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Date: June 30, 2015

Dear State Colleagues,

We have finally slogged through the Japan Bioassay Research Center (JBRC) 1998 study translations, which we sent your earlier, and in doing so have verified information from ensuing publications (Kano et al 2008, 2009) and have found information not otherwise available in English print. From this Japanese work we have developed a report (attached) that more comprehensively and accurately explains 1,4-dioxane's results in rats and mice. The regenerative liver hyperplasia MOA is conclusive in rats, showing hyperplasia preceding foci and tumors, and liver cell swelling or necrosis preceding the hyperplasia. Liver enzyme changes in rats pattern the histology. The results from the NCI (1978) study in rats without the liver enzyme changes (they were not monitored) corroborate the findings in rats from the Japanese work. All of these findings, both Japanese and U.S., show the expected changes due to this MOA and in the expected sequence, in that key events occur at lower doses than tumors.

The pattern of this MOA is also clear in mice from the results of McConnell (2013) reread of the NCI (1978) mouse study as described by Dourson et al. (2014). Unfortunately, the results are not so clear for Japanese mice when compared with either set of rat data, nor when compared with the information from McConnell. We have attempted to put all of the mouse information together from both the NCI and Japanese work, and the results are suggestive of our MOA. However, the results from the individual mouse studies are sufficiently different so as to question one data set or the other. The fact that Kano et al. (2009) specifically called out the fact that they changed their findings, may lend some substance to this difference:

> "The hepatic hyperplasia of rats and mice diagnosed in the previous report (Yamazaki et al., 1994) was re-examined histopathologically and changed to hepatocellular adenomas and altered hepatocellular foci including acidophilic, basophilic and clear cell foci in the present studies, according to the current diagnostic criteria of liver lesions in rats and mice (Mohr, 1997; Deschl et al., 2001)."

This, coupled with the fact that the Japanese lab reports do not show hyperplasia in mice [incidence in males of 5, 7, 5, 6 and in females of 2, 2, 1, 1, for control, low, medium and high doses, respectively], lead us to suspect that this lab report has been modified as stated above. We are attempting to procure additional pictures of mouse liver slides, so as to confirm this suspicion. Until this information is received, we are

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inclined to use the mouse findings of McConnell (2013) in preference to the Japanese mouse findings for liver tumors, since Kano et al. (2009) may be including precursors to tumors in the tumor incidence data. Opinions of two independent pathologists also lend support to our preference to use of the re-read of the NCI mouse liver tumors findings of McConnell (2013). The first opinion is found on the International Toxicity Estimates for Risk (*ITER*) file for 1,4-dioxane, and specifically:

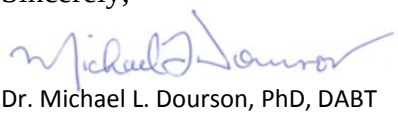
> *"One of the panelists stated that, in general, Japanese pathologists tend to diagnosis disease which most US pathologists would consider as background. This might explain why the Japanese mouse studies tend to show more toxicity [tumors] in the liver than the NCI (1978) bioassays."*

The other pathologist stated at a recent British Society of Toxicology meeting that it would be unlikely for the MOA to differ among rodent species to a chemical that caused liver tumors. The implication is that if the MOA is clear in rats, then it is likely to be the same MOA in mice. We will be asking this pathologist to give a written statement to this effect, since the implications are supportive of the hypothesized MOA.

At this point, we would highly value your comments on this *work-in-progress* report and a further discussion of its merits, and invite you to participate in the completion of this draft in any manner that is appropriate and consistent with your scientific interests. We are also happy to send you the excel spreadsheets that were used to create the graphs. Also, we will also be sending this draft report to the Ontario Ministry of the Environment (OMOE), who in contrast to U.S. Environmental Protection Agency (EPA), has cited the work of Dourson et al. (2014) in support of its opinion that 1,4-dioxane causes cancer in a threshold manner. Health Canada and the Australian government's National Industrial Chemicals Notification and Assessment Scheme are also in agreement with the OMOE.

Finally, several of us think that resolution among agencies as to whether 1,4-dioxane causes tumors in a threshold or non-threshold manner might more likely occur through a scientific discussion under the auspices of the Alliance for Risk Assessment (*ARA;* www.allianceforrisk.org). Your comments on this aspect would also be valuable. Feel free to contact Ms. Patricia Nance, of Toxicology Excellence for Risk Assessment (TERA) at nance@tera.org with any questions or comments.

Sincerely,



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Attachment A

Dioxane State Translation Project Timeline

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 study request letter to the Japanese government for copies of the full studies.
- 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 receive and then submitted for translation

December 2014

- Received English translation of the Japanese studies.

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.

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.

Attachment B

References

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- Kano, H., Umeda, Y., Kasai, T., Sasaki, T., Matsumoto, M., Yamazaki, K., Nagano, K., Arito, H., Fukushima, S. 2009. Carcinogenicity studies of 1,4-dioxane administered in drinking-water to rats and mice for 2 years. Food Chem. Toxicol. 47(11), 2776-2784.

- McConnell, G., 2013. Report on the review of liver slides from the National Cancer Institute's Bioassay of 1,4-Dioxane for Possible Carcinogenicity conducted in 1978 (NCI, 1978). Submitted to Toxicology Excellence for Risk Assessment. January/March 2013.

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