INITIAL STATEMENT OF REASONS
TITLE 27, CALIFORNIA CODE OF REGULATIONS

PROPOSED AMENDMENTS TO
SECTION 25805(b), SPECIFIC REGULATORY LEVELS: CHEMICALS CAUSING REPRODUCTIVE TOXICITY

MAXIMUM ALLOWABLE DOSE LEVEL (ORAL EXPOSURE) FOR ETHYLENE GLYCOL (INGESTED)

PURPOSE AND BACKGROUND OF PROPOSED AMENDMENT

PURPOSE

This proposed regulatory amendment is to adopt a Maximum Allowable Dose Level (MADL) for oral exposure to ethylene glycol (EG) under Proposition 65[1] in Title 27, California Code of Regulations, section 25805(b) [2]. The proposed MADL was derived using scientific methods outlined in Section 25803. The proposed oral MADL for EG is 8,700 micrograms per day.

PROPOSITION 65 AND LISTING OF EG

Proposition 65 was enacted as a ballot initiative on November 4, 1986. The Office of Environmental Health Hazard Assessment (OEHHA) within the California Environmental Protection Agency is the lead state entity responsible for the implementation of Proposition 65[3]. OEHHA has the authority to promulgate and amend regulations to further the purposes of the Act[4].

The Act requires businesses to provide a warning when they cause an exposure to a chemical listed as known to the state to cause cancer or reproductive toxicity. The Act also prohibits the discharge of listed chemicals to sources of drinking water. Warnings are not required and the discharge prohibition is not in force when exposures are sufficiently small, as specified in the Act[5].

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[1] The Safe Drinking Water and Toxic Enforcement Act of 1986, codified at Health and Safety Code section 25249.5 et. seq., hereafter referred to as “Proposition 65” or “The Act”.
[2] All subsequent citations are to Title 27, California Code of Regulations, unless otherwise noted.
[3] Health and Safety Code, section 25249.12 and Cal. Code of Regs., Title 27, section 25102(o).
[4] Health and Safety Code, section 25249.12(a).
[5] Health and Safety Code, section 25249.9(b) and 25249.10(c).

On June 19, 2015, EG (ingested) was added to the Proposition 65 list as known to the state to cause reproductive toxicity (developmental toxicity endpoint). The listing is based on formal identification of EG by the National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR) as causing reproductive toxicity (developmental endpoint)[6]. NTP-CERHR is one of several institutions designated as authoritative for the identification of chemicals as causing reproductive toxicity under Proposition 65[7].

STUDY SELECTION

To establish the scientific basis for the proposed regulation, OEHHA reviewed the studies identified in the NTP-CERHR Monograph[8] that provide the basis for the listing, and conducted a literature search for any other relevant studies or reports published after the NTP-CERHR review was completed. Additional relevant studies were identified and reviewed by OEHHA.

Human Studies

No human data relevant for establishing a MADL based on the developmental effects of EG were identified by NTP-CERHR[9] or in the subsequent literature search by OEHHA.

Studies in Laboratory Animals

The lowest observable effect levels (LOELs) and no observable effect levels (NOELs) from laboratory animal studies of sufficient quality that may provide the basis for the establishment of the MADL are discussed below.

The NTP-CERHR Monograph[10] reviews a number of studies in mice, rats, and rabbits that investigated the developmental effects of EG following prenatal

[6]NTP-CERHR (2004). NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Ethylene Glycol. Research Triangle Park, NC, National Toxicology Program, Center for the Evaluation of Risks to Human Reproduction: NIH Publication No. 04 – 4481. Available online at http://ntp.niehs.nih.gov/?objectid=4980AA81-E919-4E85-60B789CA36E59FA5

[7] Section 25306(l).

[8] NTP-CERHR (2004). NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Ethylene Glycol. Research Triangle Park, NC, National Toxicology Program, Center for the Evaluation of Risks to Human Reproduction: NIH Publication No. 04 – 4481. Available online at http://ntp.niehs.nih.gov/?objectid=4980AA81-E919-4E85-60B789CA36E59FA5

[9] *Ibid.*

exposure through the oral route of exposure. The prenatal developmental study in CD-1 mice by Neeper-Bradley et al. (1995[11]) reported a significant increase in the incidence of total malformations in litters exposed to 500 milligrams EG per kilogram body weight per day (mg/kg-day) by oral gavage from gestational day 6 to 15. At 150 mg/kg-day, no developmental effect was observed. In rats, prenatal oral exposure to EG at doses ≥1,000 mg/kg-day resulted in axial skeletal malformations, reduced body weights, external malformations, and increased post-implantation loss. The highest oral NOEL for developmental effects in CD rats was 500 mg/kg-day (Neeper-Bradley et al., 1995). Prenatal administration of EG at doses of up to 2,000 mg/kg-day by daily oral gavage from gestational day 6 to 19 in New Zealand white rabbits did not induce any obvious developmental effects (Tyl et al. 1993). Comparison of the prenatal oral route studies included in the NTP-CERHR Monograph identifies 500 mg/kg-day in CD-1 mice as the LOEL of EG for developmental toxicity, and 150 mg/kg-day as the NOEL.

OEHHA also identified several studies published after release of the NTP-CERHR Monograph through comprehensive literature searches. None of the studies identified reported a developmental LOEL that is lower than 500 mg/kg-day in mice. Hence, the study reported by Neeper-Bradley et al. (1995) is identified as the most sensitive study of sufficient quality and used as the basis for calculation of the MADL.

Study Basis for the MADL calculation

The study by Neeper-Bradly et al. (1995) provides a LOEL and a NOEL of 500 and 150 mg/kg-day, respectively, for the developmental toxicity of EG. Briefly, timed-pregnant Crl:CD-1 (ICR) BR mice (30/dose group) received a daily gavage dose of ethylene glycol (100% purity) in deionized water at 0, 50, 150, 500 or 1,500 mg/kg-day on gestational days 6–15. The dams (19-24 per group) were sacrificed on gestational day 18, and each live fetus was examined for external, visceral, and skeletal malformations. No chemical-related maternal toxicity, including effects on body weight, water intake, and liver and kidney weight, was observed at any dose level. No significant effects were noted on the number of

[10]NTP-CERHR (2004). NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Ethylene Glycol. Research Triangle Park, NC, National Toxicology Program, Center for the Evaluation of Risks to Human Reproduction: NIH Publication No. 04 – 4481. Available online at http://ntp.niehs.nih.gov/?objectid=4980AA81-E919-4E85-60B789CA36E59FA5

[11] Neeper-Bradley, T. L., Tyl, R. W., Fisher, L. C., Kubena, M. F., Vrbanic, M. A. and Losco, P. E. Determination of a no-observed-effect level for developmental toxicity of ethylene glycol administered by gavage to CD rats and CD-1 mice. Fundam Appl Toxicol 1995; 27: 121-130.

corpora lutea per dam or the number of total nonviable or viable implants per litter. At 1,500 mg/kg-day dose, fetal body weights per litter were significantly reduced. Total skeletal malformations and the incidences of 23 individual skeletal variations (i.e., poorly ossified thoracic and lumbar centra, extra lumbar ribs) were significantly increased. Skeletal malformations included fused or extra ribs and fused thoracic or lumbar arches. At 500 mg/kg-day, the incidence of total malformations, and the incidence of one individual skeletal variation (extra lumbar rib) were significantly increased, but no individual type of malformation was reported to be statistically significant at that dose level. At doses of 150 and 50 mg/kg-day, no significant developmental effect was observed. The doses of 500 and 150 mg/kg-day were identified as the LOEL and NOEL, respectively, for the developmental effects of EG in this study.

MADL CALCULATION

The following calculations were performed in accordance with Section 25803 to derive the oral MADL for EG:

- The NOEL in the study for purposes of assessment was demonstrated to be as follows:

  150 mg/kg-day

- To calculate the NOEL dose as an intake, a 58 kg body weight for a woman is assumed:

  150 mg/kg-day $\times$ 58 kg = 8700 mg/day

- The MADL is derived by dividing the NOEL expressed in mg/day by one thousand (Section 25801(b)(1)):

  $MADL_{oral}$ = 8,700 mg/day ÷ 1000 = **8,700 micrograms/day**

This MADL applies to exposure to EG by the oral route.

PROPOSED REGULATORY AMENDMENT

The proposed change to Section 25805(b) is provided below in underline:

Chemical name	*Level (micrograms per day)*
…	
Ethylene glycol (ingested)	8,700 (oral)
…	

PROBLEM BEING ADDRESSED BY THIS PROPOSED RULEMAKING

Proposition 65 does not provide guidance regarding how to determine whether a warning is required or a discharge is prohibited. OEHHA is the implementing agency for Proposition 65 and has the authority and expertise to examine the scientific literature and calculate a level of exposure, in this case a MADL, that does not require a warning or at which a discharge is not prohibited.

NECESSITY

This proposed regulatory amendment would adopt an oral MADL that conforms with the Proposition 65 implementing regulations and reflects the currently available scientific knowledge about EG. The MADL provides assurance to the regulated community that exposures or discharges at or below it are considered not to pose a significant risk of developmental or reproductive harm. Exposures at or below the MADL are exempt from the warning and discharge requirements of Proposition 65[12].

BENEFITS OF THE PROPOSED REGULATION

See "Benefits of the Proposed Regulation" under ECONOMIC IMPACT ANALYSIS below

TECHNICAL, THEORETICAL, AND/OR EMPIRICAL STUDIES, REPORTS, OR DOCUMENTS

OEHHA reviewed the 2004 NTP-CERHR "Monograph on the Potential Human Reproductive and Developmental Effects of Ethylene Glycol"[13]. OEHHA determined that the most sensitive study deemed to be of sufficient quality is the oral prenatal toxicity study in mice reported by Neeper-Bradley et al. (1995), and

[12] Health and Safety Code sections 25249.9(b) and 25249.10(c)
[13] NTP-CERHR (2004). NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Ethylene Glycol. Research Triangle Park, NC, National Toxicology Program, Center for the Evaluation of Risks to Human Reproduction: NIH Publication No. 04 – 4481. Available online at http://ntp.niehs.nih.gov/?objectid=4980AA81-E919-4E85-60B789CA36E59FA5

that there were no subsequently published studies that were more sensitive. OEHHA used the values from this study as the bases for calculating the oral MADL for EG proposed for adoption into Section 25805(b). A copy of the 2004 NTP-CERHR EG monograph and the study by Neeper-Bradley et al. (1995) will be included in the regulatory file for this action, and are available from OEHHA upon request. OEHHA also relied on the attached Economic Impact Assessment in developing this proposed regulation.

REASONABLE ALTERNATIVES TO THE REGULATION AND THE AGENCY'S REASONS FOR REJECTING THOSE ALTERNATIVES

The MADL provides a "safe harbor" value that aids businesses in determining if they are complying with the law. The alternative to the amendment to Section 25805(b) would be to not adopt a MADL for the chemical. Failure to adopt a MADL would leave the business community without a safe harbor level to assist in complying with Proposition 65. No alternative that is less burdensome yet equally as effective in achieving the purposes of the regulation in a manner that achieves the purposes of the statute has been proposed.

REASONABLE ALTERNATIVES TO THE PROPOSED REGULATORY ACTION THAT WOULD LESSEN ANY ADVERSE IMPACT ON SMALL BUSINESSES

OEHHA is not aware of significant cost impacts that small businesses would incur in reasonable compliance with the proposed action. Use of the proposed MADL by businesses is voluntary and therefore does not impose any costs on small businesses. In addition, Proposition 65 is limited by its terms to businesses with 10 or more employees (Health and Safety Code, section 25249.11(b)) so it has no effect on very small businesses.

EVIDENCE SUPPORTING FINDING OF NO SIGNIFICANT ADVERSE ECONOMIC IMPACT ON BUSINESS

Because the proposed MADL provides a "safe harbor" level for businesses to use when determining compliance with Proposition 65, OEHHA does not anticipate that the regulation will have a significant statewide adverse economic impact directly affecting businesses, including the ability of California businesses to compete with businesses in other states.

EFFORTS TO AVOID UNNECESSARY DUPLICATION OR CONFLICTS WITH FEDERAL REGULATIONS CONTAINED IN THE CODE OF FEDERAL REGULATIONS

Proposition 65 is a California law that has no federal counterpart. There are no federal regulations addressing the same issues and, thus, there is no duplication or conflict with federal regulations.

ECONOMIC IMPACT ANALYSIS
Gov. Code section 11346.3(b)

It is not possible to quantify any monetary values for this proposed regulation given that its use is entirely voluntary and it only provides compliance assistance for businesses subject to the Act.

Impact on the Creation, Elimination, or Expansion of Jobs/Businesses in California: This regulatory proposal will not affect the creation or elimination of jobs within the State of California. Proposition 65 requires businesses with ten or more employees to provide warnings when they expose people to chemicals that are known to cause cancer or developmental or reproductive harm. The law also prohibits the discharge of listed chemicals into sources of drinking water. EG (ingested) is listed under Proposition 65; therefore, businesses and individuals who manufacture, distribute or sell products with EG in the state must provide a warning if their product or activity exposes the public or employees to this chemical.

Impact on the Creation of New Businesses or Elimination of Existing Businesses within the State of California

This regulatory action will not impact the creation of new businesses or the elimination of existing businesses within the State of California. The regulatory proposal does not create additional compliance requirements, but instead provides a “safe harbor” value that aids businesses in determining if they are complying with the law.

Impact on Expansion of Businesses within the State of California

This regulatory action will not impact the expansion of businesses within the State of California. The regulatory proposal does not create additional compliance requirements, but instead provides a “safe harbor” value that aids businesses in determining if they are complying with the law.

Benefits of the Proposed Regulation: The MADL provides a “safe harbor” value that aids businesses in determining if they are complying with the law. Some businesses may not be able to afford the expense of establishing a MADL and therefore may be exposed to litigation for a failure to warn or for a prohibited discharge of the listed chemical. Adopting this regulation will save these

businesses those expenses and may reduce litigation costs. By providing a safe harbor level, this regulatory proposal does not require, but may encourage, businesses to lower the amount of the listed chemical in their product to a level that does not cause a significant exposure, thereby providing a public health benefit to Californians.

Problem being addressed by this proposed rulemaking: Proposition 65 does not provide specific guidance regarding how to determine whether a warning is required or a discharge is prohibited. OEHHA is the implementing agency for Proposition 65 and has the resources and expertise to examine the scientific literature and calculate a level of exposure that does not require a warning or trigger the discharge prohibition.

How the proposed regulation addresses the problem: The proposed regulation would adopt a specific regulatory level for EG (ingested) to provide compliance assistance for businesses that are subject to the requirements of the Act. While OEHHA is not required to adopt such levels, adopting them provides a "safe harbor" for businesses and provides certainty that they are complying with the law without providing a warning if the exposures or discharges that businesses cause are below the established level.

Reasonable alternatives to the proposed regulation: OEHHA determined that the only alternative to the proposed regulation would be to not adopt a MADL for this chemical. This alternative was rejected because it would fail to provide businesses with the certainty that the MADL can provide.

Results: By providing a MADL, this regulatory proposal spares businesses the expense of calculating their own MADL and may also enable them to reduce or avoid litigation costs. In addition, the MADL does not require, but may encourage, businesses to reduce the amount of the listed chemical in their products to a level that does not cause a significant exposure, thereby providing a public health benefit to Californians.