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Submitted Electronically to:
P65Public Comments@oehha.ca.gov

October 20, 2015

Ms. Esther Barajas-Ochoa
Office of Environmental Health Hazard Assessment
P.O. Box 4010, MS-19B
Sacramento, California 95812-4010

Re: Notice of Intent to List (NOIL) Malathion by the Labor Code Mechanism as a Compound Known to the State of California to Cause Cancer Under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65)

Dear Ms. Barajas-Ochoa:

On behalf of Cheminova A/S (EPA Company No.: 4787)), we are writing to comment on the California Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) Notice of Intent to List malathion as a chemical known to the State of California to cause cancer pursuant to the "Labor Code" listing mechanism, Health and Safety Code section 25249.8(a) and Title 27, Cal. Code of Regs, section 25904.

Cheminova A/S is sole manufacturer and supplier of all the technical malathion used in the United States (U.S.) to produce end-use products containing malathion as the active ingredient, and is the primary producer and owner of the data that support the registration of this product in the U.S., and globally. As such, we are very familiar with the toxicological database for malathion. We are grateful for the opportunity to comment on the Notice of Intent to List malathion as a known carcinogen under Proposition 65.

Cheminova submits the enclosed comments in opposition to this listing because the identification of malathion does not meet the requirements of 27 CCR section 25904. Specifically, malathion does not qualify for listing under Labor Code section 6382(b)(1) because it can be excluded via Section 6382(a) of the Labor Code and is not an appropriate Labor Code listing.

Summary of Listing and Applicable Statutes and Regulation

OEHHA's Notice of Intent to List asserts that Malathion meets the criteria for listing pursuant to 27 CCR section 25904(b)(2) as a carcinogen based upon its placement on the list of Agents Classified by the International Agency for Research on Cancer (IARC) Monographs as Group 2a, probably carcinogenic to humans with sufficient evidence of carcinogenicity in experimental animals. This category is used when there is limited evidence of carcinogenicity in humans.

The statutory authority for this regulation is derived from Section 25249.8(a) of the Health and Safety Code which provides:

> "(a) On or before March 1, 1987, the Governor shall cause to be published a list of those chemicals known to the state to cause cancer or reproductive toxicity within the meaning of this chapter, and he shall cause such list to be revised and republished in light of additional knowledge at least once per year thereafter. Such list shall include at a minimum those substances identified by reference in Labor Code Section 6382(b) (1) and those substances identified additionally by reference in Labor Code Section 6382(d)."

Labor Code Section 6382(b) (1) provides that substances listed as human or animal carcinogens by the IARC shall be listed, subject to the exclusion provision contained in section 6382(a) which states:

> "(a) Any substance designated in any of the following listings in subdivision (b) shall be presumed by the director to be potentially hazardous and shall be included on the list; provided, that the director shall not list a substance or form of the substance from the listings in subdivision (b) if he or she finds, upon a showing pursuant to the procedures set forth in Section 6380, that *the substance as present occupationally is not potentially hazardous to human health; and provided further, that a substance, mixture, or product shall not be considered hazardous to the extent that the hazardous substance present is in a physical state, volume, or concentration for which there is no valid and substantial evidence that any adverse acute or chronic risk to human health may occur from exposure."* (Emphasis added).

Cheminova asserts that malathion is excluded from listing pursuant to this section.

Basis for Exclusion Pursuant to Labor Code section 6382(a)

Malathion does not meet the criteria for listing because:

1. The United States Environmental Protection Agency (US EPA) registers products under the Federal, Insecticide, Fungicide and Rodenticide Act (FIFRA). Under this law, EPA may not register a pesticide if it cannot ensure that the product, when used in accordance with its labeling, will cause unreasonable risks to human health. EPA has approved many malathion labels under FIFRA, and continues to do so. Therefore, these labels comply with the FIFRA requirement that malathion does not pose unreasonable risk to human health.

2. In the critical rodent carcinogenicity studies on malathion, the US EPA and the California Department of Pesticide Regulation have identified that there is a clear threshold of malathion exposure at which no tumors form. Tumors observed in the animal studies have been shown to occur only at very high doses that exceeded the maximum tolerated dose as evidenced by the severe clinical signs of toxicity and death. These signs of toxicity occur only with exposures that are well above those to which humans may be exposed when using malathion in accordance with its government-approved labels.

3. Labels approved by US EPA under FIFRA are supported by risk assessments. Those risk assessments are based on the use of red blood cell cholinesterase inhibition as the critical effect. Reference doses for risk assessment are generally set based on a 10% change in cholinesterase inhibition. This level of inhibition occurs at exposure levels that are lower than the exposures causing toxicological effects in the animal studies and far lower than those that caused tumor formation. Therefore, the use of the cholinesterase endpoint in risk assessment is considered to be sufficiently protective of all other toxicological endpoints of concern, including cancer. As such, there is no substantial evidence that any adverse acute or chronic risk to human health may occur from exposures when products containing malathion are used in accordance with labels approved by the US. EPA.

4. The State of California, Canada Pest Management Regulatory Agency, as well as experts within the European Union have all concluded that risk assessments based on cholinesterase inhibition as the crucial affect demonstrate no risks of concern from exposure to malathion to humans when it is used in accordance with approved labels.

5. The review conducted by IARC was only a rudimentary assessment of potential hazard. By definition, hazard assessment does not consider exposure and does not include a risk assessment. Without identifying how the hazards identified by IARC relate to expected human exposures, IARC is not able to conclude that exposure to a product will cause adverse health effects, including cancer, in humans. As such, the IARC review provides no valid and substantial evidence that adverse acute or chronic risk to human health may occur from exposures to malathion when products containing malathion are used in accordance with labels approved by the US EPA.

In light of the fact that malathion clearly does not qualify for listing pursuant to the Labor Code mechanism and California law, we request that OEHHA rescind the Notice of Intent to list malathion as a known carcinogen.

By reference, we incorporate comments on the proposed listing of Tetrachlorvinphos, Parathion, Malathion, and Glyphosate to be submitted by CropLife America and the Joint Glyphosate Task Force.

If you have any questions regarding this submission, or if you need additional information, please do not hesitate to call me at 703-373-8885.

Sincerely,

Paul Whatling
Cheminova

Enclosure

c: David Menotti, Crowell and Moring
Kristian Lystbæk, Cheminova A/S

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COMMENTS FROM CHEMINOVA CONCERNING THE INTENT OF OEHHA TO LIST MALATHION AS A CHEMICAL KNOWN TO THE STATE OF CALIFORNIA TO CAUSE CANCER UNDER PROPOSITION 65

OCTOBER 20, 2015

EXECUTIVE SUMMARY

The California Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) has issued a Notice of Intent to List malathion as a chemical known to the State of California to cause cancer pursuant to the "Labor Code" listing mechanism, Health and Safety Code section 25249.8(a) and Title 27, Cal. Code of Regs., section 25904. Cheminova opposes this listing because the identification of malathion does not meet the requirements of 27 CCR section 25904. Specifically, malathion does not qualify for listing under Labor Code section 6382(b)(1) because it can be excluded via Section 6382(a) of the Labor Code and is not an appropriate Labor Code listing.

SUMMARY OF LISTING AND APPLICABLE STATUTES AND REGULATION

OEHHA's Notice of Intent to List asserts that malathion meets the criteria for listing pursuant to 27 CCR section 25904(b)(2) as a carcinogen based upon its placement on the list of Agents Classified by the International Agency for Research on Cancer (IARC) Monographs as Group 2a, probably carcinogenic to humans with sufficient evidence of carcinogenicity in experimental animals. This category is used when there is limited evidence of carcinogenicity in humans.

The statutory authority for this regulation is derived from Section 25249.8(a) of the Health and Safety Code which provides:

> "(a) On or before March 1, 1987, the Governor shall cause to be published a list of those chemicals known to the state to cause cancer or reproductive toxicity within the meaning of this chapter, and he shall cause such list to be revised and republished in light of additional knowledge at least once per year thereafter. Such list shall include at a minimum those substances identified by reference in Labor Code Section 6382(b) (1) and those substances identified additionally by reference in Labor Code Section 6382(d)."

Labor Code Section 6382(b) (1) provides that substances listed as human or animal carcinogens by the IARC shall be listed, subject to the exclusion provision contained in section 6382(a) which states:

> "(a) Any substance designated in any of the following listings in subdivision (b) shall be presumed by the director to be potentially hazardous and shall be included on the list; provided, that the director shall not list a substance or form of the substance from the listings in subdivision (b) if he or she finds, upon a showing pursuant to the procedures set forth in Section 6380, that *the substance as present occupationally is not potentially hazardous to human health; and provided further, that a substance, mixture, or product shall not be considered hazardous to the extent that the hazardous substance present is in a physical state, volume, or concentration for which there is no valid and substantial evidence that any adverse acute or chronic risk to human health may occur from exposure."* (Emphasis added).

Cheminova asserts that malathion is excluded from listing pursuant to this section.

BASIS FOR EXCLUSION PURSUANT TO LABOR CODE SECTION 6382(A)

Malathion does not meet the criteria for listing because:

1. The United States Environmental Protection Agency (US EPA) registers products under the Federal, Insecticide, Fungicide and Rodenticide Act (FIFRA). Under this law, EPA may not register a pesticide if it cannot ensure that the product, when used in accordance with its labeling, will cause unreasonable risks to human health. EPA has approved many malathion labels under FIFRA, and continues to do so. Therefore, these labels comply with the FIFRA requirement that malathion does not pose unreasonable risk to human health.

2. For the critical rodent carcinogenicity studies on malathion, the US EPA and the California Department of Pesticide Regulation have identified that there is a clear threshold of malathion exposure at which no tumors form. Tumors observed in the animal studies have been shown to occur only at very high doses that exceeded the maximum tolerated dose as evidenced by the severe clinical signs of toxicity and death. These signs of toxicity occur only with exposures that are well above those to which humans may be exposed when using malathion in accordance with its government-approved labels.

3. Labels approved by US EPA under FIFRA are supported by risk assessments. Those risk assessments are based on the use of red blood cell cholinesterase inhibition as the critical effect. Reference doses for risk assessment are generally set based on a 10% change in cholinesterase inhibition. This level of inhibition occurs at exposure levels that are lower than the exposures causing toxicological effects in the animal studies and far lower than those that caused tumor formation. Therefore, the use of the cholinesterase endpoint in risk assessment is considered to be sufficiently protective of all other toxicological endpoints of concern, including cancer. As such, there is no substantial evidence that any adverse acute or chronic risk to human health may occur from exposures when products containing malathion are used in accordance with labels approved by the US. EPA.

4. The State of California, Canada Pest Management Regulatory Agency (PMRA), as well as experts within the European Union (EU) have all concluded that risk assessments based on cholinesterase inhibition as the critical effect demonstrate no risks of concern from exposure to malathion to humans when it is used in accordance with approved labels.

5. The review conducted by IARC was only a rudimentary assessment of potential hazard. By definition, hazard assessment does not consider exposure and does not include a risk assessment. Without identifying how the hazards identified by IARC relate to expected human exposures, IARC is not able to conclude that exposure to a product will cause adverse health effects, including cancer, in humans. As such, the IARC review provides no valid and substantial evidence that adverse acute or chronic risk to human health may occur from exposures to malathion when products containing malathion are used in accordance with labels approved by the US EPA.

In light of the fact that malathion clearly does not qualify for listing pursuant to the Labor Code mechanism and California law, we request that OEHHA rescind the Notice of Intent to list malathion as a known carcinogen.

INTRODUCTION

On September 4, 2015, the California Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) issued a notice of its intent to list malathion as a chemical "known to the state to cause cancer" under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65)[1]. According to the notice published on September 4, 2015, OEHHA is proposing this action pursuant to the "Labor Code" listing mechanism[2].

In its notice, OEHHA points out that Health and Safety Code 25249.8(a) incorporates California Labor Code section 6382(b)(1) into Proposition 65. This section of the law requires that certain substances identified by the International Agency for Research on Cancer (IARC) be listed as known to cause cancer under Proposition 65. Labor Code section 6382(b)(1) refers to substances identified as human or animal carcinogens by IARC. As the lead agency for implementation of Proposition 65, OEHHA evaluates whether listing a chemical is required under Proposition 65.

OEHHA has asked the public to provide comments on whether malathion meets the requirements for listing as causing cancer specified in Health and Safety Code section 25249.8(a) and Labor Code section 6382(b)(1). OEHHA states that because this is a ministerial listing, the comments from the public should be limited to whether IARC has identified malathion as a known or potential human or animal carcinogen. OEHHA further states that under this mechanism, OEHHA cannot consider scientific arguments concerning the weight or quality of the evidence considered by IARC when it identified malathion and will not respond to such comments if they are submitted.

Cheminova A/S is sole manufacturer and supplier of all the technical malathion used in the United States (US) to produce end-use products containing malathion as the active ingredient, and is the primary producer and owner of the data that support the registration of this product in the US, and globally. As such, we are very familiar with the toxicological database for malathion. In addition, Cheminova was an observer during the IARC meetings held earlier this year. Thus, we are uniquely qualified to comment on the IARC review and conclusions and on OEHHA's notice of intent to list malathion as a known carcinogen under Proposition 65.

As mentioned it its notice of intent to list, OEHHA has severely restricted the kind of comments it will consider during the assigned comment period as it applies to Health and Safety Code section 25249.8(a) and Labor Code section 6382(b). Cheminova does not believe that malathion satisfies the criteria for listing as causing cancer as specified in Health and Safety Code section 25249.8(a) and Labor Code section 6382(b) because, as demonstrated by

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[1] Health and Safety Code section 25249.5 *et seq*.

[2] Health and Safety Code section 25249.8(a) and Title 27, Cal. Code of Regs., section 25904.

our comments, it does not satisfy the prerequisite conditions listed under Labor Code section 8382(a).

On the pages that follow, we review some of the critical issues related to the carcinogenicity potential of malathion, including some of the limitations of the IARC review. We then offer an opinion on whether malathion meets the criteria for listing as a chemical known to cause cancer under the Labor Code mechanism of Proposition 65.

Observations and Concerns about the IARC Evaluation

IARC, an agency of the World Health Organization (WHO), has assembled and reviewed a selected set of data in order to evaluate the carcinogenicity of malathion. According to the General Principles and Procedures of its Preamble as published on its website[3], IARC does not necessarily consider all the mechanistic literature concerning the agent being evaluated. Rather, only those data considered by IARC to be relevant to making the evaluation are included. With regard to epidemiological studies, cancer bioassays, and mechanistic and other relevant data, only reports that have been published or accepted for publication in the openly available scientific literature are reviewed. However, the preamble states that data from government agency reports that are publically available are also considered[4]. Cheminova could not locate a set of criteria used by IARC to determine which data on malathion were considered and which data were not.

Thus, this lack of transparency and selective data review is a serious concern about the review procedures employed by IARC. And, it calls into question whether IARCs conclusions are without bias, and whether the data are of sufficient strength to support its conclusions.

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[3] The website may be accessed using the following link:
http://monographs.iarc.fr/ENG/Preamble/currenta4data0706.php

[4] **Cheminova observation made during the Work Group meeting in Lyon:** Via a request made to US EPA under the Freedom of Information Act (FOIA), some regulatory cancer study reports in mice and rats were available to the working groups, but the complete set of regulatory cancer data had not been retrieved for the meeting and none of the regulatory genotoxicity data had been retrieved. The full cancer evaluation by EPA (2000) was provided by Cheminova's observer during the Lyon meeting. No agency reviews of mutagenicity /genotoxicity were provided to the experts; and the IARC did not at all consider publically available reviews from other agencies such as EFSA. Thus the data for the IARC review were selected in a way that precluded full evaluation of the available regulatory toxicology studies on malathion (done according to EPA/OECD-guidelines and GLPs, etc.). Therefore the IARC hazard conclusion was founded on a selected and incomplete data set, which is less complete than the data set available to the OEHHA.

A summary of IARC's final evaluation conclusions for malathion, along with a short rationale for those conclusions, has been published online in The Lancet Oncology[5]. IARC has stated that its detailed assessment for malathion will be published as part of Volume 112 of the IARC Monographs. To date, the IARC has not yet published a Monograph for malathion; therefore, it is impossible for Cheminova, OEHHA or other stakeholders to review and comment on the details of the IARC review or the data it used (or excluded) to justify its conclusions. The public currently only has access to the very limited information which was published in the Lancet Oncology. That text from the Lancet Oncology is reproduced below.

> "The insecticides malathion and diazinon were classified as "probably carcinogenic to humans" (Group 2A). Malathion is used in agriculture, public health, and residential insect control. It continues to be produced in substantial volumes throughout the world. There is limited evidence in humans for the carcinogenicity of malathion. Case-control analyses of occupational exposures reported positive associations with non-Hodgkin lymphoma in the USA (Waddell, et al, 2001), Canada (McDuffie, et al, 2001), and Sweden (Erickson, et al, 2008), although no increased risk of non-Hodgkin lymphoma was observed in the large Agricultural Health Study cohort (AHS). Occupational use was associated with an increased risk of prostate cancer in a Canadian case-control study (Band, et al, 2011) and in the AHS, which reported a significant trend for aggressive cancers after adjustment for other pesticides (Koutros, et al, 2013). In mice, malathion increased hepatocellular adenoma or carcinoma (combined) (US EPA, 1998). In rats, it increased thyroid carcinoma in males, hepatocellular adenoma or carcinoma (combined) in females, and mammary gland adenocarcinoma after subcutaneous injection in females (Cabello, 2001). Malathion is rapidly absorbed and distributed. Metabolism to the bioactive metabolite, malaoxon, is similar across species. Malaoxon strongly inhibits esterases; atropine reduced carcinogenesis-related effects in one study (Cabello, 2001). Malathion induced DNA and chromosomal damage in humans, corroborated by studies in animals and *in vitro*. Bacterial mutagenesis tests were negative. Compelling evidence supported disruption of hormone pathways. Hormonal effects probably mediate rodent thyroid and mammary gland proliferation."

Fortunately, Cheminova attended the evaluation work group meetings as an observer and can offer relevant observations about the discussions and evaluation procedures that occurred at the work shop. We also identify some new/additional data not considered by IARC.

It is important to note that the IARC conclusion was driven by the observation that malathion has been found to produce tumors in some long-term studies in rats and mice - but only at very high dose levels. The IARC review criteria did not consider the dose at which the tumors occur. The fact is that there is a clear threshold for malathion exposure below which tumors

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[5] The Lancet publication can be accessed using this website:
http://weedcontrolfreaks.com/wp-content/uploads/2015/03/GlyphosateWHOIARC2ALancetOncology.pdf

have never been observed. OEHHA is aware of this fact since it has in its possession the same rodent carcinogenicity studies that were evaluated by IARC, including the pathology working group and peer review reports that Cheminova provided to OEHHA with its letters dated April 19, 1999 and August 26, 2000 (Dahl, B., 1999 and Whatling, 2000). Indeed, the Medical Toxicology Branch of the California Department of Pesticide Regulation noted these same thresholds in its review of the rodent carcinogenicity studies dated April 30, 1997 (CalEPA, 1997).

It is also important for OEHHA to understand and acknowledge that IARC's assessment of malathion was strictly "Hazard-identification". In other words, the IARC review was entirely focused on the effects seen in animal studies of malathion conducted using extreme dose levels; the IARC review did not consider the probability that effects observed at high doses in animal studies will occur in humans during realistic exposure conditions. As described by the World Health Organization on its website[6], IARC's hazard classification of substances in terms of carcinogenicity "is the first step of the risk assessment process". A risk assessment, taking into account how and to what levels humans are exposed to malathion, was not conducted by IARC; therefore, it is impossible for IARC to conclude that malathion, or any other chemical it evaluates, will cause cancer in humans when the product is used in accordance with approved labels.

REGULATORY BACKGROUND ON MALATHION IN THE UNITED STATES

Malathion is a broad-spectrum organophosphate (OP) insecticide first registered in the US in 1956. It is used in agriculture for various food and feed crops, homeowner outdoor uses, ornamental nursery stock, building perimeters, pastures and rangeland, and regional pest eradication and suppression programs. It is also a critical component to public health programs designed to combat vector-transmitted diseases such as malaria, dengue fever, chikungunya, West Nile virus, and encephalitis. Finally, malathion plays an important role in integrated pest management (IPM) programs designed to offset the growing resistance of insects to the pyrethroid class of chemicals used in agriculture and in public health protection programs.

In June of 2009, United States Environmental Protection Agency (US EPA) issued its revised Reregistration Eligibility Decision (RED) for malathion (US EPA, 2009). Based on a thorough review of the toxicology, and the conduct of detailed human health risk assessments (US EPA, 2006), US EPA concluded that malathion was eligible for reregistration under the U.S. Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) because it did not pose "unreasonable" risk to humans and the environment.

[6] http://monographs.iarc.fr/ENG/News/Q&A_ENG.pdf

In making its decision to reregister malathion under FIFRA, US EPA considered the toxicology database for malathion to be complete and of acceptable quality to assess the potential hazard to humans. The database includes prenatal developmental toxicity studies in rats and rabbits, a two-generation reproductive toxicity study in rats, an acute delayed neurotoxicity study in hens, an acute neurotoxicity study in rats, a subchronic neurotoxicity study in rats, a developmental neurotoxicity study in rats, and a comparative cholinesterase (ChE) study in adult and immature rats. Additionally, an extensive database of guideline toxicology studies, as required in 40 CFR Part 158.340 (i.e., acute, sub chronic, chronic, carcinogenicity, and metabolism studies) have been submitted. More recently, a guideline immunotoxicity study has been conducted and malathion has been fully evaluated for potential effects on the endocrine system via US EPA's Endocrine Disruptor Screening Program (EDSP). The test substance used in these studies was typically the technical grade of the active ingredient (TGAI) malathion, and the strength, purity, composition, and stability of each test material was adequately documented.

It is worth noting that the carcinogenicity studies were reviewed by the Medical Toxicology Branch of the California Environmental Protection Agency (CalEPA, 1996). In that review, CalEPA concluded that the oncogenicity No Observed Effect Level (NOEL) in the rat 2-year chronic toxicity/oncogenicity study was 500 ppm and the Lowest Observed Effect Level (LOEL) was 6000 ppm. In its review of the 18-month mouse oncogenicity study, Cal EPA concluded that the oncogenicity NOEL was 800 ppm and the LOEL was 8000 ppm. Based on these reviews, California acknowledges that there is a clear threshold of oncogenic effects – in other words, the studies identified exposure levels at which there were no oncogenic responses. This is the same conclusion reached by US EPA and other regulatory bodies throughout the world.

THE IMPORTANCE OF IMPURITIES AND FORMULATION INERTS IN DETERMINING RELEVANCE OF TOXICITY DATA TO THE UNITED STATES

Impurities are of special importance to defining the toxicological profile for malathion. Certain impurities are known to influence the toxicity of malathion (Aldridge et al., 1979; Pellegrini and Santi, 1972; Talcott et al., 1977; Toia et al., 1980; and Umetsu et al., 1977). The amount of certain impurities in technical grade malathion primarily depend on and can be controlled by the manufacturing process, but a few impurities may also increase when the product is stored improperly for long periods of time at high temperatures. Indeed, the state of California recognized this when it designed its exposure monitoring program and conducted its risk assessments related to the aerial spraying of malathion in exotic fruit fly eradication efforts (Brown, et al, 1993; CalEPA, 1997). Also in recognition of the importance of controlling impurities in pest control products, impurity limits are being established for many pesticides via the Food and Agriculture Organization (FAO) of the United Nations. FAO specifications

are developed with the basic objective of promoting, as far as practicable, the manufacture, distribution and use of pesticides that meet basic quality requirements. FAO specifications have been developed for malathion (FAO, 2013). The US EPA regulates the amount of these impurities by setting legal limits in the technical grade of malathion it approves for registration in the US. Thus, these limits are important to determining the relevance of toxicological studies, particularly those reported in the open literature, because the authors often do not present any information about the impurity profile of the malathion test material used.

Similarly, toxicity studies on formulated end-use products must also be considered with caution. In addition to containing an active ingredient, formulated end-use products contain various solvents, emulsifiers and other intentionally added chemicals. These are often referred to as "inerts". Many of these chemicals have their own toxicological properties and some may enhance the toxicity of the active ingredient. Because countries around the world have different laws and regulations that govern what chemicals are permitted to be used in the manufacture of formulated end-use products, and because these laws and regulations change with time, it is important to know the composition of these formulated products when used in toxicological studies in order to determine relevance to specific countries, including the US. There is no evidence that IARC considered the impurity profile or composition of formulations when selecting, reviewing and citing literature to support its position. Without such an evaluation, the validity and relevance of the IARC assessment and conclusions to the US cannot be determined[7].

GENERAL TOXICOLOGY

Malathion exhibits low acute toxicity via the oral, dermal, and inhalation routes (Toxicity Category III or IV). Malathion, like other members of the OP common mechanism group, inhibits ChE as a mode of toxic action. Malathion is metabolically activated to its ChE inhibiting oxon metabolite, malaoxon (oxidation of the P~S moiety to P=O), in insects and mammals. Both malathion and malaoxon are detoxified by carboxyesterases leading to polar, water-soluble, compounds that are excreted. Mammalian systems show greater

[7] **Cheminova observation made during the Working Group meeting in Lyon:** It was obvious during the Working Group meeting in Lyon that the evaluations did not always distinguish whether the test substance used in a study was the active ingredient or a formulated end-use product. During plenary discussions, Cheminova's observer specifically asked whether information on test substance (purity and/or whether it was technical material or formulated end-use product) could be added to the data tables. The IARC secretariat said they would add this information in the final monograph. However, since the monograph has not yet been published, and without this information, it is not possible to determine if the studies considered by IARC were conducted with test materials that are relevant to the U.S. As such, it would not be appropriate for OEHHA to simply accept the IARC conclusions and use them to list malathion as a known carcinogen under Prop 65.

carboxyesterase activity, as compared with insects, so that the toxic agent malaoxon builds up more in insects than in mammals. This accounts for the increased toxicity of malathion in insects compared to mammals and humans (US EPA, 2006). Based on an analysis conducted by U.S. EPA and presented in its Updated Cumulative Risk Assessment for the OPs, malathion was shown to have the lowest potency to inhibit brain cholinesterase activity compared to all other OPs (see Figures 1 and 2).

PHARMACOKINETICS

In a rat metabolism study, malathion was excreted in the urine (80-90%) in the first 24 hours of exposure (Reddy et al, 1989). At 72 hours, the highest concentration of radioactivity was observed in the liver (<0.3% of the administered dose). Radioactivity did not bioaccumulate in any of the organ/tissues analyzed. Similarly, in a study where a single dose of 15 mg/kg bw malathion was administered to fully informed groups of healthy male and female human volunteers under carefully controlled clinical conditions, elimination of malathion occurred extremely rapidly in urine with approximately 90% of the total amount of urinary excretion occurring within the first 12 hours after dosing. Plasma levels of malathion and malaoxon remained below detectable levels (<ca100 ng/ml) at all times after administration, indicating the degree of protection afforded by first-pass hepatic metabolism (Gillies, D. and Dickson, J., 2000). The half-life of malathion in human blood has been reported to be 2.89 hours (Lyon, et al, 1987). The very quick half-life of malathion *in vivo* is partially responsible for the low toxicity of malathion in mammals and humans.

CARCINOGENICITY

It should be relevant to OEHHA that the US EPA has classified malathion as having "suggestive evidence of carcinogenicity" in accordance with the US EPA Proposed Guidelines for Carcinogen Risk Assessment (US EPA, 1999). The classification is based on the following evidence:

1) the occurrence of liver tumors in mice and rats only at excessive doses;
2) the presence of a few rare tumors in rats, which cannot be distinguished as either treatment related or due to random occurrence;
3) the evidence for mutagenicity is not supportive of a mutagenic concern in carcinogenicity; and
4) malaoxon, a structurally related chemical, is not carcinogenic in rats.

The carcinogenic potential of malathion was also reviewed by the FIFRA Scientific Advisory Panel (SAP) on August 17-18, 2000. According to the final SAP report, the Panel was almost

equally divided between recommending a classification of "suggestive" and "not likely to be carcinogenic to humans" (FIFRA SAP, 2000). In fact, the panel members overwhelmingly did not support a conclusion that malathion was a likely human carcinogen (US EPA, 2005). The Agency subsequently considered the SAP recommendations and concluded that the cancer classification should be "suggestive." Additionally, the US EPA Carcinogenicity Assessment Review Committee (CARC) evaluated a publication by Cabello et al. (2001) and concluded that the paper provided insufficient basis for revising the cancer classification for malathion. Ultimately, EPA concluded that its risk assessments based on cholinesterase inhibition as the critical effect is considered protective of other toxicological endpoints of concern, including carcinogenic effects (US EPA, 2009).

It should also be relevant to OEHHA that the carcinogenicity potential of malathion has also been recently reviewed by the Canadian Pest Management Agency and its regulatory conclusions were published in 2012 (PMRA, 2012). Based on a review of the same data available to IARC, PMRA concluded "Malathion was not found to be genotoxic or teratogenic. Based on the scientific evidence, malathion is unlikely to pose a carcinogenic risk for humans."

Finally, OEHHA should also be aware the carcinogenicity potential of malathion has been reviewed in the European Union. Based on the same critical studies, "no classification with regards to carcinogenicity" has been proposed by the EU experts (EFSA, 2004, 2006, 2009; UK COM/COC, 2003).

Regarding the IARC review of malathion, the IARC Preamble says IARC only reviews and considers reports that have been published or accepted for publication in the openly available scientific literature. In addition, data from government agency reports that are publically available are also considered. It is important to note that none of the citations included in the Lancet Oncology were for regulatory studies[8]. For malathion, it appears that IARC accessed a few, but not all, of the US EPA regulatory reviews that are available online. Likewise, there appears to be no standardized search or selection criteria used to obtain data from the open literature, especially for what is referred to as mechanistic data, including genotoxicity studies, where the IARC consider only "representative studies" (without defining what this would be). The exclusion of regulatory studies and the undefined "selective" review of data from the open literature raise serious concerns about whether the conclusions of the IARC reflect an un-biased evaluation process. There are other issues as well, which are discussed below.

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[8] The Lancet Oncology did refer to a data evaluation record prepared by EPA for an 18-month mouse oncogenicity study; however, as discussed later, that DER is outdated and does not reflect final agency conclusions about the study.

In the Lancet Oncology publication, the IARC states with reference to "US EPA, 1998":

> "In mice, malathion increased hepatocellular adenoma or carcinoma (combined)[10]"

Cheminova believes that there are several problems with this statement and the citation provided by IARC.

First, the statement is a misleading statement because IARC chose to ignore the important fact that the US EPA concluded that these tumors were seen only at "excessive dose levels". Second, in making this statement, IARC cites a data evaluation record (DER) produced by a former (retired) US EPA scientist in the Health Effects Division. The citation provided by IARC in the Lancet Oncology is as follows:

> "US Environmental Protection Agency. Peer review of malathion: 18-month carcinogenicity study in mice. http://www.epa.gov/opp00001/chem_search/cleared_reviews/csr_PC-057701_undated_004.pdf (accessed March 6, 2015)."

There are several problems with this citation. First, the citation suggests that the link provided will allow the reader to access a peer review conducted by US EPA on the 18-month mouse carcinogenicity study on malathion. In fact, the link does not access a peer review report at all. Rather, the link is for a data review conducted by a former US EPA scientist back in the 1990s after the study had been submitted to US EPA. Subsequent to our receipt of this DER from US EPA, a Pathology Working Group (PWG) was convened to conduct a peer review of the lesions of the liver observed in the mouse oncogenicity study. A report from the PWG peer review was submitted to US EPA and the same former US EPA scientist subsequently wrote a DER for the peer review which was issued by the US EPA in 1998. The DER for the peer review can be accessed via the following link: http://www.epa.gov/pesticides/chemicalsearch/chemical/foia/cleared-reviews/reviews/057701/057701-125.pdf. From the information provided in the Lancet Oncology, it is not clear if IARC had accessed the DER for the peer review or even considered it during their deliberations.

In any event, IARC will have erred in citing either one of these DERs as reflecting the final position of the US EPA. Subsequent to the PWG peer review, the EPA's SAP met in 2000 to consider the carcinogenicity classification for malathion. The US EPA considered the opinions of the SAP, and the final US EPA position was published in the US EPA revised human health risk assessment document (US EPA 2006). IARC did not cite the US EPA 2006 revised human health risk assessment document in the Lancet Oncology; thus, it does not appear that IARC had accessed or considered this important document during their review of malathion.

Regarding the carcinogenicity study in rats, IARC states the following in the Lancet Oncology:

> 'In rats, it [malathon] increased thyroid carcinoma in males, hepatocellular adenoma or carcinoma (combined) in females, and mammary gland adenocarcinoma after subcutaneous injection in females[4]".

This statement is made with reference to a tumor-promoter study from the open literature (Cabello, et al, 2001). However, in making its conclusion on carcinogenic potential in *rats*, the IARC chose to ignore US EPA's ultimate conclusions on the rat cancer studies. A few examples are provided below.

First, in regards to the increased thyroid carcinoma in males mentioned by IARC, the US EPA agreed with the SAP conclusions that the most appropriate assessment of this tumor is to examine the adenomas/carcinomas combined. The reason for this is that this tumor is a continuum in its natural history, i.e., progresses from hyperplasia, to adenoma to carcinoma. The SAP noted that while there was a pair-wise statistical difference for carcinomas at the high dose, this was not apparent when adenomas and carcinomas were combined, nor was there any dose trend. As such, this effect was not considered by the SAP experts and US EPA to be related to malathion exposure.

Second, regarding the hepatocellular adenoma or carcinoma incidence in female rats, IARC does not acknowledge that these tumors only occurred at the two highest dose levels where excessive toxicity was observed in these rats. There were no treatment-related tumors observed at the lower dose levels. This was confirmed by the Pathology Working Group review of these data, as well as by the FIFRA SAP review. The IARC criterion for classification does not consider dose-response relationships, thresholds or other measures of potency of a chemical for producing tumors. Thus, the IARC's methodology for cancer classification is solely and extremely hazard based. Nevertheless, this is an important piece of information because it is critical to determining whether these dose levels are relevant to expected human exposure scenarios and ultimately whether malathion will be carcinogenic to humans and this fact should not be ignored by the OEHHA.

As mentioned above, IARC refers to a study from the open literature that reported the formation of mammary gland adenocarcinoma after subcutaneous injection in females (Cabello, 2001). The study apparently showed that subcutaneous injections of malathion directly into mammary tissues can have a tumor-promoting effect. The IARC does not explain why it gives so much weight on this very special study conducted using a study design (injection) that is obviously not relevant for the human exposure situation. With a letter submitted to OEHHA on August 26, 2010, Cheminova provided OEHHA with a critical review of this paper (O'Shaughnessy and Hauswirth, 2003). As stated in our review, Cheminova has serious concerns about the design of the studies included in the publication and

the author's interpretation of those results. The US EPA has also reviewed this paper and concluded that it does not provide sufficient basis for reconsidering the US EPA cancer classification of malathion (US EPA, 2009).

Based on the numerous issues (as described above) identified with the limited information that IARC provided in the Lancet Oncology, we believe that OEHHA would be premature to proceed with its proposal to list malathion as a "known" carcinogen. The IARC review appears to contain errors, inconsistencies, misunderstandings, a lack of transparency, and a lack of general scientific credibility. In addition, because the review does not consider dose, and only represents a preliminary "hazard identification' phase for risk assessment, it would be scientifically inappropriate to use the IARC review to conclude that malathion is a chemical known by the state of California to cause cancer.

MUTAGENICITY AND GENOTOXICITY

IARC states in the Lancet Oncology that malathion induced DNA and chromosomal damage in humans and is corroborated by studies in animals and *in vitro*. Although not stated in the Lancet Oncology, as an observer during the IARC meetings, Cheminova understands that IARC considers the data reviewed to provide strong evidence of the mechanism of carcinogenicity of malathion and it is one of the major factors used by IARC to classify malathion the way it did.

Although there have been reports of positive genotoxicity in the literature, EPA's Cancer Assessment Review Committee (US EPA, 2000) cautioned that data from the open literature should be interpreted with care because positive clastogenic results were found in studies that were compromised by a lack of purity information on the test article, testing with commercial or 50% malathion formulations or finding positive responses at precipitating concentrations or at cytotoxic concentrations. Still others had technical shortcomings that precluded drawing meaningful conclusions from the data. In addition, studies showing induction of chromosome aberrations at cytotoxic levels (60% reduced cell confluence) in conjunction with the increased occurrence of unstable chromosome aberrations (e.g., chromatid and chromosome breaks), which generally lead to cell death are not considered to be adequate evidence of a positive response or supportive of a direct DNA reactive mutagenic capability of the agent.

In reviewing the same basic set of data as IARC, US EPA stated in its revised human health risk assessment (US EPA, 2009) that the mutagenicity database for malathion indicates that there is only weak evidence of a mutagenic effect in mammalian cells but only at high and cytotoxic concentrations. Negative mutagenic responses were noted for the guideline *in vitro* bacterial reverse mutation assay, the *in vivo* bone marrow cytogenetic assay, *in vivo* rat hepatocyte DNA-Repair assay, *in vivo* Micronucleus study in mice, and the *in vitro* primary rat

hepatocytes unscheduled DNA synthesis (UDS) assay. In an acceptable guideline *in vitro* mouse lymphoma cell gene mutation assay, and in the *in vitro* mammalian cytogenetic assay in human lymphocytes at concentrations that produced moderate cytotoxicity, malathion was mutagenic over a very narrow range of concentrations that showed moderate to marked cytotoxicity. Based on a weight of evidence review of data from both guideline studies and the open literature, US EPA concluded that the data do not support a mutagenic concern for malathion and carcinogenicity. The FIFRA SAP agreed with this conclusion (FIFRA SAP, 2000). In the EU, the EFSA Conclusion report concluded that although the *in vitro* results are inconclusive, the available data suggest that there is no genotoxic potential *in vivo* (EFSA, 2009). Cheminova agrees with these conclusions.

IMMUNOTOXICITY

Although immunotoxicity was not mentioned by IARC in the Lancet Oncology, we observed that a number of published studies on the immune system were evaluated by IARC and influenced its decisions. Like the genotoxic data, the immunotoxicity data in the open literature should also be interpreted with caution as results were likely compromised by a lack of purity information on the test article, testing with commercial formulations or finding positive responses at precipitating concentrations or at cytotoxic concentrations. This uncertainty prompted US EPA to require Cheminova to conduct a guideline immunotoxicity study to better characterize the potential effects of malathion on the immune system. Cheminova submitted an immunotoxicity study conducted in accordance with Good Laboratory Practices and according to OPPTS Guideline 870.7800. The US EPA reviewed the study and classified it as acceptable/guideline and concluded that the study revealed no effect on immune function and that "The toxicological database for malathion did not reveal any evidence of treatment related effects on the immune system" (US EPA, 2012).

Note that this information was not available to IARC during its review. Thus, this new information contradicts and possibly invalidates any conclusions that IARC made based on perceived effects of malathion on the immune system.

ENDOCRINE

In the Lancet Oncology, IARC says "Compelling evidence supported disruption of hormone pathways. Hormonal effects probably mediate rodent thyroid and mammary gland proliferation." Cheminova strongly disagrees with this conclusion. The potential of malathion to affect the endocrine systems in mammals and wildlife has recently been thoroughly evaluated via US EPA's Endocrine Disruption Screening Program (EDSP) (US EPA, 2015).

US EPA's review has been published on its website[9]. Based on weight of evidence considerations, which included a detailed review of guideline studies as well as published literature, US EPA concluded that "there was no evidence of potential interaction with the estrogen, androgen or thyroid pathways".

Note that this information was not available to IARC during its review. Thus, this new information contradicts and possibly invalidates any conclusions that IARC made based on perceived effects of malathion on the endocrine system.

EPIDEMIOLOGY

In the Lancet Oncology, IARC wrote the following:

> There is limited evidence in humans for the carcinogenicity of malathion. Case-control analyses of occupational exposures reported positive associations with non- Hodgkin lymphoma in the USA (Waddell et al, 2001), Canada (McDuffie et al, 2001), and Sweden (Erickson, et al, 2008), although no increased risk of non-Hodgkin lymphoma was observed in the large Agricultural Health Study cohort (AHS). Occupational use was associated with an increased risk of prostate cancer in a Canadian case-control study (Band, et al, 2011) and in the AHS, which reported a significant trend for aggressive cancers after adjustment for other pesticides (Koutros, et al, 2013).

Cheminova has evaluated the published epidemiology studies on malathion, including those publications evaluated by IARC (Reiss, R., 2015). Our review was recently submitted to the US EPA in July of 2015. There are two classes of epidemiologic studies relevant to malathion. We discuss their limitations in the text below.

The first set of studies uses biomonitoring to classify exposure in populations that are generally non- occupationally exposed. Some of these studies use a specific biomarker for malathion (e.g., malathion dicarboxylic acid), but others include a biomarker related to OPs generally (e.g., DAPs). The biomarkers used in most of the non-occupational studies have substantial limitations that could lead to exposure misclassification. For example: (1) most exposure to the biomarkers is from direct ingestion of preformed metabolites and not OP or malathion exposure, and (2) only one or two biomarker measurements are made during pregnancy, which may not accurately represent long-term exposure. Additionally, for associations tested with general OP biomarkers, attributing effects to malathion is tenuous at best, given that it is the least toxic OP.

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[9] The website may be accessed via the following link:
http://www2.epa.gov/sites/production/files/2015-06/documents/malathion-057701_2015-06-29_txr0057180.pdf

The second set of studies is from the Agricultural Health Study (AHS) cohort in which exposures were classified from surveying the applicators and asking them to recall their pesticide use history. The AHS study generally classifies exposure by whether the subject used or did not use malathion, but sometimes classification is by the number of days the subjects used malathion. This exposure classification methodology is extremely crude and misses many of the factors that affect exposure, such as the amount of material handled and the type of personal protective equipment and application equipment used. Therefore, exposure to malathion is probably classified with a substantial degree of error, and it is highly doubtful that the study design can differentiate effects potentially due to malathion from those of other pesticides.

Overall, the collective non-occupational and occupational epidemiologic data for malathion do not provide any convincing evidence of adverse human health effects caused by malathion exposure. The studies do not provide a reliable measure of exposure. Additionally, they have substantial methodological problems that limit their validity and interpretability. As such, reported statistical associations are most likely the result of chance than due to any actual exposures to malathion. Thus, the epidemiology data on malathion do not provide reliable evidence that malathion causes cancer in humans.

HUMAN HEALTH RISK ASSESSMENT

Humans may be exposed to malathion directly through crop or non-crop uses, or indirectly via residues in food. However, based on labeled use conditions, it is not possible to construct a realistic scenario under which humans would be exposed at levels that are high enough to produce the kind of organ toxicity and tumors that are seen in the long-term studies with rats and mice at very high dose rates. Indeed, based on the same cancer data as evaluated by IARC, major evaluating and regulatory authorities (such as the U.S. PMRA, EPA, EU, WHO and JMPR) have approved the continued use of malathion for use in agriculture and public health. Based on risk assessment that uses cholinesterase inhibition as the critical effect, these regulatory agencies have concluded that humans are not at risk of getting cancer through exposure to malathion.

SUMMARY

OEHHA has asked for the public to comment whether the IARC review satisfies the requirements for listing malathion as a "chemical known to the state to cause cancer". But the IARC has not yet issued a monograph on malathion. In fact, the only information available to the public is a short notice in the Lancet Oncology about the IARC review and conclusions. Without the existence of the detailed monograph, it is not possible for the public to effectively review and understand how IARC reached its conclusions, or evaluate whether its conclusions are supported by the available data. As such, it is premature for OEHHA to ask the public to comment on whether the IARC conclusions warrant listing under Proposition 65.

Although OEHHA has stated that comments on the weight or quality of the evidence evaluated by IARC cannot be considered under the Labor Code mechanism of listing carcinogens under Proposition 65, it did not mention whether the availability of other or new information can be considered by OEHHA in evaluating whether the IARC conclusions are supported by the available data. In these comments, Cheminova has identified procedural, data quality and relevance issues, and new information not considered by IARC. Some of the new information directly refutes many of the reasons cited in the Lancet and used by IARC to support its conclusion that malathion is a human carcinogen.

Because OEHHA has in its files the animal carcinogenicity studies, as well as the peer reviews of relevant histopathology data, OEHHA is well aware that the tumors observed in these animal studies only occurred at very high dose levels that exceeded the maximum tolerated dose for the test animals. These tumors formed because the exposure overwhelmed the metabolic system of the tested rodents causing tissue inflammation and toxicity. Such exposures are not relevant to humans when malathion products are used in accordance with government approved labels. OEHHA also is aware that these tumors occur at dose levels that far exceed the effect levels for cholinesterase inhibition for the animals in these studies. Thus, it should not be a surprise to OEHHA that risk assessments performed by regulators throughout the world, including those conducted by the California Environmental Protection Agency, demonstrated that the use of cholinesterase inhibition as the critical effect will be protective of any carcinogenicity risk from exposure to malathion. Considering the risk assessments show no concern for carcinogenicity, OEHHA and the State can reasonably argue that it "knows" malathion does <u>not</u> cause cancer in humans when products are used in accordance with the labels approved by US EPA and by California Department of Pesticide Regulation.

There are very few human epidemiology studies that specifically evaluated malathion. Our review of those studies concluded that (1) none of the studies include reliable measures of exposure, (2) several of the studies provide conflicting information for the same endpoints, (3) the design of the studies do not effectively manage inherent bias, and (4) statistical significant

associations by chance are likely and cannot be ruled out. Thus, considering the weaknesses and conflicting information in the available epidemiology data, there are no reliable data to arrive at the conclusion that malathion is a human carcinogen.

Based on the above, we do not believe that the IARC evaluation and conclusions are sufficiently reliable to warrant listing of malathion as a carcinogen known to the state of California to cause cancer. In fact, data available to OEHHA, as well as new data not considered by IARC, should allow OEHHA to conclude that malathion is not a known carcinogen when used in accordance with its label.

CONCLUSIONS AND RATIONALE TO SUPPORT NOT LISTING MALATHION AS A KNOWN CARCINOGEN UNDER THE LABOR CODE MECHANISM OF PROPOSITION 65

OEHHA has issued a Notice of Intent to List malathion as a chemical known to the State of California to cause cancer pursuant to the "Labor Code" listing mechanism, Health and Safety Code section 25249.8(a) and Title 27, Cal. Code of Regs, section 25904. Cheminova submits the following comments in opposition to this listing because the identification of malathion does not meet the requirements of 27 CCR section 25904. Specifically, malathion does not qualify for listing under Labor Code section 6382(b)(1) because it can be excluded via Section 6382(a) of the Labor Code and is not an appropriate Labor Code listing.

Summary of Listing and Applicable Statutes and Regulation

OEHHA's Notice of Intent to List asserts that Malathion meets the criteria for listing pursuant to 27 CCR section 25904(b)(2) as a carcinogen based upon its placement on the list of Agents Classified by the International Agency for Research on Cancer (IARC) Monographs as Group 2a, probably carcinogenic to humans with sufficient evidence of carcinogenicity in experimental animals. This category is used when there is limited evidence of carcinogenicity in humans.

The statutory authority for this regulation is derived from Section 25249.8(a) of the Health and Safety Code which provides:

> "(a) On or before March 1, 1987, the Governor shall cause to be published a list of those chemicals known to the state to cause cancer or reproductive toxicity within the meaning of this chapter, and he shall cause such list to be revised and republished in light of additional knowledge at least once per year thereafter. Such list shall include at a minimum those substances identified by reference in Labor Code Section 6382(b) (1)

> and those substances identified additionally by reference in Labor Code Section 6382(d)."

Labor Code Section 6382(b) (1) provides that substances listed as human or animal carcinogens by the IARC shall be listed, subject to the exclusion provision contained in section 6382(a) which states:

> "(a) Any substance designated in any of the following listings in subdivision (b) shall be presumed by the director to be potentially hazardous and shall be included on the list; provided, that the director shall not list a substance or form of the substance from the listings in subdivision (b) if he or she finds, upon a showing pursuant to the procedures set forth in Section 6380, that *the substance as present occupationally is not potentially hazardous to human health; and provided further, that a substance, mixture, or product shall not be considered hazardous to the extent that the hazardous substance present is in a physical state, volume, or concentration for which there is no valid and substantial evidence that any adverse acute or chronic risk to human health may occur from exposure."* (Emphasis added).

Cheminova asserts that malathion is excluded from listing pursuant to this section.

Basis for Exclusion Pursuant to Labor Code section 6382(a)

Malathion does not meet the criteria for listing because:

1. The United States Environmental Protection Agency (US EPA) registers products under the Federal, Insecticide, Fungicide and Rodenticide Act (FIFRA). Under this law, EPA may not register a pesticide if it cannot ensure that the product, when used in accordance with its labeling, will cause unreasonable risks to human health. EPA has approved many malathion labels under FIFRA, and continues to do so. Therefore, these labels comply with the FIFRA requirement that malathion does not pose unreasonable risk to human health.

2. In the critical rodent carcinogenicity studies on malathion, the US EPA and the California Department of Pesticide Regulation have identified that there is a clear threshold of malathion exposure at which no tumors form. Tumors observed in the animal studies have been shown to occur only at very high doses that exceeded the maximum tolerated dose as evidenced by the severe clinical signs of toxicity and death. These signs of toxicity occur only with exposures that are well above those to which

humans may be exposed when using malathion in accordance with its government-approved labels.

3. Labels approved by US EPA under FIFRA are supported by risk assessments. Those risk assessments are based on the use of red blood cell cholinesterase inhibition as the critical effect. Reference doses for risk assessment are generally set based on a 10% change in cholinesterase inhibition. This level of inhibition occurs at exposure levels that are lower than the exposures causing toxicological effects in the animal studies and far lower than those that caused tumor formation. Therefore, the use of the cholinesterase endpoint in risk assessment is considered to be sufficiently protective of all other toxicological endpoints of concern, including cancer. As such, there is no substantial evidence that any adverse acute or chronic risk to human health may occur from exposures when products containing malathion are used in accordance with labels approved by the US. EPA.

4. The State of California, Canada Pest Management Regulatory Agency, as well as experts within the European Union have all concluded that risk assessments based on cholinesterase inhibition as the crucial affect demonstrate no risks of concern from exposure to malathion to humans when it is used in accordance with approved labels.

5. The review conducted by IARC was only a rudimentary assessment of potential hazard. By definition, hazard assessment does not consider exposure and does not include a risk assessment. Without identifying how the hazards identified by IARC relate to expected human exposures, IARC is not able to conclude that exposure to a product will cause adverse health effects, including cancer, in humans. As such, the IARC review provides no valid and substantial evidence that adverse acute or chronic risk to human health may occur from exposures to malathion when products containing malathion are used in accordance with labels approved by the US EPA.

In light of the fact that malathion clearly does not qualify for listing pursuant to the Labor Code mechanism and California law, we request that OEHHA rescind the Notice of Intent to list malathion as a known carcinogen.

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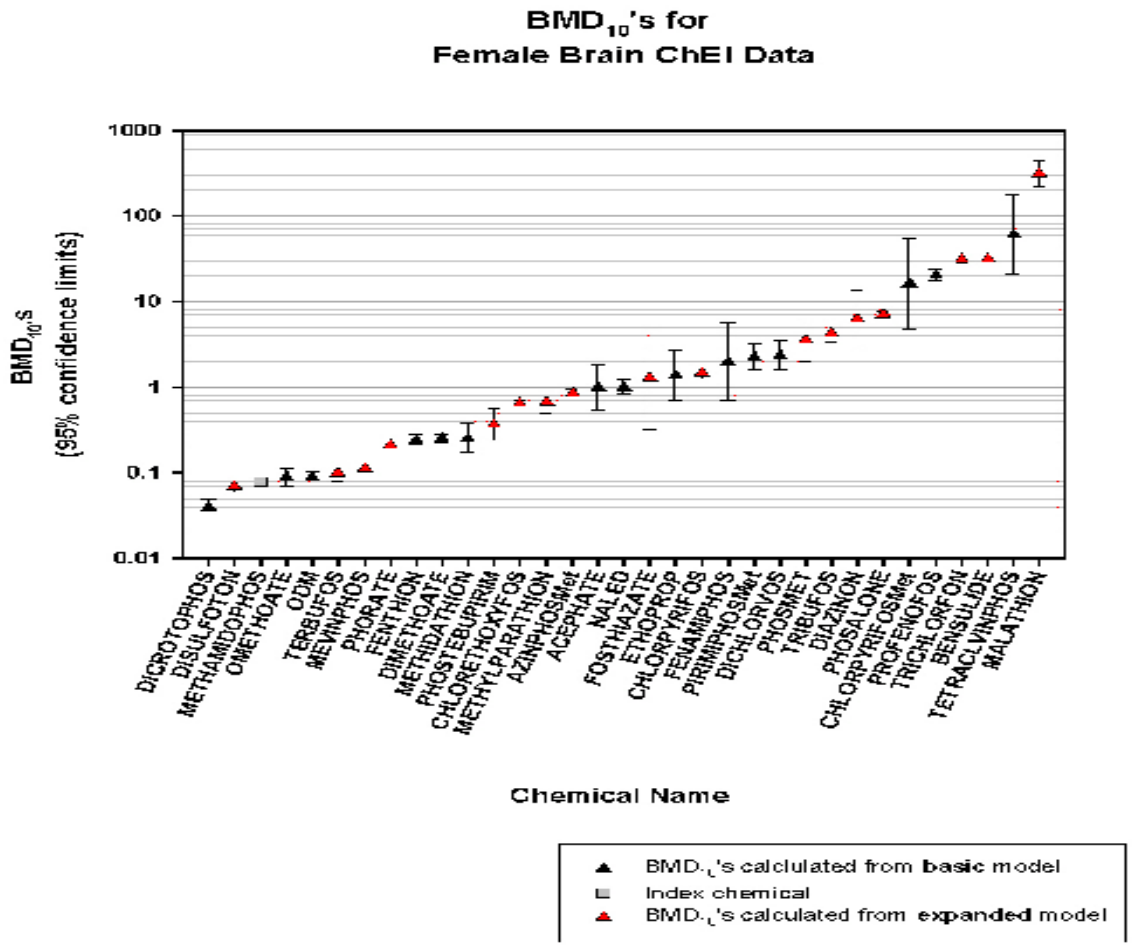
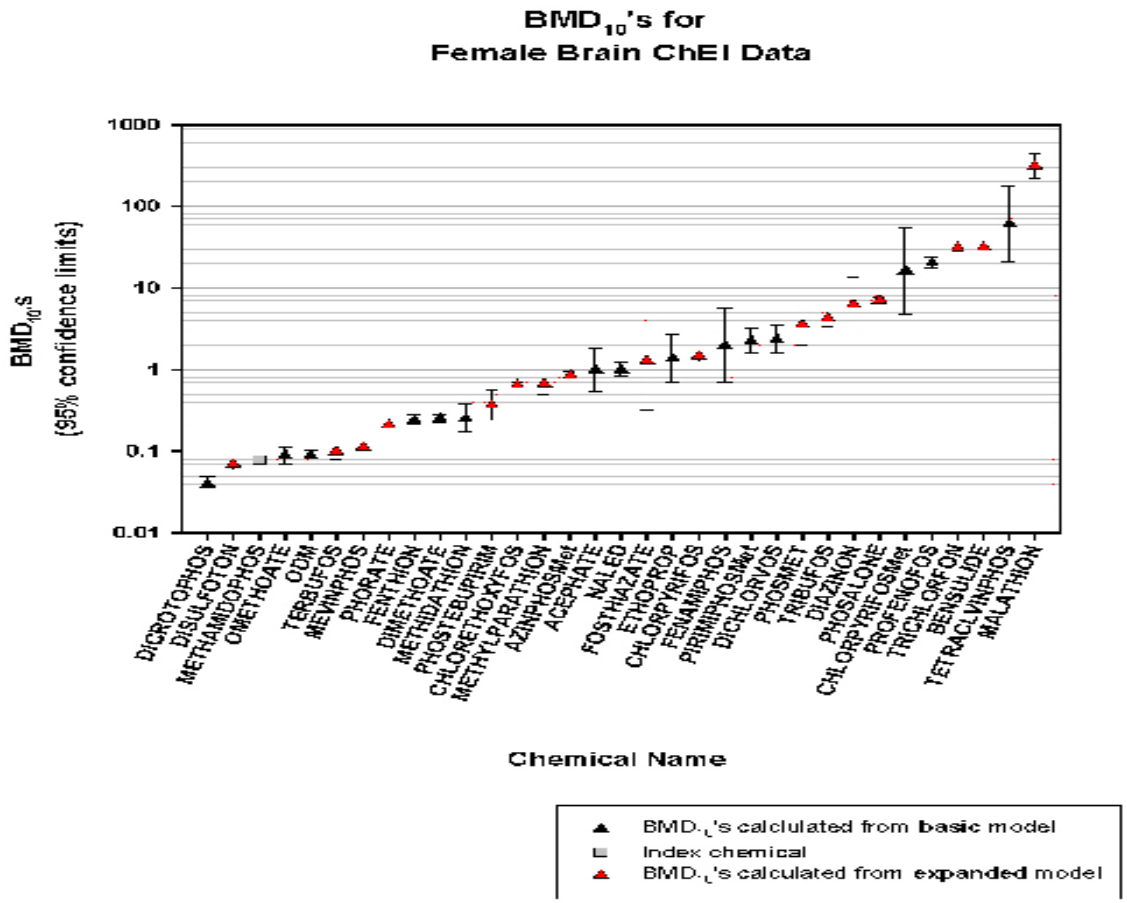
Figure I. Plot of BMD10s and the 95% confidence limits for female rat brain ChE inhibition for the OPs[11]



[11] Source: EPA, 2006. Organophosphorus Cumulative Risk Assessment 2006 Update. U.S. Environmental Protection Agency, Office of Pesticide Programs, July 31, 2006. http://www.epa.gov/oppsrrd1/cumulative/2006-op/index.htm

Figure 2: Plot of oral relative potency factors for female rat brain ChE inhibition for the OPs.[12]



[12] Source: EPA, 2006. Organophosphorus Cumulative Risk Assessment 2006 Update. U.S. Environmental Protection Agency, Office of Pesticide Programs, July 31, 2006. http://www.epa.gov/oppsrrd1/cumulative/2006-op/index.htm