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September 17, 2010

Office of Environmental Information (OEI) Docket
Mail Code 2822T
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue NW
Washington, D.C. 20460

Re: Docket ID No. EPA-HQ-ORD-2010-0395
EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments, EPA/600/R-10/038A

Email: ORD.docket@epa.gov

Dear Sir or Madam:

On May 21, 2010, EPA released the draft report entitled, "EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments" for independent external review and public review and comment (75 FR 28610) ("Draft Reanalysis"). US Magnesium LLC ("USM") appreciates the opportunity to submit comments on the Draft Reanalysis. USM submits these comments for the administrative record. USM's comments include and incorporate by this reference the attached report prepared by ToxStrategies, Inc. entitled, "Comments on EPA's Draft Dose Response Evaluation for TCDD-Suggested Improvements for Developing Toxicity Factors (September 19, 2010)" ("TS Report").

USM has a direct and substantial interest in the Draft Reanalysis. USM has invested considerable resources into understanding the characteristics, including the toxicity, of dioxin compounds and evaluating the nature and extent of dioxins in soils and sediments at its Rowley, Utah facility. USM may be significantly affected economically by the Draft Reanalysis.

The TS Report identifies 18 deficiencies in the Draft Reanalysis which warrant attention by EPA and the Science Advisory Board ("SAB") Dioxin Review Panel and correction by EPA prior to issuing any final reanalysis of dioxin toxicity issues. The TS Report points out numerous instances where EPA has failed to address the National Academy of Sciences ("NAS") 2006 Committee Evaluation of EPA's dioxin reassessment, failed to adequately explain or rationalize numerous issues related to dioxin toxicity and failed to apply the best available peer-

reviewed science, which is EPA's stated policy. Accordingly, USM requests EPA to address the comments in the TS Report in connection with issuing any subsequent dioxin toxicity reanalysis.

USM requests that these comments be placed in the administrative record for the Draft Reanalysis. In addition, USM supports and incorporates herein the comments submitted by the American Chemistry Council.

Thank you for your consideration.

Sincerely yours,

G. Thomas Tripp
Technical Services Director, US Magnesium LLC

cc: Dr. Thomas Armitage, SAB Designated Federal Officer
Dr. Timothy Buckley, Chair
Dr. Vanessa Vu, Director

# COMMENTS ON EPA'S DRAFT DOSE RESPONSE EVALUATION FOR TCDD – SUGGESTED IMPROVEMENTS FOR DEVELOPING TOXICITY FACTORS

**SEPTEMBER 19, 2010**

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## Introduction

Following review of the EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments, External Review Draft (referred to as the Draft Report), we have identified a number of issues that should be carefully evaluated by the Agency prior to finalizing the assessment. A number of these comments were also identified by the EPA Science Advisory Board (SAB) Dioxin Review Panel as well as in public comments submitted to the EPA on the Draft Report. The issues discussed in this document are related to the development of a robust evaluation for TCDD based on the best available science using procedures and guidelines set forth by the EPA. It is suggested that the Agency more fully address a number of recommendations by the National Academy of Sciences regarding the determination of a carcinogenic toxicological value (i.e., oral cancer slope factor), as well as provide additional rationale and clarification on the current approach. It is also suggested that the EPA provide additional discussion on the selection and application of data in the noncancer assessment. We urge the EPA to address these issues prior to finalizing the Draft Report.

## 1. The EPA chose a linear approach for determining a cancer slope factor; this approach was not consistent with NAS recommendations.

The National Academy of Sciences (NAS) 2006 committee evaluation of EPA's Dioxin Reassessment concluded that the scientific evidence for TCDD mode of action was "adequate to favor the use of a nonlinear model that would include a threshold response over the use of the default linear assumption" (NAS, 2006). The EPA stated that a nonlinear approach for cancer was considered and even modeled, but that there was a lack of sufficient evidence for the EPA to support a nonlinear toxicity value for cancer. This explanation by EPA is not adequate given the rich database of research available for TCDD and related compounds.

## 2. The EPA did not adequately justify its decision not to use the nonlinear approach as recommended by the NAS.

The NAS provided the EPA with four major points of evidence in support of a nonlinear approach: 1) TCDD, other dioxins, and DLCs are not directly genotoxic, 2) receptor-mediated agents have sublinear dose-response relationships, 3) evidence that liver tumors are secondary to hepatotoxicity, and 4) bioassay evidence of nonlinearity. The EPA provided limited discussion of these topics that support a nonlinear approach, and even less critical discussion was provided in support of its linear approach. Further, the Agency relied on non-consensus concepts (e.g., reactive oxygen species generation, the role of dietary and endogenous AhR agonists in additivity to background, etc.) as supporting evidence for a linear MOA. The unbalanced discussion on nonlinear and linear rationale generally suggests that the decision to use a linear approach was not supported by sound science. It should be noted that the 2006 NAS Dioxin Panel directly commented on this issue, stating that, at the very least, the EPA should provide a

comprehensive and balanced analysis for both linear and nonlinear approaches, assessing the strengths and weaknesses of both. The panel encouraged the EPA to leave the decision on the most applicable toxicological benchmark to risk managers (NAS, 2006).

## 3. The EPA was inconsistent in its use of the evidence supporting an MOA for TCDD

The EPA supported an AhR-mediated mechanism of action (MOA) for one argument but not for others. In Section 5 of the 2010 Draft Dioxin Reanalysis, the EPA stated the evidence for AhR-mediation of TCDD toxicity across species was a sound enough MOA to support the biological plausibility of TCDD being a "known human carcinogen" (EPA 2010, pg. 5-9). However, the Agency did not use this same rationale when determining the approach for evaluating TCDD dose response for quantitative assessment. For the latter, an overly strict interpretation of the 2005 Cancer Guidelines was applied. Although the 2006 NAS Dioxin Panel provided EPA with a sound, consensus-based foundation for a TCDD threshold MOA, EPA did not adopt such, and rather pursued a linear dose-response model based on lack of MOA. Further, this approach was inconsistent with the Agency's own framework (EPA, 2005) on assessing carcinogenic MOA. The EPA should make a credible attempt to develop an MOA for TCDD – particularly if the Agency is using this same argument to support the biological plausibility of TCDD carcinogenicity.

## 4. EPA does an inadequate job presenting TCDD carcinogenicity MOA

Although the EPA denied sufficient evidence for an MOA for TCDD, events in the MOA were clearly discussed throughout the draft document. Thus, the Agency provides a confusing position on the topic. The EPA described a generalized MOA for multiple tumor types, with specific key events and themes in carcinogenic processes. The Agency further stated that a receptor-mediated, carcinogenic MOA is becoming more clearly defined in laboratory animals, which is similar to that of peroxisome proliferators, phorbol esters, and estrogen. For liver, lung, and thyroid tumors, the first key event involves interaction between TCDD and AhR. In both the liver and lung hypothesized MOAs, the next key event is change in gene expression. The penultimate key event in the three tumor types appears to be cell proliferation, ultimately leading to adenomas and carcinomas. This suggests the Agency recognized a generalized MOA for three tumor types associated with TCDD in laboratory animals.

Despite the voluminous data available characterizing key events in MOA (and particularly the role of the AhR), the EPA attempts to inject uncertainty in the TCDD MOA by citing that non-AhR mediated carcinogenic effects are possible. However, only one study is referenced and the author's findings are not accurately conveyed. Thus, at a very minimum, additional data are required to support the Agency's rationale.

## 5. EPA failed to provide evidence of biological plausibility for the "all cancers" endpoint that is the basis of its OSF

The EPA selected an epidemiological study on an occupationally exposed cohort (NIOSH cohort) to derive an oral cancer slope factor (OSF) for TCDD. The Agency selected "all cancers" from Cheng et al. (2006) as the endpoint of concern. However, the EPA provided no mechanistic rationale for such an endpoint, nor did it provide any evidence that suggests analogous compounds capable of inducing cancers at all sites exist. The EPA should present sound scientific evidence that supports the biological plausibility of the "all cancers" endpoint. We are unaware of "all cancers" being an endpoint of concern for any other chemical addressed by EPA previously.

## 6. EPA failed to address uncertainties inherent in determining exposures in the NIOSH study

There are several uncertainties inherent in the exposure level estimates that have been derived for the NIOSH dioxin cohort. Estimates were based on a job exposure matrix (JEM) developed to characterize TCDD exposures. The JEM estimates of exposure were derived using uncertain TCDD exposure concentrations and subjective exposure parameters (global "contact factors" for each job description, estimates of the fractions of day each worker would have been exposed to TCDD contaminated chemical). The subjective parameters assumed that all job types involved the same degree of worker contact with the process materials regardless of the plant site NIOSH investigated; clearly a large amount of variability is likely to exist across plant sites and thus should be addressed. Essentially, EPA is using subjective estimates of human exposure in a very quantitative manner (dose response modeling) – the EPA should address the uncertainty associated with the dose estimates for the NIOSH cohort.

## 7. EPA did not address the impact of exposures to other carcinogenic compounds in its assessment of TCDD potency

Another major source of uncertainty associated with the NIOSH cohort is the effect of confounding exposures. Workers in the NIOSH cohort were exposed to more than 30 chemicals that have been classified as either known or potential human carcinogens by the EPA and IARC (Marlow et al., 1984, 1986, 1989, 1990, 1991a, 1991b, 1997; Piacitelli et al., 1990). The potential impact of these confounding exposures on the cancer mortality data, which is the foundation of the dose response analysis the EPA used to derive a proposed OSF, must be addressed.

Some of the Ranch Hand epidemiological studies (e.g., Akhtar et al., 2004; Mickalek and Pavuk, 2008) with the confounding presence of 2,4-dichlorophenoxyacetic acid (2,4-D) were excluded from quantitative analysis. However, this same pesticide was also present at three of the eight NIOSH cohort chemical plants (Plants 3, 4, and 9; Marlow et al., 1990, 1991a, 1991b), yet studies on this cohort were included in the Agency's analysis. The EPA rationalized the exclusion of the aforementioned Ranch Hand studies by stating

that it would have been "impossible" to distinguish the cancer effects of 2,4-D and TCDD-tainted 2,4,5-T. It is unclear why this rationale does not also apply to the plants studied by NIOSH. The Agency needs to address the impact of confounding exposures in the NIOSH cohort as well.

## 8. The EPA did not address the uncertainties related to deriving exposure estimates for the entire NIOSH cohort based on a small number of actual measurements

There is a great deal of uncertainty associated with the serum TCDD analytical data used to derive exposure estimates in the NIOSH cohort (Steenland et al., 1999, 2001; Aylward et al., 2005; Cheng et al., 2006). Former employees (n =170) from only one of the eight plants in the final NIOSH cohort assessment (Plant 1) were assessed for serum TCDD levels (Piacitelli et al., 2000). These data were assumed to be representative of the entire cohort, and were therefore applied to the remaining 3,300 workers at the other seven chemical plants. There is a large amount of uncertainty in this assumption, as highlighted by Aylward et al. (2005):

> *…the dose-rate regressions presented here and in Steenland et al. (2001) for this cohort are based solely on data from a small subcohort of individuals with measured serum lipid TCDD concentrations sampled in 1987–1988. These individuals were drawn from a single plant out of the 12 originally included in the NIOSH cohort (only eight plants were included in the exposure reconstruction effort by NIOSH). Thus, the results of the dose-rate regression for these individuals may or may not be representative of the exposures of cohort members from other plants.*

Because the exposure estimates were used directly in the derivation of an OSF, it is strongly recommended that these uncertainties be addressed.

## 9. The EPA relied on endpoints used as screening tools, rather than adverse effects, when deriving an RfD

The EPA relied on decreased sperm concentrations measured in males aged 1-9 years at the time of exposure as a critical effect when deriving a reference dose in its noncancer assessment. The Agency specifically noted that the values used to make this determination (unadjusted mean: 53.6 million/ml, SD: 21.8–131.8 million/ml) did not fall below the clinical level of concern (20 million/ml). However, the EPA rationalizes selecting this as an endpoint of concern by claiming there must be individuals within this group whose sperm concentrations fall below the low-end standard deviation value of 21.8 million (and therefore may have sperm concentrations that would be of clinical concern). Thus, the critical effect was based on "assumed" effects rather than documented effects of clinical concern. At a minimum, the EPA needs to verify this assumption (note: the Agency indicates that it was unable to obtain the original data even though the primary author is an SAB member).

## 10. EPA failed to present a valid analysis of variability of effects in control population

The low-end standard deviation value for the control population (31.7 million/ml) in the study used to derive the RfD was also near the level of clinical significance. This was not addressed by the Agency. Using EPA's reasoning in comment 9 above, this would suggest that a fraction of the control population has sperm concentrations of clinical concern as well (and therefore may not be different than the exposure group). The Agency needs to address these issues and provide a more scientifically robust rationale, as well as a statistical evaluation, to support its selection of a critical effect.

## 11. The EPA derived an RfD without knowing the TCDD concentrations in the people evaluated

The EPA did not have any information regarding the TCDD concentrations in the persons that may have had sperm concentrations below the low end of the standard deviation (i.e., the critical effect) – for either the exposure group or the control group. Thus, in determining the critical effect, the EPA had no information to verify that the persons with the potentially low values were associated with higher exposures to TCDD.

## 12. There is no evidence of a dose response relationship in the critical effect selected by EPA to derive the RfD

The EPA used an adjusted dataset from Mocarelli et al. 2008 (rather than the unadjusted data used to rationalize the selection of the endpoint as critical) to calculate an RfD. The original study authors conducted an analysis based on adjusted data and compared sperm concentrations by TCDD serum concentration quartile to the control group (note: the study did not evaluate TCDD serum concentrations in the control group). The EPA then selected the median serum TCDD concentration (68 ppt) in first quartile as the LOAEL, which was further evaluated in a PBPK model to determine the point of departure for the RfD derivation. However, there was no dose response relationship for this effect (and for most other effects evaluated). The Agency should provide rationale for its selection of this point of departure in the absence of a dose response relationship.

## 13. The EPA did not consider non-TCDD TEQ when evaluating exposure in the RfD calculations

When determining an RfD, the EPA did not account for exposures to dioxin like chemicals other than TCDD. Background sources of other dioxin like chemicals significantly contribute to total TEQ (note: total TEQ was not considered in the analyses). Based on studies published in the literature characterizing TEQ (e.g., Eskenazi et al. 2004), total TEQ was underestimated by approximately 55% for the concentration used as the point of departure by the EPA when calculating the RfD. Thus, the resulting RfD inappropriately assigned the effect to TCDD only.

It is of interest to note that that despite these significant background exposures to dioxin like compounds experienced in the Seveso population, the EPA still considered the Mocarelli et al (2008) study, which studied the Seveso population, as highly appropriate for RfD derivation due to the fact that it "primarily represented TCDD exposures." The Agency should account for exposures to dioxin like chemicals other than TCDD.

## 14. It is suggested that the EPA apply a consistent weight of the evidence approach when selecting and applying datasets for the development of toxicological values.

In the Draft Report, the EPA did not follow a comprehensive and unbiased evaluation of the weight of evidence when selecting epidemiological studies for both the cancer and noncancer assessments. Specifically, the Agency did not consider any studies that demonstrated a lack of association between exposure to TCDD and adverse effects (there are many such studies). Further, the Agency did not appropriately apply the Hill Criteria for causation when selecting studies – specifically, several studies lack a dose response effect as well as biological plausibility. These are key topics related to the application of a weight of evidence approach that should be considered.

## 15. The EPA did not follow guidance when selecting a PBPK model to determine dose when deriving cancer and non-cancer benchmarks

The EPA did not adhere to its own guidance when selecting and applying a PBPK model. Rather than using a PBPK model directly from the literature (several of which were available), the EPA modified a PBPK model published by Emond et al. (2006). In doing so, the EPA failed to abide by its own 2006 guidance on the issue of PBPK model selection, which specifically states studies should be peer reviewed (EPA 2006). Selecting a PBPK model that was not peer-reviewed nor validated is also inconsistent with criteria applied by the Agency for selecting studies for cancer and noncancer assessment.

## 16. The EPA did not sufficiently address NAS recommendations regarding variability and uncertainty

The NAS made two important points regarding variability and uncertainty:

1. The 2003 Dioxin Reassessment did not adequately address uncertainty and variability that resulted from the numerous decisions EPA made in deriving point estimates of cancer risk in the comprehensive risk assessment.

2. Distributions should be presented that provide clear insights about the uncertainty in the risk assessments, along with a discussion of key contributors to the uncertainty.

Further, the NAS suggested that the EPA should estimate risks associated with toxicological benchmarks derived using a variety of alternative assumptions to demonstrate the range of uncertainty and identify the parameters that have the greatest impact on these benchmarks. Specifically, NAS identified four sources of uncertainty that EPA should have incorporated into a quantitative uncertainty analysis, including:

- The full range of plausible parameter values for the dose-response functions used to characterize the dose-response relationship for NIOSH occupational cohort study selected by EPA (Cheng et al., 2006).
- Use of points of departure other then ED01.
- Alternative dose-response functional forms and goodness of fit of all models at low doses.
- Uncertainty introduced by estimation of historical occupational exposures.

The EPA did not conduct these analyses despite the NAS recommendation. Rather, the EPA concluded that such an analysis was "not feasible" and therefore, the Agency did not provide clear evaluation of the impacts of uncertainty on risk estimates as recommended. Thus, the Agency effort regarding characterization of variability and uncertainty is insufficient.

It is important to note that the current SAB panel surfaced this issue on several occasions during the course of its July 13-15, 2010 public meeting. Several panel members expressed significant concern with the EPA's lack of considerations for uncertainty and variability.

## 17. Several NAS recommendations on TEFs were not addressed by the EPA

The EPA has previously addressed a number of issues in the 2009 Draft Toxic Equivalency Factor (TEF) Guidance; however, several NAS recommendations still need to be addressed by the Agency including:

- Better uncertainty analysis of TEF values
- Considerations for body burden TEFs depending on dose metric selection
- Considerations for potential effects of AhR antagonists present in complex mixtures
- An understanding of species differences in relative potencies
- Considerations for synthetic and naturally occurring non-DLC AhR agonists

The TEF recommendations made by the 2006 NAS Dioxin Panel identify important issues that need to be clarified by EPA in the final dioxin risk assessment. It is our

understanding that no additional documents will be issued by the Agency; therefore, these comments should be addressed in the dose response analysis.

## 18. The EPA position on "additivity" related to AhR agonists is unclear

As part of the rationale for applying a linear model to derive an OSF, the EPA relies on an "additivity to background" argument. This position assumes that endogenous AhR ligands as well as natural (or dietary) AhR ligands (referred to as endodioxins) are acting as AhR agonists. These are in addition to activation of the AhR by background levels of exogenous dioxins and dioxin-like compounds. As a result, the Agency suggests that any additional exposures to exogenous dioxins and dioxin-like compounds are expected to result in AhR activity at a level that will induce toxicological consequence. However, this is in contrast to the position the EPA traditionally takes on endodioxins. For these compounds, the Agency has concluded that they play an insignificant role in the health risk of dioxins because the compounds have a short half-life and are rapidly metabolized (EPA 2003). Thus, there is a clear contradiction in the EPA's position regarding the impact of endogenous and dietary AhR agonists on human health effects that should be clarified and supported with scientific data, particularly considering the importance of this topic with respect to the mathematical approach used to derive an OSF.

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