OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

# Pesticide Exposure and Risk Assessment Peer Review

## Document Review

## Department of Pesticide Regulation's Draft Risk Characterization and Exposure Assessment Documents for Methomyl

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# PREFACE

Under the authority of California Food and Agricultural Code Section 11454.1, the Office of Environmental Health Hazard Assessment (OEHHA) conducts scientific peer reviews of human health risk assessments prepared by the Department of Pesticide Regulation (DPR). DPR generally reports the risk assessment in two documents:

- The Risk Characterization Document (RCD), which summarizes the toxicology database; discusses the hazard identification and dose-response analyses performed; assesses dietary exposure, when appropriate; and characterizes the risk associated with various exposure scenarios (dietary, occupational, residential, and aggregate exposures).
- The Exposure Assessment Document (EAD), which describes the exposure scenarios and estimates the exposure levels for workers and residents.

This report is a peer review of DPR's draft RCD (dated and received November 10, 2015), which also contained the dietary and drinking water exposure assessment (dated January 2014), and the exposure assessment for workers and bystanders (dated January 2015, referred to as the EAD), for the pesticide methomyl.

This peer review report has four parts:

I. Summary of Review
II. Responses to Charge Questions provided by DPR
III. Detailed Comments on charge questions and additional comments
IV. Minor Comments

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# I. SUMMARY OF REVIEW

This report presents the review by the Office of Environmental Health Hazard Assessment (OEHHA) of the Department of Pesticide Regulation's (DPR) draft Risk Characterization Document (RCD) and two draft exposure assessments, one for worker and bystander exposures in the Exposure Assessment Document (EAD), and one for dietary and drinking water exposures presented within the RCD, for methomyl, a carbamate insecticide (DPR, 2015a, b). The draft RCD characterizes the non-cancer health risks from methomyl associated with dermal and inhalation exposure of workers, inhalation exposure of bystanders (occupational and residential), and dietary exposures of the general public from food and water. Acute, subchronic (seasonal), and chronic (annual) exposure durations were evaluated, where applicable. Overall, we find the draft RCD and exposure assessments to be well written and concise.

Our principal comments are summarized in Section I. Responses to DPR's charge questions are provided in Section II. Detailed comments are provided in Section III and minor comments are presented in Section IV.

## A. Hazard Identification and Risk Characterization

### 1. Non-cancer Endpoint Selection and Point of Departure Determination (Table 1)

- Oral exposure
    - For acute exposure, OEHHA agrees with the selected critical toxicity endpoint and point of departure (POD) of 0.03 milligram per kilogram (mg/kg) (red blood cell [RBC] cholinesterase [ChE] inhibition in humans from McFarlane et al., 1998).
    - For subchronic exposure, OEHHA agrees with selection of the subchronic dietary neurotoxicity study (Mikles, 1998a) as the critical study, but disagrees with the selected No-Observed-Effect Level (NOEL) and POD of 9 milligram per kilogram-day (mg/kg-day) based on reduced body weight and food consumption, tremors, functional observational battery (FOB) signs, and brain ChE inhibition in male rats. OEHHA suggests that DPR consider a lower POD, possibly a NOEL of 1.48 mg/kg-day, to account for statistically significant reductions in mean total movement number which occurred at doses of 3.85 mg/kg-day and higher in female rats.
    - For chronic exposure, OEHHA disagrees with selection of the two-year dog dietary study (Busey, 1968) as the critical study, with a POD at 3 mg/kg-day, the NOEL for kidney and spleen histological changes.

Instead, OEHHA recommends the use of the two-year rat dietary study (Kaplan, 1981), which is of high quality and statistical power. The critical chronic endpoints in the rat study are dose-dependent histological changes in the bone marrow, adrenal medulla, and adrenal cortex of males. These endpoints give benchmark dose ($BMDL_{05}$)[1] values between 1.03 and 1.79 mg/kg-day, lower than the selected NOEL of 3 mg/kg-day.

- Dermal Exposure

    - For all durations, DPR chose a POD of 90 mg/kg-day from a 21-day dermal study in rabbits (Finlay, 1997). It was the highest dose tested and the reported NOEL for lack of RBC and brain ChE inhibition and clinical signs. OEHHA agrees with the selection of Finlay (1997) as the critical study for the acute, subchronic, and chronic dermal POD determinations. However, OEHHA disagrees with selection of the NOEL and POD and suggests that the POD be based on brain ChE in males. Brain ChE was statistically significantly reduced with a $BMDL_{10}$ of 15.8 mg/kg-day.

    - In addition, OEHHA suggests that DPR consider a duration extrapolation factor for extrapolation of the subchronic POD to chronic POD to account for potentially lower PODs for non-ChE endpoints with repeated exposures.

- Inhalation Exposure

    - For acute exposure, OEHHA agrees with the critical study and POD (3.92 milligram/cubic meter, $mg/m^3$; 0.16 mg/kg) based on brain ChE inhibition from an acute inhalation toxicity study in rats (Weinberg, 2014).

    - For subchronic and chronic exposures, DPR used oral PODs for the respective durations. These values (9 and 3 mg/kg-day, respectively) are significantly higher than the acute inhalation POD. OEHHA recommends that DPR consider using the acute inhalation POD for subchronic and chronic inhalation exposures and applying a duration extrapolation factor. DPR should weigh the uncertainty associated with route-to-route extrapolation against that associated with duration extrapolation.

[1] For risk assessment, the BMDL (95% lower confidence limit of the benchmark dose) is generally selected as the point of departure.

**Table 1.** Non-cancer endpoint selection and points of departure.

| Human Exposure Scenarios | DPR's Draft RCD | | | OEHHA Comments |
|---|---|---|---|---|
| | POD mg/kg-day | Species Route, Critical Effect | Critical Study | |
| Oral-acute | 0.03 ($BMDL_{10}$) | Human oral RBC ChE inhibition | McFarlane et al., 1998 | Agree. |
| Oral-subchronic | 9 (NOEL) | Rat diet Reduced body weight and food consumption, tremors, FOB signs, brain ChE inhibition | Mikles, 1998a | Agree with study, but not POD or effect. Recommend NOEL of 1.48 mg/kg-day for reduced motor activity in females. |
| Oral-chronic | 3 (NOEL) | Dog diet Kidney and spleen histopathology | Busey, 1968 | Disagree. Recommend rat dietary study by Kaplan (1981) for histopathological changes in bone marrow, adrenal medulla, and adrenal cortex with POD between 1.03 and 1.79 mg/kg-day. |
| Dermal-all durations | 90 (NOEL) | Rabbit dermal No ChE inhibition or clinical signs at highest dose tested | Finlay, 1997 | Agree with study, but disagree with POD and effect. Recommend brain ChE inhibition (statistically significant) with $BMDL_{10}$ of 15.8 mg/kg-day.<br><br>Also recommend duration extrapolation factor from subchronic to chronic exposure. |
| Inhalation-acute | 0.16 ($BMDL_{10}$) | Rat inhalation Brain ChE inhibition | Weinberg, 2014 | Agree. |
| Inhalation-subchronic | 9 (NOEL) | Use oral subchronic POD | Mikles, 1998a | Disagree. Recommend using acute inhalation POD and duration extrapolation factor for acute to subchronic, and acute to chronic. |
| Inhalation-chronic | 3 (NOEL) | Use oral chronic POD | Busey, 1968 | |

## 2. Carcinogenicity Weight of Evidence

- OEHHA concurs with DPR's conclusion that methomyl has genotoxic potential, and that oncogenicity was not observed in chronic studies conducted in the dog, rat, and mouse (Busey, 1968; Kaplan, 1981; Serota, 1981; Hazleton Laboratories, 1968).

## 3. Uncertainty Factors and Sensitive Population (Table 2)

- OEHHA agrees with the use of interspecies extrapolation uncertainty factors (UFs) of 1 for acute oral exposure because the POD was based on a human study, and 10 for the other exposure routes and durations, as these PODs were based on studies in non-primate laboratory animals.

- DPR applied a UF of 10 for intraspecies extrapolation. OEHHA recommends that DPR's default pharmacokinetic UF of √10 be increased to 10 for sensitive populations. The total intraspecies UF would be 30.

- DPR has applied an additional child-protective factor of 4 to acute exposures among infants <1 year old and children 1 to 12 years of age to account for the increased sensitivity of the young to methomyl-induced brain ChE inhibition. The total UFs for the sensitive population are 40 for acute oral exposure and 400 for all other exposure scenarios. OEHHA recommends that DPR increase this additional child-protective UF based in part on OEHHA's analysis of the comparative sensitivity of the young to methomyl-induced brain ChE inhibition, which revealed a 7-fold difference in sensitivity. OEHHA suggests that this factor of 7 be increased to 10 to address the residual concerns regarding developmental neurotoxicity, as such a study has not been conducted. In addition, this UF would account for potential non-ChE mechanisms of developmental neurotoxicity. The total UF would be 300 where the POD is from a human study and 3000 where it is from a laboratory animal study.

**Table 2.** OEHHA-Recommended and DPR's uncertainty factors.

| | Interspecies UF | | Intraspecies UF | | Additional UF for sensitive subpopulations | | Total UF Adult-only/Sensitive* | |
|---|---|---|---|---|---|---|---|---|
| Exposure | OEHHA | DPR | OEHHA | DPR | OEHHA | DPR | OEHHA | DPR |
| Acute oral | 1 | 1 | 30 | 10 | 10 | 4 | 30/300 | 10/40 |
| All others | 10 | 10 | 30 | 10 | 10 | 4 | 300/3000 | 100/400 |

* Two UFs are presented, one for the general adult population and the other for children and women of child-bearing age as sensitive subpopulations. For example, for acute oral exposure, OEHHA recommends a total UF of 30/300: 30 is for the adult (non-pregnant) population and 300 is for children and women of child-bearing age as sensitive subpopulations.

### 4. Aggregate Exposure

- OEHHA agrees with DPR's concern about acute aggregate exposure but disagrees that such an assessment cannot be performed. There are sufficient data to derive additional PODs, if needed, based on the same endpoint such as ChE inhibition for acute aggregate exposure. OEHHA recommends such an assessment be conducted.

## B. Worker and Bystander Exposure Assessment

### 1. Occupational Handler Exposure Scenarios

- OEHHA agrees that exposure estimates based on Pesticide Handlers Exposure Database (PHED)-based surrogate data for occupational handlers are reasonable. However, OEHHA is concerned with the continued reliance on PHED. This database is no longer available or supported by the US Environmental Protection Agency (US EPA) and has known limitations.

- OEHHA recommends that DPR consider supplementing PHED data with data from additional sources, such as the Agricultural Handlers Exposure Task Force database, whenever possible.

### 2. Occupational Post-Application Exposure Scenarios

- OEHHA is concerned that the combined surrogate chemical- and surrogate activity-based methods used to estimate turf installer exposure may be based on studies which may not be representative of turf installation and may also result in an estimate with a higher degree of uncertainty relative to more traditional approaches (i.e., the Transferable Turf Residue [TTR] approach and the Transfer Coefficient [TC] approach). In addition, the draft EAD should acknowledge that it is based on a single study of a different chemical that, according to US EPA (2011), "may not be representative of other chemicals or activities which result in exposure."

- OEHHA recommends that an adjustment factor be included in the inhalation exposure estimates to account for the approximate 280-fold difference in vapor pressures between oxadiazon (which was used as a surrogate for methomyl) and methomyl. Also, DPR should provide justification for the choice of activity level and corresponding ventilation rate for the turf installer inhalation exposure scenario.

### 3. Worker Bystander Exposure Scenario

- OEHHA recommends that DPR reconsider the choice of activity durations and ventilation rates used in calculating the worker bystander exposure estimates. OEHHA is concerned that the worker bystander exposure assessment may underestimate exposure because activity levels and durations used in this

analysis are derived from a survey of the general population and may be lower than those of agricultural workers.

- In addition, DPR should consider using more recent exposure factor metrics in line with current US EPA recommendations.

**4. Residential Bystander Exposure Scenario**

- OEHHA concurs with DPR's general approach for estimating inhalation exposure to residential bystanders.

**5. Residential Post-Application Exposure Scenarios**

- OEHHA recommends that the exposure assessment section of the draft EAD provide additional discussion of the rationale for not assessing a child-specific residential turf exposure scenario.

- OEHHA is concerned that potential methomyl exposure via the "take home" dust scenario is not discussed in the draft EAD, and recommends that a quantitative evaluation of this scenario be included in the draft EAD.

**6. Non-Occupational Post-Application Exposure Scenarios**

- "U-Pick" Harvester - OEHHA is concerned about potential underestimation of the exposure for adult "U-Pick" sweet corn harvesters as the transfer coefficient (TC) for this setting does not differ from the Personal Protective Equipment (PPE)-corrected TC for professional harvesters. Additional justification for this assumption should be provided.

- Surface Water Swimmer - OEHHA is concerned about lack of sufficient justification for exclusion of the swimmer exposure scenario. OEHHA's analysis of surface water data suggests that the highest statewide concentrations of methomyl have been detected most often in high-use areas (e.g., Monterey County). The analysis of swimmer exposure should be based on this data. OEHHA recommends that DPR discuss the applicability of the exposure scenarios that were cited to justify exclusion of the swimmer scenario from further consideration, and include a quantitative screening level evaluation for this scenario in the draft EAD.

## C. Dietary Exposure Assessment

- OEHHA agrees in general with the approaches used to estimate the acute and chronic dietary exposures based on anticipated residues, and used for the tolerance assessment. For some input parameters, OEHHA recommends that, whenever possible, DPR use California-specific Pesticide Data Program (PDP)

residue data for foods, DPR's well-water monitoring program drinking water concentrations, and California-specific percent crop treated (PCT) values.

- The exposure analysis should be updated to include estimates for pregnant and lactating women, and should use the most current version of exposure calculation software (Dietary Exposure Evaluation Model-Food Commodity Intake Database (DEEM/FCID).

- OEHHA further recommends an explanation as to how the exposure percentiles were chosen, and which would be most appropriate to determine risk for dietary exposure only and aggregate exposures.

# II. RESPONSES TO CHARGE QUESTIONS

DPR asked OEHHA to address specific scientific assumptions, findings, and conclusions in our peer review of the draft RCD and EAD. The responses provided in this section are purposely brief with more in-depth discussion of these responses and OEHHA's other comments in Section III, Detailed Comments.

## A. Hazard Identification and Risk Characterization

***Question 1:*** *"For the acute oral endpoint, HHAB adopted the $LED_{10}$ of 0.03 mg/kg developed by US EPA's Center for Computational Toxicology (McFarlane et al., 1998; Setzer, 2006). This was based on dose-dependent inhibition of RBC ChE in human males at 0.1, 0.2 and 0.3 mg/kg."*

**Response:** OEHHA agrees with the use of the $BMDL_{10}$ developed by US EPA for assessing acute oral exposure. Note that both OEHHA and US EPA, and other DPR RCDs, use the term $BMDL_{10}$ instead of the term $LED_{10}$. For ease of reference for this peer review, OEHHA uses the same term ($LED_{10}$) as it appears in the draft RCD. OEHHA agrees that inhibition of RBC ChE is an appropriate surrogate, particularly in humans, for inhibition of brain ChE.

***Question 2:*** *"The acute inhalation critical $LEC_{10}$ was 3.92 mg/$m^3$, from which an internal dose of 0.16 mg/kg was calculated using the default rat breathing rate. This determination was based on brain cholinesterase inhibition observed at 1 hour of exposure time in phase III of an inhalation toxicity study by Weinberg (2014)."*

**Response:** OEHHA agrees with the use of the $LEC_{10}$ and calculated internal dose for assessing acute inhalation exposure. The use of brain ChE inhibition at 1 hour is supported by steady-state inhibition levels observed between hours 1 and 6 of the 6 hour exposure duration in phase II of Weinberg (2014).

***Question 3:*** *"The critical subchronic oral NOEL of 9 mg/kg/day (150 ppm in the diet) was based on reduced body weight and food consumption, tremors during the first four*

*weeks and beyond, FOB signs and brain ChE inhibition at the LOEL dose of 94.9 mg/kg/day (1500 ppm) in the 91-day rat dietary toxicity study of Mikles (1998)."*

**Response:** As described in Section I, Summary of Review, OEHHA agrees with the use of the Mikles (1998a) subchronic neurotoxicity study to assess subchronic oral exposure but believes that the critical subchronic NOEL is 1.48 mg/kg-day (20 ppm) for reduced motor activity.

***Question 4:*** *"The critical chronic oral NOEL of 3 mg/kg/day was established in the 2-year dog dietary toxicity study of Busey (1968). This was estimated from a dietary NOEL concentration of 100 ppm based on pigmentation irregularity and swelling of kidney proximal tubule cells, and pigmentation and extramedullary hematopoiesis in the spleen at the LOEL dose of 400 ppm (11 - 14 mg/kg/day)."*

**Response:** As described in Section I, Summary of Review, OEHHA disagrees with the use of the 2-year chronic dietary study in the dog (Busey, 1968) for assessing chronic oral exposure.

***Question 5:*** *"The critical acute, subchronic and chronic dermal NOEL was 90 mg/kg/day, established in the 21-day rabbit repeat-dose dermal toxicity study of Finlay (1997)."*

**Response:** As described in Section I, Summary of Review, OEHHA agrees with the use of the Finlay (1997) study for assessing acute, subchronic, and chronic dermal exposure but disagrees with the selected POD and also suggests that a factor for duration extrapolation be considered for chronic exposures.

***Question 6:*** *"There was no evidence for developmental toxicity in the rat or rabbit developmental toxicity studies reviewed for this document (rat: Rogers and Culick, 1978; rabbit: Feussner, 1983)."*

**Response:** OEHHA agrees that there was no clear evidence for developmental toxicity in the rat or rabbit developmental toxicity studies reviewed for this document (rat: Rogers and Culick, 1978; rabbit: Feussner, 1983). However, the results of these studies are difficult to interpret due to great variability in responses among the offspring. OEHHA further agrees with DPR that there is residual concern regarding developmental neurotoxicity based on evidence thereof associated with other cholinesterase-inhibiting pesticides and the lack of a developmental neurotoxicity study for methomyl.

## B. Worker and Bystander Exposure Assessment

***Question 1:*** "*In the absence of chemical-specific human dermal absorption data and acceptable animal studies for methomyl, DPR policy is to use a default value of 50% (Donahue, 1996), and this value was utilized for calculations of dermal exposures in the Exposure Assessment Document (EAD). This brings uncertainty to the dermal exposures..."*

**Response:** OEHHA agrees that a default dermal absorption rate of 50% is likely adequately health protective for pesticides that are chemically similar to those analyzed in the cited documents.

***Question 2:*** "*As no inhalation absorption data were available for methomyl, the EAD utilized the DPR default value of 100% to calculate absorbed doses by the inhalation route (Frank, 2008).*"

**Response:** OEHHA agrees with the use of the default inhalation absorption rate of 100% for assessing methomyl exposure.

***Question 3:*** "*All handler scenarios assumed methomyl use of 12 months per year. This was based on the year-round use of methomyl on lettuce (lettuce receives about 27% of the total amount of methomyl used in California) and the hypothesis that pesticide handlers can move from one field/county to another throughout the state to follow job assignments*."

**Response:** OEHHA agrees with the assumption that pesticide handlers and lettuce harvesters move throughout the state during the year, and that a 12-month per year exposure duration for all handler scenarios is reasonable.

***Question 4:*** *Reentry exposure to treated turf.*
*"When chemical-specific data for reentry worker exposure to treated crops is lacking, it is a standard practice in exposure assessment to use DFR coupled with appropriate transfer coefficients. However, there are limited data supporting a consistent relationship between turf transferable residues (TTR) and exposure (discussed in Beauvais, 2011, http://www.cdpr.ca.gov/docs/whs/memo/hsm11005.pdf). For this reason, the Human Health Assessment Branch recommends using surrogate studies to assess human exposure to treated turf when possible. In the present draft EAD, we used one such turf exposure study as a surrogate for occupational transplanting of sod. The Jazzercise® routine was used to represent the worker reentry scenario of professional landscapers installing sod."*

**Response:** As described in Section 1, Summary of Review, OEHHA is concerned that the Jazzercise-based approach used to estimate turf installer exposure may not be sufficiently representative of this activity and resulting exposure estimates may have greater uncertainty as they rely on both surrogate chemical and surrogate activity assumptions. OEHHA recommends that DPR compare the approach with a US EPA-recommended approach which applies an empirically derived transfer coefficient for this specific turf installer scenario (US EPA, 2013a).

***Question 5:*** *Bystander inhalation exposure.*
*"One occupational bystander scenario in this EAD involves workers performing agricultural or non-agricultural activities in close proximity to an application field. For this scenario, a computational approach is needed for determining the 8-hour inhalation rate for occupational bystanders. This algorithm uses a daily inhalation rate that factors in*

*proportions of the day engaged in light, moderate, and heavy activity levels (excluding sleep), according to an average daily activity pattern from surveys conducted by California Air Resources Board and referenced in Andrews and Patterson (2000). (http://www.cdpr.ca.gov/docs/whs/memo/hsm00010.pdf)."*

**Response:** As described in Section 1, Summary of Review, OEHHA disagrees with the choice of activity levels, activity durations and ventilation rates. These data, which originate in part from a survey of the general population, may not be appropriate for physically active agricultural workers. OEHHA recommends that DPR use more appropriate modeling parameters in estimating occupational bystander inhalation exposure.

***Question 6:*** *Bystander inhalation exposure.*
*"Another assumption made when calculating bystander exposures was, that the measured outdoor methomyl air concentration was equal to the indoor air concentration."*

**Response:** OEHHA agrees that the assumption that the outdoor air concentration is equal to the indoor air concentration is reasonable.

## C. Dietary Exposure Assessment

***Question 1:*** "*The Risk Assessment Section (RAS) estimated acute dietary exposure to methomyl by performing a probabilistic analysis with DEEM-FCID v. 3.18 using residue data primarily from USDA's Pesticide Data Program (PDP) for 2000 through 2011, including analysis of drinking water from municipal water treatment plants."*

**Response:** For acute exposures, OEHHA agrees with some of the input parameters and approaches in conducting probabilistic analyses. However, OEHHA recommends that DPR provide explanations for the exposure percentile selected and the use of average detection limits for drinking water. We also recommend that DPR select California-specific data, whenever possible, include exposures to pregnant and lactating women, and update the analysis using the most current version of DEEM-FCID.

***Question 2:*** "*RAS estimated chronic dietary exposure to methomyl by performing a deterministic analysis with DEEM-FCID, v. 3.18, using the same sources of residue data that were used in the acute assessment. The concentration of methomyl in drinking water was estimated in the same way as for the acute analysis, using the average LOD of PDP samples collected during the most recent three years."*

**Response:** OEHHA agrees with the deterministic analyses using average residue values. The OEHHA recommendations about California-specific data, pregnant women, and DEEM version noted in the response for Question 1 above, also apply for chronic exposure.

***Question 3:*** "*RAS evaluated whether current tolerances for methomyl are health protective by calculating the MOE of tolerance-level residues for 15 highly consumed foods at the 95th percentile of exposure for the U.S. population and eight subpopulations."*

> **Response:** OEHHA agrees with the methodology used to conduct the acute tolerance assessment.

***Question 4:*** "*When evaluating exposure to methomyl in food, RAS did not include illegal residues in the analysis. Illegal residues are residues that either exceeded the legal tolerance or residues detected on commodities for which there was no legal tolerance."*

> **Response:** OEHHA agrees with the exclusion of illegal residues from the analysis.

# III. DETAILED COMMENTS

## A. Introduction

Methomyl (methyl (1E)-N-(methylcarbamoyloxy)ethanimidothioate, CAS 16752-77-5) is a broad-spectrum N-methyl carbamate insecticide which was first registered in the US in 1968. It acts via carbamylation of a serine residue within the acetylcholinesterase active site, thereby inhibiting the enzyme and inducing characteristic signs of cholinergic hyperactivity. It is the primary metabolite of another carbamate, thiodicarb, which is no longer registered in California (DPR, 2015c). Methomyl is used to control pests in field, fruit and vegetable crops, turf, livestock quarters, commercial premises, and refuse containers (DPR, 2015a). It is also used as a molluscicide and acaricide. There are no residential uses. Commonly-used methomyl formulations are currently registered under the trade names Lannate®, Nudrin™, Corrida™, Annihilate™, and M1™. All but the fly bait products are restricted use per both California and Federal regulations (DPR, 2015d, e). Formulations are sold as water-soluble powders, liquid concentrates, or in granular form. In 1998, US EPA published the Registration Eligibility Document for methomyl (US EPA, 1998). A dietary assessment for methomyl was completed as part of US EPA's 2007 *Revised N-Methyl Carbamate Cumulative Risk Assessment* (US EPA, 2007a). Methomyl is currently under registration review, and US EPA anticipates releasing its draft risk assessment in 2016 (US EPA, 2015a).

The following sections present detailed discussion of OEHHA's principal comments and answers to the charge questions (Sections I and II, respectively), as well as additional comments regarding the draft RCD and EAD.

### 1. Physical and Chemical Properties and Environmental Fate

Methomyl is substantially more water-soluble (58 g/L) compared to other N-methyl carbamate pesticides and has a correspondingly low octanol-water partition coefficient ($K_{ow}$ = 1.239). In contrast, carbaryl (0.104 g/L) is more than 500 times less water soluble. Methomyl is classified as semi-volatile ($5.6x10^{-6}$ mm Hg at 25ºC).

OEHHA recommends that the relatively high water solubility and low lipophilicity of methomyl be discussed in greater detail. These chemical properties greatly influence key physical processes such as environmental fate and transport, relevant exposure pathways, as well as absorption, distribution, metabolism and elimination.

### 2. Pesticide Use and Sales

The crops with the highest application amounts of methomyl are lettuce, onions, alfalfa, and corn for human consumption (DPR 2015f). The application is strictly limited to mechanical ground, aerial applications, or chemigation with no hand-held application. Ornamental, greenhouse, or residential use is not permitted. Most methomyl is applied between March and October.

Restrictions on use and substitution of less-toxic alternatives have reduced methomyl use over the past 20 years. Table 3 in the draft EAD shows annual methomyl usage between 2006 and 2010. OEHHA recommends that the table be updated to include the years 2011-2013.

### 3. Reported Illness

In 1998-2005, methomyl was the 10th-most common active ingredient involved in acute pesticide-related illness in the U.S. (Calvert et al., 2008). There seems to be an overall decline of the number of cases from 1993 to 2012. However, in 2002, there was a single incident involving 36 related cases of possible methomyl poisoning in grape harvesters in Kern County. It was not mentioned in the draft EAD. OEHHA recommends that this incident be added to the draft EAD.

## B. Pharmacokinetics

Information on the pharmacokinetics of methomyl was presented in both the draft RCD and EAD, and the contents differ in terms of both the studies presented and how they are presented. Since the two documents contribute toward the risk characterization analysis, OEHHA recommends consistency in the presentation.

### 1. Oral Absorption

The draft RCD describes the pharmacokinetics of methomyl in the rat and monkey by the oral route. In the rat, oral absorption was 100%, with urine (53%) and exhaled air as carbon dioxide (34-36%) as the major routes of excretion. Recovery was more limited n the male cynomolgus monkey (79% of the orally administered methomyl was recovered,

mostly in the exhaled air and urine). Based on this information, an oral absorption factor of 100% was used in the assessment and OEHHA agrees with this determination.

### 2. Dermal Absorption

No human studies were available for the direct estimation of methomyl dermal absorption. Although one study in female mice estimated 70% dermal absorption (Shah et al., 1981), the study did not meet 1998 US EPA requirements for acceptability in several areas and was not used in this assessment. Two additional *in vivo* and *in vitro* dermal absorption studies (Fasano, 2001a and 2001b) were delivered to DPR by the registrant after this draft EAD was completed. They were not discussed in this assessment and were not reviewed by OEHHA. OEHHA recommends that the revised EAD incorporate a critical assessment of these two studies and determine whether the data support or refute the default 50% dermal absorption value.

Due to the lack of both human and acceptable animal data, a default value of 50%, based on a review of 40 active ingredients, was used in the draft EAD, per standard DPR policy (DPR, 1996). Of the 40 compounds reviewed in the policy memorandum, dermal absorption data was only provided for 26 compounds. The remaining 14 pesticides could not be identified because the content of a key personal communication was not available. OEHHA recommends that the 14 pesticides mentioned in the dermal absorption policy memorandum be identified and their dermal absorption data be made public.

OEHHA agrees that a default dermal penetration rate of 50% for methomyl is likely to be health protective. However, OEHHA wants to caution that dermal absorption rate estimates derived under laboratory conditions may not always accurately capture what could happen in the field. For example, dermal absorption generally increases with ambient temperature, and methomyl use is highest during the hot summer months.

In addition, perspiration in a hot environment may elevate the total absorbed dose of water-soluble methomyl by: a) increasing the effective surface area available for transfer and absorbance; b) enhancing chemical movement through outer clothing to the skin surface and to adjacent areas (groin, armpits) with higher absorption rates; c) increased absorption due to enhanced peripheral circulation or transdermal movement via hair follicles or sweat glands; and d) allowing the clothing to act as a “reservoir” (WHO, 2006; EFSA, 2011; Williams et al., 2004; Morrison et al., 2015). In a registrant non-GLP “sweating” study in monkeys, dermal exposure to methomyl under extreme temperature conditions greatly exacerbated the acute toxicity of methomyl (DuPont, 1970).

OEHHA recommends that the draft EAD discuss that dermal absorption is a multi-step process that is influenced by the chemical properties of individual pesticides as well as physiological factors and external environment.

### 3. Inhalation Absorption

No inhalation absorption studies, either human or animal, were available and a default absorption value of 100% was applied to the inhalation exposure calculations. OEHHA agrees that this default assumption is reasonable and health-protective.

## C. Non-Cancer Toxicity Endpoint and Dose-Response Analysis

DPR determined PODs for oral, dermal, and inhalation exposures of acute, subchronic, and chronic duration, for a total of nine route-duration combinations. Each combination is discussed below.

### 1. General Comments

A benchmark response (BMR) of 10% was used for ChE inhibition in the draft RCD. OEHHA agrees with this approach because this approximates both normal ChE variation and the level of inhibition that can be detected with sufficient power. And for brain ChE, a BMR of 10% has been shown to be protective of clinical signs and behavioral effects (US EPA, 2007a; US EPA, 2015b).

### 2. Oral Exposure

#### a. Acute Oral Toxicity

In evaluating acute oral exposure, DPR considered several acute oral gavage studies: (i) a human study which employed capsules containing Lannate SP (89% methomyl) (McFarlane et al., 1998); (ii) five rat lethal dose $(LD)_{50}$ studies of methomyl technical (98% methomyl) (Sarver, 1991) or formulations (1-92% methomyl) (Kuhn, 1996; Durando, 2007; Sarver, 1996; Robbins, 1987), and three rat studies of technical methomyl; (iii) a time course study employing a single dose (Malley, 1997); (iv) the guideline neurotoxicity study (Mikles, 1998b); and (v) a comparative cholinesterase study in PND11 pups and adult rats (Malley, 2005). The $LD_{50}$s were 34/30 mg/kg (male/female) for methomyl technical and varied considerably for the formulations.

OEHHA supports DPR's decision to use an $LED_{10}$ ($BMDL_{10}$) of 0.03 mg/kg for inhibition of RBC in humans as the POD. This value was derived by US EPA using a dose-time response model (US EPA, 2007a) of the McFarlane et al. (1998) data. The McFarlane et al. (1998) data are amenable to BMD modeling and time is an important component in the consideration of methomyl toxicity due to the rapid reactivation of methomyl-inhibited ChE. The study also has many strengths, including that it was controlled, conducted in humans, employed low doses of a formulation (thereby making it more relevant to environmental exposures), included internal controls (plasma and RBC ChE activities were measured in the study subjects both pre- and post-exposure), and there were dose-response relationships in the data at many time points post-exposure. On the other hand, there were only four or five subjects per dose group, they were all male, and brain ChE was not measured. However, RBC ChE is an appropriate and widely-

accepted surrogate for brain ChE, particularly in humans where brain ChE activity cannot be measured due to ethical reasons (US EPA, 2000).

### b. Subchronic Oral Toxicity

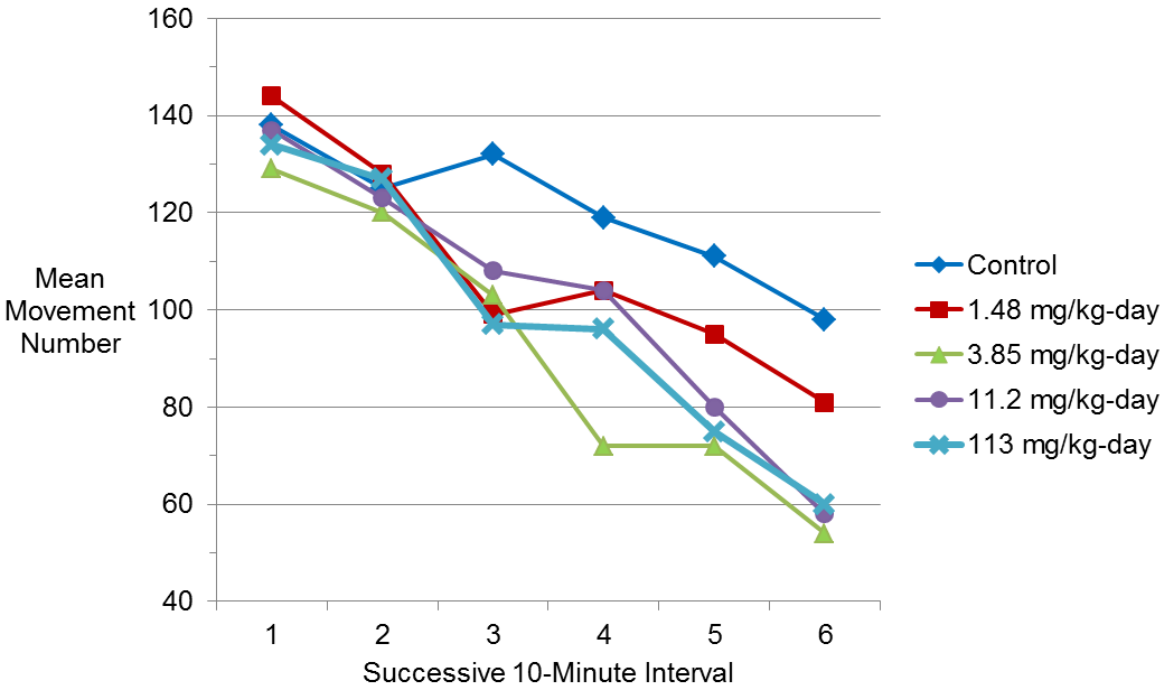
Three dietary studies, each approximately three months in duration, were considered by DPR in development of a POD for subchronic oral exposure. These included the guideline subchronic neurotoxicity study in the rat (Mikles, 1998a) and studies in the rat (Kundzin and Paynter, 1966) and dog (Sherman, 1967). According to DPR, the latter two studies did not demonstrate any toxic effects.

DPR derived a POD of 9 mg/kg-day (NOEL=150 ppm) from the Mikles (1998a) subchronic neurotoxicity study. This NOEL was based upon reduced body weight and food consumption, tremors, Functional Observational Battery (FOB) signs, and brain ChE inhibition in males at the corresponding Lowest-Observed-Effect Level (LOEL) of 1500 ppm (highest dose tested: 94.9 and 113 mg/kg-day for males and females, respectively).

OEHHA agrees with the use of the Mikles (1998a) study, as it has the lowest LOEL of the studies of sufficient duration and quality and is a comprehensive assessment of neurotoxicity by a relevant route. However, OEHHA suggests consideration of a lower POD - possibly a NOEL of 20 ppm (1.48 mg/kg-day) - for a statistically significant neurobehavioral effect at study termination at week 13. After 13 weeks of exposure, there was a statistically significant reduction in mean total movement number (mean of the sum of movement numbers from six successive 10-minute intervals) and some of the individual interval movement numbers in female rats at 50 ppm (3.85 mg/kg-day) and higher doses, when compared to control. However, this reduction did not demonstrate a dose-response relationship after 4 weeks and was not statistically significant after 8 weeks of exposure for the female rats. For the males, at week 13, the total movement numbers were increased at the two high doses, but were not statistically significant from the controls.

Although there was no dose-response relationship in the mean total movement number - the values were 90%, 76%, 84%, and 82% of control for 20 ppm, 50 ppm, 150 ppm, and 1500 ppm, respectively – a graphical representation of the data is telling because it shows the treatment effects on habituation over successive trials and time. As shown in Figure 1, all of the dosed groups habituated (demonstrated decreased activity over time) to a greater extent than the control, possibly indicative of decreased interest in their environment. The means for the dosed groups cluster with the control mean for intervals 1 and 2, separate from the control mean at interval 3, and separate from each other from interval 4 onward. Note that during intervals 5 and 6, the lowest dose group lies between the control and the higher dose groups, indicative of a dose-response relationship that plateaus at the higher doses. As the summary data were not amenable to modeling, the NOEL of 1.48 mg/kg-day may be an appropriate POD for this effect, which is consistent with the neurotoxic potential of methomyl.

**Figure 1**. Mean number of movements in successive 10-minute intervals among female rats exposed to methomyl via the diet for 13 weeks (Mikles, 1998a).




### c. Chronic Oral Toxicity

Three two-year dietary studies were considered by DPR for derivation of a POD for chronic oral exposure, one each in the rat (Kaplan, 1981), mouse (Serota, 1981), and dog (Busey, 1968). An additional 22-month dietary study in the rat (Hazleton Laboratories, 1968) was described by DPR in the 2012 (DPR, 2012a) and 2014 versions of the *Summary of Toxicology Data* for methomyl but was not mentioned in the text of the draft RCD. The chronic studies revealed that methomyl induces anemia and compensatory hematopoiesis, including bone marrow hyperplasia. The draft RCD states that RBC ChE may have roles in membrane permeability and hematopoiesis (p. 76), and thus it is possible that the anemia is related to RBC ChE inhibition. DPR selected a critical NOEL of 3 mg/kg-day (100 ppm) from the dog study (Busey, 1968) as the POD. This was based upon pigmentation irregularity and swelling of kidney proximal tubule cells, pigmentation and extramedullary hematopoiesis in the spleen, and bile duct hyperplasia observed at the LOEL of 400 ppm (11 - 14 mg/kg/day).

OEHHA questions the use of the dog study (Busey, 1968), as the Kaplan (1981) rat study is of much higher quality and statistical power. It is unclear why DPR chose Busey (1968) over Kaplan (1981), as no rationale for study selection was provided. The dog study had a small *N* of three animals/sex/dose with an additional animal/sex/dose as a one year interim sacrifice group for histopathology, as well as other deficiencies, including infrequent measurement of plasma and RBC ChE and measurement only in

control and high dose groups, lack of brain ChE determination, and changes in the purity and physical characteristics of the methomyl used over the duration of the study.

In contrast, the Kaplan (1981) rat study was well designed, implemented, and reported. It had four dose groups: 0, 50, 100, and 400 ppm with 70 animals/sex/dose, and additional groups for a one-year interim sacrifice for gross pathology and histopathology, and specifically for measurement of RBC and brain ChE activities. RBC ChE activity was measured at multiple time points throughout the study, and half of the ChE group (10 animals/sex/dose) was sacrificed at one year for determination of brain ChE and the remainder (10 animals/sex/dose) towards the end of the study. The NOEL for brain and RBC ChE inhibition is 400 ppm (highest dose tested; 16.99 and 22.71 mg/kg-day for males and females, respectively). The critical chronic endpoints in the rat study are dose-dependent increases in the incidences of bone marrow hyperplasia, focal hyperplasia in the adrenal medulla, and focal degeneration/angiectasis in the adrenal cortex of males (significant only at the high dose of 400 ppm [16.99 mg/kg-day] for all three endpoints), which give $BMDL_{05}$ values between 1.03 and 1.79 mg/kg-day, lower than the selected NOEL of 3 mg/kg-day.

## 3. Dermal Exposure

### a. Acute Dermal Toxicity

Several acute dermal $LD_{50}$ studies are described in the draft RCD (DPR, 2015a; p. 18). These show the $LD_{50}$ to be greater than the highest doses tested of 2000-5000 mg/kg.

DPR chose a NOEL of 90 mg/kg-day from a 21-day repeat dose dermal toxicity study in the rabbit (Finlay, 1997) as the POD. OEHHA agrees with the selection of the study, but not the POD, as explained below. OEHHA believes the acute POD should be 15.8 mg/kg-day, the $BMDL_{10}$ for brain ChE inhibition. While this POD was from a 21-day study, the value seems appropriate when compared to studies discussed in the draft RCD. There are two short-term studies, the Henry (1981) acute rat dermal cholinesterase study and the McAlack (1973) subacute 10-day rabbit dermal study, neither of which are discussed in the draft RCD. These studies showed NOELs of 357 mg/kg and 100 mg/kg-day, respectively. DPR may want to consider discussing these studies.

### b. Subchronic Dermal Toxicity

DPR evaluated two 21-day repeat-dose dermal toxicity studies in the rabbit (Brock, 1989; Finlay, 1997), and chose as the POD a NOEL of 90 mg/kg-day (highest dose tested) from Finlay (1997). While the two studies were conducted in a similar fashion, Finlay (1997) had more doses in the low dose range (0, 15, 30, 45, 90 mg/kg-day) compared to the wide dose range of 5, 50, and 500 mg/kg in Brock (1989).

OEHHA agrees with the use of Finlay (1997) as the critical study, but disagrees with DPR's assessment that brain ChE inhibition was not statistically significant even at the highest dose tested.

For the female data, brain ChE (94% of control) was significantly inhibited at the highest dose tested, 90 mg/kg-day.

OEHHA's pair-wise statistical analyses using both SAS® software (version 9.4, SAS Institute, Cary, NC) and Microsoft Excel® 2010 demonstrate statistically significant inhibition of brain ChE in males at 30 mg/kg-day and above (see Table 3 below), making the NOEL 15 mg/kg-day. The male brain ChE data also demonstrated a significant dose-dependent trend ($p = 0.0029$ by the ANOVA test in Excel® and $p = 0.0004$ by the Jonckheere-Terpstra Test in SAS). The $BMDL_{10}$ is 15.8 mg/kg-day, essentially identical to the NOEL. The absence of effects at the lower doses in the female rabbit may be influenced by the doses tested.

Brain ChE inhibition was observed in both male and female rabbits at 500 mg/kg in the study by Brock (1989). The brain ChE was reduced to 48% and 68% of controls in the male rabbit and female rabbits, respectively. The $BMDL_{10}$ for brain ChE in females was 14.9 mg/kg-day, with a higher value for the males. This $BMDL_{10}$ supports using the $BMDL_{10}$ as the POD from the data in Finlay (1997).

**Table 3.** Pair-wise statistical analyses of Finlay (1997) brain ChE data from male rabbits.*

| Dose (mg/kg-day) | Brain ChE (mean ± SD; U/g) (% control) | p-value from t-test† |
|---|---|---|
| 0 | 14.33 ±0.98 | - |
| 15 | 14.16 ± 0.93 (99%) | 0.76 |
| 30 | 12.91 ±0.53 (90%) | 0.0112 |
| 45 | 12.65 ± 0.71 (88%) | 0.0071 |
| 90 | 12.84 ±0.80 (90%) | 0.0167 |

* Each group had 6 rabbits.
In Excel®, two-sample t-tests assuming equal variances were performed. In SAS®, data of all groups were normally distributed by the Shapiro-Wilk, Kolmogorov-Smirnov, Cramer-von Mises, and Anderson-Darling tests, and the variance of each dose group was found to be statistically equal to the variance of the control group. Results of t-tests in SAS® and Excel® were confirmed by hand using Dunnett's test:

$$(\text{Dunnetts-t}) * s * \sqrt{(2/N)},$$

where s = pooled SD and Dunnetts-t is from one-sided using number of groups = 4 and df=25.
† Pooled p-values from SAS® and two-tailed p-values from Excel® are presented and were identical.

### c. Chronic Dermal Toxicity

In the absence of a chronic dermal toxicity study, DPR applied the subchronic dermal POD for chronic exposures (see Subchronic Dermal Toxicity section above). However, as explained above, OEHHA suggests that the POD should be 15.8 mg/kg-day, the $BMDL_{10}$ for inhibition of brain ChE in male rabbits (Finlay, 1997). It is important to note that neither of the available subchronic dermal studies evaluated neurobehavioral

endpoints or histopathology, the latter of which formed the basis of what OEHHA suggested as the critical PODs for subchronic and chronic oral exposures, respectively. Thus, an uncertainty factor to account for the possibility that brain ChE inhibition is not the most sensitive endpoint may be warranted in extrapolating from subchronic to chronic dermal exposures.

## 4. Inhalation Exposure

### a. Acute Inhalation Toxicity

In its assessment of acute inhalation exposure, DPR summarized five rat lethal concentration (LC50) studies as well as an acute inhalation cholinesterase study (Weinberg, 2014). The LC50s were 0.273/0.243 mg/L (273/243 mg/m$^3$; Male/Female) for methomyl technical and in the range of >0.053 to >1.75 mg/L (>53 to > 1750 mg/m$^3$) for the formulations.

DPR chose the results of Weinberg (2014) to (1) determine the acute inhalation POD and (2) form the basis for application of the POD to 1-, 8-, and 24-hour human exposure durations. In this study, rats were exposed nose-only to a liquid droplet aerosol atmosphere of an aqueous dilution of methomyl technical (99.4%). The study was comprised of three phases: phase I was a range-finding/maximum tolerable concentration study; phase II was a time to peak ChE (RBC and brain) inhibition study; and phase III was a dose-response study of RBC and brain ChE inhibition in which male rats were exposed for 3 hours to 36, 68, and 105 mg/m$^3$ (phase IIIA) or 0, 5.6, 14, 19, and 31 mg/m$^3$ (phase IIIB). Phase III employed only males because no appreciable difference between the sexes was observed in phases I and II.

In the draft RCD, the POD was the $LEC_{10}$ ($BMCL_{10}$) of 3.92 mg/m$^3$ for inhibition of brain ChE in male rats following a single 3-hour exposure in phase IIIB of the study. OEHHA agrees with the POD and that only the phase IIIB data should be used. The Weinberg (2014) study is of high quality, comprehensive, and is the only non-$LC_{50}$ acute inhalation toxicity study that employed more than one exposure concentration. There is no NOEL for the phase IIIB part of the study, as statistically significant inhibition of RBC (16%) and brain (13%) ChE was observed at the lowest concentration of 5.6 mg/m$^3$. Note that the study did not label the RBC value as statistically significant. This is because the author used an alpha value of 0.01. OEHHA conducted a two-sample t-test assuming unequal variances in Microsoft Excel® 2010 and both the one- and two-tailed *p* values were <0.05 (but >0.01). Apart from this value, all of the other exposure concentrations in phase IIIB were associated with statistically significant depression of RBC and brain ChE at the 0.01 level. Although salivation and lacrimation were observed at all exposure concentrations in phase IIIB, with zero incidence in controls, there was no dose-response in the salivation incidence and minimal increase in incidence for lacrimation (increasing dose: 0, 1, 2, 2, and 3 of 10 animals), despite significant RBC and brain ChE inhibition levels of 52 and 45%, respectively, at the highest dose. This suggests that at least in part, these effects were the result of port-of-entry rather than systemic effects.

DPR assumed the estimated internal dose of 0.16 mg/kg (and stable inhibition) to be applicable to 1- and 8-hour exposures, and in the absence of laboratory animal data of relevant duration, to 24-hour exposures. Phase II revealed that steady-state brain ChE inhibition levels had been achieved by hour 1 of the 6-hour exposure at 136 mg/m$^3$. DPR thus used an exposure time of one hour to estimate the effective internal dose from exposure at the $LEC_{10}$ of 3.92 mg/m$^3$. DPR also assumed 100% absorption and a default rat inhalation rate of 0.04 m$^3$/kg-hour:

$$3.92\ \frac{mg}{m^3} \times 0.04\ \frac{m^3}{kg-hour} \times 1\ hour = 0.16\ \frac{mg}{kg}$$

OEHHA agrees with DPR's analysis. In both the males and females of phase II, steady-state brain ChE inhibition levels were achieved by hour 1 of the 6-hour exposure period, with inhibition levels relative to concurrent controls of 65, 69, and 66% (males) and 65, 69, 68% (females) at 1, 3, and 6 hours of exposure, respectively. Thus, it is fair (and likely conservative) to assume that at the lower concentration of 3.92 mg/m$^3$, steady-state inhibition is achieved at 1 hour of exposure and thus the internal dose associated with 1 hour of exposure is the BMDL. If the exposure was extended to 8 or 24 hours, it is reasonable to assume that steady-state would also be achieved by hour 1 and thus the internal dose of 0.16 mg/kg would also be applicable to 8- and 24-hour exposures.

The default rat inhalation rate of 0.04 m$^3$/kg-hour is consistent with the minute volumes provided for the rat in US EPA's Physiologically-based Pharmacokinetic (PBPK) guidance document (2006: p. 3-9; 0.174 L/min for a 0.25 kg rat corresponds to 0.042 m$^3$/kg-hour) and OEHHA's *Technical Support Document for the Derivation of Noncancer Reference Exposure Levels* (2008, Appendix F: p. 2; minute volume of 0.180 L/min calculated for 0.25 kg rat using parameters provided corresponds to 0.043 m$^3$/kg-hour).

### b. Subchronic and Chronic Inhalation Toxicity

DPR stated that in the absence of a subchronic inhalation toxicity study, it would use the subchronic oral POD of 9 mg/kg-day from the subchronic dietary neurotoxicity study of Mikles (1998a) (see Subchronic Oral Toxicity section above). OEHHA's literature search located a subchronic inhalation toxicity study, but Lannate® dust was used and minimal effects were reported in males rats exposed to a single dose of 14.8 mg/m$^3$ for 3 months (Ta'Naka et al.,1987).

In the absence of a chronic inhalation toxicity study, DPR chose to use the chronic oral POD of 3 mg/kg-day from the two-year dog study (Busey, 1968; see Chronic Oral Toxicity section above) for evaluating chronic inhalation exposures.

As explained in the acute inhalation section, the Weinberg (2014) study demonstrated steady-state brain ChE inhibition levels by hour 1 of a 6-hour exposure at a high concentration (136 mg/m$^3$). Thus, it is reasonable to assume that lengthening the exposure period would not result in any further inhibition beyond steady-state. OEHHA understands that there are uncertainties associated with duration extrapolation but feels that they may not be greater than the uncertainties associated with route-to-route

extrapolation. For instance, the plasma concentration of methomyl associated with dietary exposure in the Mikles study (1998a) could be lower than that from the inhalation route (same exposure level in mg/kg-day) due to the first pass effect. The liver is the main site of metabolism for methomyl. Furthermore, the subchronic and chronic oral PODs proposed by DPR (9 and 3 mg/kg-day, respectively) are much higher than the acute inhalation POD (0.16 mg/kg-day).

OEHHA therefore suggests that DPR consider applying the acute inhalation POD of 0.16 mg/kg (derived from Weinberg, 2014) to subchronic and chronic inhalation exposures, giving both a POD of 0.16 mg/kg-day. In addition, inhalation exposure may mirror oral exposure, in that for subchronic and chronic durations, non-ChE endpoints (i.e., neurobehavioral changes and bone marrow hyperplasia) may occur at lower PODs. An uncertainty factor to account for the possibility that brain ChE inhibition is not the most sensitive endpoint may be warranted in extrapolating from acute to subchronic and chronic inhalation exposures. DPR should weigh the uncertainty associated with route-to-route extrapolation against that associated with duration extrapolation.

## D. Reproductive and Developmental Toxicity

OEHHA agrees with DPR's conclusion that the available reproductive and developmental toxicity studies do not support derivation of critical NOELs for either endpoint.

DPR evaluated the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)-compliant reproductive toxicity study, a two-generation rat study by Lu (1982), and concluded that the study did not reveal primary reproductive toxicity. OEHHA agrees with DPR's conclusion, as the pup effects (e.g., decreased mean live litter size and body weight) were observed in the presence of maternal toxicity characterized by decreased body weights and food consumption.

DPR also reviewed several subchronic oral gavage studies which investigated reproductive toxicity in male rats. OEHHA agrees with DPR's conclusion that the results of these studies are indicative of male reproductive toxicity at high doses.

DPR considered two developmental toxicity studies, one in the rat (Rogers and Culick, 1978) and the other in the rabbit (Feussner, 1983). OEHHA agrees that there was no clear evidence for developmental toxicity in these studies. However, the results are difficult to interpret due to great variability in responses among the offspring. Specifically, there was lack of a dose-response relationship for many affected offspring parameters in the rat study, and a high number of abnormalities in the control fetuses of the rabbit study.

There is a published, single-generation reproductive and developmental toxicity study in female rats which was not mentioned in the draft RCD (Mokhtar et al., 2013). The study employed oral gavage doses of a formulation at 0, 0.67, 1, and 2 mg/kg-day methomyl for 28 days, at which point exposure ceased and the females were mated. This study

demonstrated effects on both fertility and development. However, due to the rapid clearance of methomyl and reactivation of methomyl-inhibited ChE, the internal methomyl dose and ChE inhibition would have been minimal during gestation, thus undermining an association between methomyl exposure and the observed development impacts. The discrepancies between the results of this study and those described above may be related to components of the formulation (the others employed methomyl technical), or to overt toxicity resulting from the bolus dose. Also, errors within both the study text and tables call into question the quality of the study.

OEHHA further agrees that there is residual concern regarding developmental neurotoxicity based on evidence thereof associated with other cholinesterase-inhibiting pesticides, most notably chlorpyrifos (DPR, 2015a: p. 80, 88), and the lack of a developmental neurotoxicity study for methomyl.

## E. Immunotoxicity

Like DPR, OEHHA is unaware of any studies of methomyl immunotoxicity, and the US EPA reportedly waived the immunotoxicity study requirement for methomyl (DPR, 2015a: p. 80).

## F. Carcinogenicity Weight of Evidence

### 1. Genotoxicity

OEHHA concurs with DPR's conclusion that methomyl has genotoxic potential. Positive genotoxicity studies included one of four gene mutation studies (the sex-linked lethality test in *Drosophila*; the three remaining negative studies were conducted *in vitro*), seven of 10 chromosome abnormality studies (including several *in vitro* and *in vivo* micronucleus studies), and four of seven DNA damage studies (including both *in vitro* and *in vivo* studies).

### 2. Human and Experimental Animal Evidence of Oncogenicity

OEHHA agrees with DPR's conclusion that oncogenicity was not observed in the FIFRA-compliant chronic toxicity studies conducted in the dog, rat, and mouse (Busey, 1968; Kaplan, 1981; Serota, 1981). Similarly, oncogenicity was not observed in the non-compliant 22-month rat study (Hazleton Laboratories, 1968). There is no human data on methomyl oncogenicity.

## G. Extrapolation, Variability, and Uncertainty

### 1. Duration Extrapolation

As discussed previously, OEHHA recommends consideration of uncertainty factors for exposure duration extrapolation.

## 2. Uncertainty Factors

### a. Interspecies Extrapolation

OEHHA supports DPR's use of an interspecies UF of 1 for the acute oral POD, as it was based on a human study (McFarlane et al., 1998). OEHHA further supports the use of a factor of 10 for all other PODs, as these were based on studies conducted in non-primate laboratory animals.

### b. Intraspecies Extrapolation

DPR applied a default UF of 10 to account for inter-human variability in susceptibility to toxicants. However, in the absence of human kinetic data (as is the case for methomyl), OEHHA recommends an UF of 10 to account for pharmacokinetic variability among individuals (OEHHA, 2008). OEHHA believes this factor should be applied to protect sensitive subpopulations such as children, pregnant women, and the elderly. This is particularly relevant for cholinesterase-inhibiting pesticides, as certain diseases, nutritional states, and chemicals, including illicit drugs and pharmaceuticals, can lower plasma and RBC ChE levels (OEHHA, 2015). A total intraspecies UF of 30 (10 for pharmacokinetics and $\sqrt{3}$ for pharmacodynamics) is therefore recommended. As described in the next section, OEHHA recommends an additional uncertainty factor for early life exposures.

### c. Additional Uncertainty Factor

DPR applied a child-protective factor of 4 to acute exposures among infants <1 year old and children 1 to 12 years of age (DPR, 2015a: p. 8, 65) to account for the increased sensitivity of the young to methomyl-induced brain ChE inhibition. This value was based on the ratio of 3.6 between $BMD_{10}$ values of 0.36 and 0.1 mg/kg for brain ChE inhibition in adult and PND11 rats, respectively. The $BMD_{10}$ values come from US EPA's dose-time response modelling of brain ChE inhibition data from acute oral gavage studies (US EPA, 2007a). DPR stated that the analysis was based on data from the comparative cholinesterase study (Malley, 2005). This is true for the PND11 model. However, for the adult model, the dose-response data were derived from three studies - the comparative cholinesterase study, the acute oral neurotoxicity study (Mikles, 1998b), and a published dose-response study (McDaniel et al., 2007; US EPA, 2007a, Appendix II.B.2: p. 551-552). It appears that the final models were based on combined data from both sexes (US EPA, 2007a, Appendix II.B.2: p. 584-585).

OEHHA agrees with DPR's approach of using the ratio between adult and pup $BMD_{10}$ values for brain ChE inhibition. However, OEHHA's BMD analysis of only the comparative cholinesterase study resulted in a different adult:PND11 ratio of approximately 7 for the male brain ChE $BMD_{10}$ values. The adult and pup $BMD_{10}$ values were 0.49 mg/kg ($BMDL_{10}$ of 0.33 mg/kg; Exponential 3 model, Constant Variance) and 0.073 mg/kg ($BMDL_{10}$ of 0.064; Exponential 2 model, Constant

Variance), respectively. A ratio based solely on the comparative cholinesterase study, rather than a combination of studies, seems appropriate, as both age groups were treated identically apart from the doses.

Application of the child-protective factor serves to account for the increased sensitivity of the young to brain ChE inhibition. However, no developmental neurotoxicity study has been conducted for methomyl and this was considered an "uncertainty" by DPR (DPR, 2015a: p. 80). Further, the draft RCD cited recent literature which suggests that the developmental neurotoxicity of organophosphates may be independent of ChE inhibition and that certain neurotoxic effects may occur "at doses too low to induce overt clinical signs, making them difficult to detect in standardized animal testing." Given the residual concern regarding developmental neurotoxicity (see Reproductive and Developmental Toxicity section) and the potential for non-cholinergic mechanisms of toxicity, OEHHA suggests that the factor of 7 be increased to 10 and applied as an additional child-protective UF for all exposure scenarios involving children and women of child-bearing age. The total UF would be 300 when the POD is based on a human study, and 3000 when based on an animal study (Table 2).

## H. Worker and Bystander Exposure Assessment

### 1. Environmental Concentrations

#### a. Air Sources

Data from a key field monitoring study conducted near Oak Grove in San Diego County was used to estimate inhalation exposure to spray drift for both occupational and residential bystander scenarios (DPR, 1998). Before, during, and after an aerial application of methomyl and two other pesticides, air samples were collected over a 24-hour period at distances of 10-1460 meters from the treated field. Although other application site studies were described, they were not used due to analytical limitations or quality control concerns.

To estimate background exposure, four ambient air monitoring studies were conducted by the Air Resources Board (ARB) in Salinas County, Fresno County, and a three-county area (Fresno, Tulare, and Kings Counties) (DPR, 1985; DPR, 1995; ARB, 2008; ARB 2009). Of these sites, airborne methomyl levels were detected only near Mendota (ARB, 2008); however, data quality issues prevented the use of those results in the draft EAD. As a result, an ambient inhalation exposure scenario was not considered in this draft EAD.

OEHHA agrees with the use of the Oak Grove monitoring data and the appraisal of the ambient air monitoring studies. However, OEHHA recommends that the draft EAD mention whether methomyl is one of the compounds monitored in ongoing ambient air monitoring studies.

### b. Ground and Surface Water

Covering over 40 counties and nearly 600 samples per year, California ground water monitoring data from 2004-2012 was reviewed for confirmed detectable levels of methomyl. No confirmed detections were found.

OEHHA recommends that the draft EAD mention that, due to its physical properties, methomyl has the potential for groundwater contamination.

This draft EAD reviewed several surface water databases and studies. The DPR Surface Water (SURF) database found 11% of 3390 samples contained methomyl residues at levels of 0.046 to 55.3 µg/L with all methomyl-positive samples collected between July 1991 and October 2011. In two much smaller surface water studies, methomyl was detected less frequently (4% to 5.2%) at lower concentrations (0.004-0.67 µg /L) in California and in the Sacramento-San Joaquin Delta region (US EPA, 2007b; Orlando, 2013). The draft EAD concluded that methomyl surface water contamination was detected infrequently and at relatively low concentrations. US EPA recommends that swimmer exposure should only be considered if pesticides are applied directly to the water (US EPA, 1997b), and DPR concluded that this scenario did not require further assessment.

OEHHA is concerned about the potential health consequences of methomyl detected in surface waters in high-use areas. Based on the SURF data, OEHHA found that 80% of the highest 100 recorded values for methomyl (range: 0.483-55.3 µg/L) were detected after 01/01/2006. OEHHA also found that 72 out of the top 100 highest concentrations occurred in Monterey County during the high-use months. DPR's Pesticide Use Report (PUR) records show that 27% of all methomyl used in California is applied to lettuce (DPR, 2015f). Other records show that 57% of all California lettuce production came from Monterey County in 2007 (CDFA, 2013).

While few of the SURF values exceed 1 µg/L, it seems unlikely that sample collection would coincide with a time of peak methomyl contamination. Several of the highest concentrations were detected in samples collected from the same locations in Monterey County over several years, suggesting that methomyl contamination may be limited to specific watersheds or regions and, in those regions, should not be characterized as unlikely to occur. Also, the peak levels reported in SURF approached the 1-in-10-year peak estimates from recent methomyl surface water exposure assessments (99-220 µg/L; US EPA, 2010) and exceeded the US EPA's PRZM/EXAMS-modelled maximum acute exposure concentration of 30 parts per billion (ppb) noted in the Reregistration Eligibility Decision (RED) for Methomyl (US EPA, 1998: p. 38).

OEHHA recommends that DPR consider further analysis of the methomyl SURF data with respect to the increased frequency of watershed contamination in Monterey County and other regions of high methomyl use. In addition, OEHHA recommends that DPR consider including a swimmer exposure scenario in the EAD.

### c. Soil Residues

The high water solubility, low soil adsorption, and estimated soil half-life (0.5 days to 1.6 months) suggest methomyl does not persist in soil. However, some pesticides are known to be far more persistent indoors due to the lack of degradative and dissipation processes (US EPA, 1997b). Therefore, the potential for "take-home" contaminated soil to result in persistent contamination indoors should be mentioned.

OEHHA suggests that if methomyl residues in soil are not an area of concern or a potential source of exposure, the draft EAD should clearly state this conclusion and provide justification for it.

### d. Dislodgeable Foliar Residues (DFR)

Methomyl dissipation studies used in this exposure assessment were briefly discussed for cotton, corn, head lettuce, cabbage and mint. Grape studies which did not satisfy the criteria for these studies (Iwata et al., 1977; US EPA, 1996) were not acceptable for use in exposure estimates, but were sometimes used to estimate methomyl dissipation from foliage. Although methomyl use on grapes was withdrawn in 2012, grape DFR data continue to be used to provide surrogate values for other fruit and nut crops. OEHHA concurs with the DFR methodology used in this EAD; however, there is some uncertainty in using the grape data as surrogates.

## 2. Exposure Scenarios

### a. Occupational Exposure Scenarios

Three occupational exposure scenarios (handlers, reentry workers, and turf installers) were evaluated using different modeling or monitoring datasets, exposure assumptions, and exposure routes (Table 4, next page). Acute, seasonal, annual, and lifetime exposures were evaluated for reentry workers and turf installers. Acute, chronic and lifetime exposures were evaluated for handlers.

### a1. Handlers

All handler estimates were derived from surrogate exposure data from PHED (DPR, 2007). OEHHA agrees that the PHED-based surrogate data methods used to calculate occupational handler exposure estimates are reasonable and health-protective. They are more conservative than the methods outlined in the current US EPA guidance. The draft EAD also provided the PHED data used in their analysis as well as the subsequent calculations in the accompanying appendix.

While PHED is no longer supported by US EPA and has several shortcomings, the scenario data are sufficient to allow estimation of both the 95$^{th}$ percentile values, and the 90% UCL of the 95$^{th}$ percentile values. A partial replacement for PHED, the Occupational Pesticide Handler Unit Exposure Surrogate Reference Table, incorporates

additional data from more recent studies (US EPA, 2013b). However, the new reference lacks the additional data (number of observations) needed to calculate safety factor "multipliers".

**Table 4.** Occupational Exposure Scenarios for Methomyl.

| | Handlers | | | | Reentry Workers | Turf Installers |
|---|---|---|---|---|---|---|
| | Applicator | Mixer/ Loader | Flagger | Bait Handler | | |
| Location | At treated field or area | | | | At treated field after REI or PHI | At treated field after REI. $T_{1/2}$ = 1 day |
| Dermal data inputs | PHED database (US EPA) - Exposure corrected for PPE. | | | | Tiered activities, crop groups, surrogate crops, surrogate and measured DFR, TC | Surrogate chemical (*oxadiazon*) and activity (*Jazzercise*) |
| Inhalation data inputs | | | | | None | ARB (1993) and Layton (1993) |

DFR – Dislodgeable Foliar Residue, PHED – Pesticide Handlers Exposure Database, PHI – Pre-harvest Interval, PPE – Personal Protective Equipment, REI – Re-entry Interval, TC – Transfer coefficient, $T_{1/2}$ – estimated foliar half-life.

In addition, OEHHA is concerned with the continued reliance on PHED for two major reasons. As this database is no longer available or supported by US EPA, interested stakeholders will be unable to recreate PHED exposure calculations. Also, as noted in the draft EAD, PHED data has significant limitations and has been replaced for some scenarios by newer point-estimate data, which are insufficient for calculation of the safety factor multipliers. OEHHA suggests that DPR include a brief discussion of the respective deficiencies in use of PHED versus the US EPA's 2013 Exposure Surrogate Reference Table (US EPA, 2013b) in the revised EAD.

OEHHA agrees that the assumption of annual exposure for pesticide handlers and lettuce harvesters is reasonable.

### a2. Reentry Workers

Since methomyl field exposure data was either limited or unavailable for the reentry worker, DPR categorized most crops by plant form and agricultural practices (fruits and nuts, field crops, and others) to allow selection of "representative" crops (e.g., apples for all pome and stone fruits). Next, the specific work activities for each of the representative crops were evaluated for the amount of body surface exposure and then assigned to tier I (>50% body surface), II (25-50% % body surface) or III (<25% body surface). Activities with the highest potential for exposure were selected as "representative scenarios" for exposure calculations.

Acute and long-term exposures for harvesters were estimated from both measured and surrogate dislodgeable foliar residues (DFR) and transfer coefficients (TC) as described

in Tables 16 and 17 of the draft EAD. When crop-specific dissipation data was not available, a half-life ($T_{1/2}$) of one day was assumed. Both acute and long-term exposure estimates for sweet corn harvesters were 7-10-fold higher than other crops due to the high-risk transfer coefficients associated with this activity (US EPA, 1998).

OEHHA agrees with the methods used to calculate occupational reentry worker exposure via use of empirical and surrogate DFRs and TCs.

### a3. Turf Installers

Turf installer exposure was estimated via a combined structured exercise routine (SER) and surrogate chemical approach (DPR, 2012b). Subjects performed a scripted 16 minute Jazzercise routine that maximized contact with oxadiazon-treated turf. Chemical transfer was estimated from whole-body dosimetry. Personal air samples were collected at two heights to estimate inhalation exposure, but estimates of inhaled methomyl were ultimately considered too low to be included in the draft EAD (DPR, 2012b). Using this approach, DPR calculated a dose of 0.052 mg/kg-day.

OEHHA used recent US EPA guidance to estimate a dermal acute ADD of 0.019 mg/kg-day for a turf installer exposure scenario.

**Table 5.** Turf Scenario - Estimated Dermal Exposure.

| Source | DFR or TTR (µg/cm$^2$) | TC (cm$^2$/hour) | Exposure (mg/day) | Dose (mg/kg/day) |
|---|---|---|---|---|
| US EPA, 2012 and 2013a | 0.0252 (Estimated TTR) | 6,700 | 1.35 | 0.019 |
| DPR, 2015b (EAD estimate) | Combined surrogate activities and chemicals<br>Combined surrogate activities and chemicals | | 7.26 | 0.052 |

DFR – Dislodgeable foliar residue; TC – Transfer Coefficient; TTR – Turf Transfer Residue; RED- Reregistration Eligibility Decision (US EPA, 1998)

OEHHA is concerned that the SER approach did not account for the higher volatility of methomyl (vapor pressure of $5.6 \times 10^{-5}$ mm Hg @ 25°C) compared to the surrogate chemical (oxadiazon, vapor pressure of $2.0X10^{-7}$ mm Hg @ 25°C) – an approximately 280-fold difference. The SER could also underestimate the mean inhalation rate of the turf installer as it used a light activity breathing rate in its calculation. Recent guidance on ventilation rates would categorize transplanting sod as either a high intensity (farming work) or moderate intensity activity (US EPA, 2009a; US EPA, 2011). OEHHA recommends that the turf installer scenario use at least moderate activity rather than light activity breathing rates.

OEHHA recommends that the EAD further discuss the uncertainties inherent in using a combined surrogate chemical/surrogate activity approach to exposure estimation versus the TTR-based approach suggested by US EPA (US EPA, 2012; US EPA 2013b).

OEHHA also recommends that discussion of the SER method should acknowledge that it is based on a single study of a different chemical. US EPA cautioned that this method "may not be representative of other chemicals or activities which result in exposure" (US EPA, 2011).

### b. Worker Bystanders and Non-Occupational Exposure Scenarios

Three non-occupational exposure scenarios were discussed in the draft EAD – worker bystanders, residential bystanders, and "U-pick" harvesters. Only acute exposure estimates were provided in the draft EAD.

#### b1. Worker Bystanders

Inhalation is the sole route of exposure for the worker bystander scenario and it was evaluated using time-weighted average (TWA) air concentrations from a well-described application site study (DPR, 1998).

EHHA is concerned that the 8-hour worker bystander inhalation exposure estimate might have underestimated exposure for nearby agricultural workers. This analysis was based on activity levels and exposure durations from Wiley (ARB, 1991), which were based on a telephone survey of the general population that excluded non-English speakers and households without a telephone. A 2003-2004 survey of California farmworkers found that 53% spoke no English and 75% earned less than $15,000/year (Aguirre International, 2005), suggesting that the ARB survey may have largely excluded farmworkers and therefore may not accurately reflect their activity levels or durations.

Secondly, agricultural workers are ~75% male and among the most physically active of all workers (Aguirre International, 2005; Proper et al., 2006; Steeves et al., 2015). Therefore, using mean activity levels and durations values derived from a survey of the general population will likely contribute to an underestimation of exposure for these workers. Also, mean activity duration values for men are consistently ~10% higher than those for women and mean weight-adjusted ventilation rates measured during moderate intensity activities are also ~10% higher in men (US EPA, 2011). OEHHA recommends that DPR use default point estimate 8-hour breathing rates based on the mean and 95$^{th}$ percentile of moderate intensity activities, 170 and 230 L/kg-8-hrs, respectively, for adults 16-70 years old (OEHHA, 2012a).

OEHHA recommends that DPR reconsider the choice of activity durations and ventilation rates used in calculating the worker bystander exposure estimates. As these are acute exposure values, it may make sense to use an exposure estimate based on the 95$^{th}$ percentile ventilation rate for workers.

#### b2. Residential Bystanders

One-hour Absorbed Daily Dose (ADD) estimates for residential bystanders assumed high activity inhalation rates for adults and one-year-old children and methomyl air

concentrations measured during an aerial application. The 24-hour ADD estimates were based on daily activity rates and the 24 hour TWA concentration measured during and following aerial application.

OEHHA concurs with the methodology used to calculate one and 24-hour ADD exposure estimates for the residential bystander scenario.

### b3. "U-pick" Harvesters

A single non-occupational re-entry scenario was considered for "U-pick" crops (sweet corn, nectarines, peaches, and blueberries) where the general public enters the field or orchard to pick their own produce. It was assumed that children worked for 2 hours and adults worked 4 hours, so child-specific exposure estimates were 50% lower than those for adults (US EPA, 1997b).

Adult "U-pick" blueberry, nectarine, and peach harvester exposures estimates were calculated with a transfer coefficient (TC) of 10,000 $cm^2$/hour derived from the occupational TC for fruit tree harvesting (1,500 $cm^2$/hour) (DPR, 2009a). The higher TC reflects the likelihood for higher dermal exposure due to the lack of protective clothing provided to commercial harvesters.

Applying a similar adjustment to the occupational TC (17,000 $cm^2$/hour) for hand-harvested sweet corn would give an extremely high TC value of 110,000 $cm^2$/hour. Instead, by assuming that "U-pick" harvesters would wear more clothing due to the abrasive foliage and work less vigorously than professional harvesters, no adjustment was made for this exposure scenario and the same occupational TC was applied to the "U-pick" sweet corn scenario. The cited sweet corn TCs were from a 2000 US EPA policy document (DPR, 2009a). US EPA recently updated TCs (US EPA, 2013b) and the sweet corn harvesting TC was revised lower (8800 $cm^2$/hour).

Sweet corn is harvested during warm weather. We agree that the more experienced pickers would wear more protective garments. However, inexperienced harvesters would be less likely to wear long pants and long-sleeved shirts, and therefore might receive little or no protection from their clothing. We also agree that "U-pick" harvesters would be unlikely to work as vigorously as occupational farm workers and there is likely considerable variability in the actual exposure duration as some crops (corn) might be harvested relatively quickly while others (blueberries) might take longer for inexperienced "pickers".

OEHHA recommends that DPR reconsider the TC used for this scenario as well as the rationale for using the same TC for occupational and "U-pick" harvesters.

### b4. Other Non-occupational Exposure Scenarios not Addressed in the Draft EAD

<u>Child-specific turf scenario</u>

A scenario for children playing on newly-transplanted turf was not included in the draft EAD as it was considered to be a rarely-encountered situation and exposure would be significantly less than that estimated for the turf installer scenario. Although dermal exposure estimates would certainly be lower than those for turf installers due to residue dissipation, factors such as a lack of protective clothing, hand-to-mouth transfer, object-to-mouth transfer, and incidental ingestion of soil or plant material, as well as age-specific surface area to body weight ratios and age-specific ventilation rates, would be anticipated to enhance exposure. OEHHA recommends that the draft EAD either include the child-specific residential turf exposure scenario or state the reasons why it is not needed.

Swimmer scenario

A swimmer exposure scenario was not included in the draft EAD. The rationale for excluding this scenario was based on the US EPA Standard Operating Procedures (SOPs) for Residential Exposure Assessments (US EPA, 1997b), which provides guidance for estimating exposure from intentional addition of pesticides to swimming pools.

OEHHA is concerned that these guidelines may not be applicable to a scenario where a swimmer is exposed to pesticide residues from spray drift or run-off in surface water. Community swimming pools or access to them are often lacking in rural communities, so residents may instead swim in local surface water for recreational purposes. Furthermore, guidance for addressing the latter scenario appears to be available (US EPA, 2004).

OEHHA recommends that DPR reconsider the applicability of the cited US EPA guidelines and example scenarios (US EPA, 1997b; US EPA, 2004; OEHHA, 2012b) for swimmer exposure to contaminated surface water and also calculate a combined dermal and ingestion exposure estimate for surface water swimmers.

Take home dust

Exposure to “take home” indoor dust is not addressed by the draft EAD. Homeowners, farmworkers, and their families may be exposed to methomyl via “take home” dust exposure. A number of studies suggest that incidental (non-dietary) ingestion of pesticide-contaminated dust may occur frequently in the homes of California farmworkers (Bradman et al., 2007; Colt et al., 2004; Quirós-Alcalá et al., 2011; Thompson et al., 2014). One study found the carbamates carbaryl and propoxur in house dust (Colt et al., 2004).

OEHHA recommends that “take home” dust exposure be discussed in the draft EAD. While the house dust studies do not directly implicate methomyl, they do suggest that exposure via incidental ingestion of pesticide-contaminated house dust may contribute to residential exposure of farmworkers and their families and could contribute to significant health effects.

# I. Dietary Exposure Assessment

The complete dietary exposure assessment was presented in Appendix IV to the RCD, and portions were repeated in the Exposure Assessment and Risk Characterization sections of the RCD. However, the major findings were absent in the Conclusion sections (pages 5 and 94 of the RCD). OEHHA suggests that these be included in the Conclusion sections.

## 1. Anticipated Residue Assessment

Dietary (food and drinking water) exposure assessments were conducted for methomyl using the DEEM-FCID™, Version 3.18 for both acute and chronic exposures for the general US population, infants, young children, youth, adults (20-49 and 50-99 years), and females 13-49 years. DEEM v.3.18 uses food consumption data from the National Health and Nutrition Examination Survey (NHANES) 2003-2008 in conjunction with user-provided residue data to derive methomyl intake (µg methomyl per kg body weight per day). The consumption rates are estimated for specific commodities to which methomyl can be applied. Two types of assessments were conducted based on the assignment of residue level to specific commodities: the first used anticipated residues (e.g., measurements of detected residues, or, when residues were not detected, estimated residue values) while the other used tolerance levels. The tolerance assessment was only conducted for acute exposures of 15 commonly consumed commodities. On the other hand, the anticipated residue assessment used food residue data from samples collected across the US by the US Department of Agriculture PDP from 2000-2011 combined with percent crop treated data from US EPA's 2009 Screening Level Usage Analysis for methomyl (US EPA, 2009b). The drinking water residue used was the average of the last 3 years of the PDP Limit of Detection (LOD) of treated municipal drinking water. For acute exposures, exposure estimates were derived using probabilistic analysis and statistical distributions of residues while for chronic exposures average residue values were used. Analyses were conducted for food plus water and food alone. Because the tolerance for grape will be withdrawn at the end of 2016, analyses were conducted for food with grape and food without grape.

### a. Residue Data

#### a1. Food Commodities

The assessment was very thorough in describing the food commodities and residue data source. OEHHA has questions regarding barley and avocado. The draft assessment included barley, probably because the dietary exposure assessment was completed prior to the cancellation of the use effective in 2015. OEHHA recommends that this commodity and associated foodforms be removed from the analysis. The data source for avocado residue was not provided. Avocado has been found by the tolerance assessment to "not be health protective" for all age groups. OEHHA suggests clarification about these two commodities.

### a2. Pesticide Data Program (PDP) data

OEHHA agrees with the use of PDP data for the DPR analyses. The PDP is a national program with protocols designed to provide realistic residue data (i.e., fruits are washed and peeled) for dietary exposure assessment. However, the PDP samples used in the assessment include those collected in states besides California. OEHHA recommends that PDP data for samples collected in California be used, if available and the sample size is sufficient.

### a3. Percent Crop Treated (PCT) data

The percent crop treated (PCT) (acres treated with methomyl per total acres planted for a specific commodity) can be used to help assign zeros or LOD-based values (e.g., ½ LOD) for the non-detect samples in probabilistic acute exposure assessments. For chronic exposures, PCT affects the average residue level and thus the exposure estimate.

DPR selected PCT values from the US EPA Screening Level Usage Analysis (US EPA, 2009b) for years prior to 2009. The use of these values is inconsistent with DPR's Guidance for Dietary Exposure Assessment, which recommends that data most reflective of current use (preferably the most recent 5 years) be used (DPR, 2009b). OEHHA suggests the PCT value be derived from data, such as those in the Pesticide Use Report, when available.

### a4. Drinking Water Concentration

The DPR draft methomyl dietary exposure assessment used the average LOD of the last three years of recent PDP sampling of drinking water (2003 to 2011) as the point estimate (5.3 parts per trillion, ppt; or 0.0053 ppb) (DPR, 2015a; Table 10 of Appendix IV). The range of LODs for those years was 1.8 to 7.3 ppt, but it was unclear how the 5.3 ppt value was calculated. DPR states that this value likely underestimates acute exposure. OEHHA concurs with this concern because available California data showed much higher LODs. The average LOQ ranged from 0.059 to 0.274 ppb for the DPR surface water monitoring program (2003 to 2012) (DPR, 2015a; Table 8 of Appendix IV). The highest detected sample was 55.3 ppb in 2010, with no data for 2011 and 2012. As cited in the draft RCD, the DPR ground water monitoring of wells for methomyl showed only one detection (15 ppb in 2006), while all other samples (2003 to 2012) were below the LODs. For this time period, the maximum LODs ranged from 0.03 ppb to 5 ppb. These data suggest that drinking water can have methomyl levels greater than 5.3 ppt, but could not be detected due to the LOD. OEHHA suggests that DPR consider using California-specific methomyl well water LODs.

## b. Exposure Calculation

### b1. DEEM-FCID

The DPR draft methomyl dietary exposure assessment derived exposure estimates using DEEM-FCID v. 3.18, which used NHANES dietary consumption data from 2003-2008. A more recent version of DEEM-FCID (v. 4.02) is available and uses consumption data from 2005-2010. Food consumption patterns for some food items might have changed during that time. Consumption rate differences could result in differences in acute exposure estimates for a subpopulation which consumes relatively large amounts of a commodity with high residue levels. OEHHA suggests revising the assessment using the more recent consumption database.

### b2. Subpopulations

The current methomyl dietary exposure assessment does not include an evaluation of pregnant or lactating women. Because there is potential for neurodevelopmental toxicity with methomyl (as discussed in the draft RCD), it would be health protective to evaluate exposures of pregnant women. On the other hand, methomyl was not found to distribute into milk in the two lactating animals studied (goat and cow; DPR, 2015a), suggesting that human exposure via lactation is not likely. Nonetheless, both pregnant and lactating women have higher food consumption rates per kg body weight suggesting that they may have higher methomyl intakes. A pregnant woman who also nurses her child could potentially have higher methomyl intake for about 15 months (9 months of pregnancy plus approximately 6 months of lactation). It is noted that methomyl intake depends on the consumption rates of specific commodities and the residues in those commodities. OEHHA recommends that exposures of pregnant and lactating women be addressed separately from the general population in the exposure assessment. OEHHA acknowledges that DEEM v. 4.02 will provide exposure estimates for pregnant women via the custom definition but lacks the capability to analyze lactating women's exposures.

### b3. Eating Occasion

In the draft RCD, the acute dietary exposure level was aggregated by eating occasion rather than over 24 hours due to the specific mechanism of action of methomyl. OEHHA considers this a reasonable approach since humans often consume food at multiple times during the day and therefore could be exposed to methomyl several times during a 24 hour period. Because methomyl has a short half-life in the body, acute methomyl exposure can be considered the peak methomyl level during the day derived from summing overlapping exposures from each eating occasion. For this approach, the half-life estimation of the chemical is a critical factor. OEHHA suggests that for transparency the methomyl half-life value used should be identified in the draft RCD.

### b4. Exposure Percentiles

The draft RCD lacked a clear explanation of the exposure percentiles used in the assessment. For acute exposure using anticipated residues, three exposure estimates and their associated MOEs were provided: 95th, 99th, and 99.9th percentile (Tables 13 to 15). While the 95th and 99th percentiles of exposure were below the acute

population adjusted dose (aPAD), the 99.9th percentile exposures of young children subgroups exceeded the aPAD. In comparison, only the 95th percentile exposure estimates were used for tolerance assessment (Table 20). In Table 11, the theoretical concentration of methomyl in drinking water for each population subgroup was calculated using the 99.9th percentile of food only exposure, but a 95th percentile acute water consumption value. OEHHA recommends an explanation for why a specific percentile was chosen for a particular exposure scenario, and clarify which exposure estimates would be most appropriate to determine dietary and aggregate exposure risks.

### 2. Tolerance Assessment

The commodities included in the acute tolerance assessment were selected based on their high consumption rates or high contribution to exposure in US EPA's dietary exposure assessment for N-methyl carbamates (US EPA 2007a). Overall, the commodities selected for acute tolerance assessment are appropriate.

### 3. Illegal Residues

Illegal residues were found in certain samples that were destined for consumer consumption. Though some foods with illegal residues will reach consumers, the number of PDP illegal residues has been very low in the last few years. Also, the DPR illegal residue findings were mostly in samples that did not represent the portions of a commodity to which consumers are likely to consume (e.g., unwashed, inedible parts of the commodity). OEHHA concurs that it is appropriate to exclude illegal residues in chronic exposure assessments.

## J. Risk Characterization

### 1. Targets for Acceptable Exposure

As discussed in the Uncertainty Factors section, OEHHA supports the use of an interspecies UF of 1 for acute oral exposures and 10 for the remainder, as the acute oral POD was based on a human study (McFarlane et al., 1998). However, OEHHA recommends that the intraspecies UF be raised from 10 to 30 to account for increased susceptibility of certain subpopulations. OEHHA further recommends that an additional UF be applied which would address the concerns of increased sensitivity of children as well as potential non-ChE mechanisms of developmental neurotoxicity. These recommendations are summarized in Table 2. The total UFs constitute acceptable MOEs.

### 2. Aggregate Risk Assessment

Aggregate risk assessment is important for methomyl because exposure occurs through multiple routes and scenarios (occupational, residential, and dietary). However, DPR did not conduct an aggregate risk assessment (DPR, 2015a: p. 86).

For acute exposure, DPR explained that it would be unclear which target MOE would be appropriate since the acute oral POD was from humans and the acute dermal and inhalation PODs were from laboratory animals. Furthermore, the three PODs in the draft RCD were based on toxicity endpoints from different target organs.

OEHHA disagrees with the above reasons. OEHHA believes the database is sufficient for deriving PODs for the same toxicity endpoints such as ChE inhibition for acute exposure. While extrapolation may be needed for some of these PODs, the concern about aggregate exposure needs to be addressed. The draft RCD already raised concerns regarding underestimation of the acute risk due to the lack of aggregate assessment (DPR, 2015a: p. 86). It is reasonable not to conduct aggregate exposure assessment for subchronic or chronic durations since it is unlikely that a person would be exposed to methomyl from all three routes repeatedly over time.

### 3. Cumulative Risk Assessment

The draft RCD described the findings of the US EPA's 2007 *Revised N-Methyl Carbamate Cumulative Risk* Assessment, which evaluated the cumulative risk from 10 carbamates (including methomyl) from food, drinking water, and residential (non-occupational) exposures. On account of recent risk mitigation and risk reduction efforts, US EPA concluded that "there is a reasonable certainty that no harm will result from exposure to the NMC pesticides covered by this assessment, taking into account the cumulative effects of such residues" (US EPA, 2007a: p. 11). However, during the recent (and ongoing) registration review of methomyl, US EPA identified unacceptable risks due to drinking water concerns, leading to voluntary cancellation of methomyl use on barley, oat, and rye, limits on its use on wheat, and reductions in application number and rate on certain vegetable crops (US EPA, 2015a).

OEHHA recommends a continual reassessment of cumulative risk for this class of pesticides used in California.

## IV. MINOR COMMENTS

### A. Draft RCD

- The first two sentences of page 27 have the citations paired with the wrong studies.

- In the footnote to Table III-7 (page 30), there is an editorial statement that needs to be removed.

- The first sentence of page 3 erroneously states $LEC_{10}$ instead of $LED_{10}$.

- There are some inaccuracies in the language used to describe the acute inhalation POD. The second paragraph of page 65 states the following: "…if the relevant

adverse effects were observed in human experimental toxicity studies, as was this case with methomyl for acute oral and inhalation exposures." Since the inhalation toxicity study was conducted in rats, the latter part of the sentence should be changed to "as was the case with methomyl for acute oral exposures." Similarly, the third paragraph on this page states that "The 100X factor applied to all adult exposure scenarios considered for this document except acute oral and inhalation." This sentence should be rewritten as "The 100X factor was applied to all adult exposure scenarios considered for this document except for acute oral exposure." On page 72, OEHHA suggests that "calculated absorbed doses" be changed to "estimated absorbed doses" and "$LEC_{10}$" should be replaced with "$LED_{10}$" when expressed as dose. In the second paragraph of page 94, the sentence "Using the calculated absorbed doses and the critical inhalation NOEL of 0.16 mg/kg-day…" should be changed to "Using the critical inhalation $LED_{10}$ of 0.16 mg/kg-day…"

- In the first sentence of page 80, the word "acute" should be removed.

- On page 45, DPR states that the purity of the methomyl used in Shalaby et al (2010) was not provided. However, the study says that Methomex, a formulation, was used. Also, the listed effects of muscle tremors, abdominal cramps, etc. at the bottom of page 45 were from an $LD_{50}$ study, not from the reproductive toxicity part of the study (which employed smaller doses).

- The first sentence of page 39 erroneously states "Two of four" gene mutation studies as being positive when it is "One of four." The HGPRT forward mutation assay was negative for methomyl (although it was positive for *N*-nitroso-methomyl). Similarly, page 80 states that "two of five" gene mutation studies were positive instead of "one of four."

- On pp. 21 and 65, the $BMD_{10}$ values are mistakenly referred to as $LED_{10}$ values.

- Appendix IV: The text on page 8 states "Table 1a is a summary of primary PDP data used in Residue Distribution File (RDF) construction." Table 1a contains data on ½*LOD values. It would be helpful to clarify how the ½*LOD values are used. Some commodities in Table 1a have a "CT" (presumably the same as PCT) values. It would be helpful to list CT/PCT for all commodities or add a footnote to describe unlisted CT/PCT values.

- Appendix IV: Treatment of blended versus non-blended commodities should also be described, particularly in regards to the determination of the PCT. Nonblended commodities are those that are consumed as an individual unit (an individual apple). Blended commodities are those in which the individual commodity unit is comingled with other units of the same commodity (e.g., using apples from different farms to make apple juice). It is surprising to see that in Table 1a, peanut butter is given a PCT value when it would seem that peanut butter would be considered blended and

no PCT value would be used in a probabilistic assessment. PCT values are more visibly listed in Table 1b (commodities that have translated anticipated residues), which is helpful.

### B. Draft EAD

- The turf installer exposure scenario estimate was based in part on a 2011 DPR memorandum (page 59). This memorandum was subsequently revised in 2012, replacing the 2011 memorandum. The draft EAD should be updated so that it refers to the 2012 document.

- The subheading near the bottom of page 72 is misspelled and should read "Bystander".

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