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*SUBMITTED VIA ELECTRONIC MAIL*

Cynthia Oshita  
1001 I Street  
P.O. Box 2815  
Sacramento, CA 95812-2815  
E-mail: [coshita@oehha.ca.gov](mailto:coshita@oehha.ca.gov)  
Tel.: 916-322-2068  
Fax: 916-323-8803

Subject: Comments for the Proposition 65 Carcinogen Identification Committee's evaluation on tris(1,3-dichloro-2-propyl) phosphate

Dear Ms. Oshita,

We appreciate the opportunity to provide comments for the Carcinogen Identification Committee's (CIC)'s consideration when it evaluates the carcinogenicity of tris(1,3-dichloro-2-propyl) phosphate (TDCPP). Our comments were prepared in response to the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment's (OEHHA)'s carcinogenicity evaluation of TDCPP. Herein, we have provided summary information, along with supporting documents, which we believe the CIC will find helpful at making its determination whether the scientific data on TDCPP satisfy the regulatory requirements for listing this substance as a carcinogen under Proposition 65.

Our comments are focused on five primary areas:

- I. TDCPP does not meet the "sufficient evidence" requirements as articulated by OEHHA for listing as a carcinogen under Proposition 65;
- II. The rat bioassay performed using TDCPP was confounded because tumors with human relevance only occurred above the maximum tolerated dose (MTD);
- III. OEHHA incorrectly assigned "neoplastic nodules" as "hepatocellular adenomas" when evaluating liver tumors in the rat bioassay on TDCPP;
- IV. TDCPP is non-genotoxic *in vivo*; and
- V. OEHHA incorrectly utilized a structure-activity relationship from various phosphorus flame retardants to inform the metabolism, carcinogenicity, and genotoxicity of TDCPP.

A summary of the above items is provided below, whereas in-depth details are provided in Appendix 1 with key cites to the supporting information.

**I. TDCPP does not meet the “sufficient evidence” requirements as articulated by OEHHA for listing as a carcinogen under Proposition 65.**

OEHHA considers the following as strong or suggestive evidence of carcinogenicity (see pp. 6-9, Appendix 1):

STRONG EVIDENCE OF CARCINOGENICITY

1. International Agency for Research on Cancer (IARC):
  - a. Group 1 – “The agent is *carcinogenic to humans*”
  - b. Group 2A – “The agent is *probably carcinogenic to humans*”
  - c. Group 2B – “The agent is *possibly carcinogenic to humans*”
2. Globally Harmonized System of Classification and Labelling of Chemicals (GHS):
  - a. Group 1A – “Known to have carcinogenic potential to humans”
  - b. Group 1B – “Presumed to have carcinogenic potential to humans”
3. Recognition as a known or potential carcinogen by an authoritative organization (*e.g.*, the European Chemicals Agency, ECHA)
4. Proposition 65
  - a. Listed carcinogens – “Sufficient evidence of carcinogenicity...”

SUGGESTIVE EVIDENCE OF CARCINOGENICITY

1. IARC:
  - a. Group 3 – “The agent is *not classifiable as to its carcinogenicity to humans*”
2. GHS:
  - a. Group 2 – “Suspected human carcinogens”
3. Recognition as a suspected carcinogen by an authoritative organization (*e.g.*, ECHA).

OEHHA recognizes the ECHA as an “authoritative organization” for evaluating the carcinogenic potential of a substance (see pp. 8-9, Appendix 1). Though not evaluated by IARC, ECHA evaluated TDCPP in 2010 and classified it as a GHS Group 2 “Suspected human carcinogen” (see pp. 8-9, Appendix 1).

**Conclusion:** OEHHA recognizes substances listed as carcinogens under Proposition 65 as having strong evidence of carcinogenicity, whereas it considers compounds classified as GHS Group 2 carcinogens by an authoritative organization as having suggestive evidence of carcinogenicity. Therefore, utilizing the hazard criteria articulated by OEHHA, TDCPP does not meet the “sufficient evidence” standard for listing as a carcinogen under Proposition 65.

**II. The rat bioassay performed using TDCPP was confounded because tumors with human relevance only occurred above the maximum tolerated dose (MTD).**

A single bioassay was performed on TDCPP at three dose levels in which male and female rats in the high dose groups experienced excessive toxicity, which manifested as a greater than 20% decrease in body weight at study termination (see pp. 9-14, Appendix 1).

The U.S. Occupational Safety and Health Administration (OSHA) interprets doses at which excessive toxicity (*e.g.*, greater than 10% decrease in body weight) is observed as having “doubtful potential” for evaluating the carcinogenic potential to humans (*see* p. 12, Appendix 1).

The U.S. OSHA’s interpretation is consistent with the established views of other international organizations. For example, the Organisation for Economic Co-operation and Development and the International Conference on Harmonization have concluded that a decrease in body weight of greater than 10% indicates that the MTD has been exceeded (*see* pp. 11-12, Appendix 1).

When evaluating the carcinogenic potential of TDCPP, the ECHA recognized that the MTD was exceeded in the rat bioassay and that tumors occurring in the high dose group were of questionable relevance for classification and labeling (*see* p. 11, Appendix 1). However, OEHHA utilized the tumor incidence data in the high dose animals as support for its position that TDCPP should be listed as a carcinogen under Proposition 65.

Since the functional relevance of tumors occurring at dose levels in excess of the MTD is unclear for assessing the carcinogenic potential of a substance, it is necessary to evaluate the tumor incidence data at the two lower dose levels where the MTD was not exceeded. The tumor types that were increased in the bioassay for groups in which the MTD was not exceeded were renal cortical adenomas in male and female rats in the middle dose group and testicular interstitial cell tumors in male rats in the middle dose group (*see* pp. 11-14, Appendix 1). These benign tumors (*i.e.*, non invasive) are reflective of sustained proliferative hyperplasia (*i.e.*, renal cortical adenomas) and testosterone dysregulation (*i.e.*, testicular interstitial cell tumors). The latter tumor type occurs *via* a mode of action that is of questionable relevance to humans (*see* p. 13, Appendix 1).

**Conclusion:** OEHHA relied upon the tumor incidence data for groups of animals that received TDCPP in excess of the MTD. For the dose levels where the MTD was not exceeded, only benign tumors of the kidneys and testes were observed. No decrease in latency nor progression to malignancy was observed for these tumor types. When evaluated *in toto*, these data do not satisfy the “sufficient evidence” standard for listing as a carcinogen under Proposition 65.

### **III. OEHHA incorrectly assigned “neoplastic nodules” as “hepatocellular adenomas” when evaluating liver tumors in the rat bioassay on TDCPP.**

Prior to 1986, hepatoproliferative lesions were classified in the rat as “neoplastic nodules” or “hepatocellular carcinomas.” This classification scheme was utilized for the bioassay that was performed on TDCPP and finalized in 1981.

The U.S. National Toxicology Program (NTP) noted that the term “neoplastic nodule” “...permitted some potentially useful drugs and chemicals to be unfairly categorized as carcinogens...” (*see* p. 14, Appendix 1).

In recognition of the above problem, the U.S. NTP replaced the term “neoplastic nodule” in 1986 with “hepatocellular hyperplasia” and “hepatocellular adenoma” (*see* p. 14, Appendix 1).

The hepatoproliferative lesions in the rat bioassay on TDCPP have not been re-evaluated using the current pathological classification scheme. Despite this, OEHHA listed the lesions identified as “neoplastic nodules” by the study pathologist in 1981 as “hepatocellular adenomas” (*see* p. 14, Appendix 1).

**Conclusion:** OEHHA’s re-classification of “neoplastic nodules” as “hepatocellular adenomas” was arbitrary and not based on the conclusions of a diagnostic pathologist. OEHHA’s identification of statistical significance in liver tumors of animals receiving TDCPP at doses in excess of the MTD was likely impacted by this re-classification.

#### **IV. TDCPP is non-genotoxic *in vivo*.**

TDCPP’s genotoxicity database has been critically evaluated by the European Union (EU) under its Risk Assessment Report (RAR) program, the U.S. Agency for Toxic Substances and Disease Registry under its Toxicological Profiles, and the ECHA Working Group on classification and labeling. These evaluations were performed on the screening *in vitro* assays and the definitive *in vivo* assays. Based on the strengths and limitations of these studies, the foregoing agencies concluded that TDCPP is not genotoxic *in vivo* (*see* pp. 15-16, Appendix 1).

The above conclusions, which placed greater ‘weight’ on the *in vivo* (versus *in vitro*) genotoxicity tests, are consistent with the U.S. Environmental Protection Agency’s *GUIDELINES FOR MUTAGENICITY RISK ASSESSMENT* and its *GUIDELINES FOR CARCINOGEN RISK ASSESSMENT* (*see* p. 16, Appendix 1). They are also consistent with the tiered-testing approach utilized under the European Commission’s chemical control law known as “REACH” (*i.e.*, Registration, Evaluation, Authorisation and Restriction of Chemicals), which utilizes *in vitro* genotoxicity studies as a screening approach to determine whether definitive *in vivo* genotoxicity studies need to be performed (*see* pp. 16-17, Appendix 1).

Though OEHHA determined that TDCPP has genotoxic potential, it did not list any criteria from which it ‘weighed’ one genotoxicity study against another. This oversight is significant and undermines OEHHA’s conclusions (*see* pp. 17, Appendix 1).

**Conclusion:** TDCPP’s genotoxicity database has been peer-reviewed by several regulatory/public health agencies. Each concluded that TDCPP is not genotoxic *in vivo*. In contrast, OEHHA concluded that TDCPP is genotoxic, but did not evaluate the quality and reliability of the genotoxicity studies. Rather, OEHHA merely considered positive studies, without considering negative studies, and without providing even a cursory evaluation of the strengths and limitations of the underlying data from each study.

**V. OEHHA incorrectly utilized a structure-activity relationship from various phosphorus flame retardants to inform the metabolism, carcinogenicity, and genotoxicity of TDCPP.**

OEHHA utilized structure-activity relationships (SARs) from tris(2,3-dibromopropyl) phosphate (TDBPP), tris(2-chloroethyl) phosphate (TCEP), and tris(1-chloro-2-propyl) phosphate (TCPP) to inform various endpoints on TDCPP for which experimental data were already available (*see* pp. 19-26, Appendix 1). However, when the EU was preparing RARs on TDCPP, TCEP, and TCPP, it concluded “a quantitative read-across for carcinogenicity from either TDCP or TCEP to TCPP may not be appropriate, including a quantitative read across for the purpose of classification and labelling” (*see* p. 19, Appendix 1).

**Conclusions:** Though SARs may be useful at informing various endpoints on substances for which experimental data do not exist, OEHHA incorrectly utilized this approach to inform endpoints on TDCPP for which experimental data were available. The EU under its RAR program evaluated several of the structurally related compounds (*i.e.*, TCEP and TCPP) independently because they have distinctly different toxicological profiles to TDCPP.

In closing, we appreciate the opportunity to provide our individual views for the CIC’s consideration.

Respectfully yours,

/s/

Marek Banasik, M.D., Ph.D.  
Director & Medical Scientist  
Institute for Public Health and  
Environmental Protection  
Warsaw, Poland

Raymond D. Harbison, Ph.D., ATS  
Professor & Director  
University of South Florida  
Tampa, Florida, U.S.A.

Nepolina K. Chhetri, B.S., M.E.M.  
Program Manager  
Albemarle Corporation  
Baton Rouge, Louisiana, U.S.A.

Richard V. Lee, M.D.  
Professor of Obstetrics and Medicine  
State University of New York  
Buffalo, New York, U.S.A.

Julie E. Goodman, Ph.D., DABT  
Principal Scientist  
Gradient Corporation  
Cambridge, Massachusetts, U.S.A.

Todd Stedeford, Ph.D., J.D., DABT  
Toxicology Advisor & In-house Counsel  
Albemarle Corporation  
Baton Rouge, Louisiana, U.S.A.

**Disclosure of conflicts of interest:** MB and JEG have received compensation from Albemarle Corporation in the past for their contributions on projects involving brominated flame retardants. No form of remuneration was provided for their contribution on these comments. RDH and RVL have no conflicts related to the subject matter of these comments. NKC and TS are employed by Albemarle Corporation, a specialty chemical manufacturer whose product line includes brominated flame retardants. The views and opinions expressed in these comments are those of the signatories and not necessarily those of their respective employers.

## APPENDIX 1

Under Proposition 65, there are four separate mechanisms by which a substance may be listed as a carcinogen.<sup>1</sup> First, the state’s qualified experts (*i.e.*, Carcinogen Identification Committee or CIC) may determine that the substance causes cancer.<sup>2</sup> Second, a substance may be listed if “a body considered to be authoritative” has “formally identified” it as causing cancer.<sup>3</sup> Third, a substance may be listed if a state or federal agency has required it to be listed as causing cancer.<sup>4</sup> Finally, substances may be listed if they are identified as carcinogens under the California Labor Code<sup>5</sup> (*i.e.*, the Labor Code mechanism).<sup>6</sup> The focus of our present evaluation is on the first mechanism (*i.e.*, qualified experts) and the relevant information compiled by the California Environmental Protection Agency’s Office of Environmental Health Hazard Assessment (OEHHA)<sup>7</sup> to inform the CIC’s recommendation. OEHHA (2011a) claimed to utilize a weight-of-evidence approach for evaluating the carcinogenic potential of tris(1,3-dichloro-2-propyl) phosphate (TDCPP or TDCP), which included an evaluation of the following: 1) chronic repeated-dose toxicity, 2) genotoxicity, and 3) structure-activity relationships (SARs). Each of these is discussed further below, but first, the hazard criteria articulated by OEHHA are discussed as they relate to the “sufficient evidence” requirement for listing as a carcinogen under Proposition 65.

### ***1. TDCPP DOES NOT MEET THE “SUFFICIENT EVIDENCE” REQUIREMENTS AS ARTICULATED BY OEHHA FOR LISTING AS A CARCINOGEN UNDER PROPOSITION 65.***

The CIC utilizes the following criteria when evaluating whether or not a substance satisfies the regulatory requirements for listing as a carcinogen:<sup>8</sup>

Sufficient evidence of carcinogenicity exists from studies in experimental animals. For purposes of this paragraph, “sufficient evidence” means studies in experimental animals indicate that there is an increased incidence of malignant tumors or combined malignant and benign tumors in

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<sup>1</sup> Safe Drinking Water and Toxic Enforcement Act of 1986 (California Health and Safety Code §25249.5 *et seq.*) (hereinafter “Proposition 65”).

<sup>2</sup> *Id.* at §25249.8(b).

<sup>3</sup> *Id.*

<sup>4</sup> *Id.*

<sup>5</sup> California Labor Code §6382(b)(1) and (d).

<sup>6</sup> Proposition 65, *supra* note 1, at §25249.8(a).

<sup>7</sup> OEHHA (2011a). *Evidence on the carcinogenicity of tris(1,3-dichloro-2-propyl) phosphate*, Reproductive and Cancer Hazard Assessment Branch, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, 38 pp., available at [http://oehha.ca.gov/prop65/hazard\\_ident/pdf\\_zip/TDCPP070811.pdf](http://oehha.ca.gov/prop65/hazard_ident/pdf_zip/TDCPP070811.pdf) (accessed on September 5, 2011).

<sup>8</sup> Proposition 65, *supra* note 1, at §25306(e)(2).

multiple species or strains, in multiple experiments (e.g., with different routes of administration or using different dose levels), or, to an unusual degree, in a single experiment with regard to high incidence, site or type of tumor, or age at onset.

When formulating its opinion, the CIC determines if the above criteria have been “clearly shown, through scientifically valid testing according to generally accepted principles”.<sup>9</sup> We note that the above requirements for “sufficient evidence” are identical in content to the threshold requirements established by the International Agency for Research on Cancer (IARC) for demonstrating carcinogenicity in experimental animals. IARC’s requirements for *sufficient evidence of carcinogenicity* include the following:<sup>10</sup>

The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide *sufficient evidence*.

A single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites.

When the evidence of carcinogenicity in humans is “limited” or “inadequate”, but the evidence in experimental evidence is “sufficient”, IARC classifies these substances as either Group 2A “The agent is *probably carcinogenic to humans*” or Group 2B “The agent is *possibly carcinogenic to humans*”.<sup>11</sup>

Though not present in Proposition 65, IARC provides an additional category of requirements for substances with *limited evidence of carcinogenicity* in experimental animals. These requirements include the following:<sup>12</sup>

The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

IARC classifies substances with “inadequate” evidence of carcinogenicity in humans and “inadequate” or “limited” evidence of carcinogenicity in experimental animals as Group 3 “The agent is *not classifiable as to its carcinogenicity to humans*”.<sup>13</sup>

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<sup>9</sup> *Id.* at §25305(a)(1).

<sup>10</sup> IARC (2006). *Preamble*, IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS, International Agency for Research on Cancer, World Health Organization, 27 pp., at p. 20, available at <http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf> (accessed on September 5, 2011).

<sup>11</sup> *Id.* at pp. 22-23.

<sup>12</sup> *Id.* at p. 21.

As discussed below, the OEHHA has already determined that an IARC classification of Group 2B or higher (*i.e.*, Group 1 or Group 2A) meets the “sufficient evidence” criteria under Proposition 65, whereas an IARC classification of Group 3 or lower (*i.e.*, Group 4) does not.

With regard to TDCPP, the European Chemicals Agency (ECHA) classified this substance as a “Carcinogen Category 2”,<sup>14</sup> under the European Commission’s (EC’s) implemented version (*i.e.*, Regulation No. 1272/2008; *a.k.a.*, CLP)<sup>15</sup> of the Globally Harmonized System of Classification and Labelling of Chemicals (*a.k.a.*, GHS).<sup>16</sup> A substance classified as a Carcinogen Category 2 “Suspected human carcinogens” meets the following criteria, which are comparable to an IARC Group 3 classification:<sup>17</sup>

The placing of a substance in Category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A [*i.e.*, “known to have carcinogenic potential for humans”] or 1B [*i.e.*, “presumed to have carcinogenic potential for humans”], based on strength of evidence together with additional considerations [referenced section of CLP omitted]. Such evidence may be derived either from limited [footnoted section to CLP omitted] evidence of carcinogenicity in human studies or from **limited evidence of carcinogenicity in animals studies** [emphasis added].

Though Proposition 65 is silent on the comparable classifications under, for example, IARC or GHS, OEHHA has provided an interpretation of the various classifications. Under the State of California’s Green Chemistry Initiative, OEHHA (2011b) proposed the following IARC or GHS classifications and “authoritative organization” recognition as **strong evidence** for carcinogenicity:<sup>18</sup>

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<sup>13</sup> *Id.* at p. 23.

<sup>14</sup> ECHA (2010). *Committee for Risk Assessment, RAC, opinion proposing harmonised classification and labelling at Community level of TDCP (Tris[2-chloro-1-chloromethyl]ethyl]phosphate)*, ECHA/RAC/DOC No CLH-0-000000953-71-03/F, adopted 3 September 2010, European Chemicals Agency, Helsinki, Finland, 48 pp., at p. 2.

<sup>15</sup> EC (2008). *Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 (Text with EEA relevance)*, L 353, OFFICIAL JOURNAL OF THE EUROPEAN UNION, vol. 51, 1355 pp., at p. 104 (Table 3.6.1).

<sup>16</sup> UNECE (2007). *Carcinogenicity*, chapter 3.6, pp. 165-174, at p. 165, GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION AND LABELLING OF CHEMICALS (GHS), United Nations Economic Commission for Europe (UNECE), available at [http://live.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs\\_rev02/English/03e\\_part3.pdf](http://live.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev02/English/03e_part3.pdf) (accessed on September 5, 2011).

<sup>17</sup> EC (2008), *supra* note 15.

<sup>18</sup> OEHHA (2011b). *Modified text of proposed regulations, July 2011, Division 4.5, Title 22, California Code of Regulations, Chapter 54. Green chemistry hazard traits*, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, 27 pp., at p. 6, available at <http://www.oehha.ca.gov/multimedia/green/pdf/072911RevisedGC.pdf> (accessed on September 5, 2011).

1. Meeting the [IARC] criteria for Group 1, 2A, or 2B classification,
2. Meeting the criteria for being classified as a “Category 1 Known [A] or Presumed Carcinogen [B]” under the United Nation’s [GHS], or
3. Recognized as a known or potential carcinogen by an authoritative organization [*e.g.*, ECHA].

OEHHA (2011b) further ranked the following IARC classification and “authoritative organization” recognition as ***suggestive evidence*** of carcinogenicity:<sup>19</sup>

1. Meeting the [IARC] criteria for limited evidence [*i.e.*, Group 3] of carcinogenicity in animals, or
2. Recognition as a suspected carcinogen [*i.e.*, GHS Category 2] [by] an authoritative organization.

When developing its Green Chemistry Hazard Traits criteria, OEHHA stated the following under *Evidence for Carcinogenicity Hazard Trait*:<sup>20</sup>

***Proposition 65*** is updated at least annually and ***is a good source to find chemicals with strong evidence of carcinogenicity*** [emphasis added].

Therefore, it stands to reason that if OEHHA (2011b) only considers IARC Groups 1, 2A, or 2B, GHS Categories 1A or 1B, or Proposition 65 listed carcinogens as strong evidence of carcinogenicity, then the ECHA’s classification of TDCPP as a GHS Category 2 carcinogen does not meet the threshold criteria of “sufficient evidence” for listing under Proposition 65.

**Conclusions:** OEHHA (2011b) recognizes the ECHA as an “authoritative organization”, which classified TDCP as a Category 2 “suspected human carcinogen”. OEHHA (2011b) considers compounds recognized as “suspected human carcinogens” by an “authoritative organization” as ***suggestive evidence*** of carcinogenicity. However, OEHHA (2010) recognizes Proposition 65 listed carcinogens as ***strong evidence*** of carcinogenicity, not ***suggestive evidence***. Therefore, TDCPP does not meet the Proposition 65 requirements for listing as a carcinogen.

## **2. CHRONIC REPEATED-DOSE TOXICITY.**

One long-term carcinogenicity study was completed on TDCPP in 1981; the complete details of the study are not available.<sup>21</sup> However, Freudenthal and Henrich (2000)<sup>22</sup> subsequently

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<sup>19</sup> *Id.* at pp. 6-7.

<sup>20</sup> OEHHA (2010). *Initial statement of reasons, Proposed Division 4.5, Title 22, Cal. Code of Regulations, Chapter 54 Green Chemistry Hazard Traits*, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, 121 pp., at p. 24, available at [http://oehha.ca.gov/multimedia/green/pdf/GC\\_ISOR121710.pdf](http://oehha.ca.gov/multimedia/green/pdf/GC_ISOR121710.pdf) (accessed on September 5, 2011).

<sup>21</sup> OEHHA (2011a), *supra* note 7, at 28, citing: Bio/dynamics, Inc. (1981), *A two year oral toxicity/carcinogenicity study on Fyrol FR-2 in rats (Final report)*, vol. V, submitted to Stauffer Chemical Co. by Bio/dynamics, Inc., project No. 77-2016, Sept. 21, 1981.

published a summary of these data. The European Union (EU) also conducted a critical evaluation of these data in its Risk Assessment Report (RAR) on TDCPP.<sup>23</sup> Table 1 contains the tumor incidence data at 12 and 24 months, as listed in the EURAR (2008a)<sup>24</sup> and OEHHA (2011a).<sup>25</sup>

**TABLE 1. TUMOR INCIDENCE IN SPRAGUE-DAWLEY RATS FED TDCPP IN A 2-YEAR CARCINOGENICITY STUDY**

Organ	Tumor type	Timed evaluation (months)	Sex	Dose group (mg/kg-bw/day)			
				0	5	20	80
Liver	Adenoma <sup>†</sup>	12	Male	0/15 (0%)	0/12 (0%)	0/13 (0%)	3/14 (21%)
			Female	0/11 (0%)	0/13 (0%)	0/9 (0%)	1/10 (10%)
		24	Male	2/45 (4%)	7/48 (15%)	1/48 (2%)	<b>13/46<sup>a,b</sup></b> (28%)
			Female	1/49 (2%)	1/47 (2%)	4/46 (9%)	<b>8/50<sup>a,c</sup></b> (16%)
	Carcinoma	12	Male	0/15 (0%)	0/12 (0%)	0/13 (0%)	0/14 (0%)
			Female	0/11 (0%)	0/13 (0%)	0/9 (0%)	0/10 (0%)
		24	Male	1/45 (2%)	2/48 (4%)	3/48 (6%)	<b>7/46<sup>c,z</sup></b> (15%)
			Female	0/49 (0%)	2/47 (4%)	2/46 (4%)	4/50 (8%)
	Adenoma/carcinoma (combined)	12	Male	0/15 (0%)	0/12 (0%)	0/13 (0%)	3/14 (21%)
			Female	0/11 (0%)	0/13 (0%)	0/9 (0%)	1/10 (10%)
		24	Male	3/45 (7%)	9/48 (19%)	4/48 (8%)	<b>20/46<sup>b</sup></b> (43%)
			Female	1/49 (2%)	3/47 (6%)	6/46 (13%)	<b>12/50<sup>b</sup></b> (24%)
Kidney	Cortical adenoma	12	Male	0/15 (0%)	0/12 (0%)	0/13 (0%)	0/13 (0%)
			Female	0/11 (0%)	0/13 (0%)	0/9 (0%)	0/10 (0%)
		24	Male	1/45 (2%)	3/49 (6%)	<b>9/48<sup>a,c</sup></b> (19%)	<b>32/46<sup>a,b</sup></b> (70%)
			Female	0/49 (0%)	1/48 (2%)	<b>8/48<sup>a,b</sup></b> (17%)	<b>29/50<sup>a,b</sup></b> (58%)
Adrenal	Cortical adenoma	12	Male	0/15 (0%)	---	---	2/13 (15%)
			Female	5/11 (45%)	---	---	1/10 (10%)
		24	Male	5/44 (11%)	3/14 (21%)	5/16 (31%)	3/44 (7%)
			Female	8/48 (17%)	5/27 (19%)	2/33 (6%)	<b>19/49<sup>a,c</sup></b> (39%)
Testes	Interstitial cell tumor	12	Male	0/14 (0%)	0/12 (0%)	3/13 (23%)	3/11 (27%)
		24		7/43 (16%)	8/48 (17%)	<b>23/47<sup>a,b</sup></b> (49%)	<b>36/45<sup>a,b</sup></b> (80%)

<sup>22</sup> 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, vol. 19, pp. 119-125.

<sup>23</sup> EURAR (2008a). *Tris[2-chloro-1-(chloromethyl)ethyl] phosphate (TDCP)*, CAS No: 13674-87-8, EINECS No: 237-159-2, Risk assessment, EUROPEAN UNION RISK ASSESSMENT REPORT (EURAR), 294 pp., at pp. 159-161, available at [http://echa.europa.eu/doc/trd\\_substances/tris\\_2\\_chloro\\_1\\_chloromethyl\\_ethyl\\_phosphate\\_tcdp/rar/trd\\_rar\\_ireland\\_tdep.pdf](http://echa.europa.eu/doc/trd_substances/tris_2_chloro_1_chloromethyl_ethyl_phosphate_tcdp/rar/trd_rar_ireland_tdep.pdf) (accessed on September 5, 2011).

<sup>24</sup> *Id.* at p. 160 (Table 4.46).

<sup>25</sup> OEHHA (2011a), *supra* note 7, at p. 6 (Table 1).

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† Note, although these liver lesions are listed as adenoma, the pathologist from the Bio/dynamics (1981) study described these lesions as “neoplastic nodules”.<sup>26</sup> The significance of this is discussed under §2.B.

‡ Note, OEHHA (2011a) reported statistical significance in this group; however, the EURAR (2008a)<sup>27</sup> and Freudenthal and Henrich (2000)<sup>28</sup> did not identify statistical significance in this group.

<sup>a</sup> Statistical significance ( $p < 0.05$ ), as reported in the EURAR (2008a).<sup>29</sup>

<sup>b</sup> Statistical significance ( $p < 0.01$ ), as reported by OEHHA (2011a).<sup>30</sup>

<sup>c</sup> Statistical significance ( $p < 0.05$ ), as reported by OEHHA (2011a).<sup>31</sup>

<sup>d</sup> Animals not evaluated at 12 months.

As shown in Table 1, the animals at terminal sacrifice had statistically significantly increased incidences of hepatocellular adenomas (high dose groups; male and female), hepatocellular carcinomas (high dose group; male only), hepatocellular adenomas/carcinomas (combined) (high dose groups; male and female), renal cortical adenomas (mid- and high dose groups; male and female), adrenal cortical adenomas (high dose group; female only), and testicular interstitial cell tumors (mid- and high-dose groups; male only).

At first glance, the data for hepatocellular carcinomas (high dose group; male only) and hepatocellular adenomas/carcinomas (combined) (high dose group; male and female) appear to meet the “sufficient evidence” criteria for listing under Proposition 65; however, as discussed below, there are two issues that preclude such a determination.

#### *2.A. THE RAT BIOASSAY PERFORMED USING TDCPP WAS CONFOUNDED BECAUSE TUMORS WITH HUMAN RELEVANCE ONLY OCCURRED ABOVE THE MAXIMUM TOLERATED DOSE (MTD).*

The body weights of the male and female rats in the high dose groups were decreased by greater than 20% compared to the controls at terminal sacrifice.<sup>32</sup> When the ECHA issued its opinion on the proposed classification and labeling for TDCPP, it noted that the limit dose of 80 mg/kg-bw/day exceeded the MTD for the study; this information along with EHCA’s conclusion that TDCPP is not genotoxic was used to classify TDCPP as a “suspected human carcinogen” (*i.e.*, GHS category 2).<sup>33</sup> The ECHA’s opinion is consistent with current validated test guidelines for conducting carcinogenicity studies on industrial chemicals and pharmaceuticals, which state.<sup>34,35</sup>

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<sup>26</sup> *Id.* at p. 17.

<sup>27</sup> EURAR (2008a), *supra* note 23, at p. 160 (Table 4.46).

<sup>28</sup> Freudenthal RI and Henrich RT (2000), *supra* note 22, at p. 124 (Table 5).

<sup>29</sup> EURAR (2008a), *supra* note 23, at p. 160 (Table 4.46).

<sup>30</sup> OEHHA (2011a), *supra* note 7, at p. 6 (Table 1).

<sup>31</sup> *Id.*

<sup>32</sup> EURAR (2008a), *supra* note 23, at p. 159; *see also*: OEHHA (2011a) *supra* note 1, at p. 9.

<sup>33</sup> ECHA (2010), *supra* note 14, at p. 4.

<sup>34</sup> OECD (2009). *Carcinogenicity studies*, Test Guideline 451, OECD GUIDELINE FOR THE TESTING OF CHEMICALS, 15 pp., at p. 5 (para. 22).

[T]he highest dose level should normally be chosen to elicit evidence of toxicity, as evidenced by, for example, depression of body weight gain (approximately 10%).

The top dose or maximum tolerated dose is that which is predicted to produce a minimum toxic effect over the course of the carcinogenicity study. Such an effect can be predicted from a 90-day dose range-finding study in which minimal toxicity is observed. Factors to consider are alterations in physiological function which would be predicted to alter the animal's normal life span or interfere with interpretation of the study. Such factors include: ***no more than 10% decrease in body weight gain relative to controls***; target organ toxicity; significant alterations in clinical pathological parameters [emphasis added].

Further, the U.S. Occupational Safety and Health Administration (OSHA) stated the following about tumors occurring in animals at dose levels causing severe toxicity:<sup>36</sup>

Tumors occurring only at excessive doses associated with severe toxicity generally have doubtful potential for carcinogenicity in humans.

Therefore, the Bio/dynamics (1981) study does not clearly demonstrate TDCPP carcinogenicity through scientifically valid testing. Because the MTD was exceeded, the incidences of tumors in the high dose groups occurred against the background of excessive toxicity, thereby confounding the relevance of these data for evaluating the carcinogenic hazard of TDCPP. We also note that the tumors occurring with statistical significance in the kidney, adrenal gland, and testes of the high-dose animals were non invasive (*i.e.*, benign). No statistically significant increases in invasive tumors (*i.e.*, malignancies) were identified in these organs at any dose level.

Since excessive toxicity was not observed in the low- and mid-dose groups, any statistically significantly increased incidences of tumors at these dose levels are relevant for determining whether TDCPP meets the "sufficient evidence" criteria for listing as a carcinogen. Excluding the high-dose groups, no malignant tumors were identified. However, the incidences of benign tumors were statistically significantly increased in the kidney (middle dose; males and females) and the testes (middle dose; males only) and are discussed below.

The percentages of male and female rats in the middle dose groups (*i.e.*, 20 mg/kg-bw/day) with benign renal cortical adenomas were increased by 17% compared to the respective controls at study termination (Table 1). The increased incidence was statistically significantly different; however, no increase in the incidence of these lesions in male or female rats was observed at the interim (12 months) sacrifice at any dose level, including the limit dose. Therefore, TDCPP did not cause a decrease in the time to tumor formation. The EURAR (2008a) noted that at 24

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<sup>35</sup> ICH (2008). *Dose selection for carcinogenicity studies of pharmaceuticals SIC(R2)*, ICH Harmonized Tripartite Guideline, INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE, 12 pp., at pp. 2-3.

<sup>36</sup> OSHA (2009). *Hazard communication, proposed rule*, FEDERAL REGISTER, vol. 74, pp. 50279-50549, at *Confounding effects of excessive toxicity or localized effects* under Appendix F to §1910.1200- Guidance for Hazard Classifications Re: Carcinogenicity (Non-Mandatory), available at [http://www.osha.gov/pls/oshaweb/owadis.show\\_document?p\\_table=FEDERAL\\_REGISTER&p\\_id=21110](http://www.osha.gov/pls/oshaweb/owadis.show_document?p_table=FEDERAL_REGISTER&p_id=21110) (accessed on September 5, 2011).

months, hyperplasia of the convoluted tubule epithelium was found in females in the high dose group and in males of all treatment groups.<sup>37</sup> Thus, the renal cortical adenomas were likely the result of treatment-related sustained hyperplasia, which did not progress to invasive tumors at any dose level.

The incidence of benign testicular interstitial cell tumors in male rats was statistically significantly increased at the middle dose, by up to 33% above the control values (Table 1). Historically, the spontaneous occurrence of these lesions in the Sprague-Dawley rat strain is approximately 4% (*cf.* 16% in the Bio/dynamics, 1981, study).<sup>38</sup> Though these types of nonlethal tumors are common in rats and steadily increase with age,<sup>39</sup> the reported human incidence of this tumor type is approximately 132,500-fold less than the spontaneous incidence observed in CD rats, which have a historical incidence (*i.e.*, 5.3%) at about the same level as Sprague-Dawley rats.<sup>40</sup> The discrepancy in the susceptibility of rodents versus humans to this type of tumor is likely due to the mode of action by which these tumors develop in rodents, which is of questionable relevance to humans.<sup>41</sup> For example, rodents lack ‘sex hormone binding globulin’ (SHBG), a protein that binds testosterone.<sup>42</sup> In humans, SHBG is synthesized by the liver and binds approximately 95% of testosterone in the peripheral blood, which minimizes testosterone metabolism and clearance.<sup>43</sup> Human SHBG maintains a balance between free and bound testosterone, which makes it difficult to perturb peripheral testosterone levels in man.<sup>44</sup> Because rodents lack SHBG, rat testes are more susceptible to xenobiotic-induced disruption of testosterone levels.<sup>45</sup> Cook *et al.* (1999) noted “[a] similar analogy has been described for the thyroid gland, where rats lack thyroid binding globulin and its absence, which contributes to the species differences in response to long-term alterations in the thyroid axis [citation omitted].”<sup>46</sup>

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<sup>37</sup> EURAR (2008a), *supra* note 23, at p. 161.

<sup>38</sup> Derelanko MJ (2002). *Carcinogenesis*, chapter 16, pp. 621-647, at p. 628 (Table 16.5), IN: HANDBOOK OF TOXICOLOGY, Second Edition (Eds. Derelanko MJ and Hollinger MA), 1414 pp., CRC Press LLC, Boca Raton, Florida, U.S.A.

<sup>39</sup> Haseman JK, Young E, Eustis SL, *et al.* (1997). *Body weight-tumor incidence correlations in long-term rodent carcinogenicity studies*, TOXICOLOGIC PATHOLOGY, vol. 25, pp. 256-263, at p. 261.

<sup>40</sup> Cook JC, Klinefelter GR, Hardisty JF, *et al.* (1999). *Rodent Leydig cell tumorigenesis: a review of the physiology, pathology, mechanisms, and relevance to humans*, CRITICAL REVIEWS IN TOXICOLOGY, vol. 29, pp. 169-261, at p. 233.

<sup>41</sup> *Id.* at pp. 233-237.

<sup>42</sup> *Id.* at p. 234.

<sup>43</sup> *Id.*

<sup>44</sup> *Id.*

<sup>45</sup> *Id.*

<sup>46</sup> *Id.*

**Conclusions:** The Bio/dynamics (1981) carcinogenicity study utilized an upper limit dose that exceeded the MTD. No statistically significant differences in the incidence of malignant tumors or the combined incidences of benign/malignant tumors were observed at any dose levels, where the MTD was not exceeded.

*2.B. OEHHA INCORRECTLY ASSIGNED “NEOPLASTIC NODULES” AS “HEPATOCELLULAR ADENOMAS” WHEN EVALUATING LIVER TUMORS IN THE RAT BIOASSAY ON TDCPP.*

OEHHA (2011a) described the liver lesions from the Bio/dynamics (1981) study as “hepatocellular adenomas”; however, the study pathologist from the Bio/dynamics (1981) study classified the liver lesions as “neoplastic nodules”.<sup>47</sup> The distinction between the two classifications is significant. In 1986, the U.S. National Toxicology Program (NTP) adopted a revised classification scheme for hepatocellular proliferative lesions.<sup>48</sup> NTP stated the following about the adopted change:<sup>49</sup>

[H]epatocellular hyperplasia and hepatocellular adenoma are to be used for lesions which were previously combined under the diagnosis of neoplastic nodule.

NTP noted the following about the term “neoplastic nodule”:<sup>50</sup>

[T]he imposition of [the] new, misunderstood term, *neoplastic nodule*... essentially left the less decisive diagnostic pathologist off the hook. If not convinced, call it neoplastic nodule, rather than hyperplastic nodule, and the diagnosis would not likely be challenged by reviewing panels. This allowance for lack of confidence and self-discipline has permitted some potentially useful drugs and chemicals to be unfairly categorized as carcinogens, sometimes to be reassigned by a more discerning group of pathologists at a later review.

**Conclusions:** The hepatocellular lesions identified by OEHHA (2011a) as adenomas were actually diagnosed by the study pathologist as “neoplastic nodules”. Since a re-evaluation of these tissues has not been performed under the current pathological classification scheme, the neoplastic potential of “neoplastic nodules” is unclear because when this terminology was in use, it included both non-neoplastic (*i.e.*, hyperplasia) and neoplastic (*i.e.*, adenoma) lesions. Therefore, the assignment of “neoplastic nodules” under the rubric of “hepatocellular adenomas” is simply incorrect. Regardless, the lesions identified as “hepatocellular adenomas” were only statistically significantly increased in male and female rats fed TDCPP in excess of the MTD.

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<sup>47</sup> OEHHA (2011a), *supra* note 7, at p. 17; *see also*: Freudenthal RI, and Henrich RT (2000), *supra* note 22, at p. 124.

<sup>48</sup> Maronpot RR, Montgomery CA Jr., Boorman GA, *et al.* (1986). *National Toxicology Program nomenclature for hepatocellular lesions of rats*, TOXICOLOGIC PATHOLOGY, vol. 14, pp. 263-273.

<sup>49</sup> *Id.* at p. 263.

<sup>50</sup> *Id.*

### 3. TDCPP IS NON-GENOTOXIC *IN VIVO*.

The genotoxicity database on TDCPP has been extensively evaluated and peer reviewed by an independent consultant and a number of regulatory/public health agencies.<sup>51,52, 53,54</sup> The conclusions from these evaluations are presented below:

□ EBRC (2005):<sup>55</sup>

[T]he data base on genotoxicity of TDCPP can be considered as comprehensive and adequate for assessment, and by applying a “weight-of-evidence” approach based on the ranking of the individual results according to their reliability, it is reasonable to assume that ***TDCPP is void of genotoxic potential*** [emphasis added].

□ EURAR (2008a):<sup>56</sup>

There is some evidence to suggest that TDCPP is mutagenic *in vitro*. However, *in vivo* mutagenicity studies were negative, indicating that, ***in vivo, TDCPP is non-genotoxic*** [emphasis added].

When the EU evaluated the carcinogenicity data along with the genotoxicity data, it concluded the following:<sup>57</sup>

***TDCPP may be assumed to be a threshold carcinogen*** [emphasis added].

□ ATSDR (2009):<sup>58</sup>

For the most part, ***the phosphate ester flame retardants*** [*i.e.*, TDCPP, tris(2-chloroethyl) phosphate (TCEP), tributyl phosphate, tributoxyethyl phosphate, triphenyl phosphate, tris(1-chloro-2-propyl) phosphate (TCPP), and triisobutyl phosphate] ***subject of this profile have provided negative evidence of mutagenicity in in vitro tests*** with prokaryotic organisms (*i.e.*, *Salmonella typhimurium*) and mammalian cell systems. ***In vivo studies have, for the most part, also provided negative results*** [emphasis added].

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<sup>51</sup> EBRC (2005). *Review of genotoxicity studies, Tris[2-chloro-1(chloromethyl)ethyl]phosphate*, EBRC Consulting GmbH (EBRC), Hannover, Germany, 13 pp.

<sup>52</sup> EURAR (2008a), *supra* note 23, at pp. 151-159.

<sup>53</sup> ATSDR (2009). *Draft toxicological profile for phosphate ester flame retardants*, Agency for Toxic Substances and Disease Registry (ATSDR), Public Health Service, U.S. Department of Health and Human Services, 359 pp., at pp. 137-143.

<sup>54</sup> ECHA (2010), *supra* note 14, at Annex 1, pp. 11-14.

<sup>55</sup> EBRC (2005), *supra* note 51, at p. 2.

<sup>56</sup> EURAR (2008a), *supra* note 23, at p. 163.

<sup>57</sup> *Id.*

<sup>58</sup> ATSDR (2009), *supra* note 53, at p. 137.

□ ECHA (2010):<sup>59</sup>

Regarding notably the five negative *in vivo* assays, it is considered that *TDCP is not genotoxic in vivo* and thus no classification for mutagenicity is proposed [emphasis added].

The above conclusions are based in large part on the *in vivo* genotoxicity data. Though all of the genotoxicity data (*i.e.*, *in vitro* and *in vivo*) were considered, greater “weight” was placed on the definitive *in vivo* studies, rather than the screening *in vitro* studies. This approach—that is, placing greater emphasis on *in vivo* studies, is consistent with the recommendations of the U.S. Environmental Protection Agency (EPA) in its *GUIDELINES FOR MUTAGENICITY RISK ASSESSMENT*<sup>60</sup> and its *GUIDELINES FOR CARCINOGEN RISK ASSESSMENT*.<sup>61</sup> It is also consistent with the tiered-testing approach utilized under the European Commission’s chemical control law known as “REACH” (*i.e.*, Registration, Evaluation, Authorisation and Restriction of Chemicals).<sup>62</sup> As shown in Table 2, *in vitro* studies are used as a screening to determine whether definitive *in vivo* studies need to be performed.

**TABLE 2. TIERED-TESTING REQUIREMENTS FOR GENOTOXICITY UNDER REACH**

<i>Quantity manufactured or imported per year (tonnes)</i>	<i>Standard information requirement</i>	<i>Specific rules for adaptation from column 2</i>
≥ 1	<u>Test 1:</u> <i>In vitro</i> gene mutation study in bacteria. <sup>63</sup>	Further mutagenicity studies shall be considered in case of a positive result.
≥ 10	<u>Test 2:</u> <i>In vitro</i> cytogenicity study in mammalian cells or <i>in vitro</i> micronucleus study.	The study does not usually need to be conducted – if adequate data from an <i>in vivo</i> cytogenicity test are available, or – the substance is known to be carcinogenic category 1 or 2 or mutagenic category 1, 2 or 3. <sup>64</sup>
	<u>Test 3:</u> <i>In vitro</i> gene mutation study in mammalian cells, if a negative result in Test 1 and Test 2.	The study does not usually need to be conducted if adequate data from a reliable <i>in vivo</i> mammalian gene mutation test are available. Appropriate <i>in vivo</i> mutagenicity studies shall be considered in case of a positive result in any of the genotoxicity studies for Test 1, Test 2, or Test 3. <sup>65</sup>

<sup>59</sup> ECHA (2010), *supra* note 14, at Annex 1, p. 14.

<sup>60</sup> EPA (1986). *Guidelines for mutagenicity risk assessment*, EPA/630/R-98/003, Risk Assessment Forum, U.S. Environmental Protection Agency, 23 pp., at p. 12.

<sup>61</sup> EPA (2005). *Guidelines for carcinogen risk assessment*, EPA/630/P-03/001F, Risk Assessment Forum, U.S. Environmental Protection Agency, 166 pp., at p. 2-36.

<sup>62</sup> EC (2007). *Corrigendum to Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC*, L 136, OFFICIAL JOURNAL OF THE EUROPEAN UNION, vol. 50, 278 pp.

<sup>63</sup> *Id.* at p. 106.

<sup>64</sup> *Id.* at p. 107.

<p>≥ 100</p>	<p><u>Test 4:</u> <i>In vivo</i> somatic cell genotoxicity study.</p> <p><u>Test 5:</u> <i>In vivo</i> germ cell mutagenicity study.</p>	<p>If there is a positive result in any of the <i>in vitro</i> genotoxicity studies in Test 1, Test 2, or Test 3 and there are no results available from an <i>in vivo</i> study already, an appropriate <i>in vivo</i> somatic cell genotoxicity study shall be proposed by the registrant.</p> <p>If there is a positive result from an <i>in vivo</i> somatic cell study available, the potential for germ cell mutagenicity should be considered on the basis of all available data, including toxicokinetic evidence. If no clear conclusions about germ cell mutagenicity can be made, additional investigations shall be considered.<sup>66</sup></p>
<p>≥ 1,000</p>	<p><u>Test 6:</u> <i>In vivo</i> somatic cell genotoxicity study (2nd study).</p> <p><u>Test 5:</u> <i>In vivo</i> germ cell mutagenicity study (if not already performed under the ≥ 100 tonnes tier).</p>	<p>If there is a positive result in any of the <i>in vitro</i> genotoxicity studies in Test 1, Test 2, or Test 3, a second <i>in vivo</i> somatic cell test may be necessary, depending on the quality and relevance of all the available data.</p> <p>If there is a positive result from an <i>in vivo</i> somatic cell study available, the potential for germ cell mutagenicity should be considered on the basis of all available data, including toxicokinetic evidence. If no clear conclusions about germ cell mutagenicity can be made, additional investigations shall be considered.<sup>67</sup></p>

OEHHA (2011a) summarized many of the genotoxicity studies on TDCPP,<sup>68</sup> however, it did not perform an evaluation of the quality, relevance, and reliability of the data from these studies. In contrast to the conclusions from EBRC (2005), EURAR (2008a), ATSDR (2009), and ECHA (2010) that TDCPP is not genotoxic, OEHHA stated the following about the genotoxicity of TDCPP:<sup>69</sup>

TDCPP is genotoxic in multiple *in vitro* studies of bacterial and mammalian cells. It induced mutations in *Salmonella* and mouse lymphoma cells, induced chromosomal aberrations in mouse lymphoma and Chinese hamster fibroblast cells, and induced sister chromatid exchange (SCE) in mouse lymphoma cells. There is also evidence for DNA binding in mouse kidney, liver and muscle following *in vivo* exposure. TDCPP induced malignant cell transformation of Syrian hamster embryo cells in culture.

OEHHA (2011a) did not list any criteria from which it ‘weighed’ one genotoxicity study against another. This oversight is significant and undermines OEHHA’s conclusions. The ECHA recognized the importance of evaluating the relevance and reliability of studies and stated the following in its REACH guidance document on evaluating data:<sup>70</sup>

***The knowledge of how a study was carried out and consequently its relevance and reliability, is a prerequisite for the subsequent evaluation of information*** [emphasis added].

<sup>65</sup> *Id.* at p. 108.

<sup>66</sup> *Id.* at p. 112.

<sup>67</sup> *Id.* at p. 116.

<sup>68</sup> OEHHA (2011a), *supra* note 7, at pp. 7-13.

<sup>69</sup> *Id.* at p. 1.

<sup>70</sup> ECHA (2008). *Guidance on information requirements and chemical safety assessment, Chapter R.4: Evaluation of available information*, GUIDANCE FOR THE IMPLEMENTATION OF REACH, 23 pp., at p. 7.

A number of regulatory agencies have recognized the problem of not utilizing objective and transparent criteria from which to evaluate data, and have formally issued specific screening criteria for assessing the quality, reliability, and relevancy of data used in support of regulatory decisions. For example, the ECHA formally adopted the criteria, originally set forth by Klimisch *et al.* (1997),<sup>71</sup> whereas European Food Safety Authority (EFSA) recommended the Klimisch approach as an alternative screening option.<sup>72,73</sup>

Since non-industry research goes “...through [a] rigorous, multistage scientific review that is normal for academic data funded by federal agencies and published in the peer-reviewed literature”,<sup>74</sup> an obvious question is why should government agencies have to expend time and resources with screening studies or performing additional critical reviews of published peer-reviewed science? The answer is simple. Researchers make mistakes,<sup>75</sup> journal reviewers overlook overt deficiencies in studies,<sup>76</sup> and some researchers fabricate data.<sup>77</sup>

**Conclusions:** TDCPP’s genotoxicity database has been peer-reviewed in the EURAR (2008a), ATSDR (2009), and ECHA (2010). These regulatory/public health agencies evaluated the quality and reliability of the data and concluded that TDCPP is not genotoxic. An independent consultant came to the same conclusion. In contrast, OEHHA concluded that TDCPP is genotoxic, but did not evaluate the quality and reliability of the genotoxicity studies. Rather, OEHHA did not conduct a true weight of evidence analysis, instead it emphasized positive

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<sup>71</sup> Klimisch H-J, Andreae M, and Tillman U (1997). *A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data*, REGULATORY TOXICOLOGY AND PHARMACOLOGY, vol. 25, pp. 1-5.

<sup>72</sup> ECHA (2008), *supra* note 70, at p. 9.

<sup>73</sup> EFSA (2011). *Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009*, EFSA JOURNAL, vol. 9, 49 pp., at p. 28.

<sup>74</sup> Myers JP, vom Saal FS, Akingbemi BT, *et al.* (2009). *Why public health agencies cannot depend on Good Laboratory Practices as a criterion for selecting data: the case of bisphenol A*, ENVIRONMENTAL HEALTH PERSPECTIVES, vol. 117, pp. 309-315, at p. 309.

<sup>75</sup> *See, e.g.*, Ford CE, Ekström EJ, and Anderson T (2010). *Retraction for “Wnt-5a signaling restores tamoxifen sensitivity in estrogen receptor-negative breast cancer cells”*, PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, vol. 107, p. 22360. “During efforts to extend this work, we re-examined the laboratory records for all figures and found that the Excel files on which Fig. 4C was based contained serious calculation errors; the first author of the paper takes full responsibility for these inaccuracies. Considering the importance of this figure for the conclusions drawn, the authors hereby retract the work.”

<sup>76</sup> *See, e.g.*, Hong SK, Sohn KH, Kim IY, *et al.* (2010). *Polybrominated diphenyl ethers orally administration to mice were transferred to offspring during gestation and lactation with disruptions on the immune system*, IMMUNE NETWORK, vol. 10, pp. 64-74, at p. 65 (*e.g.*, 1. gavage volume not stated; 2. no mention of whether litters were culled; 3. no justification for doses of 2,500 mg/kg-bw/day or 12,500 mg/kg-bw/day; *etc.*).

<sup>77</sup> *See, e.g.*, Dyer C (2010). *Wakefield was dishonest and irresponsible over MMR research, says GMC*, BRITISH MEDICAL JOURNAL, vol. 340, p. c593.

studies and essentially ignored negative studies, without providing an evaluation of the strengths and limitations of the underlying data from each study.

#### **4. OEHHA INCORRECTLY UTILIZED A SAR FROM VARIOUS PHOSPHORUS FLAME RETARDANTS TO INFORM THE METABOLISM, CARCINOGENICITY, AND GENOTOXICITY OF TDCPP.**

When the EU was developing RARs on TDCPP, TCEP and TCPP, it concluded the following about performing a read across for these compounds.<sup>78</sup>

[I]t is considered that there is sufficient information from the structures, physical-chemical properties, toxicokinetics and mutagenic profiles of TCEP, TDCP and TCPP to support a qualitative read-across for carcinogenicity. However, based on the available data, there are some differences in the metabolism, target organs, the severity of the effects observed and the potency of the three substances, which indicate that ***a quantitative read-across for carcinogenicity from either TDCP or TCEP to TCPP may not be appropriate, including a quantitative read across for the purpose of classification and labelling*** [emphasis added].

##### **4.A. METABOLISM.**

OEHHA (2011a) stated: “[s]everal compounds [*i.e.*, 1,3-dichloro-2-propanol (1,3-DCP) and 3-monochloropropane-1,2-diol (3-MCPD)] that are potential products of the metabolism of TDCPP are known to cause cancer [reference to figures omitted].”<sup>79</sup> This qualitative statement fails to consider the quantitative differences in absorption, distribution, metabolism, and excretion of these compounds. OEHHA (2011a) devotes nearly a page of text to discuss the carcinogenicity and genotoxicity of the metabolites of 1,3-DCP (*i.e.*, 3-MCPD, epichlorohydrin, 1,3-dichloroacetone, and glycidol).<sup>80</sup> Though evaluating the toxicity of potential metabolites of TDCPP may be appropriate in the absence of data on TDCPP, it is simply unacceptable to use this approach when experimental data on TDCPP exist, which inform its potential for carcinogenicity and genotoxicity. Further, OEHHA (2011a) relied primarily on a review article by Ulsamer *et al.* (1980) as support that 1,3-DCP was “the only metabolite detected in the urine of TDCPP-treated animals (rats and rabbits; [citation omitted]).”<sup>81</sup> However, OEHHA (2011a) noted that “[e]xperimental details were not provided [in Ulsamer *et al.*, 1980].”<sup>82</sup> Subsequent studies confirmed bis(1,3-dichloro-2-propyl) phosphate (BDCPP) and 1,3-dichloro-2-propyl phosphate (MDCPP) as major and minor metabolites, respectively.<sup>83,84</sup> OEHHA (2011a) noted this in the last paragraph of its discussion on TDCPP Metabolites by stating:

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<sup>78</sup> EURAR (2008b). *Tris(2-chloro-1-methylethyl) phosphate (TCPP)*, CAS No: 13674-84-5, EINECS No: 237-158-7, *Risk assessment*, EUROPEAN UNION RISK ASSESSMENT REPORT, 408 pp., at p. 225, available at [http://echa.europa.eu/doc/trd\\_substances/tris\\_2\\_chloro\\_1\\_methylethyl\\_phosphate\\_tcpp/rar/trd\\_rar\\_ireland\\_tcpp.pdf](http://echa.europa.eu/doc/trd_substances/tris_2_chloro_1_methylethyl_phosphate_tcpp/rar/trd_rar_ireland_tcpp.pdf) (accessed on September 5, 2011).

<sup>79</sup> OEHHA (2011a), *supra* note 7, at p. 18.

<sup>80</sup> *Id.*

<sup>81</sup> *Id.* at p. 14.

<sup>82</sup> *Id.*

The primary metabolite of TDCPP found in the urine of exposed animals is the diester BDCPP. This compound has not been tested for carcinogenicity in experimental animals. Limited testing in *S. typhimurium in vitro* has provided no evidence for mutagenicity.

The above quote is significant because two separate studies identified BDCPP as the primary metabolite in urine, accounting for 67% or 63% of the applied dose.<sup>85</sup> Nomeir *et al.* (1981) hypothesized that “[t]he lack of further metabolism of [BDCPP] is thought to be due to the polarity of the acid formed by the dealkylation. This polar metabolite should partition out of the microsomes into aqueous phase making it unavailable for further metabolism.”<sup>86</sup>

**Conclusions:** The major metabolite identified in rats dosed with TDCPP is a stable diester with no evidence of mutagenicity. This finding is consistent with absence of progression to malignancy for the benign tumor types diagnosed in the TDCPP rat bioassay at dose levels where the MTD was not exceeded.

#### 4.B. CHEMICALS STRUCTURALLY-RELATED TO TDCPP.

OEHHA (2011a) relied upon the structural similarity of the phosphorus flame retardants listed in Table 3 as supporting information for its conclusion that TDCPP should be listed as a carcinogen.<sup>87</sup>

**TABLE 3. STRUCTURES OF TDCPP, TDBPP, TCEP, AND TCPP**

<i>Substance name</i>	<i>CASRN</i>	<i>Structure</i>
Tris(1,3-dichloro-2-propyl) phosphate (TDCPP)	13674-87-8	
Tris(2,3-dibromopropyl) phosphate (TDBPP)	126-72-7	
Tris(2-chloroethyl) phosphate (TCEP)	115-96-8	

<sup>83</sup> Nomeir AA, Kato S, and Matthews HB (1981). *The metabolism and disposition of tris(1,3-dichloro-2-propyl) phosphate (Fyrol FR-2) in the rat*, TOXICOLOGY AND APPLIED PHARMACOLOGY, vol. 57, pp. 401-413, at p. 410.

<sup>84</sup> Lynn RK, Wong K, Garvie-Gould C, *et al.* (1981). *Disposition of the flame retardant, tris(1,3-dichloro-2-propyl) phosphate, in the rat*, DRUG METABOLISM AND DISPOSITION, vol. 9, pp. 434-441, at p. 436.

<sup>85</sup> OEHHA (2011a), *supra* note 7, at p. 13 (citing Nomeir *et al.*, 1981) and p. 14 (citing Lynn *et al.*, 1981).

<sup>86</sup> Nomeir AA, Kato S, and Matthews HB (1981), *supra* note 83, at p. 411.

<sup>87</sup> OEHHA (2011a), *supra* note 7, at pp. 18-19.

Tris(1-chloro-2-propyl) phosphate (TCPP)	13674-84-5	
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#### 4.B.1. TDBPP.

SARs are useful for informing data *gaps* on structurally similar compounds; however, it is inappropriate to use this approach to inform endpoints when experimental data exist for the substance under evaluation. For example, OEHHA (2011a) stated the following about TDBPP:<sup>88</sup>

[TDBPP], a brominated analogue of TDCPP, is a phosphate triester that is halogenated with bromine instead of chlorine [citation to table omitted]. TDBPP is carcinogenic in both sexes of rats and mice, inducing tumors at multiple sites in mice, and is genotoxic *in vitro* and *in vivo* [citation omitted].

If taken at face value, the above statement may lead one to conclude that the carcinogenicity and genotoxicity of TDCPP is similar to that of TDBPP. This conclusion would be incorrect. The metabolism, carcinogenicity, and genotoxicity of TDCPP and TDBPP are distinctly different. Lynn *et al.* (1980) determined that Sprague-Dawley rats intravenously administered TDCPP or TDBPP excreted ~54% or ~57% of the radiolabeled dose in urine by 120 hours, respectively.<sup>89</sup> Though MDCPP was the major diester metabolite of TDCPP, accounting for ~62% of the radiolabelled dose in urine, the corresponding diester metabolite for TDBPP (*i.e.*, bis(2,3-dibromopropyl)phosphate) accounted for ~8% of the radiolabelled dose in urine.<sup>90</sup>

TDBPP has been evaluated for carcinogenicity in rats and mice.<sup>91</sup> A summary of the tumor incident data for these species is provided in Table 4.

**TABLE 4. TUMOR INCIDENCE IN F344 RATS AND B6C3F1 MICE FED TDBPP IN CARCINOGENICITY STUDIES**

RATS					
Organ	Tumor type	Sex	Dose group (mg/kg-bw/day) <sup>†</sup>		
			0	2	4
Kidney <sup>92</sup>	Adenoma	Male	0/53 (0%)	<b>26/54<sup>a</sup></b> (48%)	<b>26/54<sup>a</sup></b> (48%)
		Female	0/52 (0%)	4/54 (7%)	<b>10/54<sup>a</sup></b> (19%)
	Carcinoma	Male	0/53 (0%)	0/54 (0%)	3/54 (6%)
		Female	0/52 (0%)	0/54 (0%)	0/54 (0%)

<sup>88</sup> OEHHA (2011a), *supra* note 7, at pp. 18.

<sup>89</sup> Lynn RK, Wong K, Dickinson RG, *et al.* (1980). *Diester metabolites of the flame retardant chemicals, tris(1,3-dichloro-2-propyl)phosphate and tris(2,3-dibromopropyl)phosphate in the rat: identification and quantification*, RESEARCH COMMUNICATIONS IN CHEMICAL PATHOLOGY AND PHARMACOLOGY, vol. 28, pp. 351-360, at p. 355.

<sup>90</sup> *Id.* at pp. 355 and 358.

<sup>91</sup> NCI (1978). *Bioassay of tris (2,3-dibromopropyl) phosphate for possible carcinogenicity*, CAS No. 126-72-7, NCI-CG-TR-76, CARCINOGENESIS TECHNICAL REPORT SERIES, No. 76, National Cancer Institute (NCI), National Institutes of Health, Public Health Service, U.S. Department of Health, Education, and Welfare, 126 pp.

<sup>92</sup> *Id.* at p. A-4 (male rats) and p. A-9 (female rats).

		MICE			
		Sex	0	70	140
Adenoma/carcinoma (combined)		Male	0/53 (0%)	<b>26/54<sup>a</sup></b> (48%)	<b>29/54<sup>a</sup></b> (54%)
		Female	0/52 (0%)	4/54 (7%)	10/54 (19%)
<i>Organ</i>	<i>Tumor type</i>	<i>Sex</i>	<i>Dose group (mg/kg-bw/day)<sup>†</sup></i>		
			0	70	140
Kidney <sup>93</sup>	Adenoma	Male	0/54 (0%)	3/50 (6%)	9/49 (18%)
		Female	0/55 (0%)	2/50 (4%)	2/46 (4%)
	Carcinoma	Male	0/54 (0%)	1/50 (2%)	<b>5/49<sup>c</sup></b> (10%)
		Female	0/55 (0%)	0/50 (0%)	0/46 (0%)
	Adenoma/carcinoma (combined)	Male	0/54 (0%)	4/50 (8%)	<b>14/49<sup>a</sup></b> (29%)
		Female	0/55 (0%)	2/50 (4%)	2/46 (4%)
Fore stomach <sup>94</sup>	Squamous-cell papilloma	Male	0/51 (0%)	10/47 (21%)	11/48 (23%)
		Female	2/53 (4%)	10/48 (21%)	18/44 (41%)
	Squamous-cell carcinoma	Male	0/51 (0%)	0/47 (0%)	2/48 (4%)
		Female	0/53 (0%)	<b>4/48<sup>d</sup></b> (8%)	<b>4/44<sup>e</sup></b> (9%)
	Papilloma/carcinoma (combined)	Male	0/51 (0%)	<b>10/47<sup>a</sup></b> (21%)	<b>13/48<sup>a</sup></b> (27%)
		Female	2/53 (4%)	<b>14/48<sup>a</sup></b> (29%)	<b>22/44<sup>d</sup></b> (50%)
Lung <sup>95</sup>	Alveolar/bronchiolar adenoma	Male	6/54 (11%)	11/44 (25%)	12/50 (24%)
		Female	3/55 (5%)	8/50 (16%)	14/50 (28%)
	Alveolar/bronchiolar carcinoma	Male	6/54 (11%)	8/44 (18%)	<b>13/50<sup>f</sup></b> (26%)
		Female	1/55 (2%)	1/50 (2%)	3/50 (6%)
	Alveolar/bronchiolar adenoma/carcinoma (combined)	Male	12/54 (22%)	<b>19/44<sup>e</sup></b> (43%)	<b>25/50<sup>h</sup></b> (50%)
		Female	4/55 (7%)	9/50 (18%)	<b>17/50<sup>d</sup></b> (34%)
Liver <sup>96</sup>	Adenoma	Male	4/54 (7%)	11/49 (22%)	4/49 (8%)
		Female	4/54 (7%)	11/50 (22%)	15/49 (31%)
	Carcinoma	Male	24/54 (44%)	20/49 (41%)	19/49 (39%)
		Female	7/54 (13%)	12/50 (24%)	<b>20/49<sup>b</sup></b> (41%)
	Adenoma/carcinoma (combined)	Male	28/54 (52%)	31/49 (63%)	23/49 (47%)
		Female	11/54 (20%)	<b>23/50<sup>f</sup></b> (46%)	<b>35/49<sup>a</sup></b> (71%)

<sup>93</sup> *Id.* at p. B-4 (male mice) and p. B-8 (female mice).

<sup>94</sup> *Id.*

<sup>95</sup> *Id.* at p. B-3 (male mice) and p. B-7 (female mice).

<sup>96</sup> *Id.* at p. B-4 (male mice) and p. B-8 (female mice).

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<sup>†</sup> Note: the dose conversion was calculated and reported by the NCI (1978).<sup>97</sup>

<sup>a</sup> Statistical significance ( $p < 0.001$ ), as reported in NCI (1978).<sup>98</sup>

<sup>b</sup> Statistical significance ( $p = 0.001$ ), as reported in NCI (1978).<sup>99</sup>

<sup>c</sup> Statistical significance ( $p = 0.022$ ), as reported in NCI (1978).<sup>100</sup>

<sup>d</sup> Statistical significance ( $p = 0.048$ ), as reported in NCI (1978).<sup>101</sup>

<sup>e</sup> Statistical significance ( $p = 0.039$ ), as reported in NCI (1978).<sup>102</sup>

<sup>f</sup> Statistical significance ( $p = 0.043$ ), as reported in NCI (1978).<sup>103</sup>

<sup>g</sup> Statistical significance ( $p = 0.038$ ), as reported in NCI (1978).<sup>104</sup>

<sup>h</sup> Statistical significance ( $p = 0.003$ ), as reported in NCI (1978).<sup>105</sup>

<sup>i</sup> Statistical significance ( $p = 0.005$ ), as reported in NCI (1978).<sup>106</sup>

There are several notable differences between the findings in animals fed TDBPP (Table 4) compared to the findings in animals fed TDCPP (Table 1). First, the time-weighted average daily dose for rats fed TDBPP was 2 or 4 mg/kg-bw/day compared to 5, 20, or 80 mg/kg-bw/day for rats fed TDCPP. Second, the MTD was not exceeded in rats fed TDBPP, and a statistically significant increase in the incidence of renal tubule carcinomas and adenomas/carcinomas (combined) was observed with male rats from the high dose group. In contrast, no renal tubule carcinomas were present in male or female rats fed TDCPP, even at dose levels that exceeded the MTD. Third, the target organ for TDBPP-induced tumors was the kidney in both male and female rats, whereas the target organ for TDCPP-induced benign tumors was the kidney in male and female rats and the testes in male rats at dose levels, where the MTD was not exceeded. Finally, the target organs for TDBPP-induced tumors in mice were the kidney, forestomach, lung, and liver. A progression was observed in each of these tissues from benign to malignant tumors. It should be noted that it appeared as though the MTD may have been exceeded in the high dose mice;<sup>107</sup> however, statistically significantly increased incidences of carcinomas and/or adenomas/carcinomas (combined) were still observed in the low dose mice in the forestomach, lung, and liver (Table 4).

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<sup>97</sup> *Id.* at p. 8.

<sup>98</sup> *Id.* at p. 25 (Table 3) (male rats; kidney), p. 44 (Table 5) (male mice; forestomach), p. 45 (Table 5) (male mice; kidney), p. 48 (Table 6) (female mice; forestomach), p. 49 (Table 6) (female mice; lung), and p. 50 (Table 6) (female mice; liver).

<sup>99</sup> *Id.* at p. 29 (Table 4) (female rats; kidney) and p. 50 (Table 6) (female mice; liver).

<sup>100</sup> *Id.* at p. 45 (Table 5).

<sup>101</sup> *Id.* at p. 48 (Table 6).

<sup>102</sup> *Id.*

<sup>103</sup> *Id.* at p. 44 (Table 5).

<sup>104</sup> *Id.* at p. 45 (Table 5).

<sup>105</sup> *Id.*

<sup>106</sup> *Id.* at p. 50 (Table 6).

<sup>107</sup> *Id.* at p. 36 (Figure 3).

As noted previously, an independent consultant and several regulatory/public health agencies concluded that TDCPP was not genotoxic *in vivo*. In contrast, the IARC summarized the *in vivo* genotoxicity of TDBPP as follows:<sup>108</sup>

[TDBPP] is mutagenic (in somatic and germ cells), clastogenic and recombinogenic in *Drosophila melanogaster* and induces bone-marrow micronuclei in mice and hamsters, liver micronuclei in rats and gene mutations in mouse kidney *in vivo*.

Based on the foregoing carcinogenicity and genotoxicity data, IARC concluded:

[t]here is *sufficient evidence* in experimental animals for the carcinogenicity of [TDBPP].

[TDBPP] is *probably carcinogenic to humans (Group 2A)*.

**Conclusions:** The metabolism, carcinogenicity, and genotoxicity of TDBPP are distinctly different than the data on these endpoints for TDCPP. Though the comparison of TDBPP to TDCPP may be convenient by way of structural similarity, it is scientifically invalid to suggest, as does OEHHA (2011a),<sup>109</sup> that these two compounds have comparable toxicological profiles.

#### 4.B.2. TCEP.

OEHHA (2011a) stated the following about TCEP:<sup>110</sup>

[TCEP] is a chlorinated phosphate triester. TCEP induces tumors in both sexes of rats and mice, inducing tumors at multiple sites in rats, and is genotoxic *in vitro* and *in vivo* (IARC, 1999).

Though OEHHA (2011a) attributed the above statements to IARC (1999), these statements are misleading. IARC summarized the genotoxicity of TCEP as follows:<sup>111</sup>

[TCEP] was not mutagenic to bacteria in the absence of an exogenous metabolic system but gave equivocal results in the presence of an exogenous metabolic system [citation omitted]. It caused cell transformation and, in single studies, sister chromatid exchanges but not chromosomal aberrations or mutations in rodent cells *in vitro*. In single studies, it gave equivocal results in a micronucleus test in Chinese hamsters and caused dominant lethal mutations in rats *in vivo*.

The EU also evaluated the genotoxicity database on TCEP. It concluded the following:<sup>112</sup>

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<sup>108</sup> IARC (1999). *Tris(2,3-dibromopropyl) phosphate*, in: Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide, IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS, Vol. 71, pp. 905-921, at p. 912.

<sup>109</sup> OEHHA (2011a), *supra* note 7, at pp. 18-19.

<sup>110</sup> *Id.* at p. 19.

<sup>111</sup> IARC (1999), *supra* note 108, at *Tris(2-chloroethyl) phosphate*, pp. 1543-1548, at p. 1546.

<sup>112</sup> EURAR (2009). *Tris (2-chloroethyl) phosphate, TCEP, CAS-No.: 115-96-8, EINECS-No.: 204-118-5, Risk assessment, July 2009, Final approved version*, EUROPEAN UNION RISK ASSESSMENT REPORT, 213 pp., at p. 116.

*Overall, it can be concluded that there is no relevant evidence for mutagenicity of [TCEP]* [emphasis added].

IARC stated the following for its evaluation and overall conclusion on the carcinogenicity of TCEP:<sup>113</sup>

[t]here is *limited evidence* for the carcinogenicity of [TCEP] in experimental animals.

[TCEP] is *not classifiable as to its carcinogenicity to humans (Group 3)*.

Similarly, the EU concluded the following:<sup>114</sup>

The carcinogenic effect of [TCEP] is thought to be related to non-genotoxic (epigenetic) mechanisms.

According to the decision in the EU C&L WG [*i.e.*, Classification and Labelling Working Group] [TCEP] will be classified as a carcinogen, category 3 [*i.e.*, “some evidence from appropriate animal studies, but this is insufficient to place the substance in Category 2 (*i.e.*, “sufficient evidence”)]<sup>115</sup>

**Conclusions:** IARC and the EU evaluated the carcinogenic potential of TCEP in humans. Each concluded independently that the evidence was “insufficient”.

#### 4.B.3. TCPP.

OEHHA (2011a) stated the following about the genotoxicity of TCPP, based on the EURAR for this substance:<sup>116</sup>

TCPP is genotoxic in *in vitro*, but not *in vivo* assays [citation omitted].

The above statement was correctly conveyed—that is, the EURAR (2008b) concluded “...TCPP is not genotoxic *in vivo*.”<sup>117</sup> However, OEHHA (2011a) did not perform a weight-of-evidence evaluation on the *in vitro* and *in vivo* genotoxicity data, as was done for the EURAR (2008b).

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<sup>113</sup> IARC (1999), *supra* note 108, at p. 1546.

<sup>114</sup> EURAR (2009), *supra* note 112, at pp. 141-142.

<sup>115</sup> EC (2003). *Guidelines for setting specific concentration limits for carcinogens in Annex I of Directive 67/548/EEC, Inclusion of potency considerations*, Commission on Working Group on the Classification and Labelling of Dangerous Substances, 29 pp., at p. 4, available at <http://ec.europa.eu/environment/chemicals/dansub/pdfs/potency.pdf> (accessed on September 5, 2011).

<sup>116</sup> OEHHA (2011a), *supra* note 7, at p. 19.

<sup>117</sup> EURAR (2008b), *supra* note 78, at p. 224.

**Conclusions:** As indicated by the EU in its RARs on TDCPP, TCEP, and TCPP, it is inappropriate to utilize SAR from TCPP to TDCPP. Even if this approach were used, however, the EU concluded that TCPP, like TDCPP, is not genotoxic *in vivo*.