Methanol & Proposition 65

Response of the Methanol Institute to California's Request for Comment on the Proposed Maximum Allowable Daily Levels of Methanol with regards to the Listing of Methanol as a Reproductive Toxicant

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By

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Summary

On March 16, 2012, CalEPA's Office of Environmental Health Hazard Assessment (OEHHA) announced that methanol is added to the Proposition 65 list of chemicals known to the state to cause developmental toxicity. At the same time, OEHHA also proposed a Maximum Allowable Daily Level (MADL) of 23,000 micrograms/day for oral ingestion and 47,000 micrograms/day for inhalation exposures. The listing was based on the Authoritative Bodies mechanism in light of a 2003 report by the US NTP Center for the Evaluation of Risks to Human Reproduction (CERHR) that stated there is clear evidence for "high dose" developmental effects in laboratory animals exposed to methanol, but minimal concern for humans if the blood level of methanol is less than 10 mg/L. The Methanol Institute finds that neither the listing decision nor the MADLs published by OEHHA are supported by the data.

OEHHA reviewed the literature since 2003 and chose to ignore significant new data published since 2003 that impacts the listing decision and the calculation of MADLs.

We believe that a review of the literature is warranted as recent studies demonstrate that OEHHA's suggested MADL is unduly conservative.

Listing Criteria

The CERHR evaluated a series of studies by Nelson et al. and Rogers et al., showing developmental effects in mice and rats at exposure levels of greater than 1000 ppm in mice and 10,000 ppm in rats.

> *"Data from animal prenatal exposure studies are sufficient to demonstrate that methanol is a developmental toxicant following inhalation exposures resulting in blood methanol levels of 537 mg/L in the mouse and 1,840 mg/L in the rat. Studies in mice sufficiently demonstrated the same developmental pattern of response following oral or inhalation exposures resulting in equivalent blood levels of methanol.*
>
> *Studies that evaluated neurobehavioral effects in Long-Evans rats exposed prenatally and/or during the neonatal stage are sufficient to demonstrate that methanol blood levels of 555 mg/L in dams and 1,260 mg/L in offspring are associated with adverse neurological effects." (CERHR, page ii-99 – ii-100)*

The CERHR concluded the following relative to the potential onset of developmental effects from methanol exposure in humans.

> *"The Panel concluded that there is sufficient evidence to assume that methanol could be a developmental toxicant in humans. The Panel also noted that the blood methanol concentrations that have been associated with developmental toxicity in rodents are in the range associated with formate accumulation, metabolic acidosis, and other signs of acute toxicity in humans." (CERHR, 2003, page ii-105)*

The CERHR summarized their conclusion regarding humans on page 3 of the monograph with the following question and answer

> **"*Are Current Exposures to Methanol High Enough to Cause Concern?***
> *Probably Not. The general U.S. population presently appears to be exposed to methanol at levels that are not of immediate concern for causing adverse reproductive or developmental effects. However, there are studies to suggest that maternal exposure to acutely toxic doses of methanol may produce developmental effects in children. …"*

The CERHR concluded that only under conditions of extreme exposures to methanol would any concern regarding developmental toxicity be triggered (i.e., at acutely toxic doses). This conclusion was further reiterated on the same page (3) with the following statement

"The panel noted that the maternal blood concentration at which developmental effects were observed in mice, approximately 500 mg/L, has been observed in humans suffering acute methanol poisoning. Therefore, there may be overlap between methanol doses that result in clinical signs of methanol toxicity in humans and doses that result in developmental toxicity in rodents."

Based on the data available in 2003, the CERHR concluded that methanol was the likely proximate toxicant and that the data were likely relevant for human risk assessment. *("While formate is responsible for the acute toxicity of methanol, it appears that methanol itself results in the developmental toxicity observed in rodents." CERHR, 2003, p.3*) **Given the high blood level of methanol associated with these developmental effects, the CERHR concluded there was minimal concern for developmental effects in humans unless the blood methanol exceeded 10 mg/L. They noted that the "*safe level might actually be much higher than 10 mg/L*".**

Since the CERHR evaluation, a series of studies conducted at the University of Toronto led by Dr. Peter Wells and published in peer-reviewed scientific journals indicate that methanol is NOT the likely proximate toxicant in rodents, but it is more likely to be reactive oxygen species created by the metabolism of high doses of methanol by catalase in rodents.

In both rodents and non-rodents, methanol is metabolized to formaldehyde at about the same rate. The difference between rodents and non-rodents is not the rate of metabolism, but the enzymes and byproducts involved. Non-rodents metabolize methanol via alcohol dehydrogenase and the byproduct is water. In rodents methanol is metabolized primarily by catalase, which produces hydrogen peroxide (H_2O_2) and other reactive oxygen species. Dr. Wells' research has indicated that methanol does not produce developmental effects in the absence of catalase activity. In rabbits (non-rodent) exposed to 2000 mg/kg methanol, methanol is not metabolized by catalase and there were no developmental effects. (*Sweeting, J. N., Siu, M., Wiley, M. J. and Wells, P. G. Species- and strain-dependent teratogenicity of methanol in rabbits and mice. Reproductive Toxicology: 31(1): 50-58, 2011.)*

In response to comments submitted by the Methanol Institute that Dr. Wells' research demonstrated that developmental toxicity from methanol was related to catalase-derived reactive oxygen species, OEHHA dismissed the research because the CERHR review concluded before the research was conducted and therefore without the ability to evaluate

it, NTP found that "it appears that methanol itself" was the proximate toxicant in rodents. If the CERHR Panel were evaluating the data after Dr. Wells' research, they most likely would reach a different conclusion.

The US EPA developed a draft IRIS Assessment of methanol and based proposed lifetime reference levels on developmental effects in rodents. Several members of the EPA IRIS Peer Review Panel on the non-cancer assessment commented that more attention needs to be paid to the role of catalase in rodents and it relevance to man. The majority of the Panel did not support EPA's proposed mode of action or quantitative risk approach.

In summary, OEHHA has cited data that supports its pre-determined conclusion and dismissed the data that does not support it. It cited conclusions of a panel that considered methanol effects in 2003 to dismiss contrary research published in 2011. We recommend an oral MADL of 40,000 micrograms/day based on mouse inhalation data or 116,000 micrograms/day based on rabbit oral data.

Proposed MADL

OEHHA indicates a MADL for oral ingestion of 23,000 micrograms/day. For the standard 58 kg human female used by OEHHA, this translates to 23 mg/day/58 kg = 0.4 mg/kg/day. According to the PBPK model used by EPA in the draft IRIS assessment of methanol, this amounts to an increase in the blood methanol of less than 0.04 mg/L. The background level of methanol in the human population ranges between 0.25 and 4.7 mg/L. Thus for a person with low background, the blood level of methanol from exposure at the MADL will increase from 0.25 to 0.29, which is 94% below the high end of the normal range of unexposed persons. For a person with a high background methanol level, exposure at the MADL will increase blood methanol from 4.70 to 4.74 mg/L, a 1% increase. It is not scientifically or even logically defensible to suggest that a 1% increase in blood methanol above background represents a risk of developmental toxicity. Based on the proposed MADL, the blood methanol of all Californians, without exposure to external methanol, represents a developmental risk.

Five of the seven peer reviewers of the EPA non-cancer IRIS assessment criticized EPA's proposed RfD of 0.4 mg/kg/day as being indefensible scientifically. Only one person supported it. OEHHA's MADL is equally indefensible scientifically. As panel member Dr. McMartin noted:

> *"The RfD and RfC values have been appropriately derived based on the BMD/PBPK analysis utilizing "standard EPA procedures", but the resulting values lack scientific credence and are not logical in the sense of the exposures expected for humans. The problem scientifically is that the resulting values reflect a methanol exposure that does not increase the blood methanol concentration in the exposed human. Because of the background level of methanol in all humans lies in the range of 2 mg/L, the projected increase in methanol level from the RfC/RfD exposure is only 0.04 mg/L, i.e. a level that is really indistinguishable from the background. The implications of this include that all humans would be susceptible to developmental effects of methanol no matter what exposure they had experienced – not a suitable endpoint for risk assessment. As stated above, presuming that endogenous levels of methanol do not contribute to adverse effects*

and an exposure does not produce an increase above background levels, how can that exposure lead to an adverse effect? The conundrum occurs because the PBPK model itself has built-in conservatism, the BMD calculation has built-in conservatism and then a 100-fold uncertainty is applied. All of these factors contribute to bring the "RfC/RfD exposure" down to the levels where there is essentially no exposure-induced increase in methanol levels above the endogenous, background level, which means there is essentially no risk. So in this case of an endogenous chemical, the numbers are more conservative than necessary."

For the proposed MADL, "standard OEHHA procedures" are being employed to utilize a 1000-fold which like the "standard EPA procedures" highlighted by Dr. McMartin has produced in the case of methanol an end result that purports to identify "safe" exposure levels where there is "essentially no risk." During the EPA external peer review public hearing, one of the panelists commented that the proposed RfD and RfC were so overly stringent that the levels threatened not only the credibility of the draft methanol assessment, but the overall credibility of the IRIS program. Here too, in setting a proposed MADL that is well within normal background levels for methanol in all humans, you significantly risk damaging the credibility of OEHHA and the Proposition 65 program.

Under the Prop. 65 law, MADLs for developmental effects are determined based on the No Observable Effect Level (NOEL) in relevant animal studies. OEHHA based the oral MADL on a single exposure level in mice by Rogers et al. (1993) and applied a 10-fold adjustment because that level was not a NOEL. This is not a robust data set and should not be used for calculation of a MADL. If an oral MADL is to be calculated from mouse data, it should be based on the complete inhalation dataset by Rogers and translation into oral equivalency, as follows:

1. Current proposed MADL (inhalation) = 47,248 µg/day

2. Absorption Rates:
   Mouse Inhalation Absorption [Based on Perkins et al. (1995)]: 85%
   Human Oral Absorption [Based on several citations]: 100%

3. Proposed New MADL (oral) = 47,248 µg/day x (85%/100%) = 40,161 µg/day or = 40,000 µg/**day**

Recent data indicates that developmental studies in mice are not relevant for human risk and therefore, should not be used as the basis for an MADL. Metabolism of methanol in rabbits is more like that in humans; hydrogen peroxide and other reactive oxygen species is not produced from methanol in rabbits or humans. The MADL should be based on relevant developmental studies in rabbits, not rats or mice. Sweeting et al. (200x) demonstrated a blood level of 800 mg/L and a NOEL for developmental effects from a dose of 2000 mg/kg/day. *(Sweeting JN; Siu M; McCallum GP; Miller L; Wells PG (2010). Species differences in methanol and formic acid pharmacokinetics in mice, rabbits and primates. Toxicol Appl Pharmacol. 247: 28-35.)*

Based on a NOEL of 2000 mg/L in rabbits, the MADL is:

1. Calculation of NOEL dose for a 58 kg woman: 2000 mg/kg/ day * 58 kg = 116,000 mg/day,

2 The MADL is derived by dividing the NOEL by one thousand (Section 25801(b)(1)). Thus, the adjusted NOEL was divided by 1,000 to obtain the MADL: **MADL oral** = 116,000 mg/day ¸ 1000 = **116,000 micrograms/day.**

We recommend a MADL be calculated based on a NOEL of 2000 mg/kg/day in rabbits. The citizens of California deserve a more thoughtful review of the CERHR study and the latest available science.