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Arthur L. Lawyer, Ph.D.
President

June 25, 2012

Methanol: Proposition 65:
Comments on Proposed MADLs

Ms. Susan Luong
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
1001 I Street
Sacramento, California 95814

Dear Ms. Luong,

We are providing comments on the Office of Environmental Health Hazard Assessment's (OEHHA) March 16, 2012 "Notice of Proposed Amendment to Section 25805(b), Specific Regulatory Levels: Chemicals Causing Reproductive Toxicity: Methanol". We truly appreciate the opportunity to comment on the proposed MADLs. These comments are being submitted on behalf of a coalition that includes the following initial members; The Methanol Institute, The Chemical Specialty Products Association, and The International Food Additives Council. Other members will be indicating their support of the efforts in the near future but were unable to complete their internal approval processes due to the limited time that the final comments were available for their review.

We request that OEHHA modify the $MADL_{oral}$ from the currently proposed 23,000 micrograms per day to 40,000 micrograms per day. This proposed adjustment to the $MADL_{oral}$ is based on the best science and the method proposed applies to methanol only because of the unique nature of the database. We proposed the use of the inhalation-route NOEL as the basis for the $MADL_{oral}$. The inhalation-route NOEL is already being used by OEHHA to generate the proposed $MADL_{inhalation}$. The $MADL_{oral}$ that we are proposing uses the best estimate of the inhalation absorption rate in the mouse (85%), along with the common presumption that methanol is completely absorbed when ingested in humans (100%), to transform OEHHA's proposed $MADL_{inhalation}$ into our proposed $MADL_{oral}$. Our proposed approach is not less conservative than the approach proposed by OEHHA given the limitations of the oral study that is used to establish OEHHA's proposed $MADL_{oral}$.

As our attached document details, we believe that adjusting the $MADL_{oral}$ in this manner is scientifically justified and will reduce the burden that the currently proposed MADL would have on California businesses.

Request for Meeting. We also request a meeting with OEHHA staff so that we can discuss the technical details of our comments, along with their impact on California business.

We appreciate being provided the opportunity to communicate these comments to OEHHA. Please contact me if you have any questions or need further information.

Sincerely

Attachments
ALL:/Methanol Comments Cvr Ltr - June 25 2012.docx

Cc: George Alexeeff, OEHHA
Methanol Institute
International Food Additive Council
Consumer Specialty Products Association
Files

Comments on
Notice of Proposed Amendment to Section 25805(b), Specific Regulatory Levels: Chemicals Causing Reproductive Toxicity: Methanol Dated March 16, 2012

June 25, 2012

I. Executive Summary.

We are providing comments to the Office of Environmental Health Hazard Assessment (OEHHA) on the March 16, 2012 Notice (OEHHA, 2012a)that proposed Maximum Allowable Dose Levels (MADLs) for methanol under the Safe Drinking Water and Toxics Enforcement Act of 1986 (Proposition 65). We appreciate the opportunity to comment on the proposed MADLs and request that OEHHA modify the $MADL_{oral}$ from the currently proposed 23,000 micrograms per day to 40,000 micrograms per day. This modification would be based on the use of the inhalation-route NOEL, which is already being used by OEHHA to generate the proposed $MADL_{inhalation}$, as the basis for the $MADL_{oral}$. The $MADL_{oral}$ that we are proposing uses the best estimate of the inhalation absorption rate in the mouse (85%), along with the common presumption that methanol is completely absorbed when ingested in humans (100%), to transform OEHHA's proposed $MADL_{inhalation}$ into our proposed $MADL_{oral}$.

The "safe harbor" level (MADL) proposed by OEHHA for oral-route exposures under Proposition 65 was generated using a single reliable oral-route data point from Rogers et al. (1993). We believe that the resulting $MADL_{oral}$ is unnecessarily conservative because the small, single point study by Rogers et al. (1993) did not result in a NOEL, and as a consequence, OEHHA used a factor of 10 to provide a crude estimate of the oral NOEL for methanol. As Rogers et al. (1993) state, the oral data, from which the LOEL is derived by OEHHA, was a "small study" designed to assess the significance of the route of exposure and the role of stress in the mice. The data were not designed to establish a NOEL for the oral route in contrast to the much larger and robust inhalation data generated by the same authors in a study which was designed specifically to establish a strong and precise NOEL for the inhalation route. Therefore, we propose that the inhalation NOEL from Rogers et al. (1993) be used as the basis for the $MADL_{oral}$. Adjusting the $MADL_{inhalation}$ by using an inhalation absorption rate for the mouse of 85%, as established by Perkins et al. (1995a), and an oral absorption rate for humans of 100%, changes the currently-proposed $MADL_{oral}$ for methanol from 23,000 to 40,000 micrograms per day. We believe that our proposed approach is not less conservative than the approach proposed by OEHHA given the limitations of the oral study that is used to establish OEHHA's currently proposed $MADL_{oral}$.

We believe that adjusting the $MADL_{oral}$ in this manner is scientifically justified and will reduce the burden that the currently proposed MADL would have on California businesses. Our proposed adjustment is based on the best science and the method proposed applies to methanol only because of the unique nature of the database.

II. The NOEL Derived from Inhalation Data should be used to Generate the Oral MADL.

OEHHA's Proposed MADL. OEHHA's March 16, 2012 "Notice of Proposed Amendment to Section 25805(b), Specific Regulatory Levels: Chemicals Causing Reproductive Toxicity: Methanol," proposed MADLs of 23,000 and 47,000 micrograms per day for oral and inhalation route exposures, respectively (OEHHA, 2012a). These proposed MADLs were derived from the NOEL for developmental effects observed in a mouse developmental toxicity study by Rogers et al. (1993). The OEHHA Initial Statement of Reasons for the proposed MADL (OEHHA, 2012b), states that the mouse study by Rogers et al. (1993) was identified by CERHR and OEHHA as the most sensitive study deemed to be of sufficient quality. The NOELs for inhalation exposures and the LOEL for oral exposures to mice in Rogers et al. (1993) were transformed into the proposed MADLs by OEHHA (OEHHA, 2012b).

The NOEL for inhalation in Rogers et al. (1993) was derived from exposures to CD-1 mice for 7 hours a day during gestation days 6 - 15 at six different levels of methanol (1,000, 2,000, 5,000, 7,500, 10,000, and 15,000 ppm) in groups of 30 to 79 animals. A clear LOEL of 2,000 ppm and NOEL of 1,000 ppm (814.6 mg/kg/day) were established from these inhalation data.

The LOEL for oral exposures in Rogers et al. (1993) was based on a "small study" conducted "to evaluate the significance of route of exposure and the possible role of stress from the inhalation exposure procedure" in which a group of 20 mice (only 8 of which were determined to be pregnant) were exposed to a total of 4,000 mg/kg/day during gestation days 6-15. Four dams served as the control animals. This single dose level was the "LOEL" for oral exposures in Rogers et al. (1993). There was no NOEL established because the authors purposefully selected a dose that would result in blood methanol levels that "would approximate those seen at the higher exposures levels used in the inhalation studies" (i.e., inhalation doses that resulted in developmental toxicity). OEHHA (2012b) generated the NOEL for oral exposures for the purpose of established a MADL by dividing the LOEL by 10, as required by regulations under Proposition 65 for converting a LOEL to a NOEL when an experimental NOEL has not been estalished. This resulted in a calculated NOEL of 400 mg/kg/day.

Inhalation Data from Rogers et al. (1993) is Strong and Generates a Precise NOEL. The focus of Rogers et al. (1993) was inhalation exposures of methanol to pregnant mice and the potential for developmental toxicity. Multiple doses and thorough controls were utilized (including sham/air, unhandled, fed ad libitum, and food deprived controls). The group sizes were robust. The use of six dosing levels and the sham control enabled the authors to clearly identify a NOEL, with only a 2-fold difference between the LOEL and the NOEL. The inhalation data generated by Rogers et al. (1993), and the developmental NOEL they were able to identify, were utilized by OEHHA (2012b) as the most sensitive study deemed to be of sufficient quality (27 CCR 25803(a)(4)). The spectrum of developmental effects observed with inhalation exposures to methanol by Rogers et al. (1993) were the same as those observed by the laboratory in the limited study they performed by the oral route.

The inhalation data generated by Rogers et al. (1993) provides a stronger, more precise basis for the NOEL for oral exposures than the "small study" that the laboratory performed where only a single dosing regime was used, a NOEL was not identified, and the study design was not intended to result in a NOEL for the oral route. Certainly, if the single oral data point for Rogers et al. (1993) did not exist, OEHHA would have likely used the robust inhalation NOEL from the Rogers study, along with the proper absorption data, to generate the oral MADL.

Oral Data from Rogers et al. (1993) are Not a Strong Foundation for Establishing the Oral MADL. As discussed above, the single data point generated with oral exposures to pregnant mice did not generate a NOEL for this route, but the limited data, nonetheless, did establish that the developmental effects caused by methanol exposures to mice were the same, regardless of the route of exposure. This conclusion, in fact, was the primary purpose of the "small study" conducted by Rogers et al. (1993) on the oral route. Because the developmental effects are comparable, the more robust and precise data generated with inhalation exposures should be used as the basis of generating the $MADL_{oral}$ under Proposition 65.

Oral Data from Other Publications Assessing Methanol's Developmental Toxicity are Not Adequate for Use in Generating the Oral NOEL. In addition to Rogers et al. (1993), there are three publications that report on the potential developmental effects of methanol from oral exposures. None of them are of sufficient quality to be considered as the basis for generating the oral MADL.

These studies are all in the rat, and the rat is presumed to be less sensitive to methanol than mice based upon the Perkins modeling and the CERHR expert panel (Perkins et al., 1995b; CERHR, 2003). The study designs and outcomes are not very comparable. None of the studies other than Rogers et al. (1993) exposed pregnant animals to methanol through most of the critical period of gestation (gestation days 6 through 15 in mice and rats).

Cummings (1993), an EPA study, is negative after rats were treated at dose levels up to 3,200 mg/kg on gestation days 1 - 8. The 3,200 mg/kg/day dose level was associated with decreased maternal weight gain. Different groups of dams were sacrificed on gestation days 9, 11, or 20. No consistent evidence of developmental toxicity was observed among groups, and the NOEL for developmental toxicity is considered to be 3200 mg/kg/day. However, groups sizes were small, and it is not clear that the litter was considered to be the proper statistical unit. The NTP Panel's confidence in these data "is low due to weaknesses in the study."

Infurna and Weiss (1986) is a study of post-natal behavior after prenatal dosing. Dams were dosed either on gestation days 15-17 or days 17-19. This was a single dose (2500 mg/kg/day) drinking water study; thus, a dose-response relationship could not be evaluated. The CERHR Expert Panel (CERHR, 2003) noted that there were no consistent effects and the slight changes in a few parameters could be due to normal variability (there are, according to the authors, behavioral effects in the two groups associated with their different gestational periods). The CERHR (2003) Expert Panel stated: "The utility of the study may be limited by uncertainty

implicit in any toxicological response where there is no dose response data and the inability to place these behavioral effects in the context of other potential positive controls."

Youssef et al. (1997) gave a single oral (gavage) dose on day 10 of gestation to rats and reported anomalies and decreased fetal weight at all dose levels. This study is not considered to be a study of sufficient quality for purposes of developing a MADL. The number of dams is small (n = 10-13), and it is not clear whether the fetus or litter was considered to be the statistical unit. The fetal examination was limited to an external exam (no visceral or skeletal examinations). In addition, there was a pre-dosing with mineral oil that may have enhanced oral absorption. The fetal body weights don't appear to show a dose-relationship and the anomalies are improperly pooled to show effects at all dose levels (which led to the conclusion that the LOEL was the lowest dose tested, 1,023 mg/kg/day), a dose still above the NOEL in the Rogers et al. (1993) study.

NOEL from Inhalation Data Generated by Rogers et al. (1993) should be used to Generate the Oral MADL for Methanol. We conclude that the inhalation data from Rogers et al. (1993) provide a stronger basis for establishing not only the $MADL_{inhalation}$, but also the $MADL_{oral}$. The inhalation results are the data from the most sensitive study deemed to be of sufficient quality, provide a more precise NOEL, and are relevant to both routes of exposure. The spectrum and relative intensity of the developmental effects observed with both routes of exposure in Rogers et al. (1993) were substantially the same. Because the limited oral exposure data generated by Rogers et al. (1993) were not designed to generate a NOEL, using these data would result in an unnecessarily conservative MADL. In contrast, using the robust inhalation exposure data generated by Rogers et al. (1993) to generate the $MADL_{oral}$ would be scientifically defendable and provide a much needed margin of compliance for California businesses.

III. An Inhalation Absorption Rate of 85% from Perkins et al. (1995a) Should be Used

Perkins et al. (1995a) Determined the Inhalation Absorption Rate for Mice Using Exposure Chamber and Blood Measurements Along with Modeling Presumptions. The most scientifically sound estimate of inhalation absorption in mice is developed in Perkins et al. (1995a). The study is cited by CERHR (2003) and the estimated absorption rate of 85% is consistent with the scientific literature on methanol and the expectation of what the absorption rate should be for a small molecular weight compound that is miscible in water and has a negative log octanol-water partition coefficient (K_{ow}).

The inhalation absorption rates calculated in Perkins et al. (1995a) are based on a mass balance approach derived from a combination of measured values (chamber input and output concentrations, V_{max}, V_d, K_m, air flow rate, blood concentrations) and modeling of animal uptake and excretion over time based on the measured values. Absorption is calculated from a series of equations with the final equation being the uptake value (modeled from measured values such as air concentrations) divided by the hypothetical uptake value that would result from

100% inhalation absorption. Though the series of equations leading up to the estimation of the inhalation absorption rate are complex, they are based on a set of simple logical assumptions. The CERHR (2003) noted that the experiments and modeling effort of Perkins et al., (1995a; 1995b) used appropriate techniques to measure blood methanol, good study design and justification of the models. The CERHR made the following conclusion regarding the collective work of Perkins and others in the laboratory of G. M. Pollack (CERHR, 2003, page II-33)

> "The Panel concluded that the PBPK studies described above represent an extensive series of carefully conducted experiments to develop pharmacokinetic models for rodents exposed to methanol and to begin to apply the results to humans. The strengths of these studies are the use of appropriate techniques to measure blood methanol, good study design, and justification of the models. This work has the most utility for understanding rodent toxicity studies."

Absorption is calculated in Perkins et al. (1995a) based on the following equation:

$$\phi = \frac{(X'_E + X'_B) / 2}{X'_U}$$

Where ϕ = absorption
X'_E = the mass calculated to be extracted from the airstream
X'_B = the body burden
X'_U = the mass extracted from the airstream assuming complete absorption

The input variables are each ultimately calculated from measured data. For example, X'_B at any given time is calculated from the blood methanol concentration, the volume of distribution (V_d), maximum velocity of elimination (K_m) and the calculated blood methanol concentration at which the velocity is half maximal. The model is validated by the comparison of measured blood methanol concentrations with those calculated by modeling.

The conclusions regarding the inhalation absorption rate for mice are summarized in Table 2 of Perkins et al. (1995a), a copy of which is provided below.

Perkins et al (1995): TABLE 2

Absorption Fraction (Φ) Calculated Using Chamber Model (Eq. (12)) for Each Individually Exposed Mouse

Exposure, ppm[a]	2500	5000	10,000	15,000
Subject				
1	1.15	0.86	0.76	0.97
2	0.76	0.89	0.76	0.94
3	0.78	0.72	0.97	0.61
4	0.75	0.94		
Mean ± SD	0.86 ± 0.19	0.85 ± 0.09	0.83 ± 0.12	0.84 ± 0.20
cv	0.22	0.11	0.145	0.24
Pooled average: 0.85 ± 0.14				
Average CV: 0.18				

[a] Nominal exposure concentration.

Key publications in the development of the model that determines the absorption fraction (phi) are the following:

- Perkins et al. (1996a) describes the experimental challenges in measuring inhalation absorption of small gaseous or vapor-phase xenobiotics and, therefore, the rationale for incorporating simple, logical modeling into calculations of inhalation absorption. These calculations (modeling) are necessary to determine the amount of material being administered under conditions where the concentration of exhaled xenobiotics must be accounted for – and can only be accounted for by estimating the level based on kinetic parameters, blood levels, and simple presumptions. Additionally, these calculations are a necessary part of determining how the test animals respond to these type of xenobiotics over longer periods of exposure (e.g., 6-8 hours) that mimic the workplace exposures via inhalation and, most importantly, are relevant to the 7 hour exposures used in Rogers et al. (1993)

- Perkins et al. (1996b) undertakes the foundational experimentation that is used to validate the modeling presumptions used in Perkins et al. (1995a) and other studies in this series. This paper is thorough in describing how the laboratory works towards identifying the factors that are required to establish the model that can predict absorption of methanol. This article illustrates the ways in which the laboratory is able to manipulate ventilation rates in the rat to assess their impacts on absorption rate. It is this study in rats, and the model developed in this publication for rats, that was used to generate the model for Perkins et al. (1995a). Recall that Perkins et al. (1995a) is the pivotal study on absorption in mice. The study compares the results in mice, where absorption is steady over a large spectrum of exposure levels, and the rat, where the percent absorption changes with the exposure levels.

- Ward et al. (1995) further compares the toxicokinetics of methanol in mice and rats, and provides a clear discussion of the differences between the species and helps explain the details of the pharmacokinetics of methanol in the mouse, which is the key species for the development of MADL for methanol under Proposition 65. The research described in this publication determines V_{max}, K_m and other kinetic parameters that are important in the understanding of the body burden and steady state plasma concentrations of methanol in mice.

The inhalation absorption rate was generated, in part, using of the model described above. The model uses a mixture of the experimental measurement of modeling that is necessary to compensate for the inability to directly measure the inhalation rate of methanol via inhalation. For longer periods of exposure that are analogous to those used in study described in Rogers et al. (1993) (6 to 8 hours per day), and lower dosing levels that are most relevant to the NOEL and LOEL for developmental toxicity determined by Rogers et al. (1993), the model by Perkins et al. (1995a) fits the experimental data well (see Figure 3 in Perkins et al., 1995a) for use in the dosing levels and time of exposure that are relevant to the NOEL and LOEL for developmental effects reported by Rogers et al. (1993). The fit of the model is better at lower concentrations (2,500 and 5,000 ppm) than it is at the highest concentration (10,000 ppm) due, mostly likely, to saturation of metabolism at high concentrations.

Differences in First-Pass Metabolism of Methanol via Inhalation and Ingestion. The use of Inhalation NOEL in generating the oral MADL is, in fact conservative. If anything, the first pass kinetics of methanol associated with oral exposure would result in more rapid metabolism (and clearance) of methanol due to the relative contribution of the liver when comparing inhalation to oral exposures. Since methanol itself is presumed by both the CERHR (2003) and OEHHA (2012b) to be the determinant of developmental toxicity, if that presumption is assumed, our proposed use of the absorption rates for mouse inhalation and human ingestion, as detailed below, is conservative.

Rogers et al. (1993), the CERHR (2003) expert panel, and Perkins et al. (1995a) all conclude that there is no difference in metabolism between the inhalation and oral routes of dosing. In any case, the CERHR expert panel concluded that methanol per se was the proximate toxicant and, if that is the case, oral dosing of methanol would be expected to more rapidly detoxify methanol due to first pass metabolism. Therefore, we are being conservative by proposing the use of an absorption factor to the inhalation NOEL.

Relatively High Inhalation Absorption Rate is Expected for Methanol. A high inhalation absorption rate would be expected for a small molecular weight compound that is miscible in water, chemically stable under the conditions found in the respiratory tract, and has a log K_{ow} of around -0.75. As described above, direct measurement of inhalation absorbance of xenobiotics that are gaseous or in the vapor phase is not directly obtainable by experimentation. Validated modeling is required to complete the estimate of the absorption rate for these xenobiotics. Because of this scrutiny, methanol has received in the scientific literature, due to the work of the laboratories of Pollack and others, we are in the unique

position of being able to quantitatively illustrate the high absorption level in rodents. Although very few analogous compounds have been similarly scrutinized, we would expect to be able to predict the behavior of compounds with characteristics similar to methanol. Diffusion of this molecule would be expected to occur more slowly through the thicker membranes of the human respiratory tract and there are data showing that absorption is, in fact, lower in humans (Sedivec et al., 1981).

IV. The Oral MADL Should be Based on the Difference in Absorption Rates

Oral Absorption of Methanol in Humans is Essentially Complete. The scientific literature support the conclusion that methanol is rapidly and essentially completely absorbed into the blood when ingested (CERHR, 2003). Accordingly, the oral absorption rate is presumed to be 100%. This is also the default value that would be used by OEHHA.

The $MADL_{oral}$ Can Be Determined Using the Relevant Absorption Rates in Mice and Humans. The $MADL_{oral}$ can be estimated by using the absorption rate for inhalation exposures in mice, as reported by Perkins et al. (1995a) and the absorbance rate for oral exposures in humans. The resulting $MADL_{oral}$ is 40,000 µg/day, as calculated below:

Current proposed MADL (inhalation) =	47,248 µg/day
• Based on OEHHA (2012b)	
Absorption rates:	
Mouse Inhalation Absorption:	85%
• Based on Perkins et al. (1995a)	
Human Oral Absorption:	100%
• Based on several citations on methanol (CERHR, 2003)	
New MADL (oral) =	40,000 µg/day
47,248 µg/day x (85%/100%) =	40,161 µg/day

V. Conclusions:

We request that OEHHA modify the proposed MADL for the oral route from the current 23,000 micrograms per day to 40,000 micrograms per day by using the inhalation-based data from Rogers et al. (1993), which is already used by OEHHA to generate the proposed $MADL_{inhalation}$ route (47,000 µg/day), as the basis of the $MADL_{oral}$. The $MADL_{oral}$ we are proposing uses the best estimate of absorption via inhalation by the mouse (85%, from Perkins et al., 1995a) and the absorption via ingestion by humans (100%). These terms adjust OEHHA's inhalation MADL to a MADL for the oral route.

The "safe harbor" level (MADL) proposed by OEHHA for oral-route exposures under Proposition 65 was generated using the single reliable oral-route data point found in the scientific literature (from Rogers et al., 1993). There was no NOEL generated from this limited experimentation. We believe that the resulting $MADL_{oral}$ is unnecessarily conservative because of the 10-fold factor required under Proposition 65 in cases where there is no experimental NOEL, as was the case with this limited data set used to estimate the $MADL_{oral}$. The NOEL generated from the inhalation route studies of Rogers et al. (1993) provides a substantially stronger and more precise basis for the MADLs, for both routes. Therefore, we propose that the inhalation-route NOEL from Rogers et al. (1993) be used as the basis for the oral-route MADL and that the $MADL_{oral}$ for methanol be adjusted to 40,000 micrograms per day. Our proposed approach is not less conservative than the approach proposed by OEHHA given the limitations of the oral study that is used to establish OEHHA's proposed $MADL_{oral}$.

We believe that adjusting the $MADL_{oral}$ in this manner is scientifically justified and will reduce the burden that the currently proposed MADL would have on California businesses. This proposed adjustment is based on the best science and the method proposed applies to methanol only because of the unique nature of the database.

Request for Meeting. We request a meeting with OEHHA to discuss our comments. The database on methanol is large and unique and we wish to ensure that the information we are providing OEHHA with these comments is sufficient for enabling OEHHA to modify the $MADL_{oral}$ as we are proposing.

We appreciate being provided the opportunity to communicate these comments to OEHHA. Please contact us if you have any questions or need further information. We look forward to hearing from you.

VI. References:

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