FINAL STATEMENT OF REASONS
TITLE 27, CALIFORNIA CODE OF REGULATIONS

SECTION 25705(b) SPECIFIC REGULATORY LEVELS POSING NO SIGNIFICANT RISK

NO SIGNIFICANT RISK LEVEL: MALATHION

This is the Final Statement of Reasons for the adoption of a No Significant Risk Level (NSRL) for malathion. On May 20, 2016, the Office of Environmental Health Hazard Assessment (OEHHA) announced the listing of malathion as a chemical known to the state to cause cancer for purposes of Proposition 65[1]. On January 20, 2017, OEHHA issued a Notice of Proposed Rulemaking to adopt a proposed amendment to Section 25705, Specific Regulatory Levels Posing No Significant Risk, identifying an NSRL of 180 micrograms per day (µg/day) for malathion under Title 27, California Code of Regulations, section 25705(b)[2]. The Initial Statement of Reasons sets forth the grounds for the amendment to the regulation. A public comment period was provided from January 20 to March 6, 2017. On February 7, 2017, OEHHA received a request for a two-week comment period extension from Kahn, Soares & Conway, LLP, representing FMC Corporation. The comment period was extended to March 20, 2017. OEHHA received written public comments on the proposed rulemaking from the following organizations:

1. FMC Corporation (FMC). The comments are comprised of FMC's comment letter prepared by Kahn, Soares and Conway, LLP, and an attachment: "Response to OEHHA's Listing of Malathion as a Carcinogen under Proposition 65 and Proposed No Significant Risk Level", prepared for FMC Corporation by Exponent, Inc.
2. Combined comments from California's unified agricultural industry (CUAI), including California Citrus Mutual, California Walnut Commission, California Cotton Ginners and Growers, Western Agricultural Processors Association, California Fresh Fruit Association, and California Strawberry Commission.
3. Combined comments from Caroline Cox (Center for Environmental Health), Mark Weller (Californians for Pesticide Reform), Anne Katten (California Rural Legal Assistance Foundation), and Margaret Reeves (Pesticide Action Network).

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

PEER REVIEW

On February 22, 2017, OEHHA provided the notice of proposed rulemaking and the initial statement of reasons for the proposed NSRL for malathion to the members of the Carcinogen Identification Committee for their review and comment as required by Section 25701(e). The committee was given at least 45 days to comment. No comments were received from any committee members.

SUMMARY AND RESPONSE TO COMMENTS RECEIVED

In developing the NSRL for malathion, 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"[3], which summarizes the available data from rodent carcinogenicity studies of malathion, as well as other information relevant to the carcinogenic activity of this chemical. The NSRL is based upon the results of the most sensitive scientific study deemed to be of sufficient quality[4].

OEHHA's responses to the comments received throughout this rulemaking process are incorporated within this Final Statement of Reasons (FSOR). Some of the comments submitted during the regulatory process included observations or opinions regarding the use of malathion or regarding the carcinogenicity of the metabolite malaoxon; such remarks do not constitute an objection to or recommendation specifically directed at the proposed action or the procedures followed in this rulemaking action. Accordingly, OEHHA is not required under the Administrative Procedure Act to respond to such comments in this FSOR. Because OEHHA is constrained by limitations upon its time and resources, and is not obligated by law to respond to irrelevant comments[5], OEHHA does not provide responses to all of these remarks in this FSOR. However, the absence of responses to such remarks should not be construed to mean that OEHHA in any way agrees with them.

A summary of the relevant comments received is provided below, along with OEHHA's responses to those comments. As explained in detail in the responses to comments, OEHHA declines to change the proposed NSRL based on the comments.

[3] 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
[4] Section 25703(a)(4)
[5] California Government Code section 11346.9(a)(3)

COMMENT 1 (FMC): Default cancer modeling approach is not supported

"While OEHHA relies upon the default methods to derive an NSRL value that is referenced in the regulations, alternative approaches are supported. 'Nothing in this article shall preclude a person from using evidence, standards, risk assessment methodologies, principles, assumptions or levels not described in this article to establish that a level of exposure to a listed chemical poses no significant risk.' "

Response 1

The question at hand is whether there is an approach more scientifically appropriate for derivation of the NSRL for malathion than the default procedure used by OEHHA. Section 25703 sets forth a default approach, using a multistage model for deriving a cancer potency estimate, which is used "in the absence of principles or assumptions scientifically more appropriate"[6].

OEHHA used the Benchmark Dose (BMD) method, as described both in OEHHA's guidance[7] and in the US Environmental Protection Agency (US EPA) guidelines[8], applying a multistage mathematical model to describe the relationship between the risk of cancer and the dose. As part of the procedure OEHHA used for determining the cancer potency using the BMD method, a determination is made as to the proper type of extrapolation from the point of departure (typically the 95% lower confidence limit of the ED_{05} or ED_{10} for tumor induction) to low doses. OEHHA considered whether there was a more scientifically appropriate method for the NSRL derivation than linear extrapolation, but did not identify one. As noted in the Initial Statement of Reasons:

> "In the 2015 review of the mechanistic data for malathion, IARC[9] concluded: 'Overall, the mechanistic data provide strong support for carcinogenicity findings of malathion. This includes strong evidence for genotoxicity, hormone-mediated effects, oxidative stress, and cell proliferation. There is evidence that these effects can operate in humans.'"

[6] Section 25703(a)
[7] OEHHA (2009). Technical Support Document for Cancer Potency Factors. Available at http://oehha.ca.gov/air/crnr/technical-support-document-cancer-potency-factors-2009
[8] US EPA (2005). Guidelines for Carcinogen Risk Assessment, March 2005. Risk Assessment Forum, US Environmental Protection Agency, Washington, DC.
[9] 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

> "Based on consideration of the available mechanistic information on malathion and the above conclusions reached by IARC, the default approach using a linearized multistage model is applied to derive a cancer potency estimate for each of the three studies. There are not principles or assumptions scientifically more appropriate, based on the available data, than this default."[10]

COMMENT 2 (FMC and CUAI): The proposed NSRL does not meet regulatory standards

FMC comment:

"OEHHA's NSRL calculation was based upon the liver tumor incidences as noted in the rodent carcinogenicity studies of malathion discussed by IARC. These studies demonstrate increased liver tumor incidence only at excessively high doses of malathion that were considered by the U.S. EPA to be "inadequate to assess carcinogenicity." By relying upon these high doses OEHHA's calculation fails to represent exposures that are realistic for humans and fails to meet the generally accepted scientific principles required by Proposition 65 regulations when conducting a quantitative risk assessment by failing to address the degree to which dosing resembles the expected manner of human exposure.

The 800 ppm (unlike the 8000 and 16000 ppm for male and female rice [*sic*] and 12000 ppm for female rats) was considered adequate to assess the carcinogenic potential of malathion in mice and there was no indication of liver toxicity at 800 ppm. Accordingly, the observed high dose liver tumors are not relevant to human risk assessment at the environmental doses and not an appropriate basis for calculating the NSRL."

CUAI comment:

"Now OEHHA proposes an NSRL that is based upon the same unrealistic high doses that were the basis for IARC's erroneous decision. Such an NSRL does not meet the Proposition 65 regulatory standards for quantitative risk assessments."

"OEHHA's NSRL calculation was based upon the rodent carcinogenicity studies of malathion discussed by IARC. These studies demonstrate an increased liver tumor incidence only at excessively high doses of malathion that are unrealistic to any real

[10] OEHHA (2017). Initial Statement of Reasons, Title 27, California Code of Regulations, Proposed Amendment to: Section 25705(b) Specific Regulatory Levels Posing No Significant Risk. Malathion. Available at https://oehha.ca.gov/proposition-65/crnr/notice-proposed-rulemaking-amendment-section-25705-malathion

world scenario of exposure. As a result OEHHA's NSRL calculation results in an overly conservative assessment unnecessary for the protection of human health."

Response 2

Section 25701(a) states "The determination of whether a level of exposure to a chemical known to the state to cause cancer poses no significant risk for purposes of Section 25249.10(c) of the Act shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause cancer."

Malathion was listed under Proposition 65 via the "Labor Code" listing mechanism, based on IARC's[11] classification of malathion as *probably carcinogenic to humans* (Group 2A), and its conclusion that there is *sufficient evidence* of carcinogenicity in experimental animals for malathion. The 18-month male B6C3F1 mouse study[12] was one of multiple studies that contributed to IARC's conclusion of sufficient evidence in experimental animals: IARC found the increased incidence of hepatocellular adenoma and carcinoma (combined) observed in the 18-month male mouse study to be treatment-related. IARC did not consider the doses used in the study to be excessive; noting a significant reduction in body weight but no effect on survival associated with treatment in the study.

OEHHA notes that it is common for doses used in animal cancer bioassays to be higher than anticipated human exposure levels, sometimes markedly so. The purpose of including high doses is not to model expected human exposures, but to maximize the power of the study to detect a carcinogenic effect definitively[13,14]. The BMD method can then be employed to characterize the dose-response relationship by fitting the

[11] 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

[12] US EPA (1994). Malathion: 18-month carcinogenicity study in mice, International Research and Development Corporation. MRID 43407201. HED Doc No. 011455. Slauter RW, author. Peer reviewed by EPA. Washington (DC): Office of Pesticides and Toxic Substances, United States Environmental Protection Agency. Available from: https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/057701/057701-004.pdf

US EPA (2000). Cancer assessment document. Evaluation of the carcinogenic potential of malathion. Final report. Washington DC: Cancer Assessment Review Committee, Health Effects Division, Office of Pesticide Programs, United States Environmental Protection Agency.

[13] US EPA (2005). Guidelines for Carcinogen Risk Assessment, March 2005. Risk Assessment Forum, US Environmental Protection Agency, Washington, DC.

[14] National Toxicology Program (NTP, 2015). Handbook for Preparing Report on Carcinogens Monographs. July 20, 2015. Office of the Report on Carcinogens, Division of the National Toxicology Program, National Institute of Environmental Health Sciences, US Department of Health and Human Services.

multistage cancer model to the bioassay data, allowing for estimation of risk in the low dose region.

Thus, OEHHA's use of the 18-month male B6C3F1 mouse study in the derivation of the NSRL is consistent with the Proposition 65 regulations, as this study is among the scientifically valid studies IARC relied on in making its determination of sufficient evidence of carcinogenicity in experimental animals, and it is the most sensitive scientific study of sufficient quality.

COMMENT 3 (FMC): Genotoxicity

"IARC based its conclusion primarily on open literature studies, which are confounded by the use of test samples of unknown purity, presence of potential genotoxic constituents in the formulations, and use of test systems that are not adequately validated. Unfortunately, IARC did not seem to consider most, if any, of the high quality, GLP and guideline-compliant studies sponsored by Cheminova A/S."

"An objective analysis of the available data indicates the following:

• Malathion does not induce gene mutations in bacteria.

• Malathion does not induce gene mutations in mammalian cells in culture (see recently conducted study by Schreib, 2017).

• Malathion induces chromosomal damage (clastogenicity) in mammalian cells in culture, but malathion is not a clastogen in mammalian cells *in vivo*.

• Overall, the weight of evidence indicates that malathion is not an *in vivo* genotoxin."

Response 3

OEHHA disagrees with the commenter's conclusions regarding the genotoxicity of malathion. There are numerous scientific studies of the genotoxicity of malathion in the peer-reviewed scientific literature. IARC (2015)[15] summarized this body of literature as follows:

"The overall evidence for genotoxicity of malathion is strong. The potential for malathion to exert genotoxicity has been studied in a variety of assays and model

[15] 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

systems. Various types of genotoxic damage have been evaluated in humans exposed to mixtures of pesticides containing malathion in occupational settings, and in cases of acute intoxication with malathion-containing formulations. The effects observed range from DNA damage to various types of chromosomal damage including micronucleus formation, chromosomal aberrations, and sister-chromatid exchanges. The majority of studies reported positive results that were consistent in terms of the types of end-point observed. These results in studies in humans are corroborated by multiple positive in studies in experimental animals in vivo, and in human and animal cells in vitro. The findings in standard tests for genotoxicity in bacteria were negative."

Genotoxicity may occur as a result of gene mutations, chromosomal effects (e.g., breaks, rearrangements, loss), and other types of DNA damage. While evidence for the genotoxic effects of malathion comes primarily from chromosomal effects and DNA damage, gene mutations have also been observed in some studies[16].

The commenter's conclusion that malathion does not induce gene mutations in bacteria is not accurate. While malathion tested negative in standard tests for mutagenicity in bacteria (e.g., *Salmonella* reverse mutation assays), it did induce mutations in the TKJ6321 strain of *Bacillus subtilis* in a mutation spot test (IARC, 2015, p. 81).

The commenter referenced an unpublished report by Schreib (2017) to support the conclusion that malathion does not induce gene mutations in mammalian cells in culture. OEHHA does not have access to the Schreib (2017) report, and thus could not evaluate the quality or findings of this study. However, OEHHA disagrees with the commenter's conclusion, as malathion has been shown to induce mutations at the hypoxanthine-guanine phosphoribosyltransferase *(HPRT)* locus in cultured human T lymphocytes exposed *in vitro* (Pluth *et al.*, 1996, as cited by IARC, 2015, p. 74).

The commenter's conclusion that malathion does not induce chromosomal damage (clastogenicity) in mammalian cells *in vivo* is not accurate. As summarized above in the passage quoted from IARC, and as shown in Table 4.3 (pp. 75-77) of the IARC monograph, multiple *in vivo* mammalian studies have found that malathion induces chromosomal damage including: increases in chromosomal aberrations in the bone marrow of rats in one study, increases in chromosomal aberrations in the bone marrow of mice in seven studies (some of these studies also reported increases in chromosomal aberrations in spermatogonia, spermacytes, and spleen cells), increases

[16] *Ibid*.

in micronucleus formation in the bone marrow of mice in three studies, and increases in sister chromatid exchange in spleen cells and bone marrow of mice in two studies.

COMMENT 4 (FMC): 18 Month Correction Factor

"To derive the NSRL, OEHHA (2017) estimated the animal cancer potency (i.e., cancer slope factor, CSF_{animal}) from the malathion rodent experiments described above. For mice, they employed a correction factor to extrapolate from the 78 week (18 month) exposure to 104 weeks (two years); however, this is not appropriate. There is no scientific justification for extrapolating tumor responses observed in a terminal 18-month mouse study to what may have been found at 24 months, and this extrapolation increases and likely overestimates tumor incidences. Further, the use of an 18-month exposure duration in mice is considered appropriate for lifetime carcinogenicity testing according to current standardized OECD (2009) and U.S. EPA (2005) guidelines, and therefore, should not necessitate adjustment for a lifetime exposure. The OEHHA adjustment results in a 2.4-fold underestimate of the NSRL using mouse data."

Response 4

The standard lifespan of rats and mice is generally accepted to be two years[17]; this is in agreement with the standard testing protocol of the National Toxicology Program in its toxicology and carcinogenicity studies in rodents. When the duration of a carcinogenicity study is shorter than the natural lifespan of the test species, the number of tumors observed will be reduced and consequently the potency will also be reduced[18]. This is because animals in experiments of shorter duration are at a lower risk of developing tumors than those in the standard bioassay.

OEHHA follows the procedure described by the US EPA Carcinogen Assessment Group in Anderson *et al*. (1983) to adjust the potency to more accurately reflect the lifetime cancer risk posed by chemical carcinogens[19]: To estimate the animal cancer potency from experiments of duration less than the natural life span of the animals, it is assumed that the lifetime incidence of cancer increases with the third power of age.

An equivalent method of taking into account the less-than-lifetime duration of an animal carcinogenicity study is to adjust the doses used in the potency estimation, rather than adjusting the potency at the end of the calculation.

[17] Gold LS, Zeiger E (1997). Handbook of Carcinogenic Potency and Genotoxicity Databases. CRC Press, Inc., Boca Raton.
[18] *Ibid*.
[19] Anderson EL and the U.S. Environmental Protection Agency Carcinogen Assessment Group (1983). Quantitative approaches in use to assess cancer risk. Risk Analysis 3:277-295.

Contrary to the assertion of the commenter, the US EPA does make adjustments in the calculation of cancer potency estimates to account for less-than-lifetime study duration. For example, in estimating the cancer potency for 1,1,2,2-tetrachloroethane from a less-than-lifetime animal cancer study, the US EPA explained the need to adjust the doses as follows: "Because the study duration (90 weeks) was less than the animal lifespan (104 weeks), the scaled dose was then multiplied by the cubed ratio of experimental duration to animal lifespan to complete the extrapolation to a lifetime exposure in humans"[20].

COMMENT 5 (FMC): Inability to Replicate Cancer Slope Factors

"FMC was unable to reproduce the Cancer Slope Factor for humans for male mice, which was the basis of the NRSL. When utilizing a linearized multistage model with a 5% point of departure per OEHHA guidance, the corresponding NSRL is 280 ug [*sic*]/day compared to OEHHA's value of 180 ug [*sic*]/day."

Response 5

In reviewing the Benchmark Dose Software (BMDS) output provided by the commenter, OEHHA noted that the commenter failed to assess the goodness-of-fit of the multistage cancer model to the liver tumor data from male mice treated with malathion. The modeling approach used by the commenter results in a model that fails to meet each of the three goodness-of-fit criteria described in the resources provided by US EPA regarding use of BMDS, such as the Benchmark Dose Training Module on Cancer Models[21] and the BMDS Technical Guidance[22]. According to US EPA guidance, model fit is assessed via the global goodness-of-fit p-value, examination of the scaled residuals, and visual inspection of the plot of the data and the fitted curve. A p-value greater than 0.05[23], scaled residuals less than two in absolute value, and a plot in which the curve appears to fit the data appropriately are the markers of sufficient goodness-of-fit. Fitting the multisite cancer model in BMDS to the liver tumor data from all treatment groups in the male mouse study results in a global goodness-of-fit p-value less than 0.05 ($p = 0.0023$). Further, the scaled residual corresponding to the second highest

[20] US EPA (2010). IRIS Toxicological Review of 1,1,2,2-Tetrachloroethane (Final Report). U.S. Environmental Protection Agency, Washington, DC, EPA/635/R-09/001F. Available from: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0193tr.pdf

[21] US EPA (2014). Module 5: Benchmark Dose Modeling - Cancer Models [Webinar]. In *Benchmark Dose Software (BMDS) Training Webinars.* Retrieved from: https://clu-in.adobeconnect.com/_a1089459318/p3a32k3l8of/?launcher=false&fcsContent=true&pbMode=normal&archiveOffset=488800

[22] US EPA (2012). Benchmark Dose Technical Guidance. Washington, DC: US EPA. Available from: https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf

[23] This is the standard significance level used for models selected *a priori*, such as the multistage cancer model, when modeling cancer dose-response data.

dose group (-2.682) was greater than two in absolute value and the scaled residual corresponding to the high dose group was also very high (1.932). Finally, the plot of the curve fitted to the data confirms the numerical measures of goodness-of-fit, showing a clear visual lack of fit.

In cases where dichotomous data is not well fit by the model of choice, US EPA recommends removal of the high dose in an attempt to improve model fit[24]. This guidance is consistent with longstanding US EPA cancer dose-response practice[25].

The commenter was not able to reproduce OEHHA's cancer slope factor and NSRL calculations because they did not assess the goodness-of-fit of the multistage cancer model to the data and did not take the appropriate follow-up action (i.e., removal of the high dose) to attain sufficient goodness-of-fit. As described by OEHHA in the Initial Statement of Reasons, removal of the high dose results in a model that meets each of the three criteria identified by US EPA to demonstrate sufficient goodness-of-fit.

COMMENT 6 (FMC): Alternative options

On page 12 of the attachment, FMC suggests several alternative options for OEHHA to consider as summarized here:

1. Do not set an NSRL for malathion because observed liver tumors in the malathion assays occurred at doses irrelevant for human risk assessment, and the oral cavity tumors were incidental.
2. Set the NSRL using a value for liver tumors of 636 µg/day based on female rats.
3. Set the NSRL as 2900 µg/day based on oral cavity tumors.

Regarding the oral cavity tumors mentioned in options 1 and 3, FMC noted the following in the attachment:

> "Based on IARC's conclusion, OEHHA also determined that oral cavity tumors in the rat study were treatment-related….The IARC review provides very little discussion about these tumors, other than to note that they are 'rare.' Beyond

[24] US EPA (2012). Benchmark Dose Technical Guidance. Washington, DC: US EPA. Available from: https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf
[25] Anderson EL and the U.S. Environmental Protection Agency Carcinogen Assessment Group (1983). Quantitative approaches in use to assess cancer risk. Risk Analysis 3:277-295.

> that the OEHHA document also provides no discussion on why these tumors would be considered treatment-related."
>
> "However, the EPA SAP concluded that these tumors are actually not that rare (U.S. EPA, 2000b): "Tumors in the oral cavity of the F344 rat are uncommon but not rare as judged by recent NTP historical controls." (page 17)…Therefore, the oral cavity tumors occurred at incidence rates similar to historical controls and were not statistically significant, and thus it is concluded that these tumors were incidental and not due to treatment."

FMC noted the following rationale for option #3:

> "…an NSRL based on oral cavity tumors would have fewer scientific weaknesses because, unlike the liver tumors, there is no evidence that any putative effects occur at doses that are not relevant for human risk assessment. For liver tumors, effects occurred at doses where there is a clear mechanism that is only applicable at very high doses, whereas the two oral cavity carcinomas occurred at the low and high doses. While the lack of dose-response and statistical significance significantly reduces the possibility that the oral cavity tumors are treatment-related, there is at least no clear evidence that these would only occur at doses irrelevant for human risk assessment."

Response 6

OEHHA considers the increased incidence of liver tumors in the male mouse study to be treatment-related and finds this study to be the most sensitive; thus, none of the three alternative options proposed by the commenter is preferable over the approach taken by OEHHA in setting the NSRL.

As indicated in the response to Comment 2, the male mouse liver tumor findings are part of the basis for IARC's determination that there is sufficient evidence in experimental animals for the carcinogenicity of malathion[26], and the male mouse liver tumor dose-response data are appropriate for use in deriving a human cancer slope factor and NSRL.

According to the regulations, the NSRL is based upon the results of the most sensitive scientific study deemed to be of sufficient quality[27]. As shown in Table 3 of the Initial Statement of Reasons, among the three studies identified as being sensitive studies of

[26] 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

[27] Section 25703(a)

sufficient quality for dose-response assessment, the male mouse study is the most sensitive, as it gives the highest human cancer slope factor, and the female rat study is the least sensitive.

Regarding the squamous cell carcinomas of the oral cavity observed in the female Fischer 344 rat study (in one low-dose female and one high-dose female), the commenter correctly notes that the Initial Statement of Reasons identifies these tumors as being rare, as do IARC[28] and Haseman *et al*. (1998)[29]. Therefore, the two rare squamous cell carcinomas of the oral cavity seen in the malathion-treated female rats are considered treatment-related. However, the tumor incidence data used to estimate cancer potency from the female rat study consisted solely of the data on hepatocellular adenoma and carcinoma (combined). OEHHA did not conduct a multi-site cancer potency analysis with the female rat liver and oral cavity tumor data because the low incidence of these rare oral cavity tumors, which occurred in only two of the treated rats, will not contribute appreciably to the potency estimate based solely on the liver tumor data.

COMMENT 7 (Caroline Cox *et al*.)

"We strongly support your efforts to help Californians protect themselves from this hazardous pesticide…We believe that the Office of Environmental Health Hazard has followed the standard procedures for establishing a safe harbor level for a Proposition 65 carcinogen for malathion."

Response 7

OEHHA acknowledges the comment.

COMMENT 8 (Caroline Cox *et al*.)

"We believe that the proposed safe harbor level could be improved by using the data that was removed for model-fitting purposes (male mouse high dose group). If that is not feasible, a more detailed explanation of why it was removed is important."

[28] 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

[29] Haseman JK, Hailey JR, Morris RW (1998). Spontaneous neoplasm incidences in Fischer 344 rats and B6C3F1 mice in two-year carcinogenicity studies: a National Toxicology Program update. Toxicol Pathol. 1998 May-Jun;26(3):428-41. Haseman et al. (1998) shows that spontaneous squamous cell carcinoma of the oral cavity is rare, with a 0.4% (6/1351) spontaneous incidence in control F334 rats from NTP carcinogenicity studies (feeding studies).

Response 8

As described in detail in Response 5 above, the high dose group was removed in modeling the liver tumor data in male mice treated with malathion to achieve sufficient goodness-of-fit of the multistage cancer model. This is in accordance with the US EPA guidance on use of BMDS in estimating cancer potency, and is consistent with the longstanding practice of OEHHA[30,31] and US EPA[32].

ALTERNATIVES DETERMINATION

In accordance with Government Code section 11346.9(a)(4), OEHHA has, throughout the adoption process of this regulation, considered available alternatives to determine whether any alternative would be more cost effective in carrying out the purpose for which the regulation was proposed, or would be as cost effective and less burdensome to affected private persons than the proposed action. FMC suggested alternatives to the regulation which are summarized in Comment 6 above, and OEHHA's rationale for rejecting those alternatives is summarized in the response to Comment 6. OEHHA has determined that no reasonable alternative considered by OEHHA or that has otherwise been identified or brought to the attention of OEHHA would either be more effective in carrying out the purpose for which the action is proposed, or would be as effective and less burdensome to affected private persons, or would be more cost-effective to affected private persons and equally effective in implementing the statutory policy or other provision of law than the proposed regulation.

For chemicals listed under the Act as known to cause cancer, the Act exempts discharges to sources of drinking water and exposures of people without provision of a warning if the exposure poses "no significant risk" of cancer (Health and Safety Code, section 25249.10(c)). The Act does not specify numerical levels of exposure that represent no significant risk of cancer.

The purpose of this regulation is to establish a No Significant Risk Level for malathion. At or below this level, the Act does not require a warning or prohibit discharges of the chemical to sources of drinking water. Thus, adopting this level will allow persons

[30] OEHHA (2002). No Significant Risk Levels (NSRLs) for the Proposition 65 Carcinogens 3,3'-Dimethylbenzidine and 3,3'-Dimethylbenzidine Dihydrochloride. Available at: https://oehha.ca.gov/media/downloads/proposition-65/chemicals/dimethylbenzidinensrlaug2002.pdf

[31] OEHHA (2001). Expedited Cancer Potency Values and No Significant Risk Levels (NSRLs) for Six Proposition 65 Carcinogens: Carbazole, MeIQ, MeIQx, Methylcarbamate, 4-Nitrosomethylamino-1-(3-pyridyl)-1-butanone, and Trimethyl phosphate. Available at: https://oehha.ca.gov/media/downloads/proposition-65/chemicals/expedited2001.pdf

[32] Anderson EL and the U.S. Environmental Protection Agency Carcinogen Assessment Group (1983). Quantitative approaches in use to assess cancer risk. Risk Analysis 3:277-295.

subject to the Act to determine whether a given discharge to sources of drinking water or a given exposure to this chemical is subject to the warning requirement or discharge prohibition provisions of the Act (Health and Safety Code, section 25249.5 and 25349.6).

Although Section 25703 describes principles and assumptions for conducting risk assessments to derive No Significant Risk Levels, some businesses subject to the Act do not have the resources to perform these assessments. Yet each business with ten or more employees must determine whether its activities or products are subject to the discharge prohibition or warning requirements of the Act. Adopting an NSRL for this chemical provides an efficient way of determining if a business is in compliance with the Act.

LOCAL MANDATE DETERMINATION

OEHHA has determined this regulatory action will not pose a mandate on local agencies or school districts, nor does it require reimbursement by the State pursuant to Part 7 (commencing with Section 17500) of Division 4 of the Government Code. OEHHA has also determined that no nondiscretionary costs or savings to local agencies or school districts will result from this regulatory action. Proposition 65 provides an express exemption from the warning requirement and discharge prohibition for all state and local agencies. Thus, these regulations do not impose any mandate on local agencies or school districts.