May 21, 2012

Ms. Susan Luong
Office of Environmental Health Hazard Assessment
P.O. Box 4010, MS-19B
Sacramento, California 95812-4010

Re: Amendment to Section 25805, Specific Regulatory Levels: Chemicals Causing Reproductive Toxicity Methanol

Dear Ms. Luong:

The American Forest & Paper Association (AF&PA) and the American Wood Council (AWC) wish to provide comments on the proposed Proposition 65 Maximum Allowable Daily Level (MADL) for methanol of 47,000 micrograms per day for inhalation.

The AF&PA is the national trade association of the forest products industry, representing pulp, paper, packaging and wood products manufacturers, and forest landowners. Our companies make products essential for everyday life from renewable and recyclable resources that sustain the environment. The forest products industry accounts for approximately 5 percent of the total U.S. manufacturing GDP. Industry companies produce about $190 billion in products annually and employ nearly 900,000 men and women, exceeding employment levels in the automotive, chemicals and plastics industries. The industry meets a payroll of approximately $50 billion annually and is among the top 10 manufacturing sector employers in 47 states.

AWC is the voice of North American traditional and engineered wood products, representing over 60 percent of the industry. As a renewable resource that absorbs and sequesters carbon, the wood products industry makes products that are essential to everyday life and employs about one-third of a million men and women in well-paying jobs. AWC's engineers, technologists, scientists, and building code experts develop state-of-the-art engineering data, technology, and standards on structural wood products for use by design professionals, building officials, and wood products manufacturers to assure the safe and efficient design and use of wood structural components. AWC also provides technical, legal, and economic information on wood

design, green building, and manufacturing environmental regulations advocating for balanced government policies that sustain the wood products industry. AF&PA and AWC members have facilities in California that release methanol in the production processes, and therefore, have a direct interest in the proposed rulemaking.

A. The Proposed MADL for Methanol Fails a Reality Test

To place the proposed MADL of 47 milligrams per day (mg/d) in biological perspective, we have conducted an analysis by estimating the incremental blood methanol levels in humans that would result from an exposure of 47 mg/d of methanol. We have used the methanol pharmacokinetic model of Bouchard et al. (2001) as employed by Starr and Festa (2003). Starr and Festa present the following steady-state equation, which relates human external methanol exposure and human blood methanol levels.

Where C^{ss} is the steady-state airborne methanol concentration in milligrams per cubic meter (mg/m^3), ΔB^{ss} is the human steady-state blood methanol increment in milligrams per liter (mg/L) arising from continuous inhalation exposure to C^{ss}, and the pharmacokinetic parameters are values as presented in the following table.

(1) $C^{ss} = 1000 * (K_{ex} + K_{meth} + K_m) * V_d * BW / (F_{abs} * VR) * \Delta B^{ss}$

(2) $C^{ss} = 41.5 * \Delta B^{ss}$

<u>Human parameter values utilized in the Bouchard et al. (2001) model</u>

Parameter	Symbol	Human value
Ventilation rate	VR	833.3 L/h
Absorption fraction	F_{abs}	0.577
Exhalation rate	K_{ex}	5.1×10^{-2} h^{-1}
Rate of metabolism to formaldehyde	K_{meth}	0.4h^{-1}
Urinary excretion rate	K_m	2.0×10^{-3} h^{-1}
Volume of distribution	V_d	0.7 L/kg
Body weight	BW	70 kg

We first converted the methanol MADL into an airborne concentration using a daily inhalation rate for women in the age bracket 21 – 41 years (obtained from the U.S. Environmental Protection Agency Exposure Factor Handbook, 2011 edition). The 95th percentile inhalation rate for the age bracket of 21 – 31 is given in the Handbook as 17.50 cubic meter per day (m^3/d), and 16.58 m^3/d for the age bracket 31 – 41 years.

The average of these two values, 17.04 m^3/d, was used as the estimated inhalation rate for the 21-41 age bracket. Dividing the MADL by this inhalation rate yields a corresponding airborne steady-state concentration of 2.8 mg/m^3.

From equation (2), we calculate the incremental steady-state blood level.

$$\Delta B^{ss} = C^{ss} /41.5 = 2.8 \text{ mg/m}^3/41.5 = 0.067 \text{ mg/L}$$

For body weight in equation (1), we used 58 kg for women. We also calculated an inhalation rate in liters per hour (L/h) as shown below:

$$17.04 \text{ m}^3\text{/d} * 1\text{d/24h} * 1 \text{ m}^3\text{/1000L} = 710 \text{ L/h}$$

Other parameters in the above table remain the same.

From equation (1), we calculate the incremental steady-state blood level to be 0.073 mg/L.

$$\Delta B^{ss} = 2.8 \text{ mg/m}^3/38.2 = 0.073 \text{ mg/L}$$

The National Toxicology Program Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR) Monograph on the Potential Human Reproductive Effects of Methanol (NTP-CERHR 2003) presents data on background blood methanol levels in humans. The report presents data for 22 adults on restricted diet (no methanol containing or methanol producing foods for 24 hours), the mean blood methanol was 1.8 ± 2.6 (S.D.) mg/L. **This mean background blood methanol value of 1.8 mg/L is 25 times greater than the blood methanol value of 0.073 mg/L corresponding to the MADL exposure.**

The NTP Monograph on the Potential Human Reproductive Effects of Methanol also states that "[t]he dietary exposure is pervasive in the general population and has been characterized through survey studies. It is generally believed that dietary sources contribute to the observed background blood methanol concentrations (<5-10 mg/L)." At a background blood level of 5 mg/L for example, the incremental blood level corresponding to the MADL exposure of 0.073 mg/L is only 1.5 percent of background. **From these observations, it is quite clear that the proposed MADL that would result in a blood level of 0.073 mg/L does not make sense from both a biological and toxicological point of view since a mean blood background level is around 25 times greater (1.8 mg/L to 5 mg/L).** We believe OEHHA should revise their MADL to take into consideration background blood methanol concentrations. If OEHHA chooses to stay with the proposed MADL for inhalation, OEHHA should provide justification for setting a MADL at a level much less than normal thresholds of methanol found in human blood.

B. The Legislative Mandate for a 1,000 Fold Exposure Multiplier Is Inconsistent With the Use of the Best Available Science

California's Proposition 65 legislative mandate requiring no observable effect at 1,000 times an exposure level is inconsistent with the best available science. Using a safety factor of 1000 significantly diminishes the value of employing best available science, such as when using a physiologically-based pharmacokinetic (PBPK) model to reduce uncertainties interspecies extrapolation, and when using other biological data to narrow uncertainties in pharmacodynamics and inter-individual variability. As we have illustrated above, use of such an arbitrary 1000-fold multiplier can lead to results that are highly aberrant. For the foregoing reasons, we urge OEHHA not to adopt the proposed MADL but instead set a less stringent MADL that takes in account naturally occurring blood levels of methanol. Regarding a more scientific approach, we refer OEHHA to the previously cited Starr and Festa (2003) publication in which a physiologically-based pharmacokinetic (PBPK) model with blood methanol as a dose metric is used to derive a scientifically-based reference concentration for methanol.

We appreciate the opportunity to comment on the proposed MADL for methanol inhalation. If you have any questions, please contact Laurie Holmes at 202-463-5174 or laurie_holmes@afandpa.org.

Sincerely,

Paul Noe
Vice President, Public Policy
American Forest & Paper Association

Robert Glowinski
President
American Wood Council

References

Starr TB, Festa JL. A proposed inhalation reference concentration for methanol. Regulatory Toxicology Pharmacology. 2003 Oct;38(2):224-31.

U. S. Environmental Protection Agency, Exposure Factors Handbook: 2011Edition.