

**INITIAL STATEMENT OF REASONS  
TITLE 27, CALIFORNIA CODE OF REGULATIONS**

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

**GLYPHOSATE**

**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 glyphosate under Proposition 65<sup>1</sup> in Title 27, California Code of Regulations, section 25705(b)<sup>2</sup>. The proposed NSRL of 1100 micrograms per day ( $\mu\text{g}/\text{day}$ ) is based on a carcinogenicity study in rodents and was derived using the methods described in Section 25703.

Proposition 65 was enacted as a ballot initiative on November 4, 1986. The Office of Environmental Health Hazard Assessment (OEHHA) within the California Environmental Protection Agency is the lead state entity responsible for the implementation of Proposition 65<sup>3</sup>. OEHHA has the authority to adopt and amend regulations to implement and further the purposes of the Act<sup>4</sup>.

The Act requires businesses to provide a warning when they cause an exposure to a chemical listed as known to the state to cause cancer or reproductive toxicity. The Act also prohibits the discharge of listed chemicals to sources of drinking water. When exposures are insignificant, warnings are not required and the discharge prohibition does not apply. The NSRL provides guidance for determining when this is the case for exposures to chemicals listed as causing cancer.

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<sup>1</sup> 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".

<sup>2</sup> All further regulatory references are to sections of Title 27 of the Cal. Code of Regs., unless otherwise indicated.

<sup>3</sup> Section 25102(o).

<sup>4</sup> Health and Safety Code, section 25249.12(a).

A Notice of Listing for glyphosate as known to the state to cause cancer under Proposition 65 was published on our website on March 27, 2017. *Glyphosate* (CAS No. 1071-83-6) will be added to the list of chemicals known to the state to cause cancer for purposes of Proposition 65. The effective date of this listing will be determined following a decision from the Court of Appeal regarding a request for a stay in the pending case *Monsanto v OEHHA*.<sup>6</sup> A separate Notice will be published, along with an updated Proposition 65 list, when the chemical is added to the list.

## DEVELOPMENT OF PROPOSED NSRL

To develop the proposed NSRL for glyphosate, OEHHA relied on Volume 112 in the series of International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans entitled “Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos”<sup>7</sup>, which summarizes the available data from rodent carcinogenicity studies of glyphosate, as well as other information relevant to the carcinogenic activity of the chemical. The NSRL is based on the results of the most sensitive scientific study deemed to be of sufficient quality<sup>8</sup>.

### Selection of Study Used to Determine Cancer Potency

OEHHA reviewed the available data from the rodent carcinogenicity studies of glyphosate discussed by IARC<sup>9</sup>, and determined that the two-year study conducted in male CD-1 mice fed glyphosate (purity, 98.6%) in the diet met the criterion in Section 25703 as the most sensitive study of sufficient quality.

The two-year diet study of glyphosate conducted in CD-1 male mice was performed by Inveresk Research International and summarized in the 2006 Joint FAO/WHO Meeting

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<sup>5</sup> The Safe Drinking Water and Toxic Enforcement Act of 1986, Health and Safety Code, section 25249.5, et seq.

<sup>6</sup> *Monsanto et al v OEHHA et al.*, Fresno County Superior Court case #16CECG00183, recently appealed to the California Court of Appeal (5<sup>th</sup> District). A case number has not yet been assigned.

<sup>7</sup> International Agency for Research on Cancer (IARC, 2015). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 112, Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos. IARC, World Health Organization, Lyon, France. Available at: <http://monographs.iarc.fr/ENG/Monographs/vol112/index.php>

<sup>8</sup> Section 25703(a)(4)

<sup>9</sup> International Agency for Research on Cancer (IARC, 2015). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 112, Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos. IARC, World Health Organization, Lyon, France. Available at: <http://monographs.iarc.fr/ENG/Monographs/vol112/index.php>

on Pesticide Residues report<sup>10</sup> and by IARC<sup>11</sup>. In this study, groups of 50 male CD-1 mice were fed a diet containing glyphosate (purity, 98.6%) at concentrations intended to achieve dose rates of 0, 100, 300, or 1000 milligrams of glyphosate per kilogram of body weight per day (mg/kg-day) for two years<sup>12</sup>. Survival was not affected by treatment with glyphosate at any dose in the study<sup>13</sup>. A glyphosate treatment-related increase in hemangiosarcomas was observed, with a statistically significant positive trend<sup>14</sup>. The tumor incidence data used to estimate cancer potency from this study are presented in Table 1.

**Table 1. Tumor incidences<sup>a</sup> of treatment-related lesions in male CD-1 mice administered glyphosate in the diet for two years (IARC, 2015; JMPR, 2006)**

Tumor type	Dose group (mg/kg-day)				Trend test p-value <sup>b</sup>
	0	100	300	1000	
Hemangiosarcoma	0/50	0/50	0/50	4/50	p = 0.0036

<sup>a</sup> Data as reported by IARC (2015) and JMPR (2006).

<sup>b</sup> Exact test for linear trend.

### Estimation of Cancer Potency in Mice Using the Multistage Model

In the 2015 review of the mechanistic data for glyphosate, IARC<sup>15</sup> concluded:

“Overall, the mechanistic data provide strong evidence for genotoxicity and oxidative stress. There is evidence that these effects can operate in humans.”

Based on consideration of the available mechanistic information on glyphosate and the above conclusions reached by IARC<sup>16</sup>, a multistage model is applied to derive a cancer

<sup>10</sup> Joint FAO/WHO Meeting on Pesticide Residues (JMPR, 2006). Glyphosate. In: Joint FAO/WHO Meeting on Pesticide Residues. Pesticide residues in food – 2004: toxicological evaluations. Report No. WHO/PCS/06.1. Geneva: World Health Organization; pp. 95–169. Available from: [http://apps.who.int/iris/bitstream/10665/43624/1/9241665203\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/43624/1/9241665203_eng.pdf), accessed January 19, 2016.

<sup>11</sup> International Agency for Research on Cancer (IARC, 2015). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 112, Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos. IARC, World Health Organization, Lyon, France. Available at: <http://monographs.iarc.fr/ENG/Monographs/vol112/index.php>

<sup>12</sup> International Agency for Research on Cancer (IARC, 2015). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 112, Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos. IARC, World Health Organization, Lyon, France. Available at: <http://monographs.iarc.fr/ENG/Monographs/vol112/index.php>

<sup>13</sup> *Ibid.*

<sup>14</sup> *Ibid.*

<sup>15</sup> *Ibid.*

<sup>16</sup> *Ibid.*

potency estimate, following the guidance in Section 25703. There are no principles or assumptions scientifically more appropriate, based on the available data, than this approach.

The lifetime probability of a tumor at a specific site given exposure to the chemical at dose  $d$  is modeled using the multistage polynomial model:

$$p(d) = \beta_0 + (1 - \beta_0) \left( 1 - \exp[-(\beta_1 d + \beta_2 d^2 + \dots + \beta_j d^j)] \right)$$

where the background probability of tumor,  $\beta_0$ , is between 0 and 1 and the coefficients  $\beta_i$ ,  $i = 1 \dots j$ , are positive. The  $\beta_i$  are parameters of the model, which are taken to be constants and are estimated from the data. The parameter  $\beta_0$  provides the basis for estimating the background lifetime probability of the tumor.

In order to derive a measure of the cancer response to glyphosate (per mg/kg-day) in the male mouse study described above, the dose associated with a 5% increased risk of developing a tumor was calculated and the lower bound for this dose was estimated using the multistage polynomial model for cancer in US EPA's Benchmark Dose Software (BMDS)<sup>17</sup>. The ratio of the 5% risk level to that lower bound on dose is known as the "animal cancer slope factor ( $CSF_{\text{animal}}$ )", or the "animal cancer potency".

The animal cancer slope factor calculated from the male mouse study summarized in JMPR (2006) and IARC (2015) and described above is  $0.00000897 \text{ (mg/kg-day)}^{-1}$ .

#### 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 ( $CSF_{\text{human}}$ ) is achieved by multiplying the animal potency ( $CSF_{\text{animal}}$ ) by the ratio of human to animal body weights ( $bW_{\text{human}}/bW_{\text{animal}}$ ) raised to the one-fourth power when  $CSF_{\text{animal}}$  is expressed in units  $(\text{mg/kg-day})^{-1}$ :

$$CSF_{\text{human}} = CSF_{\text{animal}} \times (bW_{\text{human}} / bW_{\text{animal}})^{1/4}$$

<sup>17</sup> US EPA Benchmark Dose Software (BMDS) Version 2.6.0.1 (Build 88, 6/25/2015). National Center for Environmental Assessment. Available from: <http://bmds.epa.gov>

The default human body weight is 70 kg. In the absence of animal body weight data from the male mouse study, the default<sup>18</sup> average body weight of 0.03 kg for male mice was used. The derivation of the human cancer slope factor using the default body weight values and the animal cancer slope factor of 0.0000897 (mg/kg-day)<sup>-1</sup> is shown below:

$$CSF_{\text{human}} = 0.0000897 \text{ (mg/kg-day)}^{-1} \times (70 \text{ kg} / 0.03 \text{ kg})^{1/4} = 0.00062 \text{ (mg/kg-day)}^{-1}$$

### Calculation of No Significant Risk Level

The NSRL can be calculated from the cancer slope factor as follows. The Proposition 65 no-significant-risk value is one excess case of cancer per 100,000 people exposed, expressed as 10<sup>-5</sup>. 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<sup>-5</sup> 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<sup>19</sup>. The intake can be converted to a µg per day amount by multiplying by 1000. This sequence of calculations can be expressed mathematically as:

$$NSRL = \frac{10^{-5} \times 70 \text{ kg}}{CSF_{\text{human}}} \times 1000 \text{ µg/mg.}$$

As indicated previously, the slope factor for glyphosate derived from the male mouse study data and exposure parameters presented in Table 1 is 0.00062 per mg/kg-day. Inserting this number into the equation above results in an NSRL of 1129 µg/day; rounding yields an NSRL of 1100 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:

<sup>18</sup>Gold LS, Zeiger E (1997). Handbook of Carcinogenic Potency and Genotoxicity Databases. CRC Press, Inc., Boca Raton.

<sup>19</sup> Section 25703(a)(8)

Chemical name	Level (micrograms per day)
Acrylonitrile	0.7
...	
<u>Glyphosate</u>	<u>1100</u>
...	

## **PROBLEM 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.

## **ECONOMIC IMPACT ASSESSMENT (see below)**

### **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 glyphosate. The NSRL provides assurance to the regulated community that exposures at or below this level 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<sup>20</sup>.

### **BENEFITS OF THE PROPOSED REGULATION**

See “Benefits of the Proposed Regulation” under ECONOMIC IMPACT ANALYSIS below.

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

The 2015 IARC monograph entitled “Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos”<sup>21</sup>, was relied on by OEHHA for calculating the NSRL for glyphosate. It includes data used in

<sup>20</sup> Health and Safety Code sections 25249.9(b) and 25249.10(c)

<sup>21</sup> International Agency for Research on Cancer (IARC, 2015). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 112, Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos. IARC, World Health Organization, Lyon, France. Available from: <http://monographs.iarc.fr/ENG/Monographs/vol112/index.php>

the potency calculation and on mechanisms of carcinogenesis that are relevant to evaluating the most appropriate method for deriving the NSRL in the context of Section 25703. OEHHA also relied on information on the animal carcinogenicity studies of glyphosate presented in the 2006 Joint FAO/WHO Meeting on Pesticide Residues report<sup>22</sup>, and on the default male mouse body weight value of Gold and Zeiger<sup>23</sup>. Copies of these documents will be included in the regulatory record for this proposed action. These documents are available from OEHHA upon request.

OEHHA also relied on the attached Economic Impact Analysis in developing this proposed regulation.

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

The 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 an NSRL would leave the business community without a “safe harbor” level to assist businesses in complying with Proposition 65. No alternative that is less burdensome yet equally as effective in achieving the purposes of the regulation in a manner that achieves the purposes of the statute has been proposed.

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

OEHHA is not aware of significant cost impacts that small businesses would incur in reasonable compliance with the proposed action. Use of the proposed NSRL by businesses is voluntary and therefore does not impose any costs on small businesses. In addition, Proposition 65 is limited by its terms to businesses with 10 or more employees (Health and Safety Code, section 25249.11(b)) so it has no effect on very small businesses.

### **EVIDENCE SUPPORTING FINDING OF NO SIGNIFICANT ADVERSE ECONOMIC IMPACT ON BUSINESS**

Because the proposed 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

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<sup>22</sup> Joint FAO/WHO Meeting on Pesticide Residues (JMPR, 2006). Glyphosate. In: Joint FAO/WHO Meeting on Pesticide Residues. Pesticide residues in food – 2004: toxicological evaluations. Report No. WHO/PCS/06.1. Geneva: World Health Organization; pp. 95–169. Available from: [http://apps.who.int/iris/bitstream/10665/43624/1/9241665203\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/43624/1/9241665203_eng.pdf) , accessed January 19, 2016.

<sup>23</sup> Gold LS, Zeiger E (1997). Handbook of Carcinogenic Potency and Genotoxicity Databases. CRC Press, Inc., Boca Raton.

businesses, including the ability of California businesses to compete with businesses in other states.

**EFFORTS TO AVOID UNNECESSARY DUPLICATION OR CONFLICTS WITH  
FEDERAL REGULATIONS CONTAINED IN THE CODE OF FEDERAL  
REGULATIONS**

Proposition 65 is a California law that has no federal counterpart. There are no federal regulations addressing the same issues and, thus, there is no duplication or conflict with federal regulations.



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## **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 or Elimination of Jobs 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 knowingly and intentionally 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. *Glyphosate* (CAS No. 1071-83-6) will be added to the list of chemicals known to the state to cause cancer for purposes of Proposition 65<sup>24</sup>. The effective date of this listing will be determined following a decision from the Court of Appeal regarding a request for a stay in the pending case *Monsanto v OEHHA*.<sup>25</sup> A separate Notice will be published, along with an updated Proposition 65 list, when the chemical is added to the list.

One year after the date of listing, businesses that manufacture, distribute or sell products with glyphosate in the state must provide a warning if their product or activity exposes the public or employees to significant amounts of this chemical. The regulatory proposal does not create additional compliance requirements, but instead provides a “safe harbor” value that aids businesses in determining whether a warning is required for a given exposure.

**Impact on the Creation of New Businesses or Elimination of Existing Businesses within the State of California:** This regulatory action will not impact the creation of new businesses or the elimination of existing businesses within the State of California. The regulatory proposal does not create additional compliance requirements, but instead provides a “safe harbor” value that aids businesses in determining if they are complying with the law.

**Impact on Expansion of Businesses within the State of California:** This regulatory action will not impact the expansion of businesses within the State of California. The

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<sup>24</sup> The Safe Drinking Water and Toxic Enforcement Act of 1986, Health and Safety Code, section 25249.5, et seq.

<sup>25</sup> *Monsanto et al v OEHHA et al.*, Fresno County Superior Court case #16CECG00183, recently appealed to the California Court of Appeal (5<sup>th</sup> District). A case number has not yet been assigned.

regulatory proposal does not create additional compliance requirements, but instead provides a “safe harbor” value that aids businesses in determining if they are complying with the law.

**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.