PRE-REGULATORY DRAFT – FOR DISCUSSION PURPOSES ONLY
SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT OF 1986
PROPOSITION 65

POSSIBLE AMENDMENTS TO SECTION 25805 SPECIFIC REGULATORY LEVELS: CHEMICALS CAUSING REPRODUCTIVE TOXICITY

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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On July 3, 2015, the Office of Environmental Health Hazard Assessment (OEHHA) received a "Petition by Center for Environmental Health for Administrative Rulemaking to repeal or amend Proposition 65 regulations pertaining to the Maximum Allowable Dose Level (MADL) for lead," which was filed pursuant to Government Code section 11340.6.

Following review of the Petition and related materials, OEHHA decided to set a hearing on the Petition to allow all interested stakeholders to provide input concerning the request for repeal or amendment of the existing MADL for lead set out in Title 27, Cal. Code of Regs., section 25805(b). *As a starting point for discussion*, OEHHA has developed a possible set of amendments to the existing regulations which are being published for public comment. This document provides a general discussion of those possible amendments.

The regulatory amendments would do three things.

- They would clarify OEHHA's intent that all the existing MADLs for listed chemicals are set as the highest exposures that can occur in a single day. These values, when multiplied by 1000, are deemed to cause no observable effect, and hence are exempt from the Proposition 65 warning requirements pursuant to Health and Safety Code section 25249.10.
- They would create a new subsection 25805(b)(2) that would establish MADLs for certain chemicals for intermittent exposures that, when multiplied by 1000, are deemed to pose no observable effect.
- They would repeal and replace the existing MADL for lead with MADLs in the new subsection (25805(b)(2)). The levels are expressed as maximum levels of exposure to lead that could occur for different exposure frequencies. For

example, one MADL value is for an exposure that occurs every day and a different value when an exposure occurs once every 7 days.

GENERAL BACKGROUND

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[1]. OEHHA has the authority to amend and adopt regulations to further the purposes of the Act[2].

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 does not apply when exposures are sufficiently low, as specified in the Act[3]. Specifically:

> "An exposure for which the person responsible can show … that the exposure will have no observable effect assuming exposure at one thousand (1000) times the level in question for substances known to the state to cause reproductive toxicity, based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of such chemical pursuant to subdivision (a) of Section 25249.8."

PROPOSITION 65 LISTING OF LEAD AS KNOWN TO CAUSE REPRODUCTIVE TOXICITY

Lead was added to the Proposition 65 list on February 27, 1987, as known to the state to cause reproductive toxicity, pursuant to Labor Code Section 6382(d), which is incorporated by reference in Health and Safety Code Section 25249.8(a). The listing included all three categories of reproductive endpoints: male reproductive toxicity, female reproductive toxicity and developmental toxicity.

On November 22, 2013, OEHHA changed the basis of the listing to the "formally required to be labeled or identified" listing mechanism. This was done because of changes to the federal regulations that affected the basis for the original listing of

[1] Health and Safety Code section 25249.12 and Cal. Code of Regs., Title 27, section 25102(o)
[2] Health and Safety Code, section 25249.12(a).
[3] Health and Safety Code, section 25249.9 (b) and 25249.10(c)

lead, as described by OEHHA in public notices on the change in the basis for listing[4] and responses to comments on the action.[5] Lead is required by federal Occupational Safety and Health Administration (OSHA) regulations to be identified or labeled to communicate a risk of reproductive toxicity[6].

The current listing of lead is based on three separate provisions of OSHA regulations, described by OEHHA in the notice of intent to change the basis in listing materials[7]. One requires warning of reproductive effects in areas where the Permissible Exposure Limit (PEL) established by OSHA is exceeded. A second requires that warnings be placed on bags of protective clothing or equipment contaminated with lead[8]. The third is the OSHA requirement that workers exposed to any level of lead be provided the following information, contained in "Appendix A to §1910.1025-Substance Data Sheet for Occupational Exposure to Lead":[9]

> "(2) Long-term (chronic) overexposure. Chronic overexposure to lead may result in severe damage to your blood-forming, nervous, urinary and reproductive systems…
> "Chronic overexposure to lead impairs the reproductive systems of both men and women. Overexposure to lead may result in decreased sex drive, impotence and sterility in men. Lead can alter the structure of sperm cells raising the risk of birth defects. There is evidence of miscarriage and stillbirth in women whose husbands were exposed to lead or who were exposed to lead themselves. Lead exposure also may result in decreased fertility, and abnormal menstrual cycles in women. The course of pregnancy may be adversely affected by exposure to lead since lead crosses the placental barrier and poses risks to developing fetuses. Children born of parents either one of whom were exposed to excess lead levels are more likely to have birth defects, mental retardation, behavioral disorders or die during the first year of childhood."

PROPOSITION 65 MAXIMUM ALLOWABLE DOSE LEVELS

The MADLs adopted by OEHHA provide a "safe harbor" in that any exposure that does not exceed the adopted value is deemed not to require a warning and any discharge

[4] California Regulatory Notice Register (Register 2013, No. 38-Z, pp 1471-1474) September 20, 2013
[5] OEHHA, Response to Comments Pertaining to the Notice of Intent to Change the Basis for Listing for 1,2-Dibromo-3-Chloropropane (DBCP), Ethylene Oxide and Lead to the Formally Required Listing Mechanism under Proposition 65, November 2013
[6] Title 29, Code of Federal Regulations Part 1910, Subpart Z, section 1910.1025
[7] California Regulatory Notice Register (Register 2013, No. 38-Z, pp 1471-1474) September 20, 2013
[8] 1910.1025(g)(2)(vii)(A)
[9] Appendix A to §1910.1025, IIB(2)

that does not exceed the adopted value is not subject to the discharge prohibition. Thus, a person knowingly and intentionally causing an exposure in the course of doing business that conforms to this limit has certainty that no warning is required. In cases where exposure to a chemical exceeds the MADL, that protection no longer applies. In such a case, the person causing the exposure must either provide a warning or be prepared to demonstrate that there will be no observable effect assuming exposure at one thousand (1,000) times the level of exposure being caused, as required by the Act. All existing MADLs developed by OEHHA were derived to be the maximum level of exposure that could occur on any single day, whether the exposure occurs on a daily basis or an intermittent basis.

POSSIBLE MADLS FOR LEAD

The MADL for lead was developed in 1989 by the California Health and Welfare Agency, then the designated lead agency for the implementation of Proposition 65. The lead MADL was established at 0.5 microgram per day (µg/day). Since the adoption of this MADL, numerous studies have been conducted of the reproductive toxicity of lead. A major review of those studies was recently released by the US Environmental Protection Agency (US EPA)[10]. In addition, OEHHA in 2013[11] published a physiologically based pharmacokinetic model that can be used to calculate levels of lead intake that result in a given concentration of lead in human blood. Many studies evaluating the health effects of lead use blood lead as a measure of lead exposure.

Level of Lead Exposure with No Observable Effect

The US EPA released the Integrated Science Assessment for Lead in June 2013 for its National Ambient Air Quality Standards (NAAQS) program. In that report, US EPA reviewed the extensive epidemiological and toxicological literature on the health effects of lead and made causal determinations between exposure to lead and health effects. In developing the potential new MADLs for lead, OEHHA used this report as a source of recent information on the dose-response relationships for lead, focusing on reproductive endpoints identified by OSHA in its warning language.

US EPA has long recognized the reproductive toxicity of lead at high exposure levels. In its 1986 NAAQS review[12], the section “The Effects of Lead on Reproduction and

[10] US Environmental Protection Agency, Integrated Science Assessment for Lead, US EPA Office of Research and Development, National Center for Environmental Assessment, EPA/600/R010/075F

[11] Office of Environmental Health Hazard Assessment (OEHHA), Estimating Workplace Air and Worker Blood Lead Concentration using an Updated Physiologically-based Pharmacokinetic (PBPK) Model, California Environmental Protection Agency, OEHHA , Air, Community, Environmental Research Branch, October 2013.

[12] US EPA, Air Quality Criteria for Lead, Volume IV of IV, Environmental Criteria and Assessment Office, Office of

Development" began with a historical overview of the effects of high-dose lead on these endpoints. US EPA's 2006 NAAQS update[13] began its review of reproductive toxicity with a summary of the 1986 findings, noting:

> "Lead has been implicated as a risk factor for reproductive outcomes for over a century (Rom, 1976; Oliver, 1911). As early as 1860, increased rates of stillbirths and spontaneous abortions were found in women with occupational Pb exposure (usually in the ceramics industry) and in women with husbands employed in the Pb industry, compared to unexposed women (Rom, 1976). Other early investigations found increased rates of physically and mentally "retarded" offspring among these same groups. In 1910, these findings resulted in the first Pb-related occupational regulation; the British Committee on Occupational Health recommended that women not be employed in the Pb industry (Oliver, 1911). These observations, however, were based on exposure levels far above those considered acceptable today, and current research now focuses on substantially lower exposure levels."

US EPA's 2013 review also focused on epidemiological and animal evidence below levels causing frank symptoms of lead poisoning, generally blood lead levels in humans below 40 µg/dL. The 2013 review found a causal relationship between male reproductive function and exposure to lead but did not find a causal association for female reproductive function. The review noted that the epidemiological evidence for developmental toxicity from in utero exposure is inconsistent and that findings from experimental animal studies are mixed. While US EPA clearly recognized that postnatal exposure to lead affects the neurodevelopment of children, this is not an endpoint covered by Proposition 65, and so could not be used as the basis of the MADL determination. Therefore, OEHHA used evidence for adverse effects on male reproductive function to calculate the possible MADLs.

The use of animal studies is problematic in developing an updated MADL for lead. OEHHA determined that the most sensitive animal study of sufficient quality for male effects was a study in cynomolgus macaques (Foster et al. 1998[14] Singh et al. 1993[15]). Ultrastructural and histological damage resulted in the testes and seminiferous tubules in animals exposed to 1.5 milligrams of lead per kilogram of body weight per day (mg/kg-d) of lead acetate, equivalent to daily doses of 0.955 mg/kg lead. A no observed effect level (NOEL) was not reported, as this was the only dose used. Using the default

Research and Development, EPA 600/8-83/028dF, June 1986, page 12-192.

[13] US EPA, Air Quality Criteria for Lead, Volume I of II, National Center for Environmental Assessment-RTP Division, Office of Research and Development, EPA 600/R-05/144aF, October 2006, page 6-155

[14] Foster WG, Singh A, McMahon A, Rice DC (1998). Chronic lead exposure effects in the cynomolgus monkey (Macaca fascicularis) testis. Ultrastruct Pathol. 22(1):63-71

[15] Singh A, Cullen C, Dykeman A, Rice D, Foster W (1993). Chronic lead exposure induces ultrastructural alterations in the monkey testis.J Submicrosc Cytol Pathol. 25(4):479-86.

approach to derivation of safe harbors in section 25803, the lowest observed effect level was divided by 10 to obtain a surrogate NOEL (section 25803(a)(8)). This was multiplied by the male body weight of 70 kg (section 25803(b)). Dividing this by the 1000-fold factor (section 25803(a)) results in the value of 6.7 µg/day as a possible MADL. However, because the half-life of lead is shorter in macaques than in humans, humans exposure to 1000 times this value would result in male reproductive effects, because daily exposure to 6700 µg of lead would result in blood levels exceeding 60 µg/dL in humans[16]. US EPA stated in its 2013 review that consistent associations in studies of occupational exposures are observed for male reproductive effects in humans at blood lead levels of 25 µg/dL and greater[17]. This statement updated US EPA's 2006 conclusion that effects on male reproductive function appear at blood lead levels greater than 45 µg/dL. Thus the value of 6.7 µg/day cannot be selected as a MADL. Calculating a MADL from human evidence is thus necessary.

US EPA emphasizes the "consistent evidence from studies of occupational cohorts with high [lead] levels" in identifying the blood lead levels of 25 µg/dL and above as associated with male reproductive effects. However, while lead clearly affects male reproductive function in humans and animals, there is uncertainty regarding the no observed effect level. US EPA notes that "results from occupational cohorts may have been confounded by other workplace exposures, which were not adjusted for in the epidemiological studies." US EPA also notes, "There is uncertainty related to exposure patterns resulting in likely higher past [lead] exposures." (p 4-711 [Chapter 4, page 711])

Of the human studies, US EPA found the strongest evidence for adverse effects on sperm and semen. The epidemiological evidence comes primarily from studies of workers and studies from fertility clinics that characterized the reproductive effects of lead at different blood lead levels. Studies of men at fertility clinics may suffer from selection bias and US EPA noted that these studies are not generalizable (US EPA, 2013, p 4-668). In considering the worker studies as the basis for identifying a blood level with no observable effect, it is important to address the potential for confounding, which was not described in many studies. However, there are three occupational studies in the literature reporting adverse effects of lead on sperm that adjusted for factors that affect sperm. These are the cross-sectional studies of Mahmoud et al. (2005)[18], Bonde et al. (2002)[19] and Telisman et al. (2000)[20].

[16] Calculated using OEHHA's physiologically based pharmacokinetic model, described below.

[17] US EPA 2013 Integrated Science Assessment for Lead, page lxxxvi

[18] Mahmoud A, Kiss P, Vanhoorne M, De Bacquer D, Comhaire F (2005). Is inhibin B involved in the toxic effect of lead on male reproduction? Int J Androl. 28(3):150-5

[19] Bonde JP, Joffe M, Apostoli P, Dale A, Kiss P, Spano M, Caruso F, Giwercman A, Bisanti L, Porru S, Vanhoorne M, Comhaire F, Zschiesche W (2002).Sperm count and chromatin structure in men exposed to inorganic lead: lowest adverse effect levels. Occup Environ Med.59(4):234-42. Full paper available at:

Bonde et al. studied 486 male workers from the United Kingdom, Italy and Belgium. Mean sperm density and sperm count were reduced in workers with blood lead levels of 50 µg/dL or more compared to the referent group. These sperm parameters were not significantly affected in groups exposed to 10.1-20 or 20.1-30 or 30.1-40, or 40.1-50 µg/dL. The authors calculated a threshold dose of 44 µg/dL. In contrast, Mahmoud et al. (2005) in a study of lead smelter workers in Belgium found significantly reduced sperm concentration compared to the referent group in workers with a mean blood lead level of 31 µg/dL compared to the referent group. This study did not identify a no observed effect group.

Telisman et al. (2000) found significantly reduced sperm counts in lead-exposed industrial workers from Zagreb, Croatia. Telisman et al. recruited 98 men who had been occupationally exposed to low or moderate levels of lead, but not to other metals. A total of 51 subjects involved in product assembly from a machine tool factory served as the referent group. This cross-sectional study was well designed, with data collection on questionnaires by physicians for each study subject. Also an andrologic physical examination was conducted by an andrologist blinded by the exposure category of the study subject. Subjects were employed for at least two years in the current workplace, and those with medical conditions known to be associated with male reproductive dysfunction (e.g., cryptorchisdism, genital trauma) were excluded. Reduced sperm count was observed in men with blood lead levels of approximately 25, 35, or 55 µg/dL, but not in the grouping with mean blood lead level of approximately 15 or 45 µg/dL. This analysis does not appear to have been adjusted for potential confounders such as smoking and cadmium exposure, both of which were somewhat different between the exposed and unexposed samples; however, adjustments for smoking and cadmium exposure appear to have been unnecessary in regression models with blood lead (log-transformed) and sperm parameters. The blood lead level of 15 µg/dL is taken as the blood lead level with no observed effect for the purposes of calculating a MADL, since it comes from the most sensitive study deemed to be of sufficient quality (Section 25803(a)(5)).

Modeling the Exposure Using the Blood Lead Level

Lead differs from most chemicals in that the concentration of lead in blood that results from exposure is used in characterizing human-dose response relationships for health effects. OEHHA recently developed a pharmacokinetic model that enables the

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1740274/

[20]Telisman S, Cvitković P, Jurasović J, Pizent A, Gavella M, Rocić B (2000). Semen quality and reproductive endocrine function in relation to biomarkers of lead, cadmium, zinc, and copper in men. Environ Health Perspect. 108(1):45-53. Full paper available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1637869/

estimation of blood concentrations of lead for adults exposed under various exposure conditions. That model was developed to support the work of the California Department of Public Health's Occupational Lead Poisoning Prevention Program in its reconsideration of lead standards for California workers. The model is described in the 2013 OEHHA report "Estimating Workplace Air and Worker Blood Lead Concentration using an Updated Physiologically-based Pharmacokinetic (PBPK) Model" [21]. The model received extensive public comment and review and scientific peer review[22].

OEHHA is considering the use of its lead PBPK model for the development of MADLs for lead. OEHHA has calculated lead intake levels that would result in blood concentrations at the blood lead level with no observable effect. The starting point of the modeling exercise and the development of possible MADLs would be based on ascertaining exposures that result in a mean blood lead level of 15 µg/dL, and dividing these exposure levels by 1000 as required by Proposition 65 to identify a level of lead exposure that is exempt from the warning requirement. Different patterns of exposure to lead can result in the same maximal blood level. Thus, OEHHA developed multiple possible MADLs to address different patterns of exposure.

Calculation of Possible MADLs

Using its PBPK model, OEHHA has calculated intakes for different exposure levels and frequencies that result in maximum blood lead levels of 15 µg/dL, and divided them by 1000. Under this approach, the MADLs for lead for different exposure frequencies were calculated. For example, a maximum blood level of 15 µg/dL results from an exposure one day in every four days to 670 µg. Dividing this by 1000 and rounding results in a MADL of 0.7 µg when exposure occurs on one day in every four days. The blood level of 15 µg/dL also results from an exposure one day in every seven days to 1141 micrograms. Dividing this by 1000 and rounding to one significant figure results in a MADL of 1 µg for exposures that occur in one day out of every 7 days. Thus, possible MADLs for lead are calculated that depend on the frequency of exposure. OEHHA has calculated such values for differing frequencies of exposure.

The OEHHA PBPK model used in this analysis – the Leggett+ model – incorporates new information about the pharmacokinetics of lead in the adult body into an existing lead model developed by Dr. Leggett in 1993[23]. The software code for the model is

[21] Office of Environmental Health Hazard Assessment (OEHHA), Estimating Workplace Air and Worker Blood Lead Concentration using an Updated Physiologically-based Pharmacokinetic (PBPK) Model, California Environmental Protection Agency, OEHHA , Air, Community, Environmental Research Branch, October 2013.
[22] Ibid., page ii
[23] Estimating Workplace Air and Worker Blood Lead Concentration Using Updated physiologically-based Pharmacokinetic (PBPK) Model. Office of Environmental Health Hazard Assessment, October 2013.

available on OEHHA's website[24]. Each simulation assumed a pre-exposed blood lead level of zero, and modeled the rise and fall of blood lead levels during episodic exposures for 10 years.

Use of MADLs for Determining Need for Warnings for Intermittent Exposures

The lead MADLs described above represent a significant change from the way MADLs have been previously derived by OEHHA. All the current MADLs for reproductive toxicants, including lead, have identified single-day exposure levels that would not require warnings. By identifying levels of lead exposure for periods of time ranging from one day to as many as 120 days that would be exempt from the warning requirements of Proposition 65, the potential MADLs provide a new approach for determining if a given lead exposure requires a Proposition 65 warning. The OEHHA PBPK+ model provides the scientific basis for making the calculations to support this approach. This approach is scientifically more appropriate for lead exposures because a single exposure at the levels and frequencies set out in the potential regulation will not raise the individual's blood lead level above the no observed effect level.

COMPARISON OF THE POSSIBLE MADLS WITH OTHER PUBLIC HEALTH GUIDANCE VALUES

OEHHA has developed a guidance value for lead for use in developing the California drinking water standard. OEHHA's guidance level is called a "Public Health Goal for Drinking Water", or PHG. The effect of lead on the neurobehavior of children, namely lead effects on IQ, was the basis of the determination. This is not an endpoint covered by Proposition 65 because the studies on which it is based focus on measures of exposure in the postnatal period, and so could not be used as the basis of the MADL determination.

The method to calculate the Public Health Goal is different from that used by Proposition 65 for reproductive toxicants, and more similar to that used for Proposition 65 carcinogens. The slope of the dose-response curve for lead vs. IQ decrement was used to derive public health protective values: The change in one IQ point due to change in blood lead concentrations, and hence change in intake, was used. Lead associated with a one IQ point change in a child was calculated to be a daily intake of 2.86 µg. To derive the PHG this intake was then divided by 3 to take into account:

[24] OEHHA, Leggett Plus Part A computer code; OEHHA, Leggett Plus Part B computer code. Available at: http://oehha.ca.gov/air/legget.html

> "the uncertainty with regard to the degree of protection offered at this level, considering the lack of a threshold. The uncertainty factor of three also accounts for the extrapolation from the small sample size used in the main study of Lanphear et al. (2005) to the large, diverse population of children in California."

The daily intake was also multiplied by 0.2 to take into account the non-drinking water sources of lead. Thus the public health protective PHG is equivalent to a child intake of 0.19 µg every day. This is similar to the draft MADL for daily exposure of 0.2 µg.

The no significant risk level for cancer effects under Proposition 65 is 15 µg per day. The US Food and Drug Administration's Provisional Total Tolerable Intake Level for chronic exposures from all sources of lead is a daily intake of 6 µg for young children, and a daily intake of 25 µg per day for childbearing women[25].

INPUT ON THE POSSIBLE MADLS

OEHHA is seeking public input concerning this potential new approach to calculating a MADL for lead. Stakeholders are encouraged to participate in all aspects of the rulemaking process.

[25] US Food and Drug Administration, Survey Data on Lead in Women's and Children's Vitamins, August 2008, available online at: http://www.fda.gov/Food/FoodborneIllnessContaminants/Metals/ucm115941.htm; Carrington CD, Bolger PM (1992). An assessment of the hazards of lead in food. *Regul Toxicol* Pharmacol, 16, 265-272