TERA

Report of the Expert Peer Review of Sulfolane Reference Doses for the Alaska Department of Environmental Conservation

Volume Two - Appendix

Expert Panel:

Dr. Andrew Maier (Panel Chair)

Dr. Susan Griffin

Dr. Richard Hertzberg

Dr. Michael Luster

Dr. Deborah Oudiz

Dr. Stephen Roberts

Independent

Non-Profit

Science

For Public Health Protection

Toxicology Excellence for Risk Assessment

December 18, 2014

Appendix A. Meeting Handouts (panel biographical sketches, conflict of interest information, charge questions, agenda, and additional handouts)

Welcome

Welcome to this expert peer review meeting of a toxicological reference dose (RfD) for sulfolane. This handout includes an agenda, as well as information about how the peer review has been organized, ground rules for the meeting, and panel biographical sketches and conflict of interest information.

The scientific documents and public technical comments for the sulfolane RfD review are posted on the web at: http://www.tera.org/Peer/sulfolane/index.html.

Agenda

Location: University of Alaska, Fairbanks
Wood Center, Conference Room EF

Tuesday, September 16, 2014

8:00am **Arrival & Registration**

8:30am **Meeting Convenes**[1]
Welcome, Ms. Jacqueline Patterson, TERA
Panel Introductions and Conflict of Interest/Bias Disclosures, Panel
Meeting Process and Ground Rules, Panel Chair

9:00am **Background**
Presentation, Tamara Cardona, Contaminated Sites Program, Division of Spill Prevention and Response, Alaska DEC and Stephanie Pingree Buss, SPB Consulting for Alaska DEC
-- Clarifying Questions from the Panel
-- Clarifying Questions and Comments from RfD Authors

9:45am **Panel Discussion**

12:00pm **Lunch**

1:00pm **Panel Discussion, continued**

5:00pm **Meeting Adjourns**

Wednesday, September 17, 2014

8:00am **Registration**

8:30am **Meeting Reconvenes**

8:45am **Panel Discussion, continued**

1:00pm **Lunch**

2:00pm **Panel Discussion, continued**

4:00pm **Meeting Adjourns**

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[1] The Chair will call a break mid-morning and mid-afternoon. At the end of each session, RfD authors will have an opportunity to ask the panel clarifying questions.

Ground Rules for Meeting Observers

The peer review meeting is open to the public and interested persons are invited to attend as observers. Observers are invited to listen and are expected to remain quiet during the meeting. Because the panel review is a scientific meeting, there will be no public comment period during the meeting, however Alaska Department of Environmental Conservation (ADEC) personnel will be available to answer general questions on the sulfolane project after the panel concludes their deliberations each day.

It is important that the meeting attendees remember that the panel members must remain independent and should not be influenced by any party. Therefore, we ask observers to refrain from discussing the RfDs or related issues with the panel members during the breaks unless a panel member initiates the discussion. Panel members will be asked to summarize any relevant conversations for the rest of the panel and audience when the meeting reconvenes after the break.

No pictures, audio, or visual recording, are allowed at the meeting.

The purpose of the meeting is to obtain the consensus opinion of the panel of experts as a whole after their full deliberation and discussion of the RfDs. During the meeting, panelists will make statements and ask questions as they work through the issues to form their individual and collective opinions. Statements or opinions expressed during the discussions may not reflect the panelist's or the panel's final thinking on the subject. Therefore, it would be inappropriate to quote individual expert's statements from the meeting. The final meeting report will contain the official recommendations and conclusions of the panel.

Peer Review Process

ADEC has tasked Toxicology Excellence for Risk Assessment (TERA) with conducting an independent, expert peer review of the available RfDs for sulfolane. A sulfolane RfD will be used by ADEC to develop cleanup levels for groundwater in North Pole, Alaska. TERA is an independent non-profit organization with a mission to protect public health through the best use of toxicity and exposure information in the development of human health risk assessments. As a non-profit organization, TERA organizes independent peer reviews on chemical assessments or other risk assessment work products to meet the needs of public and private sponsors.

The purpose of the peer review is to convene a group of experts to evaluate the scientific basis and appropriateness of the document(s) and related conclusions. Peer review is a critical review of a work product that is conducted by qualified individuals who are independent of those who performed the work, but are collectively equivalent in technical expertise (i.e., peers) to those who performed the work. The peer review involves an in-depth assessment of the assumptions, calculations, alternate interpretations, methodology, and conclusions of the material under review.

ADEC, as the sponsor of the peer review, is paying for the direct costs of conducting the peer review meeting and TERA's labor costs to organize and convene the peer review. TERA's responsibilities include identifying and recruiting scientists with relevant expertise, identifying and managing conflict of interest and bias issues, organizing and conducting the meeting, and drafting and finalizing the meeting report. The peer reviewers for this meeting have been offered and accepted an honorarium for their service.

TERA has developed its peer review and consultation program following principles highlighted by the U.S. Office of Management and Budget (OMB) and utilizing approaches used by U.S. EPA, the National Academy of Sciences, EPA's Science Advisory Board, and the International Life Sciences Institute (ILSI) Policies and Procedures for its Model Peer Review Center of Excellence.

Selection of the Panel and Evaluation of Potential Conflict of Interest and Bias Issues

The sulfolane peer reviewers are recognized technical experts who have been selected for their relevant scientific technical knowledge and independence. Collectively, the panel has expertise in toxicology, immunology, human health risk assessment, RfD methods and derivation, contaminated site assessments, biostatistics, and benchmark dose modeling. The experts have background and experience with the government, university, industry, and non-profit sectors. Each selected expert has been screened for potential conflicts of interest and every effort was made to avoid conflicts of interest and biases that would prevent a panel member from giving an independent opinion on the subject.

TERA, as the independent group convening the peer review, was solely responsible for selecting the panel. TERA's final selection of the panel members was based upon the candidates' scientific experience and credentials, the overall need for coverage of the charge questions, conflict of interest and bias considerations, and the individuals' interest and availability. Experts serve on the panel as individuals and provide their personal scientific opinions on the issues under discussion during the meeting; they do not serve as representatives of their employers or any other group with whom they may be affiliated.

In order to protect the independence of the panel's review, the experts' names are not being shared or released prior to the meeting. TERA has not identified the panel members to ADEC or anyone other than the panel. Panel members have been asked to refrain from discussing the review with others.

Development of the Charge

TERA has reviewed the group of RfDs and the background document prepared by ADEC and developed the charge to peer reviewers. The purpose of the charge is to identify the important relevant scientific issues and questions, and provide a framework for the panel discussions. The sulfolane panel charge covers the key aspects and decision points for the derivation of an RfD. The charge also includes open ended questions to insure that the experts will cover all relevant issues in their discussions.

Prior to the Peer Review Meeting

TERA sent a package of review materials to the panel approximately one month prior to the meeting. The review package included the ADEC background document, copies of the RfDs, key references, and the peer review charge. The panel reviewed these materials prior to the meeting. The meeting materials have been posted on the meeting web page - http://www.tera.org/Peer/sulfolane/index.html. The authors of the subject RfDs and others were invited to provide written technical comments on the materials. These technical public comments have been posted to the web page and shared with the panel.

The Peer Review Meeting

The purpose of the peer review meeting is to have the expert panel evaluate the RfDs and reach conclusions based on the science. Therefore, the discussions will be limited to the panel members. During their discussions, the panel may seek clarification on the individual RfDs from the RfD authors. At several points in the agenda, the chair will ask the attending RfD authors in they have any clarifying questions for the panel.

The meeting chair will facilitate the panel in their discussions to cover the issues and questions from the charge. Individual panelists will be asked to share their opinions and defend them with scientific data and analysis. The panel will attempt to achieve consensus on the key points and charge questions. If unanimous consensus is not achieved, the meeting report will discuss minority opinions to reflect the full range of opinions of the panel.

Meeting Report

TERA scientist(s) will work with the panel to prepare a draft meeting report that will summarize the panel's discussions, conclusions, and recommendations. This report will not be a transcript of the meeting; rather it will summarize the key discussions and conclusions. The report text will not attribute comments to specific panelists as it is the consensus opinion of the panel as a whole that is the important result of the peer review. During the finalization of the meeting report, the panel may clarify their conclusions; the panel's conclusions and recommendations are not final until the final meeting report is released.

The final meeting report will be the official record of the peer review and include copies of any presentation slides, a list of attendees, panel biographical sketches and conflict of interest/bias information, handouts from the meeting, and any public comments. The final meeting report will be made available on the TERA meeting web page.

Expert Panel Biographic Sketches

Dr. Susan Griffin

Dr. Griffin is a Senior Toxicologist with the Superfund Program at the U.S. Environmental Protection Agency (EPA) in Denver, Colorado. Dr. Griffin has a doctorate in Veterinary Toxicology and Pharmacology from the University of California, Davis and is a Diplomate of the American Board of Toxicology. Dr. Griffin has extensive experience in assessing human health risks and communicating the results to diverse parties. She has completed several hundred human health baseline risk assessments for hazardous waste sites, provides expert toxicological and risk assessment advice to EPA and the Department of Justice on Superfund sites, and designs and manages research investigations to obtain scientifically sound bases for risk assessment activities. She chaired the workgroup that developed the Integrated Exposure Biokinetic Uptake Model for Lead for the U.S. Superfund Program and has served as an expert consultant to the Food and Drug Administration (FDA) on the Dental Products Panel. She is actively involved in writing and developing U.S. Superfund guidance documents, and developing chemical toxicity values for EPA's Integrated Risk Information System (IRIS) data base as a consensus reviewer. Dr. Griffin has worked with U.S. Agency for International Development in Romania and has consulted with the Chilean Ministry of Mines on arsenic exposures and health effects at the Chuquicamata Mine. Dr. Griffin has published on risk assessment issues and methods.

Dr. Richard Hertzberg

Dr. Richard Hertzberg has a special term appointment with the Argonne National Laboratory, Environmental Science Division, developing methods and case studies for cumulative health risk assessment. He is also an adjunct professor in the Department of Environmental Health at Emory University, where he teaches graduate courses in risk assessment. In addition, he works as a private consultant focusing on dose-response modeling, cumulative risk assessment, and statistical approaches for toxic interactions in chemical mixtures, and he is a Toxicology Excellence for Risk Assessment (TERA) Fellow. Dr. Hertzberg received his doctorate in biomathematics from the University of Washington. Dr. Hertzberg retired from the EPA in 2006. As a Senior Scientist at EPA's National Center for Environmental Assessment (NCEA) he led the research program on mixture risk assessment and was instrumental in writing the EPA mixture risk guidelines. He initiated the use of categorical regression for dose-severity modeling, and the interaction-based hazard index for mixture risk assessment. Dr. Hertzberg has extensive experience with mathematical modeling for quantitative risk assessment, specializing in bio-mathematical dose-response models of human toxicology, quantitative health risk estimation of chemical mixtures, quantitative methods for cumulative risk assessment of chemical and nonchemical stressors for cumulative risk assessment, and teaching of quantitative methods for health risk assessment. He has served on external review and advisory panels to the U.S. Geologic Survey, the Agency for Toxic Substances and Disease Registry (ATSDR), the Health Council of the Netherlands, The Lovelace Respiratory Research Institute, and the National Institute of Occupational Health

(NIOSH). Dr. Hertzberg was awarded the Distinguished Achievement Medal in Environmental Statistics from the American Statistical Association.

Dr. Michael Luster

Dr. Michael I. Luster is a Research Professor in the School of Public Health at West Virginia University. Dr. Luster received his Ph.D. in Microbiology (Immunology) from Loyola University of Chicago. He retired as Chief of the Toxicology and Molecular Biology Branch at NIOSH in 2006. His work at NIOSH included studies on the effects of environmental and occupational agents on the immune system, including applied research (development of methods and mathematical models to minimize uncertainties in risk assessment) and basic research. He has authored or co-authored over 360 publications and eight books in the area of immunotoxicology and is on the editorial board of numerous journals. Dr. Luster has served on advisory committees for the National Academy of Sciences, EPA, FDA, U.S. Consumer Product Safety Commission, International Life Sciences Institute (ILSI), World Resource Institute, Soap and Detergent Association, and others. He was a member of the World Health Organization (WHO) Committee on Immunotoxicology in Risk Assessment and EPA's committee to develop immunotoxicology assessment guidelines. He is a recipient of the Alice Hamilton Award for excellence in occupational safety and health research from NIOSH and the Frank Blood Award from the Society of Toxicology.

Dr. Andrew Maier

Dr. Andrew Maier is an Associate Professor of Environmental Health at the University of Cincinnati, where he has led a research program on occupational toxicology and risk assessment since 2013. Previously he served as the Director for the non-profit organization TERA and currently he serves as Chair of the TERA Fellows Program. Dr. Maier also works with NIOSH as a Toxicology Fellow. Dr. Maier has a Ph.D. in Toxicology from the University of Cincinnati with a focus on the molecular mechanisms of toxicity. In his capacity as a toxicologist and risk assessor, he has evaluated the toxicity of hundreds of chemicals and prepared toxicity assessments including derivation of reference doses and occupational exposure limits, critical examination of mode of action and human relevance considerations in support of dose-response assessments, and estimation of cancer risk. He is certified in comprehensive industrial hygiene practice by the American Board of Industrial Hygiene (CIH) and is a Diplomate of the American Board of Toxicology (DABT). Dr. Maier has served on many advisory and peer review panels and has chaired workshops and peer reviews on toxicity and risk assessments, risk methods and frameworks, and occupational health research.

Dr. Deborah Oudiz

Dr. Deborah Oudiz has been retired for the last five years. Prior to retirement, she was a Senior Toxicologist for the California Department of Toxic Substances Control in the California Environmental Protection Agency. She received her Ph.D. from the University of Cincinnat, Department of Environmental Health, followed by a National Cancer Institute (NCI) Postdoctoral Traineeship at University of California, San Francisco and further postdoctoral work at the University of California, Davis. Her research interests include male reproductive toxicology and work with mouse chimera models for determining maternal and paternal contributions to early embryonic deaths. During her tenure with California EPA, she oversaw and developed risk assessments in support of remediation of hazardous waste sites. Dr. Oudiz was instrumental in establishing a program for the evaluation of school sites for hazardous chemicals. She was responsible for developing guidance for these programs on a variety of toxicology and human exposure issues including lead-based paint, arsenic, naturally occurring asbestos, pesticides, and PAHs (poly aromatic hydrocarbons). In addition she has extensive experience in risk communication with communities, press, and other interested parties. Dr. Oudiz currently lives in Homer, Alaska where she is on the board of the Alaska Center for Coastal Studies and is a member of Cook Inletkeeper.

Dr. Stephen Roberts

Dr. Stephen Roberts is Director of the Center for Environmental & Human Toxicology at the University of Florida, and a Professor with joint appointments in the College of Veterinary Medicine, the College of Medicine, and the College of Public Health and Health Professions. He received his Ph.D. from the University of Utah College of Medicine and subsequently completed a National Institutes of Health (NIH) individual postdoctoral fellowship in pharmacokinetics at the State University of New York Buffalo. He has previously served on the faculties of the University of Cincinnati and the University of Arkansas for Medical Sciences. Dr. Roberts conducts research in a number of areas of toxicology, including mechanisms of toxicity, toxicokinetics, nanotoxicology, and risk assessment. His research has been funded by several federal agencies, including the National Institutes of Health (NIH), the EPA, and the Department of Defense. His teaching responsibilities at the University of Florida include graduate courses in toxicology and risk assessment, as well as invited lectures in other graduate and professional courses. Dr. Roberts has served on numerous advisory boards and committees. He currently serves as an advisor to the Florida Department of Environmental Protection, and he is a member the Chemical Assessment Advisory Committee of the Science Advisory Board for the EPA. He receives funding from government and private parties to conduct basic and applied research on toxicology and risk assessment. Dr. Roberts is a Fellow of the Academy of Toxicological Sciences (ATS).

Conflict of Interest Screening

To facilitate the evaluation of potential conflict of interest (actual and perceived) and bias situations for the peer review candidates, TERA identified a list of individuals and other parties that have been involved with derivation of sulfolane toxicity values or the evaluation of sulfolane toxicity for this site. This list included potentially responsible parties (current owner is Flint Hills Resources of Alaska - a wholly-owned subsidiary of Koch Industries - and former owner is the Williams Company) and their consultants who have worked on sulfolane or the site assessment, those individuals or organizations who have developed toxicity values for sulfolane that are being evaluated in this peer review, and Alaska state agencies and those organizations who have provided support to DEC on sulfolane. The candidates were asked to consider their recent financial and other relationships with these parties when completing the conflict of interest questionnaire, as well as any current and past activities or interest in sulfolane.

TERA evaluated each candidate expert for conflict of interest and determined that **none of the panel members has any conflicts of interest for their participation on this peer review.** None of the six selected experts has a current financial interest or involvement with any of these parties that would constitute a conflict of interest. TERA also evaluated the potential for each candidate to be biased or less than objective in their scientific opinions for this review. Some of the selected panel members have past or current professional relationships with one or more of the identified parties. TERA evaluated these situations and concluded that none of these relationships would cause the panel member to be biased for this review. In the interests of transparency, the following information is being provided.

Dr. Susan Griffin is a Senior Toxicologist with the Region 8 Superfund Program of the U.S. EPA. The EPA's National Center for Environmental Assessment (NCEA) office developed a sulfolane value (PPRTV) that is being considered by the panel. Dr. Griffin did not participate in the development or any review of the PPRTV. She works in Region 8, which is not part of EPA's Office of Research and Development where NCEA is located. Dr. Griffin and TERA do not believe that her employment by the EPA will interfere with her objective and critical review of all the sulfolane values.

Dr. Richard Hertzberg provided scientific support on chemical mixtures to EPA's NCEA from his retirement in 2006 until 2013. None of this work was related to the EPA sulfolane PPRTV. Dr. Hertzberg and TERA do not believe that his previous employment or consulting with NCEA will interfere with his objective and critical review of all the sulfolane values.

Dr. Michael Luster. None.

Dr. Andrew Maier. None

Dr. Debbie Oudiz. None

Dr. Stephen Roberts. None

Toxicology Excellence for Risk Assessment (TERA). TERA has organized this peer review for the State of Alaska. TERA is being paid for this work under a subcontract with ERM Alaska, Inc. TERA has no current financial or other interest with sulfolane or the North Pole Refinery. TERA has no previous financial or other interest or involvement with the refinery and has not done any work on sulfolane in the past. TERA currently has a project with a law firm representing Koch Industries Inc. (Flint Hills Resources of Alaska is a subsidiary of Koch Industries) that involves a facility outside the State of Alaska and a different chemical substance. TERA discussed this situation with Alaska DEC and Koch Industries and neither had concerns or issues with TERA not being able to organize this peer review for DEC in an objective and unbiased manner. TERA is disclosing this information in the interests of transparency.

Charge Documentation

Introduction

ADEC has tasked TERA with conducting an independent, expert peer review of the available RfDs for sulfolane. A sulfolane RfD will be used by ADEC to develop cleanup levels for groundwater in North Pole, Alaska.

Background from ADEC webpage: "The discovery in late 2009 of sulfolane in drinking water wells near the North Pole Refinery, about 15 miles east of Fairbanks, has led to an extensive investigation of contaminated groundwater. The plume is nearly 2.5 miles wide and 3 miles long, one of the largest in the state. Flint Hills Resources of Alaska, the current refinery owner, responded quickly to offer affected residents an alternate drinking water source. Sulfolane, an emerging contaminant, was at first not officially listed as a hazardous chemical, and its long-term health effects from exposure have not yet been studied. This event has been unprecedented for the Contaminated Sites Program due to the number of properties affected with private drinking water wells and the size of the plume. For an overview in more detail, see Frequently Asked Questions (http://dec.alaska.gov/spar/csp/sites/north-pole-refinery/index.htm)."

Reference Doses

- Canadian Council of Ministers of the Environment (CCME). 2006. "Canadian Environmental Quality Guidelines for Sulfolane: Water and Soil (Scientific Supporting Document)." PN 1368.
- Agency for Toxic Substances and Disease Registry (ATSDR). 2010. "Health Consultation: Sulfolane." February 3.
- ATSDR. 2011. "Health Consultation: Sulfolane." May 2.
- Haney, J. [Texas Commission on Environmental Quality (TCEQ)]. 2011. Sulfolane (CASRN 126-33-0) [re: Update of March 9, 2011 toxicity factor documentation with a slightly revised benchmark dose (BMD)]. September 6.
- United States Environmental Protection Agency (US EPA). 2012. "Provisional Peer Reviewed Toxicity Values for Sulfolane (CAS No. 126-33-0)." National Center for Environmental Assessment (NCEA), Superfund Health Risk Technical Support Center, January 30.
- Magee, B. [ARCADIS U.S., Inc.]. 2012. Memorandum to Flint Hills Resources Alaska re: Assessment of dose response information for sulfolane. May 21.
- Thompson, CM; Gaylor, DW; Tachovsky, JA; Perry, C; Carakostas, MC; Haws, LC. 2013. "Development of a chronic noncancer oral reference dose and drinking water screening level for sulfolane using benchmark dose modeling." J. Appl. Toxicol. 33(12):1395-1406.
- Health Canada. 2014. "Drinking Water Guidance Value for Sulfolane." March 17.

Charge to Peer Reviewers

The peer reviewers are asked to use independent professional scientific judgment to evaluate the reference doses. The panel should draw upon US EPA risk methods and guidance for

BMD modeling, as these are the commonly accepted methods used in the US to derive RfDs that are used to develop protective cleanup levels for contaminated sites.

The following questions and topics should be used to frame your discussion of the scientific information and issues regarding derivation of a RfD for sulfolane and to identify the most adequate RfD.

1. The subject RfDs selected HLS (2001) or Zhu et al. (1987) as the principal study. Discuss the strengths and weaknesses of the key studies and the available toxicity data on sulfolane. Are there additional relevant references that should be considered for the RfD and if so, explain the reasoning for considering them.

2. Discuss the endpoints and effects seen in the toxicity studies and potential mode(s) of action.

   a. Based on assessment of toxicological relevance, which endpoints should be considered for derivation of a RfD?
   b. What dosimetric adjustments should be made for the relevant endpoints?
   c. Discuss the no and lowest observed adverse effect levels (NOAELs and LOAELs). Evaluate the endpoints for suitability for benchmark dose (BMD) modeling and discuss model fit.
   d. Which is the most scientifically defensible point of departure (POD) for a sulfolane RfD?

3. Discuss the basis for selection of uncertainty factors. What are the most appropriate values for the standard factors commonly used?

4. Please identify any additional scientific issues or questions that the panel should discuss.

5. Please discuss which of the RfDs reflects the best use of the currently available data, and why.

6. Discuss the overall confidence in the selected RfD(s) and what additional studies or analyses, if any, would help reduce uncertainty or increase confidence.

References

Huntingdon Life Sciences Ltd. (HLS). 2001. "Sulfolane Toxicity Study by Oral Administration via the Drinking Water to CD Rats for 13 Weeks. Volumes One and Two." Report to Shell Canada, Calgary, Alberta. October 16.

Zhu, ZH; Sun, ML; Li, ZS; Yang, ZC; Zhang, TB; Heng, ZC; Xiao, BL; Li, QQ; Peng, QY; Dong, YH; Jiang, S; Jiang, J. 1987. "An investigation of maximum allowable concentration of sulfolane in surface water." J. West China Univ. Med. Sci. 18(4):376-380.

Registered Meeting Attendees

Marcia Bailey
US EPA

Joshua Banks
Alaska State Legislature

Chad Blystone*
NIEHS

Brandon Brefczynski
ADEC

Stephanie Buss
SPB Consulting

Matt Buxton
Fairbanks Daily News-Miner

Tamara Cardona
ADEC

Cindy Christian
ADEC

James Clark
Law Office of James F. Clark

Kim DeRuyter
ADEC

Katie Diedrich
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James Durant*
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William Farland
William H Farland Consulting

Sheila Fleming*
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Annette Gatchett*
US EPA

Mark Gebbia
Williams

Richard Guillaume
Landowner

David Guttenberg
Alaska Legislature

Ali Hamade
State of Alaska Department of Health and Social Services

Laurie Haws
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Tammie Wilson
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Ted Wu
ADEC

Jay Zhao*
US EPA

Appendix B Slides from ADEC presentation

Sulfolane Reference Doses

TERA Peer Review of Sulfolane RfDs Meeting

September 16, 2014

THE STATE of ALASKA

GOVERNOR SEAN PARNELL

Alaska Department of Environmental Conservation

Division of Spill Prevention and Response

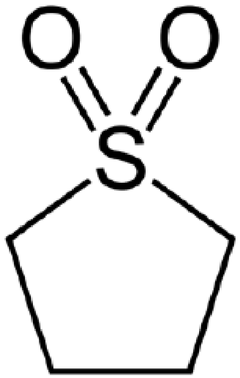
Contaminated Sites Program

Tamara Cardona, PhD

Stephanie Pingree Buss*

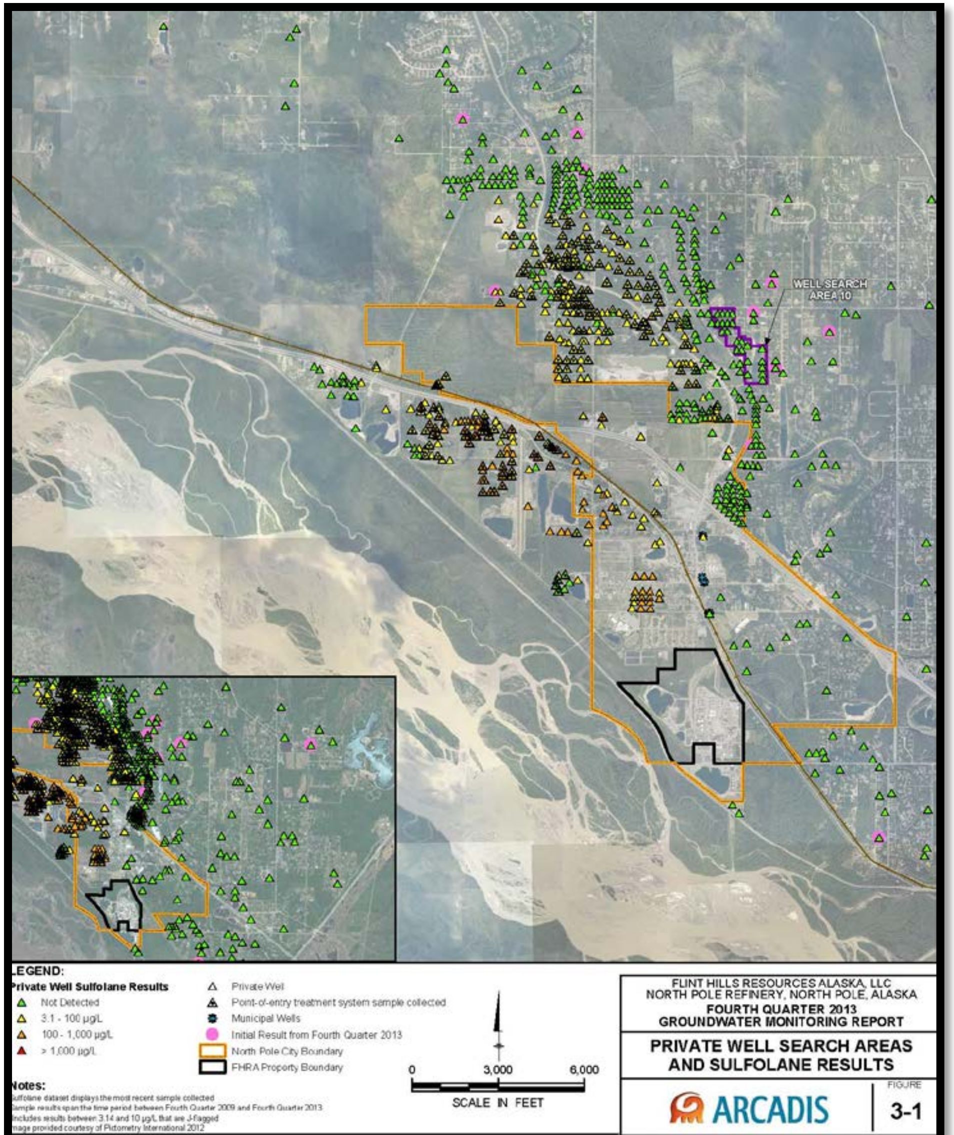
What is sulfolane?

Property	Value
Molecular weight	120.18
Freezing point	27.4 – 27.8 °C
Specific Gravity (30/20 °C)	1.265
Vapor Pressure (27.6 °C)	0.0062 mm Hg
Henry's Law constant	4.6 X 10^{-6} atm-m^3/mole
Solubility in water (25 °C)	≥100 g/L



- Industrial solvent used during gasoline production
- Used to separate aromatic compounds from hydrocarbon mixtures and to purify natural gas
- Low vapor pressure
- Highly soluble in water
- Not well absorbed through skin

Sulfolane in North Pole, Alaska



- Sulfolane discovered in private drinking water wells in 2009
- Alternative water supplies
- Current sulfolane plume approx. 2.5 miles wide by 3 miles long.

Why an Expert, Peer-Review?

- Developing a cleanup level involves many steps. For DEC, the reference dose is a key component in the calculation that determines a cleanup level.

- To ensure the most scientifically sound groundwater cleanup level for sulfolane, DEC is seeking the panel's expert, independent recommendation on the oral, chronic reference dose.

Key Studies

Zhu et al. 1987

- 6-month study in guinea pigs
- Hepatic effects, change in cell counts, dispersion of spleen white pulp
- No effect level = 0.25 mg/kg-d

Huntingdon Life Sciences 2001

- 13-week study in rats
- Reduction in lymphocytes, monocytes, LUC counts in females
- No observed effect level= 2.9 mg/kg-d

Zhu et al. 1987

- Acute toxicity in mice, white rats, and guinea pigs

Species	LD_{50}
Mice	2504 mg/kg
Rats	2343 mg/kg
Guinea pigs	1445 mg/kg

- 90-day study in white rats and guinea pigs
  - Guinea pigs were more sensitive to sulfolane than rats
- **6-month study in guinea pigs**
- Mutagenicity Test (Ames, mice marrow erythrocyte micronucleus, SCE assay)
- Teratogenicity test

Zhu et al. 1987 – 6 month toxicity study

- Guinea pigs – 40 each dose group, equal numbers male/female
- Dose groups: 0.25, 2.5, 25, 250 mg/kg and control
- Biochemical and pathological evaluations
- Change rates in fatty deposits showed dose-response relationship
- Dose groups 2.5, 25 and 250 mg/kg
  - Fatty deposits change in the liver tissue
  - Shrinkage of spleen white pulp
  - Decreasing cell counts in spinal marrow
- Authors noted:
  - Chronic threshold at 2.5 mg/kg
  - No effect dose at 0.25 mg/kg

Huntingdon Life Sciences, 2001

- 13-week exposure in drinking water
  - CD rats, 20 animals per dose group (10 males/10 females)
  - Good Laboratory Practices
  - Battery of tests conducted
  - Males – hydrocarbon nephropathy at 400 mg/L or more
  - Females – reduced lymphocytes, monocyte, LUC counts at 100 mg/L or more
    - Not seen in males
  - No observed effect level = 8.8 mg/kg –d for males and 2.9 mg/kg-d for females

DW conc. (mg/L)	0	25	100	400	1,600
Male dose (mg/kg-d)	0	2.1	8.8	35.0	131.7
Female dose (mg/kg-d)	0	2.9	10.6	42.0	191.1

Available Sulfolane RfDs

Source	Principal Study	Test Species	Endpoint	Modeling Approach	Point of Departure (mg/kg-day)	Composite Uncertainty Factor	Reference Dose (mg/kg-day)
CCME, 2006	HLS 2001	Rat (female)	WBC counts	NOAEL	NOAEL = 2.9	300	0.0097
ATSDR, 2010	Zhu et al. 1987	Guinea pig	Hepatic effects, changes in serum ALP, WBC counts	NOAEL	NOAEL = 0.25	100	0.0025
ATSDR, 2011	Zhu et al. 1987	Guinea pig	Dispersion of spleen white pulp	BMD	$BMDL_{10}$ = 1.5	1,000	0.002
TCEQ, 2011	HLS 2001	Rat (female)	WBC counts	BMD	$BMDL_{1SD}$ = 16.1 $BMDL_{HED}$ = 3.9	300	0.013
US EPA, 2012	HLS 2001	Rat (female)	WBC counts	NOAEL	NOAEL = 2.9	3,000	0.001
Magee, 2012	HLS 2001	Rat (female)	WBC counts	BMD	BMDL = 11.64	1,000	0.01
Thompson et al., 2013	HLS 2001	Rat (female)	WBC counts	BMD	$BMDL_{1SD}$ = 16 $BMDL_{HED}$ = 3.9	300	0.01
Health Canada, 2014	HLS 2001	Rat (female)	Lymphocytes	BMD	$BMDL_{1SD}$ = 4.12	1,000	0.00412

Uncertainty Factor Differences

Source (By Date)	UF_A	UF_D	UF_H	UF_L	UF_S	UF_C
CCME, 2006	10	3*	10	--	--	300
ATSDR 2010	10	--	10	--	--	100
ATSDR, 2011	10	--	10	--	10	1,000
TCEQ (Haney), 2011	--	3	10	--	10	300
US EPA, 2012	10	3	10	1	10	3,000
Magee, 2012	10	--	10	--	10	1,000
Thompson et al., 2013	3	3	3	--	10	300
Health Canada, 2014	10	10	10	--	--	1,000

Notes:
* - Based on the CCME application of uncertainty factors, this value was used to account for adequate, but not extensive dataset; subchronic-chronic extrapolation; and serious effects concerns (CCME 2006).

Questions

Appendix C Slides from panel discussion on model selection

Method for Choosing a Model

Remove those where:

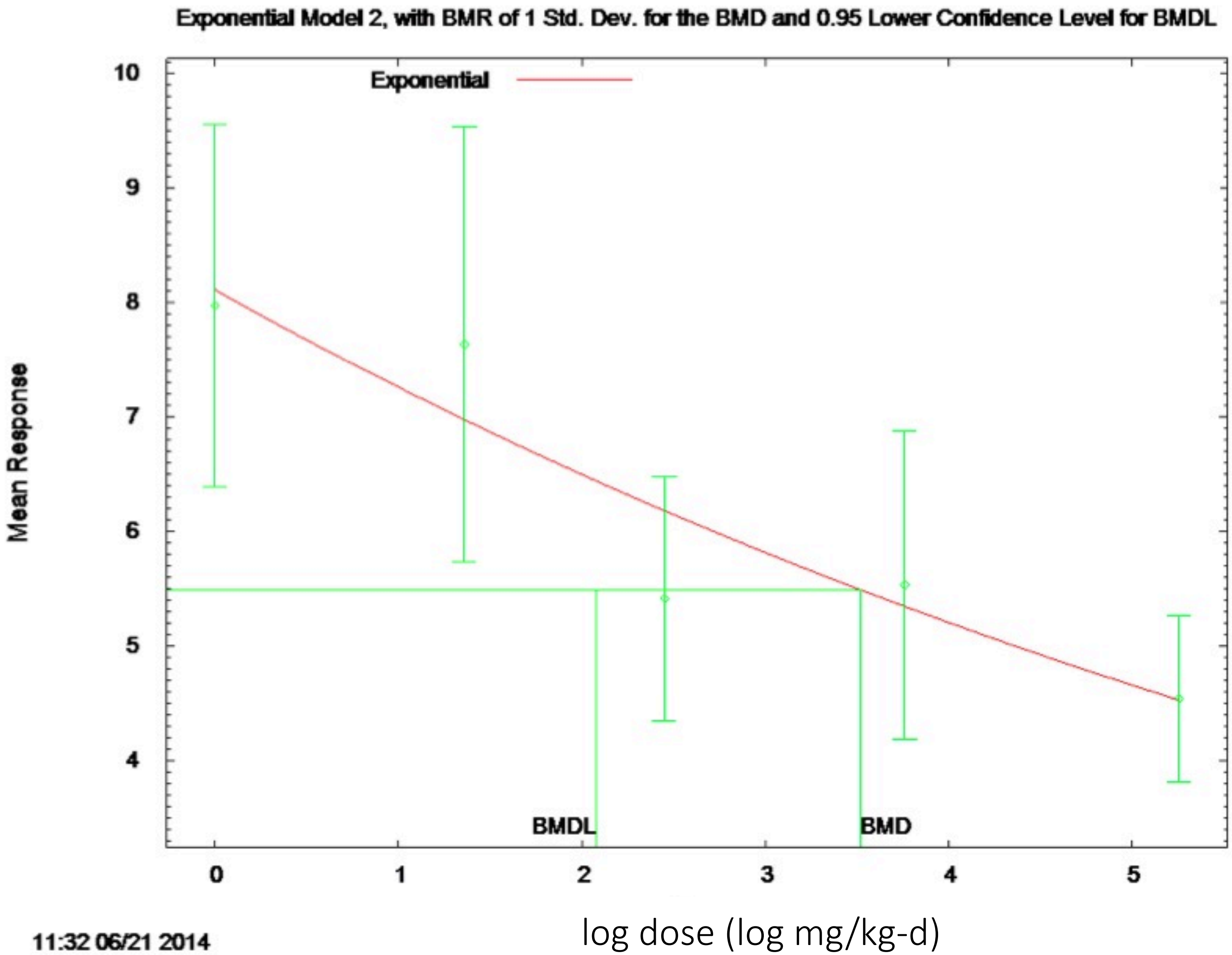
1- Numerical problems (wrong variance model)

2- Unacceptable lack of fit p-value (if LoF<0.1)

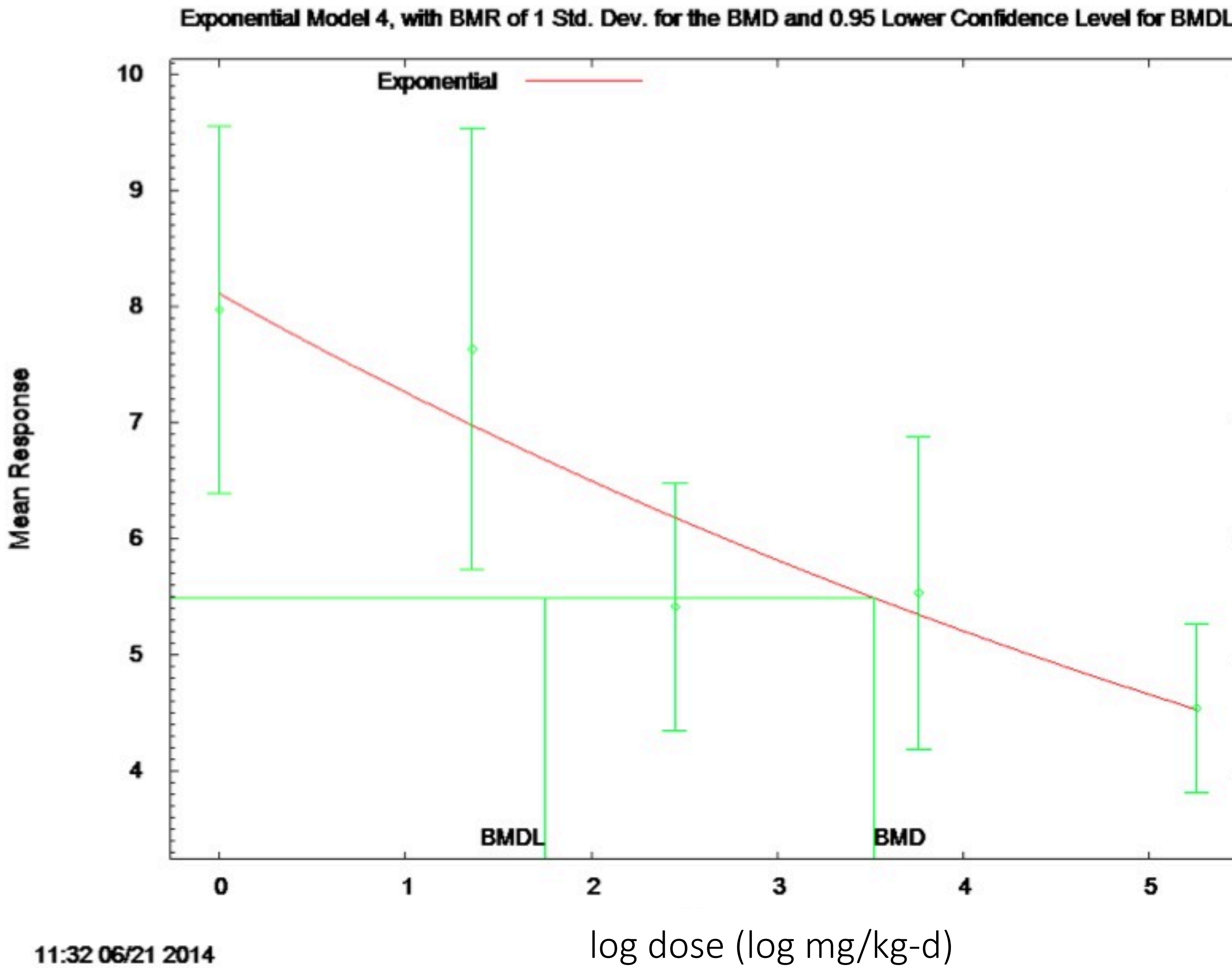
3- Over-specified model (higher order polynomials are identical to linear)

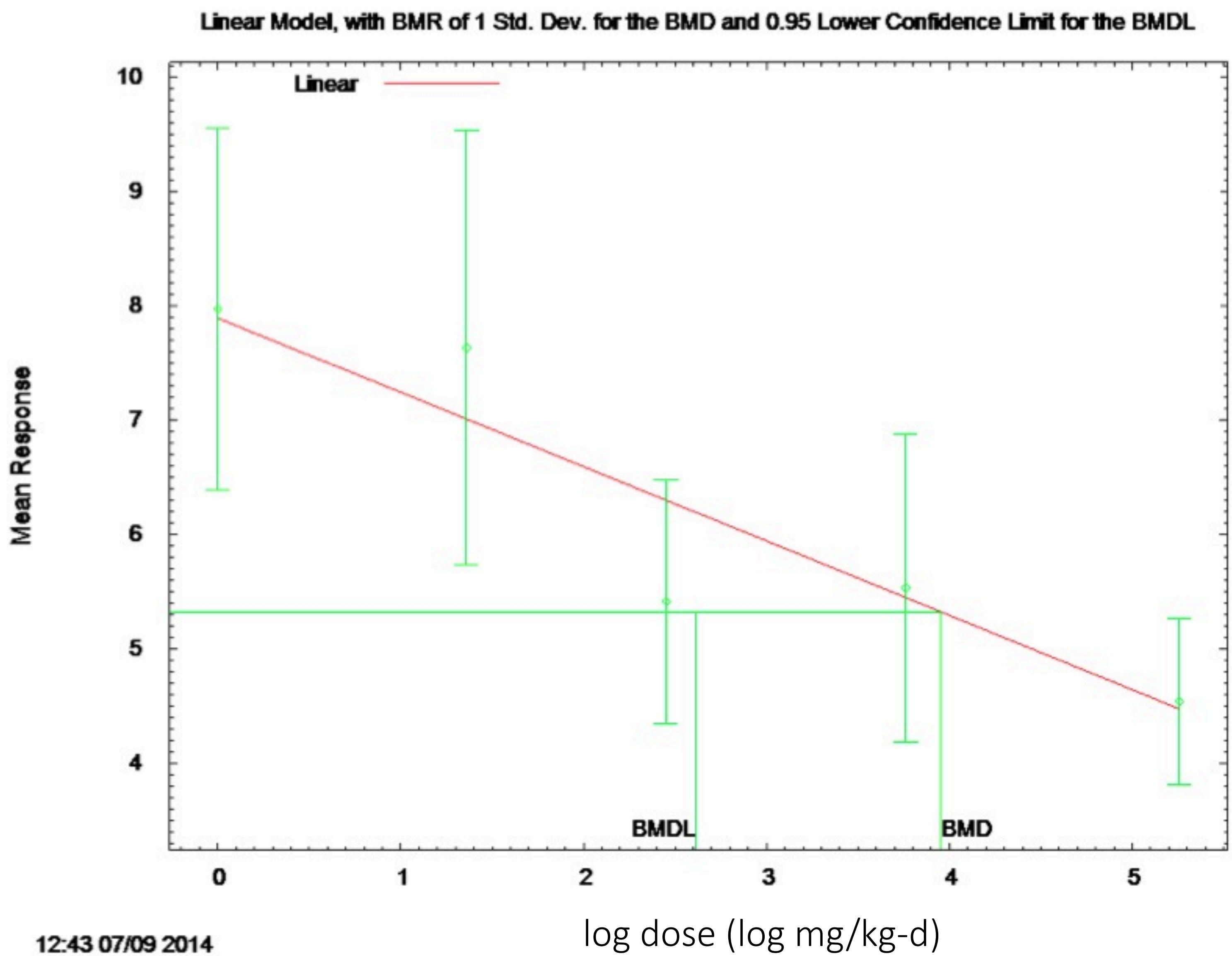
(Remaining models have very close AIC's)

4- Scaled residuals too high



Exponential Model 2, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL
Exponential
Mean Response
10
9
8
7
6
5
4
BMDL
BMD
0
1
2
3
4
5
log dose (log mg/kg-d)
11:32 06/21 2014


Exponential Model 4, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL
Exponential
Mean Response
10
9
8
7
6
5
4
BMDL
BMD
0
1
2
3
4
5
log dose (log mg/kg-d)
11:32 06/21 2014



Linear Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL
Linear
Mean Response
10
9
8
7
6
5
4
BMDL
BMD
0
1
2
3
4
5
log dose (log mg/kg-d)
12:43 07/09 2014

Table 3.2 BMDS Model Results Summary for White Blood Cell Count (Log-transformed Doses, Concurrent Controls)

Model Type	Constant Variance Model (Y/N)	Homogeneity Variance (p-value)	Goodness of Fit (p-value)	AIC	Scaled Residual Near BMD	BMD/ BMDL Ratio	BMD (mg/kg-day)		BMDL (mg/kg-day)		BMDS Wizard Notes[b,c]
							Ln	Nm[a]	Ln	Nm[a]	
Exp. (M2)	Y	0.036	0.391	113.87	-1.24	1.52	2.32	9.18	1.52	3.58	Unusable (wrong variance model)
Exp. (M3)	Y	0.036	0.227	115.83	-1.31	1.61	2.46	10.67	1.53	3.60	Unusable (wrong variance model)
Exp. (M4)	Y	0.036	0.223	115.87	-1.22	2.08	2.30	8.95	1.11	2.02	Unusable (wrong variance model)
Exp. (M5)	Y	0.036	0.237	116.26	-1.87E-05	1.53	2.10	7.20	1.37	2.95	Unusable (wrong variance model)
Hill	Y	0.036	0.254	116.16	-0.16	1.47	2.03	6.59	1.38	2.98	Unusable (wrong variance model)
Power	Y	0.036	0.357	114.10	-1.44	1.39	2.73	14.29	1.97	6.14	Unusable (wrong variance model)
Poly. (4°)	Y	0.036	0.357	114.10	-1.44	1.39	2.73	14.29	1.97	6.14	Unusable (wrong variance model)
Poly. (3°)	Y	0.036	0.357	114.10	-1.44	1.39	2.73	14.29	1.97	6.14	Unusable (wrong variance model)
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Linear	Y	0.036	0.357	114.10	-1.44	1.39	2.73	14.29	1.97	6.14	Unusable (wrong variance model)
Exp. (M2)	N	0.036	0.130	109.17	0.394	1.70	3.53	32.96	2.08	6.99	Alternate (viable model)
Exp. (M3)	N	0.036	0.0679	110.90	0.252	1.83	3.90	48.43	2.13	7.42	Questionable (GoF p < 0.1)
Exp. (M4)	N	0.036	0.130	109.17	0.394	2.01	3.53	32.96	1.75	4.75	Alternate (lowest BMDL)
Exp. (M5)	N	0.036	0.022	112.76	0.494	2.58	3.64	37.26	1.41	3.10	Questionable (GoF p < 0.1)
Hill	N	0.036	0.0276	112.37	0.0849	1.57	2.29	8.92	1.46	3.32	Questionable (GoF p < 0.1)
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Notes:

Full data, WBC, log(dose+1), concurrent controls

Table 3.2 BMDS Model Results Summary for White Blood Cell Count (Log-transformed Doses, Concurrent Controls)

Model Type	Constant Variance Model (Y/N)	Homogeneity Variance (p-value)	Goodness of Fit (p-value)	AIC	Scaled Residual Near BMD	BMD/ BMDL Ratio	BMD (mg/kg-day)		BMDL (mg/kg-day)		BMDS Wizard Notes[b,c]
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wrong variance model

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Questionable fit

Table 3.2 BMDS Model Results Summary for White Blood Cell Count (Log-transformed Doses, Concurrent Controls)

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Notes:

Overparameterized (all reduce to linear)

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(but not screened because of AIC values: were too close)

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Poly. (4°)	Y	0.036	0.357	114.10	-1.44	1.39	2.73	14.29	1.97	6.14	Unusable (wrong variance model)
Poly. (3°)	Y	0.036	0.357	114.10	-1.44	1.39	2.73	14.29	1.97	6.14	Unusable (wrong variance model)
Poly. (2°)	Y	0.036	0.357	114.10	-1.44	1.39	2.73	14.29	1.97	6.14	Unusable (wrong variance model)
Linear	Y	0.036	0.357	114.10	-1.44	1.39	2.73	14.29	1.97	6.14	Unusable (wrong variance model)
Exp. (M2)	N	0.036	0.130	109.17	0.394	1.70	3.53	32.96	2.08	6.99	Alternate (viable model)
Exp. (M3)	N	0.036	0.0679	110.90	0.252	1.83	3.90	48.43	2.13	7.42	Questionable (GoF p < 0.1)
Exp. (M4)	N	0.036	0.130	109.17	0.394	2.01	3.53	32.96	1.75	4.75	Alternate (lowest BMDL)
Exp. (M5)	N	0.036	0.022	112.76	0.494	2.58	3.64	37.26	1.41	3.10	Questionable (GoF p < 0.1)
Hill	N	0.036	0.0276	112.37	0.0849	1.57	2.29	8.92	1.46	3.32	Questionable (GoF p < 0.1)
Power	N	0.036	0.0630	111.05	0.147	1.54	4.02	54.88	2.62	12.68	Questionable (GoF p < 0.1)
Poly. (4°)	**N**	0.036	**0.136**	**109.06**	**0.177**	**1.51**	**3.96**	**51.23**	**2.61**	**12.66**	**Recommended (lowest AIC)**
Poly. (3°)	**N**	0.036	**0.136**	**109.06**	**0.177**	**1.51**	**3.96**	**51.23**	**2.61**	**12.66**	**Recommended (lowest AIC)**
Poly. (2°)	**N**	0.036	**0.136**	**109.06**	**0.177**	**1.51**	**3.96**	**51.23**	**2.61**	**12.66**	**Recommended (lowest AIC)**
Linear	**N**	0.036	**0.136**	**109.06**	**0.177**	**1.51**	**3.96**	**51.23**	**2.61**	**12.66**	**Recommended (lowest AIC)**

Residuals too high

Table 3.2 BMDS Model Results Summary for White Blood Cell Count (Log-transformed Doses, Concurrent Controls)

Model Type	Constant Variance Model (Y/N)	Homogeneity Variance (p-value)	Goodness of Fit (p-value)	AIC	Scaled Residual Near BMD	BMD/ BMDL Ratio	BMD (mg/kg-day)		BMDL (mg/kg-day)		BMDS Wizard Notes[b,c]
							Ln	Nm[a]	Ln	Nm[a]	
Exp. (M2)	Y	0.036	0.391	113.87	-1.24	1.52	2.32	9.18	1.52	3.58	Unusable (wrong variance model)
Exp. (M3)	Y	0.036	0.227	115.83	-1.31	1.61	2.46	10.67	1.53	3.60	Unusable (wrong variance model)
Exp. (M4)	Y	0.036	0.223	115.87	-1.22	2.08	2.30	8.95	1.11	2.02	Unusable (wrong variance model)
Exp. (M5)	Y	0.036	0.237	116.26	-1.87E-05	1.53	2.10	7.20	1.37	2.95	Unusable (wrong variance model)
Hill	Y	0.036	0.254	116.16	-0.16	1.47	2.03	6.59	1.38	2.98	Unusable (wrong variance model)
Power	Y	0.036	0.357	114.10	-1.44	1.39	2.73	14.29	1.97	6.14	Unusable (wrong variance model)
Poly. (4°)	Y	0.036	0.357	114.10	-1.44	1.39	2.73	14.29	1.97	6.14	Unusable (wrong variance model)
Poly. (3°)	Y	0.036	0.357	114.10	-1.44	1.39	2.73	14.29	1.97	6.14	Unusable (wrong variance model)
Poly. (2°)	Y	0.036	0.357	114.10	-1.44	1.39	2.73	14.29	1.97	6.14	Unusable (wrong variance model)
Linear	Y	0.036	0.357	114.10	-1.44	1.39	2.73	14.29	1.97	6.14	Unusable (wrong variance model)
Exp. (M2)	N	0.036	0.130	109.17	0.394	1.70	3.53	32.96	2.08	6.99	Alternate (viable model)
Exp. (M3)	N	0.036	0.0679	110.90	0.252	1.83	3.90	48.43	2.13	7.42	Questionable (GoF p < 0.1)
Exp. (M4)	N	0.036	0.130	109.17	0.394	2.01	3.53	32.96	1.75	4.75	Alternate (lowest BMDL)
Exp. (M5)	N	0.036	0.022	112.76	0.494	2.58	3.64	37.26	1.41	3.10	Questionable (GoF p < 0.1)
Hill	N	0.036	0.0276	112.37	0.0849	1.57	2.29	8.92	1.46	3.32	Questionable (GoF p < 0.1)
Power	N	0.036	0.0630	111.05	0.147	1.54	4.02	54.88	2.62	12.68	Questionable (GoF p < 0.1)
Poly. (4°)	**N**	0.036	**0.136**	**109.06**	**0.177**	**1.51**	**3.96**	**51.23**	**2.61**	**12.66**	**Recommended (lowest AIC)**
Poly. (3°)	**N**	0.036	**0.136**	**109.06**	**0.177**	**1.51**	**3.96**	**51.23**	**2.61**	**12.66**	**Recommended (lowest AIC)**
Poly. (2°)	**N**	0.036	**0.136**	**109.06**	**0.177**	**1.51**	**3.96**	**51.23**	**2.61**	**12.66**	**Recommended (lowest AIC)**
Linear	**N**	0.036	**0.136**	**109.06**	**0.177**	**1.51**	**3.96**	**51.23**	**2.61**	**12.66**	**Recommended (~~lowest AIC~~)**

Notes:

Recommended!

Method for Choosing a Model

Remove those where:

1- numerical problems (wrong variance model)

2- unacceptable lack of fit p-value (if $LoF<0.1$)

3- over-specified model (higher order polynomials are identical to linear)

4- Scaled residuals too high

5- Winner? Linear model, using log(dose)

In preparing the meeting report, the presenting panel member noted the following clarification on this presentation:

2- unacceptable lack of fit p-value (if $LoF<0.1$)

Would be more clearly communicated by using p instead of LoF:

2- unacceptable lack of fit p-value (if $p<0.1$)

Please note that the lack of fit p-value works in reverse to the usual significance p-value, in that higher p indicates acceptable fit, thus screening out models (removing from consideration) would use $p < 0.1$.