INITIAL STATEMENT OF REASONS
TITLE 27, CALIFORNIA CODE OF REGULATIONS

PROPOSED AMENDMENT TO SECTION 25703, SUBSECTION (a)(6)
QUANTITATIVE RISK ASSESSMENT

SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT OF 1986
PROPOSITION 65

PURPOSE OF PROPOSED AMENDMENT OF REGULATION

This proposed regulatory amendment updates the method used for interspecies conversion used in calculating No Significant Risk Levels ("NSRL") under Proposition 65[1]. Interspecies conversion is applied when the data used in calculating an NSRL are from animal experiments. This amendment would make this regulation consistent with current methods used by the drinking water and air toxics programs within the Office of Environmental Health Hazard Assessment (OEHHA) and by the U.S. Environmental Protection Agency (U.S. EPA) for cancer risk assessments when exposure is via the oral route.

Methods, principles and assumptions used to calculate an NSRL are provided in Title 27, California Code of Regulations, section 25703(a)(6) [2], which was originally adopted in 1989 and amended in 1990. Section 25703(a)(6) provides the approach to be used for interspecies conversion. This calculation converts estimates of animal cancer potency to human cancer potency estimates. It uses an interspecies surface scaling factor. The underlying assumption in surface area scaling is that chemical doses are equivalent in different species when they are expressed as an amount (e.g., a milligram quantity) divided by the surface area for the species of animal providing the data for the cancer potency calculation. In this case the same dose divided by bodyweight to the two-thirds power is assumed equivalent in different species. This assumption leads to the method for interspecies conversion given in the current regulation of multiplying animal cancer potency by the ratio of human to animal bodyweight, taken to the one-third-power. The proposed amendment to the regulation assumes that dose expressed as an amount divided by the bodyweight to the three-fourth power is equivalent across species. This amendment would change the existing regulatory provision to a ratio for human to animal bodyweight to one-fourth power for interspecies conversion and delete the provision giving specific scaling factors for mice and rat data.

In 2009, after peer review by the state's Scientific Review Panel on Toxic Air Contaminants, OEHHA adopted updated methods for calculating cancer potency

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[1] The Safe Drinking Water and Toxic Enforcement Act of 1986, which is codified at Health and Safety Code section 25249.5 et seq.

[2] All further references are to sections of Title 27 of the California Code of Regulations.

values for risk assessments conducted pursuant to the 1987 Air Toxics "Hot Spots" Information and Assessment Act[3]. Supporting documentation is given in OEHHA's May 2009 "Technical Support Document for Cancer Potency Factors: Methodologies for derivation, listing of available values, and adjustments to allow for early life stage exposures",[4] a copy of which will be included in the rulemaking file for this proposed amendment. For interspecies scaling, the 2009 OEHHA document states on page 4: "OEHHA will use scaling based on body weight to the ¾ power, rather than to the ⅔ power." The primary basis for the change was to be consistent with the U.S. EPA.

In 2005 the U.S. EPA in its "Guidelines for Carcinogen Risk Assessment,"[5] explained its interspecies scaling procedure, termed "cross-species" scaling:

> "3.1.3 Cross-species Scaling Procedures
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> "Standard cross-species scaling procedures are available when the data are not sufficient to support a toxicokinetic model or when the purpose of the assessment does not warrant developing one. The aim is to define exposure levels for humans and animals that are expected to produce the same degree of effect (U.S. EPA, 1992b), taking into account differences in scale between test animals and humans, such as size and lifespan."
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> "3.1.3.1. Oral Exposures
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> "For oral exposures, administered doses should be scaled from animals to humans on the basis of equivalence of $mg/kg^{3/4}$-d (milligrams of the agent normalized by the 3/4 power of body weight per day) (U.S. EPA, 1992b). The 3/4 power is consistent with current science, including empirical data that allow comparison of potencies in humans and animals, and it is also supported by analysis of the allometric variation of key physiological parameters across mammalian species. It is generally more appropriate at low doses, where sources of nonlinearity such as saturation of enzyme activity are less likely to occur. This scaling is intended as an unbiased estimate rather than a conservative one."

The current surface scaling factor established in Section 25703(a)(6) was based on the 1986 California Department of Health Services "Guidelines for Chemical Carcinogen Risk Assessments" and the U.S. EPA's 1986 guidelines for

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[3] Health and Safety Code Section 44300, et seq.

[4] Office of Environmental Health Hazard Assessment (OEHHA). Technical Support Document for Cancer Potency Factors: Methodologies for derivation, listing of available values, and adjustments to allow for early life stage exposures, California Environmental Protection Agency, OEHHA, Air Toxicology and Epidemiology Branch, May 2009, available online at: http://www.oehha.ca.gov/air/hot_spots/tsd052909.html

[5] U.S. Environmental Protection Agency (U.S. EPA), Guidelines for Carcinogen Risk Assessment, EPA/630/P-03/001B, U.S. EPA Risk Assessment Forum, Washington DC, March 2005, available online at: http://www.epa.gov/ttn/atw/cancer_guidelines_final_3-25-05.pdf

carcinogen risk assessment.[6] Since this regulation was adopted, the U.S. EPA has changed its interspecies scaling factor and other California risk assessment programs, including those within OEHHA, have followed suit. The OEHHA program that develops drinking water Public Health Goals[7] uses three-quarters scaling and has adopted a number of Public Health Goals employing the scaling method after subjecting the documents to external scientific peer review. Examples include: public health goals for methyl tertiary butyl ether (MTBE)[8], benzo(a)pyrene[9], and 1,2,3-trichloropropane[10]. Similarly, after review by the external Scientific Review Panel, the air program formally adopted the approach, as noted above. The unit cancer risk value for ethylbenzene was developed using the new approach, and was adopted following review by the Scientific Review Panel and public comment.[11] [12] The U.S. EPA has employed the scaling factor in peer-reviewed assessments as well, for example in the 2010 "Toxicological Review for 1,1,2,2-Tetrachloroethane."[13]

Section 25703(a) requires that all risk assessments be based upon evidence and standards of comparable scientific validity to the evidence and standards which formed the basis for the listing of the chemical. The regulation goes on to provide certain default assumptions or principles for calculating No Significant Risk Levels. However, the regulation provides that other assumptions, principles or data sets should be used where scientifically more appropriate. Thus, the default interspecies conversion scaling factor can be replaced by an alternative method when scientifically justified.

An example of when an alternative method should be applied is when pharmacokinetic data are sufficient to support cross-species scaling based on a

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[6] U.S. Environmental Protection Agency (U.S. EPA) (1986). Guidelines for Carcinogen Risk Assessment. Federal Register 51:33992-34003. Available online at: http://www.epa.gov/cancerguidelines/guidelines-carcinogen-risk-assessment-1986.htm

[7] Health and Safety Code section 116365(c)(1)

[8] Office of Environmental Health Hazard Assessment (OEHHA), Public Health Goal for Methyl Tertiary Butyl Ether (MTBE) in Drinking Water, California Environmental Protection Agency, OEHHA, March 1999, available online at: http://www.oehha.ca.gov/water/phg/index.html

[9] Office of Environmental Health Hazard Assessment (OEHHA), Public Health Goal for Benzo(a)pyrene in Drinking Water, September 2010, available online at: http://www.oehha.ca.gov/water/phg/pdf/091610Benzopyrene.pdf

[10] Office of Environmental Health Hazard Assessment (OEHHA), Public Health Goal for 1,2,3-Trichloropropane in Drinking Water, California Environmental Protection Agency, OEHHA, August 2009, available online at: http://www.oehha.ca.gov/water/phg/pdf/082009TCP_phg.pdf

[11] Office of Environmental Health Hazard Assessment (OEHHA), Long Term Health Effects of Exposure to Ethylbenzene, California Environmental Protection Agency, OEHHA, November, 2007, available online at: http://oehha.ca.gov/air/hot_spots/pdf/Ethylbenzene_FINAL110607.pdf

[12] Office of Environmental Health Hazard Assessment (OEHHA), Notice of Adoption of Unit Risk Value for Ethylbenzene, California Environmental Protection Agency, OEHHA, November, 2007, available online at: http://oehha.ca.gov/air/hot_spots/pdf/111407memo.pdf

[13] U.S. Environmental Protection Agency, Toxicological Review for 1,1,2,2-Tetrachloroethane (CAS No. 79-34-5): In Support of Summary Information on the Integrated Risk Information System (IRIS), EPA/635/R-09/001F, U.S. EPA, Washington DC, September 2010, page 97, available online at: http://www.epa.gov/iris/toxreviews/0193tr.pdf

physiologically based pharmacokinetic (PBPK) model. In such a case, an approach could be employed like that used in the calculation of an alternative unit risk value for ethylbenzene.[14] It took into account both pharmacokinetics and pharmacodynamics in interspecies conversion. This calculation was reviewed by the Scientific Review Panel. A copy of this document will be included in the regulatory file for this action.

This proposed amendment to the Proposition 65 method for interspecies conversion does not require a revision of the existing cancer potencies and NSRLs that have already been adopted. However, as these cancer potency values and NSRLs are reviewed and updated, the new method will be applied as appropriate along with a review of the relevant scientific data on dose response.

PROPOSED REGULATORY AMENDMENT

The proposed change to the regulation is provided below in underline and strikeout:

25703. Quantitative Risk Assessment

(a)(6) Human cancer potency shall be derived from data on human or animal cancer potency. Potency shall be expressed in reciprocal milligrams of chemical per kilogram of bodyweight per day. Interspecies conversion of animal cancer potency to human cancer potency shall be determined by multiplying by a ~~surface area~~ scaling factor equivalent to the ratio of human to animal bodyweight, taken to the one~~-third~~ fourth power. ~~This is equivalent to a scaling factor of 14 when extrapolating from mouse data and a scaling factor of 6.5 when extrapolating from rat data.~~

NECESSITY

This proposed regulatory amendment will update the default approach established in the existing regulation to bring it in line with the current interspecies scaling factor used by the U.S. Environmental Protection Agency and the OEHHA air and drinking water programs. The adoption of this approach is necessary in order to ensure that the regulation uses scientific methodology that is consistent with methods used within OEHHA and by other agencies such as U.S. EPA.

BACKGROUND

[14] Office of Environmental Health Hazard Assessment (OEHHA), Appendix B of the Air Toxics Hot Spots Risk Assessment Guidelines Part II: Technical Support Document for Cancer Potency Factors, California Environmental Protection Agency, OEHHA, May 2009, available online at: http://www.oehha.ca.gov/air/hot_spots/tsd052909.html

The Office of Environmental Health Hazard Assessment (OEHHA) within the California Environmental Protection Agency is the state entity responsible for the implementation of Proposition 65. OEHHA has the authority to promulgate and amend regulations to further the purposes of Proposition 65.[15]

Proposition 65 prohibits a person in the course of doing business from knowingly and intentionally exposing any individual to a chemical that has been listed as known to the State to cause cancer or reproductive toxicity, without first giving clear and reasonable warning to such individual[16]. The Act also prohibits a business from knowingly discharging a listed chemical into water or onto or into land where such chemical passes or probably will pass into a source of drinking water. The Act provides an exemption from the warning requirement if a person in the course of doing business is able to demonstrate that an exposure for which the person is responsible poses no significant risk of cancer[17]. 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[18].

Section 25701 describes alternative methods for making a determination that a given exposure poses no significant risk. One such method is the application of a specific regulatory level for the chemical in question established in section 25705(b). Regulations previously adopted by OEHHA provide guidance for determining whether an exposure to, or a discharge of, a chemical known to cause cancer meets either of the statutory exemptions[19]. 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, methods and assumptions described in Section 25703 to derive a NSRL, which is defined as the level of exposure to the chemical which is calculated to result in no more than one excess case of cancer in an exposed population of 100,000, assuming exposure over a 70-year lifetime (10^{-5} lifetime risk of cancer); or
2. By application of the specific regulatory level adopted for the chemical in Section 25705(b) that are developed following guidance in 25703; 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 25703(a).

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[15] Health and Safety Code section 25249.12(a)

[16] Health and Safety Code, section 25249.5

[17] Health and Safety Code, sections 25249.10 and 25249.11

[18] Health and Safety Code, sections 25249.9 and 25249.11

[19] Title 27, California Code of Regulations, sections 25701-25721

The proposed amendment modifies one of the methods and assumptions in Section 25703(a)(6) to bring it in line with current scientific methodology used by the agency for other risk assessment programs.

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

OEHHA relied on the 2005 U.S. EPA Guidelines for Carcinogen Risk Assessment, and OEHHA's 2009 Technical Support Document for Cancer Potency Factors,"[20] [21] and recent cancer risk assessment documents that include dose response assessments that have been peer reviewed, as cited above. A copy of these documents will be included in the regulatory file for this action.

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

OEHHA is proposing by this amendment to harmonize its approach to scaling results from animals to humans in cancer risk assessment with other OEHHA programs. OEHHA is not aware of any reasonable alternatives to the proposed regulatory action.

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

The proposed regulatory action will not adversely impact small business. The proposed regulation identifies a level below which businesses are exempt from Proposition 65 warning requirements and the discharge prohibition. It does not impose any mandatory requirement upon any business, including small business.

EVIDENCE SUPPORTING FINDING OF NO SIGNIFICANT ADVERSE ECONOMIC IMPACT ON BUSINESS

The regulation will not have a significant statewide adverse economic impact directly affecting businesses, including the ability of California businesses to compete with businesses in other states. The proposed amendment updates a method used to identify a level below which businesses are exempt from Proposition 65 warning requirements and the discharge prohibition. No costs or expenses are incurred by businesses to comply with the proposed regulation. There is no significant adverse economic impact on any business. In fact, the proposed regulatory action makes it easier for affected businesses to comply

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[20] Office of Environmental Health Hazard Assessment (OEHHA). Technical Support Document for Cancer Potency Factors: Methodologies for derivation, listing of available values, and adjustments to allow for early life stage exposures, California Environmental Protection Agency, OEHHA, Air Toxicology and Epidemiology Branch, May 2009, available online at: http://www.oehha.ca.gov/air/hot_spots/tsd052909.html

[21] U.S. Environmental Protection Agency (U.S. EPA), Guidelines for Carcinogen Risk Assessment, EPA/630/P-03/001B, U.S. EPA Risk Assessment Forum, Washington DC, March 2005, available online at: http://www.epa.gov/ttn/atw/cancer_guidelines_final_3-25-05.pdf

with Proposition 65 by helping them determine when the warning and discharge requirements may apply.

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.