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 FOR METHAM SODIUM

PURPOSE AND BACKGROUND OF PROPOSED AMENDMENT

PURPOSE

This proposed regulatory amendment is to adopt a Maximum Allowable Dose Level (MADL) for metham sodium[1] under Proposition 65[2] in Title 27, California Code of Regulations, section 25805(b)[3]. The proposed MADL was derived using scientific methods outlined in Section 25803. The proposed MADL for metham sodium is 290 micrograms per day.

PROPOSITION 65 AND LISTING OF METHAM SODIUM

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[4]. OEHHA has the authority to promulgate and amend regulations to further the purposes of the Act[5].

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[6].

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[1] Synonyms include metam sodium and sodium N-methyldithiocarbamate.
[2] 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".
[3] All subsequent citations are to Title 27, California Code of Regulations, unless otherwise noted.
[4] Health and Safety Code, section 25249.12 and Cal. Code of Regs., Title 27, section 25102(o).
[5] Health and Safety Code, section 25249.12(a).
[6] Health and Safety Code, section 25249.9(b) and 25249.10(c).

On May 15, 1998, metham sodium was added to the Proposition 65 list as known to the state to cause reproductive toxicity (developmental endpoint). The listing is based on formal identification of metham sodium by the US Environmental Protection Agency (US EPA) as causing developmental toxicity. The US EPA is one of several institutions designated as a body recognized as authoritative for the identification of chemicals as causing reproductive toxicity under Proposition 65[7].

STUDY SELECTION

Relevant studies that provide information on the developmental toxicity of metham sodium were identified by US EPA[8,9] in the materials that formed the basis for listing metham sodium as causing reproductive toxicity[10]. OEHHA also conducted a literature search to identify relevant studies published subsequent to the studies used by US EPA. All of these studies were reviewed as the possible basis for establishing a MADL for metham sodium[11,12]. The most sensitive studies deemed to be of sufficient quality were selected to provide a basis for the MADL[13].

[7] Section 25306(l).

[8] Hellwig, J. and B. Hildebrand 1987. Report on the study on the prenatal toxicity of metam-sodium in rats after oral administration (gavage). BASF Aktiengesellschaft, D-6700 Ludwigshafen, West Germany, Reg. Doc. No. (BASF) 87/0128. A summary of the study is contained in the US Environmental Protection Agency (US EPA) Office of Pesticides and Toxic Substances Memorandum of August 16, 1991 from YM Ioannou to S Lewis, Subject: Metam Sodium – Review of Two Developmental Toxicity Studies in Rats and Rabbits Submitted by the Registrant.

[9] Hellwig, J. 1987. Report on the study of the prenatal toxicity of metam-sodium (aqueous solution) in rabbits after oral administration (gavage). Final Report Dated July 15, 1987. BASF Aktiengesellschaft, D6703 Limburgerhof, Federal Republic of Germany, Reg. Doc. (BASF) 87/0255. A summary of the study is contained in the US EPA Office of Pesticides and Toxic Substances Memorandum of August 16, 1991 from YM Ioannou to S Lewis, Subject: Metam Sodium – Review of Two Developmental Toxicity Studies in Rats and Rabbits Submitted by the Registrant.

[10] US Environmental Protection Agency (US EPA, 1994a) Proposed Rule: Addition of Certain Chemicals; Toxic Chemical Release Reporting; Community Right to Know. Federal Register (59 FR 1788).
US Environmental Protection Agency (US EPA, 1994b) Final Rule: Addition of Certain Chemicals; Toxic Chemical Release Reporting; Community Right to Know. Federal Register (59(229) FR 61432).

[11] Tinston, D.J. 1993. Metam sodium developmental toxicity study in the rat. Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Report No. CTL/P/4052. A summary of the study is contained in the US Environmental Protection Agency (US EPA) Office of Prevention, Pesticides and Toxic Substances, Memorandum from TF McMahon to L Deluise, Subject: Metam Sodium: Review of a Rat Developmental Toxicity Study Submitted by the Registrant under FIFRA Section 6(a)(2) and Review of a Rabbit Developmental Toxicity Study Submitted by the Registrant, December 8, 1993. [https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/039003/039003-052.pdf]

[12] Hodge, M.C.E. 1993. Metam Sodium: Developmental Toxicity Study in the Rabbit. Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Report No. CTL/P/4035, Study No. RB0623, 9/6/93. A summary of the study is contained in the US EPA, Office of Prevention, Pesticides and Toxic Substances, Memorandum from TF McMahon to L Deluise, Subject: Metam Sodium: Review of a Rat Developmental Toxicity Study Submitted by the Registrant under FIFRA Section 6(a)(2) and Review of a Rabbit Developmental Toxicity Study Submitted by the Registrant, December 8, 1993. [https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/039003/039003-052.pdf].

[13] Section 25803(a)(5).

Human Studies

No human data were identified in the literature search by OEHHA.

Studies in Laboratory Animals

Four developmental toxicity studies, two in rabbits and two in rats, were examined; all involved the oral route of exposure. Developmental toxicity studies by the inhalation or dermal routes of exposure were not identified.

Ingestion of chemicals following inhalation exposure occurs in humans, as illustrated by the abundance of reports in the literature of GI effects in humans following inhalation exposures to a variety of chemicals, including metal dusts and aerosols[14,15,16].

There is some concern that inhalation exposure may result in more efficient absorption and, due to bypass of first-pass detoxification processes in the liver, greater toxicity than oral exposure (EPA, 2007[17]). However, because no developmental toxicity studies of metham sodium using the inhalation route of exposure were identified, OEHHA relied on oral developmental toxicity studies of metham sodium for estimating effects that may occur via either oral or inhalation exposures. This is consistent with the approach taken by US EPA (2007) and the California Department of Pesticide Regulation (DPR) (DPR, 2004[18]).

Brief summaries of major findings on dose-response from the four developmental toxicity studies are presented in Table 1. The studies are available to the public in their entirety at DPR headquarters, 1001 I Street, Sacramento, California 95812[19].

All the studies identified were reviewed and considered by OEHHA for the establishment of the MADL. The doses reported in Table 1 reflect the administered dose of metham sodium based on the purity and stability of the compound, and in some

[14] ATSDR 2012. Toxicological profile for Chromium. US Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.
[15] Cooco PC, Ward MH, Buiatti E 1996. Occupational risk factors for gastric cancer: an overview. Epidemiologic Reviews, 18:2.
[16] Hansen et al. 2008. Risk of Adverse Gastrointestinal Events from Inhaled Corticosteroids. Pharmacotherapy, 28(11): 1325-1334.
[17] US EPA 2007, Metam Sodium: Phase 5 Revised Chapter of the Reregistration Eligibility Decision Document
[18] California Department of Pesticide Regulation (DPR) 2004 Metam Sodium (Sodium N-Methyldithiocarbamate) Risk Characterization Document, Medical Toxicology Branch, DPR, California Environmental Protection Agency, July 21, 2004 [http://www.cdpr.ca.gov/docs/risk/rcd/metam.pdf].
[19] Information on requesting access to these studies from DPR is available at http://www.cdpr.ca.gov/docs/registration/PRbrochure.pdf.

cases the percentage of metham sodium present as the active ingredient in the specific formulation administered.

Table 1. Metham Sodium Developmental Toxicity: Dose-Response Findings

STUDY (SPECIES)	EXPOSURE	FINDINGS	NOEL/LOEL
Hellwig & Hildebrand, 1987[20] Developmental Study (Wistar Rat)	0, 10, 40, or 120 mg/kg-day aqueous solution, administered by gavage on gestation days 6-15 (Active ingredient reported as 42.2%, resulting in doses of metham sodium of 4.2, 16.9 or 50.6 mg/kg-day)	Early resorption loss and post-implantation loss in the low and high dose group. Reduced fetal weights at the high dose. 2 fetuses had a neural tube closure effect (meningocele) at the high dose, an effect not observed in the historical control. Reduced food consumption, maternal weight and weight gain at mid dose.	Neither a NOEL nor a LOEL for developmental toxicity could be reliably identified in this study because of uncertainty in the dose response relationship due to lack of increased post implantation loss in the mid dose group.
Tinston, 1993[21] Developmental Study (Alpk:ApfSD, a Wistar-derived Rat)	0, 5, 20 or 60 mg/kg-day, administered in aqueous solution daily by gavage on gestation days 7-16	Decreased fetal weights and skeletal developmental delays at 20 mg/kg-day and an increase in meningocele, anophthalmia, hydrocephaly at 60 mg/kg-day; increase in clinical signs and reduced food consumption, maternal weight and weight gain at 20 mg/kg-day. Maternal toxicity evident at 20 and 60 mg/kg-day in an increased incidence of salivation, vaginal bleeding, and oral staining and at 60 mg/kg-day in an increased incidence of piloerection, eye discharge, subdued behavior, and urinary incontinence.	Developmental NOEL = 5 mg/kg-day Maternal NOEL = 5 mg/kg-day

[20] Hellwig and Hildebrand, 1987, full citation provided in footnote 8.
[21] Tinston, 1993, full citation provided in footnote 11.

Table 2. Metham Sodium Developmental Toxicity: Dose-Response Findings (continued)

STUDY (SPECIES)	EXPOSURE	FINDINGS	NOEL/LOEL
Hellwig, 1987[22] Developmental Study (Himalayan Rabbit)	0, 10, 30 or 100 mg/kg-day aqueous solution administered daily by gavage on gestation days 6-18 (Active ingredient reported to be 42.2%, resulting in estimated administered doses of metham sodium of 4.2, 12.7 or 42.2 mg/kg-day)	Increased early resorptions significantly increased in all dose groups on a fetal basis but on a litter basis only significant at the high dose. At the low and mid doses they were marginally significant (p=0.06 and 0.07 respectively). Dead implantations were significantly increased in the mid and high dose groups on a fetal basis and at the high dose group on a litter basis. Two fetuses with a neural tube closure defect (meningocele + spina bifida) at 42.2 mg/kg-day. At 42.2 mg/kg-day slightly decreased food consumption in dams during the treatment period (~93% of controls), mean placental weight increased by 14%.	Neither a NOEL nor a LOEL for developmental toxicity could be reliably identified in this study because of uncertainty in the dose response relationship.
Hodge, 1993[23] Developmental Study (NZW Rabbit)	0, 5, 20, or 60 mg/kg-day by gavage (adjusted for active ingredient 43.14% w/w in liquid form)	Decreased maternal food consumption with significantly decreased body weights at ≥ 20 mg/kg-day and increased post-implantation loss, early intra-uterine deaths and total litter resorptions at 60 mg/kg-day. Increase in skeletal variations at ≥ 20 mg/kg-day and an increased incidence of cleft palate and meningocele in fetuses along with decreased mean live litter size, and mean litter and fetal weight at 60 mg/kg-day.	Developmental NOEL = 5 mg/kg-day Maternal NOEL = 5 mg/kg-day

[22] Hellwig, 1987, full citation provided in footnote 9.
[23] Hodge, 1993, full citation provided in footnote 12.

Comparison of the studies in Table 1 identifies 5 mg/kg-day in rats (based on the decrease in fetal weights and the appearance of skeletal developmental delays at 20 mg/kg-day that were statistically significant on a litter basis in the study by Tinston (1993)) and rabbits (based on an increase in skeletal variants at 20 mg/kg-day in the study by Hodge (1993)) as the highest reliable NOEL for developmental toxicity of metham sodium that does not exceed a reliable LOEL.

Reliable developmental NOELs and LOELs could not be determined in the rat study by Hellwig and Hildebrand (1987)[24] and the rabbit study by Hellwig (1987)[25]. There is uncertainty about the dose response relationship in those studies (see Table 1); also US EPA noted that the investigators' statement that the content of metham sodium was 42.2% could not be substantiated[26].

The studies reported by Tinston (1993)[27] and Hodge (1993)[28] provide an accurate NOEL of 5.0 mg/kg-day administered by gavage. OEHHA has reviewed the Tinston (1993) and the Hodge (1993) studies and deemed them to be of sufficient quality. In its discussion of the Hodge 1993 study, US EPA[29] stated, "No specific deficiencies were noted that affected the outcome of this study." US EPA[30] noted that the Tinston 1993 study satisfied the test guideline requirements for a developmental study in rats. Both studies provide the basis for calculation of the MADL.

STUDY BASIS FOR THE MADL CALCULATION

The study by Tinston (1993)[31] provides a developmental NOEL of 5 mg/kg-day in Wistar rats. Developmental effects at the LOEL of 20 mg/kg in this study included decrease of fetal body weights and skeletal developmental delays. The maternal effects included clinical signs (salivation, vaginal bleeding, and oral staining), and lowered body weight gain and food consumption. The same NOEL of 5 mg/kg-day is also identified in the

[24] Hellwig, J. and B. Hildebrand 1987, full citation provided in footnote 8.
[25] Hellwig, J. 1987, full citation provided in footnote 9.
[26] Metam Sodium - Review of Two Developmental Toxicity studies in Rats and Rabbits Submitted by the Registrant. US EPA, 1991. Available at https://www3.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-039003_16-Aug-91_029.pdf
[27] Tinston 1993, full citation provided in footnote 11.
[28] Hodge 1993, full citation provided in footnote 12.
[29] Metam Sodium: Review of a Rat Developmental Toxicity Study Submitted by the Registrant under FIFRA Section 6(a)(2) and Review of a Rabbit Developmental Toxicity Study Submitted by the Registrant. US EPA, 1993. Available at https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/039003/039003-052.pdf.
[30] *Ibid*.
[31] Tinston, D.J. 1993, full citation provided in footnote 11.

developmental toxicity study in NZW rabbits (Hodge, 1993)[32] in which an increase in skeletal variants was noted at the LOEL of 20 mg/kg-day.

MADL CALCULATION

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

- Calculation of NOEL in mg/day for a 58 kg pregnant woman:

  5 mg/kg-day × 58 kg = 290 mg/day

- Calculation of the maximum allowable dose level for metham sodium by dividing the NOEL expressed in mg/day by one thousand (Section 25801(b)(1)):

  290 mg/day ÷ 1000 = 290 micrograms (µg)/day

MADL = **290 micrograms/day**

PROPOSED REGULATORY AMENDMENT

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

Chemical name	*Level (micrograms per day)*
Metham Sodium	290

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.

[32] Hodge, M.C.E. 1993, full citation provided in footnote 12.

NECESSITY

This proposed regulatory amendment would adopt a MADL that conforms with the Proposition 65 implementing regulations and reflects the currently available scientific knowledge about metham sodium. A MADL provides assurance to the regulated community that exposures or discharges at or below it is 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[33].

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

In determining the evidence and standards that formed the basis for listing metham sodium under Proposition 65, OEHHA reviewed the US EPA documents and additional literature. These documents included numerous studies of the effects of metham sodium, including *in vivo* studies in experimental animals that provide additional evidence of developmental toxicity.

OEHHA relied on two studies: Tinston, D.J. 1993. "Metam sodium developmental toxicity study in the rat". Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Report No. CTL/P/4052 and Hodge, M.C.E. 1993. "Metam Sodium: Developmental Toxicity Study in the Rabbit." Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Report No. CTL/P/4035, Study No. RB0623, 9/6/93. Tinston (1993) provides a NOEL of 5 mg/kg-day in rats, based on the decrease in fetal weights and the appearance of skeletal developmental delays at 20 mg/kg-day which were statistically significant on a litter basis. Hodge (1993) provides the same NOEL of 5 mg/kg-day in rabbits, based on an increase in skeletal variants at 20 mg/kg-day.

Copies of the publicly available documents and studies reviewed in development of the MADL will be included in the regulatory file for this action, and are available from OEHHA upon request. Copies of the studies identified as summarized by US EPA, and available at DPR can be accessed in their entirety at 1001 I Street, Sacramento CA

[33] Health and Safety Code sections 25249.9(b) and 25249.10(c).

95812 by members of the public upon completion of the affirmation required under Government Code section 6254.2.
OEHHA also relied on the attached Economic Impact Analysis 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 promulgate a MADL for the chemical. Failure to promulgate a MADL would leave the business community without a safe harbor level to assist businesses in determining compliance 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 because 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. Metham sodium is listed under Proposition 65; therefore, businesses and individuals who manufacture, distribute or sell products with metham sodium 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 “safe harbor” values that aid businesses in determining if they are complying with the law with respect to metham sodium.

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 “safe harbor” values that aid 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.

How the proposed regulation addresses the problem: The proposed regulation would adopt specific regulatory levels for a listed chemical 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 if the exposures or discharges they 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 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.