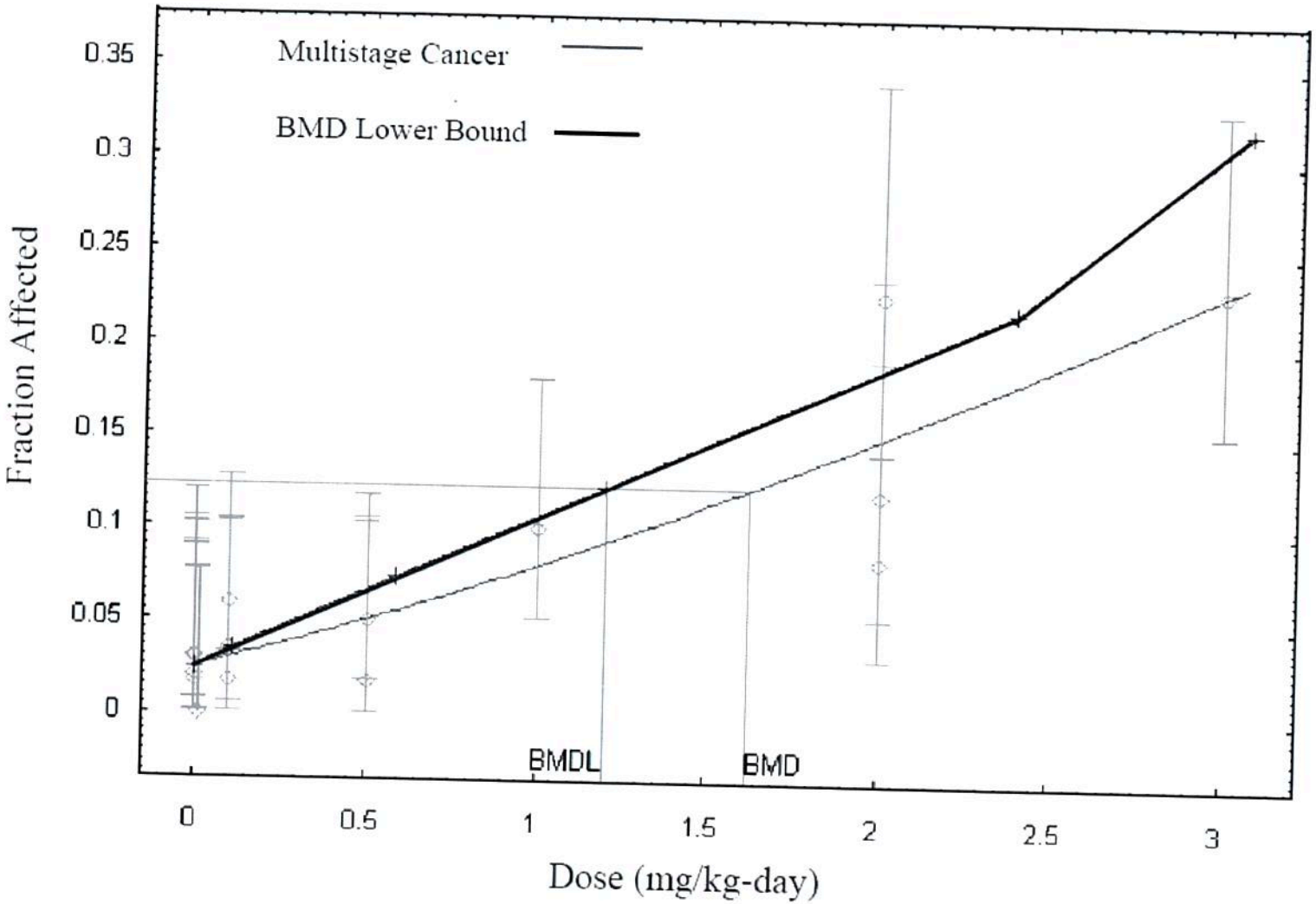
Contemporary: BMD

Clear advantages and disadvantages exist in the use of a benchmark dose (BMD)

- Uses responses near the range of observation.
- Includes a measure of variability in the response.
- Determines a consistent measure of response.
- Applies to fewer, more robust, toxicity data sets.
- Accounts for more dose response of critical effect.

Casarett and Doull (Sixth Edition) page 94

Figure 2a. Multistage Model Fitted To Pooled Thyroid Tumors, Showing Small Change In Slope Between Low & High Doses



Dourson M.L., R. Hertzberg, B. Allen, L. Haber, A. Parker, O. Kroner, A. Maier, and M. Kohrman, 2008

Figure 2b. Probit Model Fitted To Pooled-all Thyroid Tumor Data, Showing Differing Slopes Between The Low & High Doses

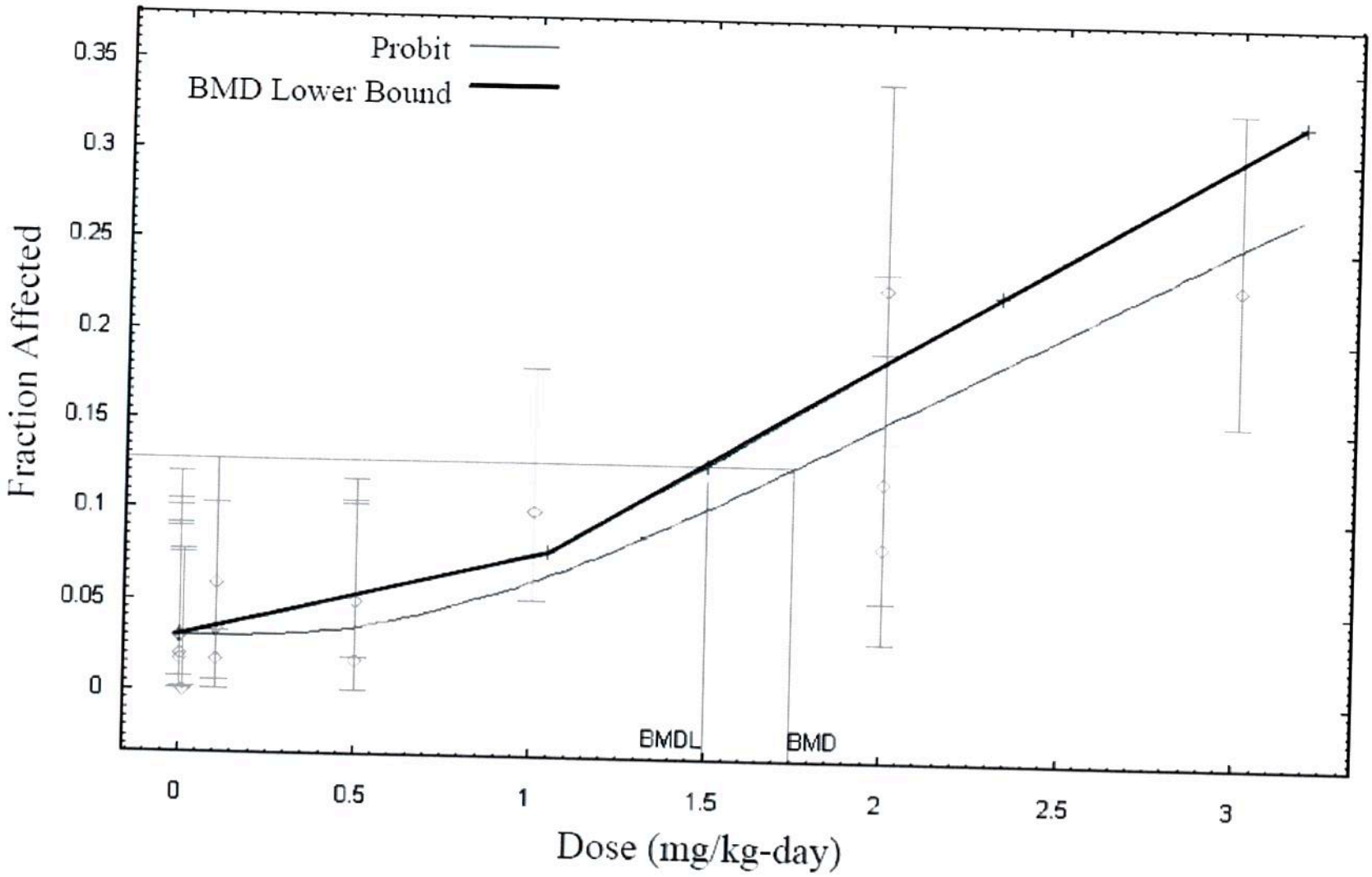


Table 5. Comparison Of 2% BMD, BMDL & Slope Factors (SF) For Acrylamide's Thyroid Tumors In Rats

Data Set	Model	BMD_{02}	SF BMD_{02}	$BMDL_{02}$	SF $BMDL_{02}$	BMD/BMDL
All pooled tumors	Multistage	0.39	0.052	0.23	0.087	1.7
Low-dose pooled tumors	Multistage	0.80	0.025	0.23	0.088	3.5
All pooled tumors	**Probit**	**0.81**	**0.025**	**0.69**	**0.029**	**1.2**
All pooled tumors	Weibull	0.82	0.024	0.72	0.028	1.1
Low-dose pooled tumors	Weighted linear regression	0.92	0.022	0.33	0.061	2.8

P-values for all regressions exceed 0.1 and thus are acceptable; AICs and residuals for the multistage and probit models with all pooled tumors were comparable, however, BMD/BMDL ratios (above) and visual fit differ (see Figure 2a,b). Bold printed row indicates model chosen for extrapolation to humans.

Contemporary: Categorical Regression

RfD Definition

"without appreciable risk"
"is likely to be"
"deleterious effect"

Regression model

$r < 10^{-2}$
$P(*) > 0.95$
severity = moderate or frank

New RfD Definition

$P (r < 10^{-2}$ at dose<RfD $) > 0.95$

where $r = P$ (severity >1)

Hertzberg R.C. and M.L. Dourson, 1993

Aldicarb Clinical Studies

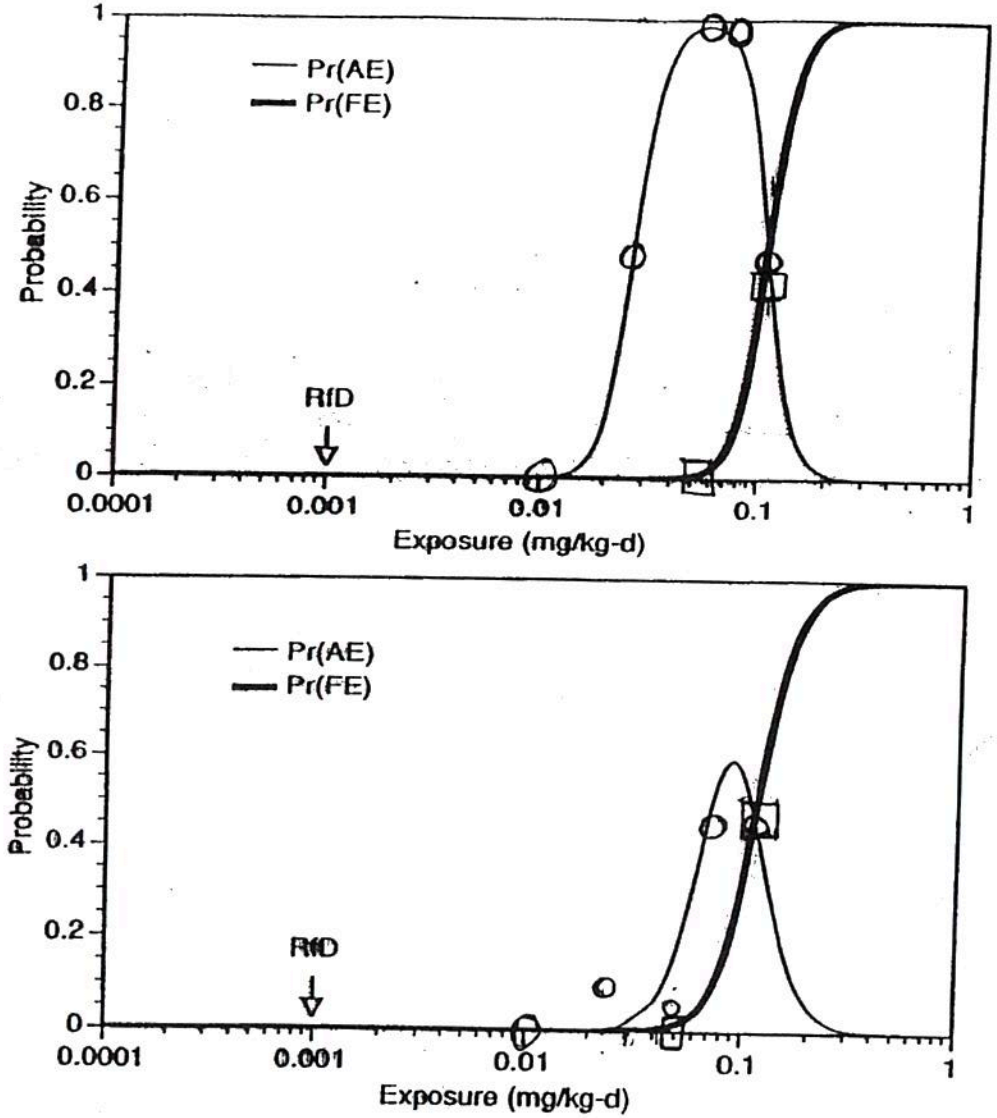
Frequency of Clinical Signs or Blood Cholinesterase				
Study	**Dose (mg/kg-day)**	**Group Size**	**Clinical Signs**	**Blood Cholinesterase Inhibition[a]**
Haines, 1971	0.025	4	1 Apprehension	4 Whole blood
	0.05	4	1 Runny nose[c]	4 Whole blood
	0.10	4	4 Weakness and sweating, Nausea in 2 individuals	4 Whole blood
Wyld et al., 1992[b]	0	22	0	0 Plasma & 0 RBC
	0.010	8	2 Headaches[c]	0 Plasma & 0 RBC
	0.025	12	1 Sweating	12 Plasma & 11 RBC
	0.050	12	1 Sweating	1 Plasma & 1 RBC
	0.06	1	1 Sweating	1 Plasma & 1 RBC
	0.075	3	1 Lightheadedness	3 Plasma & 3 RBC

Dourson, M.L., L.K. Teuschler, P.R. Durkin and W.M. Stiteler, 1997

Effect Categories of Aldicarb Exposure in Humans

Frequency of Categories of Effect Associated with Aldicarb Exposure in Humans						
Study	Dose (mg/kg/day)	Group Size	Frequency of Responders within Categories of:			
			NO Effects	Non-adverse Effects	Adverse Effects	Frank Effects
Wyld	0.0	22	**22 (22)**	0 (0)	0 (0)	0 (0)
Wyld	0.010	8	**8 (0)**	0 (0)	0 (0)	0 (0)
Wyld	0.025	12	0 (0)	**8 (11)**	**4 (1)**	0 (0)
Wyld	0.025	4	0 (0)	**0 (3)**	**4 (1)**	0 (0)
Wyld	0.50	12	0 (0)	**1 (11)**	**11 (1)**	0 (0)
Wyld	0.50	4	0 (0)	**0 (4)**	**4 (0)**	0 (0)
Wyld	0.075	4	0 (0)	**0 (2)**	**4 (2)**	0 (0)
Haines	0.10	4	0 (0)	0 (0)	**2 (2)**	**2 (2)**

Probability of Category with Aldicarb

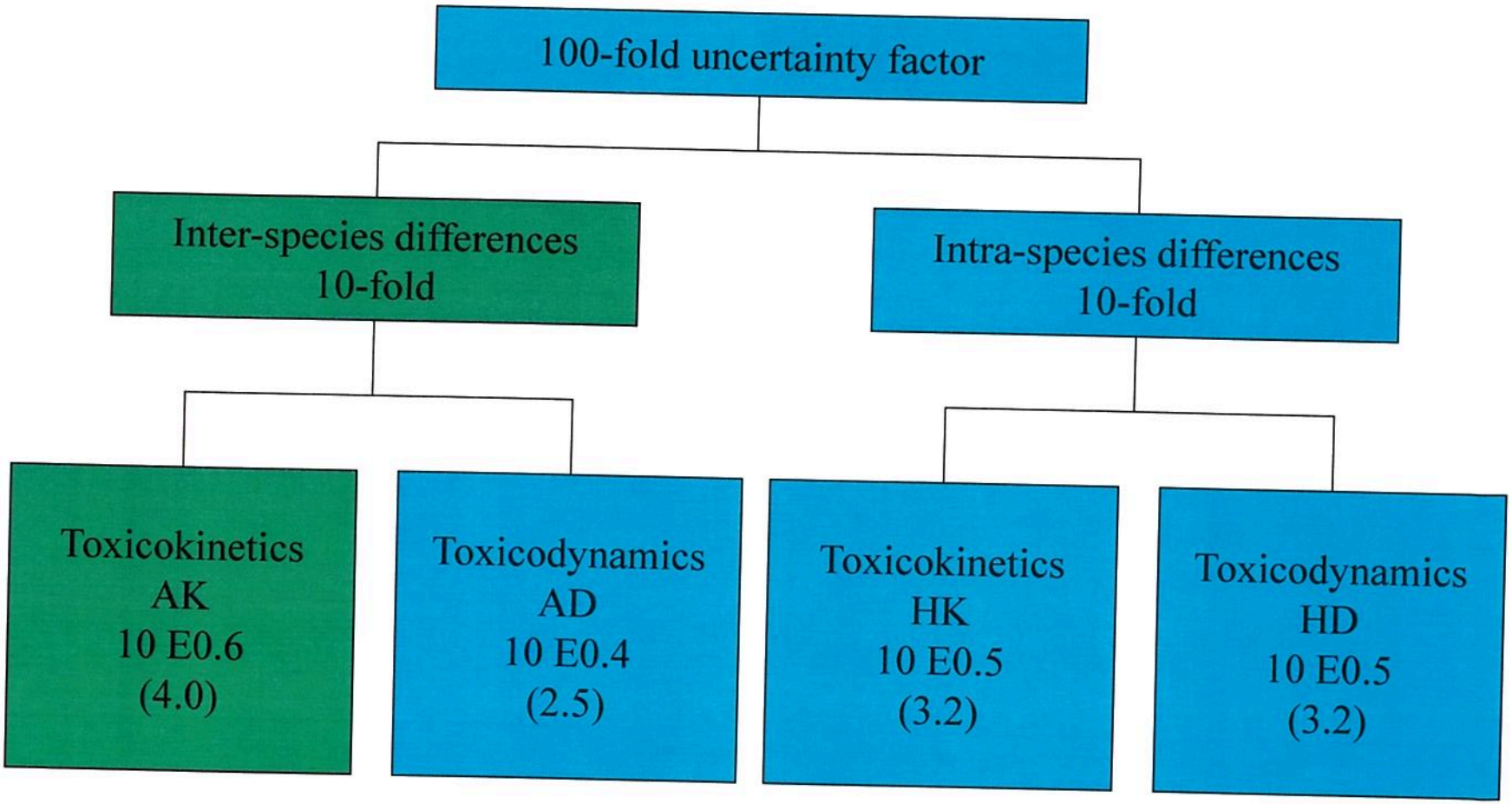


Contemporary: Categorical Regression

- Advantages:
  - provides a consistent basis for calculating risk above the RfD
  - all useful data can be categorized
  - accounts for severity of toxic effect
- Limitations:
  - animal to human extrapolation is still needed
  - data are transformed into categories which loses information

Patty's Toxicology, Volume 1 (Fifth Edition) pages 209-213

Contemporary: Chemical Specific Adjustment Factor (CSAF)



International Programme on Chemical Safety (IPCS). 2005.

Boron…	CSAF	Justification
Absorption	1	Absorption is complete.
Distribution	1	Distribution occurs by passive diffusion.
Metabolism	1	No metabolism.
Elimination	4	Clearance is 3 to 4 times faster in rats than humans.
Total kinetics (default is 4)	4	Interspecies differences in kinetics were dominated by elimination.
Dynamics (default is 2.5)	2.5	Default of 2.5 was retained.
Interspecies	10	Factor to be applied.

Dourson, M.L., A. Maier, B. Meek, A. Renwick, E. Ohanian and K. Poirier. 1998.

Boron Area	CSAF	Justification
Absorption	1	As above
Distribution	1	As above
Metabolism	1	As above
Elimination	1.8	Elimination dominated by the glomerular filtration rate, a 1.8 fold variation between the average pregnant woman and two standard deviations below that.
Total kinetics (default is 3.2)	1.8	See note under elimination above.
Dynamics (default is 3.2)	3.2	Default of 3.2 was retained.
Intraspecies	5.7	Factor to be applied.



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Final CSAF for Boron

$$CSAF = AK_{AF} \times AD_{AF} \times HK_{AF} \times HD_{AF}$$

$$= 4 \times 2.5 \times 1.8 \times 3.2$$

$$= 57 \text{ (rounded to 60)}$$

EPA IRIS (2009) uncertainty factor is

$$= 3.3 \times 3.16 \times 2 \times 3.16$$

$$= 66$$

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Contemporary: PBPK

- It is now routine to ask folks whether or not a PBPK model is available for the chemical of interest.
- Numerous PBPK papers; some have been given top awards (RASS of SOT papers of the year):
  - Sweeney, L. et al. (2001). Proposed occupational exposure limits for select glycol ethers using PBPK models and Monte Carlo simulation. Toxicol. Sci. 62(1):124-139.
  - Kirman, C.R., et al. (2004). Addressing nonlinearity in the exposure-response relationship for a genotoxic carcinogen: cancer potency estimates for ethylene oxide. Risk Anal. 24:1165-1183.

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Create the Future: Collaborate/Research

- Risk Information Exchange (RiskIE)
- International Toxicity Estimates for Risk (*ITER*)
- Alliance for Risk Assessment (*ARA*)
- CRADAs, testing of mutational MOA with NCTR
- Genomics
- NAS (2008)
- Peer review

RiskIE

Risk Information Exchange

www.allianceforrisk.org/RiskIE.htm



- An interactive Database to Communicate In-Progress Risk & Toxicity Assessments
- Includes over 7000 projects being conducted by more than 27 organizations representing 13 countries
- Available at the Alliance for Risk Assessment (*ARA*) website

ITER

International Toxicity Estimates for Risk

www.tera.org/ITER
http://toxnet.nlm.nih.gov

- Provides chronic human health risk values and cancer classifications from organizations around the world for over 650 chemicals
- Includes a synopsis that explains the underlying basis and rationale for each risk value and differences in risk values
- A link to each organization's website or source document
- A forum through which independent parties can share their peer reviewed risk values

Alliance for Risk Assessment (*ARA*) (www.allianceforrisk.org)

Stakeholder Process

States, Fed. Agencies, Public Interests, Industry

Initiation of Risk Issue

Document Draft

Peer Reviews

Release to Public



Risk Information Exchange (RiskIE)

ARA Process

Steering Committee

Non-profit Collaborators

Risk Document Development

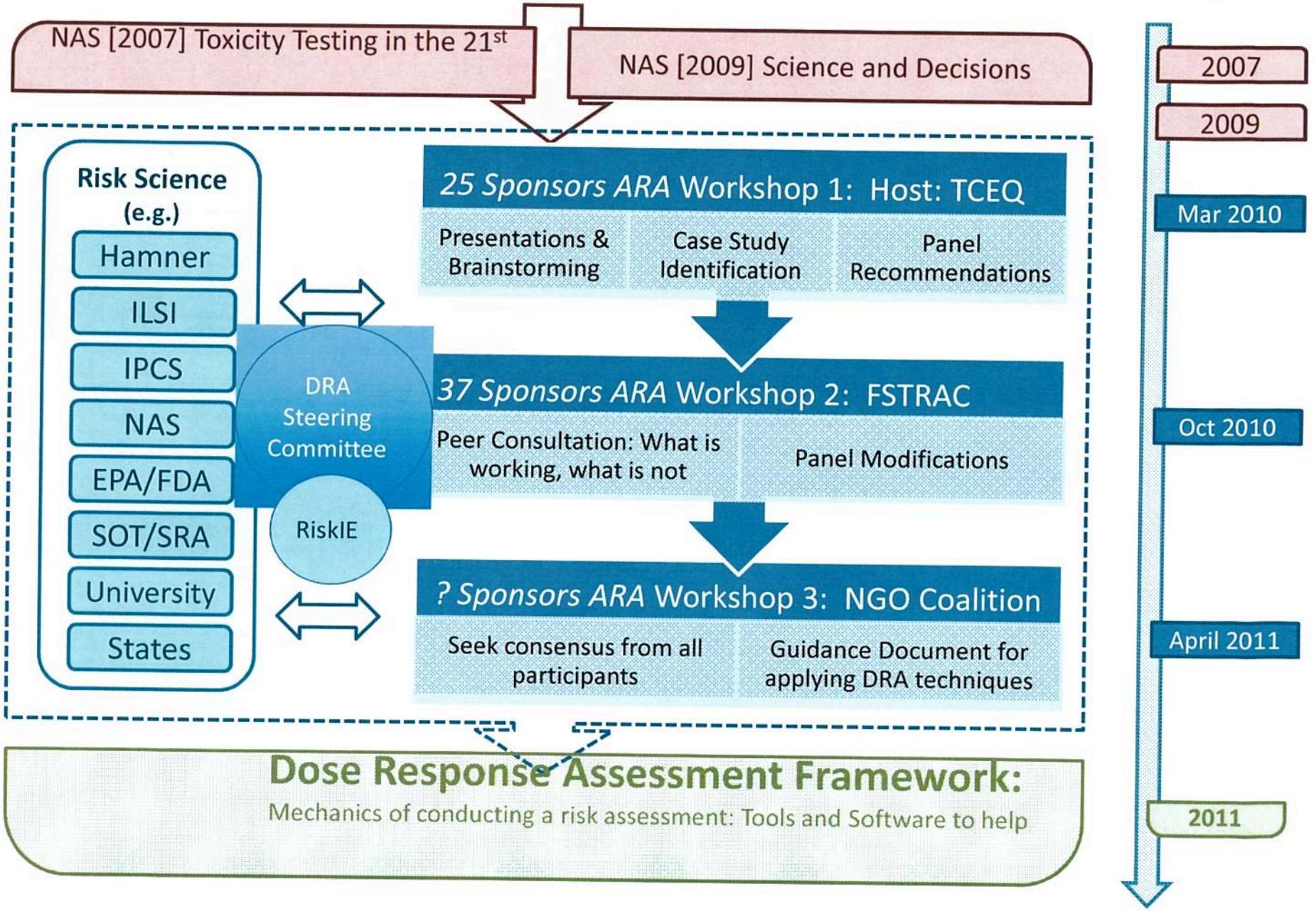
Training and Certification

Risk Communication

Risk Research And Tools

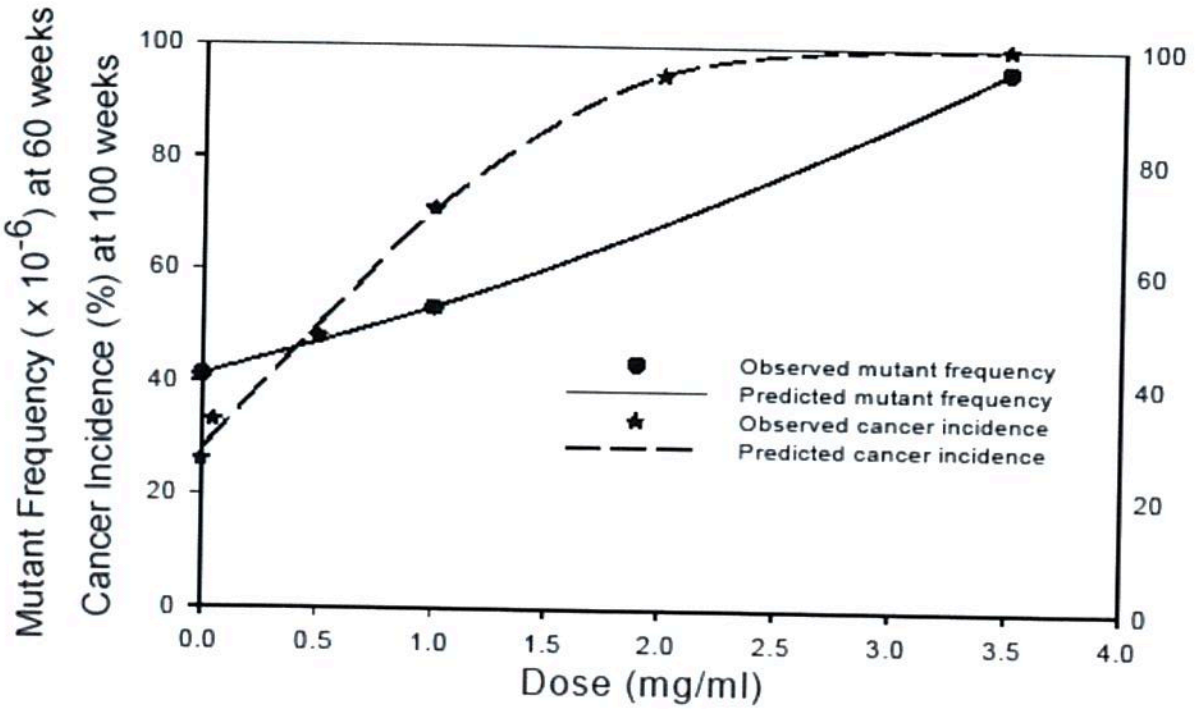
Peer Review & Consult

Beyond Science and Decisions: Problem Formulation to Dose Response



National Center for Toxicological Research: CRADA

Case study 2: Dose-Response Analysis for Dichloroacetic Acid



Genomics in Risk Assessment

Bowyer et al., 2008. Subchronic acrylamide exposure in Fischer 344 rats.

Region	Gene Expressed	Expression Levels		
		% Relative to Control[a]	Relative to GADPH	P value[d]
Thyroid	Glyceraldehydephosphate dehydrogenase (GAPDH)	83±12%	NA	NA
Thyroid	Thyroglobulin	102±18%	54.6-fold	0.97
Thyroid	Thyroid peroxidase	102±18%	0.278-fold	0.77
Thyroid	Sodium iodide symporter	142±22%	0.0218-fold	0.12
Thyroid	Type I 5′-deiodinase	142±38%	0.295-fold	0.48
Thyroid	Type II 5′-deiodinase	189±33%	0.0181-fold	0.034
Thyroid	Type III 5′-deiodinase	113±18%	0.00139-fold[b]	0.53
Thyroid	Mki67	109±14%	0.0619-fold	0.71
Pituitary	Thyroid stimulating hormone β	108%	12.31	0.30
Pituitary	Thyroid hormone receptor α	103%	8.53	0.57
Pituitary	Thyroid hormone receptor β	109%	8.74	0.73

Statistically significant

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Science and Decisions:
Advancing Risk Assessment (NAS 2009)

- Gave suggestions on hiring, training and planning
- Suggests incorporation of background exposures, stressors, and/or diseases in modeling efforts
- Suggests common dose response approach for all endpoints; default is a no threshold model
- These latter two suggestions are controversial
  - Background exposures and diseases are included in control groups
  - Including background exposures/stressors obviates tier the "Component" part of EPA mixtures guidelines
  - Ignoring thresholds is not consistent with most toxicology
- Several current methods were overlooked

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Risk Assessment Peer Review

- Cornerstone principles
  - Scientific robustness
  - Selection of appropriate panel expertise
  - Transparency
  - Independence
- Distinguish conflict-of-interest from bias
  - Avoid COI
  - Balance biases
- Rule of thirds; ~1/3 of the panel should be
  - Experience risk assessors
  - Chemical or related-chemical experts
  - Effect experts
- Balanced affiliations

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Summary

- Know traditional risk methods cold
  - Involve clinicians
  - Challenge non-experts
- Use contemporary methods often
  - BMD, Categorical Regression, CSAF, PBPK
- Create future by collaboration and research
  - Hang together, or hang separately
  - Focus on collaboration among agencies

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- Extra slides



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Thresholds

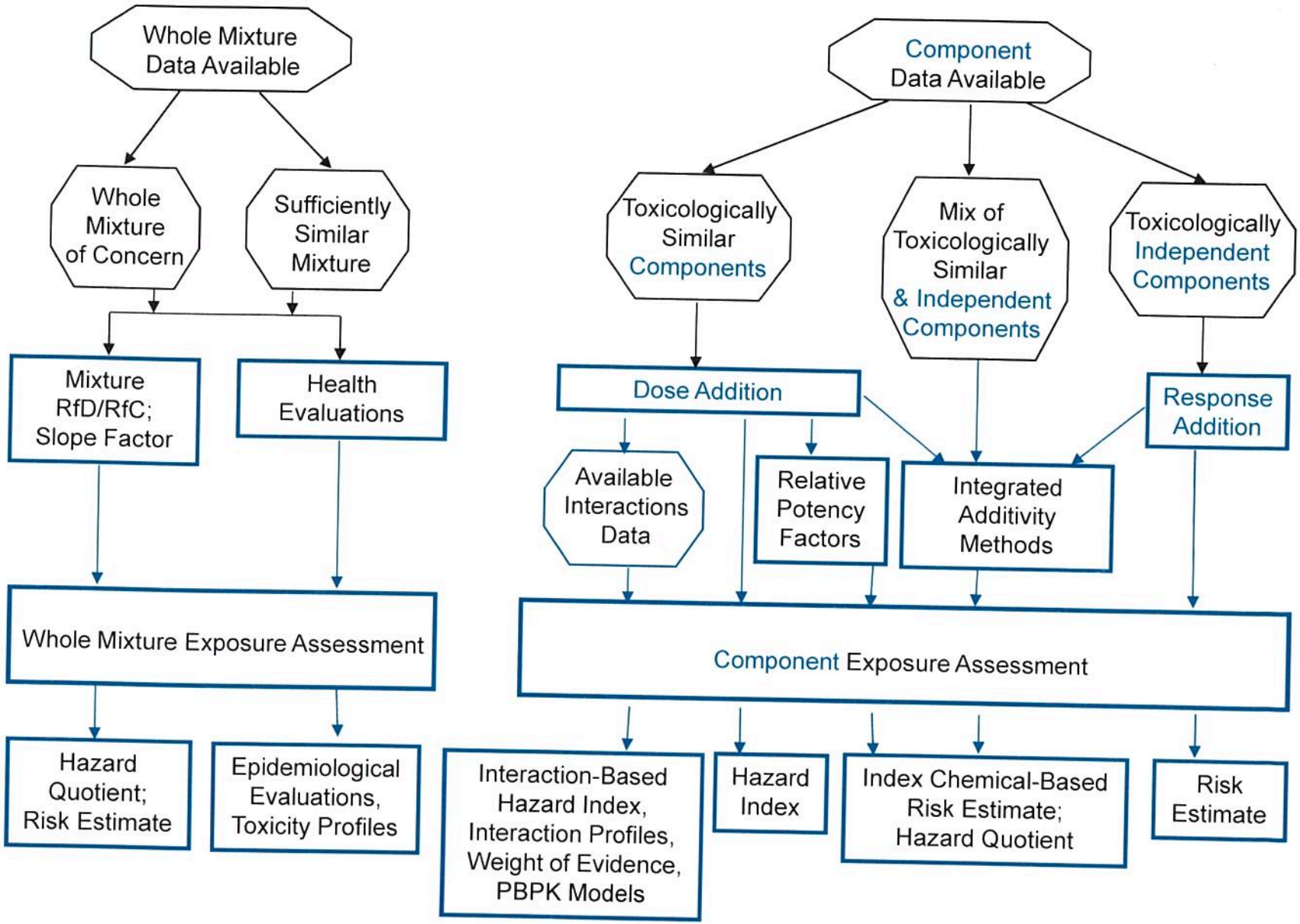
Wikipedia: Point where one mentally or physically is vulnerable in response to provocation or to particular things in general, as in emotions, stress, or pain.

Word software: Level at which effect starts

Casarett & Doull (2008—page 23): …some dose below which the probability of an individual responding is zero.

The question is not whether a chemical has a threshold for an adverse effect---since all chemicals do---but rather can it be that this threshold is one molecule.

Flow Charts for Evaluating Chemical Mixtures



Defining the range of the reference dose: imprecision versus uncertainty.

Dourson ML, Gadagbui B, Pfau E, Thompson R, Lowe J*

* *Alliance for Risk Assessment (ARA); Toxicology Excellence for Risk Assessment; Hull & Associates, Inc.; Alliance for Site Closures; CH2M-Hill*

Hazard Range and Problem Formulation

- The development of a hazard range should help to address the following problems:
  - Hazardous waste site remedial objectives for chronic exposures
  - Communicating risk/hazard of exposure above RfC
  - Prompt/short term exposure action levels
  - Inform the confounding effects of assessing ambient background concentrations in air

TCE Residential Indoor Air Acceptable Exposure Levels

- Based on CalEPA values (2000)
  - HQ = 1: 630 $\mu g/m^3$
  - ELCR = 1 x 10^{-6}: 1.2 $\mu g/m^3$
  - ELCR = 1 x 10^{-5}: 12 $\mu g/m^3$
  - ELCR = 1 x 10^{-4}: 120 $\mu g/m^3$

- Based on US EPA IRIS (October 2011)
  - HQ = 1: 2.1 $\mu g/m^3$
  - ELCR = 1 x 10^{-6}: 0.48 $\mu g/m^3$
  - ELCR = 1 x 10^{-5}: 4.8 $\mu g/m^3$
  - ELCR = 1 x 10^{-4}: 48 $\mu g/m^3$

Risk Assessment and Risk Management

- Excess Lifetime Cancer Risk (ELCR) Range: 10^{-6} to 10^{-4}
  - Provides risk managers flexibility to balance acceptable exposure levels with closure needs:
    - Technical feasibility
    - Implementability
    - Timeliness
    - Economic considerations
    - Cultural or other concerns
- **How may a similar evaluation be performed with respect to the non-cancer endpoint?**

Problem Response: Alliance for Risk Assessment (*ARA*)

- *ARA* TCE Workgroup formed in the Fall of 2012
  - Open invitation, broad interest and participation
  - Trichloroethylene (TCE) Risk Assessment Guidance for Contaminated Sites (April 2013)
  - Webcast: Practical Guidance for Contaminated Sites: TCE Risk Assessment Case Study (November 4, 2013)
  - Observers: over 300 scientists from multiple international organizations, including government, industry, academia and NGOs, on 6 conference calls and one webinar.

NAS (2014) & IRIS Process

- "**Finding**: EPA could improve documentation and presentation of dose-response information.

- **Recommendation**: EPA should clearly present two dose-response estimates: **a central estimate (such as a maximum likelihood estimate or a posterior mean) and a lower-bound estimate for a POD from which a toxicity value is derived.** The lower bound becomes an upper bound for a cancer slope factor but remains a lower bound for a reference value." [emphasis added]

NAS (2014) & IRIS Process

- "**Finding**: IRIS-specific guidelines for consistent, coherent, and transparent assessment and communication of uncertainty remain incompletely developed. The inconsistent treatment of uncertainties remains a source of confusion and causes difficulty in characterizing and communicating uncertainty.

- **Recommendation**: Uncertainty analysis should be conducted systematically and coherently in IRIS assessments. To that end, EPA should develop IRIS-specific guidelines to frame uncertainty analysis and uncertainty communication. Moreover, uncertainty analysis should become an integral component of the IRIS process."

Reference Dose (IRIS)

- "The RfD (expressed in units of mg of substance/kg body weight-day) is defined as an estimate (**with uncertainty spanning perhaps an order of magnitude**) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime." [emphasis added]

- That is, the RfC/RfD is expected to be below the actual threshold for adverse effect in a sensitive subgroup.

Uncertainty vs. Imprecision

- Alternative interpretations:
  - Imprecision of a RfC is on both sides of the RfC. This is because a 2nd expert group might estimate a RfC higher or lower than the 1st group, if given the same information.
  - Uncertainty in a RfC, in contrast, lies mainly above the RfC. This is because RfCs are based on lower bounds on PODs and UFs are known to be protective.
  - For risk management decisions, uncertainty in the RfC is generally more important than imprecision.
  - Managers are interested in making decisions that protect public health and uncertainties in a RfC are generally more informative.

Hazard Range Development

- Hazard Range
  - Floor
  - Intermediate value (Midpoint)
  - Ceiling

Floor of the Hazard Range

- Identified as the RfC/RfD based on a single candidate value
- In the case of an RfC/RfD based on two or more candidate values
  - identified as the candidate RfC/RfD with the higher(est) confidence.
    - The reference value is not likely to change with further testing, except for mechanistic studies that might affect the interpretation of prior test results.
    - RfC could be modified if refined data are obtained to modify uncertainty factors – e.g., kinetic data for chemical-specific adjustment factors.

Floor of the Hazard Range

- The RfC/RfD is developed:
  - using UFs that are protective based on the observed behaviors of a typical toxicant
    - so that the RfC/RfD is an underestimate of the expected threshold value.
  - The floor of the hazard range may be denoted as a point below which risk managers are unlikely to recommend remedial action or exposure control.

Ceiling of the Hazard Range

- Is defined as the adjusted point of departure (POD_{adj})
- POD based on the critical concentration/dose of chosen study.
- Managers likely to take regulatory action above this ceiling since specific toxic effects can sometimes be seen.

Ceiling: Adjusted POD

- Adjustments for the dosing regime in the critical study, such as…

- Toxicokinetic differences between the test organism and humans
- Database quality, lack of NOAEL, and study duration; reductions are based on available data, or a factor of 3 used as a default for each area.
- The intent of these adjustments and reductions is to estimate the likely ceiling of the RfD/C by using the median value of the Ufs.

Midpoint of the Hazard Range

- Unlikely to be associated with adverse effects in a human population, based on…
  - Greater understanding of the range of uncertainty associated with RfC/RfD development and
  - Consistent with the definition of "uncertainty of up to an order of magnitude" impacts the RfC/RfD
- It is a plausible estimate of the upper concentration or dose that is likely to be protective of the general population, including sensitive subpopulations

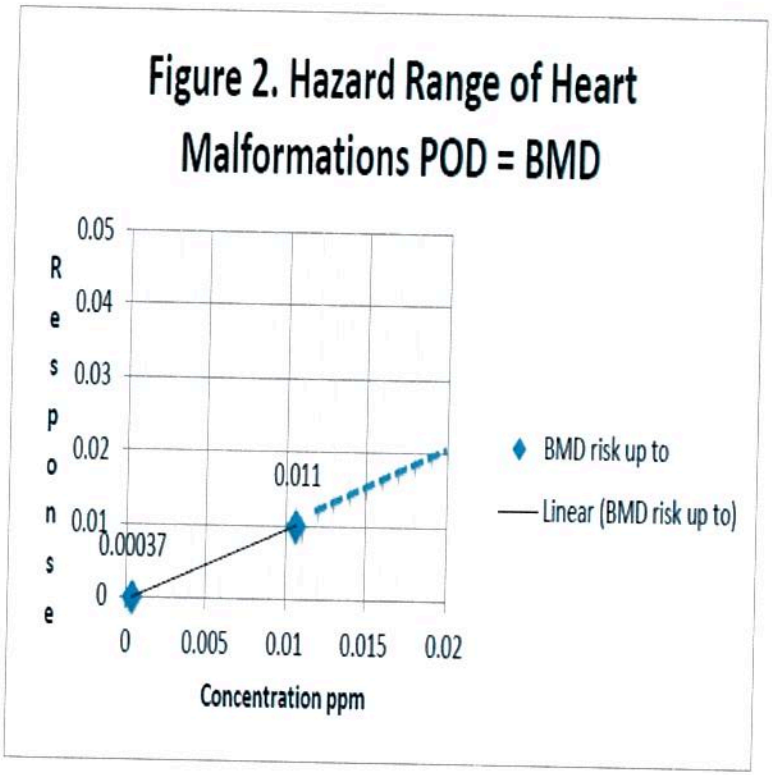
Midpoint of the Hazard Range

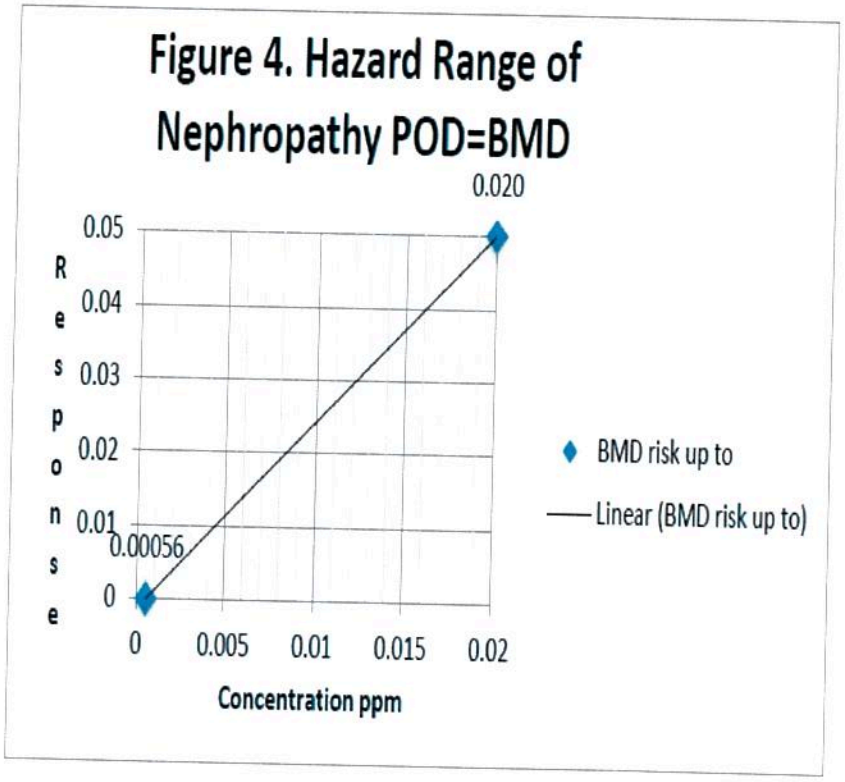
- Is a judgment that meshes four considerations:
  - Collective magnitude of the UFs
  - Steepness of the hazard slope describing exposures above the RfC/RfD
  - The confidence in the selection of the critical effect
  - The confidence in the POD

Johnson et al., 2003
RfC = 2 μg/m^3

- Fetal malformation endpoint
  - Intermediate value of 10 μg/m^3 is judged to be 5-fold above the candidate RfC due to:
    - Its small UF of 10,
    - Shallower hazard slope,
    - Low confidence in the critical effect, and
    - Low confidence in the choice of a benchmark response of 1% ($BMDL_{01}$)

Hazard Ranges of Two Candidate RfCs for TCE (as per Gentry et al.)





NTP, 1988
RfC = 3 μg/m^3

- Toxic nephropathy endpoint
  - Intermediate value of 9 μg/m^3 is judged to be 3-fold above the candidate RfC due to:
    - Its small UF of 10,
    - Steeper hazard slope,
    - Medium confidence in the critical effect, and
    - Medium to low confidence in the choice of a benchmark response of 5% ($BMDL_{05}$)

Keil et al., 2009
RfC = 2 µg/m^3

- Decreased thymus weight endpoint
  - Intermediate value of 20 µg/m^3 is judged to be 10-fold above the candidate RfC due to:
    - Its larger UF of 100,
    - The effect shown by Keil et al. (2009) does not lend itself to dose-response modeling, so steepness of the slope was not assessed
    - Medium confidence in the critical effect, and
    - Medium to low confidence in its choice of a LOAEL as the POD

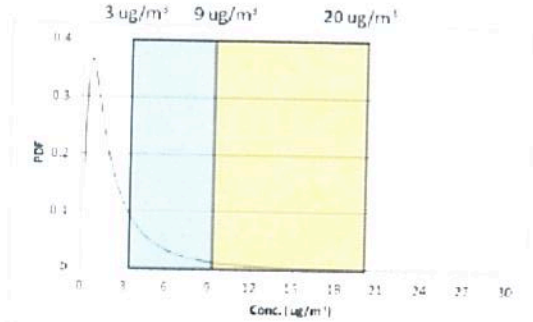
TCE as an Example

Table 7. Different uncertainty ranges for different TCE RfCs. All values are in $\mu g/m^3$. Shaded areas indicate best **overall uncertainty range** for risk management purposes.

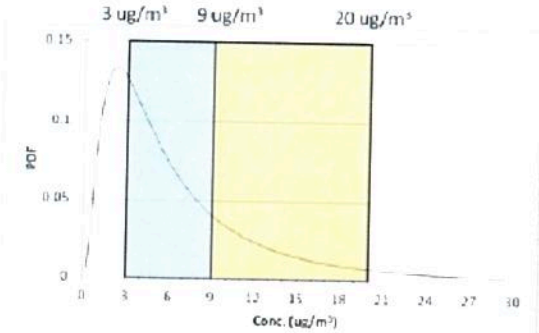
Study	Endpoint	IRIS UF [a]	Steep [b] Slope	Confidence		Uncertainty Ranges		
				Critical [c] Effect	Point of [d] Departure	Floor	Intermediate	Ceiling
Johnson et al (2003)	Fetal malformation	10	Lower	Low	Low	2	10	20
NTP (1988)	Toxic nephropathy	10	Higher	Medium	Medium to Low	3	9	30
Keil et al. 2009	Decreased thymus weight	100	NA	Medium	Medium to Low	2	20	60

a. Size of the uncertainty factor as on IRIS
b. Steepness of the hazard slope (*i.e.*, the slope of the line describing hypothetical population responses at concentrations above the RfC), as per Section 3.
c. Confidence in the choices of critical effect, as per Section 4.
d. Confidence in the POD, as per Section 4.

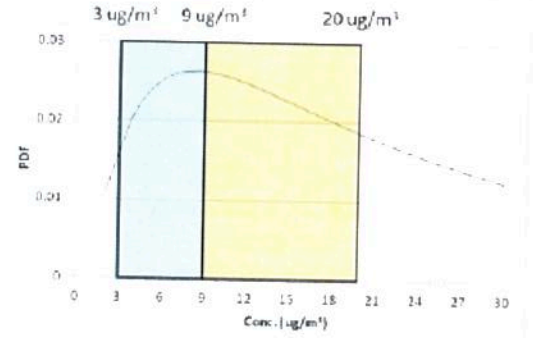
Practical Application of the Hazard Range for TCE



ES Figure 1a. Exposure distribution of indoor air concentrations primarily below the 3 $\mu g/m^3$ to 20 $\mu g/m^3$ hazard range. Relatively small proportion of exposures is higher than 3 $\mu g/m^3$. Nominal actions or no further action may be warranted for risk management.



ES Figure 1b. Exposure distribution of indoor air concentrations falling within the 3 $\mu g/m^3$ to 20 $\mu g/m^3$ hazard range. Relatively small proportion of exposures is higher than 9 $\mu g/m^3$. Limited action may be warranted for risk management



ES Figure 1c. Exposure distribution of indoor air concentrations primarily above the 3 $\mu g/m^3$ to 20 $\mu g/m^3$ hazard range. Actions to reduce exposures may be warranted for risk management.

For more information http://www.allianceforrisk.org/Projects/TCE.html

Guidance for Contaminated Sites: Trichloroethylene Case Study. Gadagbui, et al., SOT, 53rd Annual Meeting & ToxExpo, 23-27 March 2014, Phoenix, AZ.

Development of a Non-cancer Hazard Range for Effective Risk Assessment and Risk Management of Contaminated Sites: A Case Study with TCE and Other Chemicals, Beyond Science & Decisions: Problem Formulation to Dose-Response Assessment, Workshop VIII, 21-22 May 2014, Austin, TX.

Thank You!

TCE Criteria: *Through the Years*

- Withdrawn US EPA IRIS (1989)
  - Inhalation Unit Risk = 1.7×10^{-6} $(\mu g/m^3)^{-1}$
- CalEPA values (2000)
  - Chronic inhalation REL = 600 $\mu g/m^3$
  - Inhalation Unit Risk = 2×10^{-6} $(\mu g/m^3)^{-1}$
- Draft US EPA TCE Assessment (2001)
  - Prov. RfC = 0.04 mg/m^3 = 40 $\mu g/m^3$
  - Prov. Inhalation Unit Risk = 5.7×10^{-6} $(\mu g/m^3)^{-1}$ to 1.1×10^{-4} $(\mu g/m^3)^{-1}$
- US EPA IRIS (October 2011)
  - RfC = 0.002 mg/m^3 = 2 $\mu g/m^3$
  - Inhalation Unit Risk = 4.1×10^{-6} $(\mu g/m^3)^{-1}$

Consequences of the New TCE Toxicity Values (Problem Formulation)

- Risk-based indoor air levels now based upon non-cancer endpoint (RfC)
- The RfC is based on both chronic and developmental endpoints
- Prompt/short term exposure action levels based on the RfC
  - Prompt action exposure concentrations
  - Application of lifetime RfC to acute and subchronic exposures
- Confounding effects of assessing ambient background concentrations of TCE in air

NAS *Science and Decisions: Advancing Risk Assessment* (2009)

- "For noncancer end points, it is assumed that homeostatic and defense mechanisms lead to **a dose threshold** (that is, there is low-dose nonlinearity), below which effects do not occur or are extremely unlikely. For these agents, risk assessments have focused on defining the reference dose (RfD) or reference concentration (RfC), a putative quantity that is 'likely to be without an appreciable risk of deleterious effects' (EPA 2002a, p. 4-4)." [emphasis added]

- That is, the RfC/RfD is expected to be below this actual threshold for adverse effect.

NAS *Science and Decisions: Advancing Risk Assessment* (2009)

"The "hazard quotient" (the ratio of the environmental exposure to the RfD or RfC) and the "hazard index" (HI)... An HI less than unity is generally understood as being indicative of lack of appreciable risk, and a value over unity indicates some increased risk.

The larger the HI, the greater the risk, but the index is not related to the likelihood of adverse effect except in qualitative terms: 'the HI cannot be translated to a probability that adverse effects will occur, and is not likely to be proportional to risk' (EPA 2006a)." [emphasis added]

NAS (2009) & Hazard Assessment

- NAS (2009):
  - Suggested that methods for assessing non-cancer toxicity have the capability of determining hazard ranges.
- ARA project "Beyond Science and Decisions: From Problem Formulation to Dose Response"
  - Built on NAS (2009) report
  - Six of its cases studies are about evaluating noncancer *risk* (at different doses)
    - Each was vetted by a Science Panel
- We focus on:
  - modeling risk above the RfC/RfD using the benchmark dose method (Gentry *et al.*, 2011).

Problem Response: Alliance for Risk Assessment (ARA)

- *Guidance for Contaminated Sites: Trichloroethylene Case Study*. Gadagbui, *et al.*, SOT, 53rd Annual Meeting & ToxExpo, 23-27 March 2014, Phoenix, AZ.

- *Development of a Non-cancer Hazard Range for Effective Risk Assessment and Risk Management of Contaminated Sites: A Case Study with TCE and Other Chemicals,* Beyond Science & Decisions: Problem Formulation to Dose-Response Assessment, Workshop VIII, 21-22 May 2014, Austin, TX.

Yes, "Thresholdable" Carcinogens are Still Delaney Carcinogens

Michael Dourson, PhD, DABT, ATS
TERA Center
University of Cincinnati

Life is Chemistry…

- We are all exposed to a sea of chemicals daily.
  - Coffee with ~1000 chemicals; 20 to 30 of them known to be either mutagenic or carcinogenic
  - No pure water anywhere
  - Acrylamide, a known carcinogen, in ~40% of our cooked food
  - Pharmaceuticals in our waterways
  - Mixtures of diverse chemicals in our air due to just living in a house, working in a city, or playing soccer on artificial turf
  - Soils are a complex mixtures of living and dying organisms each with its own stew of chemistries…

Adding to this Complexity are Four Things to Remember

- Dose matters
- Timing is critical
- People differ
- Things change

[Hayes, Kruger, and Clemens, 2016]

Fortunately…

- These 1000+ chemicals each have a safe or virtually safe dose.
  - For noncancer toxicity this can be an ADI, RfD, MRL, TDI, DNEL, OEL, TLV, PEL, REL, etc… based on a NOAEL, LOAEL, BMD, or HED, HEC with associated SF, UF, CSAF, DDEF, or AF, etc.
  - For cancer toxicity this can be a VSD or RSD, with associated CIs, based on a POD, SF, or Q1*, etc.
- These doses can be use with exposure assumptions to determine for either cancer or noncancer toxicity a…
  - MRL, HQ, MOE, MOS, HI, DWEL, etc…
- ***Fortunately…?***

So What of All This Science?

- The overriding goal of federal policies governing the use of chemicals is- *and should be*- consumer safety.
- Fess up. Doesn't your family only want to know at dinner whether the chemical highlighted in the daily news is safe?
- And isn't this question asked everywhere else in the country?
- And somehow do you think that US Congress is any different?
- *Au contraire*! And this is why the **Delaney amendment** was passed. Science is complex and safety is paramount.

So…Is It safe?

- For some toxicities the answer is easy… For example, one chemical is:
  - A well known flame retardant
  - An established neurotoxin
  - An endocrine disruptor for sure…
- *And a macronutrient*… a Reference Dose (RfD) is appropriate

- But for other toxicities like cancer…

US has 7th-highest-cancer-rate-in-world

- Jan 24, 2011 -- About 300 of every 100,000 Americans develop cancer each year, earning us 7th place!
  - The new rankings were compiled using World Health Organization (WHO) estimates.
- We are higher than we should be, and it's not the type of list on which you want to be on top, says Alice Bender, MS, RD.
  - Due to lifestyle? Americans are more likely overweight from eating too much food, drinking to much alcohol and being less active.
- So has the "war on cancer" reduced our rates?

And What About Idiopathic disease?

one that exists without any connection with any known cause.

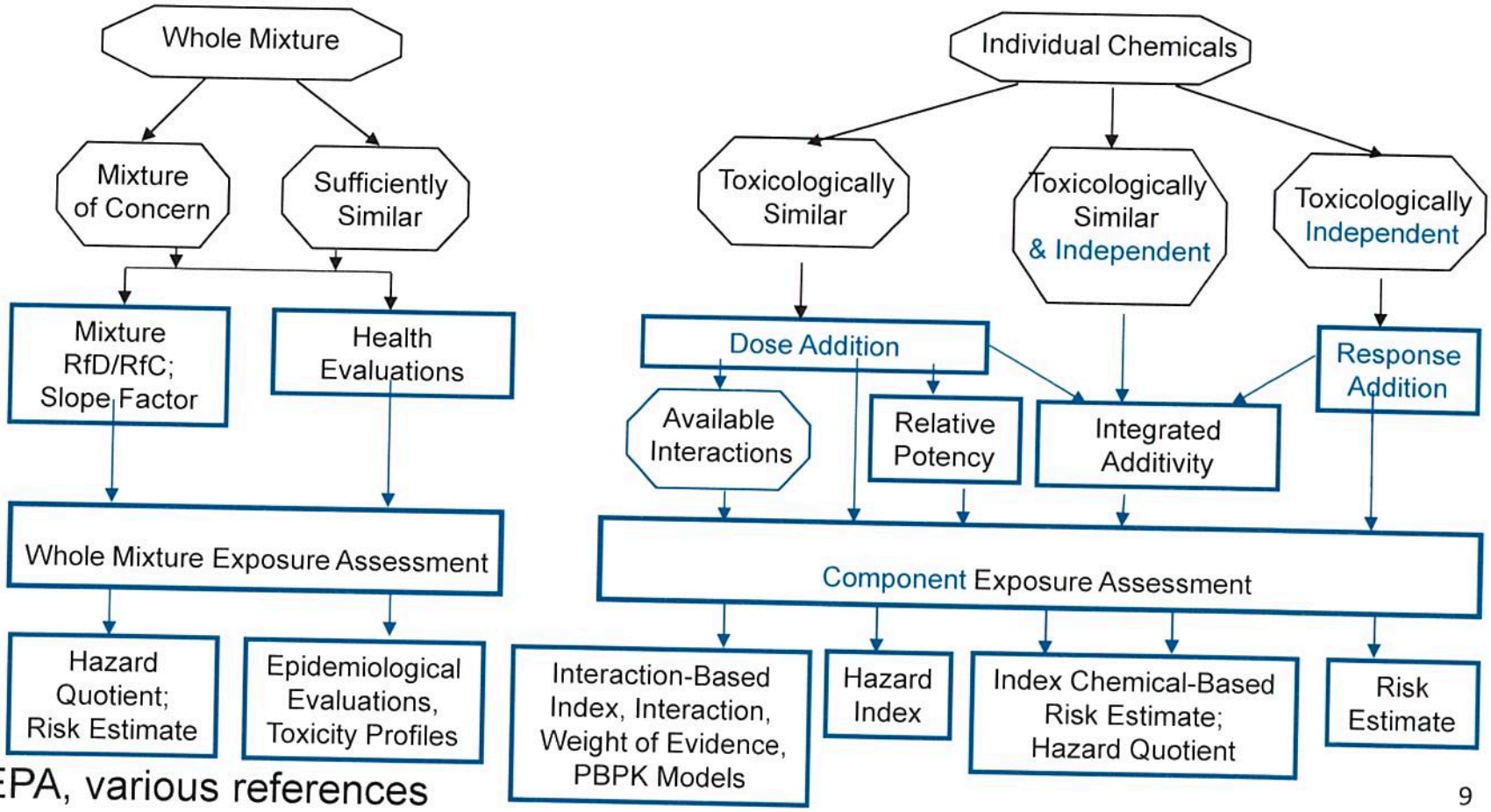
[http://medical-dictionary.thefreedictionary.com/idiopathic+disease]

Idiopathic Diseases (partial listing):

- Alabama rot
- Condylar resorption
- Diffuse idiopathic skeletal hyperostosis
- Idiopathic giant-cell myocarditis
- Idiopathic infantile arterial calcification
- Inflammatory demyelinating diseases of the central nervous system
- Idiopathic interstitial pneumonia
- Idiopathic pulmonary fibrosis
- Immune thrombocytopenic purpura
- Juvenile idiopathic arthritis
- Multifocal fibrosclerosis
- Pellucid marginal degeneration
- Systemic-onset juvenile idiopathic arthritis

[https://en.wikipedia.org/wiki/Category:Idiopathic_diseases]

Or Evaluating Chemical Mixtures?



EPA, various references

Legislative Answer? Chemicals are not Safe Unless Proven Otherwise

- Repeal Delaney? One needs to find a legislative replacement.
  - Perhaps an 95% upper-bound, one in a million, lifetime, excess, cancer risk, where the risk is unlikely greater, but likely lower and perhaps 0.
- Delaney prevents beneficial product development?
  - A simple walk around the grocery store readily disputes this claim.
- But opposition to Delaney may be based on misunderstanding
  - Allows discretion if substance induces cancer when ingested in tests which are appropriate. Expert judgment needed here.
  - Once "induced" limit of science is reached. Delany assures safety.

To the Rescue!

- The Society of Toxicology (SOT) mission is to create a safer and healthier world by advancing the science of toxicology and increasing the impact on society from these advances.

- Specialty Sections are formed to help with understanding risk assessment and regulatory and safety evaluation.

- Better communication to the public and Congress is needed.

Health Risk Assessment for Perchlorate: New Direction in EPA's Modeling Approach for Establishing Standards

Michael Dourson, Ph.D., DABT, FATS, FSRA
John Reichard, PhD, PharmD
University of Cincinnati, College of Medicine

EPA (2016) Perchlorate Model

- EPA's Science Advisory Board (SAB, 2013) recommended crafting a model on perchlorate's effects on sensitive lifestages to assist the agency in determining an appropriate maximum contaminant level goal (MCLG).
- In an effort to fulfill the recommendations of this panel, EPA (2016) showcased a model, which is the first step in a two step process to develop an MCLG.
- EPA choose hypothyroxinemia as the critical effect, that is the first adverse effect or its known precursor, as part of this modeling effort.

EPA's External Peer Review

- The peer reviewers identified a number of areas for improvement of the proffered model:
  - Develop a plan for further actions in order to maximize the benefit of any model revisions.
  - Develop a model that is fit for the intended purpose. Specifically, how the model outputs would be used in developing the MCLG.
- Changes in hormones are precursors of the critical effect that leads to neurotoxicity. Models should facilitate:
  - Linkages between perchlorate exposure and iodine handling and impacts on thyroid hormone levels, and
  - Relationships between thyroid hormone status and neurodevelopment in critical fetal, especially 1st trimester, and post-natal periods.

EPA's External Peer Review

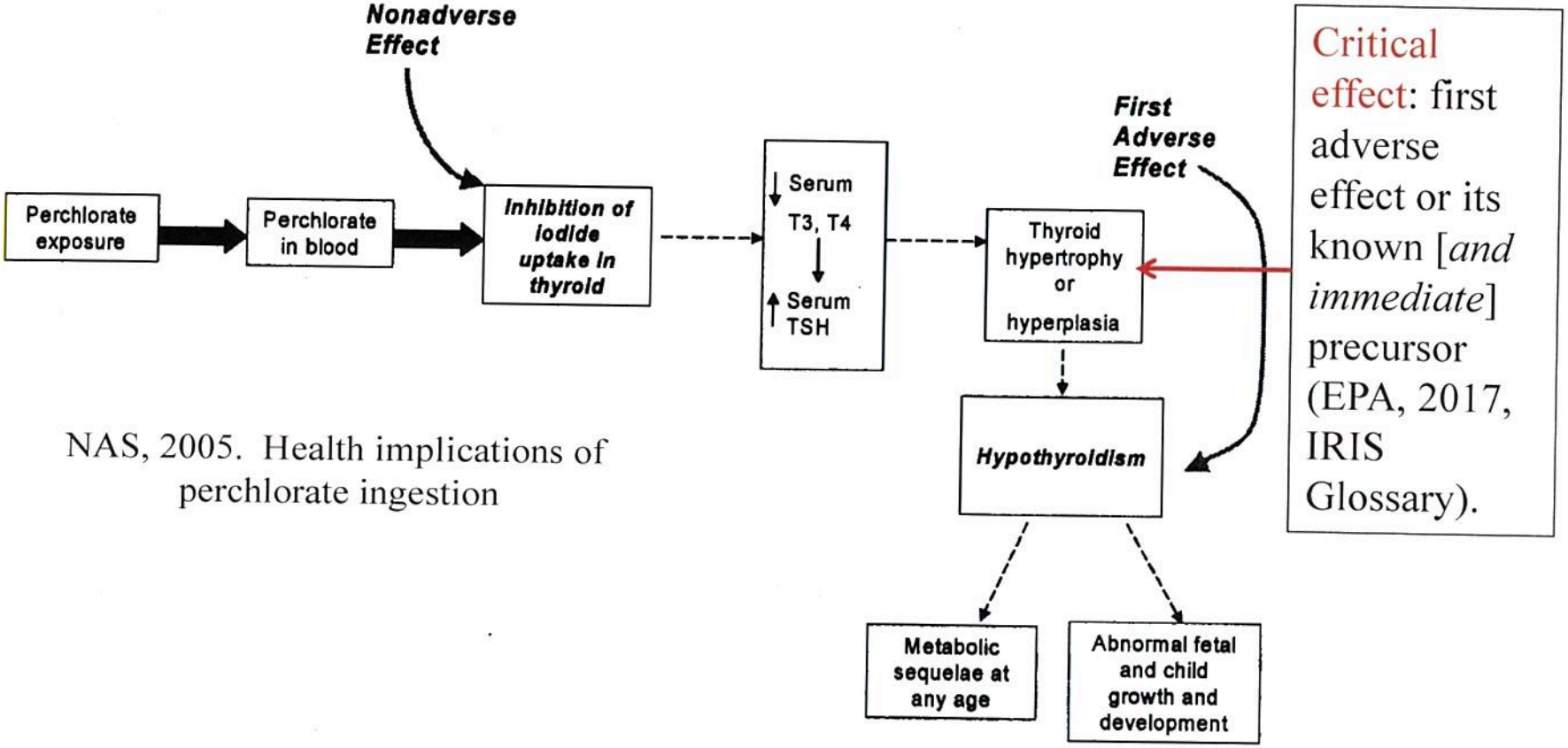
- EPA should establish an interaction with clinicians and epidemiologists with expertise in thyroid function and neurodevelopment.
- EPA should clearly convey the scope of the modeling effort, the biology the model addresses, and the model applications.
- EPA needs to clearly state why the current model, which likely could always be improved given additional time and resources, represents a fit-for-purpose solution applicable to current efforts to develop regulatory standards for perchlorate.

External Comments

- The physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) model of EPA accounts for differences in exposure and biology across life stages, and is a good start at understanding iodine nutrition and perchlorate exposures.
- However, EPA needs to explain thyroid changes as critical effects, in contrast to NAS (2005) and its own definition.
- EPA also needs to support its assumption of 2.5th to 10th percentile of fT4 as a hypothyroxinemia range, and incorporate symporter up-regulation in the model.

University of Cincinnati, College of Medicine, November 23, 2016

The Critical Effect as per NAS/EPA



NAS, 2005. Health implications of perchlorate ingestion

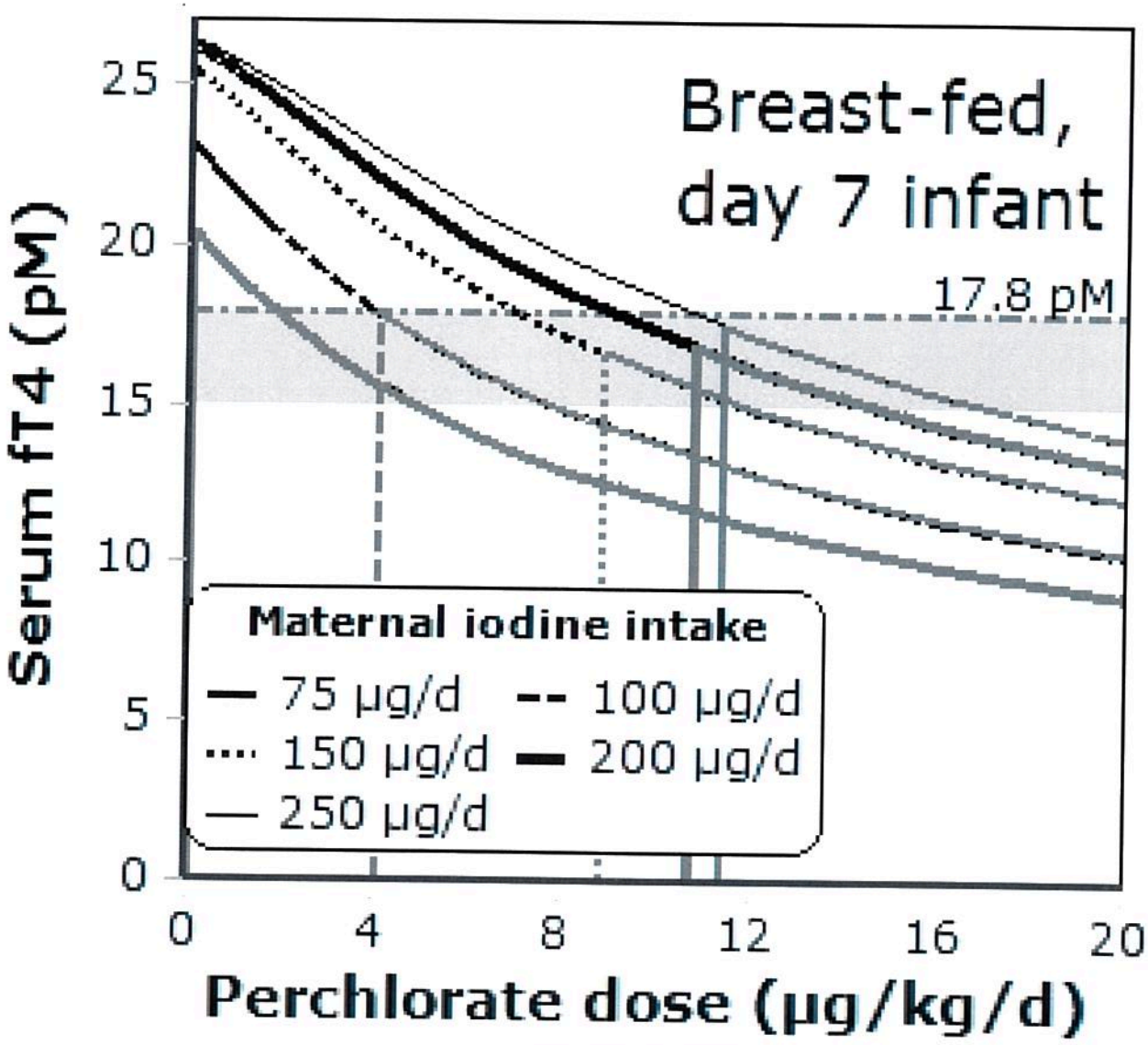
FIGURE 5-2 Committee's suggested mode-of-action model for perchlorate toxicity in humans indicating first adverse effect in the continuum.

One Way Forward?

- EPA could select as the critical effect a lower 2.5th percentile of free T4 in the chosen sensitive population.
- Although not technically the critical effect, this percentile may be a reasonable surrogate for increase in TSH, which would be necessary for thyroid hyperplasia and hypertrophy, which are the known precursors to the first adverse effect from perchlorate, and therefore the critical effect (NAS, 2005, page 111).

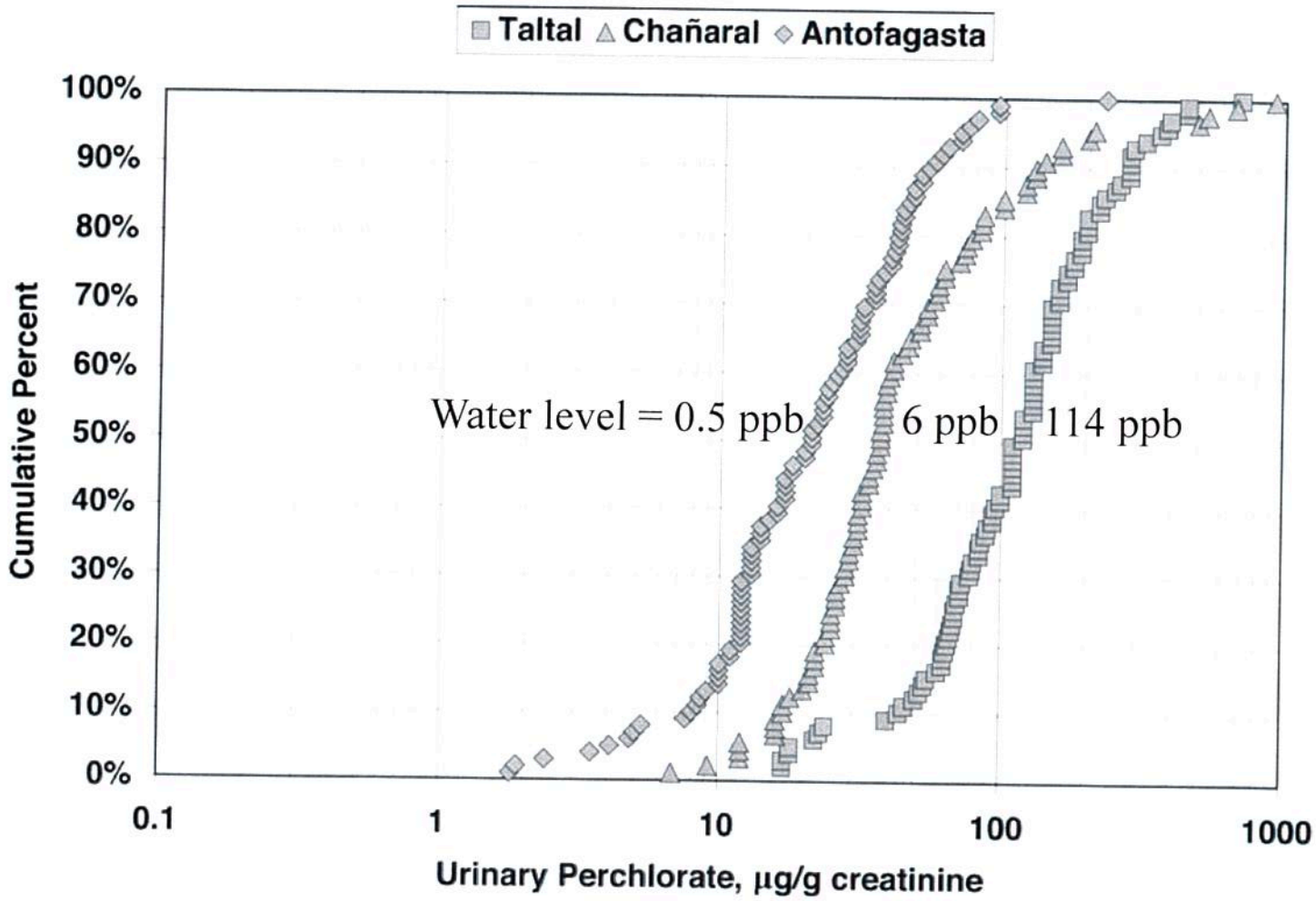
EPA, 2016, page 75

Biologically Based Dose Response Models for the Effect of Perchlorate on Thyroid Hormones in the Infant, Breast Feeding Mother, Pregnant Mother, and Fetus: Model Development, Revision, and Preliminary Dose-Response Analyses



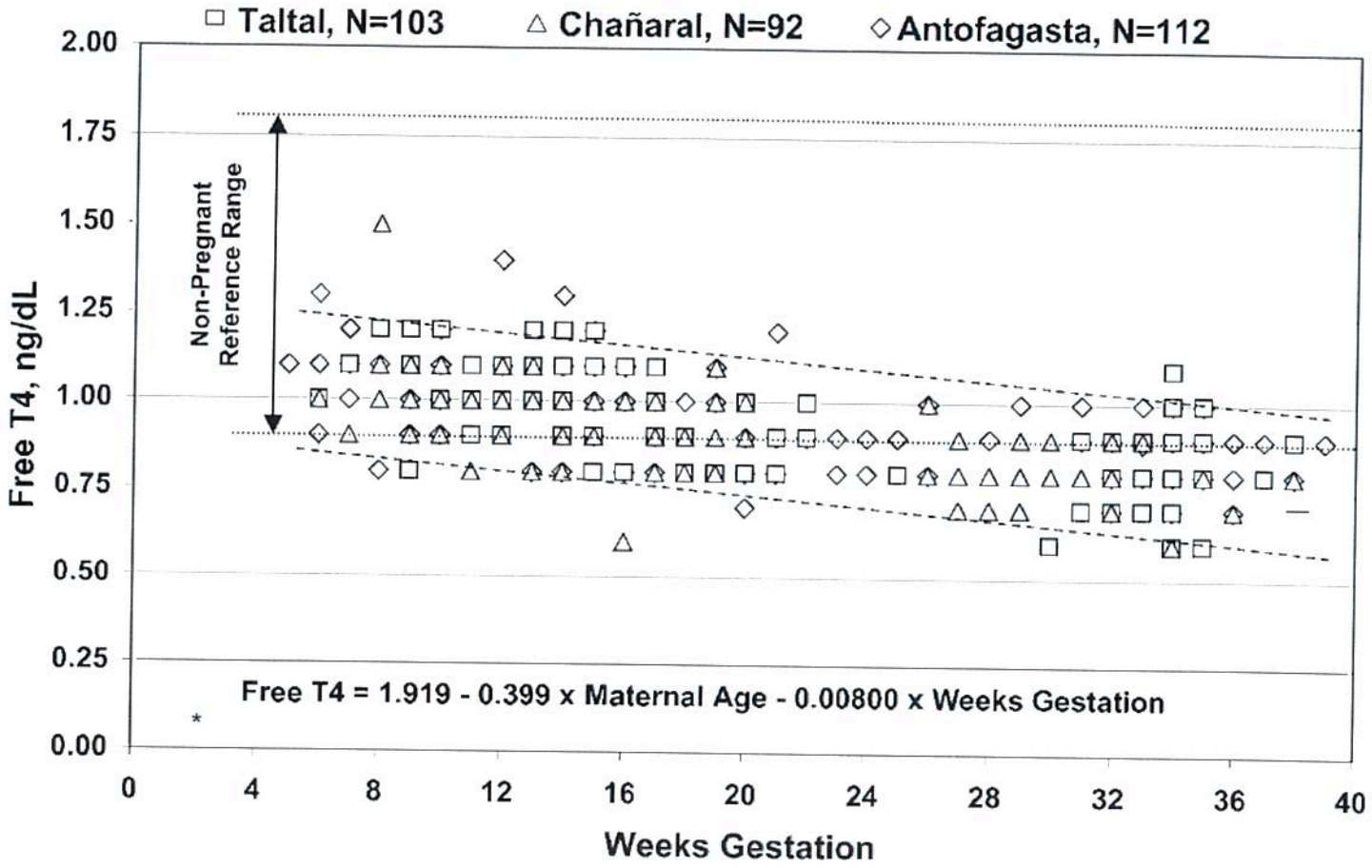
One Way Forward

- If EPA selects an iodine-deficient subpopulation as the basis for its MCLG, then this choice reduces the need for an uncertainty factor for within human variability.
- EPA should consider observations from prospective epidemiology studies, specifically Tellez et al. (2005) for applicability to the US, consistent with NAS (2005, page 69).
- EPA should consider how the model might be modified by up-regulation of symporter expression in the perchlorate dose range of interest, or if not possible, then un-modeled up-regulation leads to a more conservative or MCLG.



Tellez et al., 2005. Long-Term Environmental Exposure to Perchlorate Through Drinking Water and Thyroid Function During Pregnancy and the Neonatal Period . THYROID Volume 15, Number 9, 2005.

MATERNAL PERCHLORATE EXPOSURE DURING PREGNANCY



Tellez et al., 2005. Long-Term Environmental Exposure to Perchlorate Through Drinking Water and Thyroid Function During Pregnancy and the Neonatal Period . THYROID Volume 15, Number 9, 2005.

One Way Forward

- From a clinical perspective lactation is associated with iodine uptake in the breast, and, there is a well-documented clinical increase in thyroid hormone requirements during pregnancy.
- However, colleagues of the University of Cincinnati are unaware of any clinically increased rate of hypothyroidism in breast-feeding women compared to those choosing to feed their children formula. Thus, pregnancy and its increased thyroid hormone requirements appear to have a far greater impact on the mother than breast-feeding.
- EPA should explore the clinical relevance of the breast-feeding maternal population prior to choosing it for any point of departure in developing an MCLG.

Summary

- EPA's biologically based dose response model addresses many of the challenges the Agency has faced in establishing causality and uncertainty with perchlorate exposure.
- EPA's peer review panel highlights important limitations in the model that impact its viability in developing of an MCLG, the most important perhaps is whether the "critical effect" should be multiple steps before any adverse effect, and whether a 1st trimester fetus is more sensitive. A second peer review is planned for later this summer.
- However, EPA has a good basis for the sensitive population; thus, the need for uncertainty factor for within human variability is lessened.

Extra Slides

Practical Guidance on a Non-cancer Hazard Range for Effective Risk Management of Contaminated Sites: A Case Study with Trichloroethylene and other Chemicals

Tri-Service Environmental Risk Assessment Work Group
January 21, 2015

Pfau EJ, Thompson R, Gadagbui BK, Gillay D, Lowe J, Dourson M;*

**Hull & Associates, Inc.; Alliance for Site Closures; TERA; Barnes & Thornburg, LLP; CH2M-Hill; Alliance for Risk Assessment*

NAS (2009) & Hazard Assessment

- NAS (2009):
  - Suggested that methods for assessing non-cancer toxicity have the capability of determining hazard ranges.
- *ARA* project "Beyond Science and Decisions: From Problem Formulation to Dose Response"
  - Built on NAS (2009) report
  - Six of its cases studies are about evaluating noncancer *risk* (at different doses)
    - Each was vetted by a Science Panel
- We focus on:
  - modeling risk above the RfC/RfD using the benchmark dose method (Gentry *et al.*, 2011).

NAS (2014) & IRIS Process

- "**Finding:** EPA could improve documentation and presentation of dose-response information.

- **Recommendation:** EPA should clearly present two dose-response estimates: **a central estimate (such as a maximum likelihood estimate or a posterior mean) and a lower-bound estimate for a POD from which a toxicity value is derived.** The lower bound becomes an upper bound for a cancer slope factor but remains a lower bound for a reference value."
[emphasis added]

NAS (2014) & IRIS Process

- **"Finding:** IRIS-specific guidelines for consistent, coherent, and transparent assessment and communication of uncertainty remain incompletely developed. The inconsistent treatment of uncertainties remains a source of confusion and causes difficulty in characterizing and communicating uncertainty.
- **Recommendation:** Uncertainty analysis should be conducted systematically and coherently in IRIS assessments. To that end, EPA should develop IRIS-specific guidelines to frame uncertainty analysis and uncertainty communication. Moreover, uncertainty analysis should become an integral component of the IRIS process."

Reference Dose (IRIS)

- "The RfD (expressed in units of mg of substance/kg body weight-day) is defined as an estimate (**with uncertainty spanning perhaps an order of magnitude**) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime." [emphasis added]
- That is, the RfC/RfD is expected to be below the actual threshold for adverse effect in a sensitive subgroup.

Uncertainty vs. Imprecision

- Alternative interpretations:
  - Imprecision of a RfC is on both sides of the RfC. This is because a 2nd expert group might estimate a RfC higher or lower than the 1st group, if given the same information.
  - Uncertainty in a RfC, in contrast, lies mainly above the RfC. This is because RfCs are based on lower bounds on PODs and UFs are known to be protective.
  - For risk management decisions, uncertainty in the RfC is generally more important than imprecision, because managers are interested in making decisions that protect public health.

Hazard Range Development

- Hazard Range
  - Floor
  - Midpoint
  - Ceiling

Floor of the Hazard Range

- Identified as the RfC/RfD based on a single candidate value
- In the case of an RfC/RfD based on two or more candidate values
  - identified as the candidate RfC/RfD with the higher(est) confidence.
    - The reference value is not likely to change with further testing, except for mechanistic studies that might affect the interpretation of prior test results.
    - RfC could be modified if refined data are obtained to modify uncertainty factors – e.g., kinetic data for chemical-specific adjustment factors.

Floor of the Hazard Range

- The RfC/RfD is developed:
  - using UFs that are protective based on the observed behaviors of a typical toxicant
    - so that the RfC/RfD is an underestimate of the expected threshold value.
  - The floor of the hazard range may be denoted as a point below which risk managers are unlikely to recommend remedial action or exposure control.

Ceiling of the Hazard Range

- Is defined as the adjusted point of departure (POD_{adj})
- POD based on the critical concentration/dose of chosen study.
- Managers likely to take regulatory action above this ceiling since specific toxic effects can sometimes be seen.

Ceiling: Adjusted POD

- Adjustments for the dosing regime in the critical study, such as…

- Toxicokinetic differences between the test organism and humans
- Database quality, lack of NOAEL, and study duration; reductions are based on available data, or a factor of 3 used as a default for each area.
- The intent of these adjustments and reductions is to estimate the likely ceiling of the RfD/C by using the median value of the Ufs.

Midpoint of the Hazard Range

- Unlikely to be associated with adverse effects in a human population, based on…
  - Greater understanding of the range of uncertainty associated with RfC/RfD development and
  - Consistent with the definition of how "uncertainty of up to an order of magnitude" impacts the RfC/RfD

- It is a plausible estimate of the upper concentration or dose that is likely to be protective of the general population, including sensitive subpopulations

Midpoint of the Hazard Range

- Is a judgment that meshes four considerations:
  - Collective magnitude of the UFs
  - Steepness of the hazard slope describing exposures above the RfC/RfD
  - The confidence in the selection of the critical effect
  - The confidence in the POD

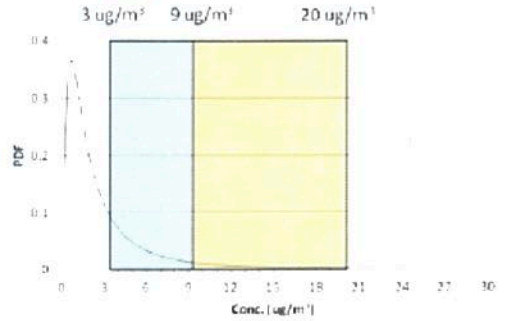
TCE as an Example

Table 7. Different uncertainty ranges for different TCE RfCs. All values are in $\mu g/m^3$. Shaded areas indicate best **overall uncertainty range** for risk management purposes.

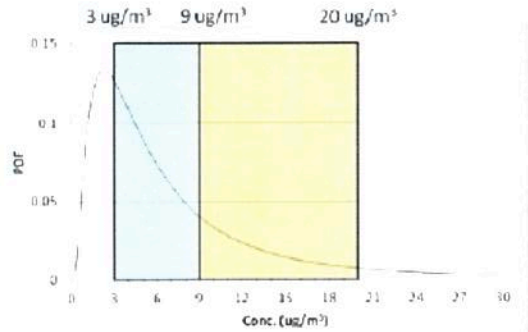
Study	Endpoint	IRIS UF [a]	Steep Slope [b]	Confidence		Uncertainty Ranges		
				Critical Effect [c]	Point of Departure [d]	Floor	Intermediate	Ceiling
Johnson et al (2003)	Fetal malformation	10	Lower	Low	Low	2	10	20
NTP (1988)	Toxic nephropathy	10	Higher	Medium	Medium to Low	3	9	30
Keil et al. 2009	Decreased thymus weight	100	NA	Medium	Medium to Low	2	20	60

a. Size of the uncertainty factor as on IRIS
b. Steepness of the hazard slope (*i.e.*, the slope of the line describing hypothetical population responses at concentrations above the RfC), as per Section 3.
c. Confidence in the choices of critical effect, as per Section 4.
d. Confidence in the POD, as per Section 4.

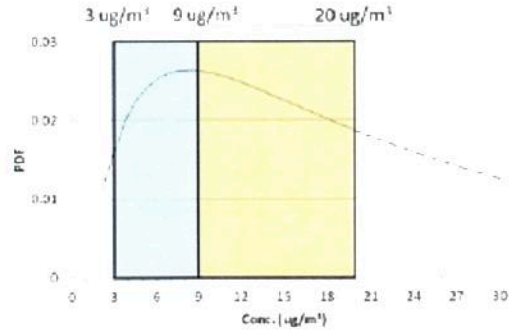
Practical Application of the Hazard Range for Noncancer Effect (e.g., TCE)



ES Figure 1a. Exposure distribution of indoor air concentrations primarily below the 3 $\mu g/m^3$ to 20 $\mu g/m^3$ hazard range. Relatively small proportion of exposures is higher than 3 $\mu g/m^3$. Nominal actions or no further action may be warranted for risk management.



ES Figure 1b. Exposure distribution of indoor air concentrations falling within the 3 $\mu g/m^3$ to 20 $\mu g/m^3$ hazard range. Relatively small proportion of exposures is higher than 9 $\mu g/m^3$. Limited action may be warranted for risk management



ES Figure 1c. Exposure distribution of indoor air concentrations primarily above the 3 $\mu g/m^3$ to 20 $\mu g/m^3$ hazard range. Actions to reduce exposures may be warranted for risk management.

Summary of data for the Development of the Hazard Range for the Arsenic

Chemical	IRIS RfD (mg/kg-day)	IRIS POD (mg/kg-day)	IRIS UF[a]	Steep Slope[b]	Confidence		Hazard Ranges (mg/kg-day)		
					Critical Effect[c]	POD[d]	Floor	Midpoint (Inter-mediate)	Ceiling
Arsenic*	3E-4	8E-4	3	Low	High	Medium	1E-4*	3E-4	8E-4*

a. Size of the uncertainty factor as on IRIS
b. Steepness of the hazard slope (*i.e.*, the slope of the line describing hypothetical population responses at concentrations above the RfC), as per Section 3.
c. Confidence in the choices of critical effect, as per Section 4.
d. Confidence in the POD, as per Section 4.

Summary of data for the Development of the Hazard Range for the Chromium (VI)

Chemical	IRIS RfD	IRIS POD	IRIS UF[a]	Steep Slope[b]	Confidence		Hazard Ranges (mg/kg-day)		
	(mg/kg-day)				Critical Effect[c]	POD[d]	Floor	Midpoint (Inter-mediate)	Ceiling
Chromium (VI)	3E-3	2.5	300 x 3	Low	Low	Low	3E-3	3E-2	3E-1***

a. Size of the uncertainty factor as on IRIS
b. Steepness of the hazard slope (*i.e.*, the slope of the line describing hypothetical population responses at concentrations above the RfC), as per Section 3.
c. Confidence in the choices of critical effect, as per Section 4.
d. Confidence in the POD, as per Section 4.

***Range judged to be 100 (see text under *"Evaluation"*)

Summary of data for the Development of the Hazard Range for the Tetrachloroethylene

Chemical	IRIS RfD (mg/kg-day)	IRIS POD (mg/kg-day)	IRIS UF[a]	Steep Slope[b]	Confidence		Hazard Ranges (mg/kg-day)		
					Critical Effect[c]	POD[d]	Floor	Midpoint (Inter-mediate)	Ceiling
Tetrachloroethylene	6E-3	6E-0	1000	Low	High	Low	6E-3	6E-2	6E-1**

a. Size of the uncertainty factor as on IRIS
b. Steepness of the hazard slope (*i.e.*, the slope of the line describing hypothetical population responses at concentrations above the RfC), as per Section 3.
c. Confidence in the choices of critical effect, as per Section 4.
d. Confidence in the POD, as per Section 4.

**Range judged to be 100 (see text under *"Evaluation"*)

Panel and Audience Comments

- Midpoint" may not be an appropriate term, but rather a best estimate of the sensitive human LOAEL. The authors noted the intent for the "midpoint" was to identify a value that will protect sensitive populations, based upon greater understanding of uncertainty.
- When greater uncertainty exists, one might want the "midpoint" to be closer to the RfD, rather than farther. The authors noted that larger uncertainty suggests a larger range between the floor and the ceiling.
- Regardless, all agreed that it is important to clearly communicate that the value is a judgment.

More comments at:
http://www.allianceforrisk.org/Workshop/WS8/DR8_Meeting_Report_and_Appendices.pdf

Hazard Range and the Problem Formulation

- Does the development of a hazard range help to address the following problems:
  - Hazardous waste site remedial objectives for chronic exposure levels
  - Communicating risk/hazard of exposure above RfC/RfD
  - Prompt/short term exposure action levels
    - Prompt action exposure concentrations
    - Application of lifetime RfC/RfD to acute and subchronic exposures
  - Confounding effects of assessing ambient background concentrations in air (TCE, Petroleum)

Summary

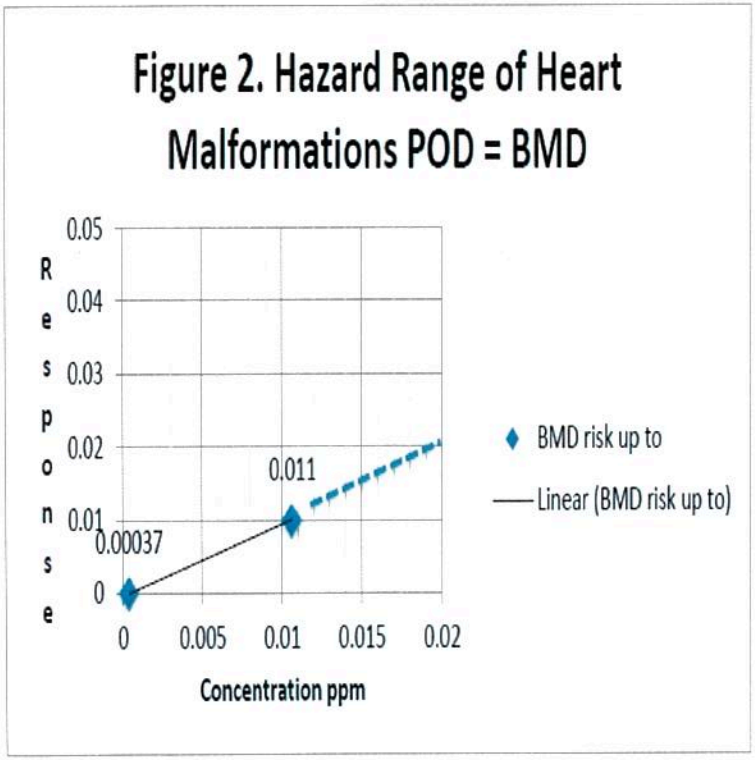
- The suggested method allows the development of a range in a non-cancer health risk value based on readily available information.
- The development of floor, midpoint and ceiling of the suggested range is consistent with the problem formulations of risk managers at waste sites. This range may be helpful with other contaminated media.
- Science Panel comments suggested several improvements including the possible integration with the work offered by Dr. Nancy Beck in the presentation on "Understanding Uncertainties and Confidence in Hazard Databases: An Example Using IRIS."

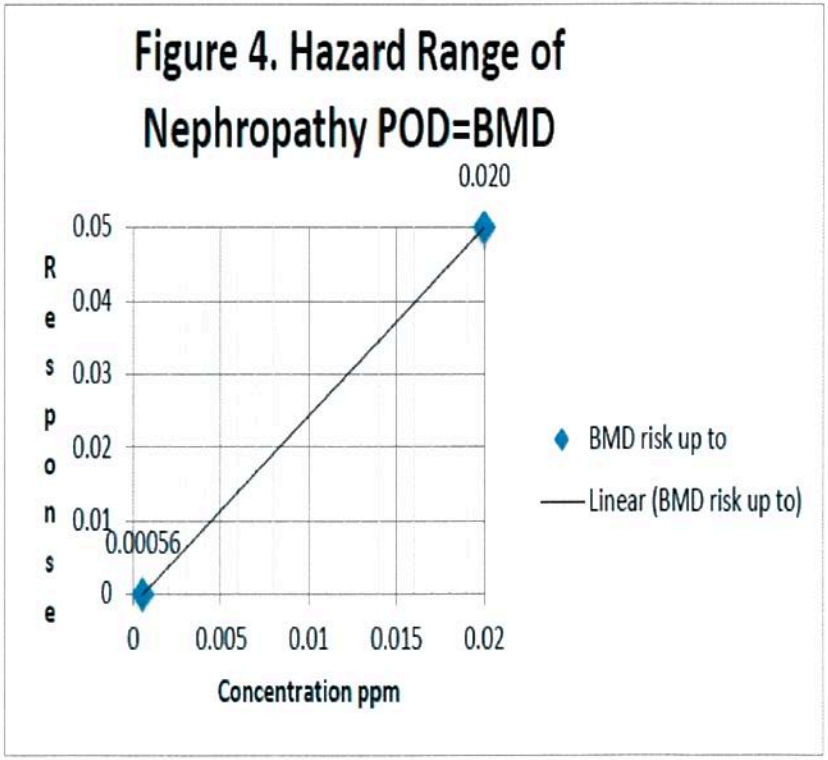
Extra Slides

Johnson et al., 2003
RfC = 2 μg/m^3

- Fetal malformation endpoint
  - Midpoint of 10 μg/m^3 is judged to be 5-fold above the candidate RfC due to:
    - Its small UF of 10,
    - Shallower hazard slope,
    - Low confidence in the critical effect, and
    - Low confidence in the choice of a benchmark response of 1% ($BMDL_{01}$)

Hazard Ranges of Two Candidate RfCs for TCE (as per Gentry et al.)





NTP, 1988
RfC = 3 μg/m^3

- Toxic nephropathy endpoint
  - Midpoint of 9 μg/m^3 is judged to be 3-fold above the candidate RfC due to:
    - Its small UF of 10,
    - Steeper hazard slope,
    - Medium confidence in the critical effect, and medium to low confidence in the choice of a benchmark response of 5% ($BMDL_{05}$)

Keil et al., 2009
RfC = 2 μg/m^3

- Decreased thymus weight endpoint
  - Midpoint of 20 μg/m^3 is judged to be 10-fold above the candidate RfC due to:
    - Its larger UF of 100, medium confidence in the critical effect, and medium to low confidence in its choice of a LOAEL as the POD
    - The effect shown by Keil et al. (2009) does not lend itself to dose-response modeling, so steepness of the slope was not assessed

Arsenic as an Example

Oral RfD Summary (after IRIS)

Critical Effect	**Experimental Doses**	**UF**	**MF**	**RfD**
Hyperpigmentation, keratosis and possible vascular complications Human Chronic oral exposure Tseng, 1977; Tseng *et al.*, 1968	NOAEL: 0.009 mg/L, converted to 0.0008 mg/kg-day LOAEL: 0.17 mg/L, converted to 0.014 mg/kg-day	3	1	3E-4 mg/kg-day

Chromium (VI)

Oral RfD Summary (after IRIS)

Critical Effect	Experimental Doses	UF	MF	RfD
None Reported Rat, 1-year drinking water study MacKenzie et al., 1958	NOAEL: 25 mg/L of chromium as K_2CrO_4 2.5 mg/kg-day (adj.)	300	3	3E-3 mg/kg-day

Tetrachloroethylene

Oral RfD Summary (after IRIS)

Principal Study/Critical Effect	POD (mg/kg-day)*	UF	Candidate RfDs (mg/kg-day)	RfD (mg/kg-day)**
Echeverria *et al.* (1995): neurotoxicity (reaction time, cognitive effects) in occupationally-exposed adults	LOAEL = 9.7	1,000[a]	0.0097	0.006
Cavalleri *et al.* (1994): neurotoxicity (color vision) in occupationally-exposed adults	LOAEL = 2.6	1,000[a]	0.0026	

*Derived by route-to-route extrapolation from inhalation exposure using PBPK model of Chiu and Ginsberg (2011).

**The RfD is supported by the two principal studies, as a midpoint of the range of available values (then rounded to one significant figure).

[a]Judged to be 100 (see text under "*Evaluation*")

Table 1. Summary of data for the Development of the Hazard Range for the Arsenic, Tetrachloroethylene and Chromium (VI) RfDs on IRIS (2014).

(All values for these ranges are in mg/kg-day).

Chemical	IRIS RfD	IRIS POD	IRIS UF[a]	Steep Slope[b]	Confidence		Hazard Ranges (mg/kg-day)		
	(mg/kg-day)				Critical Effect[c]	Point of Departure[d]	Floor	Midpoint (Intermediate)	Ceiling
Arsenic*	3E-4	8E-4	3	Low	High	Medium	1E-4*	3E-4	8E-4*
Tetrachloroethyl-ene	6E-3	6E-0	1000	Low	High	Low	6E-3	6E-2	6E-1**
Chromium (VI)	3E-3	2.5	300 x 3	Low	Low	Low	3E-3	3E-2	3E-1***

*The floor to ceiling range as found on IRIS

**Range judged to be 100 (see text under *"Evaluation"*)

***Range judged to be 100 (see text under *"Evaluation"*)

a. Size of the uncertainty factor, as per IRIS

b. Steepness of the hazard slope (*i.e.*, the slope of a hypothetical line describing population responses at concentrations above the RfD), as per Section 3 of eth case Study Report.

c. Confidence in the choices of critical effect, as per Section 4 of the Case Study Report.

d. Confidence in the point of departure, as per Section 4 of eth Case Study Report.

The concept of hormesis and application in risk assessment

Michael Dourson with help from Ed Calabrese
Risk Science Center (aka, TERA Center)
University of Cincinnati, College of Medicine

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Abstract

- Low dose non-monotonic (LDNM) behavior occurs routinely in biological systems. Such behavior can be due to essentiality, toxicology masking or hormesis.
- Hormeisis is characterized by low-dose adaptive effect and high-dose adverse effect.
- As with other LDNM, hormesis depends on endpoint measured and chemical mode of action (MOA).
- Because the hormetic biphasic dose response may represent a general pattern of biological responsiveness, or is otherwise part of the adverse outcome pathway of many chemicals, it should become progressively more significant within risk assessment practice.

HORMESIS CONCEPT

- Low doses of numerous stressors (e.g. exercising, intermittent fasting, hypoxia, heat, cold, ionizing/non-ionizing radiation, electricity, toxins, chemicals/drugs) can stimulate a wide range of adaptive responses
- Calabrese, numerous citations

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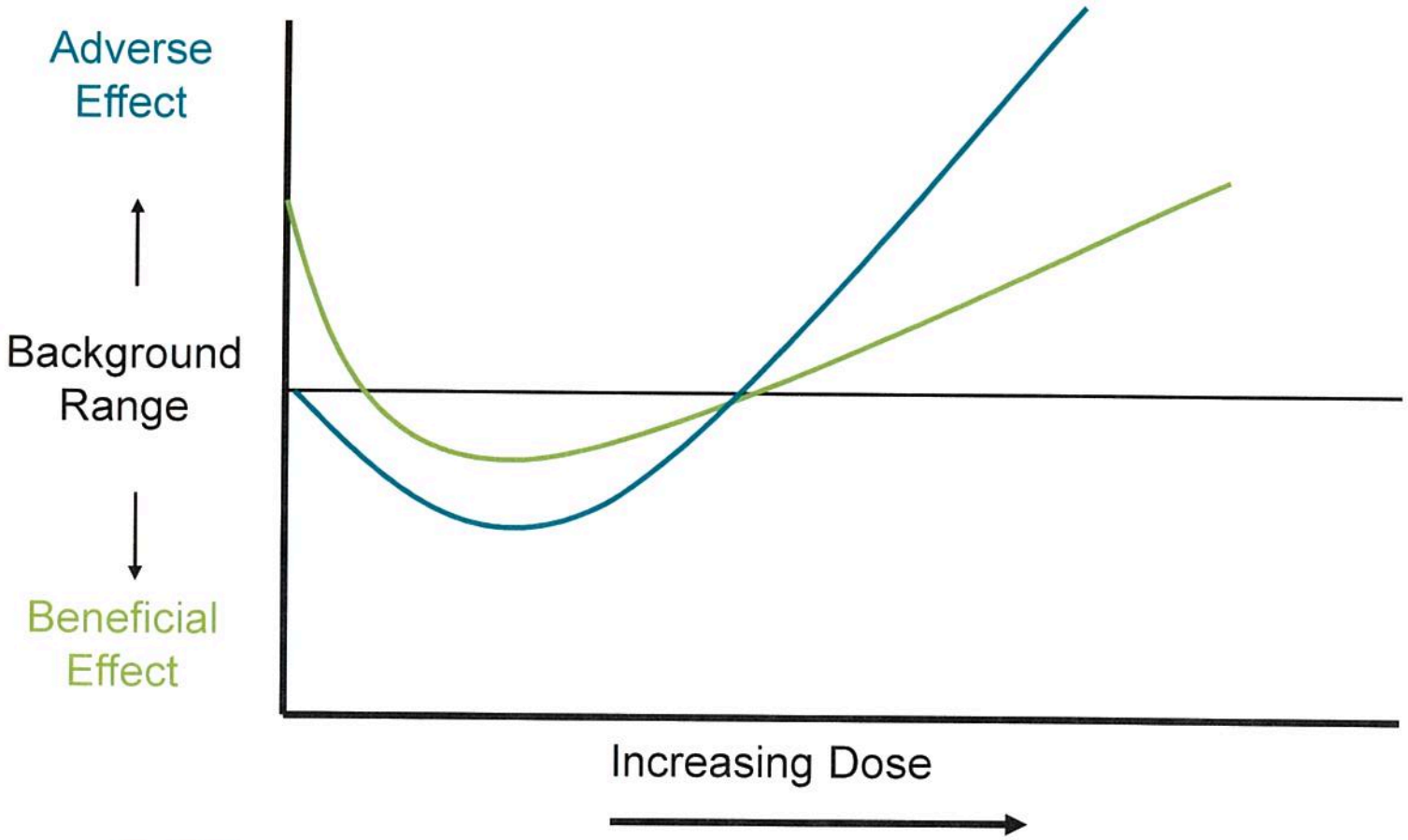
General Form of the Essentially/Hormesis Curves



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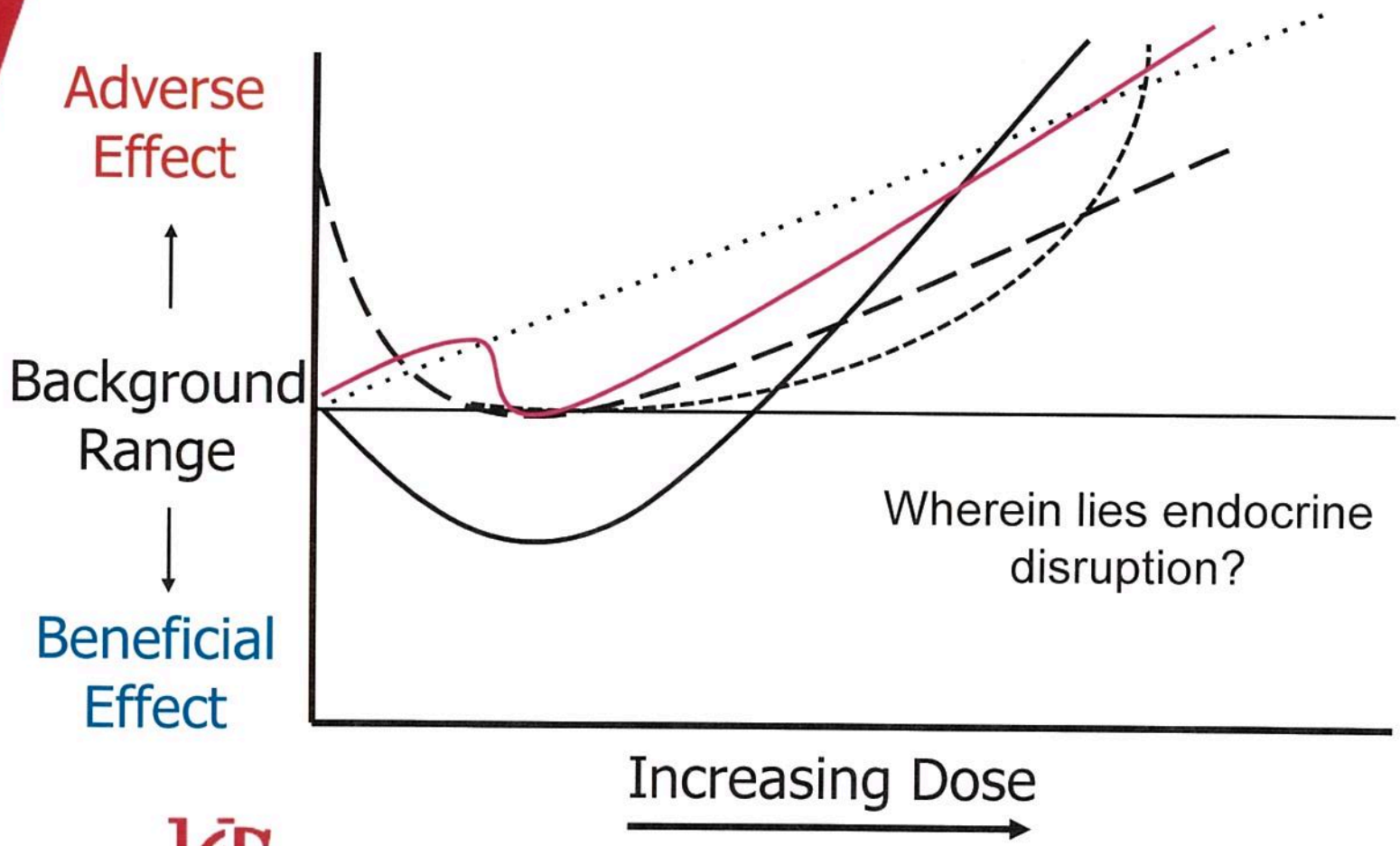
A Variety of Possibilities
Essentially (– –), Hormesis (–), Toxicity (---), Cancer (...) LDNM (red)



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Mechanisms for LDNM (partial)

- Essential nutrients – such as chromium & copper
- Overcompensation & induction of protective responses – increased heat shock proteins from mild heat stress or gutathione from oxidative stress
- Benefits and risks to different organs---low dose ethanol benefits in heart, but high dose problems in CNS & liver
- Shifts in response spectrum – cyclophosphamide increased resistance to flu; decreased resistance to tumors.
- Stimulatory and inhibitory receptors within same organ (apomorphine)
- Masking---antimicrobial stimulation of growth masking overall toxicity measured by changes in body weight

A Way Forward?

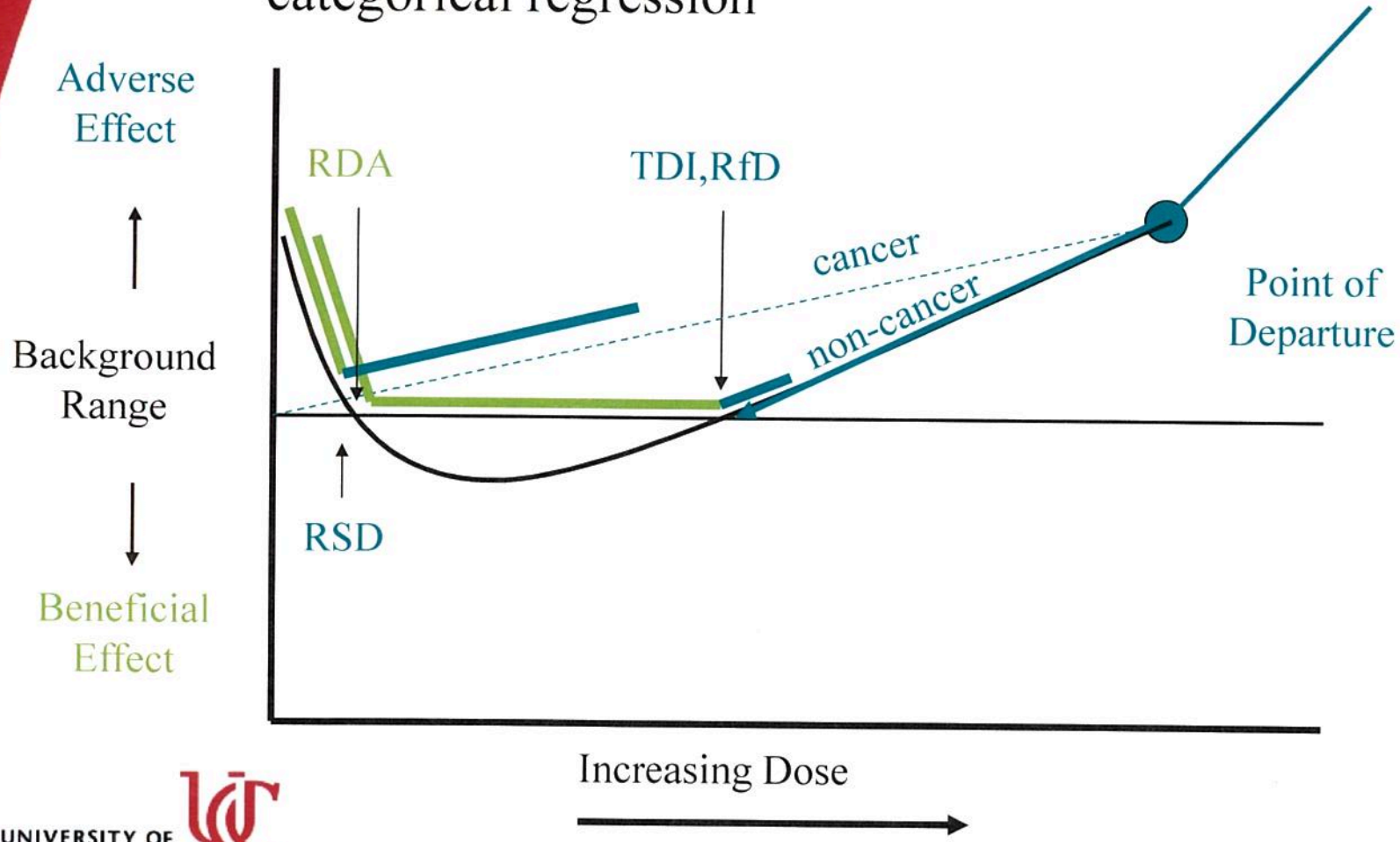
Case by Case (current approach for essential nutrients)

A Mode of Action (MOA) approach: Are MOAs the same and effect severities similar?

- No and No? Develop "RDA" and RSD/RfD, allow overlap if biology indicates, or plot composite effect/benefit curve by categorical regression
- No and Yes? Plot composite data using new models, determine nadir
- Yes and No? Plot composite effect/benefit curve by addressing severity via categorical regression
- Yes and Yes? Plot with new models, determine nadir

Is mechanism the same? Effect severity similar?

No and No: Develop RDA, and RSD, TDI or RfD; combine curves (as below) or model via categorical regression



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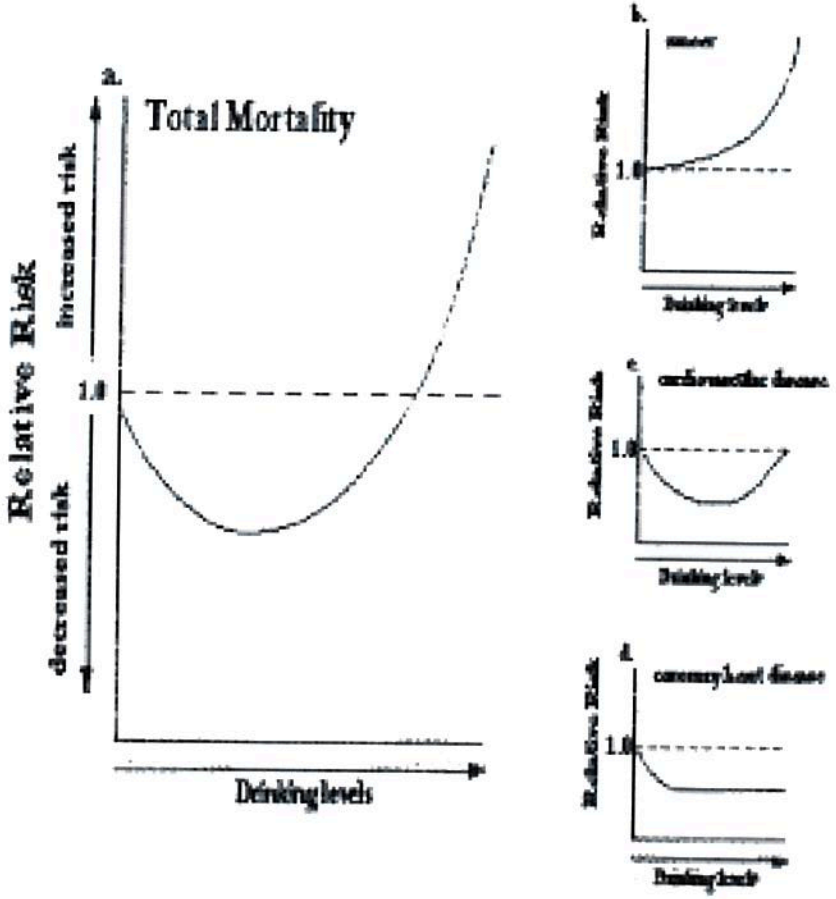
Is mechanism the same? Effect severity similar?

No and Yes: Plot composite data using new models, determine nadir

- Total mortality: J-shape response for ethanol intake
- Cancer: no apparent increase until higher drinking levels
- Cardiovascular: U-shaped response
- Coronary Heart Disease: L-shaped threshold effect



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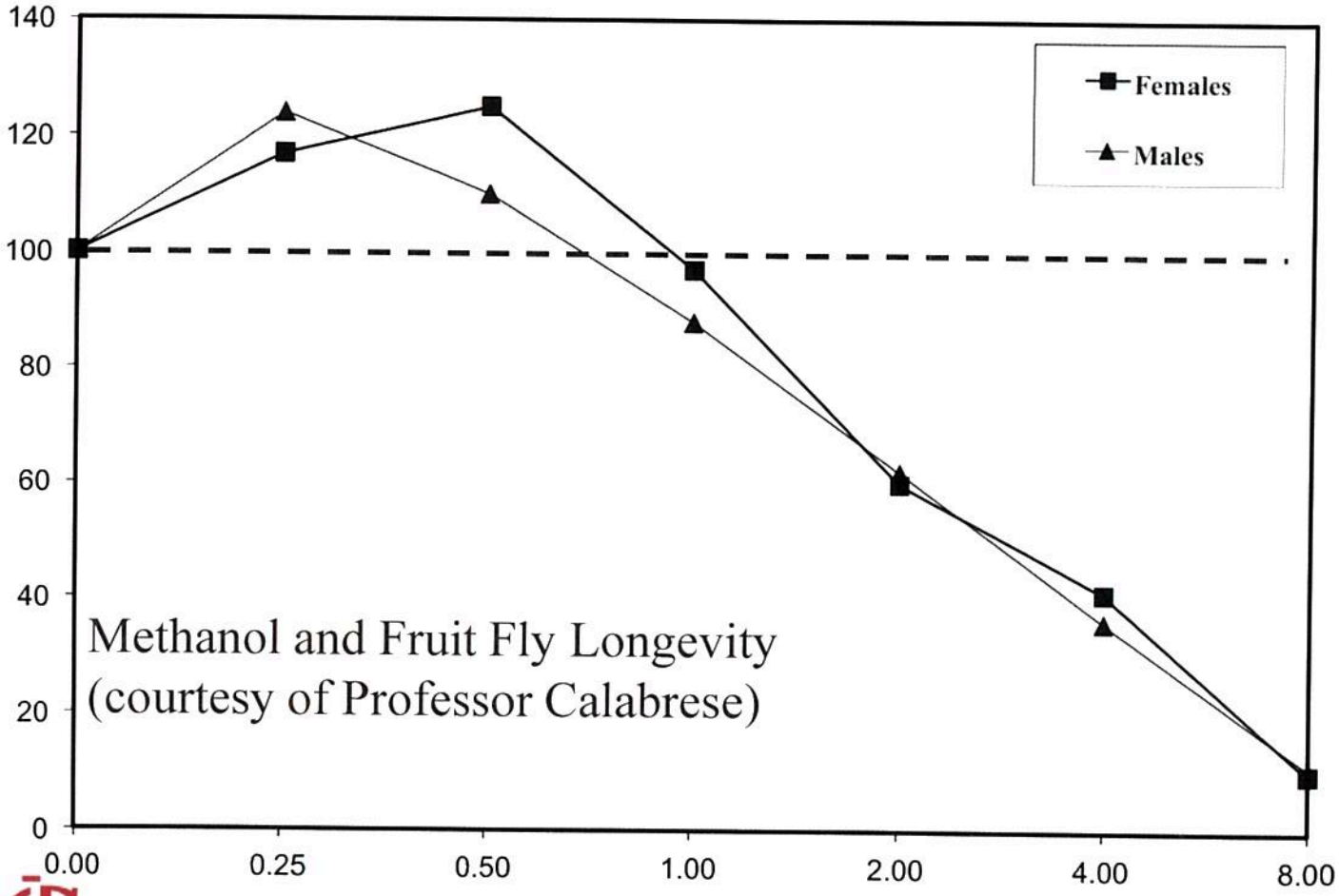
Is mechanism the same? Effect severity similar?

No* and Yes:* Plot composite data using new models, determine nadir



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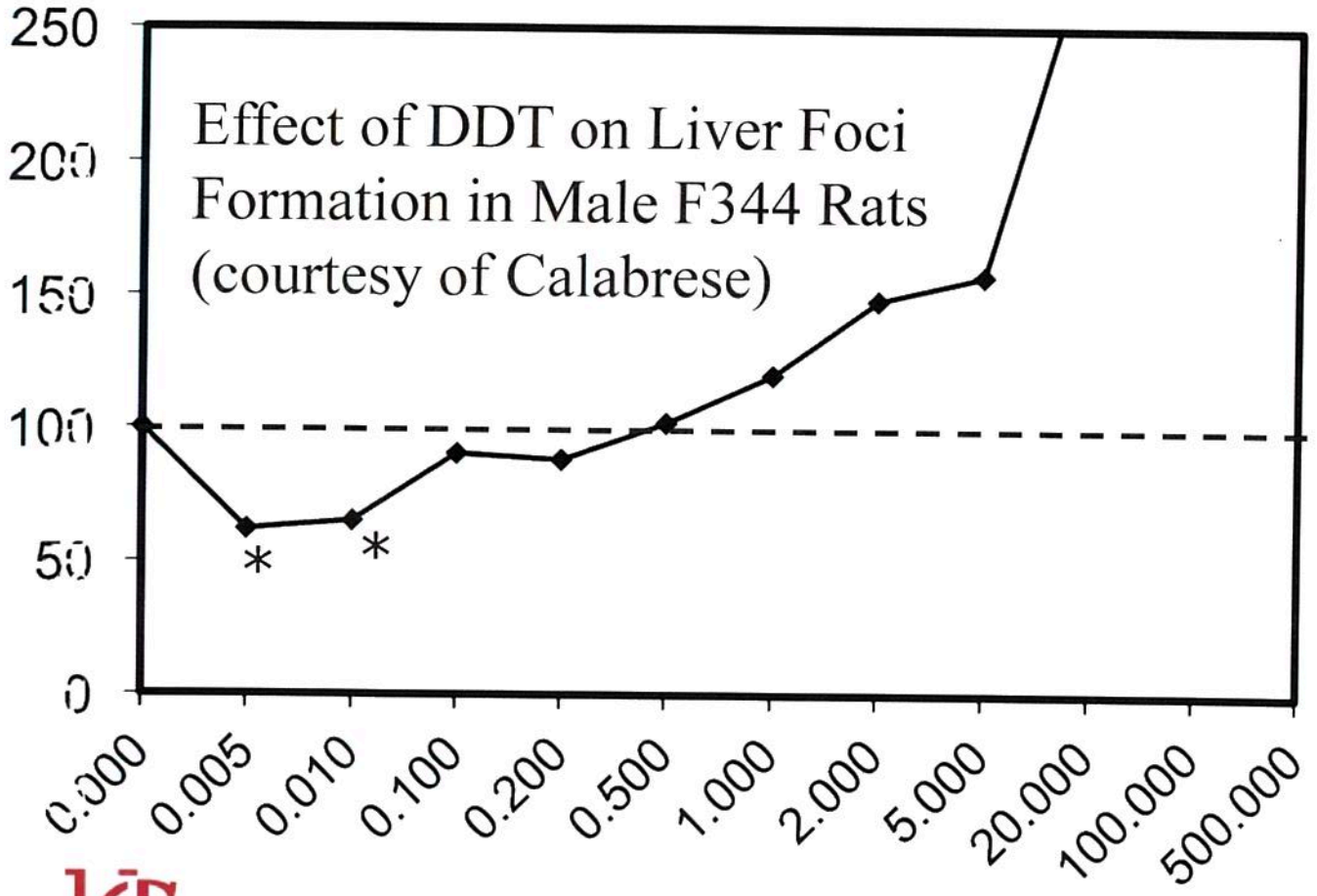
Is mechanism the same? Effect severity similar?

Yes and No: Plot composite effect/benefit curve by addressing severity via categorical regression.



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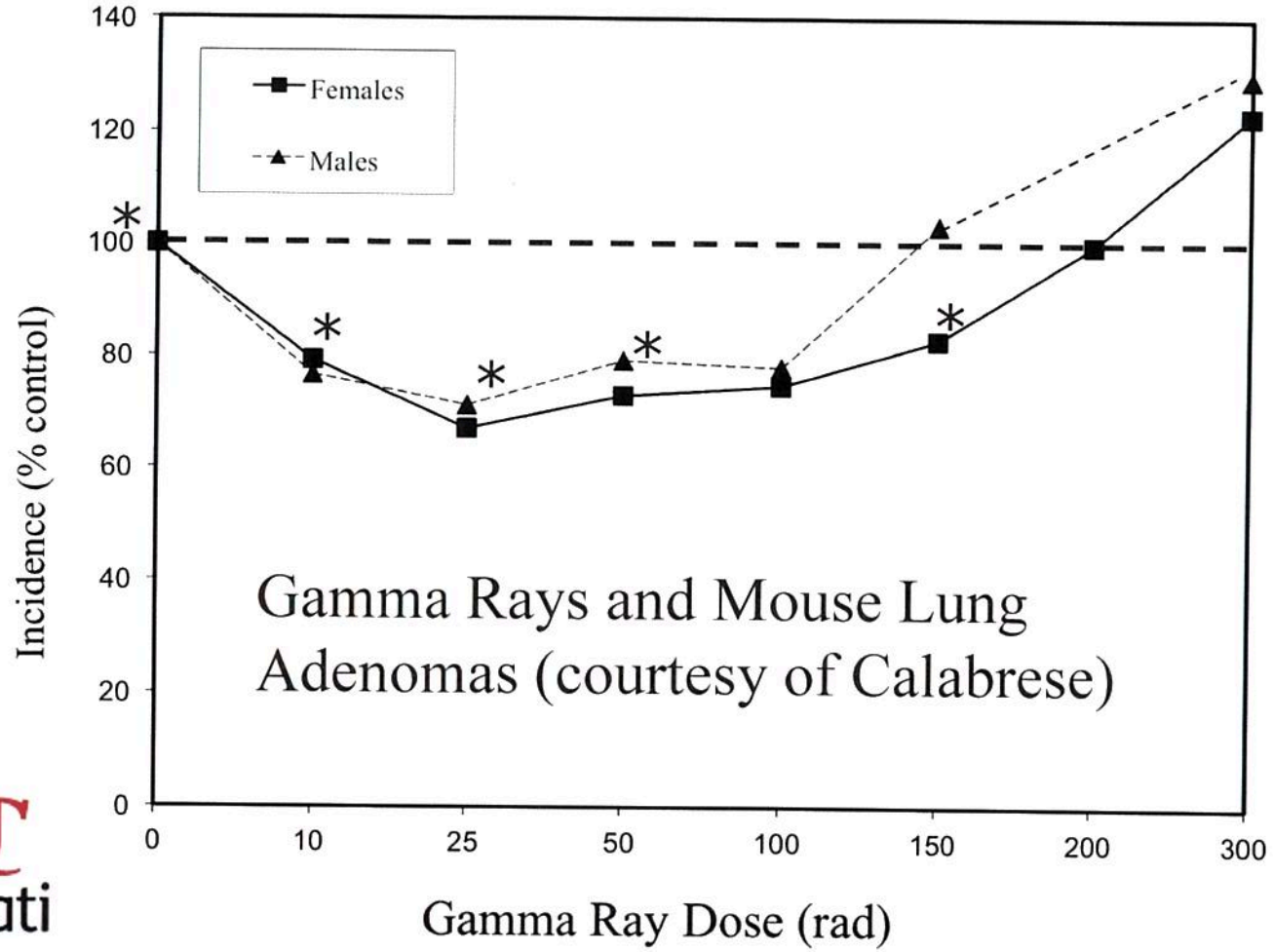
Is mechanism the same? Effect severity similar?

Yes and No: Plot composite effect/benefit curve by addressing severity via categorical regression.



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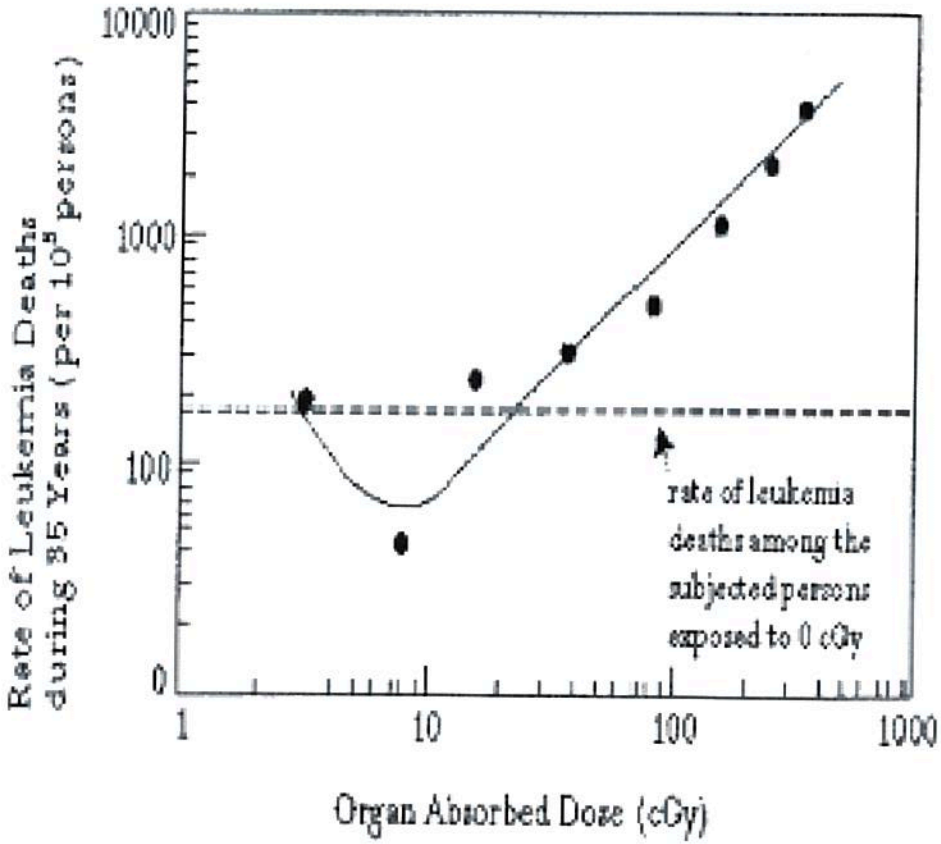
Is mechanism the same? Effect severity similar?

Yes and Yes: Plot using new models and determine nadir

- Survivors of Hiroshima and Nagasaki
- Radiation hormesis
- 8 cGy is optimum for suppression of leukemia
- Dr. Luckey's claim that "low dose radiation is stimulating and essential for life!"



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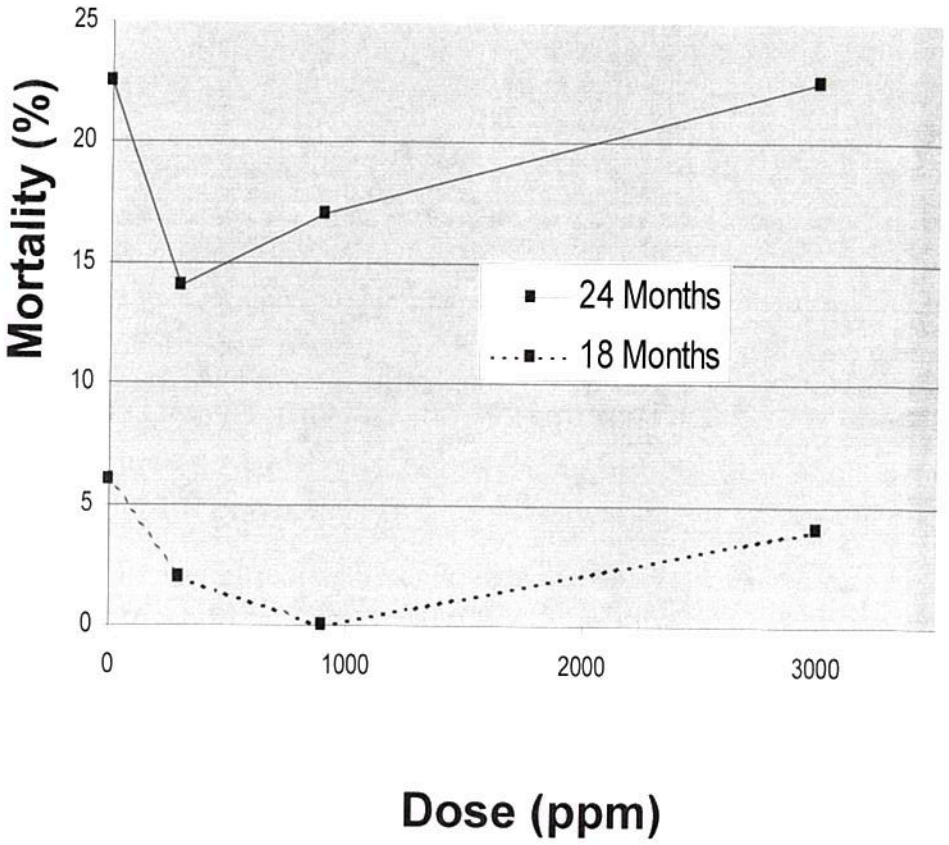
Is mechanism the same? Effect severity similar?

Yes and Yes: Plot using new models and determine nadir

- DR curve with minima at the middle dose at 18 mos. And a minima at the low does at 24 mos.
- Survival at 0 dose keeps deteriorating with age.
- Mortality is inhibited at the medium doses of compound.



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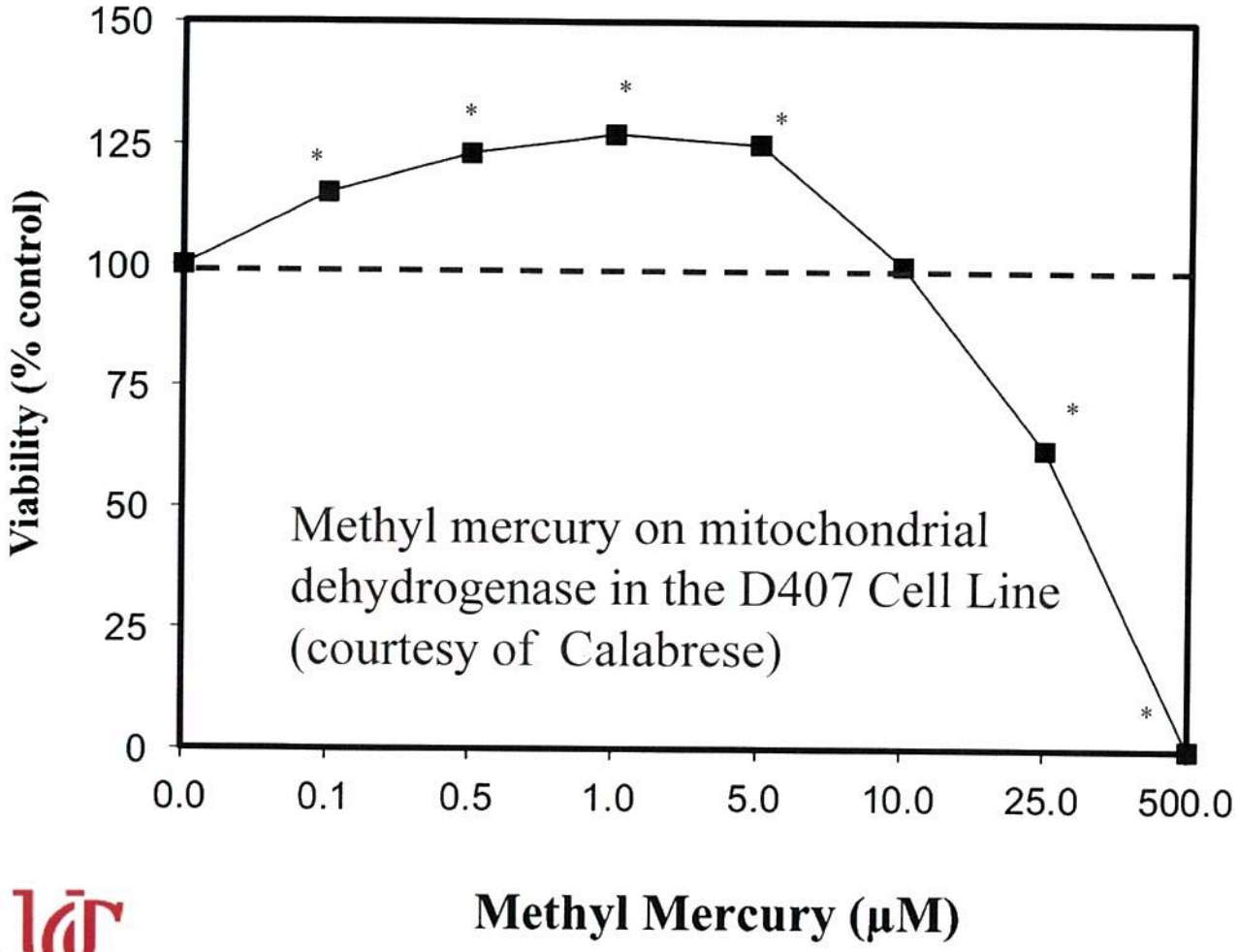
Is mechanism the same? Effect severity similar?

Yes and Yes: Plot using new models and determine nadir



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Current Issues and Activities:

Critical Effect & Point of Departure

Trend: better characterizing dose response of critical effect in low-dose region. For example,

- Benchmark dose (BMD), categorical regression and Markov-Chain Monte Carlo for toxicokinetic models (Andersen and Clewell, multiple publications).
- Cooperative agreements to address dose-response approaches for mutagenic chemicals (Moore and Haber, 2006).
- Evaluation of severity, adversity, adaptation, compensation, hormesis and essentiality in critical effect.

Current Issues and Activities:

Use of Precursor Data and Adverse Outcome Pathways

Trend: increasing use of precursor data to judge mode of action. For example,

- Meek et al. (2008, 2014) Mode of action frameworks for evaluating experimental animal evidence in relationship to humans.
- U.S. National Institute for Occupational Safety and Health research for evaluating biomarkers; includes Bayesian network for using biomarker data.
- U.S. Environmental Protection Agency (EPA) research on the pathology-physiological progression to develop criteria to categorize endpoints (AOPs).

Current Issues and Activities:

Uncertainty Factors

Trend: using chemical data to move from default values of 10-fold. For example,

- International Programme on Chemical Safety (Meek et al., 1994; IPCS, 2005; EPA, 2013) methods for using chemical-specific adjustment factors (CSAFs).
- SOT Award-winning papers on implications of genetic polymorphisms for development of uncertainty factors and CSAFs (Nauman et al., 1998; Haber et al., 2002).
- The default is to use data; use 10-fold reluctantly.

Implications for Essentiality Risk Characterization

A Risk Assessment Definition for Essential Elements…

> Statistical or biological significant increases in adverse effects at both lower and higher doses from an optimal or background point in the dose response curve.

A Risk Assessment Definition for Hormesis…

> Statistical or biological significant decreases in adverse effects below background in the low dose region.

With either definition, low, but yet still measurable doses, exhibit a positive, beneficial effect.

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Conclusions

- The existing risk assessment & management model is general and can incorporate essential elements, but it lacks precision.
- Hormesis is a general biological concept. It represents an adaptive strategy through which biological performance is enhanced and mediated.
- A mode of action framework may provide approaches for characterizing risk and benefit of hormetic and other LDNM elements, but must address the differing severity of effects, perhaps through categorical regression.

Extra Slides

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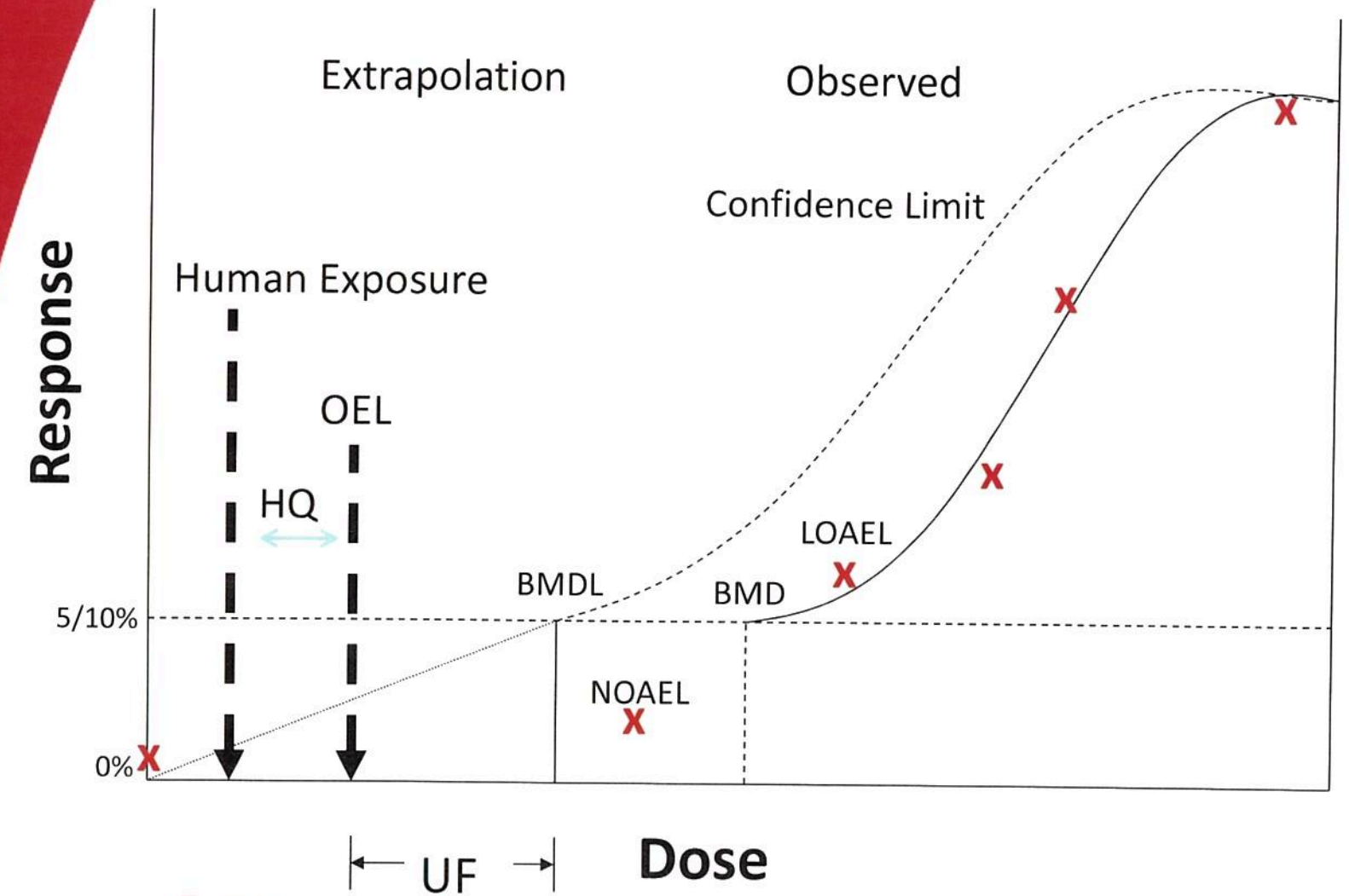

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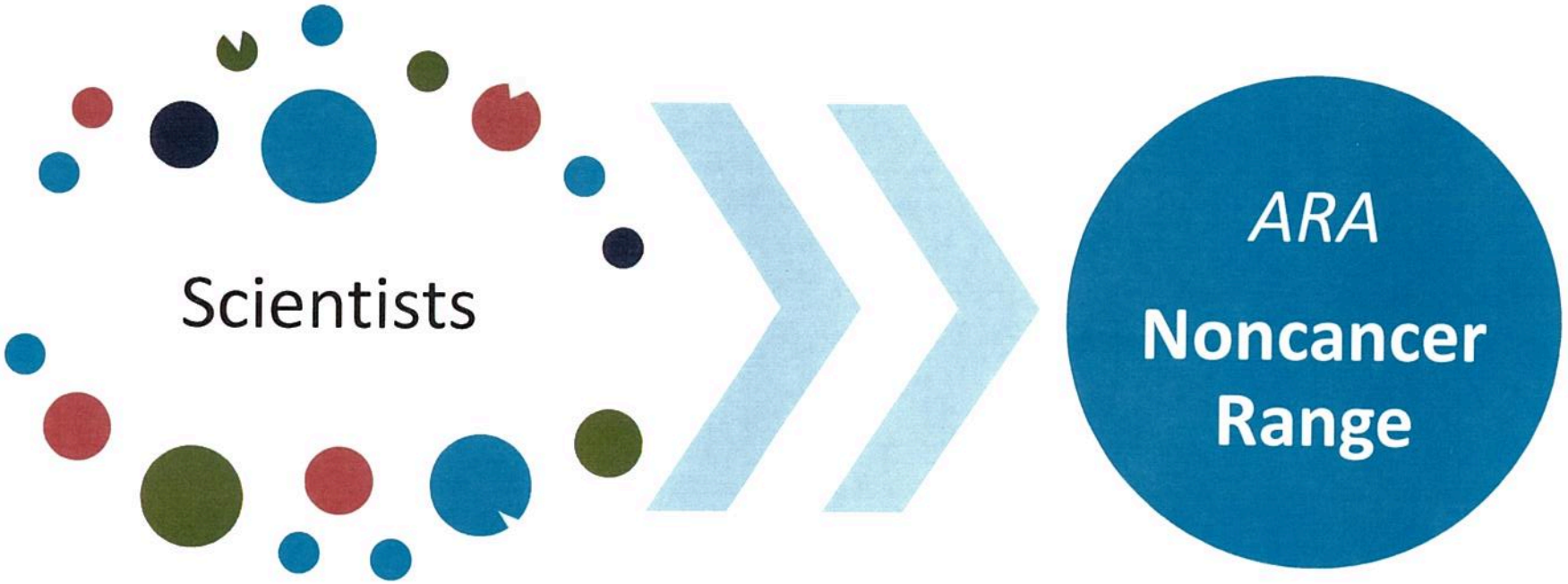
Managing the Non-Cancer Risks at Hazardous Waste Sites: Trichloroethylene (TCE) as a Case Study



Michael Dourson, Risk Science Center, U.Cin.
Rod Thompson, Risk Options, LLC
Edward Pfau, Hull and Associates

Abstract

- The 2011 EPA reference concentration (RfC) TCE presents risk managers evaluating vapor intrusion with two challenges:
  - Discerning TCE concentrations that are attributable to subsurface contamination, and
  - Selecting remedial objectives that result in acceptable indoor TCE levels.
- RfCs exhibit several precautionary adjustments, but do not show a range as for cancer (i.e., 10^{-4} to 10^{-6}). Thus, risk managers do not often consider an RfC range when deciding.
- A method for determining the safety range for noncancer hazard is presented:
  - Comparable to the cancer risk range
  - Consistent with the uncertainty inherent in EPA's RfC calculation.
  - TCE Safety range was judged to be 3 to 30 ($\mu g/m^3$).

State's Relocation or Immediate Response Action Levels

Problem Formulation: So which "safe" levels are correct?

State	Urgent/Immediate Action Residential	Urgent/Immediate Action Commercial	Imminent Action Residential	Imminent Action Commercial
Alaska	2	8.4		
California	6	(24)		
Connecticut	5	8		
Indiana	20			
Massachusetts	6	24	20	60
New Hampshire	2	8.8		
New Jersey	4	18		
New York	20			
Ohio	6.3	26	20	60
Region 09	6	24		
Region 10	2	8		
Region 7	2	8		

State's Very Rapid Response Action Levels

All of these are in the safe range for the appropriate group!

State	Urgent/Immediate Action Residential	Urgent/Immediate Action Commercial	Imminent Action Residential	Imminent Action Commercial
Alaska	2	8.4		
California	6	(24)		
Connecticut	5	8		
Indiana	20			
Massachusetts	6	24	20	60
New Hampshire	2	8.8		
New Jersey	4	18		
New York	20			
Ohio	6.3	26	20	60
Region 09	6	24		
Region 10	2	8		
Region 7	2	8		

Problem Response: Alliance for Risk Assessment (*ARA*)

- *ARA* Steering Committee accepts proposal Summer 2012
  - United States Army Corps of Engineers, Oregon Department of Environmental Quality, Indiana Department of Environmental Management, U.S. Environmental Protection Agency (EPA), University of Cincinnati, College of Medicine, Texas Commission on Environmental Quality, Agency for Toxic Substance & Disease Registry, Neptune & Company, Inc.
- TCE Workgroup formed in the Fall of 2012
  - Open invitation, broad interest and participation
  - Trichloroethylene (TCE) Risk Assessment Guidance for Contaminated Sites (April 2013)
  - Webcast: Practical Guidance for Contaminated Sites: TCE Risk Assessment Case Study (November 4, 2013); over 300 scientists from multiple international organizations, including government, industry, academia and NGOs, on 6 conference calls and one webinar.
  - Alliance for Risk Assessment (*ARA*) review Summer of 2015
  - Publication in the Spring of 2016

ARA Science Panel
Thoughts and Response

Purpose: Guidance for Noncancer Range at Contaminated Sites

- Develop a range in noncancer risks, similar to the range used for cancer risks in management of waste sites, using readily available information from U.S. EPA and elsewhere.

- Create range to enable evaluation of uncertainty in the noncancer benchmark.

- Demonstrate confidence in this range so that the range can be considered in the determination of management choices.

NAS (2014) & IRIS Process

- **Finding:** EPA could improve documentation and presentation of dose-response information.

- **Recommendation:** EPA should clearly present two dose-response estimates: **a central estimate (such as a maximum likelihood estimate or a posterior mean) and a lower-bound estimate for a POD from which a toxicity value is derived.** The lower bound becomes an upper bound for a cancer slope factor but remains a lower bound for a reference value."

NAS (2014) & IRIS Process

- **Finding**: IRIS-specific guidelines for consistent, coherent, and transparent assessment and communication of uncertainty remain incompletely developed. The inconsistent treatment of uncertainties remains a source of confusion and causes difficulty in characterizing and communicating uncertainty.

- **Recommendation**: Uncertainty analysis should be conducted systematically and coherently in IRIS assessments. To that end, EPA should develop IRIS-specific guidelines to frame uncertainty analysis and uncertainty communication. Moreover, uncertainty analysis should become an integral component of the IRIS process.

Developing the Range

An RfC is an estimate (**with uncertainty spanning perhaps an order of magnitude**) of a daily oral (for RfD) or continuous inhalation (for RfC) exposure to the human population (**including sensitive subgroups**) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

- Arsenic RfD on IRIS.
  - There was not a clear consensus among Agency scientists on the oral **RfD of 0.3 ug/kg-day**. Applying the Agency's RfD methodology, strong scientific arguments can be made for various values within a factor of 2 or 3 of the currently recommended **RfD value, i.e., 0.1 to 0.8 ug/kg-day**. It should be noted, however, that the RfD methodology, by definition, yields a number with inherent uncertainty spanning perhaps an order of magnitude.

Developing the Range (con't)

- In the IRIS Summary for TCE, U.S. EPA identified three candidate RfC values from principal and supporting studies for the noncancer inhalation toxicity of TCE. These are:
  - Candidate RfC of 2 $\mu g/m^3$ based on decreased thymus weight in female mice (Keil *et al.*, 2009);
  - Candidate RfC of 2 $\mu g/m^3$ based on fetal heart malformations in rats (Johnson *et al.*, 2003); and
  - Candidate RfC of 3 $\mu g/m^3$, based on toxic nephropathy in female rats (NTP, 1988).
- Each of these candidate RfCs may be evaluated with respect to the imprecision and the uncertainty inherent in its derivation.

Imprecision Versus Uncertainty

- **Imprecision** of a RfC is on both sides of the RfC. This is because a 2nd expert group might estimate a RfC higher or lower than the 1st group, if given the same information.
- **Uncertainty** in a RfC, in contrast, lies mainly above the RfC. This is because RfCs are based on lower bounds on points of departure & uncertainty factors are known to be protective.
- For risk management decisions, uncertainty in the RfC is generally more important than imprecision. Managers are interested in making decisions that protect public health and uncertainties in a RfC are generally more informative.

Different Uncertainty Ranges for TCE RfCs

Table 7. Uncertainty ranges for different TCE RfCs in $\mu g/m^3$. Shaded areas indicate best **overall uncertainty range** for risk management.

Study	IRIS UF [a]	Steep Slope [b]	Confidence		Uncertainty Ranges		
			Critical Effect [c]	Point of Departure [d]	Floor	Intermediate	Ceiling
Johnson et al (2003)	10	Lower	Low	Low	2	10	20
NTP (1988)	10	Higher	Medium	Medium to Low	3	9	30
Keil et al. 2009	100	NA	Medium	Medium to Low	2	20	190

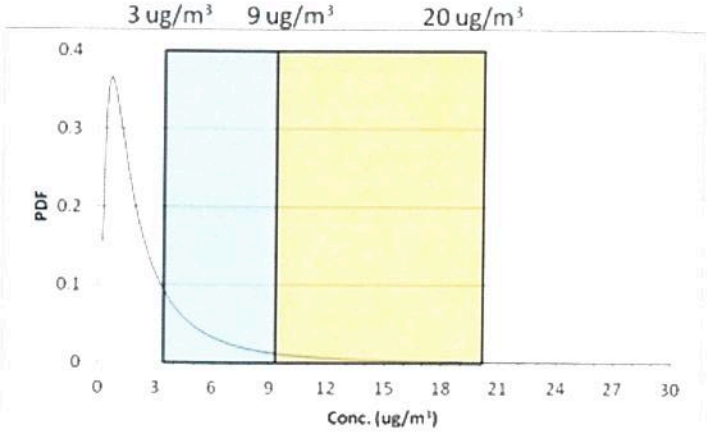


Figure 3a. Exposure distribution of indoor air concentrations primarily below the 3 µg/m^3 to 20 ug/m^3 hazard range. Relatively small proportion of exposures is higher than 3 µg/m^3. Nominal actions or no further action may be warranted for risk management.

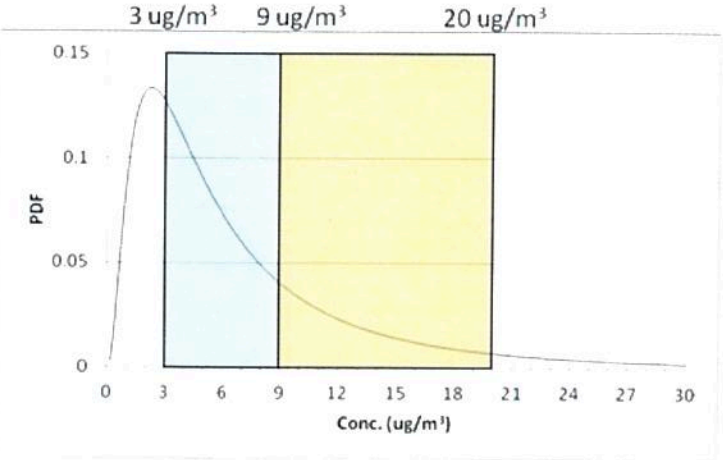


Figure 3b. Exposure distribution of indoor air concentrations falling within the 3 µg/m^3 to 20 µg/m^3 hazard range. Relatively small proportion of exposures is higher than 9 µg/m^3. Limited action may be warranted for risk management.

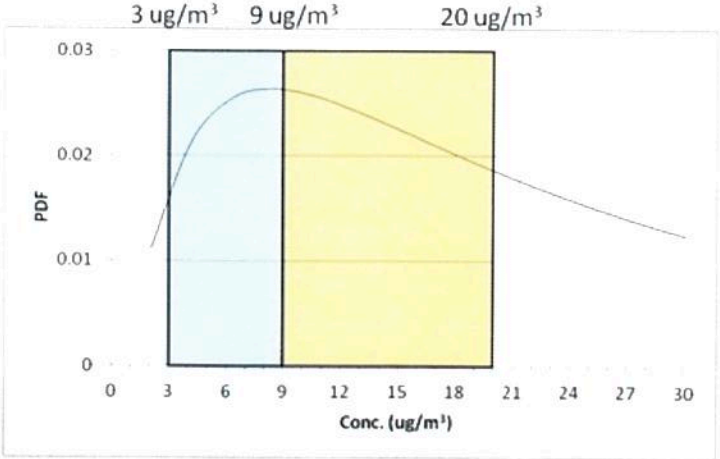


Figure 3c. Exposure distribution of indoor air concentrations freqeuently above the 3 µg/m^3 to 20 µg/m3 hazard range. Actions to reduce exposures may be warranted for risk management.

TCE Action Level Decision Matrix

Exposure Scenario	Chronic Response ug/m^3	Accelerated Response ug/m^3	Prompt Action ug/m^3
Residential	>3.2 but < 9.4	> 9.4 but < 21	> 21
Commercial (8 hr)	> 13 but < 39	> 39 but < 88	> 88
Response Action	Within months coordinate with local or state personnel to communicate risk from long-term exposures.	Within weeks coordinate with local and state personnel to communicate risk from short term exposure.	Within days coordinate with local and state personnel to communicate risk from several days exposure.
	Based on chronic exposures, remedial objectives can be based anywhere in the range of 3.2-9.4 ug/m^3 (residential) or 13-39 ug/m^3 (commercial) within 6 months.	Based on short term exposures, remedial objectives can be based anywhere in the range of 3.2-9.4 ug/m^3 (residential) or 13-39 ug/m^3 (commercial) within 10 days to 3 months.	Based on acute exposures, remedial objectives can be based anywhere in the range of 3.2-9.4 ug/m^3 (residential) or 13-39 ug/m^3 (commercial) within a matter of days.

Summary: Noncancer Range at Contaminated Sites

- A noncancer range was developed for the TCE RfCs. Range included floor, midpoint and ceiling.
- Range for EPA's TCE RfC was judged to be ***3 to 30 µg/m³***.
  - The results of the NTP study-based RfC were used to determine the floor and midpoint of this uncertainty range.
  - The highly controversial results from the Johnson et al. (2003) study-based RfC, while associated with low confidence, were considered for the ceiling level, but journal peer review recommended against this.
  - This 3 µg/m³ to 30 µg/m³ range was entirely within the wider individual uncertainty range from the Keil et al. (2009) study; therefore, this latter study was considered to be confirmatory.

Need for Further Effort

- Continue this dialogue regarding vapor intrusion risk assessment issues, including agencies and responsible parties.
- Study the proposed method for the noncancer risk range.
- Resolve discrepancies in TCE fetal heart findings from one lab compared with negative findings in all other labs.
- Determine appropriate TCE safe range & averaging time.

For more information go to:

http://www.allianceforrisk.org/Projects/TCE.html

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513 558-7949



ARA *Building a Risk Assessment Community*

Collaboration thru *ARA* brings:



Credibility

Publicity

Efficiency

Trust

ARA – Building a Risk Assessment Community

Perchlorate Reference Dose (RfD)

Joan Dollarhide

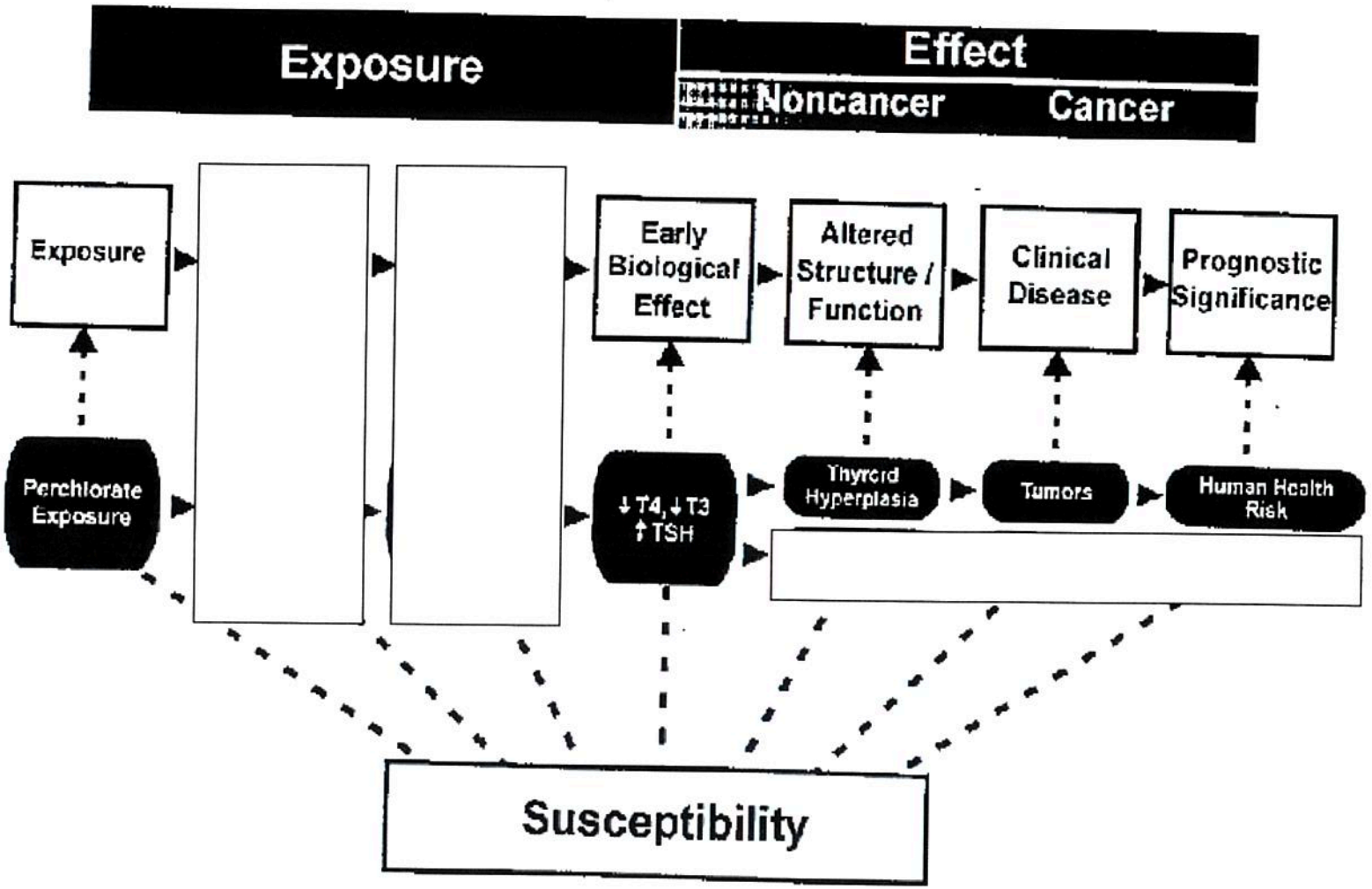
Jay Zhao

Mike Dourson

Toxicology Excellence for Risk Assessment
(*TERA*)

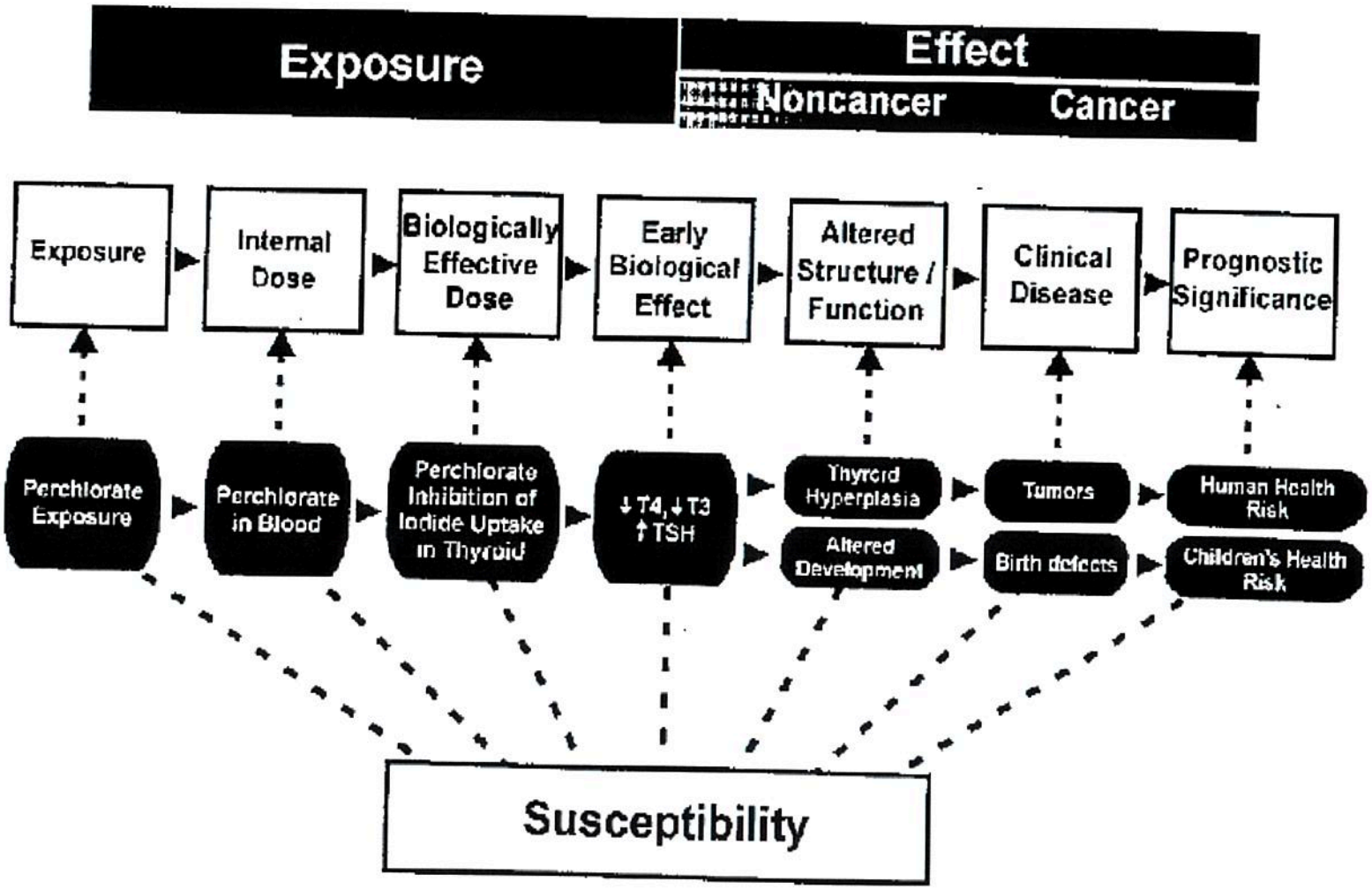
Perchlorate Response Continuum

(EPA, 1992)



Perchlorate Response Continuum

(EPA, 2002)

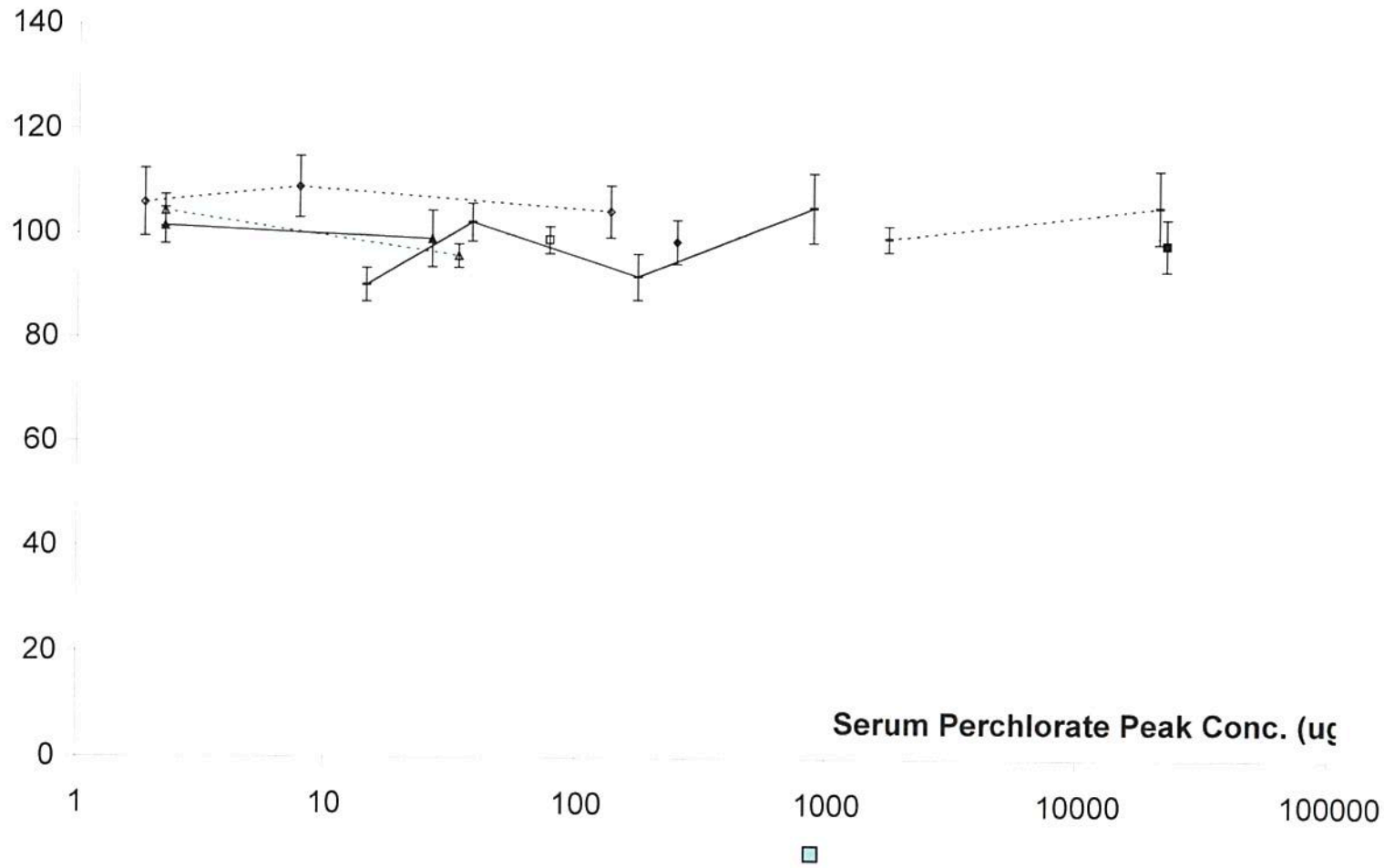


Decreased T4 is Critical Effect

- Mode of action analysis shows inhibition of iodine uptake is biologically effective dose and altered hormones early biological effect
- In humans, decreased T4 in both pregnancy and infancy known to increase potential for thyroid and nervous system toxicity; no such knowledge for iodine inhibition
- In perchlorate rodent studies, altered hormones occur at lower doses than other thyroid and nervous system effects. Pregnant rats have most dramatic response.
- Decreased T4 not adverse itself – changes in this hormone occur every day. Rather decreased T4 is a precursor to an adverse effect.
- Basing an RfD on decreased T4 will prevent all subsequent potential adverse effects.

Human Studies Most Appropriate Critical Studies

- Several well-conducted human studies available, including occupational, epidemiology, clinical studies.
- One of the sensitive subpopulations, neonates/children, well studied.
- Although kinetics appear similar between rodents and humans, dynamics dramatically different (i.e., 10-fold)
- In humans, no decrease in T4 observed at any dose tested, even when serum perchlorate levels sufficient to result in up to 70% iodine uptake inhibition, compared to rats.
- Iodine uptake inhibition different in humans and rats.


Human T4 Response to Perchlorate D
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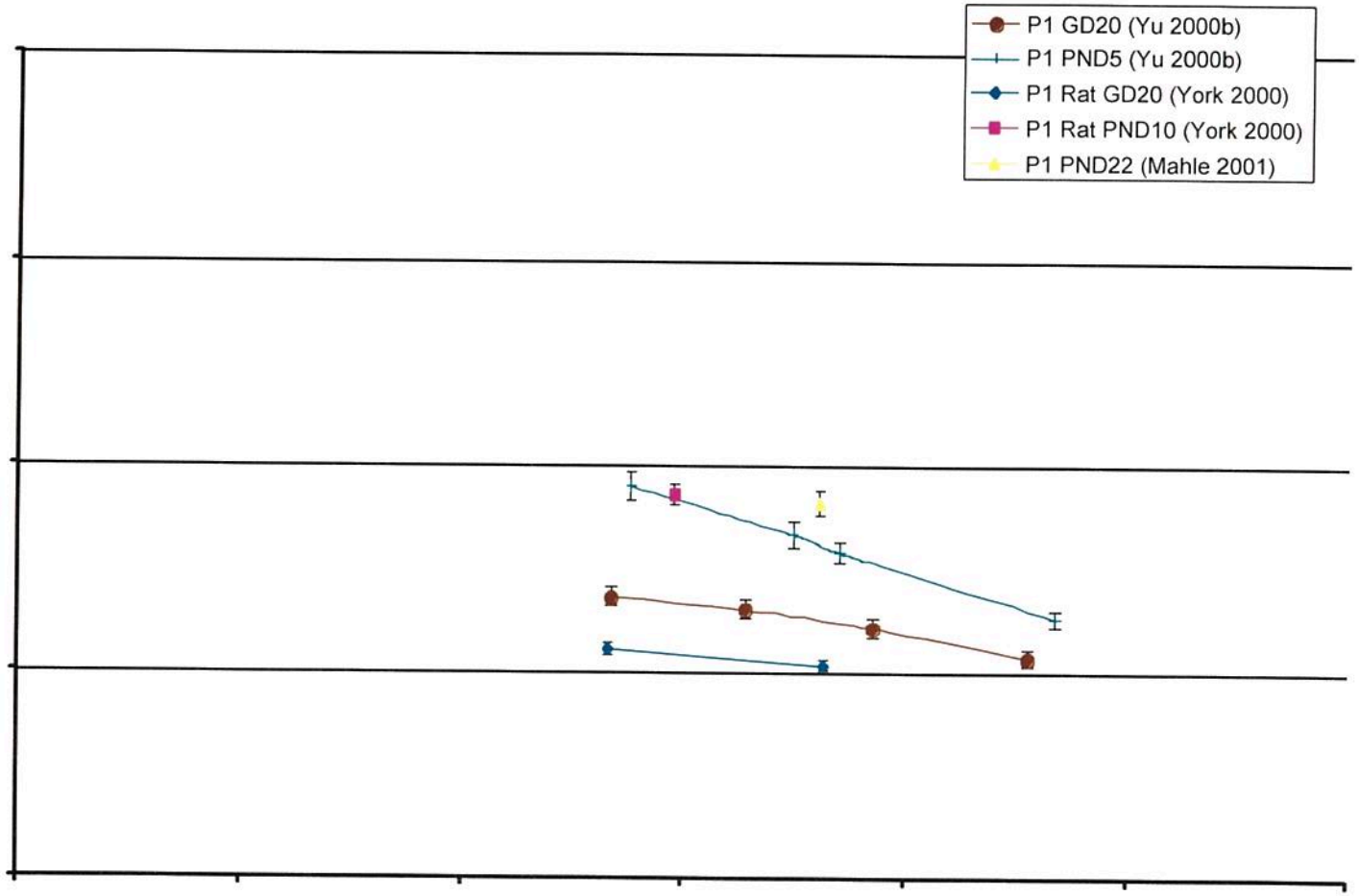
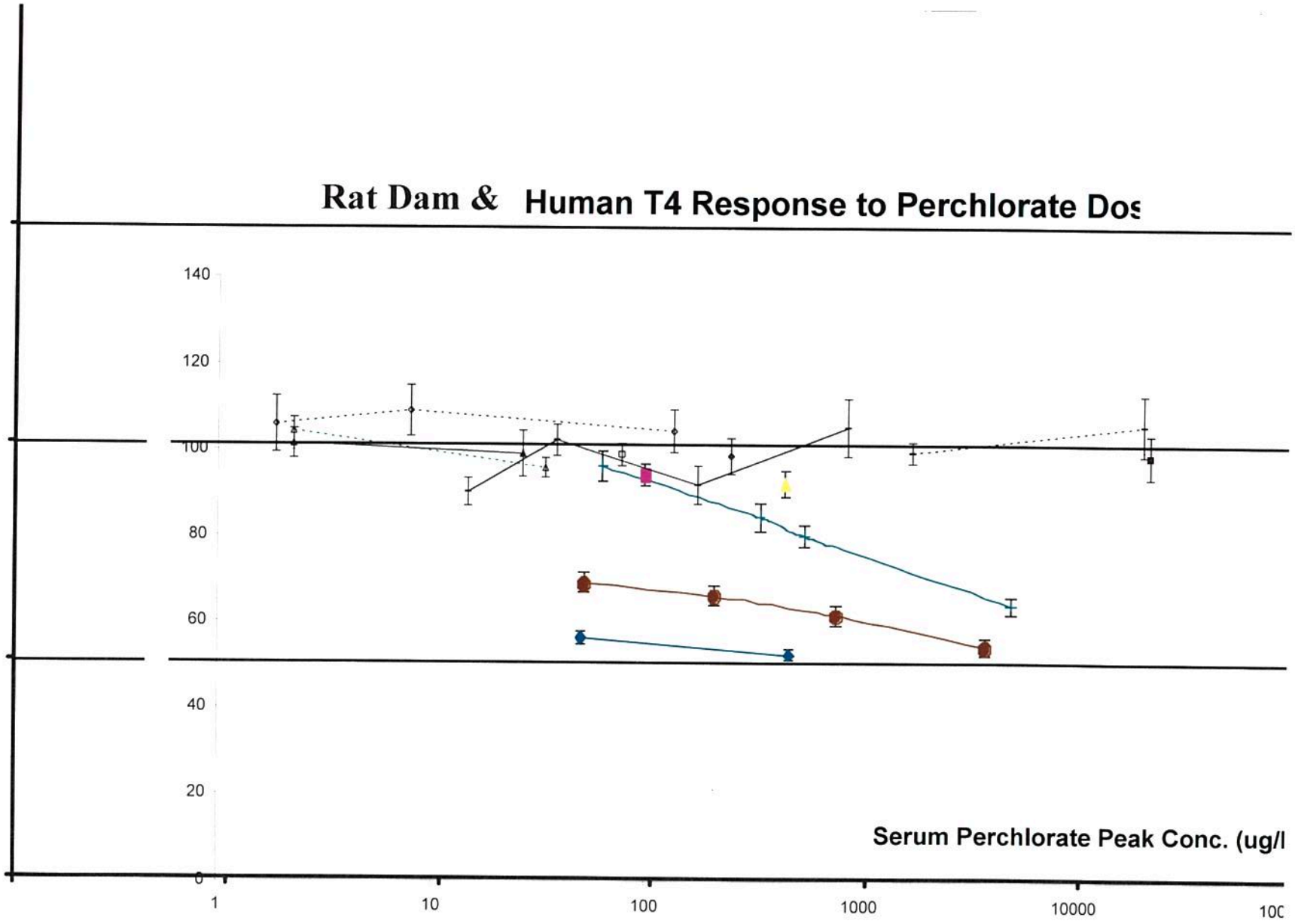

P1 GD20 (Yu 2000b)
P1 PND5 (Yu 2000b)
P1 Rat GD20 (York 2000)
P1 Rat PND10 (York 2000)
P1 PND22 (Mahle 2001)


Rat Dam & Human T4 Response to Perchlorate Dos
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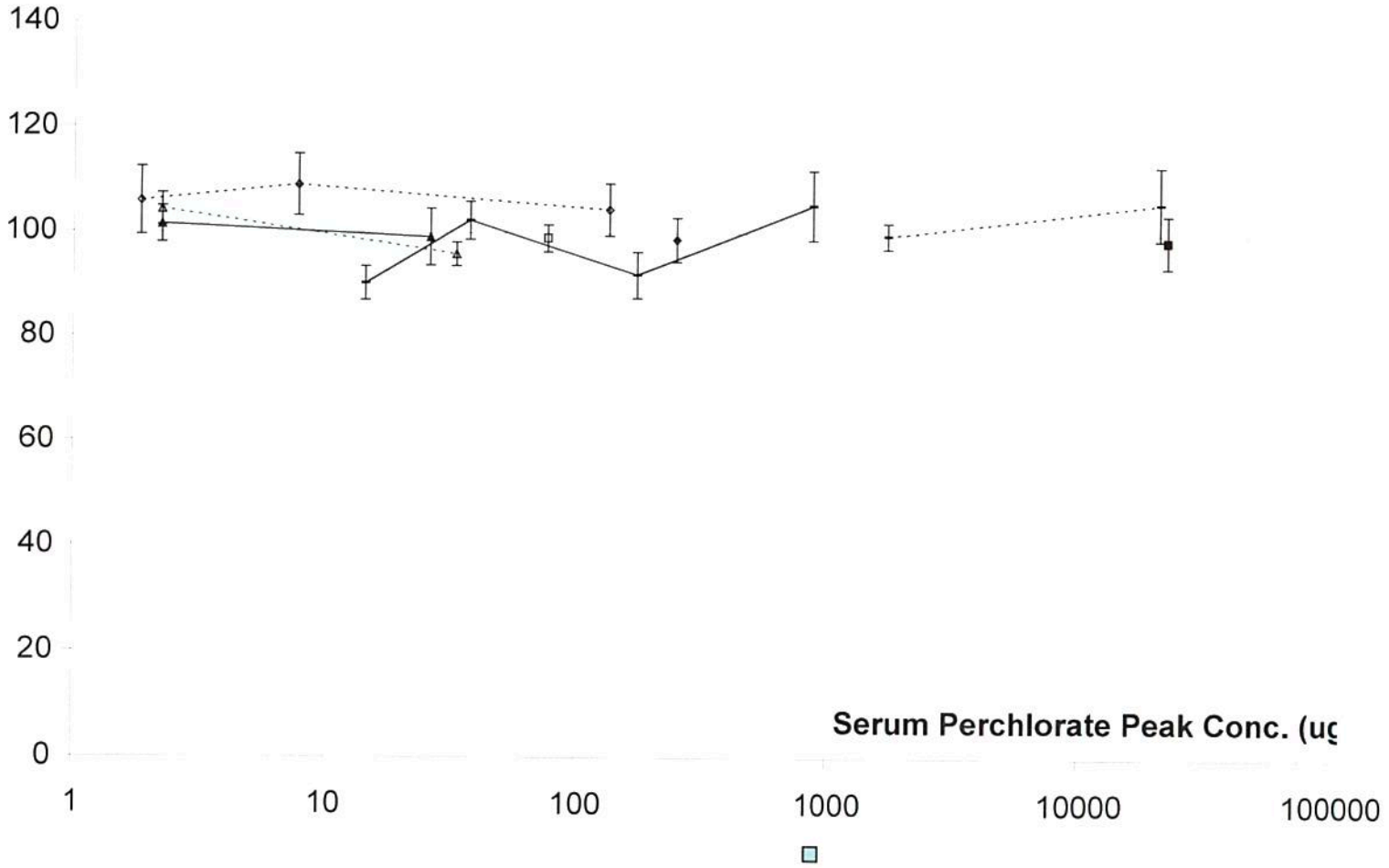
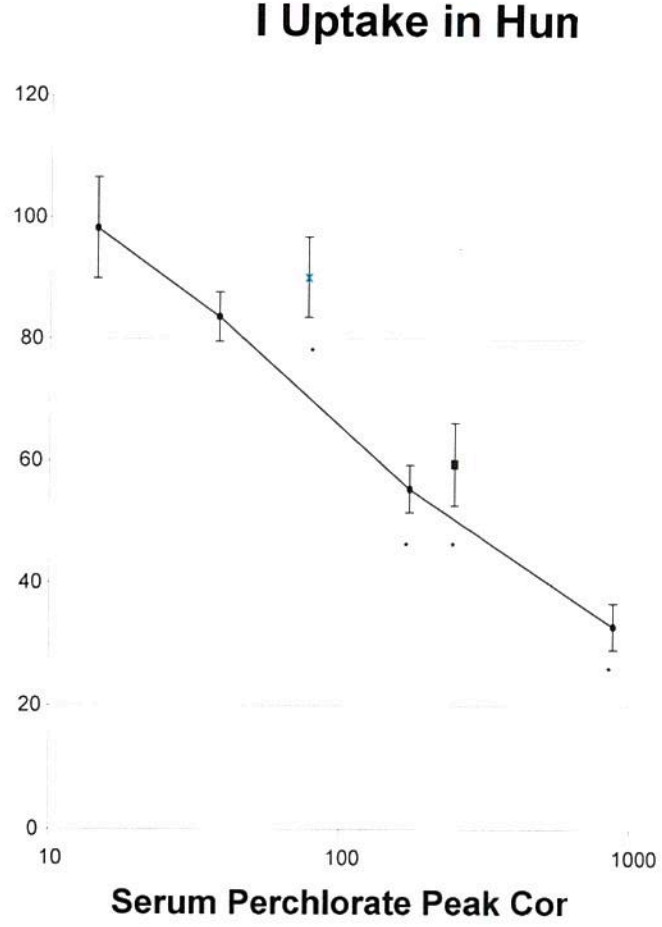
Serum Perchlorate Peak Conc. (ug/l

Human T4 Response to Perchlorate D

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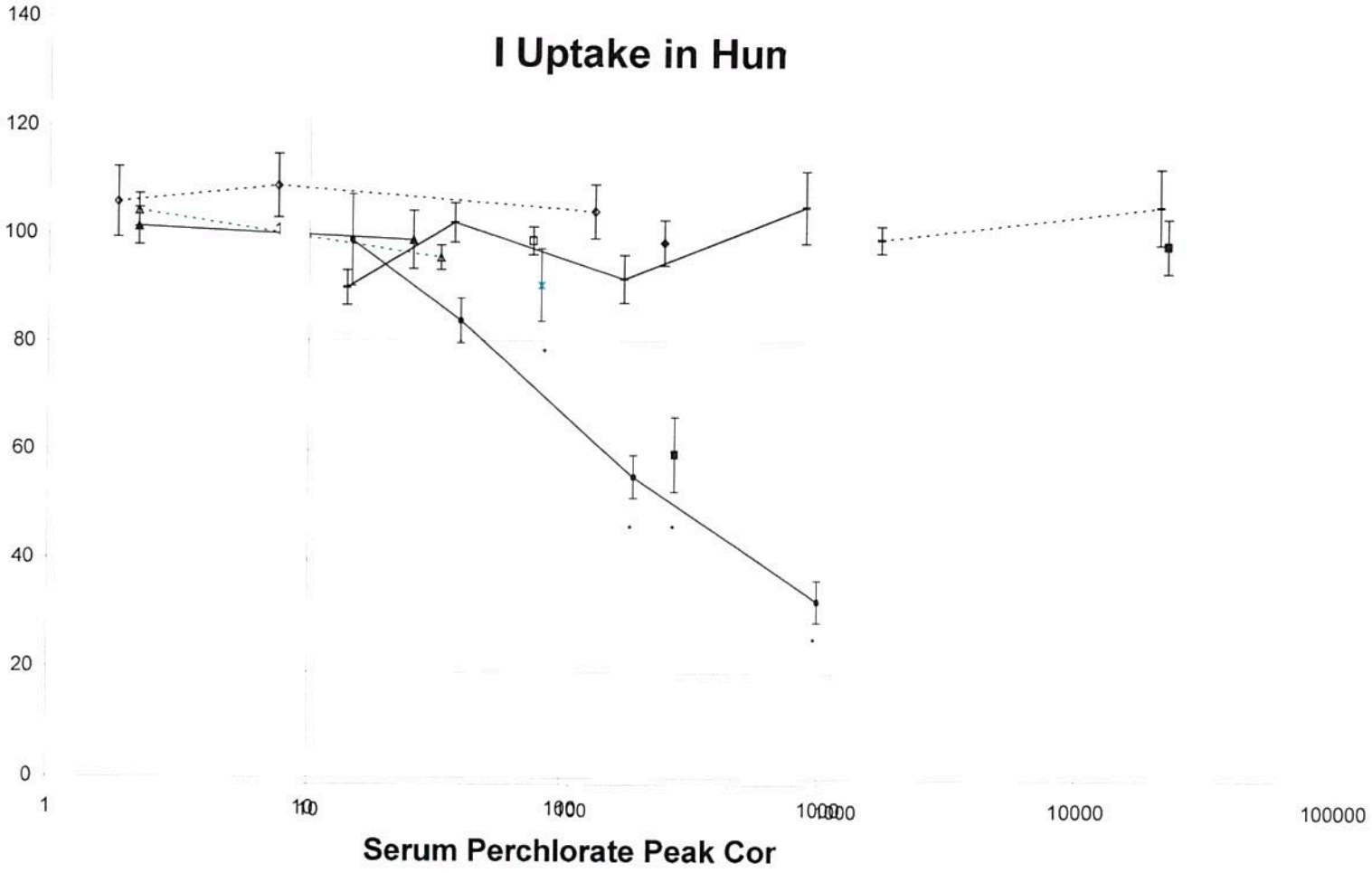
Human T4 Response to Perchlorate D



Co-critical Study: Crump et al., 2000

- Epidemiology study of 9784 neonates and 162 school-age children.
- TSH and free T4 measured compared in residents of 3 cities in Chile. Measured perchlorate concentrations:

  Taltal – 100-120 ug/L

  Chanaral – 5-7 ug/L

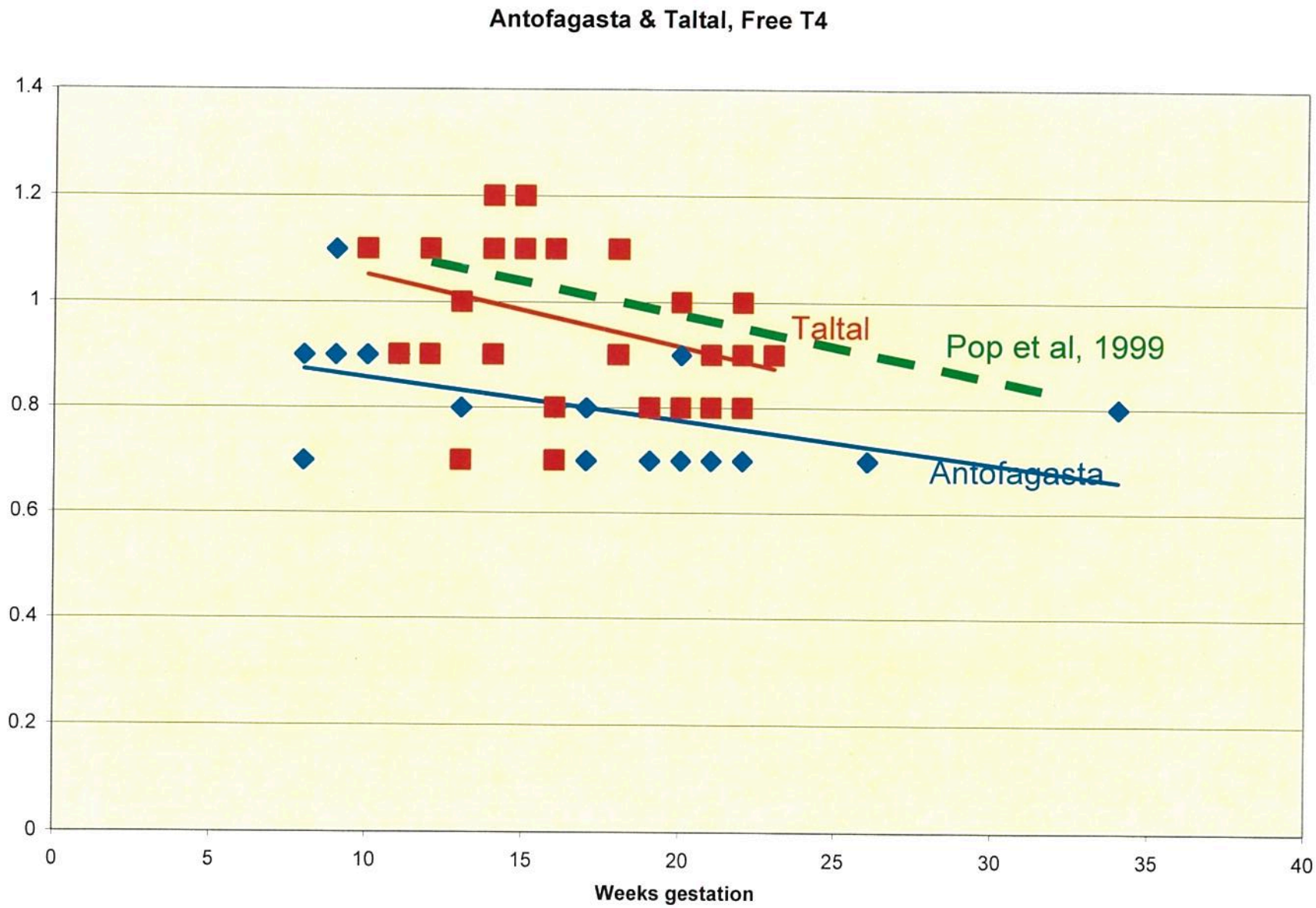
  Antofagasta - <4ug/L
- No effect on TSH or T4 observed in neonates or children in any city.
- Freestanding NOAEL of 0.006 mg/kg-day estimated based on estimated child drinking water consumption of 1.5 L/day and body weight of 28 kg.

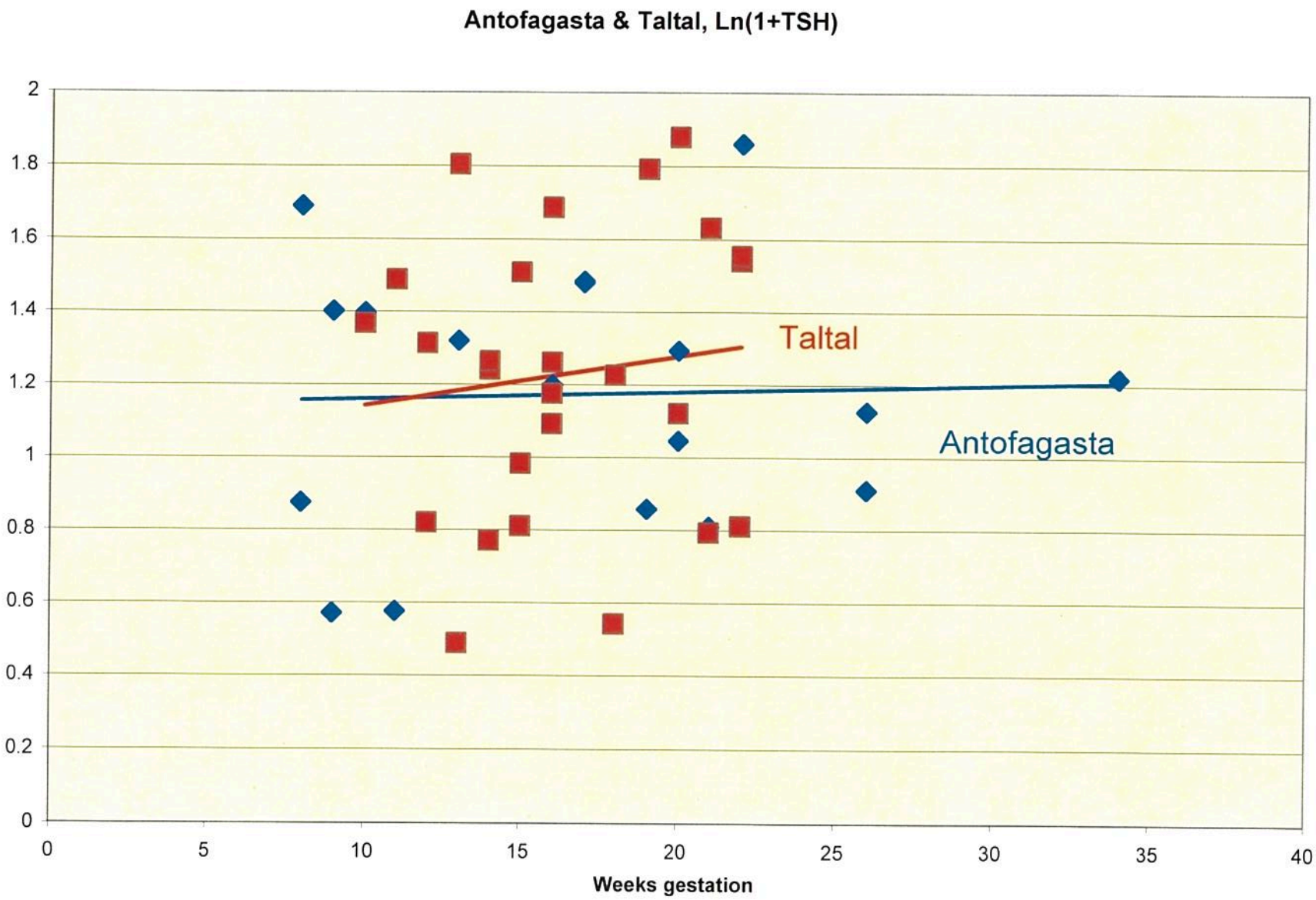
Co-critical Study: Greer et al., 2002

- Clinical study of 37 male and female healthy volunteers exposed for 14 days
- Perchlorate in drinking water at doses of 0.007, 0.02, 0.1 and 0.5 mg/kg-day
- Iodine uptake and thyroid parameters evaluated.
- No statistically significant effects on T4; good dose-response for inhibition of iodine uptake.
- Identifies a NOAEL of 0.5 mg/kg-day.
- BMD analysis of iodine uptake inhibition ($BMDL_{20}$ = 0.02 mg/kg-day) selected as conservative, quantitative NOAEL surrogate for RfD development

Different Perchlorate RfDs

Item / Group	*TERA* 2002 proposed	*TERA* 2002 supporting	EPA 2002 proposed	OEHHA 2002 proposed
Critical Effect	T4 decrease in children	Adult iodine inhibition	Several effects	Adult iodine inhibition
Study	Crump et al., 2000	3 human clinical studies	PSG, 2001	Greer et al., 2002
BMDL, NOAEL, or LOAEL (mg/kg-day)	Human NOAEL 0.006	Human $BMDL_{20}$ 0.02	Rat LOAEL 0.01	Human BMDL05 0.0037
Total Factor	3	10	300	30
RfD (mg/kg-day)	0.002	0.002	0.00003	0.0001
Confidence in RfD	High	High	Medium	NA


Antofagasta & Taltal, Free T4
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0
5
10
15
20
25
30
35
40
Weeks gestation
Taltal
Pop et al, 1999
Antofagasta


Antofagasta & Taltal, Ln(1+TSH)
2
1.8
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0
0
5
10
15
20
25
30
35
40
Weeks gestation
Taltal
Antofagasta

Acknowledgement

TERA wishes to thank the Perchlorate Study Group for its support over a number of years to study perchlorate's toxicology and assess its risk.

However, support for the development of this manuscript was provided only by internal developmental reserve funds of *TERA*, and not by any outside party.

Furthermore, our deliberations shown in this paper have not been influenced by discussions with outside parties.

History of TERA Coordinated Public/Private Partnership on Perchlorate Research

Mike Dourson, Ph.D., DABT

Toxicology Excellence for Risk Assessment (*TERA*)



T*oxicology*
E*xcellence for*
R*isk*
A*ssessment*



TERA is a non-profit 501(c)(3) corporation dedicated to the best use of toxicity data for risk assessment.



One of TERA's Activities

- Improve the practice of risk assessment by industry and government through informed and neutral guidance and advice



History of Perchlorate RfD

- EPA Superfund provisional Reference Dose 1992, revised 1995
- *TERA* RfD and expert peer review 1997 - data are inadequate, suggest specific studies
- 1997-1999 Air Force and PSG complete recommended studies
- 1999 EPA draft document and RfD based on new data peer reviewed/ peer review
- 2000-2002 Air Force and PSG completed additional studies
- 2002 EPA revised draft risk assessment and RfD/ peer review



EPA Provisional RfD 1992

- EPA Superfund Technical Support Center
- Based on acute study in patients with Graves' Disease (Stanbury and Wyngaarden, 1952)
- NOAEL 0.14 mg/kg-day - release of iodine in thyroid followed by incomplete inhibition of iodine uptake
- Uncertainty factor 1000 (10 each Uf_H, UF_S, UF_D)
- RfD of 0.0001 mg/kg-day = ground water screening level of 4 ppb



EPA Provisional RfD 1995

- EPA Superfund Technical Support Center
- Based on acute study in patients with Graves' Disease (Stanbury and Wyngaarden, 1952)
- NOAEL 0.14 mg/kg-day - release of iodine in thyroid followed by incomplete inhibition of iodine uptake
- Uncertainty factor 300 to 1000 (10 each Uf_H, UF_S, 3 to 10 for UF_D)
- RfD of 0.0001 to 0.0005 mg/kg-day = ground water screening level of 4 to 18 ppb



TERA Expert Peer Review 1997

- Additional literature search to answer outstanding questions from EPA provisional RfD
- Considered Caldwell study, not available to EPA
- Developed a RfD based on similar database as EPA's RfD, peer reviewed in 1997



TERA Expert Peer Review 1997

Conclusion:

Perchlorate database insufficient

to develop any RfD

Major unanswered questions:

- » shape of dose-response curve in humans
- » effects from long-term exposure
- » possibility of effects in organs/systems other than thyroid



Recommended Studies

- Neurobehavioral developmental
- 90-day subchronic oral bioassay
- Segment II developmental
- Two-generation reproductive
- ADME
- Genotoxicity assays
- Immunotoxicity studies
- Mechanism studies



TERA Coordinated Studies

- TERA, in association with the U.S. Air Force, U.S. EPA, the Perchlorate Study Group and others, has helped in developing a research program and protocols for studies that will fill in the data gaps that existed in the toxicology database.
- Studies were funded by the U.S. Department of Defense and Perchlorate Study Group.
- TERA monitored these studies.



EPA 1999 RfD

- Minimal LOAEL of 0.1 mg/kg-day for thyroid hypertrophy and decreased lumen size in PND5 pups (Neurodevelopmental study, Argus 1998)
- Experimental dose of ammonium perchlorate adjusted by 0.85 to estimate dose of perchlorate ion.
- RfD of 0.0009 mg/kg-day = DWEL of 32 ppb in water



Studies Conducted In Response to 1999 Peer Review Recommendations

- PWG reevaluation of all thyroid histopathology
- Predictive immunotoxicity studies
- Developmental toxicity study in rats
- "Effects study"
- Motor activity study
- Epidemiology and clinical human studies
- PBPK modeling



EPA 2002 RfD

- MOA – any transient decrease of T4 can have effect on neurodevelopment
- LOAEL of 0.01 mg/kg-day based on decreased T4 in rat dams and brain morphometry in rat pups (Effects Study, Argus, 2001)
- Supported by BMDL analysis of colloid depletion and thyroid hypertrophy in multiple studies and novel statistically analysis of motor activity studies
- LOAEL adjusted by 0.85 to estimate dose of perchlorate ion



Summary of RfDs

	EPA 1992	EPA 1995	EPA 1999	EPA 2002	TERA
Critical Study	Stanbury and Wyngaarden, 1952	Stanbury and Wyngaarden, 1952	Argus 1998, Neurodevelopmental study	Argus 2001, "Effects Study"	Crump et al., 2000 and Greer et al., 2002
Species	Human	Human	Rat	Rat	Human
Critical Effect	Release of iodine from thyroid	Release of iodine from thyroid	Thyroid histo-pathology in PND5 pups*	Decreased T4 in dams, brain morphometry in pups**	Decreased T4 in pregnant women. BMDL for iodine uptake inhibition used as NOAEL surrogate
NOAEL/ LOAEL	NOAEL, 0.14 mg/kg-day	NOAEL, 0.14 mg/kg-day	LOAEL, 0.1 mg/kg-day	LOAEL, 0.01 mg/kg-day	NOAEL, 0.006 or 0.02 mg/kg-day
UF	1000	300-1000	100	300	3-10
RfD	0.0001 mg/kg-day	0.0001 – 0.0005 mg/kg-day	0.0009 mg/kg-day	0.00003 mg/kg-day	0.002 mg/kg-day
DWEL	4 ppb	4 ppb – 18 ppb	32 ppb	1 ppb	70 ppb

*EPA conducted a "weight-of-evidence" analysis, and noted that this effect was supported by BMD analysis of hormone levels and motor activity results, but that thyroid histopathology occurred at lower doses than the other effects.

** More focus by EPA on the potential for neurodevelopmental effects. Mode of action – transient decrease of T4 can result in neurodevelopmental effects. Weight-of-evidence analysis found support for LOAEL in BMD analysis of hormones, novel statistical evaluation of two motor activity studies, tumors in 2-gen study, and immunotoxicity study.

TERA Provides Public Access to These New Study Results

- *TERA* website: www.tera.org
- Presentation at Scientific Conventions: SRA & SOT
- Provides comments on EPA's assessment
- Publications in peer reviewed journals.



TERA Website Provides Public Access to PSG Study Results

- 1997 peer review comments,
- Study designs,
- Study results,
- Data analysis,
- Related publications,
- TERA independent assessment.



New Manuscript

- Reference dose for perchlorate based on human studies.
- Submitted for publication, peer reviewer's comments received, under revision.



Data-Derived Replacement of Default Uncertainty Factor

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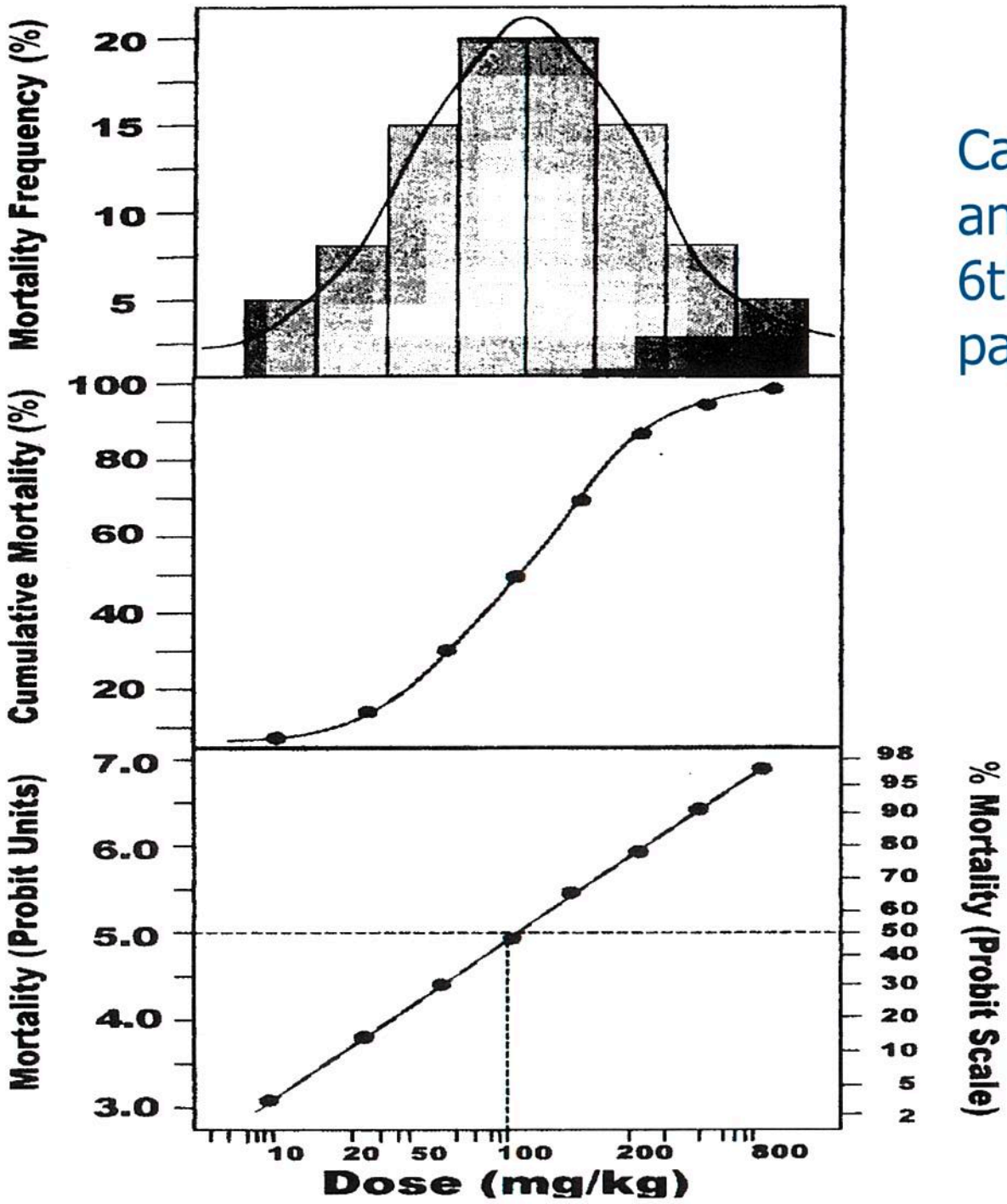
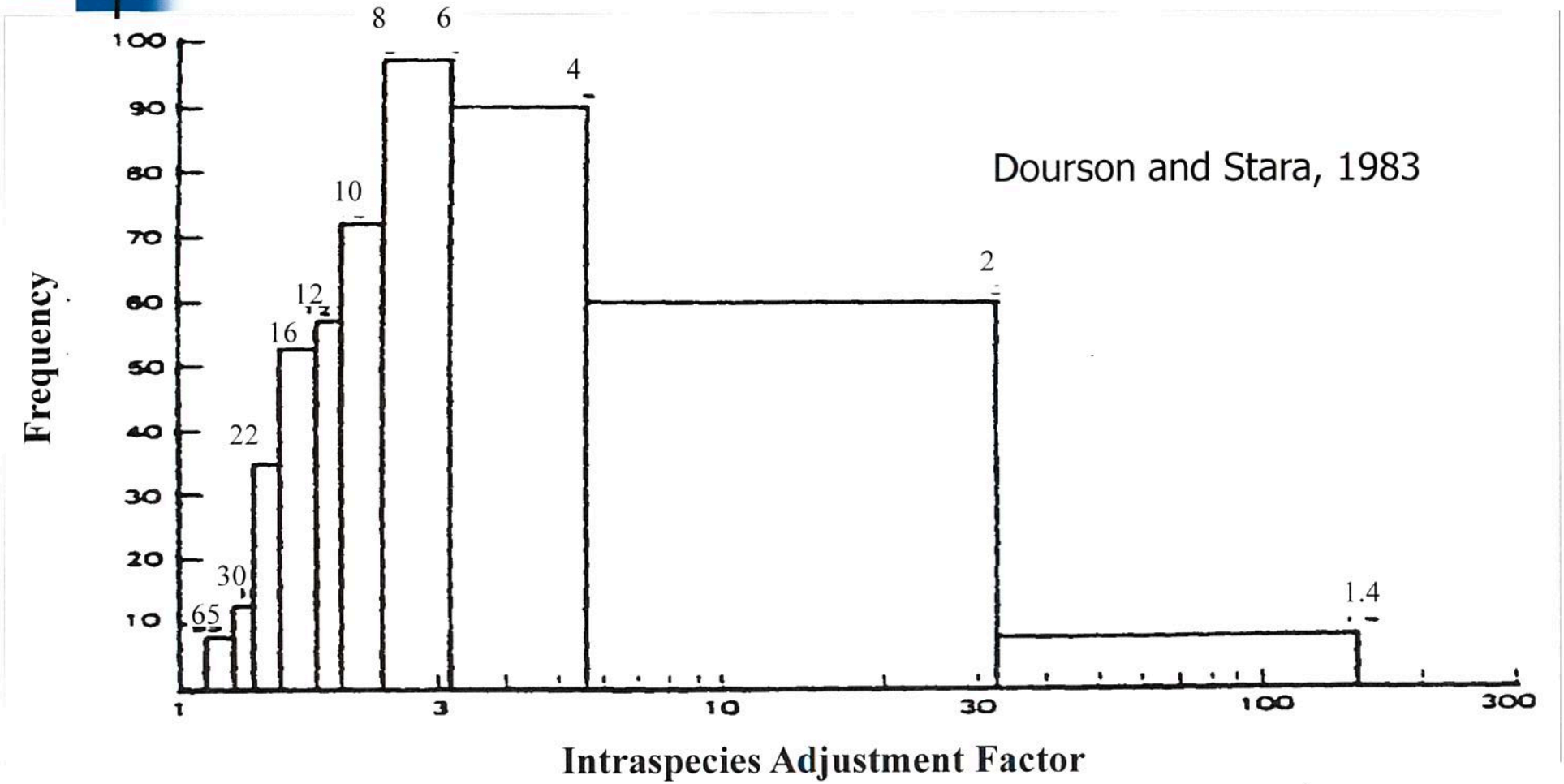
(*TERA*)



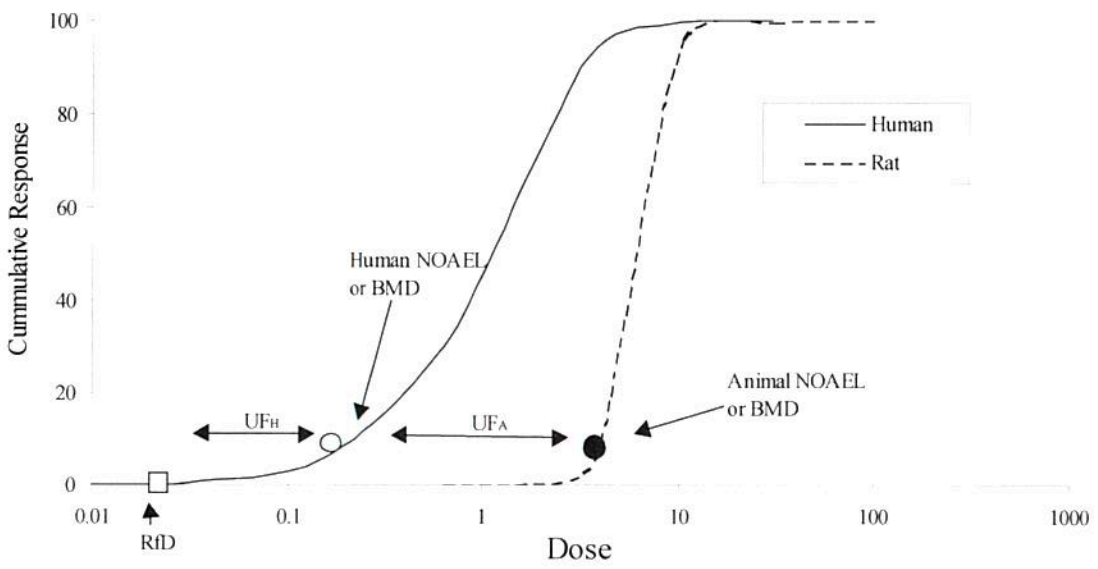
Casarett and Doull, 6th Edition, page 19

Intraspecies Variability

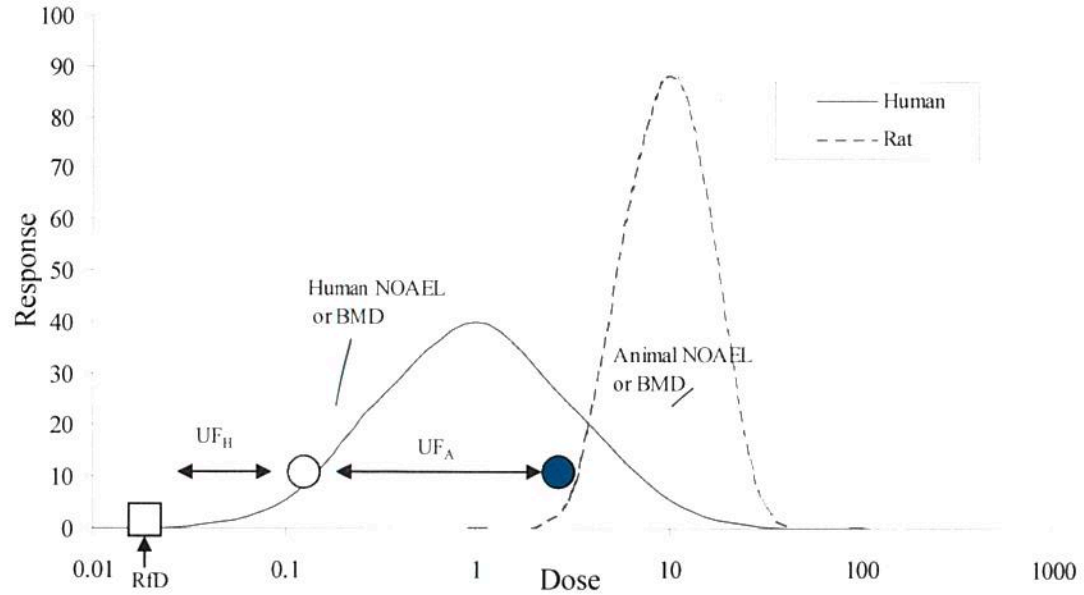


Frequency vs an intraspecies adjustment factor obtained by raising 10 to the power (3 standard deviations ÷ the probit, log-dose slope). Probit, log-dose slopes are shown within the figure

Cumulative response as a function of dose for humans and rats



Response as a function of dose for humans and rats



Dourson et al, 2002, In review

Response as a function of dose for humans of different sensitivities

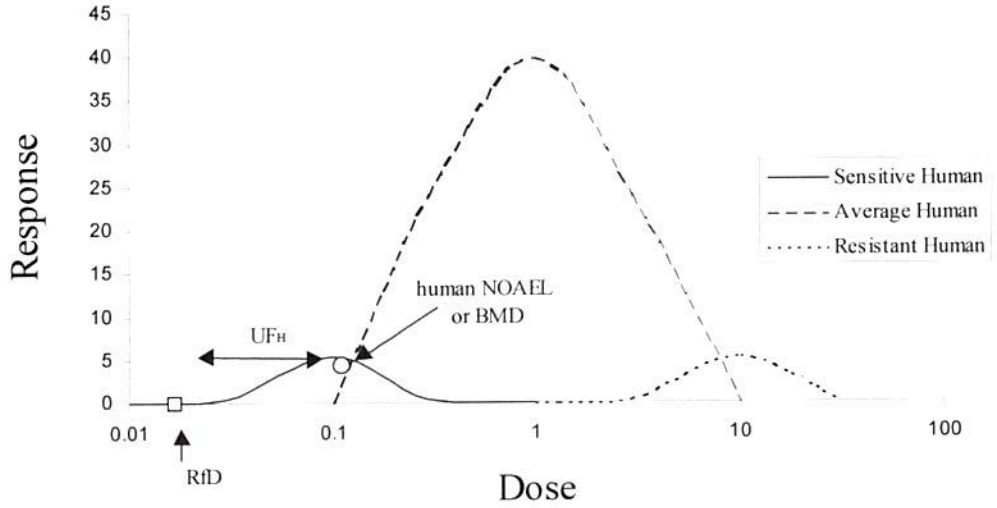
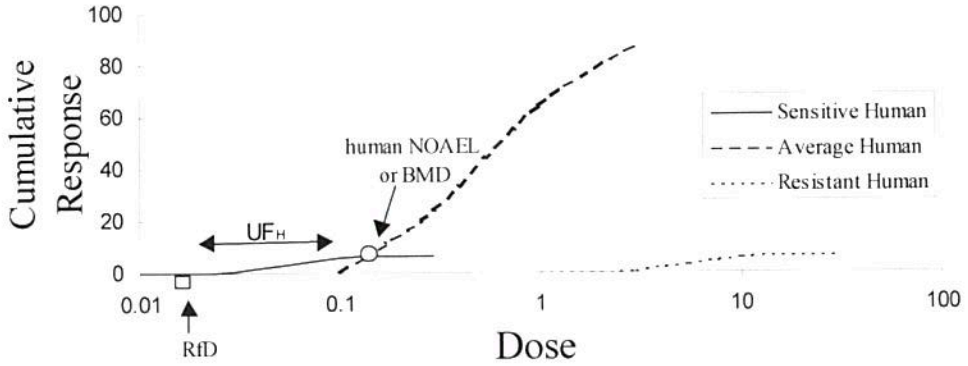


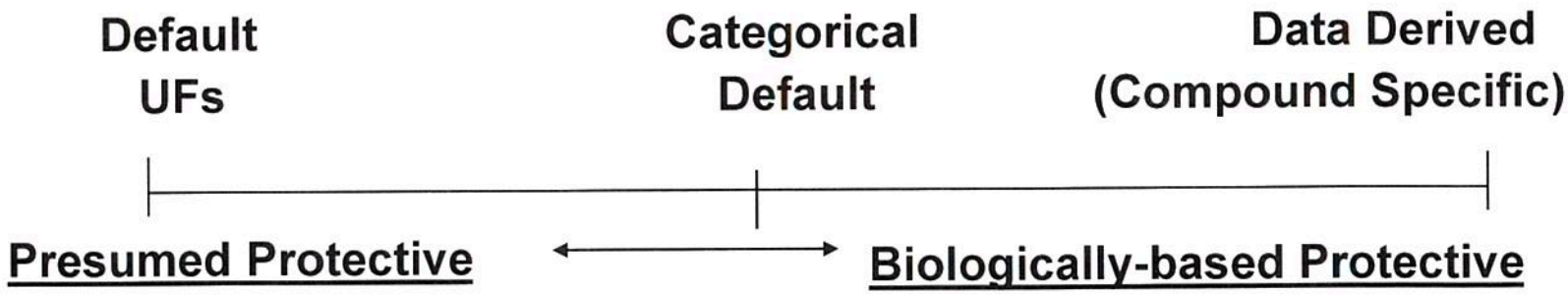
Figure 6b. Cumulative Response as a function of dose for humans of different sensitivities. Data are the same as in Figure 6a.



Dourson et al, 2002, In review

Evolution of Uncertainty Factors

- Over the last several years, scientists have begun using more data when choosing uncertainty factors
- Scientists use a number of approaches
- Methods range from default ("presumed protective") to those incorporating more biological data ("biologically-based protective")



Meek et al, 2001

Example of Default UF: Methyl Hg Oral RfD

Critical Effect	Experimental Doses*	UF	MF	RfD
Developmental neuropsychological impairment	Benchmark Dose: $BMDL_{05}$ range of 46-79 ppb in maternal	10	1	1E-4 mg/kg-day (0.0001 mg/kg-day)
Human epidemiological studies (Grandjean et al., 1997; Budtz-JØrgensen et al., 1999a)	blood for different neurological effects in the offspring at 7 years of age, corresponding to a range of maternal daily intakes of 0.857-1.472 µg/kg-day			

EPA, 2001

Dose Conversion for Methyl Hg

$$d = (\mu g/kg/day) \frac{c \times b \times V}{A \times f \times bw}$$

d	=	daily dietary intake (expressed as μg of methylmercury)
c	=	concentration in blood (expressed as μg/L)
b	=	elimination constant (expressed as days-1)
V	=	volume of blood in the body (expressed as liters)
A	=	absorption factor (expressed as a unitless decimal fraction
f	=	fraction of absorbed dose taken up by blood (unitless)
bw	=	body weight (expressed in kg)

EPA, 2001

Example of Categorical Default

- Renwick (1993) proposed breaking the interspecies and intraspecies UFs into toxicokinetic (TK) and toxicodynamic (TD) components
- This approach was modified by World Health Organization- International Programme on Chemical Safety as follows:

	Kinetics	Dynamics
*Inter*species	4.0	2.5
*Intra*species	3.2	3.2

IPCS, 1994

Interindividual Variability in Ingested MeHg

Study	Maternal Medium	50th percentile[a] (μg/kg-d)	50th percentile/5th percentile[b]	50th percentile/1st percentile[c]
Stern (1997)	hair	0.03-0.05[d] (mean = 0.04)	1.8-2.4 (mean = 2.1)	2.3-3.3 (mean = 2.7)
	blood	0.01	1.5-2.2 (mean = 1.8	1.7-3.0 (mean = 2.4)
Swartout and Rice (2000)	hair	0.08	2.2	Data not reported
	blood[e]	0.02	2.1	2.8
Clewell et al. (1999)	hair	0.08	1.5	1.8
	blood[f]	0.07	1.4	1.7

[a] Corresponding to either 1ppm Hg in hair or 1ppb in blood

NAS, 2001

Example of Data-Derived & Categorical Default for Hg

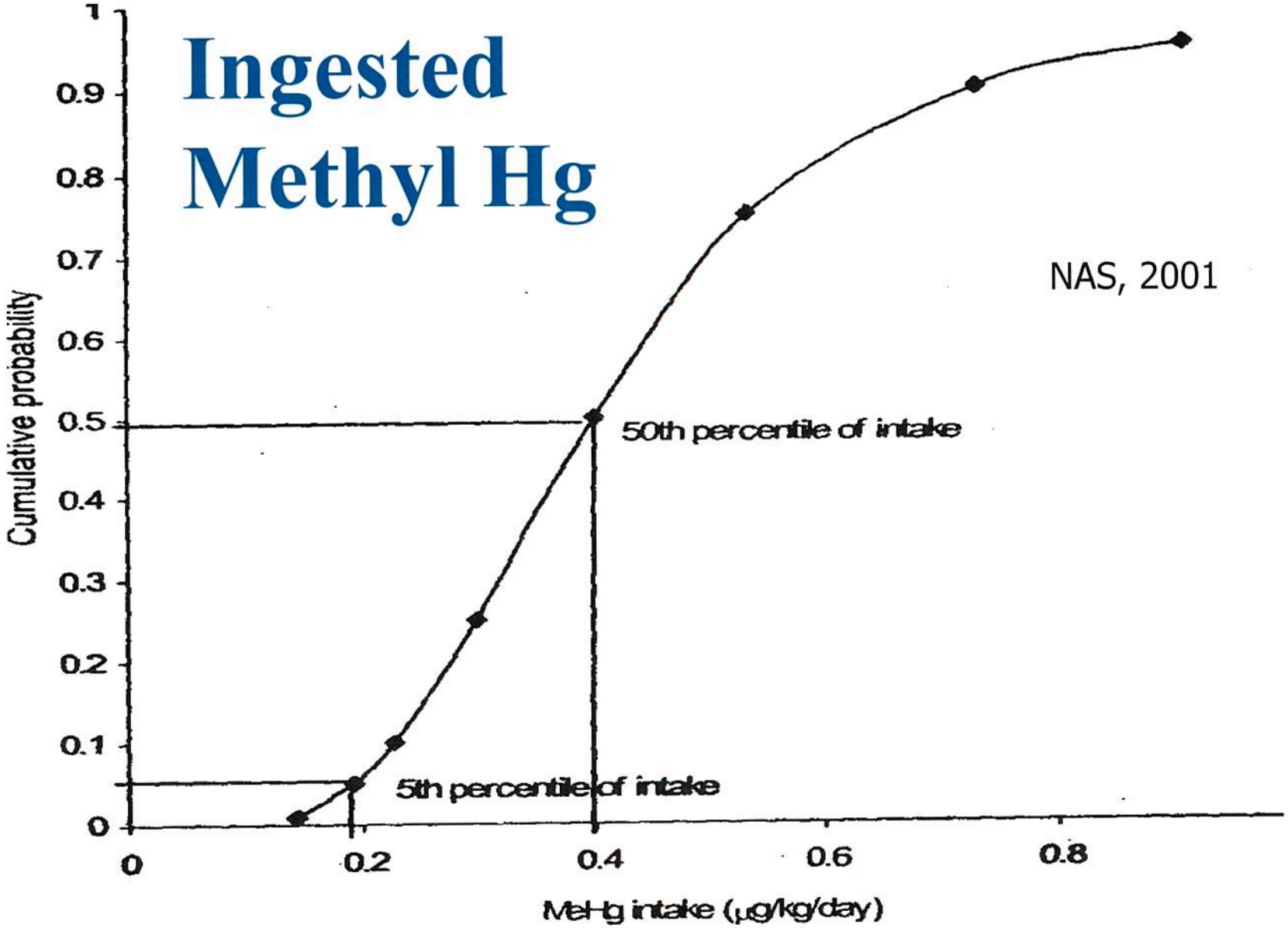
	Kinetics	Dynamics
*Inter*species	1	1
*Intra*species	1.8	3.2

Total UF = 5.8

Methyl Hg RfD = 2 E-4 mg/kg-day

Ingested Methyl Hg

NAS, 2001



Predicted mean probability of MeHg intake corresponding to 11ppm MeHg in hair.

Example of Data-Derived (or Compound Specific: Monte Carlo

- Plasma Flows
  - fraction of cardiac output
  - e.g., cardiac output, brain, kidney, liver
- Tissue Volumes
  - fraction of body weight
  - e.g., body weight, brain, plasma, kidney
- Partition Coefficients for MeHg
  - e.g., brain/blood, brain blood/plasma, gut/blood
- Kinetic Parameters
  - L/hr for 1 kg animal
  - e.g, conversion of brain MeHg to inorganic Hg, MeHg to inorganic Hg in intestine
- Fetal Kinetic Parameters
  - L/hr
  - placenta/embryo diffusion of MeHg, RBC to plasma diffusion on HeMg in Fetus

Comparison of ingestion rates (μg/kg/day) estimated using a deterministic approach to rates estimated using a Monte Carlo approach

Percentile	Monte Carlo	Deterministic
1	0.82	0.6-0.9 (Stern, 1997)
5	0.99	
10	1.10	
25	1.25	
50	1.5	1.7 (ATSDR, USEPA MC)
75	1.8	2.0 (USEPA)
90	2.19	
95	2.47	
99	3.15	

Comparison of Predicted Variability of Ingestion Rate from Monte Carlo Analysis

Ratio of Median to 5th Percentile of Distribution		
USEPA	Stern (1997)	PBPK
2.0	2.0	1.5

RfD Based on a Monte Carlo

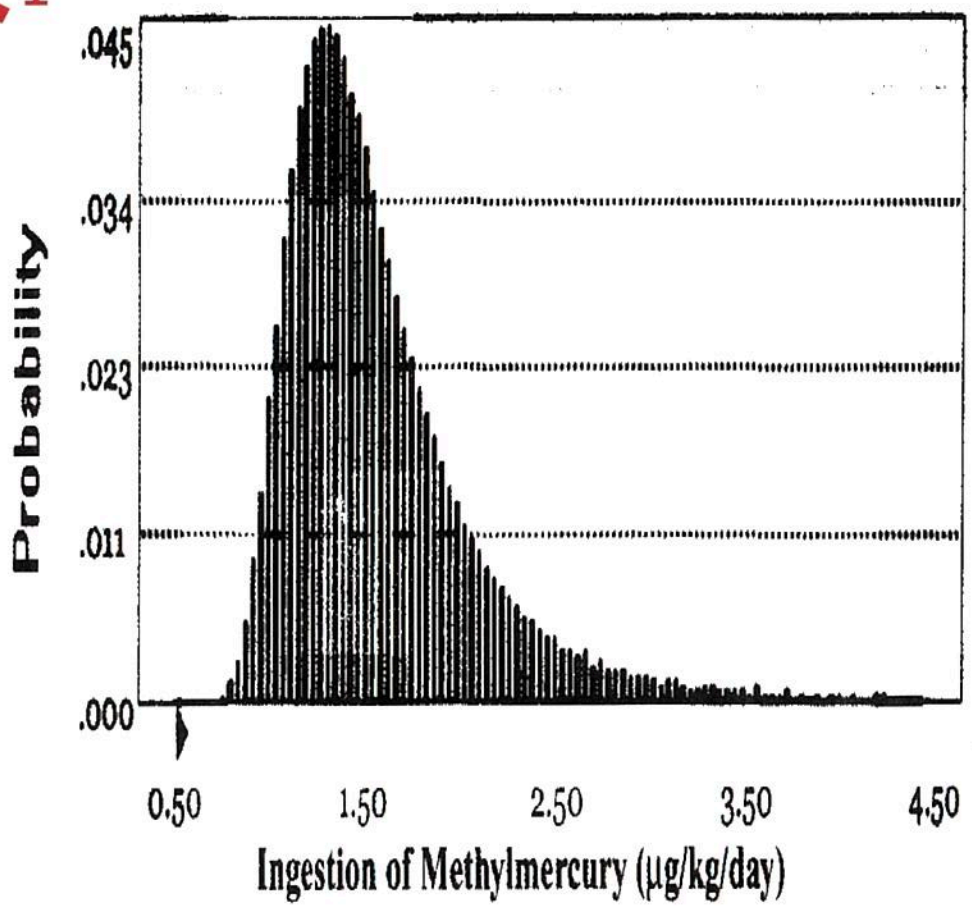
1

÷ 3 UF

2

Distribution of RfD Values

Percentile	RfD(µg/kg/day)
1	0.29
5	0.35
10	0.38
25	0.44
50	0.53
75	0.63
90	0.77
95	0.86
99	1.10



Methylmercury ingestion associated with BMDL in Seychelles population.

Summary

- Limited scientific data supports use of default uncertainty factor for intra-species variability of 10. (Hg RfD = 1 E-4)
- Newer methods on categorical defaults allow replacement of defaults with compound specific data. (Hg RfD = 2 E-4)
- Monte Carlo Analysis requires more data but allows probabilistic approach to RfD determination. (Hg RfD = 4 E-4)

Category	Date	Creditor	Credits
Awards and Grants	8/3/2015	US EPA	10,000.00
Awards and Grants	4/6/2016	US EPA	10,000.00
Awards and Grants	2/22/2017	US EPA	10,000.00
Alex Malaspina:Grant	1/20/2017	Community Fdn for Greater Atlanta	50,000.00
Contributions	9/25/2015	Am. Chemist	5,000.00
Contributions	10/13/2015	Am Beverage Assn	10,000.00
Contributions	11/30/2015	TPN Associates,LLC	25.00
Contributions	11/30/2015	The Coca-Cola Company	10,000.00
Contributions	11/30/2015	The Coca-Cola Company	10,000.00
Contributions	3/23/2016	Am Beverage Assn	5,000.00
Contributions	7/8/2016	Am Beverage Assn	5,000.00
Contributions	7/28/2016	Society of Toxicology	1,000.00
Contributions	7/22/2016	CropLife America	1,000.00
Contributions	7/14/2016	Am. Chemistry Council	5,000.00
Contributions	8/26/2016	The Coca-Cola Company	10,000.00
Contributions	8/26/2016	The Coca-Cola Company	5,000.00
Contributions	1/31/2017	The Coca-Cola Company	10,000.00
Contributions	1/31/2017	The Coca-Cola Company	10,000.00
Corporate Sponsors	7/15/2015	Procter & Gamble Company	10,000.00
Corporate Sponsors	7/31/2015	Givaudan Flavors Corporation	10,000.00
Corporate Sponsors	1/28/2016	Givaudan Flavors Corporation	10,000.00
Corporate Sponsors	1/29/2016	Firmenich Inc	10,000.00
Corporate Sponsors	1/29/2016	Intertek Scientific & Regulato	3,000.00
Corporate Sponsors	1/1/2016	Am Beverage Assn	1,000.00
Corporate Sponsors	1/1/2016	ToxStrategies Inc	3,000.00
Corporate Sponsors	1/1/2016	The Hamner Inst for Hlth Scien	1,000.00
Corporate Sponsors	1/1/2016	Novartis	10,000.00
Corporate Sponsors	1/1/2016	Procter & Gamble	10,000.00
Corporate Sponsors	1/1/2016	Am. Chemistry Council	1,000.00
Corporate Sponsors	1/1/2016	Exxon Mobil	20,000.00
Corporate Sponsors	2/23/2016	Monsanto Company	10,000.00
Corporate Sponsors	2/8/2016	Merck	3,000.00
Corporate Sponsors	2/23/2016	The Coca-Cola Company	10,000.00
Corporate Sponsors	3/9/2016	Church & Dwight Co., Inc	10,000.00
Corporate Sponsors	3/9/2016	Pepsico Inc	10,000.00
Corporate Sponsors	9/16/2016	SRC, Inc	333.00
Corporate Sponsors	9/23/2016	Mars Inc	20,000.00

Corporate Sponsors	1/3/2017	NSF International	1,500.00
Corporate Sponsors	1/10/2017	ToxStrategies, Inc	1,500.00
Corporate Sponsors	1/19/2017	Exxon Mobil	20,000.00
Corporate Sponsors	1/25/2017	Am. Chemistry Council	1,500.00
Corporate Sponsors	2/3/2017	Intertek Scientific and Regula	1,500.00
Corporate Sponsors	2/24/2017	Firmenich Inc	10,000.00
Corporate Sponsors	3/24/2017	Pepsico Inc	10,000.00
Corporate Sponsors	3/2/2017	Mars Inc	10,000.00
Corporate Sponsors	3/14/2017	Procter & Gamble	10,000.00
Corporate Sponsors	5/31/2017	Merck	3,000.00
Corporate Sponsors	5/11/2017	Givaudan Flavors Corporation	10,000.00
Grants	11/30/2015	The Coca-Cola Company	7,500.00
Grants	11/30/2015	The Coca-Cola Company	7,500.00
Mouse Liver Tumor	12/30/2015	Exxon Mobil	10,000.00
Mouse Liver Tumor	2/29/2016	BASF	10,000.00
Mouse Liver Tumor	3/23/2016	Am Beverage Assn	2,000.00
Mouse Liver Tumor	3/9/2016	The Coca-Cola Company	5,000.00
Mouse Liver Tumor	3/14/2016	Am. Chemistry Council	3,000.00
Mouse Liver Tumor	3/21/2016	Procter & Gamble	10,000.00
Mouse Liver Tumor	5/18/2016	Bayer	2,000.00
Mouse Liver Tumor	7/7/2016	Am. Chemistry Council	2,000.00
Mouse Liver Tumor	11/9/2016	USFDA	5,000.00
Mouse Liver Tumor	5/9/2017	EPA	4,125.00