

**FINAL STATEMENT OF REASONS
TITLE 27, CALIFORNIA CODE OF REGULATIONS**

**SECTION 25805, SPECIFIC REGULATORY LEVELS: CHEMICALS CAUSING
REPRODUCTIVE TOXICITY**

MAXIMUM ALLOWABLE DOSE LEVEL: SULFUR DIOXIDE

This is the Final Statement of Reasons for the adoption of a Maximum Allowable Dose Level (MADL) for sulfur dioxide (SO₂), a chemical known to the State of California to cause reproductive toxicity (developmental endpoint) under Proposition 65¹. On July 6, 2012, the Office of Environmental Health Hazard Assessment (OEHHA) issued a Notice of Proposed Rulemaking to adopt a proposed MADL of 220 micrograms per day for SO₂ under Title 27, California Code of Regulations, section 25805(b)². The Initial Statement of Reasons set forth the grounds for the amendment to the regulation. A public comment period was provided from July 6 to August 20, 2012. The Notice stated that a public hearing would be held only on request. No request for a public hearing was received. One written comment was received by OEHHA.

On March 22, 2013, OEHHA issued a Notice of Revision of Proposed Specific Regulatory Level and Augmentation of Record for the Proposed Regulation. The Notice proposed a revised MADL of 10,000 micrograms per day. The augmentation consisted of data submitted to OEHHA in comments on the proposed regulation³. As required by Government Code section 11346.8(c), and Title 1, Section 44 of the California Code of Regulations, OEHHA gave notice of this revision and augmentation. A public comment period was provided from March 22 to May 6, 2013. The Notice stated that a public hearing would be held only on request. No request for a public hearing was received. One written comment was received by OEHHA.

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 Available at http://www.oehha.ca.gov/prop65/law/pdf_zip/082812GMASo2.pdf.

PEER REVIEW

On July 3, 2012, OEHHA provided the notice of proposed rulemaking and the Initial Statement of Reasons for the proposed MADL for SO₂ to the members of the Developmental and Reproductive Toxicant Identification Committee for their review and comment as required by Section 25801(f). No comments were received from any committee members. On March 18, 2013, members of the committee received notice of the augmentation and the revised MADL. No comments were received from any members.

SUMMARY AND RESPONSE TO COMMENTS

Comments on the July 6, 2012 Notice of Proposed Rulemaking

Written comments were received from the Grocery Manufacturers Association. The comments are summarized and responses are provided below.

Comment 1

The first comment stated that there was an error in a statistic presented in the papers published in the scientific literature that provided the lowest observable effect level (LOEL) that formed the basis for the MADL^{4,5}. The comment stated that a rounding error in the statistical analysis resulted in a reduction in fetal weight being incorrectly reported as statistically significant ($p < 0.05$). The commenter subsequently provided the original data records for the study to OEHHA.

Response 1

Reanalysis of the data by OEHHA confirmed that the commenter's statement was correct, and that the change in fetal weight at this exposure level was not statistically significant.

⁴ Murray FJ, Schwetz BA, Crawford AA, Henck JW, Quast JF, Staples RE (1979). Embryotoxicity of inhaled sulfur dioxide and carbon monoxide in mice and rabbits. *Journal of Environmental Science and Health, Part C* 13(3):233-50.

⁵ Murray FJ, Schwetz BA, Crawford AA, Henck JW, Staples RE (1977). Teratogenic potential of sulfur dioxide and carbon monoxide in mice and rabbits. *Doe Symp Ser* 47: 469-478.

The study in question, by Murray et al., reported a developmental LOEL of 23.9 parts per million (ppm), based on the measured time-weighted SO₂ concentration. OEHHA now considers this level as the no observable effect level (NOEL) for the study by Murray et al.

As noted in the Initial Statement of Reasons for the proposed regulation, another inhalation study by Singh (1989)⁶ demonstrated reduced birth weight after prenatal exposure to SO₂. This effect was statistically significant for mice exposed to SO₂ at 65 ppm for 24 hours/day. At 32 ppm, a reduction in birth weight was not statistically significant. Thus, the study by Singh (1989) provided a NOEL of 32 ppm for mice exposed for 24 hours/day and, for purposes of Proposition 65, is now the most sensitive study deemed to be of sufficient quality (Section 25803(a)(4)). Consequently, OEHHA revised the proposed MADL, and gave public notice of this change in the March 22, 2013 Notice of Revision of Proposed Specific Regulatory Level and Augmentation of Record for the Proposed Regulation. The revised MADL calculation, which was also provided in the March 22, 2013 Notice, is presented below.

The following calculations were performed in accordance with Section 25803 to derive the MADL for SO₂ using data and exposure parameters from Singh (1989):

- Conversion of air concentration in ppm to milligrams per cubic meter (mg/m³) using a conversion factor of 2.64 mg/m³ per ppm⁷
(32 ppm × 2.64 [mg/m³ per ppm]) = 84.48 mg/m³
- Calculation of the NOEL dose for a 30 gram mouse (0.030 kilograms [kg]) with an inhalation rate of 0.063 m³/day^{8,9}
(84.48 mg/m³ × 0.063 m³/day) ÷ (0.030 kg) = 177.41 mg/kg/day

⁶ Singh J (1989). Neonatal development altered by maternal sulfur dioxide exposure. *Neurotoxicology* 10(3): 523-7.

⁷ Office of Environmental Health Hazard Assessment. Evidence on the Developmental and Reproductive Toxicity of Sulfur Dioxide, 2011. Available at http://www.oehha.ca.gov/prop65/hazard_ident/pdf_zip/So2HID022511.pdf.

⁸ Bond JA, Dahl AR, Henderson RF, Dutcher JS, Mauderly JL, Birnbaum LS (1986). Species differences in the disposition of inhaled butadiene. *Toxicol Appl Pharmacol* 84: 617-627.

⁹ Depledge MH (1985). Respiration and lung function in the mouse, *Mus musculus* (with a note on mass exponents and respiratory variables). *Respir Physiol* 60: 83-94.

- Calculation of the NOEL dose for a 58 kg woman
 $177.41 \text{ mg/kg/day} \times 58 \text{ kg} = 10289.78 \text{ mg/day}$,
or 10,000 mg/day after rounding
- 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:

$$\text{MADL} = 10,000 \text{ mg/day} \div 1000 = \mathbf{10,000 \text{ micrograms/day}}$$

This MADL is based on inhalation data. All of the studies that formed the basis for listing SO₂ were of exposure to SO₂ as a gas. There are currently no available studies on exposure solely to SO₂ by the oral route. However, based on review of relevant information¹⁰, OEHHA has concluded that exposure to SO₂ by the oral route is expected to pose no more risk, and may pose less risk, than exposure to the equivalent amount by the inhalation route.

This MADL applies only to the specific compound SO₂, and does not apply to sulfites, bisulfites and metabisulfites. These chemicals are not currently listed under Proposition 65 so exposure to them, at any level, is not subject to the warning and discharge provisions of Proposition 65.

Comment 2

The commenter suggested that use of a benchmark dose approach to establish a MADL for SO₂ was more appropriate than using a lowest observable effect level and supported a MADL of 2200 micrograms per day or greater based on the data from Murray et al., rather than the value of 220 micrograms per day proposed by OEHHA.

Response 2

The Murray et al. study no longer serves as the basis of the MADL. The MADL derived from the study of Singh et al. is 10,000 micrograms per day. As noted

¹⁰ Office of Environmental Health Hazard Assessment. Evidence on the Developmental and Reproductive Toxicity of Sulfur Dioxide, 2011. Available at http://www.oehha.ca.gov/prop65/hazard_ident/pdf_zip/So2HID022511.pdf.

below (Response 5), the commenter subsequently expressed support for this revised MADL.

Comment 3

The commenter stated that OEHHA should conclude that two additional chemical species, Sulfurous Acid (H_2SO_3) and Hydrated SO_2 ($\text{SO}_2 \cdot \text{H}_2\text{O}$), "should be excluded from being subject to Proposition 65 warning and discharge requirements, since neither of these chemical species existing in sulfite-containing foods is a listed substance".

Response 3

This pertains to the listing of the chemical and not to the MADL, and is therefore not relevant to the proposed regulation. As a point of clarification these two chemicals are not identified as causing reproductive toxicity under Proposition 65. See also the response to comment 1.

Comment 4

The comments provide an extensive discussion of food chemistry and sulfur dioxide, and conclude that sulfur dioxide does not exist in foods and beverages and is thus not subject to Proposition 65 requirements.

Response 4

This discussion and conclusion does not pertain to establishment of the MADL, but rather to its applicability to specific products. Thus, the comment is not relevant to the proposed regulation.

Comments on the March 22, 2013 Notice of Revision of Proposed Specific Regulatory Level and Augmentation of Record for the Proposed Regulation

Written comments were received from the Grocery Manufacturers Association. The comments are summarized and responses are provided below.

Comment 5

The commenter summarized the basis for OEHHA's proposed revision of the MADL, concluded that the revision is an appropriate regulatory action based on science and stated that the Grocery Manufacturers Association supports OEHHA's decision to increase the proposed MADL for sulfur dioxide from 220 micrograms/day to 10,000 micrograms/day.

Response 5

OEHHA acknowledges the comment.

ALTERNATIVES DETERMINATION

In accordance with Government Code section 11346.9(a)(4), OEHHA has, throughout the adoption process for this regulation, considered available alternatives to determine whether any alternative would be more cost effective in carrying out the purpose for which the regulation was proposed, or would be as cost effective and less burdensome to affected private persons than the proposed action.

In considering these alternatives, OEHHA considered the proposed alternative offered in the comments on the original notice, made changes to the initial proposed MADL and provided an additional 45-day comment period. OEHHA has determined that no other reasonable alternative considered by OEHHA or that has otherwise been identified or brought to the attention of OEHHA would either be more effective in carrying out the purpose for which the action is proposed, or would be as effective and less burdensome to affected private persons, or would be more cost-effective to affected private persons and equally effective in implementing the statutory policy or other provision of law than the proposed regulation.

For chemicals known to the state to cause reproductive toxicity, an exemption from the warning requirement is provided by the Act when a person in the course of doing business is able to demonstrate that an exposure for which the person is responsible will have no observable reproductive effect, assuming exposure at 1,000 times the level in question (Health and Safety Code sections 25249.9,

25249.10 and 25249.11). The maximum dose level at which a chemical has no observable reproductive effect is referred to as the No Observable Effect Level (NOEL). The Act also provides an exemption from the prohibition against discharging a listed chemical into sources of drinking water if the amount discharged does not constitute a "significant amount," as defined, and the discharge is in conformity with all other laws and regulatory requirements (Health and Safety Code sections 25249.9 and 25249.11). Thus, these exemptions apply when the exposure or discharge in question is at a level that does not exceed the NOEL, divided by 1,000.

Regulations previously adopted by OEHHA provide guidance for determining whether an exposure to, or a discharge of, a chemical known to cause reproductive toxicity meets the statutory exemption (Sections 25801-25821). These regulations provide three ways by which a person in the course of doing business may make such a determination: (1) by conducting a risk assessment in accordance with the principles described in Section 25803 to derive a NOEL, and dividing the NOEL by 1,000; or (2) by application of the specific regulatory level adopted for the chemical in Section 25805; or (3) in the absence of such a level, by using a risk assessment conducted by a state or federal agency, provided that such assessment substantially complies with Section 25803(a). The specific regulatory levels in Section 25805 represent one one-thousandth of the NOEL.

LOCAL MANDATE DETERMINATION

OEHHA has determined this regulatory action will not pose a mandate on local agencies or school districts nor does it require reimbursement by the State pursuant to Part 7 (commencing with Section 17500) of Division 4 of the Government Code. OEHHA has also determined that no nondiscretionary costs or savings to local agencies or school districts will result from this regulatory action. Proposition 65 provides an express exemption from the warning requirement and discharge prohibition for all state and local agencies. Thus, these regulations do not impose any mandate on local agencies or school districts.