INITIAL STATEMENT OF REASONS
TITLE 27, CALIFORNIA CODE OF REGULATIONS

PROPOSED AMENDMENT TO:
SECTION 25705(b) SPECIFIC REGULATORY LEVELS
POSING NO SIGNIFICANT RISK

TRIS(1,3-DICHLORO-2-PROPYL) PHOSPHATE (TDCPP)

SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT OF 1986
PROPOSITION 65

PURPOSE AND BACKGROUND OF PROPOSED AMENDMENTS OF REGULATION

This proposed regulatory amendment would adopt a No Significant Risk Level (NSRL) for tris(1,3-dichloro-2-propyl) phosphate (TDCPP) under Proposition 65[1] in Title 27, California Code of Regulations, section 25705(b).[2] The proposed NSRL of 5.4 micrograms per day (µg/day) is based on a carcinogenicity study in rodents and was derived using the methods described in Section 25703.

Proposition 65 was enacted as a voters' initiative on November 4, 1986. The Office of Environmental Health Hazard Assessment (OEHHA) is the lead entity responsible for the implementation of Proposition 65.[3] OEHHA has the authority to adopt 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 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 insignificant. The NSRL safe harbor provides guidance for determining when this is the case.

TDCPP was listed as known to the State to cause cancer under Proposition 65 on October 28, 2011.

[1] The Safe Drinking Water and Toxic Enforcement Act of 1986, codified at Health and Safety Code section 25249.5 et. seq., commonly known as Proposition 65, hereafter referred to as "Proposition 65" or "The Act".
[2] All further regulatory references are to sections of Title 27 of the Cal. Code of Regs., unless otherwise indicated.
[3] Title 27, Cal. Code of Regs., section 25102(o).
[4] Health and Safety Code, section 25249.12(a).

DEVELOPMENT OF PROPOSED NSRL

To develop the proposed NSRL for TDCPP, OEHHA relied on a 2011 OEHHA document entitled, "Evidence on the Carcinogenicity of Tris(1,3-dichloro-2-propyl)phosphate,"[5] which summarizes the available data from rodent carcinogenicity studies of TDCPP, as well as other information relevant to the carcinogenic activity of the chemical. The NSRL is based upon the results of the most sensitive scientific study deemed to be of sufficient quality.[6]

Selection of Study Used to Determine Cancer Potency

OEHHA determined that a two-year diet study conducted in male Sprague-Dawley CD rats by Bio/dynamics[7] and reported in the published scientific literature by Freudenthal and Henrich[8] met this criterion. In this study, male Sprague-Dawley CD rats (60/group) were fed for two years a diet containing TDCPP at concentrations intended to achieve dose rates of 0, 5, 20, or 80 milligrams of TDCPP per kilogram of body weight per day (mg/kg-day). TDCPP treatment-related increases in liver, kidney, and testicular tumors were observed. The tumor incidence data from this study are presented in Table 1 at the top of the next page. These data were used to estimate the cancer potency that serves as the basis for the NSRL.

[5] Office of Environmental Health Hazard Assessment (OEHHA), 2011. Evidence on the Carcinogenicity of Tris(1,3-dichloro-2-propyl) phosphate. California Environmental Protection Agency, OEHHA, Reproductive and Cancer Hazard Assessment Branch, July 2011, available at: http://oehha.ca.gov/prop65/hazard_ident/pdf_zip/TDCPP070811.pdf

[6] Section 25703(a)(4)

[7] Bio/dynamics, Inc., 1981. A Two Year Oral Toxicity/Carcinogenicity Study on Fyrol FR-2 in Rats (Final Report). Volume V. Submitted to Stauffer Chemical Co. by Bio/dynamics, Inc. Project No. 77-2016. Sept. 21, 1981.

[8] Freudenthal RI and Henrich RT, 2000. Chronic toxicity and carcinogenic potential of tris-(1,3-dichloro-2-propyl) phosphate in Sprague-Dawley rat. *International Journal of Toxicology* **19**(2):119-25.

Table 1. Tumor incidences[a] in male Sprague-Dawley rats administered TDCPP in the diet for two years.

Organ	Tumor type	Dose group (mg/kg/day)				Trend test p-value[b]
		0	5	20	80	
Liver	Combined hepatocellular adenoma and carcinoma	3/45	9/48	4/48	20/46[c]	p < 0.0001
Kidney	Renal cortical adenoma	1/45	3/49	9/48[d]	32/46[c]	p < 0.0001
Testes	Interstitial cell tumor	7/43	8/48	23/48[c]	36/46[c]	p < 0.0001

[a] Incidences represent the combined incidences from all unscheduled deaths plus the terminal sacrifice at two years, as reported in OEHHA, 2011.
[b] Exact test for linear trend.
[c] Statistically significant increase in incidence compared to control ($p < 0.01$, by Fisher's exact test).
[d] Statistically significant increase in incidence compared to control ($p < 0.05$, by Fisher's exact test).

Estimation of Cancer Potency in Rats Using the Linearized Multistage Model

As stated in the 2011 OEHHA document[9]:

> "Positive findings in multiple *in vitro* genotoxicity test systems indicate that TDCPP may be carcinogenic through a genotoxic mechanism. TDCPP induced mutations in multiple strains of *Salmonella typhimurium* and in mouse lymphoma cells. It induced chromosomal aberrations in mouse lymphoma cells and hamster fibroblast cells, increased the formation of SCE *[sister chromatid exchange]* in mouse lymphoma cells, and induced unscheduled DNA synthesis in rat hepatocytes. In an *in vivo* study, TDCPP bound to DNA and proteins in mouse kidney, liver and muscle."

Based on consideration of all the evidence summarized in the 2011 OEHHA document, while the mechanism(s) of carcinogenic action of TDCPP remain unknown, the available evidence suggests that genotoxicity is involved and thus the default approach using a linearized multistage model[10] is applied to derive a cancer potency estimate. There are not principles or assumptions scientifically more appropriate, based on the available data, than this default.

[9] OEHHA 2011. Evidence on the Carcinogenicity of Tris(1,3-dichloro-2-propyl) phosphate. California Environmental Protection Agency, OEHHA, Reproductive and Cancer Hazard Assessment Branch, July 2011, available at: http://oehha.ca.gov/prop65/hazard_ident/pdf_zip/TDCPP070811.pdf
[10] Section 25703

The tumor incidence data for each of the three tumor sites presented in Table 1 were fit to the multistage polynomial, $p(d) = 1 - \exp[-(q_0 + q_1d_1 + q_2d_2 + ... + q_jd_j)]$, with constraints, $q_i \geq 0$ for all i. In this model, p(d) is the lifetime probability of dying with a tumor (p) induced by an average daily dose (d), and q_i are parameters of the model, which are taken to be constants and are estimated from the animal cancer bioassay data. With four dose groups, as is the case with the male rat study of TDCPP, the default linearized multistage model has four parameters, q_0, q_1, q_2, and q_3. A four parameter model was fit to the kidney and testes tumor data. Due to modeling constraints, a three parameter model was fit to the liver tumor data. The parameter q_1 is, for small doses, the ratio of excess lifetime cancer risk to the average daily dose received.

In order to derive a measure of the total cancer response to TDCPP (per mg/kg/day) in the male Sprague-Dawley rat study, the potencies for each of the three treatment-related tumor sites shown in Table 1 are summed using a probabilistic approach. This is a way of taking into account the multisite carcinogenicity and provides a basis for estimating the cumulative risk of carcinogen treatment-related tumors. Specifically, statistical distributions of the linear term (q_1) of the multistage model are generated for each of the three sites. The distributions of q_1 for each of these sites are then statistically summed using a Monte Carlo approach and assuming independence. The sum is created by adding the linear term for each tumor site, according to its distribution, through random sampling with 100,000 trials. The upper 95% confidence bound on the summed distribution is taken as the multisite animal cancer potency estimate, referred to here as $q_{1(UCB)}$. When the experiment duration is at least two years in rats, the parameter $q_{1(UCB)}$ is taken as the animal cancer potency (q_{animal}).

Estimation of Human Cancer Potency

Human cancer potency is estimated by an interspecies scaling procedure. According to Section 25703(a)(6), dose in units of mg per kg bodyweight scaled to the three-quarters power is assumed to produce the same degree of effect in different species in the absence of information indicating otherwise. Thus scaling to the estimated human potency (q_{human}) is achieved by multiplying the multisite animal potency (q_{animal}) by the ratio of human to animal body weights (bw_h/bw_a) raised to the one-fourth power when animal potency is expressed in units $(mg/kg\text{-}day)^{-1}$:

$$q_{human} = q_{animal} \times (bw_h / bw_a)^{1/4}$$

The average body weight of 0.578 kg for male rats was obtained from information presented in Freudenthal and Henrich.[11] Briefly, a graph of body weight values plotted at 4 week intervals from that publication was digitalized, and average body weight reported for control male rats during the study was calculated. The default human body weight is 70 kg. The derivation of human cancer potency using the male rat cancer potency of 0.0387 $(mg/kg\text{-}day)^{-1}$ is shown below:

$$q_{human} = 0.0387\ (mg/kg\text{-}day)\text{-}1 \times (70\ kg\ /0.578\ kg\ )^{1/4} = 0.13\ (mg/kg\text{-}day)^{-1}$$

Calculation of No Significant Risk Level

The NSRL can be calculated from the cancer potency estimate (slope factor) as follows. The Proposition 65 no significant risk value is one excess case of cancer per one hundred thousand people exposed, expressed as 10^{-5}. This value is divided by the slope factor, expressed in units of one divided by milligram per kilogram bodyweight per day. The result of the calculation is a dose level associated with a 10^{-5} risk in units of mg/kg-day. This dose then can be converted to an intake amount in units of mg per day by multiplying by the bodyweight for humans. When the calculation is for the general population, the bodyweight is assumed to be 70 kg in NSRL calculations (Section 25703(a)(8)). The intake can be converted to a µg per day amount by multiplying by 1000. This sequence of calculations can be expressed mathematically as:

$$\text{NSRL} = \frac{10^{-5} \times 70\,\text{kg}}{\text{slope factor}} \times 1000\ \mu\text{g/mg}.$$

As indicated previously, the slope factor for TDCPP derived from the data and exposure parameters presented in Table 1 is 0.13 per mg/kg-day. Inserting this number into the equation above results in an NSRL of 5.4 µg/day.

PROPOSED REGULATORY AMENDMENT

Section 25705(b)

The proposed change to Section 25705(b) is provided below, in underline and strikeout.

(1) The following levels based on risk assessments conducted or reviewed by the lead agency shall be deemed to pose no significant risk:

[11] Freudenthal RI and Henrich RT, 2000. Chronic toxicity and carcinogenic potential of tris-(1,3-dichloro-2-propyl) phosphate in Sprague-Dawley rat. *International Journal of Toxicology* **19**(2):119-25.

Chemical name	Level (micrograms per day)
Acrylonitrile	0.7
…	
Tris(1,3-dichloro-2-propyl) phosphate (TDCPP)	5.4
…	

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 resources and expertise to examine the scientific literature and calculate a level of exposure, in this case an NSRL, that does not require a warning or for which a discharge is not prohibited.

NECESSITY

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

BENEFITS OF THE PROPOSED REGULATION

The NSRL 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 NSRL 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 an NSRL, 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.

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

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

The 2011 OEHHA document entitled "Evidence on the Carcinogenicity of Tris(1,3-dichloro-2-propyl) phosphate"[13] is the document relied on by OEHHA for calculating the NSRL for TDCPP. It includes data used in the potency calculation and on mechanism of carcinogenesis that is relevant to evaluating the most appropriate method for deriving the NSRL in the context of Section 25703. A copy of the 2011 OEHHA document will be included in the regulatory record for this proposed action, and is available from OEHHA upon request. OEHHA also relied on the male rat carcinogenicity study by Bio/dynamics, Inc.[14] and the published report of that study by Freudenthal and Henrich,[15] and these are also included in the regulatory record for this proposed action and are available from OEHHA upon request.

OEHHA 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 NSRL provides a "safe harbor" value that aids businesses in determining if they are complying with the law. The alternative to the proposed amendment to Section 25705(b) would be to not adopt a NSRL for the chemical. Failure to adopt a NSRL would leave the business community without a "safe harbor" level to assist them in determining compliance with Proposition 65.

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. 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.

[13] OEHHA, 2011 Evidence on the Carcinogenicity of Tris(1,3-dichloro-2-propyl) phosphate. California Environmental Protection Agency, OEHHA, Reproductive and Cancer Hazard Assessment Branch, July 2011, available at: http://oehha.ca.gov/prop65/hazard_ident/pdf_zip/TDCPP070811.pdf

[14] Bio/dynamics, Inc., 1981. A Two Year Oral Toxicity/Carcinogenicity Study on Fyrol FR-2 in Rats (Final Report). Volume V. Submitted to Stauffer Chemical Co. by Bio/dynamics, Inc. Project No. 77-2016. Sept. 21, 1981.

[15] Freudenthal RI and Henrich RT, 2000. Chronic toxicity and carcinogenic potential of tris-(1,3-dichloro-2-propyl) phosphate in Sprague-Dawley rat. *International Journal of Toxicology* **19**(2):119-25.

EVIDENCE SUPPORTING FINDING OF NO SIGNIFICANT ADVERSE ECONOMIC IMPACT ON BUSINESS

Because the proposed NSRL 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.

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. TDCPP is listed under Proposition 65; therefore, effective October 28, 2012, businesses and individuals who manufacture, distribute or sell products with TDCPP in the state must provide a warning if their product or activity exposes the public or employees to this chemical.

Benefits of the Proposed Regulation: The NSRL 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 an NSRL and therefore may be exposed to litigation for a failure to warn of an exposure to 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 an NSRL 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 NSRL for this chemical. This alternative was rejected because it would fail to provide businesses with the certainty that the NSRL can provide.