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 Dicrotophos

Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

LIST OF CONTRIBUTORS

Peer Reviewers

Toxicology and Risk Assessment	Worker and Bystander Exposure Assessment	Dietary Exposure Assessment
Katherine Sutherland-Ashley, Ph.D.	James Nakashima, Ph.D.	Amy Arcus-Arth, D.V.M., M.P.V.M. Katherine Sutherland-Ashley, Ph.D.

Report Reviewers

Lori Lim, Ph.D., D.A.B.T.

Charles Salocks, Ph.D., D.A.B.T.

David Ting, Ph.D.

Melanie Marty, Ph.D.

Allan Hirsch

PREFACE

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

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

This report is a review of the draft RCD (dated December 30, 2015) provided by DPR for the pesticide dicrotophos. The draft EAD was included as an appendix to the draft RCD.

This peer review report has four parts:

I. Summary of Review
II. Response to Charge Statements, provided by DPR
III. Detailed Comments on charge statements 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 Assessment (OEHHA) on the Department of Pesticide Regulation (DPR) draft Risk Characterization Document (RCD) for dicrotophos, an organophosphate pesticide not currently registered in California. The draft RCD characterizes the health risks from dicrotophos associated with a Special Local Need (SLN) registration of BIDRIN® 8 to control brown stink bugs on cotton. Workers and adult residential bystanders were evaluated for dermal, inhalation, and combined exposures. Child bystanders were evaluated for dermal, inhalation, oral, and combined exposures. Dietary and drinking water exposures were also considered for various age groups for the general public. Overall we find the document is well-written and the limited toxicological review is justified for the proposed single use on cotton.

Our principal comments are summarized in Section I. Responses to DPR's charge statements (descriptions of scientific assumptions, findings and conclusions to be addressed by peer reviewers) are provided in Section II. Detailed comments are provided in Section III and minor comments are in Section IV.

A. Hazard Identification and Risk Characterization

1. Non-cancer Endpoint Selection and Point of Departure Determination

a. Toxicity Endpoint

- The draft RCD considered brain cholinesterase inhibition (ChEI) to be the most sensitive health endpoint, and used ChEI data from laboratory animal studies for deriving points of departure (PODs) for all exposure routes and durations. OEHHA generally agrees with the approach to evaluate brain ChEI as the critical effect. However, changes in brain weight in neonatal pups from Brammer (2003) occurred at similarly low doses and DPR should re-evaluate this study and provide reasons for not using it in POD determination.

- The draft RCD showed that dicrotophos inhibition of brain ChEI reaches steady state after about 21 days of repeated dosing. Once steady-state enzyme inhibition is reached, subsequent exposure does not appear to elicit a greater response. Because of this finding, DPR determined it was unnecessary to evaluate repeated exposures using the conventional subchronic and chronic exposure scenarios, when ChEI is the critical effect. Instead, the draft RCD only evaluated acute and steady-state exposures. This is consistent with the US Environmental Protection Agency's (US EPA) risk assessment for dicrotophos (2015a) and OEHHA agrees with this approach.

- For brain ChEI, DPR considered rat pups more sensitive than adult rats for acute oral exposure. The draft RCD applied the acute oral POD derived from data for rat pups (postnatal day 8, PND8) to estimate the risk for all population subgroups in the exposure assessments as a conservative approach.

  OEHHA agrees with the application of this POD for all subpopulations. The subpopulations evaluated in the exposure assessments for dicrotophos can be divided into: sensitive population and general adult population. The sensitive population consists of infants, children, and women of child-bearing age who could be affected by the developmental neurotoxicity (DNT) of dicrotophos. Individuals in the sensitive population are in the worker (women of child-bearing age), bystander and dietary exposure scenarios. The 'general adult' population in this report include adults (age 50 to 99) for the dietary exposure scenario (this is consistent with US EPA's subpopulation classification in the 2015 risk assessment).

b. Benchmark Dose Modeling

- DPR used Benchmark Dose (BMD) modeling with a benchmark response (BMR) of 10% ($BMDL_{10}$) to establish the POD for ChEI. OEHHA agrees with the approach. This is consistent with US EPA's recommendation of a 10% BMR for brain ChEI by organophosphate pesticides (OPs) based on both statistical and biological evidence (US EPA, 2015b). OEHHA also agrees with DPR in choosing the Hill model in some of the BMD analyses. By contrast, US EPA only used the Exponential model for ChEI data. OEHHA's opinion is that model selection should be based on which model most accurately describes the data. The exponential and Hill models are typically used for receptor-mediated responses. In a number of cases described in the draft RCD, the Hill model provided a substantially better fit (higher Test 4 p values) than the exponential models.

- DPR did not provide sufficient information on why a specific BMD model was selected for POD determination. This is especially important for cases where the models selected failed one or more of the statistical tests in the Benchmark Dose Software (BMDS). As outlined by US EPA (2012a), PODs should be based on models that fit all the criteria for model selection. The draft RCD should include model outputs as well as clearly describe the criteria used for model selection.

c. Oral Exposure

- For acute oral exposure, OEHHA agrees with DPR's choice of the $BMDL_{10}$ of 0.03 milligram/kilogram-day (mg/kg-day) for brain ChEI in PND8 male rats given dicrotophos by gavage (Moxon, 2003) as the acute oral POD for the both the sensitive population and the general adult population. While

the $BMDL_{10}$ for brain ChEI from neonatal rats is lower than for adult animals in the database, OEHHA agrees that the aging brain can also be more sensitive to neurotoxicity than the healthy adult population and a POD from neonatal animals is health protective for these populations.

- OEHHA agrees with the selection of a $BMDL_{10}$ of 0.025 mg/kg-day for brain ChEI from the subchronic neurotoxicity study in adult female rats as the steady-state oral POD (Horner, 1995). The $BMDL_{10}$ of brain ChEI for each of the exposure duration (5, 9 and 14 weeks) was the same (0.025 mg/kg-day), indicating that ChEI reached a steady-state by at least 5 weeks of treatment. The $BMDL_{10}$s for males in the study were slightly higher (0.031-0.036 mg/kg-day), but reached a steady-state at about the same time.

d. Inhalation Exposure

- DPR selected a 28-day inhalation toxicity study in the rat (Blair, 2010) as the critical study and used its endpoint (brain ChEI) to assess acute and steady-state dicrotophos inhalation exposures because it was the only appropriate study. While OEHHA agrees with the study selection, OEHHA is concerned about the magnitude of the POD based on the $BMDL_{10}$ when compared to the study's No-Observed-Effect Levels (NOELs). There is a large difference between the NOEL (<0.097 mg/kg-day) and the $BMDL_{10}$ (0.41 mg/kg-day) for the female rat. OEHHA suggests additional discussion be added to address these differences and to justify the use of the $BMDL_{10}$ as the POD. Additionally, the NOEL (estimated at 0.032 µg/L when a factor of 3 is applied to the lowest dose with a significant effect) may be appropriate because of concerns regarding the BMD model selection for this endpoint.

e. Dermal Exposure

- The toxicity database for dicrotophos also lacked appropriate acute toxicity studies for dermal exposure. Thus, DPR chose a 28-day dermal toxicity study as the critical study and brain ChEI as the critical endpoint for acute and steady-state dermal dicrotophos exposures (Noakes, 2001). The POD was the $BMDL_{10}$ of 2.1 mg/kg-day. OEHHA concurs with this determination.

2. Carcinogenicity Weight of Evidence

- OEHHA agrees with DPR's weight of evidence evaluation for determining the carcinogenicity of dicrotophos. The presence of follicular cell adenomas (benign) only in male mice (Milburn, 1998) and weak mutagenicity in *in vitro* genotoxicity assays (San and Clark, 1995; Dean, 1974) are insufficient to identify dicrotophos as a carcinogen. Toxicity

ForeCaster (ToxCast™) data indicated a lack of carcinogenic potential. However, there is a published genotoxicity study which showed dicrotophos caused an increase in chromosomal aberrations (CA) in CHO-K1 cells and induced DNA damage in HepG2 cells (Wu et al., 2010). OEHHA suggests DPR include this study in their weight of evidence evaluation to reflect a greater concern for the genotoxicity potential of dicrotophos.

3. Uncertainty Factors and Sensitive Populations

- DPR applied a 10-fold interspecies uncertainty factor (UF) for the assumption that humans are 10 times more sensitive than animals. OEHHA agrees with this approach.

- In the draft RCD, DPR applied an UF of 10 for intraspecies pharmacokinetic and pharmacodynamic variability for all populations. OEHHA recommends DPR increase the intraspecies factor to 30 for the general adult population. OEHHA uses a default UF of 10 for intraspecies pharmacokinetic variability, which accounts for wide variability by age in pharmacokinetics and thus for subpopulations possibly being more sensitive than the general adult population to the toxicity of a chemical. The scientific basis for this recommendation is detailed in OEHHA's peer reviewed Air Toxics Hot Spots Risk Assessment Guidelines, Technical Support Document for the Derivation of Reference Exposure Levels (OEHHA, 2008). An UF of $\sqrt{10}$ is retained for intraspecies pharmacodynamic variability.

- For the sensitive population (pregnant women, infants, children, and women of child-bearing age), OEHHA recommends an UF of 10 for intraspecies variability. This is supported by a POD derived from effects observed in PND8 animals. However, OEHHA also recommends the use of an additional UF of 10 to protect against DNT (see below). This additional UF would offer additional protection against both pharmacokinetic and pharmacodynamic variability in the sensitive population.

- US EPA determined that there was sufficient uncertainty regarding dicrotophos' mechanism of action causing developmental neurotoxicity (DNT) that the Food Quality Protection Act (FQPA) 10-fold Safety Factor was applied in their 2015 human risk assessment for dicrotophos (US EPA, 2015a). OEHHA concurs with this concern especially when there is evidence of changes in brain weight and morphometry in pups exposed to dicrotophos *in utero* from the Brammer study (2003). OEHHA recommends including this additional uncertainty factor to protect infants.

- Total UFs recommended by OEHHA are 300 for the adult general population (10 for interspecies, 30 for intraspecies) and 1000 for the sensitive population (10 for interspecies, 10 for intraspecies, 10 for DNT).

4. Risk Characterization

- Margin of Exposure (MOE) values are calculated by dividing the POD by the estimated human exposure dose or air concentration. The draft RCD characterized whether an exposure is likely to cause adverse health effects using a target MOE of 100 for all age groups. OEHHA recommends re-evaluation of the target MOEs to take into account the recommended UFs in this report. OEHHA's suggested target MOEs are 300 and 1000 for the general adult population and sensitive population, respectively.

B. Worker and Bystander Exposure Assessment

1. Occupational Handler Exposure Scenarios

- OEHHA agrees that occupational handler exposure estimates based on the Pesticide Handlers Exposure Database (PHED) are reasonable. However, OEHHA is concerned with the continued reliance on PHED, as software for this database is no longer available or supported by US EPA. Secondly, PHED has known limitations, such as exposure estimates that are based on combinations of data from diverse studies that have different protocols, analytical methods and residue detection limits.

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

- To improve the transparency of the draft EAD, OEHHA also recommends that DPR cite the specific PHED scenarios, data and calculations used in the exposure estimates.

2. Occupational Post-Application Exposure Scenarios

- OEHHA is concerned that the values for transfer coefficient (TC) and dislodgeable foliar residue (DFR) used in the cotton scout scenario might have underestimated exposure.

- OEHHA recommends that DPR consider using a TC derived from results of a monocrotophos field study instead of the TC used in the draft EAD that was based on field data from three different pesticides. OEHHA also recommends that DPR address acute and seasonal exposure of cotton scouts, who may enter treated fields prior to the expiration of the re-entry

interval (REI) to inspect for insect damage and status of plant development.

- OEHHA disagrees with the approach taken in the draft EAD in estimating the dermal absorption value of dicrotophos. Rather than relying on a mathematically complex analysis of data from *in vivo* and *in vitro* dermal absorption studies in rats and humans, OEHHA recommends that DPR utilize the data from an *in vivo* dermal absorption study of monocrotophos in human subjects (Feldmann and Maibach, 1974).

3. **Residential Bystander Exposure Scenario**

- OEHHA is concerned about the choice of AgDRIFT input parameters for estimating groundboom-related spray drift deposition, as well as the use of the 50th percentile deposition curve output, as they may lead to underestimation of exposure. OEHHA recommends that DPR provide additional justification for these choices and cite additional literature describing current agricultural practices that support the assumption regarding the larger droplet size. OEHHA also recommends that DPR use the more conservative 90th percentile output option as there appears to be sufficient documentation of the source data and relevant calculations in the publically available literature.

4. Non-Occupational Post-Application Exposure Scenarios

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

C. Dietary Exposure Assessment

- Dietary (food and drinking water) exposure assessments were conducted for acute and steady-state exposures to dicrotophos. The only proposed use of dicrotophos is on cotton and the only food products with potential residue are cottonseed and processed cotton products (including cottonseed oil). OEHHA generally agrees with the approaches taken in the dietary assessment.

- OEHHA recommends the analysis should be updated to include the most recent version of the exposure software (DEEM-FCID v. 4.02), include exposure estimates for pregnant and lactating women, and remove or clarify the need to derive dietary exposure estimates for "workers 18-99."

- Exposure estimates were described as 95th percentile for dietary, 99.9th percentile for water, and 97.5th combined. OEHHA recommends further explanation on how these percentiles were chosen and on how the exposure estimates for food and drinking water were combined.

- In the Risk Appraisal section of the Draft RCD, DPR showed higher drinking water exposure levels estimated from surface water data than those from using Pesticide Database Program (PDP) finished drinking water data. OEHHA suggests that DPR clarify the wide differences in drinking water exposure estimates between these two data sources and provide justification on which is more appropriate.

II. RESPONSES TO CHARGE STATEMENTS

The responses to some of the charge statement are intended to be brief to avoid redundancy with the comments in Section I and detailed discussion of OEHHA's comments in Section III.

A. Hazard Identification and Risk Characterization

Statement 1: "*A benchmark dose (BMD) analysis was conducted on all of the studies with brain ChE data using the exponential models and the Hill model to identify critical NOELs."*

Response: As described in Section I, OEHHA agrees with the selection of the Hill and exponential models because they are designed for receptor-mediated responses. OEHHA recommends the inclusion of model outputs and model selection criteria.

Statement 2: "*A $BMDL_{10}$ of 0.03 mg/kg-day was selected as the critical NOEL for evaluating acute oral exposure to dicrotophos based on brain ChEI in PND8 rat pups (Moxon, 2003a)."*

Response: As described in Section III.C, OEHHA agrees with the study selected for acute oral exposure. .

In addition, in this charge statement as well as others, and in the draft RCD, $BMDL_{10}$ and NOEL were considered equivalent terms as the $BMDL_{10}$ was referred to as the critical NOEL. They are not. The draft RCD should recognize they represent two different ways to determine the POD.

Statement 3: "*A BMDL of 0.025 mg/kg-day for brain ChEI from the subchronic neurotoxicity study in adult female rats was selected as the critical NOEL to evaluate the steady-oral exposure to dicrotophos (Horner, 1995)."*

Response: As described in Section III.C, OEHHA agrees with DPR's selection of 0.025 mg/kg-day ($BMDL_{10}$) from female adult rats as the steady-state oral POD (Horner, 1995). The chosen POD was also protective of brain ChEI of neonatal animals because the $BMDL_{10}$ for PND12 rats were at similar level (0.03 mg/kg-day; Moxon, 2003b).

Statement 4: *"A $BMDL_{10}$ of 2.1 mg/kg-day from the 28-day dermal study in rats was selected as the critical NOEL to evaluate dermal exposure for both short-term and steady-state exposures (Noakes, 2001)."*

Response: As described in Section III.C, OEHHA agrees with this determination.

Statement 5: *"A $BMDL_{10}$ of 0.42 µg/L (microgram/liter) from the 28-day inhalation study in rats was selected as the critical NOEL to evaluate inhalation exposure for workers and bystanders for all exposure durations (Blair, 2010)."*

> **Response:** OEHHA agrees with the selection of Blair (2010) as the critical study to evaluate inhalation exposure to dicrotophos. However, additional discussion on $BMDL_{10}$ and NOEL values is needed to explain the significance of the large difference between these values and issues with BMD model selection (see Detailed Comments in Section III.C).

Statement 6: "*DPR RAS concluded there was insufficient evidence to conduct a quantitative assessment for carcinogenicity based on the increase in thyroid tumors in male mice observed in a 105-week oral oncogenicity study (Milburn, 1998)."*

> **Response:** As described in Section III.E, OEHHA agrees with DPR's conclusion that there is insufficient evidence to conduct a quantitative cancer analysis. However, OEHHA suggests that the result from the genotoxicity study (Wu, 2010) be included in the genotoxicity potential evaluation.

B. Exposure Assessment

Statement 7: *"Dietary and drinking water exposure were evaluated using a deterministic approach with mean residues in cottonseed oil from field trial studies and a probabilistic approach with residues in finished drinking water from the PDP database, respectively."*

> **Response:** OEHHA generally agrees with the approaches taken for dietary exposure to dicrotophos. There are no California specific residue data or drinking water concentrations so OEHHA agrees with DPRs use of registrant submitted field trial residue data and PDP drinking water data. However, OEHHA suggests additional explanation of the percentiles chosen for the dietary and water exposure estimates and the combined exposure.

Statement 8: "*A mathematical approach in qualifying in vitro dermal absorption data for use in exposure assessment is being used for the first time. Since a peer review of this approach has not been performed, a level of uncertainty is cast upon the dermal exposure estimates."*

> **Response:** The complex mathematical approach that DPR used to estimate the dermal absorption of dicrotophos does not appear to be warranted because a more direct, transparent approach is available. OEHHA recommends that DPR utilize experimental data from an *in vivo* dermal absorption study of monocrotophos in human subjects (Feldmann and Maibach, 1974) to estimate the dermal absorption of dicrotophos. This alternative approach does not require interspecies extrapolation or appraisal of the validity of *in vitro* dermal absorption methods (as discussed under Section III.B).

Statement 9: **"***Worker exposure estimates were based on PHED surrogate data and do not consider newer available data.**"***

Response: As described in Section I, Summary of Review, OEHHA agrees that exposure estimates derived using PHED-based surrogate data for occupational handlers are reasonable. However, OEHHA is concerned with the continued reliance on PHED and suggests that DPR should begin supplementing PHED data with data from other sources whenever possible. OEHHA also recommends that DPR include or cite the specific PHED scenarios, data and calculations used to generate these exposure estimates to increase the transparency of the draft EAD.

Statement 10: *"Aerial concentrations of dicrotophos from groundboom applications cannot be estimated due to limitations in the AgDRIFT model."*

Response: OEHHA concurs with DPR that the AgDRIFT model cannot be used to estimate air concentrations resulting from groundboom applications. AgDRIFT uses deposition curves derived for ground applications based on measured values that bounded 50% or 90% of the data at each point. Since there is currently no other US EPA-approved method or model for estimating air concentrations near groundboom applications, OEHHA agrees that bystander aggregate exposure near groundboom-treated fields will likely be underestimated as the current DPR approach does not account for inhalation of spray drift or post-application volatilization (as discussed under Section III.G.2).

C. Risk Characterization

Statement 11: *"DPR RAS used 10% brain ChEI in rats as the critical toxicity endpoint for short-term and steady-state exposure to dicrotophos for all scenarios. Therefore, the target MOE was 100 assuming humans are 10-fold more sensitive than rats and there is a 10-fold variation in the sensitivity of the human population."*

Response: OEHHA generally recommends the use of a UF of 10 for interspecies extrapolation and a UF of 30 for intraspecies variability. OEHHA suggests a total UF of 300 for the general adult population. In the case of dicrotophos, OEHHA also supports an additional UF of 10 to protect against DNT because of the reported changes in brain weight and morphometry in pups exposed *in utero* (Brammer, 2003). If an additional 10-fold UF is applied to protect against DNT in the sensitive population, this would offer additional protection against both pharmacokinetic and pharmacodynamic variability in fetuses, infants and children, and the intraspecies UF could be reduced to 10 rather than 30. This would then result in a total UF of 1000 for the sensitive population. This is consistent with the approach taken by US EPA (2015a) in its recent assessment of dicrotophos. See detailed discussion under Sections III.D and III.E.

Statement 12: *"DPR RAS is considering the use of an additional uncertainty factor of 10 with dicrotophos to protect infants, children and women of child-bearing (age) from potential neurodevelopmental toxicity by non-ChEI mechanisms (US EPA, 2015b)."*

Response: As stated above, OEHHA recommends DPR apply an additional 10-fold UF to protect the sensitive population. This is supported by the findings of brain weight and morphometry changes in a DNT study of dicrotophos (Brammer, 2003) and consistent with US EPA's recommendation in the "Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides" (US EPA, 2015b). See detailed discussion under Sections III.D and F.

III. DETAILED COMMENTS

A. Introduction

Dicrotophos, dimethyl phosphate of 3-hydroxy N,N-dimethyl-cis-crotonamide (CAS 141-66-2, molecular formula $C_8H_{16}NO_5P$), is an organophosphate (OP) insecticide and cholinesterase inhibitor (ChEI). Dicrotophos is a liquid that is miscible in water with formulations intended for foliar application to cotton plants or as a micro-injection treatment for ornamental and non-food bearing trees. Commonly-used dicrotophos formulations have been registered under a variety of trade names, at various concentrations and sometimes as a mixture (EXTOXNET, 1996). The current application is the only one in California; it is a Special Local Need (SLN) label registration for BIDRIN®8 (82% dicrotophos) on cotton plants.

Dicrotophos was first registered by US EPA in 1964 and the interim reregistration eligibility decision (IRED) was signed in 2002. A revised human health risk assessment for dicrotophos was published by US EPA in 2015 (US EPA, 2015a). The last registered use of dicrotophos in California was in 1991 and it is not currently registered. This draft RCD represents the first risk assessment conducted by DPR on dicrotophos.

In this review of the draft RCD and draft EAD by OEHHA, the following sections present detailed discussion of OEHHA's answers to charge statements and principal comments presented in Sections I and II.

1. Physical and Chemical Properties, and Environmental Fate

Dicrotophos is highly water soluble, but is also soluble in some less polar solvents such as xylene. The draft SLN review does not mention that BIDRIN®8 is a mixture of two isomers with 85% in the form of the pesticidally-active E-isomer (US EPA, 2006). OEHHA recommends that DPR include additional information about the chemical and physical properties of dicrotophos, emphasizing its high water solubility and the bioactivity of the E-isomer.

No fate and transport information was provided in the draft RCD or draft EAD. Considerable data on dicrotophos stability, mobility and degradation exist and should have been included in this draft EAD. OEHHA recommends that DPR include additional information about dicrotophos such as its stability in water and soil, mobility in soil, and volatilization potential.

2. Pesticide Use and Sales

Under the proposed SLN Registration (24C) for dicrotophos use on cotton, a maximum application rate of 1 pound/acre/season is allowed during the "growth period" between first bloom and 30 days before harvest. The early stages of bloom development are considered the most susceptible period for stink bug damage (VCE, 2009). A recent

survey of dicrotophos use on cotton in the southern United States reported 1-2 applications per season (US EPA, 2014c), however the registrant states that it is not uncommon “to make four to six total insecticide applications due to stink bug migration into cotton” (AMVAC, 2014). OEHHA recommends that the draft EAD provide additional California-specific details about anticipated frequencies of aerial and ground application, as well as the anticipated seasonal use and timing of application.

3. Reported Illness

Dicrotophos has not been registered for use in California since 1991. For that reason, no cases of dicrotophos-related illness in agricultural workers have been reported in the state since that time. However, the National Institute of Occupational Safety and Health Sentinel Event Notification System for Occupational Risks (NIOSH SENSOR) program identified 26 cases of dicrotophos-related illness from 1999 to 2008 in other states (US EPA, 2012b). Ten of the 26 cases were exposed in a residential setting, with 9 of the 10 residential cases classified as bystander exposures resulting from spray drift from aerial applications of cotton. OEHHA recommends that the draft EAD discuss the NIOSH SENSOR data as it appears to validate DPR and OEHHA’s concern for the bystander spray drift exposure scenario.

B. Pharmacokinetics

The absorption, distribution, metabolism, and excretion of dicrotophos are relatively simple and adequately addressed in the draft RCD. Dicrotophos causes ChEI, an effect that does not require metabolic activation. Dicrotophos is also rapidly absorbed and extensively metabolized. While most of the metabolites are readily excreted, 3% is metabolized to monocrotophos, which has similar ChEI activity as the parent compound. Oral absorption efficiency was 94-97%. There were no studies on inhalation absorption so a default absorption rate of 100% was used. OEHHA agrees with this approach.

A dermal absorption factor to estimate systemic dose via dermal exposure was calculated using a new methodology based on *in vitro* and *in vivo* data. One registrant study provided *in vivo* rat data (Gledhill, 1999) and another evaluated both human and rat *in vitro* dermal absorption (Davies, 1999). In an appendix and supporting memorandum to the draft RCD, DPR described a procedure using data from these studies to calculate a 95% upper confidence level (UCL) of 26.3% that was used as the human dermal absorption rate (DPR, 2015b; DPR 2015c).

OEHHA is concerned about the quality of the *in vitro* rat and human studies and agrees with comments provided in the supporting memorandum, describing numerous shortcomings of the Davies study such as missing data points as well as a lack of procedural and technical details (DPR, 2015c). However, the memorandum did not mention whether the study also reported skin source, skin integrity or the presence of solvents and/or co-formulants. In evaluating these studies, OEHHA recommends that

the draft EAD discuss how the *in vitro* study design differs from OECD guidelines as well as any major confounding factors.

OEHHA is also concerned with the number and quality of references provided in the draft EAD. A two-page document, "NAFTA Dermal Absorption Group Position Paper on Use of *In Vitro* Dermal Absorption Data in Risk Assessment," was cited in Charge Statement #8 to support the approach that DPR used to analyze the available dermal absorption data for dicrotophos. The members of this working group were not identified, the document was unpublished and apparently not peer reviewed, and its release date was not indicated. In our opinion, these deficiencies undermine the utility of the NAFTA document for the exposure assessment and it should not be used.

OEHHA is concerned that a complex mathematical analysis was used to estimate the dermal absorption of dicrotophos in humans (DPR, 2015b; DPR 2015c). The analysis relied heavily on the results of the *in vitro* and *in vivo* dermal absorption of dicrotophos in rats – a species that often over-predicts transdermal absorption of chemicals in humans. Therefore, OEHHA recommends that DPR use data from a dermal exposure study of monocrotophos in humans (Feldmann and Maibach, 1974) to calculate an upper end estimate of the dermal absorption of dicrotophos.

This recommendation is based on the following considerations: (1) dicrotophos and monocrotophos have comparable molecular structures, differing from one another by a single methyl group; (2) both compounds have very similar values for water solubility and K_{OW} - parameters that are critical determinants of transdermal absorption; (3) the experimental subjects in the study were humans, so interspecies extrapolation is not required; (4) the site of skin application in the study (ventral forearm) is highly relevant to the anticipated site of exposure that pesticide handlers and cotton scouts are expected to experience; and (5) the authors of this report also determined the amount of test compound excreted in the urine following intravenous administration (100% absorption) to correct incomplete urinary excretion (Feldmann and Maibach, 1974).

Feldmann and Maibach (1974) reported that the dermal absorption of monocrotophos in six human subjects was 14.7± 7.1 (mean± SD) percent. Assuming these data are normally distributed, the 95th percentile estimate from the Feldmann data is 26% (calculated with the NORMINV function in Excel®). These results are consistent with the results of DPR's analysis that produced a 95% upper confidence limit of 26.3%, and they provide a more transparent basis for estimating dermal exposure to the pesticide in humans.

C. Non-cancer Toxicity Endpoint and Dose-Response Analysis

No human toxicity studies were described in the draft RCD, and DPR chose to evaluate brain ChEI from laboratory animal studies for deriving PODs for dicrotophos for acute and steady state exposure durations. OEHHA agrees with this general approach, with the exception for the DNT study (Brammer, 2003). A variety of clinical signs of neurotoxicity were also observed in the animal studies but mostly occurred at higher

doses than the dose for ChEI. Furthermore, brain ChEI data in the animal studies are extensive and allow for comparison across multiple life stages, as well as exposure routes and durations.

Compared to previous RCDs, this draft RCD included only a brief hazard identification section highlighting the lowest- and no-observable effect levels (LOEL/NOELs) and BMD/BMDLs from available studies. Because of the limited scope of this draft RCD (SLN use on cotton only) and the decision to only evaluate brain ChEI as the critical endpoint, a complete toxicological profile was not provided. OEHHA agrees with this approach but suggests providing more details on the critical studies.

In agreement with the approach used in this draft RCD, OEHHA advocates the use of the BMD modelling over the LOEL/NOEL approach. Brain ChEI in the animal studies for dicrotophos generally showed good dose-response relationship with sufficient number of animals to permit BMD modeling. One of the major differences in the BMD analyses done by DPR and that done by US EPA for the risk assessment of dicrotophos (US EPA, 2015a) was the inclusion of the Hill model in addition to the exponential models, the only model type used by US EPA for ChEI data. OEHHA agrees with DPR in including the Hill model in the BMD analyses and not relying only on exponential models. Our opinion is that we should select the model that most accurately describes the data. In many cases in the draft RCD, the Hill model provided a substantially better fit (higher Test 4 p values) and thus should be included.

In the DPR's BMD analyses for the POD selection, there were instances where one or more of the tests had non-significant p values yet the information was not provided in the draft RCD. For transparency, OEHHA suggests DPR include the selected models for each study/endpoint and the model output results, such as p values, Akaike information criteria (AICs), and scaled residuals. For endpoints that failed one or more of the tests, OEHHA also suggests that the BMD/BMDL values should be included in the summary tables (Tables 3-5 in the draft RCD) for comparison purposes. However, only those models with significant p values that meet all the criteria for model selection should be selected for PODs. Reasons for selecting a specific model over others should also be provided in the draft RCD. Complete BMD model outputs for the critical endpoints may also be included in the appendices.

1. Acute Oral Exposure

For acute oral exposure, DPR chose a $BMDL_{10}$ of 0.03 mg/kg-day for brain ChEI in PND8 male rats as the acute oral POD (Moxon, 2003a). In this acute ChEI study, pre-weaning rats at PND8, 15 and 22 (5 pups/sex) were dosed with 0, 0.1, 0.3, 1 and 5 mg/kg dicrotophos by gavage and assessed for brain and red blood cell ChEI 2 hours after dosing. There was no clear NOEL for this study. PND8 males, PND15 males and females, and PND22 females all had ChEI even at the lowest dose (i.e., indicating a NOEL of <0.1 mg/kg-day). BMD analysis of brain ChEI data resulted in a range of $BMDL_{10}$s of 0.03 (PND8) to 0.13 (PND22) mg/kg-day. The Hill model for male PND8 brain ChEI had the lowest $BMDL_{10}$ from the acute/short-term database (0.03 mg/kg-

day), provided good model fit and met all the criteria for BMD model selection. Applying a UF of 3 to extrapolate from the lowest LOEL of 0.1 mg/kg-day to NOEL would also result in an estimated POD of 0.03 mg/kg-day, adding confidence to the $BMDL_{10}$ determination.

DPR applied the acute oral POD of 0.03 mg/kg-day to both the general adult population and sensitive population. OEHHA agrees with the application of this POD.

2. Steady-State Oral Exposure

DPR selected a $BMDL_{10}$ of 0.025 mg/kg-day for brain ChEI from a subchronic neurotoxicity study in adult female rats as the steady-state oral POD (Horner, 1995). In this 90-day neurotoxicity study, adult Alpk:APfSD rats (12/sex/dose) were fed 0, 0.5, 5 or 25 ppm dicrotophos in the diet for 13 weeks and assessed for ChEI, functional observation battery (FOB) and motor activity. Satellite groups of 6 animals/sex/dose were also assayed at 5 and 9 weeks for the same endpoints. Average doses were calculated as 0, 0.04, 0.39, and 2.03 mg/kg-day for males and 0, 0.04, 0.45, and 23.8 mg/kg-day for females. There were significant reductions in brain ChEI at all doses tested. The consistency in $BMDL_{10}$ values in females measured after 5, 9 and 13[1] weeks of exposure demonstrates ChEI had reached a steady-state at 5 weeks. The $BMDL_{10}$s for males in the study are slightly higher but ChEI also reached a steady-state following 5 or more weeks of treatment. The NOEL from the study was <0.04 mg/kg-day. BMD analyses of brain ChEI resulted in $BMDL_{10}$s of 0.025 for females and 0.031-0.036 for males. The draft RCD chose 0.025 mg/kg-day as the POD for steady-state oral exposure.

It should be noted there is a study with bolus dosing which indicates lower BMDLs (0.005 mg/kg-day for females and 0.015 mg/kg-day for males) than the POD selected. In this study, 10 adult rats/sex/group were dosed with 0, 0.008, 0.02 or 0.4 mg/kg-day dicrotophos by gavage for 28 days (Brammer, 2002). NOELs from this study based on brain ChEI were 0.02 and 0.008 mg/kg-day for males and females, respectively. Corresponding $BMDL_{10}$s were 0.015 (males) and 0.008 mg/kg-day (females). While these were lower than the BMDLs from Horner (1995), DPR did not select the POD from this study because of the concern on the route of administration. OEHHA agrees that bolus dosing resulting from gavage administration could cause greater ChEI than occurring from dietary or drinking water exposure, and that a dietary study would better represent the human exposures evaluated in the draft EAD.

3. Inhalation Exposure

There was one inhalation toxicity study for dicrotophos in the database appropriate for risk assessment. In this study, 10 Crl:CD rats/sex/group were exposed to 0, 0.097, 0.73 or 2.9 µg/L dicrotophos by nose only inhalation for 6 hours/day, 5 days per week for 4 weeks (Blair, 2010). Brain ChEI was the most notable adverse effect and was

[1] ChE activity was measured on Week 14.

significant at all doses in females and at 0.73 and 2.9 µg/L in males. Other effects included a decrease in mean reticulocytes and atrophy of the seminiferous tubules in males at 2.9 µg/L. DPR chose an average $BMDL_{10}$ of 0.42 µg/L from the male and female datasets as the POD to evaluate inhalation exposure for workers and bystanders for all exposure durations (Blair, 2010).

OEHHA has concerns regarding the BMD model selection and recommends additional discussion on the differences between NOEL/BMDL and justification for choosing a higher POD. As shown in the following table (Table 1) using information from Table 4 of the draft RCD, the NOELs for the study were 0.097 µg/L for males and <0.097 µg/L for females. The lack of a NOEL for females was due to a statistically significant reduction of brain ChE in females at the lowest dose tested.

Table 1. Brain ChEI from a 28-day inhalation toxicity study in rats (Blair, 2010).

	Brain Acetylcholinesterase Activity (percent inhibition in parentheses)				**Values from Table 4 (draft RCD)**	
Dose (µg/L)	0	0.097	0.73	2.9	NOEL (µg/L)	$BMDL_{10}$ (µg/L)
Males	23.32	23.29 (0)	20.67* (11)	15.16* (35)	0.097	0.43
Females	24.43	22.84** (7)	20.68* (15)	15.09* (38)	n/a	0.41

* p<0.001 **p<0.05

note: $BMDL_{10}$ for males is 0.652 mg/kg-day when modeled with non-constant variance.

While the biological significance of a 7% reduction in ChEI is unclear, the calculated $BMDL_{10}$ of 0.41 µg/L for females was over 4 times higher than the LOEL for females (0.097 µg/L). The BMD model selected for females also failed tests 3 and 4[2] in BMD analysis and the result is not recommended for use based on BMD model selection criteria. The $BMDL_{10}$ of 0.43 µg/L for the male rat was also over four times higher than the NOEL for males (0.097 µg/L). And the model selected for males also failed test 3 in BMD modeling. When modeled without constant variance, both the exponential M2 and M3 models have significant p values for all tests and the $BMDL_{10}$ is 0.652 µg/L, over 6 times higher than the NOEL for males. For this dataset, the NOEL/LOEL approach is appropriate. OEHHA recommends applying an UF factor of 3 to extrapolate from LOEL to NOEL, resulting in an estimated NOEL of 0.032 µg/L for females from the Blair (2010) study. Because inhalation is a major route of exposure and this is the only inhalation study to consider, additional discussion of these differences in PODs and consideration of a lower POD is warranted.

[2] Test 3 is a test to determine whether the variances are adequately modeled. Test 4 is a test on model fit of the data. From BMD software v.2.6 (US EPA)

The same subchronic inhalation toxicity study and POD was used to evaluate both short-term and seasonal inhalation exposure. For dicrotophos, OEHHA agrees that an acute exposure by the same route would likely result in a higher NOEL or POD (as is the case for oral toxicity studies) and thus using a subchronic POD to evaluate acute exposure is health-protective.

DPR assumed 100% absorption of dicrotophos by the inhalation route and a default rat breathing rate of 40 liters per hour (L/hr). In the absence of data to indicate otherwise, OEHHA agrees with the default absorption rate. The default rat inhalation rate of 40 liters per kilogram body weight-hour (L/kg-hr) is consistent with the inhalation rate calculated by US EPA for dicrotophos (43.5 L/kg-hr; US EPA, 2015a) 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 43 L/kg-hr). The slightly lower breathing rate calculated by DPR is likely due to a slightly different default rat body weight applied in the calculation.

4. Dermal Exposure

There was only one dermal toxicity study which measured brain ChEI and was appropriate for assessing acute and steady-state dermal exposure. In Noakes (2001), the skin of 15 Crl:CD rats/sex/dose were treated with 0, 2, 5, 10 or 80 mg/kg-day dicrotophos for 6 hours/day, 5 days/week for 4 weeks. ChEI (brain, plasma, and RBC) was the only treatment-related effect other than erythema in females. The subchronic dermal NOEL from the study was 5 mg/kg-day in both males and females. Calculated $BMDL_{10}$s for brain ChEI were 3.50 mg/kg-day for males and 2.13 mg/kg-day for females.

OEHHA agrees with the selection of Noakes, 2001 as the critical study to evaluate dermal exposure to dicrotophos. Because females had a lower $BMDL_{10}$, significant p value for Test 4, and a better visual fit of the data, OEHHA agrees with the selection of the $BMDL_{10}$ of 2.1 mg/kg-day as the critical POD. Note that the p value for males is not significant for Test 4 (model fit) and for females is not significant for Test 3 (model variance). This should be indicated in the summary table (Table 5 from the draft RCD) or in a separate table summarizing the outputs for the chosen models.

Similar to the case for inhalation exposure, OEHHA agrees with the use of a POD from a subchronic dermal toxicity for acute dermal exposure.

D. Reproductive and Developmental Toxicity

Dicrotophos was tested for reproductive toxicity in a multi-generation study in rats. Moxon (1997) treated 26 Wistar rats/sex/group (F_0 generation) with 0, 0.5, 5.0 or 25 ppm in the diet from 10 weeks before mating until 4 weeks of lactation. There was high mortality in the offspring from the high dose group in the F_1 generation, so the high dose was reduced to 10 ppm. The parental generations mainly had effects on body weights

and clinical signs of toxicity at 25/10 and 5 ppm. There was reduced pup viability at 5 ppm in both F_1 and F_2 generations. Both the parental and the developmental NOELs were 0.5 ppm for the study, which equated to approximately 0.05 mg/kg-day. While these are higher than the PODs chosen for the steady-state oral exposure, the toxicity data from this study demonstrate there is a concern for toxicity in young animals at low doses not mediated through the ChEI mechanism.

There are two developmental toxicity studies for dicrotophos, one in Sprague-Dawley rats (Rodwell, 1986) and one in New Zealand White rabbits (Moxon, 2001). In the first study, 25 mated female Sprague-Dawley rats/sex/group were treated with 0, 0.1, 0.5, 1.0 or 2.0 mg/kg-day dicrotophos by gavage from gestational day (GD) 6 to GD15. In the other study, 28 mated female New Zealand White rabbits were treated with 0, 0.5, 1.0, or 2.0 mg/kg-day dicrotophos by gavage from GD5 to GD29. Body weights, clinical signs, and litter outcomes were measured in each species. In both studies, developmental NOELs (2.0 and 1.0 mg/kg-day for rats and rabbits, respectively) were higher than maternal NOELs (0.5 mg/kg-day for both species) and developmental toxicity was not indicated in the rat study.

There is one DNT animal study in the dicrotophos database. Brammer (2003) dosed 30 time-mated female Wistar rats per group with 0, 0.01, 0.05, and 0.4 mg/kg-day of dicrotophos by gavage from GD7 to postpartum day 7. Pups were also dosed from PND8 to PND22. Neurotoxicity was assessed by FOB, motor activity measurements, and brain histopathology. There were no significant effects on Functional Observational Battery (FOB) or motor activity in male and female offspring. However, there were statistically significant increases in absolute brain weights of female pups at 12 days after birth at all dose groups tested. Brain weights were also assessed by analysis of covariance on final body weight by study authors. When adjusted for final body weight, brain weights were statistically increased at the highest dose, 0.4 mg/kg-day. This statistical approach is consistent with recommendations in the open literature for optimum organ weight analyses (Bailey at al., 2004).

There were also statistically significant changes in various brain morphometric measurements at 0.4 mg/kg-day, the only treated group examined, when the brains were examined on PND 12 and 63. At day 12, male pup brains exhibited significantly decreased frontal cortex height and width, while female pup brains had significantly decreased thickness of the dorsal cortex and increases in multiple measurements of the hippocampus. At day 63, male brains had decreased thalamus/cortex overall width while female brains only had decreased width of the thalamus. Females also had decreased hypothalamus length from the midline.

In the draft RCD, this study was presented only by the NOEL of 0.4 mg/kg-day and a notation of “No adverse effects” in Table 4 (page 10; DPR, 2015d). DPR stated in their Summary of Toxicological Data for dicrotophos (DPR, 2015d) that there were no consistent effects on brain structure and established the maternal and developmental NOELs at the highest dose tested (0.4 mg/kg-day). On the other hand, US EPA

established a developmental No-Observed-Adverse-Effect Level (LOAEL) of 0.05 mg/kg-day for changes noted in the brain at 0.4 mg/kg-day (US EPA, 2015a).

OEHHA believes that the effects on the brain are important and they were not adequately analyzed in the draft RCD. The brains of PND12 female rats showed the most significant changes and their results are summarized in Table 2. Absolute brain weight is statistically significant for PND12 females at 0.01 mg/kg-day. The absolute brain weight data were not amenable to BMD modeling. Based on statistical significance of increased absolute brain weight in females at the lowest dose tested, there was no clear NOEL from the study. OEHHA's practice is to apply a UF of up to 10-fold to extrapolate from LOEL to NOEL. In this case a factor of 3 seemed sufficient since the dose-response relationship is shallow with only a 2-fold increase (105% to 109% of control) over a 40-fold dose range (from 0.01 to 0.4 mg/kg-day). Furthermore, while increases in brain weight resulting from *in utero* exposures to dicrotophos are concerning, the toxicological significance at this magnitude of change is unclear. Applying a 3-fold UF factor would result in an estimated NOEL of 0.003 mg/kg-day for this endpoint. OEHHA suggests that DPR re-examine the results of this study in determining the oral POD for the sensitive population and in considering the need for an additional UF to protect against DNT (see Section III.F.2.c).

Table 2. Female rat brain weight and morphometric measurements on in F1 generation on day 12 (Brammer, 2003).

Females – Day 12	Dose (mg/kg-day)			
	0	0.01	0.05	0.4
Terminal body weight (g)	21.0±3.1	22.4±2.4	24.0±2.6	24.1±3.1
Brain weights				
Brain weight (g) % of control	1.03±0.08	1.08±0.07* 105%	1.09±0.04* 106%	1.12±0.05** 109%
Brain weight to body weight ratio (%)	4.95±0.45	4.86±0.33	4.59±0.44	4.72±0.48
Brain weight adjusted for body weight	1.09	1.09	1.07	1.10*
Brain morphology (in millimeters)				
Level 3 -dorsal cortex 1 – thickness	1.42±0.09	NA	NA	1.33±0.12*
Level 4 – hippocampus – width dentate gyrus	0.49±0.05	NA	NA	0.53±0.03*
Level 4 – hippocampus – length dentate gyrus	1.30±0.06	NA	NA	1.39±0.13*
Level 5 – hippocampus – width dentate gyrus	0.70±0.10	NA	NA	0.77±0.05*
Level 5 – hippocampus – width overall	1.33±0.13			1.43±0.07*

* p<0.05,** p<0.01. All values are mean± standard deviation with N=11 animals. NA=not available because the brains were not examined.

E. Carcinogenicity Weight of Evidence

1. Genotoxicity

Dicrotophos was positive for mutagenicity in a mouse lymphoma forward mutation assay with and without metabolic activation (San and Clark, 1995). Dicrotophos was negative in other guideline genotoxicity assays. However, positive results were reported by Wu et al. (2010) for chromosome aberrations in CHO-K1 cells and DNA damage in comet assay for HEPG2 cells. Also, structurally similar monocrotophos, a metabolite of dicrotophos, showed positive genotoxicity evidence (DPR, 2015d). In the draft RCD, DPR stated there is "no strong evidence of genotoxicity." While the registrant submitted studies were only weakly indicative of genotoxicity, the study by Wu et al. (2010) demonstrated the genotoxic potential of dicrotophos. OEHHA suggests DPR include an evaluation Wu et al. (2010), and any other relevant open literature studies for a more thorough evaluation and a greater concern for the genotoxicity potential of dicrotophos.

2. Human and Experimental Animal Evidence

There are no human data on the carcinogenic potential of dicrotophos. DPR reviewed two chronic laboratory animal studies in two species for evidence of carcinogenicity of dicrotophos. There was no evidence of tumors in rats (Fifty two Alpk:APfSD rats/sex/dose) fed 0, 0.5, 5.0, or 25 ppm dicrotophos in the diet for 2 years (Allen, 1998).

There was, however, a dose-related increase in follicular cell adenomas of the thyroid gland (Table 3) in a study with mice (55 C57BL/10JfCD-1 Alpk mice/sex/dose) fed dicrotophos in their diet at 0, 5, 10 or 50 ppm, for 105 weeks (Milburn, 1998). The doses were equivalent to 0, 0.02, 0.25 and 1.42 mg/kg-day for males and 0, 0.03, 0.32, and 1.74 mg/kg-day for females. The increase of the follicular cell adenomas in male mice was statistically significant by trend analysis ($p < 0.01$) and by pairwise comparison ($p<0.05$). These tumors were found at the study termination (105 weeks). Male mice also had a minimal increase in follicular epithelial hyperplasia of the thyroid gland at the high dose. Two of the high dose males had both hyperplasia and adenoma. Historical control incidence of thyroid adenoma was low (range from 0% to 3.4% from 1984 to 1996). This study did not measure thyroid hormone levels and provided no information on the mode of action. Female mice in this study did not show a significant increase in these tumors or any other tumors, but they did have a reduced survival rate which could have affected the results. Females had a dose dependent increase in mortality after 1 year, with the high dose group having the greatest early mortality. Mortality in the males was unaffected by dicrotophos treatment but was in excess of 40% for all dose groups, including the controls. There is no evidence of thyroid effects in the database.

Table 3. Thyroid lesion incidences in 2 year dietary study in mice (Milburn, 1998).

	Male				Female			
Dose (mg/kg-day)	0	0.02	0.25	1.42	0	0.03	0.32	1.74
Animals on study	55	56	55	55	55	55	55	55
Animals surviving to termination	31	33	31	31	30	33	21	14
Thyroid lesion for in animals at terminal sacrifice								
Examined	31	33	29	27	30	33	20	13
Missing	0	0	2	4	0	0	1	1
Follicular Cell Adenoma (Benign)	0++	0	1	5*	1	2	2	0
Thyroid hyperplasia	1+	1	1	4	0	1	1	1
Thyroid lesion for all animals in study								
Examined	54	53	53	49	54	53	49	52
Missing	1	2	2	6	1	2	6	3
Follicular Cell Adenoma (Benign)	0++	0	1	5*	1	3	3	0

*p<0.05 by Fisher Exact test; ++ p<0.01 or + p<0.05 by trend analysis

3. Other Evidence

Dicrotophos is structurally similar to monocrotophos, another OP insecticide. DPR reviewed the oncogenicity studies of monocrotophos and found no evidence of tumors in mouse or rat bioassays. There was minimal positive genotoxicity evidence (positive reverse mutation assay, forward mutation assay as well as few *in vitro* assays for DNA damage) but none met US EPA's current guidelines for genotoxicity assays.

DPR also reviewed ToxCast™ data for dicrotophos in the draft RCD. There were positive assays suggesting some upregulated inflammatory responses, effects on one of the cytochromes (Cyp2C19), human butylcholinesterase, and an estrogen response element. While the inflammatory responses and effects on Cyp2C19 could be involved in the increased incidence of thyroid tumors, DPR concluded that the limited evidence did not support determining dicrotophos as a carcinogen. OEHHA concurs with DPR on this determination.

4. Potency Determination Approach

OEHHA agrees with DPR that there is insufficient *in vivo* evidence to derive a cancer potency.

F. Extrapolation, Variability, and Uncertainty

1. Duration Extrapolation

For the oral exposure scenario, no extrapolation for length of exposure was necessary. DPR chose a POD from an acute oral toxicity study (Moxon, 2003a) and no extrapolations for length of exposure were necessary. For steady-state oral exposure, DPR selected a POD from a 90-day dietary (subchronic) study. The selected $BMDL_{10}$ of 0.025 mg/kg/day was the same $BMDL_{10}$ calculated for females at 5, 9 and 14 weeks in the study, suggesting that ChEI reaches steady-state following subchronic exposure.

As previously discussed, for inhalation and dermal exposure scenarios, POD from the respective route subchronic toxicity studies were used to evaluate both acute and steady-state exposures for bystanders and short-term and seasonal exposure for workers/handlers. For dicrotophos, OEHHA agrees that an acute exposure by the same route would likely result in a higher NOEL or POD and thus using a subchronic POD to evaluate acute exposure is health-protective.

2. Uncertainty Factors

a. Interspecies Extrapolation

OEHHA supports DPR's use of an interspecies UF of 10 because all PODs were derived from laboratory animal studies.

b. Intraspecies Extrapolation

In the draft RCD, an intraspecies UF of 10-fold was applied to account for pharmacokinetic and pharmacodynamics differences within the human population. OEHHA recommends that this factor be increased to 30 (total of 10 for pharmacokinetics and √10 for pharmacodynamics). For non-cancer effects, OEHHA's view is that there are many factors affecting human variability in response to a chemical exposure (OEHHA, 2008; Zeise et al. 2013). Thus, based on analyses of human pharmacokinetic variability, OEHHA's practice is to increase the traditional intraspecies pharmacokinetic UF of √10 to 10 (OEHHA, 2008). This increase would account for the wide variability in pharmacokinetics in the population, especially among subpopulations such as infants and children, pregnant women, and the elderly. However, if an additional 10-fold UF is applied to protect against DNT in the sensitive population, this additional UF would offer additional protection against both pharmacokinetic and pharmacodynamic variability in fetuses, infants and children. Thus, in this case, a total intraspecies UF of 10 for intraspecies pharmacodynamic and pharmacokinetic variability, in combination with the additional UF of 10 for DNT, would be sufficient.

c. Additional Uncertainty Factor

Dicrotophos is a known neurotoxicant and can potentially cause developmental neurobehavioral effects. The DNT animal study by Brammer (2003) showed significant effects in the brain of female pups at the lowest dose tested, 0.01 mg/kg-day (Table 3, Section III.D). While there were no FOB effects measured in the study, it is unknown if the brain changes observed could potentially cause long-term neurobehavioral changes.

OEHHA concurs with US EPA on their concerns about developmental neurotoxicity. US EPA published a systematic literature review on the neurodevelopmental toxicity of OPs supporting a policy decision to apply an additional 10-fold FQPA safety factor to human risk assessments for all OPs (US EPA, 2015b). The basis for their concern were *in vivo* laboratory studies demonstrating long term behavioral effects from early life exposures as well as multiple human epidemiology studies showing associations between OP exposure and developmental neurobehavioral effects in young children. US EPA determined that there was sufficient uncertainty regarding the mode of action and the human dose response relationship of OPs and DNT to support the 10-fold UF. They applied this additional UF in their risk assessment for dicrotophos (US EPA, 2015a).

OEHHA agrees that brain ChEI is a preferable endpoint for deriving a POD than a small, albeit statistically significant increase in absolute brain weight (Brammer, 2003). However, the effects on brain weight and morphometric measurements from the Brammer study heightened the concern on DNT. Therefore, OEHHA suggests that DPR apply an additional 10-fold UF to protect against DNT in the sensitive population.

G. Worker and Bystander Exposure Assessment

1. Occupational Exposure Scenarios

a. Handlers

Acute and seasonal occupational handler (applicators, mixer/loaders, flaggers) exposures were estimated via the PHED. Based on monitoring study data, PHED provides generic exposure estimates for specific uses which are not chemical-specific. A major underlying assumption for these estimates is that worker exposure is primarily a function of the formulation type and the handling activities (e.g., packaging type, mixing/loading/application method or clothing scenario), rather than chemical-specific properties.

Since 2011, US EPA has replaced PHED with the Occupational Pesticide Handler Unit Exposure Surrogate Reference Table (OPHUESRT), which combines PHED point estimates with additional data from industry sources (US EPA, 2015c). However, DPR defines PHED-derived exposure estimates as the 90% UCL on the 95th percentile for short-term exposure and the 90% UCL on the arithmetic mean for intermediate- and long-term exposures. A known effective sample size is required to calculate both the 95^{th} percentile and 90% UCL (DPR, 2007), and these data are not included in OPHUESRT.

OEHHA concurs with DPR's approach to calculating acute and long-term exposure estimates and agrees that exposure estimates based on PHED data are reasonable.

OEHHA is concerned with the continued reliance on PHED due to its acknowledged shortcomings. OEHHA commends DPR's decision to review newer studies included in OPHUESRT for use in later EADs.

OEHHA recommends DPR identify the specific PHED scenarios used in this draft EAD to provide additional transparency to the analysis and consider including both PHED data and related calculations as a separate appendix. Recent draft EADs included all this information in a separate appendix instead of simply citing a memorandum containing all PHED scenarios.

b. Reentry Workers

Although hand weeding and thinning activities may also result in potential reentry worker exposure, cotton scouting is considered a crucial factor in limiting crop losses. Scouts handle and collect samples as frequently as twice a week (UGA, 2015). For dicrotophos, the current reentry interval (REI) is 6 days, the pre-harvest interval (PHI) is 30 days and the minimum application interval between applications is 14 days. Short-term dermal exposure estimates for cotton scouts assumed that reentry occurred no earlier than 6 days post-application based on the REI. Seasonal exposure was based on a DFR calculated for 13 days post-application (REI + 7 days).

OEHHA is concerned that DPR evaluated the cotton scouting scenario only at or after the 6-day post-application REI and did not consider exposure that may occur earlier. Some cotton industry guidance states that fields should be scouted every 5-7 days and that some scouts may inspect twice a week (UGA, 2015: Monk et al., 2012; Bacheler, 2012). Within the REI, cotton scouts would be required to use personal protective equipment (PPE) but the DFR would be expected to be higher. OEHHA recommends that DPR provide acute and seasonal estimates of cotton scout exposure, assuming a reasonable frequency of post-application re-entry prior to expiration of the REI.

DPR selected a DFR from a Texas field study (Prochaska, 1998) due to concerns about rainfall impacting study results. OEHHA concurs with the choice of the Texas study data for DFR estimation.

DPR used a TC of 2000 cm^2/hr derived from studies of cotton scouts based on dermal exposure to three organophosphate pesticides (DPR, 1990), when estimating dicrotophos dermal exposure. OEHHA is concerned that the TC used in the draft EAD, while more health-protective than the value used by US EPA (US EPA, 2013b), may still lead to underestimation of dermal exposure.

Instead of using a TC derived from an analysis of three different pesticides, OEHHA recommends that DPR consider applying a TC derived with only the monocrotophos data, found in the same analysis cited in the draft EAD (DPR, 1990). Monocrotophos is a structural analog of dicrotophos, and the chemical and physical properties of these

two compounds are very similar. OEHHA has determined that if the TC was based only on the monocrotophos data, the estimated exposure for cotton scouts would increase by 2.3-fold above the exposure estimate calculated in the draft EAD (Table 4).

Table 4. Mean dermal transfer coefficients (TC) for cotton scouts by body part.

	Mean TC (cm^2/hr) from 3 pesticides** (DPR, 1990)	**Mean TC (cm^2/hr) Monocrotophos data** (DPR, 1990)
Bare Hands	950	1824
Upper Body*	102	983
Lower Body*	964	1757
Total TC	**2016**	**4564**

* Includes 90% protection factor, TC= transfer coefficient

** The three pesticides are monocrotophos, ethyl parathion, and methyl parathion.

2. Residential Exposure of Adults and Children to Spray Drift

A major area of concern in this draft EAD and recent US EPA guidance is the off-target drift and deposition of dicrotophos onto residential or public areas with the potential for direct and indirect exposure of adults and children (US EPA, 2013a; US EPA, 2014a; US EPA, 2014b).

In spray drift-specific guidance, US EPA stated that "for regulatory purposes… this document focuses on compliant application events. In compliant application events no individual should be directly sprayed, given existing label language and requirements for worker protection, which means direct dermal and inhalation exposures to sprays will not be considered" (US EPA, 2013a). DPR's rationale differed from that of US EPA in that DPR chose to estimate direct inhalation exposure when it was possible to do so (for aerial applications). OEHHA supports DPR's decision and suggests the draft EAD discuss the rationale for including estimates of direct inhalation exposure.

In the draft EAD, specific inputs such as meteorological conditions and field size were used to give the highest deposition and air concentration estimates for spray drift under California conditions. OEHHA concurs with DPR's use of these "worst-case" assumptions in estimating dicrotophos exposure from spray drift.

DPR chose two sentinel populations: Children 1-2 years of age and adults. DPR employed the modified US EPA Standard Operating Procedure for Residential Pesticide Exposure Assessment (US EPA, 2013a) in estimating the residential exposure to spray drift. OEHHA concurs with these choices.

Recently, US EPA released a preliminary screening level analysis for bystander exposure to volatilized conventional pesticides and dicrotophos was shown to exceed

the concentration of concern for the cole crop scenario at all field sizes (US EPA, 2014e).

OEHHA is concerned about this additional exposure pathway for residential bystanders, particularly since dicrotophos use will occur during the warmest months of the year in the three Southern California counties where dicrotophos use is being proposed. OEHHA recommends that DPR discuss whether inhalation of dicrotophos vapor would contribute materially to the aggregate exposure for residential bystanders.

a. Spray Drift Exposure Estimates from Aerial Applications

The AGDISP model, which tracks droplets and adjusts for turbulence, evaporation and weather conditions (Teske et al., 2002), was used to calculate all inhalation and deposition estimates for adults and children near aerial application sites. Estimates were generated for two application rates and two types of aircraft. Details of the application input parameters used in the draft EAD can be found in a separate memorandum (DPR, 2015a) and closely match those found in draft US EPA guidance documents (US EPA, 2013a: US EPA, 2014f).

The AGDISP software used in the draft EAD differs functionally from the AgDRIFT software used in the US EPA 2014 dicrotophos exposure assessment. AgDRIFT algorithms were designed primarily to model the motion of large droplet distributions (US EPA, 2014b; Teske et al., 2009). Recent versions of AGDISP incorporate updated algorithms that more accurately predict fine droplet motion, resulting in greater near field (< 400m) deposition and a decrease in far field (> 400 m) deposition (Teske et al., 2009).

OEHHA concurs with DPR's aerial spray drift model selection, input parameters and the resulting exposure estimates.

b. Spray Drift Exposure Estimates from Ground Applications

Only indirect dermal and oral exposures were estimated for ground applications. Since the AgDRIFT groundboom module is based entirely on field study data to predict spray drift deposition, it is not able to estimate air concentrations (Teske et al., 2002).

As described in a supporting memorandum, DPR used two boom heights, a fine-to-medium/coarse droplet spectrum distribution and the 50th percentile options in estimating exposure. The rationale stated by DPR for choosing the 50th percentile was to "maintain uniformity with orchard airblast" and the "derivation of the 90th percentile is not clear" and the AgDRIFT documentation provided insufficient mathematical detail (DPR, 2015a).

OEHHA is concerned about the choice of input parameters for estimating groundboom-related spray drift deposition. The US EPA chose more conservative options (fine to very fine spray inputs and outputs based on the 90th percentile deposition curve) in their exposure assessment (US EPA, 2014b) that resulted in risk estimates for children at

distances of 50 feet or less, while the DPR analysis found only exposures of concern at 25 feet.

OEHHA agrees that the AgDRIFT user manual does not fully document the calculation of the 90th percentile estimates for groundboom. However, it does contain the curve-fitting formula and curve shape parameters used in the data analysis (Teske et al., 2003). Both the AgDRIFT user manual, and the 1999 background document for the FIFRA SAP review of the AGDRIFT groundboom module indicate that these deposition curves were based on the measured values that bounded either 50% or 90% of the data at each distance (Teske et al., 2003; US EPA, 1999a).

OEHHA recommends that DPR provide additional rationale for these choices and cite any additional references which would support the use of the medium/coarse droplet size distribution. OEHHA also recommends that DPR use the more conservative 90th percentile output option as the ground application deposition algorithms were evidently based on measured values that bounded the data at each point (US EPA, 1999a; US EPA, 1999b; Teske et al., 2003).

The draft EAD states that "studies showed that the ambient air concentrations of other organophosphates (e.g., chlorpyrifos) measured after a ground-based application could be similar (within a factor of ~2) to the simulated values from an aerial application of chlorpyrifos (CARB, 1998)." The cited chlorpyrifos field study data appear to be from an airblast application at an orange grove at an application rate of 6 pounds AI/acre.

OEHHA is concerned with the apparent lack of approved methodology available for estimating air concentrations for nearby groundboom applications. If inhalation exposure from groundboom was roughly estimated as 25-50% of the estimated aerial inhalation exposure, then the aggregate dose would be larger for some of the groundboom exposure scenarios.

OEHHA recommends that DPR provide a comparison of estimates or range of estimates from both simulated and field study sources to further clarify this point. OEHHA also recommends that DPR consider using AGDISP or other methods to estimate air concentrations for nearby ground applications. A recent study demonstrated that AGDISP v8.27 air concentration estimates closely approximated measured concentrations from application site air sampling data (Nsibande et al., 2015), while a box model approach may not be suitable for this exposure scenario (US EPA, 2014d).

3. Other Non-occupational Exposure Scenarios Not Addressed in the Draft EAD

Exposure to "take home" indoor dust was not addressed by the draft EAD. Homeowners, farmworkers, and their families may be exposed to dicrotophos 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; Quirós-Alcalá et al., 2011). OEHHA recommends that "take home" dust exposure be discussed in the draft EAD.

H. Dietary Exposure Assessment

The dietary exposure assessment was included in the main body of the draft RCD. The analysis included acute and steady-state exposures to dicrotophos in food, drinking water, and combined exposures. Exposure estimates included subgroups of the population segregated out by age, sex, and workers status.

There are only two tolerances established for dicrotophos residues in food, cottonseed (0.2 ppm) and cotton gin by-products (2 ppm). Exposures were calculated based on a residue value for cottonseed oil, the only food product consumed by people resulting from dicrotophos treatment of the cotton plant.

1. Residue Data

a. Food Residues

DPR used cottonseed residue data from two registrant submitted studies (Prochaska, 1998a; Prochaska, 1998b). One study analyzed raw commodities (undelinted cottonseed and cotton gin by-products) while the other study analyzed the processed cotton products (refined cottonseed oil, meal, and hulls). The studies were not described in detail in the draft RCD. It is unclear which commodities, or if all commodities had residues and what the residues were. DPR stated that the two studies gave an average of 0.0367 ppm for cottonseed oil (the end product consumed by humans) and used this value in acute and steady-state dietary exposure. However, only one of the two residue studies are described as including cottonseed oil among the commodities analyzed. OEHHA questions the approach used in calculating the residue level in cottonseed oil. US EPA used a cottonseed oil residue value of 0.043 ppm in their 2015 risk assessment but did not report the source of the data. OEHHA suggests DPR provide additional description of the residue studies and provide justification for how the cottonseed oil residue value was determined. DPR may also wish to contact USEPA to get their source of cottonseed oil data.

b. Drinking Water Concentration

DPR used dicrotophos levels in finished drinking water (post-treatment ready for consumption) samples from USDA's PDP 2008-2013 to estimate the drinking water exposure. Monitoring data before 2008 were not used because the detection limits were 10- to 100-fold higher than the current values. Residue values (400 samples) from multiple states were used to develop the distribution needed for the probabilistic assessment. However, of the 400 samples, only four were detects, ranging from 1.5 to 3.4 parts per trillion (ppt) and the LOD was 0.9 ppt. Given the quality of the database, OEHHA questions the benefit of conducting the probabilistic assessment of drinking water exposure.

US EPA in their 2014 and revised 2015 risk assessments for dicrotophos estimated both surface water and ground water exposure concentrations. The estimated surface water concentrations were orders of magnitude higher than estimated for groundwater and were chosen as the driver for risk. OEHHA agrees with DPR that surface water exposure estimates grossly overestimate drinking water exposure and agree with DPR's choice to use finished drinking water samples as most appropriate because it is more commonly consumed by the public. However, because of the very large differences between surface, ground, and finished drinking water estimates, additional justification for choosing the least conservative of the 3 should be included. Because dicrotophos is water soluble and has been detected in the groundwater of some other states (US EPA, 2015a), OEHHA also suggests DPR include a discussion on the potential for dicrotophos to contaminate groundwater.

2. Exposure Calculation

a. DEEM-FCID

The DPR draft dicrotophos dietary exposure assessment derived exposure estimates using DEEM-FCID v. 3.16, which used National Health and Nutrition Examination Survey (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. DEEM-FCID v. 4.02 has two out of six years of more recent data relative to v. 3.16. Because consumption rates are only needed for one commodity (cotton seed oil) and because cottonseed oil is a blended commodity typically used in small amounts in various food products, it is unlikely that consumption of cottonseed oil will have changed substantially from 2003-08 to 2005-2010. However, OEHHA suggests using the most current data and software to derive exposures.

DPR used the two-day average food consumption data from NHANES for estimating the acute exposure. OEHHA disagrees with this approach as it would lead to under-estimating the exposure. OEHHA recommends using the one-day consumption data of consumers only. Two-day averages are more appropriate for steady-state exposure scenarios.

b. Subpopulations

The current dicrotophos dietary exposure assessment does not include an evaluation of pregnant women. Because there is a concern for DNT, it would be prudent to include this sensitive population.

c. "Workers 18-99"

Tables 8 and 9 in the draft EAD presented exposure estimates and MOEs for various subpopulations including "workers 18-99" years old. Elsewhere in the document "workers" refers to occupational exposures. It is unclear how 'worker' food and water

consumption data were derived from the NHANES dataset. OEHHA recommends the procedure be better described or this group be removed.

d. Exposure Percentiles

The exposure estimates used to calculate MOEs for each acute and steady state exposure from dietary (food only), drinking water, and combined (dietary plus drinking water) pathways are listed in Table 8 of the draft EAD. This table shows that a 95th-, a 99.9th-, and a 97.5th-percentile value was used for dietary, drinking water, and combined exposures, respectively. OEHHA recommends the reasoning for selecting these percentiles be provided in the RCD.

The method by which the combined exposure estimates in Table 8 were derived was not explained. OEHHA suggests DPR provide a clear description of how the combined exposure estimates (dietary plus drinking water) were calculated.

I. Risk Characterization

1. Targets for Acceptable Risk

DPR considered the target MOE of 100 (which is the total UF) as health protective for all exposure groups and durations. This was based on 10-fold UF for interspecies extrapolation and 10-fold for intraspecies variability. As previously discussed, OEHHA recommends the target MOEs of 300 for the general adult population and 1000 for the sensitive population. The same UFs should be applied for acute and steady state exposures of all routes.

2. Combined Exposure

In the draft RCD, acute exposures to dicrotophos by multiple routes (referred to as combined exposures or aggregate exposure) were evaluated for three scenarios: (1) dietary and drinking water for all population subgroups, (2) dermal and inhalation, exposures for workers and adult bystanders, and (3) dermal, inhalation, and incidental oral exposures (hand-to-mouth exposures) for child bystanders. The combined exposures were calculated using the MOEs for the individual routes. OEHHA agrees with this approach since all the PODs were based on the same endpoint, brain ChEI. However, OEHHA recommends DPR provide explanation for not including the dietary route in the combined exposures for workers and bystanders.

IV. MINOR COMMENTS

A. Draft RCD (Dietary and Drinking Water Exposure)

Page 5: “Conclusions” section should go after “Risk Appraisal” section.

Page 15: “Only 4 samples from North Carolina in 2012 had detectable residues...” For clarity, OEHHA suggests the sentence be revised to “The only detectable residues were 4 samples from North Carolina in 2012...”

Page 17: In Table 8, the combined steady-state exposure for infants is less than the food only steady-state exposure. This is likely a typo. OEHHA suggests reviewing the infant values in this table and revising as necessary.

Page 21: “The acute exposure estimates ranged from 1.63 ng/kg/day for adults 50-99 years old to 6.93 ng/kg/day for children 1-2 years old. The steady state exposure estimates were about a third lower ranging from 0.58 ng/kg/day for adults 50-99 years old to 2.58 ng/kg/day for children 3-5 years old.” OEHHA observes that the steady state exposure estimates are approximately a third of the acute estimates rather than one third lower. OEHHA suggests that the wording be revised to clarify the sentence.

The draft DPR 2015 dicrotophos assessment refers to “dietary” as food only while some other DPR assessments refer to “dietary” as food plus drinking water (e.g., 2015 draft methomyl RCD, 2015 draft chlorpyrifos RCD). This comment is informational only, to help if departmental consistency is desired.

B. Draft EAD

In the exposure appraisal (page 23, last paragraph), the phrase “studies showed” may imply that the two-fold difference in chlorpyrifos air concentrations between aerial and ground applications was observed experimentally and does not indicate that the air concentrations due to aerial applications were simulated (DPR, 2015a). The draft EAD should be revised to read “comparison of modelled air concentrations and field study data from ground applications”.

The title of the Barry reference (DPR, 2015a) should be corrected as the title is “Estimation of Chlorpyrifos Horizontal Deposition and Air Concentrations for California Use Scenarios”.

On page 24 of the exposure appraisal, (paragraph 2), the draft EAD stated, “Both Agencies employed the same modeling parameters for simulating drift exposures due to groundboom.” This is incorrect. US EPA used a “very fine to fine” spray type in the dicrotophos exposure assessment for groundboom (US EPA, 2014b).

In the description of the spray drift-bystander exposure scenarios, the supporting memorandum (DPR, 2015a) shows in Table 1 that the droplet distribution for groundboom exposure estimates was “medium/coarse”. However, the user manual for AGDRIFT 2.1.1, the choices for droplet distribution are shown as “very fine to fine” and “fine to medium/coarse”. This may be a typo or due to changes in the software between v2.0.05 and v2.1.1.

The website www.agdrift.com is cited as the source for several references in the Barry memorandum but is no longer active.

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