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GSA Contractor
GS-10F-3069N

March 3, 2015

Ms. Monet Vela
Office of Environmental Health Hazard Assessment
P.O. Box 4010
Sacramento, California 95812-4010

Dear Ms. Vela,

Toxicology Excellence for Risk Assessment (TERA) is a nonprofit corporation with a mission to protect public health. 2/3rds of its work is for government and other nonprofits; 1/3rd of its work is for industry and industry related. An example of the latter is the support TERA received from the American Chemistry Council for the analysis shown in this letter.

TERA develops partnerships among government, industry and other interested groups to address risk assessments of high visibility, and cooperative ventures such as VCCEP, *ITER* available at the National Library of Medicine, and the Alliance for Risk Assessment. Prior to TERA, I held several leadership roles in US EPA, including forming its IRIS. I have been humbled to received SOT's Lehman award, the International Society of Regulatory Toxicology and Pharmacology's International Achievement Award and a Fellow for the Society for Risk Analysis (SRA). I am also a past President of the American Board of Toxicology and a current member of EPA's Science Advisory Board.

The issue before us regards OEHHA's risk assessment judgment on the chemical DINP. OEHHA is depending on default risk assessment methods, methods developed by the US EPA group where I worked in 1980---35 years ago! In some respects, OEHHA realizes that these default methods are woefully inadequate, especially since some of their scientists have assisted in the development of scientifically more appropriate methods based on current risk assessment thinking. Unfortunately, OEHHA's reliance on these default methods for the DINP assessment, and not the newer science, results in a scientifically meaningless NSRL. The resulting risk-management decision is not credible.

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The risk assessment judgments of other expert bodies[1] that have evaluated DINP should be perused. Moreover, testimony of individual experts on the Mode of Action (MOA) for several of the tumors evoked by DINP should be incorporated the OEHHA analysis. These opinions are made by stellar scientists, are well wrought, and can form the foundation of well-reasoned risk management decisions. These judgments and opinions should be highly valued by OEHHA, not discarded, and deviations from them, if any, should be explained and peer reviewed by risk assessment experts.

OEHHA seems to think that since "Risk analysis shall be based on the most sensitive study deemed to be of sufficient quality" (California, 2011)[2] that it is only the most potent study or endpoint needs to be chosen. *Au contraire*. In risk assessment, the "most sensitive study" for determining the risk in humans should consider:

- Repeatability---a sensitive study will show effects in comparable studies of the same or other species/strains;[3]
- Relevance--- a sensitive study will show effects in one species that are expected to be found in humans;[4]
- Potency--- a sensitive study will show effects that occur at the lowest dose or concentration.

The "most sensitive study" does not equal…only the most potent study.

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[1] U.S. Consumer Product Safety Commission (CPSC, 2001, 2012) "The CHAP on DINP concluded that for DINP mononuclear cell leukemia is of uncertain relevance to humans." Australian Government, National Industrial Chemicals Notification and Assessment Scheme (NICNAS, 2012) "DINP exhibits little or no evidence of genotoxicity in available studies." European Chemicals Agency (ECHA, 2013)--Does not make definite conclusions for the MNCL data except that it may strengthen the selected NOAELS (15 & 88 mg/kg-day). European Commission (2003)-Due to the PPAR alpha MOA, no concern for potential carcinogenic effect in humans (for liver). For MNCL uses IARC "not classifiable as to carcinogenicity in humans." For the kidney – Not relevant due to alpha 2 globulin mechanism.

[2] California (2011): Title 27, California Code of Regulations; ARTICLE 7. NO SIGNIFICANT RISK LEVELS, § 25703. Quantitative Risk Assessment

[3] " In predicting carcinogenicity, one should consider both the sensitivity and the specificity of an assay. Sensitivity refers to the proportion of carcinogens that are positive in an assay [**that is, how well the assay is repeatable---note added**]…The word 'sensitivity' also can be used to denote the ability of an assay to detect a mutagen at a low concentration or a small change in mutation frequency; so alternative usages **[of the word "sensitivity"---note added]** must be recognized from the context." Cassarett and Doull, Fifth Edition, page 290.

[4] "Presented with data from several animal studies, the risk assessor first seeks to identify the animal model that is most relevant to humans, based on the most defensible biological rationale (for instance, using comparative pharmacokinetic data)...." (Barnes and Dourson, 1988)

In this regards, liver tumors from DINP exposure are repeatable. They are found in both sexes and multiple strains and species of rodents. In contrast, leukemia and kidney tumors are not repeatable. They are only found in one species and/or one sex of one species. Liver tumors in experimental animals are also relevant to those found in humans, although the hypothesize MOA for liver tumors in rodents is not quantitatively, and may not be qualitatively, similar to humans. In contrast, kidney tumors and leukemias are not relevant to humans. Kidney tumors are only found in male rats and are associated with a biological process (i.e., a2u) that is characteristic of only this species/sex. Although the particular kind of leukemia found in F344 rats has a matching human counterpart, the etiology of this tumor in humans is different than that found in rat. Not only are these leukemias specific to this strain of rats, but the control incidence among rat studies of this strain are enormous and variable. Moreover, the quantitative findings between rats and humans are disparate (rats are much, much more sensitive). As a result in part, NTP is recommending not using the F344 rat strain in its future bioassay program.[5] For all of these reasons, the leukemias found in these rats are not relevant to humans either.

Liver tumors evoked by DINP have sufficient potency that a dose response assessment is meaningful. Liver tumors are not as potent as the leukemias found in rats, but are more potent than the kidney tumors.

Thus, based on a consideration of tumor repeatability, relevance and potency, the "most sensitive study/endpoint" is clearly liver tumors found in rodents. A summary of this choice is found in Table 1. This effect, liver tumors, should be used as the basis of DINP's dose response assessment.

As all erudite risk assessment scientists know, dose response assessment options for DINP tumors must first explore various Modes of Action (MOAs) for tumor development. OEHHA currently does this in an unstructured way, and this approach leads to an uneven review of the available data. Rather, OEHHA should follow the guidelines of its colleagues, and, specifically, those of the International Programme on Chemical Safety (IPCS), International Life Sciences Institute (ILSI), Mode of Action (MOA), Human Relevant (HR), Weight of Evidence (WOE) Framework[6] and of U.S. Environmental Protection Agency's (EPA, 2005).[7] Following these guidelines will allow a more structured approach to the

[5] For example, here is a quote from a recent NTP meeting report "In addition, when a statistically significant tumor effect is found in test animals relative to concurrent controls, the effect may not be considered exposure-related if it falls within the range observed in historical controls." ANGELA KING-HERBERT AND KRISTINA THAYER. 2006. NTP Workshop: Animal Models for the NTP Rodent Cancer Bioassay: Stocks and Strains—Should We Switch? *Toxicologic Pathology*, 34:802–805.

[6] Several publications exist on this. One of the latest ones is: M. E. (Bette) Meek, Christine M. Palermo, Ammie N. Bachman, Colin M. North and R. Jeffrey Lewis. 2013. Mode of action human relevance (species concordance) framework: Evolution of the Bradford Hill considerations and comparative analysis of weight of evidence. Journal of Applied Toxicology. DOI 10.1002/jat.2984.

[7] U.S. Environmental Protection Agency. 2005. Guidelines for carcinogen risk assessment. Washington D.C. EPA/630/P-03/001B.

analysis, will incorporate the negative findings of mutagenicity data, and importantly, show that potential mutations and or genotoxicity at high doses cannot be a key event for this tumor development at low dose, and demonstrate that the preponderance of data supports MOAs for tumor develop that are expected to exhibit thresholds in the dose response curve. In addition, the underlying biology and appearance of liver tumors must be reanalyzed. A superficial look at the liver tumor response with dose for individual studies might lead one to suppose that the response might fit with a linear regression as shown in Figure 1. However, if the tumor response is normalized for control incidence, each of the 4 available studies on liver tumors in rats show the same results. And in contrast to the individual analysis, the combined picture clearly shows a non-linear response, with doses lower than 300 mg/kg-day showing a negative trend. While it might be argued these negative responses are not yet acceptable for a risk management decision, this analysis clearly shows that:

OEHHA's linear approach to the DINP NSRL…is not scientifically supported.

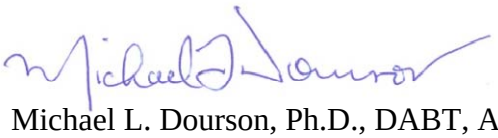
Rather, OEHHA should follow the judgments of other expert bodies, and develop a threshold for the critical effect via a NOAEL or BMD divided by appropriate uncertainty factors. The science supports a threshold for the adverse effects of DINP.

To summarize:

- The findings of expert groups and individual experts should be honored.
- The most sensitive study/effect is a liver tumor.
- A threshold approach to dose response assessment is the most scientific reasonable option for DINP's dose response assessment

I would be more than happy to work with my colleagues at OEHHA and the American Chemistry Council to develop a scientific credible position on the most appropriate NSRL for DINP. The TERA staff would also be happy to provide additional information regarding these comments.

Sincerely,



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