# 1,4-Dioxane Analysis

Project Objectives:

- Obtain additional information on mouse liver histopathology from the Japanese long term cancer bioassay on 1,4-dioxane
- Determine whether the additional analysis of the mouse liver pathology supports a non-linear (threshold) Mode Of Action (MOA) for cancers caused by 1,4-dioxane

Jeri Higginbotham of the State of Kentucky has petitioned the Alliance for Risk Assessment (*ARA*) Steering Committee to obtain additional information from the Japanese studies to inform 1,4-dioxane's cancer Mode of Action (MOA) and her request has been accepted. TERA is now forming a coalition of interested groups to obtain this information, and your group is invited to participate. However, the *ARA* Steering Committee also thought that problems might occur in gathering some of this Japanese information, since this research is now 25 years old, so we invite your group to submit any information or additional thoughts regarding the scope of this inquiry that will bear on 1,4-dioxane's cancer Mode of Action (MOA).

By way of background, EPA's IRIS 1,4-dioxane external peer review in 2012 suggested reviewing the histopathology slides from the NCI 1978 dioxane cancer bioassay in mice to ascertain whether non cancer pathology was evident, since, if evident, this would support the evaluation of a regenerative hyperplasia MOA by EPA staff. TERA scientists worked with Dr. Gene McConnell and staff of the NTP to reevaluate these mouse liver slides, and the results were sent to EPA staff in 2013 and published as Dourson et al., 2014. In brief, the reread of the slides showed extensive non cancer pathology, thus supporting the regenerative hyperplasia MOA. However, this evaluation also led to the desire to evaluate the mouse liver slides from a series of Japanese studies on 1,4-dioxane. In the summer of 2014, five US states and TERA scientists requested these full studies from our Japanese colleagues. These studies were received in the fall of 2014, and were then translated and analyzed during the winter of 2015. A report of this translation and a draft analysis was prepared and sent around to requesting states in July of 2015.

As described in this 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 criteria for liver histopathology scoring during the course of reporting their results. Thus, we are collectively at a point where a limited amount of

additional information from the Japanese studies, including potentially rereading some of the mouse liver histopathology slides, may be helpful. The intent of this *ARA* project is to obtain this limited, additional information from the Japanese studies, or other information as appropriate, in order to resolve the hypothesized MOA for 1,4-dioxane's liver tumor formation (and potentially other tumors) as described in the reports mentioned above.

# Dioxane Project Timeline

March 2013

- Review of liver slides from the National Cancer Institute's Bioassay of 1,4-Dioxane for
  Possible Carcinogenicity conducted in 1978 – McConnel 2013

Feb 2014

- Mode of action analysis for liver tumors from oral 1,4-dioxane exposures and evidence-based dose response assessment – Dourson et al., 2014

June 2014

- Contacted several state agencies to inquire about their interest in signing a request letter for three studies that were conducted by the Japanese Bioassay Research Center (JBRC) on 1,4-dioxane in mice and rats.

July 2014

- Collected signatures from 5 state agencies (MN, MO, MI, TX, and KY) to place on a request letter to the Japanese government (Ministry of Health, Labour and Welfare of Tokyo, Japan) for the Japanese studies.

August 2014

- TERA submitted a  to the Japanese government for copies of the full studies.
  - Dioxane Inhalation Study Request Letter
  - Dioxane Oral Study Request Letter

- Received the oral studies from the Japanese Ministry of Health, Labour, and Welfare. Submitted a second request for additional missing appendices.

November 2014

- Japanese studies received and then submitted for translation
  - Yamamoto 1990 1,4-dioxane_2years
  - Yamamoto 1990 1,4-dioxane_2years_photographs
  - Yamamoto 1990 1,4-Dioxane_13week_APPENDIX C-P
  - Yamamoto 1990 1,4-dioxane_acute,2weeks,13weeks_apendix B-C O
  - Yamamoto 1990 1,4-dioxane_acute,2weeks,13weeks_photographs
  - Yamamoto 1990 1,4-dioxane_2years_photographs.compressed
  - Yamamoto 1990 1,4-Dioxane_Acute_APPENDIX A
  - Yamamoto 1990 1,4-Dioxane_Cancer_APPENDIX_1
  - Yamamoto 1990 1,4-Dioxane_Cancer_APPENDIX_2
  - Yamamoto 1990 1,4-Dioxane_Cancer_PHOTOGRAPHS
  - Yamamoto 1990 1,4-Dioxane_Pre_PHOTOGRAPHS
  - Yamamoto 1990 Mouse photos only

December 2014

- Received English translation of the Japanese studies.
  - Translated study – Yamamoto 1990 Acute,2weeks, 13weeks
  - Translated study – Yamamoto 1990 2 year Carcinogenicity

January 2015

- Began review and QA of the translated studies
- Emailed translated studies to the 5 States that signed the request letter. Asked each to review and submit any comments or questions about translation.
- Dioxane Status Update Letter 23 Jan/Feb 2015

April 2015

- Draft analysis prepared on the translated Japanese studies. Missing individual experimental animal appendices requested.

June 2015

- Draft analysis sent to state and industry partners for comment. Dioxane State Letter 30 June 2015
- Reanalysis Report Dioxane Reanalysis of Japanese Findings 30 June 2015
  - Tables 1 and 2 (Revised-Tables 8 and 9)
  - Dioxane Figures

November 2015

- Nov 6, 2015 conference call notes

December 2015

- Society for Risk Analysis Dioxane poster

August 2016

- Revised 1,4-Dioxane Mode of Action paper submitted to Regulatory Toxicology & Pharmacology
  - Tables
  - Figures