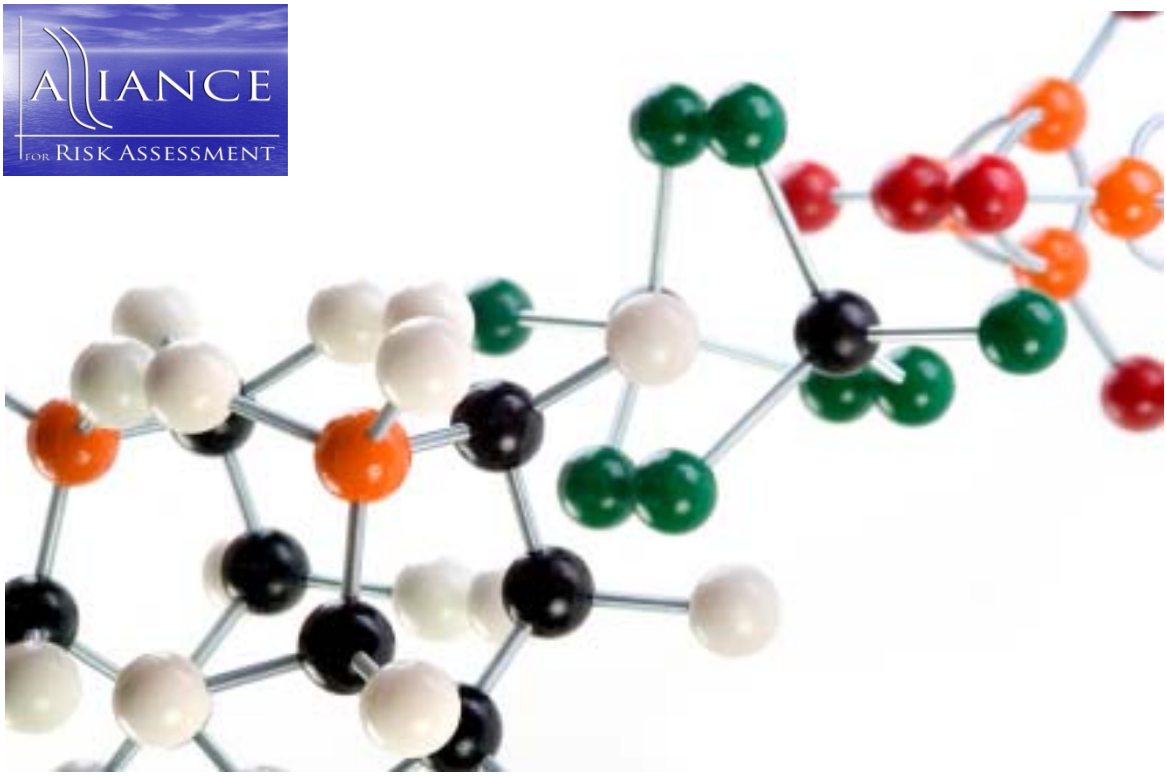

Beyond Science and Decisions:
From Problem Formulation to Dose-Response
Report from Workshop VI - Appendices

Workshop Held:
May 28, 29 &-30, 2013
Arlington, VA
at the United States Environmental Protection Agency

Appendices

October 10, 2013

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Appendix 1. Biographies for Standing Panel Members

Richard Beauchamp, Texas Department of State Health Services

Richard A. Beauchamp is the Senior Medical Toxicologist for the Texas Department of State Health Services (DSHS) with responsibility for providing advanced toxicological and risk assessment support for the Exposure Assessment, Surveillance, and Toxicology (EAST) Group. As cooperative agreement partners with the Agency for Toxic Substances and Disease Registry (ATSDR), Dr. Beauchamp and other EAST Group members are tasked with conducting Public Health Assessments at abandoned hazardous waste sites that are proposed and added to the Environmental Protection Agency's (EPA's) National Priority List (NPL) of Superfund sites in Texas. Dr. Beauchamp is also involved with conducting other medical and toxicological Public Health Consultations involving exposures to environmental hazardous substances.

After earning his medical degree at the University of Texas Health Science Center at San Antonio (1973-1977), Dr. Beauchamp completed a three year pediatric residency with the Austin Pediatric Education Program at Brackenridge Hospital in Austin, Texas (1977-1980) and began working at the Texas Department of Health as a Public Health Physician Epidemiologist (1980). Early in his career at the health department, he was tasked with developing risk assessment expertise that would be essential for the newly-formed Environmental Epidemiology Program in the evaluation of environmental and chemical exposures. With an undergraduate degree in Electrical Engineering (U.T. Austin) and a strong background in mathematics and computer sciences, Dr. Beauchamp has applied the knowledge gained through participation at numerous risk assessment conferences, symposia, and seminars (sponsored by EPA, NGA, CDC, ASTHO, NIOSH, and others) to the development of his so-called "Risk Assessment Toolkit." Dr. Beauchamp's toolkit consists of a series of Excel® spreadsheets designed for the flexible and rapid evaluation of cancer and non-cancer risks resulting from exposures to a wide variety of environmental contaminants through all of the common exposure pathways. Risks are calculated incrementally using age-specific exposure parameters, including body weights, body surface areas, respiratory daily volumes, and EPA's early-life exposure factors. Risks are integrated over the exposure duration, using up to 46 different age intervals, to insure that childhood exposures are appropriately addressed.

James S. Bus, Exponent

James S. Bus is a Senior Managing Scientist in the Center for Toxicology and Mechanistic Biology in the Health Sciences Group of Exponent, a leading global consulting firm (May 2013-present). His primary responsibilities at Exponent are to provide toxicology expertise for addressing client product stewardship and regulatory needs associated with industrial and pesticide chemicals. Prior to joining Exponent, Dr. Bus retired from The Dow Chemical Company as Director of External Technology, Toxicology and Environmental Research and Consulting (1989-2013). He also previously held positions as Associate Director of Toxicology and Director of Drug Metabolism at The Upjohn Company (1986-1989), Senior Scientist at the Chemical Industry Institute of Toxicology (CIIT, 1977-1986), and Assistant Professor of Toxicology, University of Cincinnati (1975-1977). Dr. Bus currently serves on the Boards of Directors of The Hamner Institutes (formerly CIIT) and the ILSI Research Foundation. He has also has served as Chair of the American Chemistry Council and International Council of Chemical Associations Long-Range Research Initiatives; the Board of Directors of ILSI-HESI; the USEPA Office of Research and Development Board of Scientific Counselors (1997-2003) and Chartered Science Advisory Board (2003-2009); the National Toxicology Program Board of Scientific Counselors (1997-2000); the FDA National Center for Toxicological Research Science Advisory Board (2004-2010); and the National Academy of Sciences/National Research Council Board on Environmental Studies and Toxicology (BEST; 2005-2011). He has served as an Associate Editor of *Toxicology and Applied Pharmacology*, and on the Editorial Boards of *Environmental Health Perspectives* and *Dose Response*. Dr. Bus is a member of the Society of Toxicology (serving as President in 1996-97), the American Society for Pharmacology and Experimental Therapeutics, the American Conference of Governmental and Industrial Hygienists, and the Teratology Society. He is a Diplomate and Past-President of the American Board of Toxicology and a Fellow of the Academy of Toxicological Sciences (member of Board of Directors, 2008-present; President, 2010-2011). Dr. Bus received the Society of Toxicology Achievement Award (1987) for outstanding contributions to the science of toxicology; the Society of Toxicology Founders Award (2010) for leadership fostering the role of toxicology in improving safety decisions; Rutgers University Robert A. Scala Award (1999) for exceptional work as a toxicologist in an industry laboratory; and the K.E. Moore Outstanding Alumnus Award (Michigan State University, Dept. Pharmacol. and Toxicol.). He received his B.S. in Medicinal Chemistry from the University of Michigan (1971) and Ph.D. in pharmacology from Michigan State University (1975) and currently is an Adjunct Professor in the Dept. Pharmacology and Toxicology at that institution. His research interests include mechanisms of oxidant toxicity, chemical and pesticide modes of action, defense mechanisms to chemical toxicity, relationships of pharmacokinetic and exposures information to expression of chemical toxicity, and general pesticide and industrial chemical toxicology. He has authored/co-authored over 100 publications, books, and scientific reviews.

Rory Conolly, U.S. EPA National Health and Environmental Effects Research Laboratory

Rory Conolly is a Senior Research Biologist in the Integrated Systems Toxicology Division of the U.S EPA's National Health and Environmental Effects Research Laboratory in Research Triangle Park, North Carolina, USA. His major research interests are (1) biological mechanisms of dose-response and time-course behaviors, (2) the use of computational modeling to study these mechanisms and, (3) the application of computational models to quantitative dose-response assessment. Dr. Conolly received the U.S. Society of Toxicology's (SOT) Lehman Award for lifetime achievement in risk assessment in 2005. He was a member of the National Academy of Sciences Board on Environmental Studies and Toxicology from 2004 until joining the EPA in 2005, President of the SOT Biological Modeling Specialty Section (2000 – 2001), President of the SOT Risk Assessment Specialty Section (1997 - 1998), a member of the SOT Risk Assessment Task Force (1998 - 2000) and is currently a Councilor with the Risk Assessment Specialty Section. He is Adjunct Professor of Biomathematics at North Carolina State University, Faculty Affiliate, Department of Environmental and Radiological Health Sciences, Colorado State University and has four times received awards from the SOT Risk Assessment Specialty Section (1991, 1999, 2003, 2004). Dr. Conolly was born in London, England and raised in Canada and the United States. He received a bachelor's degree in biology from Harvard College in 1972, a doctorate in physiology/toxicology from the Harvard School of Public Health in 1978, and spent a post-doctoral year at the Central Toxicology Laboratory of Imperial Chemical Industries, PLC, in Cheshire, England. He was a member of the Toxicology Faculty at The University of Michigan School of Public Health from 1979 through 1986, and worked with the U.S. Air Force Toxic Hazards Research Division, Wright-Patterson Air Force Base, Ohio from 1986 until 1989. In 1989 Dr. Conolly joined the Chemical Industry Institute of Toxicology (CIIT) and worked there until 2005, when he joined the U.S. EPA.

Mike Dourson, Toxicology Excellence for Risk Assessment

Mike Dourson is the President of Toxicology Excellence for Risk Assessment (TERA), a nonprofit corporation dedicated to the best use of toxicity data in risk assessment. Before founding TERA in 1995, Dr. Dourson held leadership roles in the U.S. Environmental Protection Agency as chair of US EPA's Reference Dose (RfD) Work Group, charter member of the US EPA's Risk Assessment Forum and chief of the group that helped create the Integrated Risk Information System (IRIS). Dr. Dourson received his Ph.D. in Toxicology from the University of Cincinnati. He is a Diplomate of the American Board of Toxicology and a Fellow of the Academy of Toxicological Sciences. Dr. Dourson has served on or chaired numerous expert

panels, including peer review panels for US EPA IRIS assessments, US EPA's Risk Assessment Forum, TERA's International Toxicity Estimates for Risk (*ITER*) independent peer reviews and consultations, FDA's Science Board Subcommittee on Toxicology, the NSF International's Health Advisory Board, and SOT's harmonization of cancer and non-cancer risk assessment. He served as Secretary for the Society for Risk Analysis (SRA) and has held leadership roles in specialty sections of SRA and SOT. He is currently on the editorial board of three journals. Dr. Dourson has published more than 100 papers on risk assessment methods, has co-authored over 100 government risk assessment documents, and has made over 100 invited presentations.

Annie M. Jarabek, U.S. EPA, Office of Research and Development

Annie M. Jarabek is a senior toxicologist in the immediate office of the National Center for Risk Assessment (NCEA) within the US EPA's Office of Research and Development (ORD). Annie is the principal author of the US EPA's Methods for Derivation of Inhalation Reference Concentrations (RfC) and Application of Inhalation Dosimetry, which introduced dosimetry and physiologically-based pharmacokinetic (PBPK) model structures and reduced forms into the RfC methods for interspecies adjustment. She has worked on several high-priority and interdisciplinary Agency assessments including the risk characterization of perchlorate ingestion and the inhalation of particulate matter (PM); and has served in an advisory capacity on other methods and assessments, including the guidance on body-weight scaling for harmonizing noncancer and cancer approaches for the interspecies adjustment of ingested chemicals. Her current research efforts focus on multi-scale modeling of dose-response and decision analysis. Annie has twice received awards for best manuscript in risk assessment application from the Risk Assessment Specialty Section (RASS) of the Society of Toxicology (SOT), along with several best abstract awards. She has also received the Lifetime Achievement Award from the University of Massachusetts, the Risk Practitioner of the Year award from the Society of Risk Analysis (SRA), the Superfund National Notable Achievement Award, and several award medals (1 gold, 1 silver and 5 bronze) and "S awards" for scientific leadership from the Agency for her various contributions. Annie has served as an elected Councilor to the Society for Risk Analysis and as the vice-president/president of the SOT RASS. Annie has also served the SOT on its awards, communications, nominations, and scientific program committees. She is currently on the editorial board of the international journal "Dose-Response."

R. Jeffrey Lewis, ExxonMobil Biomedical Sciences, Inc.

Dr. R. Jeffrey Lewis is currently Section Head of the Epidemiology, Health Surveillance and Quality Assurance group at ExxonMobil Biomedical Sciences, Inc (EMBSI). In this position, Dr Lewis is responsible for managing EMBSI's Epidemiology and Health Surveillance group, the company's laboratory quality assurance program, and for providing support to ExxonMobil scientific programs related to 1,3-butadiene, naphthalene, asphalt, legislative/regulatory affairs and regulatory impact analysis (e.g., benefit-cost analysis). He has served on a number of industry trade association scientific committees (e.g., the American Chemistry Council's 1,3-butadiene Work Group), external science advisory boards (e.g., the Alliance for Risk Assessment Expert Science Panel) and is a member of the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) Committee. Dr. Lewis also has an adjunct faculty appointment at the University of Texas School of Public Health and is Past Treasurer for the Society for Risk Analysis. Dr. Lewis received his Bachelor of Science degree in biology from the University of Kansas in 1985 and a M.S. and Ph.D. in Epidemiology from the University of Texas School of Public Health in 1987 and 1990, respectively. In addition, he earned a Master of Business Administration degree from Rutgers University in 1997.

Bette Meek, McLaughlin Centre for Population Health Risk Assessment, University of Ottawa

Bette Meek has a background in toxicology receiving her M.Sc. in Toxicology (with distinction) from the University of Surrey, U.K. and her Ph.D. in risk assessment from the University of Utrecht, the Netherlands. She is currently the Associate Director of Chemical Risk Assessment at the McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, completing an interchange assignment from Health Canada. She has extensive experience in the management of chemical assessment programs within the Government of Canada, most recently involving development and implementation of process and methodology for the health assessment of Existing Substances under the Canadian Environmental Protection Act (CEPA) and previously, programs for contaminants in drinking water and air.

With colleagues within Canada and internationally, she has contributed to or led initiatives to increase transparency, defensibility and efficiency in health risk assessment, having convened and participated in initiatives in this area for numerous organizations including the International Programme on Chemical Safety, the World Health Organization, the International Life Sciences Institute, the U.S. Environmental Protection Agency, the U.S. National Academy of Sciences and the U.S. National Institute for Environmental Health Sciences. Relevant areas have included

frameworks for weight of evidence analysis including mode of action, chemical specific adjustment factors, physiologically-based pharmacokinetic modeling, combined exposures and predictive modeling. She has also authored over 175 publications in the area of chemical risk assessment and received several awards for contribution in this domain.

Greg Paoli, Risk Sciences International

Greg Paoli serves as Principal Risk Scientist and COO at Risk Sciences International, a consulting firm specializing in risk assessment, management and communication in the field of public health, safety and risk-based decision-support. Mr. Paoli has experience in diverse risk domains including toxicological, microbiological, and nutritional hazards, air and water quality, climate change impacts, medical and engineering devices, as well as emergency planning and response for natural and man-made disasters. He specializes in probabilistic risk assessment methods, the development of risk-based decision-support tools and comparative risk assessment. Mr. Paoli has served on a number of expert committees devoted to the risk sciences. He was a member of the U.S. National Research Council committee that issued the 2009 report, *Science and Decisions: Advancing Risk Assessment*. He serves on the Canadian Standards Association Technical Committee on Risk Management, advisory committees of the National Roundtable on the Environment and the Economy, a US NRC Standing Committee on the Use of Public Health Data at the U.S. Food Safety and Inspection Service, and has served on several expert committees convened by the World Health Organization. Mr. Paoli completed a term as Councilor of the Society for Risk Analysis (SRA) and is a member of the Editorial Board of *Risk Analysis*. Recently, Mr. Paoli was awarded the Sigma Xi – SRA Distinguished Lecturer Award. He has provided training in risk assessment methods around the world, including the continuing education programs of the Harvard School of Public Health and the University of Maryland. Greg holds a Bachelors Degree in Electrical and Computer Engineering and a Master's Degree in Systems Design Engineering from the University of Waterloo.

Alan Stern, New Jersey Department of Environmental Protection

Dr. Alan H. Stern is the Section Chief for Risk Assessment in the Office of Science of the New Jersey Department of Environmental Protection; Adjunct Associate Professor in the Department of Environmental and Occupational Health of the University of Medicine and Dentistry of New Jersey-School of Public Health. He received a bachelor's degree in biology from the State University of New York at Stony Brook (1975), a master's degree in cellular and molecular biology from Brandeis University (1978), a master of public health degree (1981) and a

doctorate in public health from the Columbia University School of Public Health (1987). Dr. Stern is board-certified in toxicology by the American Board of Toxicology (Diplomate of the American Board of Toxicology). Dr. Stern's areas of expertise include risk assessment and exposure assessment including the application of probabilistic techniques to quantitative estimation of exposure and risk. His research interests have focused on heavy metals including lead, mercury, chromium and cadmium. Dr. Stern was a member of the National Research Council/National Academy of Sciences Committee on the Toxicology of Methylmercury (1999-2000) and a member of the recent USEPA Science Advisory Board panel for the National-Scale Mercury Risk Assessment for Coal- and Oil-Fired Electrical Generating Units (June-July 2011) as well as the USEPA Science Advisory Board Panel for Peer Review of the All-Ages Lead Model (Oct. 27-28, 2005). He has also served on numerous USEPA-IRIS review panels including Toxicological Review of Urea (Dec. 13, 2010, Panel Chair), Toxicological Review of Trichloroacetic Acid (Dec. 10, 2009, Panel Chair), Toxicological Review of 2-Hexanone (May 22, 2008, Panel Chair), Toxicological Review of Toluene (Feb. 5, 2004, Panel Chair). Other panels, committees and workshops include, ATSDR Toxicological Profile Review of Revised Minimal Risk Levels (MRLs) for 1,4-Dioxane (March-April, 2010), ATSDR Toxicological Profile Review of Revised Inhalation MRL for 1,4-dioxane (Sept. 2011),.USEPA Panel for the Review of Draft Exposure Factors Handbook (March 3-4, 2010), USEPA Workshop on Cardiovascular Toxicity of Methylmercury (Jan. 12-13, 2010), USEPA Panel for Review of ―Draft Child-Specific Exposure Factors Handbook (Sept. 19-20, 2007). Dr. Stern has authored numerous articles in peer-reviewed journals, and contributed a book chapter on Exposure Assessment for Neurotoxic Metals in ―Human Developmental Neurotoxicology - D. Bellinger, ed. (Taylor & Francis, New York, 2006.), and the article on *Environmental Health Risk Assessment‖ in the Encyclopedia of Quantitative Risk Assessment and Analysis*. John Wiley and Sons Ltd., 2008.

Appendix 2. Meeting Agenda

Agenda

Date: May 28, 29 & 30, 2013

Location: U.S. Environmental Protection Agency, Washington, D.C.

Purpose: To advance the recommendations of NAS (2009) and subsequent framework of *ARA* (Meek et al., 2013) on problem formulation and dose-response analysis, through review of illustrative case studies for further development of methods

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Tuesday May 28th

Welcome (1:00 to 1:15)

- Julie Fitzpatrick, U.S. Environmental Protection Agency

Introductions and Updates (1:15 to 1:30)

- Lynne Haber, TERA, on behalf of the Dose-Response Advisory Committee
- Introductions - Members of the Science Panel

Case Study: Endogenous Formation Implications for Formaldehyde Carcinogenicity (1:30 to 3:00)

- Robinan Gentry, Environ International Corporation
- Tom Starr, TBS Associates

- Jim Swenberg, University of North Carolina Chapel Hill
- Jeffry Schroeter, Applied Research Associates

Afternoon Break (3:00 to 3:30)

Case Study: Endogenous Formation Implications for Formaldehyde …continued (3:30 to 5:30)

Reception (dinner portion hors d'oeuvres, 6:30 to 8:30)

Wednesday, May 29th

Keynote Talk (8:30 to 9:30)

- Ken Olden, U.S. EPA, National Center for Environmental Assessment

Pathway-Based Regulatory Toxicology and Alternatives to Animal Testing (9:30 to 10:00)

- Thomas Hartung, Johns Hopkins Bloomberg School of Public Health (via webinar)

Morning Break (10:00 to 10:30)

International Developments on Mode of Action (10:30 to 11:00)

- Bette Meek, University of Ottawa

The HESI RISK21 Roadmap: Practical Application to Pyrethroid Human Safety Assessment (11:00 to 11:30)

- Tim Pastoor, Syngenta Crop Protection, Inc.

The HESI RISK21 Quantitative Key Events Dose Response Framework (Q-KEDRF) (11:30 to noon)

- Ted Simon, Ted Simon, LLC

Lunch (12:00 to 1:00)

Case Study: Hypothesis-Driven Weight of Evidence Review for Naphthalene Carcinogenicity (1:00 to 2:30)

- Lorenz Rhomberg, Gradient
- Lisa Bailey, Gradient

Afternoon Break (2:30 to 3:00)

Case Study: Hypothesis-Driven continued… (3:00 to 5:00)

Observer Comments (5:00 to 5:30)

Thursday, May 30th

Case Study: Interpretation of 24-hour Sampling Data (8:30 to 10:00)

- Roberta Grant, Texas Commission on Environmental Quality
- Joseph "Kip" Haney, Texas Commission on Environmental Quality
- Allison Jenkins, Texas Commission on Environmental Quality
- Denis Jugloff, Ontario Ministry of Environment
- Julie Schroeder, Ontario Ministry of Environment (in absentia)

Morning Break (10:00 to 10:30)

Case Study: Interpretation of 24-hour Sampling Data (cont) (10:30 to 12:30)

Observer Comments (12:30 to 1:00)

Adjourn (1:00**)**

Closed Panel Discussion (1:00 to 5:00)

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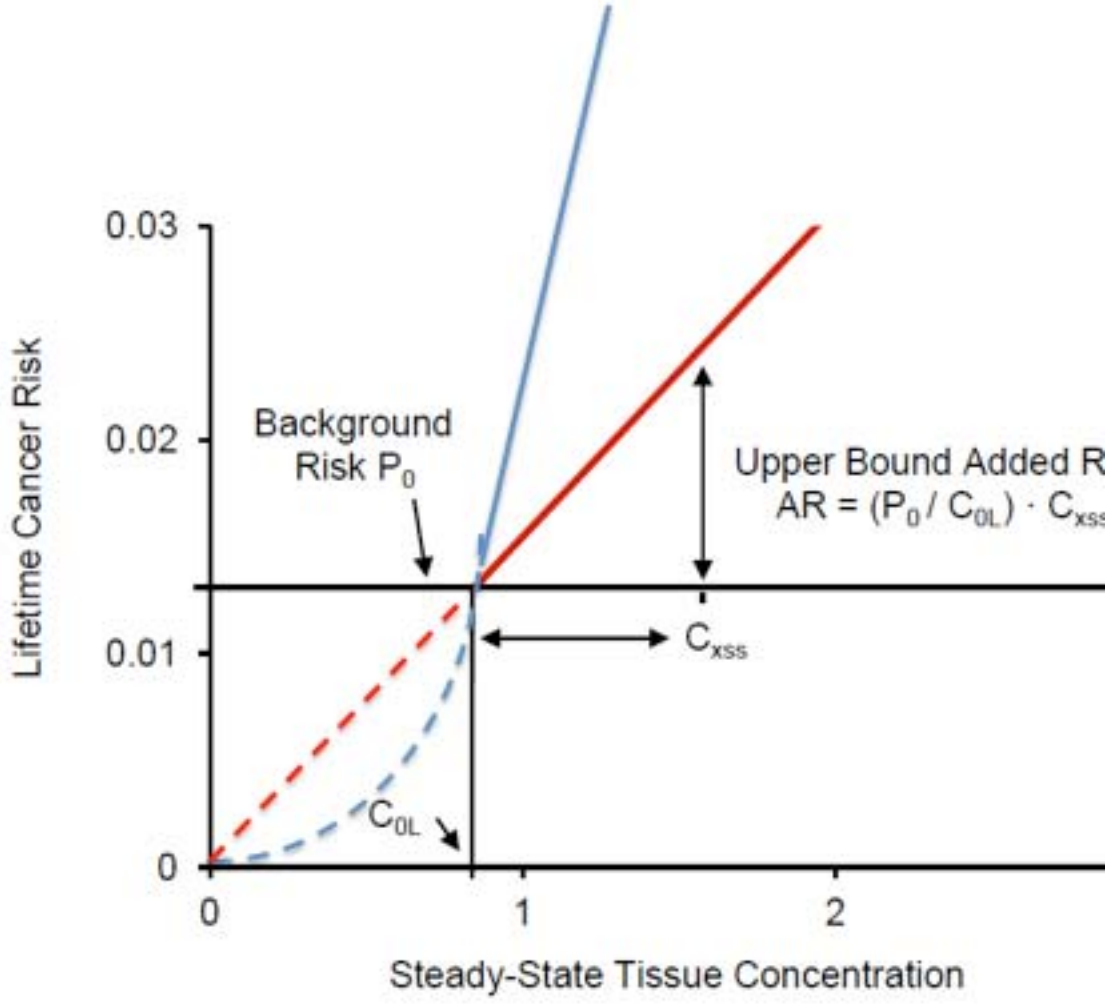
Appendix 4. Observer Comment and Author Response

Jennifer Jinot of the U.S. EPA provided the following written comment after the meeting, building on her verbal comments during the meeting:

"Though Dr. Starr's approach is presented as a bounding approach or "reality check" because it is based on conservative assumptions, there is at least one key assumption that is not conservative, and this undermines the utility of this approach as a "reality check". The claim is made that one of the conservative features of the approach is that it assumes linearity at low doses. However, the main assumption made in deriving the linear low-dose slope is not conservative. The (upper-bound) slope is calculated as P_0/C_{0L} (the background risk [P_0] divided by the [lower bound] steady-state tissue concentration of endogenous DNA adducts [C_{0L}]; (see the Appendix Figure 1 and legend, below, modified from Dr. Starr's presentation, and provided at the end of the workshop report). In other words, the low-dose slope for the risk from additional adducts (above C_{0L}) from exogenous exposure is taken as the average risk per endogenous adduct; this is essentially the same as assuming that the dose-response relationship for risk as a function of adduct level is linear over the concentration range of endogenous adducts (i.e., from 0 to C_{0L} in the Appendix Figure 1) and then extending that linear slope into the low-dose range for additional adducts from exogenous exposure. However, it seems highly plausible that the dose-response relationship over the endogenous range is sublinear (e.g., that the baseline levels of DNA repair enzymes and other protective systems evolved to deal with endogenous DNA damage would work more effectively for lower levels of endogenous adducts), i.e., that the slope of the dose-response relationship for risk per adduct would increase as the level of endogenous adducts increases (see blue dashed line in the Appendix Figure 1). If the dose-response relationship over the endogenous range is sublinear, then the slope at C_{0L} would be higher than that based on the assumed linear dose-response relationship over the endogenous range (see Appendix Figure 1). Slope at C_{0L} would be higher than that based on the assumed linear dose-response relationship over the endogenous range (see Appendix Figure 1). Thus, assuming a linear dose-response relationship over the endogenous range as the basis for an upper bound on linear low-dose risk from exogenous exposure is not a conservative assumption." See the Appendix Figure 1 below. Thus, assuming a linear dose-response relationship over the endogenous range as the basis for an upper bound on linear low-dose risk from exogenous exposure is not a conservative assumption." See the Appendix Figure 1 below.

Appendix Figure 1. Cancer Risk versus DNA Adduct Concentration, Adapted by Jennifer Jinot from Presentation by Thomas Starr



The above Figure is a modification of the figure presented by Dr. Starr (Figure 4 of the main report): the red dashed line and the blue dashed curve and solid line were added to the original figure. The red dashed line portrays the assumed linear dose-response relationship across the concentration range of the endogenous adducts; the slope of this line is basis for the assumed upper-bound slope (red line) in the presented bottom-up approach. The blue dashed curve illustrates the alternative, and highly plausible, assumption that the dose-response relationship across the concentration range of the endogenous adducts is sublinear; the blue solid line depicts the linear extension of that sublinear curve from the slope of the curve at C_{0L}. The solid blue line has a higher slope than the assumed upper-bound slope (red line) in the bottom-up approach.

Authors' response to audience comment:

This written comment with an accompanying figure (Appendix Figure 1) was presented verbally by Jennifer Jinot (US EPA) after comments on the presentations from all ARA Panel Members and after the ensuing discussion amongst Panel Members and the presenters. Before we address Jinot's comment, we briefly summarize key elements of the bottom up approach to bounding the added cancer risk that might arise from low exogenous exposure levels (see also Starr TB, Swenberg JA. 2013. A novel bottom-up approach to bounding low-dose human cancer risks from chemical exposures. *Reg Toxicol Pharmacol* 65(3):311-315).

Key Elements of the Bottom Up Approach

The approach makes use of two parameters: 1) the background cancer risk (P_0) in a specific target tissue, and 2) the background (endogenous) concentration (C_0) of a cancer-related exposure biomarker, such as a specific DNA adduct, measured in the same target tissue. After adjusting appropriately for residual statistical uncertainty by replacing central estimates of P_0 and C_0 with their corresponding upper (P_{0U}) and lower (C_{0L}) confidence bounds, respectively, the ratio P_{0U}/C_{0L} provides a conservative cancer risk slope factor that can be used to bound the added risk that might be associated with incremental steady-state exogenous exposure (C_{xss}). Assuming that the upper bound on added risk (AR) is approximately linear near C_0, our bottom up approach results in the equation: $AR = (P_{0U}/C_{0L}) \cdot C_{xss}$. Note the implicit assumption that all of the background cancer risk P_0 could be causally linked to the background endogenous exposure C_0, so the resulting bound on added risk is "worst case" in that regard.

Strengths of the bottom up approach are that it 1) is consistent with the "additivity to background" concept; 2) yields upper-bound risk estimates that are linear at all doses, and 3) requires only information regarding background risk, background (endogenous) exposure, and the additional steady-state exogenous exposure in order to be implemented. The bottom-up approach thus provides a completely independent "reality check" on low-dose risk estimates derived with the typical "top down" approach of fitting dose-response models to high-dose human or laboratory animal cancer data. The key biotechnological advance that underpins this approach is the extraordinary ability to distinguish between and separately quantify the target tissue exposure biomarkers that arise from internal background (endogenous) and external (exogenous) sources.

Response to Jinot's Comment

Jinot's comment on our bottom up approach: 1) is completely speculative, and 2) contradicts the limited inferences about cancer risk at low doses that can be drawn from the available data.

1. **Jinot's comment is speculative; there are no data to support it.**

Jinot asserts that it is "highly plausible" for the dose-response relationship between cancer risk and the steady state target tissue DNA adduct concentration to be sublinear below the endogenous level C_0, claiming further that this sublinearity forces the slope of the relationship to be greater than our bottom up estimate P_{0U}/C_{0L} (not P_0/C_{0L}, as Jinot states) that applies at total DNA adduct concentrations equal to and greater than C_0 (not C_{0L}, as Jinot states). However, there are no data regarding cancer risk below C_0, so any statements regarding the shape of the dose-response relationship below C_0, including Jinot's, can only be speculation. The dose-response relationship below C_0 cannot even be investigated, because the endogenous DNA adducts that comprise C_0 are always present, even when there is no *exogenous* exposure. This is why our bottom up approach to bounding the cancer risk at low doses includes no assumptions whatsoever regarding the shape of the dose-response curve below C_0. The plausibility of hypothetical conjectures about the shape of the dose-response curve below C_0 cannot be evaluated without data, and there are no cancer data or DNA adduct data below C_0, for formaldehyde, or for any other chemical.

2. **Jinot's comment directly contradicts the dose-response implications of the available data at and above C_0.**

Jinot contends that sublinearity of the dose-response relationship below C_0 necessarily implies that the slope of the dose-response curve at and above C_0 must be greater than our bottom up bounding slope estimate, P_{0U}/C_{0L}. However, standard top down dose-response modeling using the available rat nasal tumor data for formaldehyde provides clear evidence that this is not the case.

When we used the EPA default "top down" risk assessment approach of fitting a multistage model ($P(d) = 1–\exp(-(a_0+a_1 \cdot d+a_2 \cdot d^2+ \ldots +a_n \cdot d^n))$, with n=7) to the available rat nasal tumor data versus airborne formaldehyde concentration, the resulting maximum likelihood estimate (MLE)

of the model's slope at zero external exposure, i.e., at C_0, was identically zero as shown in Appendix Figure 2 and Table 1 below. Indeed, if the EPA default non-negativity constraint on the model's linear dose coefficient had been relaxed, the MLE of the slope at C_0 would actually be *negative*! Neither of these results (zero or a negative value) is greater than our bottom up bounding estimate of P_{0U}/C_{0L}, namely, $3.656 \cdot 10^{-4}$ per adduct per 10^7 dG, despite the fact that the fitted dose-response is highly nonlinear, and sublinear, at and above C_0, involving 6th and 7th powers of dose, as is also shown in Table 1 below. Hence, our bottom up estimate of the slope at C_0 does indeed provide an upper bound on the "best", i.e., maximum likelihood, estimate of this slope, even when the best-fitting dose-response is highly sublinear. This result clearly contradicts Jinot's assertion.

When we similarly fit the multistage model to the same rat nasal tumor data, but this time versus total DNA adducts in rat nasal tissue (Appendix Figure 3 and Table 2 below), with the exogenous DNA adduct concentrations, measured at 6 hours post exposure onset, adjusted properly with an estimated 206 hour half-life to equivalent continuous steady state values, the resulting MLE of this model's slope at zero external exposure, i.e., at C_0, was $1.976 \cdot 10^{-5}$ per adduct per 10^7 dG. This estimate is approximately 18.5-fold smaller than our bottom up bounding slope estimate ($3.656 \cdot 10^{-4}$ per adduct per 10^7 dG), again contradicting Jinot's assertion that the MLE slope would be greater than our bottom up bounding estimate.

We also fit a Weibull model, modified to allow for a non-negative linear term

($P(d) = 1 - \exp(-(a_0 + a_1 \cdot d + a_p \cdot d^p))$, with $p \geq 2$), via maximum likelihood to the same rat nasal tumor data versus total DNA adducts in rat nasal tissue, again with the measured exogenous adduct concentrations at 6 hours post exposure onset adjusted properly with an estimated 206 hour half-life to equivalent continuous steady state values. The fit of this model to the rat nasal cancer data in the low-dose region is also provided in Appendix Figure 3, as well as in Table 3, but the fit of this model is indistinguishable visually from that of the previously discussed multistage model. The resulting MLE of the slope of this model at zero external exposure, i.e., at C_0, was $1.868 \cdot 10^{-5}$ per adduct per 10^7 dG, approximately 19.6-fold smaller than our bottom up bounding estimate of $3.656 \cdot 10^{-4}$ per adduct per 10^7 dG, once again in contradiction with Jinot's comment.

Thus, each of the three "top down" dose-response modeling approaches that we have described herein independently confirms that our bottom up bounding estimate of the slope at C_0 is conservative, in the sense that our bottom up estimate exceeds by substantial margins the maximum likelihood estimates of the model-specific MLEs of the slope at C_0. These results all contradict what Jinot has asserted in her comment. It is also noteworthy that the model-specific

MLEs of the coefficient of the linear term in the three top down dose-response analyses were all equal to zero, and the models themselves were all highly nonlinear, and sublinear, depending on 6^{th} and 7^{th} powers of dose when airborne formaldehyde was used as the dose metric, and on 5^{th} and 6^{th} powers of dose, or the 5.8^{th} power of dose for the modified Weibull model, when the dose metric was comprised of total DNA adducts in rat nasal tissue.

Also noteworthy is the fact that all three fitted dose-response models had substantial and positive intercept terms (a_0), indicating that most of the background nasal cancer risk (P_0) at C_0 was attributed during the model fitting process to sources *other* than the endogenous DNA adducts. Specifically, the maximum likelihood estimate of the fraction of background risk,

$f = (1-\exp(-a_0))/P_0$, that was attributed to sources other than the endogenous DNA adducts was 0.877, 0.829, and 0.832, respectively, for the three modeling approaches discussed above. These fractions would be higher still if the coefficient of the linear term in the models had been permitted to be negative.

3. Summary

Given the available data for nasal cancer in rats exposed to formaldehyde by inhalation, our implicit assumption that the endogenous DNA adducts that are present in nasal respiratory epithelium could be responsible for *all* of the background nasal cancer risk appears to be highly conservative. In addition, our assumption that P_{0U}/C_{0L} provides a conservative upper bound on the slope of the dose-response relationship for added rat nasal cancer risk near the background endogenous DNA adduct concentration C_0 also appears to be fully confirmed by three different dose-response analyses of the available data. Our assumptions regarding the nature of the dose-response relationship near C_0 can thus be appropriately characterized as "highly plausible". In contrast, Jinot's assumptions are appropriately characterized as implausible because there are no data that support them, and because the results from multiple dose-response analyses of the data that are available for formaldehyde-induced nasal cancer in rats directly contradict them. Her comment is therefore best characterized as completely speculative.

TABLE 1. GLOBAL82 MULTISTAGE MODEL ANALYSIS OF CH2O RAT NASAL TUMOR DATA WITH AIRBORNE FORMALDEHYDE CONCENTRATION, PPM, AS THE DOSE METRIC.

GROUP 1 HAS 1 RESPONSES OUT OF 3,602 MEMBERS FOR A DOSE OF 0.0

GROUP 2 HAS 0 RESPONSES OUT OF 107 MEMBERS FOR A DOSE OF 0.7

GROUP 3 HAS 0 RESPONSES OUT OF 353 MEMBERS FOR A DOSE OF 2.0

GROUP 4 HAS 3 RESPONSES OUT OF 343 MEMBERS FOR A DOSE OF 5.8

GROUP 5 HAS 22 RESPONSES OUT OF 103 MEMBERS FOR A DOSE OF 9.9

PREDICTED AND OBSERVED RESPONSE PROBABILITIES

GROUP= 1 PREDICTED= .246252E-03 OBSERVED= .277624E-03

GROUP= 2 PREDICTED= .246274E-03 OBSERVED= .000000

GROUP= 3 PREDICTED= .258686E-03 OBSERVED= .000000

GROUP= 4 PREDICTED= .871728E-02 OBSERVED= .874636E-02

GROUP= 5 PREDICTED= .213638 OBSERVED= .213592

CHI-SQUARE GOODNESS OF FIT STATISTIC IS .132132

MAXIMUM VALUE OF THE LOG-LIKELIHOOD IS -79.9416846141

MAXIMUM LIKELIHOOD ESTIMATES OF DOSE COEFFICIENTS:

Q(0)= .246282488309E-03

Q(1)= .000000000000

Q(2)= .000000000000

Q(3)= .000000000000

Q(4)= .000000000000

Q(5)= .000000000000

Q(6)= .178971172177E-06

Q(7)= .768126937566E-08

MAXIMUM LIKELIHOOD ESTIMATE OF SLOPE AT 0 PPM = 0.00000000

TABLE 2. GLOBAL82 MULTISTAGE MODEL ANALYSIS OF CH2O RAT NASAL TUMOR DATA WITH TOTAL STEADY STATE DNA ADDUCTS PER 10^7 DG (EXOGENOUS @ 6 HRS ADJUSTED WITH 206 DAY HALF-LIFE) AS THE DOSE METRIC.

GROUP 1 HAS 1 RESPONSES OUT OF 3,602 MEMBERS AT A DOSE OF 4.70

GROUP 2 HAS 0 RESPONSES OUT OF 107 MEMBERS AT A DOSE OF 5.06

GROUP 3 HAS 0 RESPONSES OUT OF 353 MEMBERS AT A DOSE OF 6.40

GROUP 4 HAS 3 RESPONSES OUT OF 343 MEMBERS AT A DOSE OF 13.99

GROUP 5 HAS 22 RESPONSES OUT OF 103 MEMBERS AT A DOSE OF 24.89

PREDICTED AND OBSERVED RESPONSE PROBABILITIES

GROUP= 1 PREDICTED= .246756E-03 OBSERVED= .277624E-03

GROUP= 2 PREDICTED= .255253E-03 OBSERVED= .000000

GROUP= 3 PREDICTED= .324303E-03 OBSERVED= .000000

GROUP= 4 PREDICTED= .850748E-02 OBSERVED= .874636E-02

GROUP= 5 PREDICTED= .214038 OBSERVED= .213592

CHI-SQUARE GOODNESS OF FIT STATISTIC IS .158189

MAXIMUM VALUE OF THE LOG-LIKELIHOOD IS -79.9667788023

MAXIMUM LIKELIHOOD ESTIMATES OF DOSE COEFFICIENTS:

Q(0)= .230118857391E-03

Q(1)= .000000000000

Q(2)= .000000000000

Q(3)= .000000000000

Q(4)= .000000000000

Q(5)= .309576346214E-08

Q(6)= .887612832236E-09

Q(7)= .000000000000

MAXIMUM LIKELIHOOD ESTIMATE OF SLOPE AT 4.7 PER 10E+07 dG = 1.97625E-05

TABLE 3. TB STARR MODIFIED WEIBULL MODEL ANALYSIS OF CH2O RAT NASAL TUMOR DATA VS TOTAL STEADY STATE DNA ADDUCTS PER 10^7 dG (EXOGENOUS @ 6 HRS ADJUSTED WITH 206 DAY HALF-LIFE) AS THE DOSE METRIC.

GROUP 1 HAS 1 RESPONSES OUT OF 3,602 MEMBERS AT A DOSE OF 4.70

GROUP 2 HAS 0 RESPONSES OUT OF 107 MEMBERS AT A DOSE OF 5.06

GROUP 3 HAS 0 RESPONSES OUT OF 353 MEMBERS AT A DOSE OF 6.40

GROUP 4 HAS 3 RESPONSES OUT OF 343 MEMBERS AT A DOSE OF 13.99

GROUP 5 HAS 22 RESPONSES OUT OF 103 MEMBERS AT A DOSE OF 24.89

PREDICTED AND OBSERVED RESPONSE PROBABILITIES

GROUP= 1 PREDICTED= . 24599E-03 OBSERVED= .277624E-03

GROUP= 2 PREDICTED= . 25408E-03 OBSERVED= .000000

GROUP= 3 PREDICTED= . 32157E-03 OBSERVED= .000000

GROUP= 4 PREDICTED= . 86756E-02 OBSERVED= .874636E-02

GROUP= 5 PREDICTED= . 21364 OBSERVED= .213592

MAXIMUM VALUE OF THE LOG-LIKELIHOOD IS -79.9649259

MAXIMUM LIKELIHOOD ESTIMATES OF MODIFIED WEIBULL MODEL PARAMETERS:

A0= .23090E-03

A1= .00000

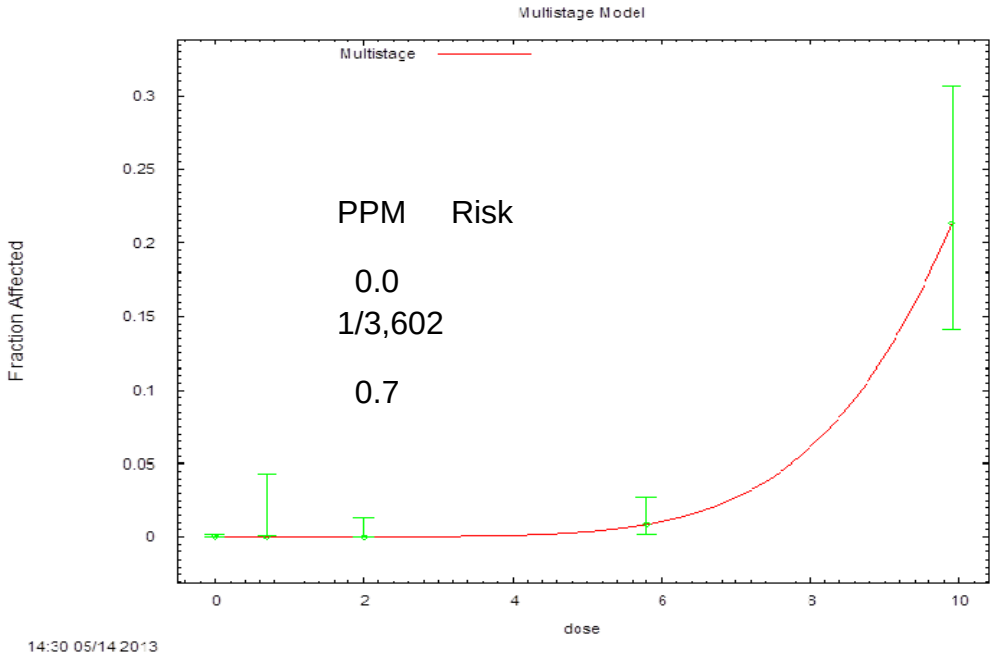
AP= .19041E-08

P= .58027E+01

MAXIMUM LIKELIHOOD ESTIMATE OF SLOPE AT 4.7 PER 10E+07 dG = 1.866798E-05

Appendix Figure 2.

Plot of predicted tumor incidence (red curve) for a multistage model fit to rat nasal tumor data by maximum likelihood using airborne formaldehyde concentration as the dose metric. See Table 1 for model parameter values.



Appendix Figure 3.

Plot of the Jinot speculation (blue curve), the linear "bottom up" confidence bound (red line), and predicted tumor incidence from multistage and modified Weibull models (green curve) fit by maximum likelihood to rat nasal carcinoma data (red squares) using total (endogenous plus exogenous) steady state formaldehyde-dG adducts per 10^7 dG as the dose metric. See Tables 2 and 3 for model parameter values. The horizontal black line depicts P_0, the background rat nasal tumor incidence estimate of 1/3,602.