Texas Commission on Environmental Quality (TCEQ) Responses to Public Comments Received on the Proposed Development Support Document for 2-Butoxyethanol October 15, 2007

The public comment period for the proposed Development Support Document (DSD) for 2-butoxyethanol ended August 17, 2007. The American Chemistry Council (ACC) submitted comments. The Toxicology Section (TS) of the Texas Commission on Environmental Quality (TCEQ) appreciates the effort put forth by ACC to provide technical comments on the proposed DSD for 2-butoxyethanol. The goal of the TS and TCEQ is to protect human health and welfare based on the most scientifically-defensible approaches possible (as documented in the DSD), and evaluation of these comments furthered that goal. ACC comments are provided below, followed by TCEQ responses. TCEQ responses indicate what changes, if any, were made to the DSD in response to the comment.

American Chemistry Council (ACC) Comments Regarding the TCEQ Development Support Document for 2-Butoxyethanol Chronic ReV and ESL Values

Comments:

It is not appropriate that the draft DSD for 2-butoxyethanol recommends using the results of Haufroid et al. (1997) as the key study. There are serious methodological limitations in Haufroid et al. (1997) occupational study. ACC comments that the study has a) poor study description; b) failure to control for potential confounding factors; c) biological plausibility. ACC indicates that there is persuasive evidence in available animal and in vitro red blood cell studies to demonstrate that the "true" NOAEL in humans may be much higher than Haufroid et al. (1997) suggests. ACC believes that the approach to deriving the chronic health-based ReV and ESL for 2-butoxyethanol as set forth in the draft DSD should be reconsidered and revised to be consistent with the methodology used by EPA in the current IRIS assessment (USEPA 1999).

TCEQ Response:

The TS appreciates ACC's comments and agrees that it is more appropriate to use the subchronic/chronic LOAEL of 31 ppm for hematological effects in female rats identified by NTP (1998) animal study and dose-response information on RBC count reported by the IRIS. Accordingly, the TS has conservatively used a human equivalent concentration (HEC) of 79 ppm calculated based on the PBPK and BMC_{05} combined modeling as POD_{HEC} for the derivation of chronic health-based ReV and ESL (NTP 1998, USEPA 1999).

From: "McLallen, Sarah" <Sarah_McLallen@americanchemistry.com>
To: <tox@tceq.state.tx.us>
Date: 8/17/2007 12:08:26 PM
Subject: Comments on Development Support Document for 2-butoxyethanol

The American Chemistry Council's Ethylene Glycol Ethers Panel submits the attached comments on the Texas Commission on Environmental Quality's June 2007 proposed Development Support Document for 2-butoxyethanol. If you have any questions or require additional information, please do not hesitate to contact me. Below, my contact information is provided.
Best regards, Sarah McLallen

Sarah Loftus McLallen

Director, Chemical Products and Technology Division

American Chemistry Council

1300 Wilson Blvd

Arlington, VA 22209

703-741-5607

Sarah_mclallen@americanchemistry.com

CC: <jlee@tceq.state.tx.us>

American® Chemistry Council

August 17, 2007

***Via* E-Mail**

Toxicology Section, MC 168
Texas Commission on Environmental Quality
P.O. Box 13087
Austin, TX 78711-3087
< tox@tceq.state.tx.us >

Re: Proposed Chronic Health-Based ReV and ESL for 2-Butoxyethanol

The American Chemistry Council's Ethylene Glycol Ethers Panel appreciates the opportunity to submit comments on the Texas Commission on Environmental Quality's (TCEQ) June 2007 proposed Development Support Document (DSD) for 2-Butoxyethanol. The Panel members are Arch Chemicals, The Dow Chemical Company, Eastman Chemical, and Equistar Chemicals LP. This submission addresses only the proposed chronic health-based inhalation reference value (ReV) and effects screening level (ESL) for 2-butoxyethanol. Specifically, as developed below, these proposed toxicity values should be reevaluated because the selection of the Haufroid (1997) study as the point of departure is not scientifically appropriate or consistent with the TCEQ (2006) Guidelines for developing the ReV and ESL criteria.

1. **Methodological Limitations in Haufroid (1997)**

The draft DSD acknowledges that humans are substantially less sensitive than laboratory animals to the potential hemolytic effects of exposure to 2-butoxyethanol, and appropriately looks first to available human data to identify an appropriate basis for developing the chronic ReV and ESL. The draft DSD identifies Haufroid (1997) as an appropriate basis despite what it calls "minor limitations" in this study.

Haufroid *et al.* compared 31 plant workers potentially exposed to 2-butoxyethanol to 21 workers with no exposure. The exposed group was well below the occupational exposure limit for the time-weighted average. Only one participant was heterozygous for the c2 allele for the p450 2E1 gene, precluding any analyses or conclusions on the influence of genetic polymorphism for cytochrome P450 on urinary BAA excretion. Of the 12 parameters reported, two means were statistically different between exposed and unexposed, the hematocrit (Hct) and the mean corpuscular hemoglobin concentration (MCHC). The authors conclude that this suggests "membrane damage" among exposed workers.

A critical review reveals that Haufroid (1997) has a number of serious flaws that should rule it out as the basis for developing chronic toxicity values for exposure to 2-butoxyethanol. The methodology of the study is weak and poorly described. The crude analyses could not take into account other confounding factors that might explain the differing means. The authors do not make a case for biological plausibility among workers with confirmed low exposure and study parameters that are within the range of normal.

a. **Poor Study Description**

The selection criteria for the participants are not described. The authors do not inform the reader how the 31 exposed and 21 controls came to be identified, recruited, and to participate. The refusal rate is not disclosed. Without such information, it is impossible to assess comparability between the groups included in the study or comparability to other exposed populations. The authors state that groups were matched for sex, age and smoking habits. However, while all 31 exposed workers were male, there is no indication that indeed all 21 controls are men. Although reportedly "matched", the controls are older, smoke less and drink more than the exposed group. This is important since these factors can influence the parameters evaluated in this study.

b. **Failure to Control for Potential Confounding Factors**

The Hct was statistically higher among the controls than the exposed (45.5 % vs. 43.9 %) as measured by a simple *t*-test to evaluate the differences between means. However, factors other than low 2-butoxyethanol exposure have been associated with this marginally lower Hct. For example, poor nutrition and blood loss may cause anemia (lower Hct), whereas chronic smoking and dehydration are associated with increased Hct (Braunwald 2001). The same factors confound the interpretation of the other statistically significant finding for MCHC, which is the ratio of hemoglobin (Hgb) to Hct.

c. **Biological Plausibility**

The hematologic, renal and hepatic parameters for both the exposed and control groups in the study are within normal ranges. The groups may have slight differences in two of the measured parameters, but such a result is not surprising in such a small study, and in any case the two groups have differences in age, smoking habits, alcohol consumption, job and, perhaps, other differences not recognized in this study. More important, there was no correlation between the Hct and MCHC findings and urinary BAA, the metabolite of 2-butoxyethanol which the draft DSD identifies as the proximate toxicant responsible for 2-butoxyethanol's hemolytic effects.

The draft DSD attempts to sidestep these difficulties by disregarding the authors' claim that the study shows an association between 2-butoxyethanol exposure and hemolytic effects, and treating Haufroid (1997) as a negative study. The DSD then derives from the study a no adverse effects level (NOAEL) of 0.6 ppm, the mean 2-butoxyethanol exposure level reported by the authors. This exposure estimate is based on extremely limited data – just a single work shift in a study population said to be exposed from one to six years, with no data offered to suggest that this solitary shift was representative. It does appear, nevertheless, that the 2-butoxyethanol exposures in Haufroid (1997) were relatively low even for an occupational setting (ACGIH 2003). Haufroid (1997) does not find a dose-response relationship, and based on information identified by the Panel, no other chronic or subchronic studies of humans establish hemolytic effects levels for 2-butoxyethanol. As a result, even if the limited exposure data collected by Haufroid et al. are accepted as valid and representative, the NOAEL established in that study represents just one data point on an otherwise completely unknown dose-response curve. Thus, the "true" NOAEL in humans may be much higher than Haufroid (1997) suggests.

As discussed in the next section, there is persuasive evidence in available animal and *in vitro* red blood cell studies indicating that this is the case.

2. The IRIS Assessment

The draft DSD does review the key animal data that might provide a point of departure for deriving ReV and ESL criteria for 2-butoxyethanol, including the reference concentration (RfC) developed in the current IRIS Assessment (EPA 1999).[1] It decides to use Haufroid (1997) to develop the toxicity values in large part because of the preference for human data contained in the TCEQ (2006) guidelines, and in part because it judges the limitations of Haufroid (1997) to be "minor," a characterization which the draft DSD suggests is shared by the IRIS assessment. However, the evaluation of Haufroid in the IRIS review indicates quite clearly that the shortcomings of the Haufroid (1997) study as the basis for deriving toxicity values are more than just "minor." The IRIS review finds that the implications of "the small erythroid effects" found in Haufroid "are unclear," and "they do not appear to be related to the more severe adverse effects observed in laboratory animals" (EPA 1999, p. 11). Accordingly, the IRIS review derives its toxicity criteria for 2-butoxyethanol from animal data "because no relevant human data exist" (EPA 1999, p. 51). Significantly, the preference for human data in the TCEQ (2006) guidelines is not absolute. The guidelines state that "When relevant human studies are not available, animal data are used to develop toxicity factors" (TCEQ 2006, p. 20).

In view of the lack of useful human chronic health effects data, the available animal studies, coupled with the extensive database on the absorption, distribution, metabolism and elimination of 2-butoxyethanol, provide a much more robust and appropriate basis for developing toxicity criteria, as the IRIS assessment (EPA 1999) demonstrates. In addition, *in vitro* red blood cell studies and physiologically-based pharmacokinetic (PBPK) modeling suggest that the approach adopted in the DSD for deriving toxicity values is inappropriate. Udden (2002) demonstrated that humans are at least 100 times even less sensitive to the potential hemolytic effects of 2-butoxyethanol than laboratory rats, significantly more resistant than found in the earlier IRIS review (EPA 1999). In addition, the PBPK model developed by Corley (1994) and used in the IRIS assessment to derive the EPA RfC predicts that the level of BAA in humans exposed continuously by inhalation to an 2-butoxyethanol-saturated atmosphere (greater than 1,000 ppm)[2] would result in maximum blood concentrations of BAA of 2mM, well below the level needed to produce hemolysis in human red blood cells (Udden 2002, EPA 1999a). Particularly in view of the serious limitations of Haufroid (1997), these data cast considerable doubt on the validity of using a NOAEL of 0.6 ppm based on that study to derive the ReV and ESL for 2-butoxyethanol.

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For the reasons presented above, the ACC Ethylene Glycol Ethers Panel believes that the approach to deriving the chronic health-based ReV and ESL for 2-butoxyethanol as set forth in the draft DSD should be reconsidered and revised to be consistent with the methodology used by EPA in the current IRIS assessment. If further information is needed with respect to these comments, please contact me.

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[1] The draft DSD also reviews a California Office of Environmental Health Hazard Assessment chronic inhalation REL based on animal data (OEHHA 1998), but that assessment was based on a subchronic intermittent exposure study and does not consider subsequent studies in rats and mice that provide more appropriate bases for deriving toxicity values, as discussed in the IRIS assessment (EPA 1999).

[2] The theoretical 2-butoxyethanol maximum airborne concentration is greater than 1,100 ppm, but in recent acute studies, the highest attainable concentrations were 600 to 700 ppm.

Sarah C. L McLallen

Sarah C. L. McLallen
Manager, Ethylene Glycol Ethers Panel
Sarah_McLallen@americanchemistry.com

cc: Dr. Jong-Song Lee (*via* e-mail to jlee@tceq.state.tx.us)

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