OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

Pesticide Exposure and Risk Assessment Peer Review

Document Review

Department of Pesticide Regulation's Draft Risk Characterization Document for Chlorpyrifos

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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 review of human health risk assessments prepared by the Department of Pesticide Regulation (DPR). This report by OEHHA is a review of the draft Risk Characterization Document (RCD, dated December 31, 2015) for the pesticide chlorpyrifos. The draft RCD on chlorpyrifos summarized the toxicology database of the chemical; discussed hazard identification and dose-response analyses; estimated the exposure under various exposure scenarios and routes of exposure, and characterized the risks associated with the exposures.

This peer review report has four parts:

I. Summary of Review
II. Responses to Charge Statements
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I. SUMMARY OF REVIEW

This report presents the review by the Office of Environmental Health Hazard Assessment (OEHHA) of the draft Risk Characterization Document (RCD) for chlorpyrifos (CPF) prepared by the California Department of Pesticide Regulation (DPR). CPF is a widely used organophosphate (OP) insecticide for pest control on agricultural crops and for public health to control mosquitos.

Overall, OEHHA finds that the RCD is limited in scope. The exposure assessment evaluated only the exposure of residential bystanders of two age groups (children 1-2 years and females 13-49 years old) to CPF from drift of spray from nearby agricultural application, dietary exposure of females 13-49 years and children (<1 to 12 years old), and the aggregate exposure (children 1-2 years old only) from drift and from food and drinking water. It did not evaluate the exposure of agricultural workers, certain plausible exposure pathways (via vapor and dust), other groups of residential bystanders, or ambient air exposure.

The points of departure (PODs) from the physiologically-based-pharmacokinetic and pharmacodynamic (PBPK-PD) model and the dietary exposure estimates were those from the 2014 risk assessment conducted by the US Environmental Protection Agency (US EPA, 2014a). OEHHA does not consider the PODs and uncertainty factors (UFs) in the draft RCD sufficiently health protective, based on OEHHA's analysis of the model and experimental animal database. Further, US EPA recently re-assessed the PODs from the PBPK-PD model and proposed a lower POD (US EPA, 2016a, 2016b).

The draft RCD has a limited discussion of the experimental animal toxicity study database. The animal database, including studies conducted in the developing organism, is extensive with many experiments designed to investigate cholinesterase inhibition and neurotoxicity induced by CPF. OEHHA recommends an analysis of the animal database to compare PODs derived from the data with those estimated from the PBPK-PD model.

Our principal comments are summarized here in Section I. OEHHA's review focuses on those issues that are likely to impact the key findings and conclusions of the assessment. 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 provided in Section IV.

A. Points of Departure and Risk Characterization

1. DPR used the PBPK-PD model-derived and human-specific PODs for red blood cell (RBC) acetylcholinesterase (AChE) inhibition from US EPA's 2014 draft Risk Assessment. DPR determined that:

- Infants, young children, and women of child-bearing age[1] are the populations of concern.
- Acute and steady-state durations are appropriate exposure durations.
- A total uncertainty factor (UF) of 100 is sufficient for all populations evaluated.

OEHHA agrees with the selection of the critical endpoint, populations of concern, and exposure durations. However, OEHHA disagrees with the total UF of 100 for the RBC AChE PODs derived from the PBPK-PD model. OEHHA recommends a total UF of at least 1,000, as discussed below.

2. DPR applied an interspecies UF of 1 by arguing that the PBPK-PD model was built from human data, including two human deliberate dosing studies.

OEHHA acknowledges that the model was built with mostly human data but key parameters were taken from animal dataset and human cadavers. OEHHA recommends retaining an interspecies/model UF of 3 to account for the uncertainty in the model because of uncertainties regarding the source of parameter values, specifically:

- Sensitivity analysis indicates that uncertainties in several model parameters derived from animal data affect model outputs.
- Key parameters for metabolism in the model were based on *in vitro* data from human post-mortem tissues. The use of these tissues raises questions of potentially different activities compared to *in vivo* activities.
- Further, OEHHA notes that the model outputs have been compared with the results of only one *in vivo* human study. However, the study is not well suited for the purpose as the subjects had little or no RBC AChE inhibition. It was an acute oral study and there is uncertainty in using the results to validate model predictions associated with inhalation and dermal exposure routes, as well as steady-state exposures.

3. DPR applied an intraspecies UF of 10 to account for human variability because:

- The PBPK-PD model did not fully account for physiological, anatomical, and biochemical changes associated with pregnancy.
- Metabolic parameters (variability of PON1 and cytochrome P450 [CYP450] enzyme activities) were based on too small a sample size to be representative of the entire population and were derived from human cadaver tissues.

OEHHA concurs with those points, but recommends a higher intraspecies UF of at least 30 because of the inter-individual human variability not capture in the PBPK-PD model regarding changes during pregnancy, genetic polymorphism, and variations in metabolism and cholinesterase activities associated with age and environmental factors.

[1] In the draft RCD, women of child-bearing age are defined as those between ages 13 and 49 years. The evaluation of this group includes pregnant women and the fetuses.

4. DPR applied an additional UF of 10 because epidemiological studies and animal toxicity studies showed an association between CPF exposures (prenatal and postnatal exposures) and long-term neurotoxicity (developmental neurotoxicity [DNT]). These effects may occur at doses below those resulting in detectable RBC AChE inhibition (RBC AChE is used as a surrogate for brain AChE inhibition). This latter point was supported by the zebrafish data.

OEHHA agrees that the additional uncertainty factor of 10 is needed to protect against DNT of CPF.

5. In the draft RCD, experimental animal toxicity studies were not evaluated for POD determination.

OEHHA recommends that the draft RCD provide a detailed analysis of the animal toxicity data. This analysis would include derivation of alternative PODs to compare with the PODs derived from the PBPK-PD model. OEHHA's analyses indicate that PODs derived from animal studies are lower, especially when an interspecies extrapolation UF of 10 is included, than those from the PBPK-PD model. This comparative analysis supports OEHHA's recommendation of increasing the total UF from 100 to at least 1,000 for the PBPK-PD model-derived PODs.

6. In the draft RCD, the proposed target MOE was 100.

OEHHA recommends that the target MOE be increased to at least 1,000 because of the following and presented above:

- Interspecies/model UF of 3 for the uncertainty in the model because of uncertainties regarding the source of parameter values.
- Intraspecies UF of 30 for inter-individual human variability not captured in the PBPK-PD model regarding changes during pregnancy, genetic polymorphism, and variations in metabolism and cholinesterase activities associated with age and environmental factors.

- Additional UF of 10 for to protect against DNT of CPF at doses below those resulting in detectable RBC AChE inhibition.
  - In addition, the PODs estimated using the PBPK-PD model are much higher than that proposed by the US EPA based on cord blood CPF and DNT data from an epidemiology study (Rauh et al., 2011). In their presentation to the Federal Insecticide, Fungicide and Rodenticide Act Scientific Advisory Panel (FIFRA SAP), the US EPA reported that these PODs from the model were not health protective (US EPA, 2016a; p. 559; 2016b). They proposed a lower POD based on cord blood CPF level associated with reduced working memory in children from an epidemiology study, referred to as the Columbia Study in this report (Rauh et al., 2011).

While OEHHA recognizes that there are issues with using the Columbia study as the critical study, results from animal data indicate the PODs estimated using the PBPK-PD model may not be health-protective.

B. Spray Drift Bystander Exposure Assessment

1. DPR did not evaluate inhalation exposure from groundboom and airblast applications. Of the exposure scenarios associated with aerial spray application evaluated in the draft RCD, inhalation contributed most to the risk.
OEHHA recommends that DPR estimate CPF air concentrations for inhalation exposure from these two ground spray applications by using modeling, field data or surrogate monitoring results.
2. The draft exposure assessment did not evaluate exposure associated with volatilization of CPF or dust contaminated with CPF.
OEHHA recommends that DPR include these two exposure scenarios in their assessment.

C. Dietary Exposure Assessment

The draft RCD included a dietary (food and drinking water) exposure assessment. OEHHA generally agrees with the dietary exposure assessment, but some of the values/approaches used may not be health protective. They include the use of non-California-specific percent of crop treated (PCT), lack of specific evaluation for formula-fed infants, and the use of drinking water rate that includes nursing infants. In addition, OEHHA recommends that exposure to infants via breast milk be assessed.

D. Exposure to CPF in Ambient Air

CPF has been detected in DPR's ambient air monitoring program at frequencies ranging from 2% to 75% at the three monitoring locations.

OEHHA suggests that the general public's exposure to this chemical be considered and evaluated as a candidate Toxic Air Contaminant (TAC).

II. RESPONSES TO CHARGE STATEMENTS

The responses to some of the charge statements are intended to be brief to avoid redundancy with the summary comments in Section I and detailed discussion of OEHHA's comments in Section III. Other issues not included in the charge statements are also covered in the Section III.

A. Hazard Identification

Statement 1: *"The critical acute and subchronic endpoints were PBPK-estimated PoDs based on 10% inhibition of the RBC AChE activity in humans. These PoDs were used for evaluating oral, dermal and inhalation exposure from diet and spray drift."*

Response: OEHHA agrees that, in general, inhibition of RBC AChE is the most sensitive adverse endpoint observed following exposure to CPF by all routes

(oral, dermal, inhalation) and durations (acute and steady-state) for which controlled studies with animals and humans are available. OEHHA further agrees that 10% is an appropriate benchmark response level for the evaluation of RBC AChE inhibition in humans for the risk assessment of CPF.

Statement 2: "*Chronic NOELs were not established separately."*

Response: In using the PBPK-PD model-derived PODs, DPR assumed that steady-state RBC AChE inhibition is achieved after 21 days of exposure, and thus steady-state PODs were sufficient to address subchronic and chronic exposure durations. OEHHA evaluated the PBPK-PD model and animal toxicity data, and concurs with this assumption.

B. Spray Drift Exposure Assessment

Statement 1: *"Due to the limitation of AgDRIFT model, aerial concentrations of CPF from orchard airblast and groundboom applications can't be estimated."*

Response: As described in Section I, Summary of Review, and Section III.G, OEHHA concurs with DPR that the AgDRIFT model cannot be used to estimate air concentrations resulting from groundboom or airblast applications.

However, since inhalation exposure has been shown to be a significant component of chlorpyrifos exposure for the aerial application scenario, OEHHA believes that inhalation exposure should be evaluated for groundboom and airblast applications. OEHHA suggests that DPR find ways to bridge this data gap by using the AGricultural DISPersal (AGDISP) model or field data (Nsibande et al., 2015; CARB, 1998; US EPA, 2013a).

C. Dietary Exposure Assessment

Statement 1: *"HHAB utilized the 2014 U.S. EPA food-only probabilistic exposure estimates to evaluate the risk from CPF exposure from food."*

Response: OEHHA generally agrees with the use of the 2014 US EPA dietary exposure estimates. However, OEHHA suggests evaluating the use of PCT data specific to California and assessing infants using non-nursing, consumer-only, consumption rates.

Statement 2: *"HHAB conducted its own acute drinking water exposure assessment employing CDPR residue data from surface and ground water in California, and PDP monitoring data for drinking water in California."*

Response: OEHHA agrees with DPR's probabilistic analysis of acute drinking water exposure using California-specific residue data from surface, ground, and finished drinking water samples. However, OEHHA suggests that steady-state

exposure should also be considered. In addition, OEHHA recommends that the food and water exposure estimates for formula-fed infants be summed together to give a dietary exposure estimate specific to this potentially highly exposed group.

D. Risk Characterization

Statement 1: *"The critical NOELs for characterizing the risk from exposure to CPF were PBPK-PD-estimated human equivalent doses. A target MOE of 100 was generally considered protective against the CPF toxicity. This target takes into account uncertainty factors of 1 for interspecies sensitivity, 10 for intraspecies variability and 10 for potential neurodevelopmental effects. When exposure occurs by more than one route and route-specific NOELs are used, a combined MOE for all routes can be calculated."*

Response: For interspecies UF, OEHHA recommends retaining an interspecies/model UF at a value of 3-fold to account for uncertainties in model parameters based on animal data, key metabolism parameters derived from post-mortem tissues, and limited validation with only a single acute oral human study. (See Section III.D.1)

OEHHA suggests increasing the intraspecies UF to *at least* 30-fold to account for deficiencies in the PBPK-PD model regarding changes during pregnancy, genetic polymorphism, and variations in metabolism and cholinesterase activities associated with age and environmental factors.

OEHHA agrees with using an additional UF for DNT, including effects which may occur at doses below those which cause detectable cholinesterase inhibition, and suggests that the UF should be *at least* 10-fold. Use of this additional UF is recommended by US EPA for all OPs (US EPA, 2015a).

Thus, OEHHA recommends a target margin of exposure (MOE) of at least 1,000, instead of 100 as proposed in the draft RCD.

Statement 2: *"For spray drift, the risk from acute (1.5 hour) dermal, inhalation, and non-dietary oral exposures was calculated using the 21-day steady state dermal, inhalation and oral PoDs for CPF."*

Response: OEHHA agrees that it is health protective to use the steady-state PODs to address the bystander exposure because the exposure scenario assumes a series of 1.5-hour exposures with a minimal interval of 10 days.

Statement 3: *"Aggregate exposure-combined MOEs were estimated for a child 1-2 years old that would be exposed at 10-1000 feet from the CPF application site potentially through inhalation, skin contact with residues (drift deposition), ingestion of residues by object-to-mouth + hand-to-mouth + incidental soil ingestion (oral exposure), and consumption of food and drinking water (oral, upper bound of exposure [99th*

percentile]). An aggregate MOE approach was used because of different exposure routes and durations, and route-specific NOELs."

Response: OEHHA agrees that aggregate exposure is important for CPF risk assessment and that the aggregate MOE approach is appropriate since the MOE for each route was calculated using a POD for the same critical endpoint (RBC AChE inhibition).

While OEHHA agrees that the pathways noted are important for the young child, OEHHA believes contribution of additional pathways, as discussed in this report, should be considered. Also, it is not clear why aggregate exposure analysis was not performed for other age groups. A screening-level assessment should be conducted to identify the most important exposure pathways and susceptible populations. In addition to acute aggregate exposure, a steady-state aggregate assessment should be considered because of the persistence of CPF in the soil and the detection of the chemical in ambient air, drinking water, and food.

For the acute aggregate MOE calculation, OEHHA agrees that CPF-induced inhibition of RBC AChE is cumulative. However, the rationale for using different duration PODs (an acute oral POD for acute dietary exposures and steady-state PODs for other routes) is unclear and needs justification.

III. DETAILED COMMENTS

A. Introduction

The draft RCD represents the first risk assessment of CPF conducted by DPR (DPR, 2015a). The US EPA has released two Human Health Risk Assessments (HHRA) on CPF and coordinated three FIFRA SAP reviews on the use of epidemiological data and PBPK-PD modeling to derive PODs for risk assessment purposes (as summarized in US EPA, 2016b). Some of the key findings and estimates in the draft RCD are the same as those in the US EPA 2014 HHRA (US EPA, 2014a, 2014b). A summary of the FIFRA SAP findings (not including the April 2016 meeting) is presented in the draft RCD (p. 26-27).

The following sections provide detailed discussion of OEHHA's principal comments and responses to charge statements presented in Sections I and II, respectively.

1. Physical and Chemical Properties and Environmental Fate

The draft RCD presented very limited information on the environmental fate of CPF. The lone citation, a 3-page book chapter, is insufficient to explain several essential phenomena (bioaccumulation, soil persistence and volatilization) important in the estimation of exposure and determination of exposure scenarios. OEHHA recommends that DPR provide additional information and discussion on physical and chemical

properties, as well as the environmental fate and transport of the chemical and its metabolites.

Additionally, the draft RCD only provides physico-chemical properties of CPF under standard laboratory conditions, such as at a temperature of 25°C. However, CPF is used year-round in areas where ambient temperatures can rise to 35 to 40°C (CARB, 1998). OEHHA suggests DPR discuss the impact of high ambient temperature on deposition, volatilization of CPF, and persistence of CPF in environmental media.

2. Pesticide Use and Sales

The draft RCD reported that 21 of the 49 CPF products with active registrations are specifically labelled for ground or aerial spray applications. In reviewing Table 2 in the draft RCD, OEHHA noted that the five crops with highest use (tree nuts, tree fruit, cotton, alfalfa, grapes) can be treated by aerial or ground spray application (US EPA, 2015b; DPR, 2016). OEHHA recommends that DPR analyze the usage data to determine the annual amounts of CPF applied by these two types of application. Such an analysis can tell us the relative importance of aerial and ground spray applications, and enable assessing the significance of the inability to evaluate inhalation exposure to CPF during and following ground spray applications.

3. Reported Illness

The draft RCD stated that the total CPF reported illnesses represented approximately 2% of all pesticide-related illness cases reported in California for 2003-2012. Exposure to pesticide drift, which includes spray, mist, fumes or odor carried from the target site by air, accounts for two-thirds (154/235) of these cases. Exposure to CPF residues, the portion of the pesticide that remains in the environment for a period of time following application or drift, represents nearly 20% of these cases (43/235). OEHHA suggests DPR utilize this information in the development of exposure scenarios. For example, though the data indicate 20% of the cases are related to CPF residues, the draft RCD did not consider the “take-home dust” exposure pathway.

B. Pharmacokinetics

Following oral administration, CPF is rapidly and completely absorbed, with rapid distribution, metabolism, and excretion. Over 50% of the administered dose is excreted in the urine as metabolites within the first 12 hours. CPF and its metabolites do not accumulate in tissues. Parent CPF is not found in urine, and is difficult to detect in blood, suggesting that nearly all CPF is quickly converted into more water-soluble metabolites.

The draft RCD stated that the external CPF concentration for dermal exposure was converted to absorbed doses using a default absorption rate of 100% for “computational purpose” (Draft RCD: p. 81). This value seemed to be overly conservative since the dermal absorption in humans is slow and incomplete at ~1-4%, based on three separate

studies (Draft RCD p. 37-38). OEHHA recommends this point be clarified. In addition, methodology on how the absorbed dose was estimated for the inhalation route should also be provided. The higher breathing rates of young children and pregnant women on a per body weight basis (OEHHA, 2008) should be accounted for in the calculation.

The draft RCD described in detail studies on the oral pharmacokinetics of CPF in the rat (Nolan et al., 1987) and the oral (Kisicki et al., 1999; Nolan et al., 1982; Griffin et al., 1999) and dermal (Nolan et al., 1982; Griffin et al., 1999; Meuling et al., 2005) pharmacokinetics in the human (Draft RCD p. 35-37). However, only the references were provided for other pharmacokinetic studies in the database. OEHHA recommends that DPR provide a more comprehensive review of the pharmacokinetic studies in the database because CPF disposition and metabolism information is important for understanding CPF toxicity as well as in the PBPK-PD model used to derive the PODs.

Pharmacokinetic data from several laboratory animal studies in which AChE activity was simultaneously monitored, allowing one to directly associate body burden with effect, were not included in the draft RCD. These studies include the comparative cholinesterase study (Marty and Andrus, 2010), in which postnatal day 11 (PND11) pups and adults were dosed by gavage with a single acute dose or for 11 days consecutively. Of particular interest is the component in which pups were exposed to a single dose of CPF in milk and adult females to a single dose in the diet to determine matrix effects on absorption. Mattsson et al. (1998) administered CPF to dams by gavage from gestation day 6 (GD6) to lactation day 10 (LD10), with pups exposed *in utero* and through milk. Blood in both dams and pups was assessed for the parent compound and metabolite levels, as was milk. Two acute inhalation studies (Hotchkiss et al., 2010, 2013) also included pharmacokinetic components. Data from these studies provide information on fetal exposure and lactational transfer of CPF in animal models and should be discussed in greater detail.

C. POD Determination Using PBPK-PD Model

DPR chose to adopt the PBPK-PD model-derived PODs established by US EPA (2014a) instead of determining PODs based on laboratory animal toxicity studies. The rationale for this approach was: (1) the PODs were derived from a human model and thus eliminated difficulties in POD estimation due to uncertainties associated with interspecies extrapolation and the lack of no-observed-effect levels (NOELs) in some of the laboratory animal studies; (2) the model had been thoroughly vetted; and (3) the model could be “adjusted based on the subpopulation exposed and the duration of exposure in a standardized manner” (Draft RCD p. 73, 75, 77-78).

US EPA used the PBPK-PD model to derive acute (single day, 24 hours) and steady-state PODs for oral dietary exposure, but only steady-state PODs for dermal and inhalation exposures; all were based on 10% RBC AChE inhibition. RBC AChE is used as a surrogate for brain AChE inhibition. DPR adopted all these PODs in the draft RCD (Table 1).

Table 1: PODs for 10% RBC AChE inhibition from the PBPK-PD model for CPF.

Exposure Routes	Age Groups	Acute Exposure PODs[a]	Steady-State Exposure PODs[a]
Oral (mg/kg-day)	Infants < 1 year	0.600	0.103
	Child 1-2 years	0.581	0.099
	Child 6-12 years	0.530	0.090
	Youths 13-19 years	0.475	0.080
	Females 13-49 years	0.467	0.078
Dermal (mg/kg-day)	Child 1-2 years	ND	134.25
	Females 13-49 years	ND	23.6
Inhalation (mg/m^3)	Child 1-2 years	ND	2.37
	Females 13-49 years	ND	6.15

[a]From Table 20 of Draft RCD (p. 78). For spray drift exposures, the risks from acute exposure were evaluated using the steady-state PODs. Abbreviations: mg/kg-day= milligram per kilogram body weight per day, mg/m^3= milligram per cubic meters, ND= not determined.

OEHHA notes that both acute and steady-state PODs for the oral route are higher for infants than for adults, which seems contrary to the general assumption of greater vulnerability of infants to chemical exposure. According to Smith et al. (2014), infants are less sensitive to RBC AChE inhibition at low acute CPF doses (<0.6 mg/kg), at the level of the POD, because the infant's higher relative liver weight (liver weight to body weight ratio) confers greater capacity to detoxify CPF-oxon than adults. In the PBPK-PD model, other metabolic parameters are set to be the same across ages based on the Smith et al. (2011) *in vitro* metabolism study:

- Infants and adults have equivalent metabolic capacity on a specific activity basis (per gram microsomal protein) on the desulfuration and dearylation of CPF by CYP2B6 and CYP2C19, respectively (Smith et al., 2011).
- There is a "constant" amount of microsomal protein per gram liver (33 mg/g) across all ages (Smith et al., 2014).

The assumption regarding age-related CYP2B6 and CYP2C19 levels is consistent with the variation in CYP ontogeny and activity over the lifespan. Hines (2013) classified CYP (and other metabolic enzyme) ontogeny into three groups: CYP isoforms that occur in the fetus and disappear after birth (Group 1), CYP (including CYP2B6, CYP2C19, CYP3A5) that are relatively constant across the lifespan (Group 2), and CYP that are not present until after birth (Group 3). The Group 3 CYP enzymes appear after birth at varying rates and there is hypervariability in the early postnatal period. CYP3A4 and carboxylesterases (which metabolize the CPF-oxon) belong to this group.

However, the assumption in the PBPK-PD model that there is a "constant" amount of microsomal protein per gram liver across all ages (Smith et al., 2014) may not be correct. There is significantly less microsomal protein per gram liver at birth and it increases slowly over time (Hines, 2013). Thus, each CYP isoform has its own pattern

of expression pre- and postnatally, and CYP metabolic capacity is generally lower in earlier life stages, particularly in children less than 1 year of age. Furthermore, the small sample size used to determine the hepatic metabolism parameters for the PBPK-PD model showed high variability over all ages (Smith et al., 2011). Smith et al. (2014) noted that the use of *in vitro* data from children in the model have not been validated by *in vivo* data from children, which OEHHA acknowledge is difficult to obtain. Thus, OEHHA cannot conclude with confidence that young children are less sensitive to CPF than adults. These concerns add to the uncertainty regarding the variability of PON1 (discussed later).

For bystander exposure to CPF, both DPR and US EPA considered only steady-state exposure. The rationale was that a bystander may have residual RBC AChE inhibition left from the prior crop treatment when crops are subsequently treated (Draft RCD: p. 78). Crop treatment may occur at 10-day intervals and RBC AChE takes approximately 26 days to recover to normal values (DPR cited Nolan et al., 1984, which is the published version of Nolan et al., 1982). OEHHA agrees with this approach.

1. Critical Endpoint

DPR concurred with US EPA in selecting the critical endpoint of RBC AChE inhibition for derivation of PODs from the PBPK-PD model. OEHHA agrees with using RBC AChE inhibition as the critical endpoint for the model. While the model can also estimate brain AChE inhibition, it is not appropriate for use as the critical endpoint since there is limited information on CPF metabolism in the human brain; the data currently available and used to build the model are based on *in vitro* studies using rat brain microsomes. Animal studies on OPs demonstrate that RBC AChE is more sensitive to CPF-induced inhibition than brain AChE, and thus a POD based on RBC AChE inhibition is protective of brain AChE inhibition.

2. PBPK-PD Model Description

The draft RCD provided a minimal description of the PBPK-PD model with little detail on its construction and parameters. For this review, OEHHA examined the original publications of the model in order to understand the construction of the model and the uncertainties and limitations therein.

The PBPK-PD model was originally proposed by Timchalk and colleagues (Timchalk et al., 2002). It underwent numerous modifications culminating in the current multi-route life-stage PBPK-PD model (Smith et al., 2014; Poet et al., 2014). It has been vetted through publication in peer-reviewed journals and review by stakeholders, the FIFRA SAP, and US EPA (Draft RCD: p. 75). Further modifications to the PBPK-PD model were made to include compartments and parameters specific to pregnancy (Poet 2015). While the latter modified model was discussed by DPR (Draft RCD: p. 41-42), it was not used to derive the PODs. OEHHA agrees that the latter modified model is not ready to be used. This model has not been peer reviewed and has not been considered by the FIFRA SAP. US EPA also expressed concerns regarding the lack of CPF-specific

pharmacokinetic data during pregnancy to test the predictive capability of the model (US EPA, 2016b). So, relative to the current model, it is not appropriate for use by DPR at this time; in time, after a thorough review process, it may be considered or incorporated into the assessment.

The PBPK portion of the model accounts for CPF disposition (absorption, distribution, metabolism, and excretion) while the PD portion relates CPF-oxon formation with changes in the activities of β-esterases (AChE, plasma butyrylcholinesterase [BuChE], and carboxylesterases). The PBPK-PD model incorporated age-dependent changes in physiological parameters (body weight, organ volume, and metabolism) to model the exposures of infants (> 6 months), children, and adults to CPF. The model describes a time course for disposition of CPF, CPF-oxon, and trichloropyridinol (TCPy) in several compartments: blood, brain, diaphragm, fat, liver, rapidly perfused tissues (sum of kidney, spleen, lung, gastrointestinal tract, and pancreas), and slowly perfused tissues (sum of muscle, skin, bone marrow, and non-fat adipose tissue), and estimates the AChE inhibition by CPF-oxon in blood, brain, liver, and diaphragm. The model was designed for oral exposures but was further refined to include dermal and inhalation routes of exposure (Poet et al., 2014). DPR considered the model sufficient for use for all three routes (Draft RCD: p. 38). OEHHA agrees with this determination. While the model's inhalation-route parameters were based mostly on extrapolated data, the model assumed 100% absorption in the airway, near-zero elimination via exhalation, and no PON1 detoxification of CPF-oxon in the lung tissue (Poet et al., 2014).

3. Use of Human Data

DPR considered the PBPK-PD model to adequately model the disposition of CPF in the human because the model was constructed using parameters predominantly derived from human data. Key human studies in the model were the *in vitro* liver and plasma metabolism study (Smith et al., 2011) and two deliberate in *vivo* dosing studies in humans (Nolan et al., 1984; Kisicki et al., 1999). Of the 128 parameters used to build the model, 90% were sourced from experimental measurements (Hays and Kirman, 2013). A majority of these measurements came from *in vitro* data from rat and human tissues. The remaining 10% of the parameters were optimized to fit available CPF exposure studies in laboratory animals and humans. Sensitivity analysis showed that four parameters from animal data contributed to the variation in the model output: partition coefficients for CPF-oxon from liver:plasma, CPF from blood:brain, CPF from blood:liver, and AChE levels in the brain (Hays and Kirman 2013).

The PBPK-PD model includes different life stages by adjusting CPF metabolism using age-specific body weight and tissue volumes. *In vitro* metabolism studies were conducted by Smith et al. (2011) using human samples (20 plasma and 30 post-mortem liver samples from individuals ranging in age from 2 weeks to 76 years). From the *in vitro* microsomal metabolism assays, the authors found no age-related differences in microsomal protein metabolism of CPF or CPF-oxon on a specific activity (per unit weight) basis. However, when scaled by organ size (based on age), there are differences because more enzyme is available as blood and organ volumes increase.

DPR expressed concerns about this study. First, the study was limited by too few samples over a large age range and did not adequately describe age-related changes in metabolism of CPF, nor inter-individual variability within an age group. Second, post-mortem tissue samples may not accurately represent the metabolic processes of live tissues since time to sampling and handling of tissue samples can result in protein degradation and loss of enzyme activity (Draft RCD: p. 122).

OEHHA agrees with DPR's concerns regarding the enzyme activity parameters being sourced from cadaver tissues as they could be different from those derived from *in vivo* studies. Also, the sample size is too small to be representative of the general population, and thus does not completely remove uncertainties associated with age-dependent or genotype variation in CPF metabolism.

The draft RCD provided brief summaries of two *in vivo* human studies important for the model. In Nolan et al. (1984), six healthy male volunteers were given an oral dose of 0.5 mg/kg CPF on a lactose tablet. TCPy in blood and urine, CPF in blood, and cholinesterase activities in plasma and RBCs were measured at various time points. After 30 days, the subjects were again dosed with 5.0 mg/kg by the dermal route. The following parameters were sourced directly from the Nolan study: intestinal absorption of CPF to the liver, dermal absorption rate, elimination rate for TCPy, degradation rate of BuChE, and transfer rate of CPF from stomach to intestine.

The main use of the second study, Kisicki et al. (1999), was to validate the model (described in Timchalk et al., 2002). Volunteers (6 male, 6 female) were administered a single oral dose of 0.5, 1, or 2 mg/kg CPF powder in capsules. Blood and urine were collected and CPF, CPF-oxon, and TCPy levels were measured, along with RBC AChE. The transfer rate of CPF from stomach to intestine from the Nolan et al. (1984) study was adjusted using the Kisicki data due to differences in the dosing formulations.

OEHHA notes the deficiencies in these studies, including the use of data from these acute dosing studies for derivation of steady-state PODs, too few participants, all of whom were adults, and variability observed in the dose-response relationship for AChE inhibition. Most of the dosed subjects did not exhibit significant RBC AChE inhibition, bringing into question the suitability of using the study for validating the PBPK-PD model in terms of RBC AChE inhibition as the critical endpoint. Nevertheless, the model output is fairly accurate for acute exposure when compared to both the Nolan and Kisicki datasets for RBC and plasma ChE inhibition and CPF and TCPy concentrations in plasma. Model output for steady-state exposure has not been validated.

D. Extrapolation, Variability, and Uncertainty

OEHHA has a greater level of doubt, compared to that expressed in the draft RCD, regarding the PBPK-PD model-derived PODs with respect to their representativeness of the heterogeneous general population and lack of agreement with the PODs from epidemiological studies of neurodevelopmental deficits. This concern is consistent with:

- The current US EPA position that the total UF applied to PODs from the PBPK-PD model should be increased to partially account for wide variability among humans (US EPA applied a total UF of 100 in their 2014 draft assessment, but has since suggested that it should be increased[2]).
- US EPA's recent proposal to base the POD on the cord blood CPF level (2.16 picogram/gram, pg/g), which would give an acute oral POD for sensitive populations ~10,000-fold lower than that from the PBPK-PD model. The estimated external oral dose associated with 2.76 pg/g (close to the proposed value of 2.16 pg/g) is 0.000029 mg/kg-day (US EPA, 2016c: Slide 150), compared to 0.467 mg/kg from the PBPK-PD model.
- Lower PODs from experimental animal toxicity studies compared to those from the PBPK-PD model.

1. PBPK-PD Model-Derived PODs

a. Interspecies Extrapolation

DPR stated that the model is based primarily on studies performed in humans or human tissues and thus the interspecies UF should be a factor of 1. OEHHA notes the complexity of the model with 128 input parameters. Several parameters were estimated from animal studies; they can affect the model outputs. Some of the key parameters were derived from cadaver tissues rather than live individuals. In addition, the PBPK-PD model has only been validated by a human *in vivo* study for acute oral exposure but not for other exposure routes or steady-state exposures. For these reasons, OEHHA recommends increasing the interspecies UF to a factor of 3 to account for the interspecies/model uncertainties in the model outputs.

b. Intraspecies Variability

DPR applied an UF of 10 to account for variability among individuals because of the following concerns: (1) the PBPK-PD model did not fully account for physiological, anatomical, and biochemical changes associated with pregnancy, and (2) metabolic parameters (e.g., variability of PON1 and CYP450 enzymes) were based on post-mortem tissues from too small a sample size, and are thus not representative of the general population.

OEHHA agrees with these concerns. However, OEHHA recommends a higher intraspecies UF of at least 30-fold because the range of activating and de-toxifying enzyme activities in the human population can be much greater than 10-fold. This recommendation is based on the following discussion of PON1 and CYP450 variations in the general population.

[2] From US EPA's presentation to the 2016 FIFRA SAP (April 19-21, 2016, Arlington, VA; US EPA, 2016a: p. 559).

Population variability is particularly important to address for PON1, the key deactivation enzyme for CPF-oxon. The draft RCD discussed variation in PON1 levels between mothers and newborns, within cord blood samples, and age-dependent changes in expression. Pregnancy lowers PON1 expression in the mother (Ferre et al., 2006; Stefanović et al., 2012) and PON1 protein levels vary between mother and child, with children's PON1 levels 4-fold lower than that in the mother (Furlong et al., 2006). Levels of PON1 rise after birth, but the age at which PON1 levels plateau has not been firmly established. According to DPR, it has been shown to be 6-15 months (Draft RCD: p. 39), while US EPA suggests that it could be as late as 9 years of age (US EPA, 2014a: p. 23). The age at which PON1 levels plateau may be linked to genotype (Cole et al., 2003). In summary, PON1 is lower in pregnant women, infants, and small children than in adults. OEHHA is concerned that these variabilities among different age groups and pregnancy conditions are not fully accounted for by the intraspecies UF of 10 proposed by DPR.

In addition to variability caused by age, there are genetic polymorphisms which alter the activity levels of metabolic enzymes. Two important genetic polymorphisms exist for PON1 (Ginsberg et al., 2009). One affects the structure of the active site and thus catalytic efficiency while the other affects expression of the enzyme. The allelic frequencies of these polymorphisms vary between ethnic groups. Ginsberg et al. (2009) performed a Monte Carlo analysis of PON1 function related to polymorphisms and showed a 4-fold difference for median values in the bimodal distribution and a 20-fold difference between the 1st and 99th percentile values within a particular ethnicity for different organophosphate substrates. The 1st percentile had 5- to 6-fold lower activity compared to the median value and there was a 100-fold difference between the extreme minimum and maximum enzyme activities.

Studies have also shown that PON1 activity in serum can vary *within* a particular genotype, generally 15-fold but up to 56-fold when comparing the lowest to the highest individuals (Ginsberg et al., 2009). This implies that there are additional factors that affect PON1 levels and activity, in turn affecting inter-individual sensitivity to CPF. These factors include therapeutic drug usage, smoking, alcohol intake, and diet. Studies in animals have also shown that stress can modulate PON1 activity. These gene-environment interactions can further increase variability among individuals. Specifically, the PBPK-PD model used point estimates of PON1 activity for each age group, and thus did not incorporate variability in PON1 activity either within age groups or related to genotype or other factors. Thus, OEHHA believes that the intraspecies UF of 10 proposed in the draft RCD is inadequate.

The draft RCD also discussed age-dependent expression and variability in CYP450 isoforms associated with CPF metabolism; they include CYP2B6 (desulfuration), CYP2C19 (dearylation), and CYP3A4 (desulfuration and dearylation) (Draft RCD: p. 38-39). Pregnancy alters expression of these enzymes in humans, resulting in an increase in CYP3A4 activity and a decrease in CYP2C19 activity (Anderson, 2005). Again, the model used only point estimates for CYP450 activity for each age group, with no

consideration of inter-individual variability due to genetic, physiological, or environmental factors.

In conclusion, it is OEHHA's opinion that model uncertainty and inter-individual variability associated with pregnancy and the wide range in enzymatic rates due to age, genetic polymorphisms, and environmental factors warrant at least a 30-fold intraspecies UF. OEHHA recommends that the results of Ginsberg et al. (2009) be discussed in the draft RCD.

c. Additional Uncertainty Factor

DPR has included an additional UF of 10 for the potential of developmental neurotoxic effects resulting from CPF exposure in the absence of detectable RBC AChE inhibition, the critical endpoint for the PODs from the PBPK-PD model. Developmental neurotoxicity was reported in a number of animal studies and epidemiology studies as summarized in the draft RCD. Three prospective epidemiological studies (referred to as the Columbia study, CHAMACOS cohort, and Mount Sinai Children's Health study; Draft RCD: p. 53-56) suggest that prenatal exposure to CPF can lead to neurodevelopmental effects such as changes in IQ and working memory in newborns and up to preadolescence. Recently, the 2016 FIFRA SAP conducted a review of the findings and interpretations of the Columbia study and determined that, although the epidemiological data is useful, it is not sufficiently reliable for deriving a POD (US EPA, 2016a). DPR also reviewed the Columbia study as well as other epidemiological studies and decided that the neurodevelopmental data are not "sufficient" to derive the POD (Draft RCD: p. 22, 126 and 127). OEHHA agrees with this decision.

OEHHA agrees that there is evidence indicating that neurodevelopmental and neurobehavioral effects can occur from pre- and post-natal exposures to CPF, and supports the application of an additional UF of 10 to protect sensitive groups against this effect. The draft RCD described numerous studies in the literature which explored alternate mode of actions (MOAs) for DNT, involving endocannabinoid, serotonergic, and dopaminergic systems, and data showing that DNT effects can occur from CPF exposures in the absence of detectable brain AChE inhibition.

2. Comparative Analysis Using Animal Toxicity Data

The draft RCD provided only summary tables covering acute, subchronic, chronic, developmental, and developmental neurobehavioral studies in animals. OEHHA recommends that DPR provide a more detailed and in-depth evaluation of the animal toxicity studies. Similar to the 2008 FIFRA SAP's suggestion to "bound" PODs for CPF from one source of data with PODs from another source (US EPA, 2012: p. 21), OEHHA suggests that PODs based on the animal data be used to "bound" those derived from the PBPK-PD model, and to support raising the total UF for the PBPK-PD model-derived PODs from 100 to at least 1,000.

US EPA noted that “[g]iven the differences across laboratory animal and epidemiology studies, the qualitative similarity in research findings is striking,” referring specifically to effects on cognition, motor control, and social behavior domains, as well as brain morphometry (US EPA, 2014a: p. 46). This consistency in the types of effects, including cholinesterase inhibition, between the animal and human studies indicates that the animal studies can be used to bound the PBPK-PD model-derived PODs based on RBC AChE inhibition. OEHHA conducted a preliminary assessment of some of the animal studies conducted using the oral route described in the draft RCD and conducted Benchmark Dose (BMD) modeling of the dose-response data for the critical effects. Note that in the following discussion we use the term “ChE” when referring to both AChE and plasma BuChE.

a. **Oral - Acute Exposure**

The draft RCD provided a table summarizing the ChE inhibition results (mostly LOELs/ NOELs) observed in animal and human studies following acute or short-term (up to 10 days) oral exposure to CPF (Draft RCD: Table 7, p. 43-44). In this table, the lowest acute NOEL based on RBC AChE inhibition is <0.3 mg/kg-day (Mattsson et al., 1998), with 0.1 mg/kg-day as the experimentally determined NOEL for other studies. OEHHA evaluated the animal studies and suggests that DPR consider the Mattsson et al. (1998) cholinesterase and pharmacokinetic study for quantitative evaluation. In this study, dams were exposed by gavage to 0, 0.3, 1, and 5 mg/kg/day CPF technical (99.8%) in corn oil from GD6 to LD10. Pups were exposed only through milk. Cholinesterase activity was determined in plasma, RBC, brain, and heart in 5 dams/dose and 5 pups/sex/dose on GD20, LD1, LD5, LD11, LD22, and LD65 (pups only). An additional 5 dams/dose and 5 pups/sex/dose were sacrificed on GD20, LD1, LD5, and LD11 for determination of CPF, CPF oxon, and TCP in blood and milk. In all compartments tested, dams were generally more sensitive to ChE inhibition than fetuses/pups. NOELs based on statistical significance ($p < 0.05$) in the dam were 0.3 mg/kg-day in the forebrain and hindbrain and <0.3 mg/kg-day in the heart, plasma, and RBC. In the draft RCD, the NOEL for this study was stated to be < 0.3 mg/kg-day. OEHHA derived a $BMDL_{10}$ (10% benchmark response[3]) of 0.04 mg/kg-day for the inhibition of RBC AChE in the rat dam on LD1.

b. **Oral - Steady-State Exposure**

DPR presented oral toxicity studies of subchronic and chronic durations (Draft RCD: Tables 8 - 11 [mislabeled as 8, 10, 11, 12]). DPR cited the most sensitive endpoint in both subchronic and chronic studies as RBC AChE inhibition in pregnant rats in the DNT study (Hoberman, 1998), with a $BMDL_{10}$ of 0.03 mg/kg-day calculated by US EPA (2011a) (Draft RCD: p. 74-76).

OEHHA identified four studies of different durations and in different species (rat and dog) in the subchronic database with $BMDL_{10}$ values of around 0.05 mg/kg-day for RBC AChE inhibition. These $BMDL_{10}$ values and source studies are: (1) $BMDL_{10}$ of 0.06 mg/ kg-day from male rats at 6 months of treatment in a chronic rat study (Young and Grandjean,1988), (2) $BMDL_{10}$ of 0.04 mg/kg-day from F1 male rats after ≥13 weeks of treatment in the 2-generation rat reproductive toxicology study (Breslin et al., 1991), (3) $BMDL_{10}$ of 0.06 mg/kg-day from male dogs after 6 weeks of exposure (Marable et al., 2001), and (4) $BMDL_{10}$ of 0.05 mg/kg-from female rats following 4 weeks of exposure (Maurissen et al., 1996).

OEHHA also reviewed chronic studies and found that the chronic POD was the same as that for subchronic exposure. Therefore, based on our preliminary analyses, the steady-state oral POD is approximately 0.05 mg/kg-day.

[3] BMDL=Benchmark Dose Lower limit (95th percentile)

c. Comparison of Points of Departure and Uncertainty Factors

As discussed above, the PODs OEHHA derived from animal toxicity studies are lower than those from the PBPK-PD model. Table 2 compares the oral PODs for children 1-2 years of age and females 13-49 years of age, which are the two main population subgroups evaluated in the draft RCD. When a default interspecies UF of 10 is applied to the animal PODs, the difference is 16 to 145-fold. However, when the OEHHA-recommended interspecies/model UF of 3 is applied to the PODs derived from the PBPK-PD model, the difference is reduced to 5- to 48-fold.

Table 2: Comparison of PODs for RBC AChE Inhibition from the PBPK-PD Model and Animal Toxicity Studies for Bounding Purposes.

Exposure Route	**Groups[a]**	**PBPK-PD Model with Default Interspecies UF of 1 Applied**		**Possible PODs from Animal Studies with Default Interspecies UF of 10 Applied**	
		Acute Exposure PODs[a]	Steady-State Exposure PODs[a]	Acute Exposure PODs[b]	Steady-State Exposure PODs[b]
Oral (mg/kg-day)	Child	0.581	0.099	0.004	0.005
	Female	0.467	0.078		

[a]Child = 1 to 2 years of age, Female =13 to 49 years of age.
[b]PODs with 10-fold default interspecies UF applied.

E. ToxCast™ and Tox21 Data

The draft RCD has an extensive description of the Toxicity ForeCaster (ToxCast™) and Toxicology in the 21st Century (Tox21) data for CPF and CPF oxon from *in vitro* high-throughput (HT) assays and *in vivo* zebrafish embryo assays (Draft RCD: p. 57-71). DPR concluded that the ToxCast™ HT *in vitro* data cannot be used for risk assessment because the true actives[4] are not related to any known specific adverse outcome pathway (AOP) and that the data do not add new information to the risk assessment (Draft RCD: p. 128). DPR also concluded that the results of the zebrafish assays provide strong weight-of-evidence that CPF causes neurodevelopmental toxicity related to learning in the embryo, and at a concentration 10-fold lower than that (0.01 versus 0.10 micromolar, µM) causing AChE inhibition (Draft RCD: p. 129). The comparison was based on statistical significance and not the PODs for these effects.

[4] True actives are assays that demonstrate an effect at concentrations below those causing cytotoxicity.

OEHHA agrees with DPR's general conclusion about the *in vitro* ToxCast™ data, and the results of zebrafish assays. OEHHA commends DPR's efforts in considering the ToxCast™ and Tox21 data in support of their assessment of toxicity of CPF.

F. Carcinogenicity Weight of Evidence

The discussion of the carcinogenic potential of CPF in the draft RCD is limited. It stated that CPF did not cause tumors in the chronic oral studies with rats and mice and that there was "no significant increase in tumors" in general in the chronic oral studies (Draft RCD: p. 15, 46).

According to US EPA, "[c]hlorpyrifos is not likely to be carcinogenic to humans, based on the lack of evidence of carcinogenicity in studies in rats and mice and the absence of a mutagenicity concern. Chlorpyrifos was not mutagenic in bacteria, or mammalian cells, but did cause slight genetic alterations in yeast and DNA damage to bacteria" (US EPA, 2011a: p. 29). The International Agency for Research on Cancer (IARC) has designated CPF as "Medium priority" for development of a cancer monograph during the period 2015-2019, stating that

> *"Increased risk of leukaemia in professional applicators has been reported in a cohort study, and of non-Hodgkin lymphoma in several case-control studies. Cancer bioassay data were also available. Mechanistic studies indicated immunotoxic, genotoxic and pro-oxidant properties related to the activation of certain signaling pathways involved in the regulation of cell proliferation and survival. Recent high-throughput screens provided new insights into the extent of biological activity (IARC, 2014: p. 31)."*

IARC was most likely referring to the Lee et al. (2004) cohort study (discussed below) but OEHHA is unaware of case-control studies on this topic. CPF is not listed as a carcinogen under California's Proposition 65.

1. Genotoxicity

There is a brief discussion of the genotoxicity data in the draft RCD (p. 47) and more detailed study descriptions in Appendix 1 (p. 185-188). Although genotoxicity assays for CPF were largely negative, CPF affected recombination in yeast and bacteria (Simmon et al., 1977a, b; Draft RCD: Appendix 1, p. 187-188) and induced DNA damage in two *in vivo* comet assays (Mehta et al., 2008; Rahman et al., 2002).

OEHHA suggests that DPR discuss whether or not the positive studies provide evidence of genotoxicity.

2. Human and Experimental Animal Evidence

In the draft RCD, the only descriptions of the four chronic toxicity animal studies were in the toxicology summary (Appendix 1). The draft noted that there was "no significant

increase in tumors" in the chronic oral toxicity studies (Draft RCD: p. 46). No human studies related to carcinogenicity were presented.

OEHHA agrees with DPR that CPF does not cause a significant increase in tumors in animal toxicity studies and that the chronic toxicity studies did not sufficiently challenge the animals. In these studies, the highest dose tested barely reached the maximum tolerated dose (MTD), generally defined as a 10% reduction in body weight. OEHHA also notes that the mouse study was only 79 weeks in duration, instead of two years or 104 weeks. The chronic animal studies were all oral studies, and thus may not be predictive of cancer risk following inhalation and dermal exposures, which are the major routes of exposure for pesticide applicators.

OEHHA reviewed publications from the Agricultural Health Study (AHS) which demonstrated an association between CPF exposure among pesticide applicators and several cancer types (Alavanja et al., 2003, 2004; Engel et al., 2005; Lee et al., 2004, 2007). The US EPA reviewed the evidence from the AHS epidemiologic evaluations and concluded that "initial findings for lung and rectal cancer, while preliminary at this time, are notable and worthy of future follow-up and analysis as additional data is obtained" (US EPA, 2011b: p. 2).

OEHHA recommends that DPR provide a weight of evidence discussion for carcinogenicity which includes the limitation of the animal toxicity studies, the positive genotoxicity findings, and the results of the human epidemiologic cancer studies.

G. Exposure Assessment

The draft RCD conducted exposure assessment of residential bystander exposure to CPF drift from nearby agricultural application. A recent comprehensive exposure assessment conducted by US EPA found 153 of 285 occupational handler scenarios presented unacceptable risks (US EPA, 2014b). However, a worker exposure assessment was not conducted in this draft RCD and no rationale was provided for this limited scope.

The Executive Summary (Draft RCD: p. 15) indicates that health risk assessments were conducted for four sentinel sub-groups. In the evaluation of the residential bystander scenario, exposure was assessed for only two groups – children 1-2 years of age and women of child-bearing age. This discrepancy should be explained or reconciled.

1. Residential Bystander Spray Drift Exposure Assessment

a. Environmental Concentrations

a1. Air Sources

In the draft RCD, the AGDISP model was used to estimate CPF air concentrations and surface deposition resulting from aerial spray applications. Although AgDRIFT was

used to estimate surface deposition for ground spray applications, air concentrations could not be estimated with this model. For this reason, inhalation exposure to CPF in air as a result of nearby ground spray application was not included in the exposure assessment. Since inhalation is one of the major exposure pathways in aerial spray application, OEHHA suggests DPR use other models or field data to estimate inhalation exposure of residential bystanders.

Similarly, there are two field studies which collected air samples during and after airblast treatment and reported peak CPF air concentrations near the edge of an orange grove and apple orchards (CARB, 1998; Fenske et al., 2009). The draft RCD should include these two field studies. They could be useful in assessing air concentrations as well as to calculate inhalation exposure of residential bystanders from ground spray applications. The Fenske study also noted that conversion of CPF to the CPF-oxon can occur during the sampling process and may not accurately reflect airborne levels. This could represent another source of uncertainty.

a2. Soil Residues

As stated in the draft RCD, CPF adsorbs strongly to soil and, once the contaminated soil has been transported indoors, may persist for months in an indoor environment (Fenske et al., 2002). However, no soil residue data was presented.

OEHHA recommends that the draft RCD include additional information on the stability of CPF in soil as it may be relevant for assessing exposure in a “take-home” dust scenario and could contribute to aggregate exposure for residential bystanders.

b. Exposure Scenarios

Table 3 summarizes the exposure scenarios DPR used for the two sentinel populations and different application types (ground versus aerial spraying). For each scenario, the exposure duration was assumed to be a series of 1.5-hour exposures with a minimal interval of 10 days. OEHHA concurs with this duration. However, OEHHA proposes additional routes to be evaluated, and they are presented in Table 3 (text in italics inside parentheses).

b1. Populations and Routes

DPR evaluated two sub-populations: children 1-2 years of age, whose activity patterns may result in higher exposure, and women of child-bearing age, whose exposure may result in developmental neurotoxicity of the fetus. OEHHA concurs with the selection of these two sentinel populations.

Table 3. Exposure Scenarios for Residential Bystanders as Evaluated in the draft RCD and proposed by OEHHA (in parentheses)[a].

		Application Method		
		Groundboom	Airblast	Aerial
Populations	Exposure Type	Exposure Routes		
Women 13-19 years old	Direct[b]	*(Dermal, Inhalation)*	*(Dermal, Inhalation)*	Inhalation *(Dermal)*
	Indirect[c]	Dermal *(inhalation)*	Dermal *(inhalation)*	Dermal *(inhalation)*
Children 1-2 years old	Direct[b]	*(Dermal, Inhalation[d])*	*(Dermal, Inhalation[d])*	Inhalation *(Dermal)*
	Indirect[c]	Dermal, Incidental Oral *(Inhalation)*	Dermal, Incidental Oral *(Inhalation)*	Dermal, Incidental Oral *(Inhalation)*

[a]Additional exposure routes proposed by OEHHA are shown as text in italics inside parenthesis

[b]Direct exposure is due to direct inhalation or dermal contact with spray drift during or immediately after the pesticide application.

[c]Indirect exposure results from spray drift that has deposited on a surface, but then is transferred to the skin, ingested as a result of hand-to-mouth activities, or inhaled as a vapor.

[d]This route was indicated for aggregate exposure (Draft RCD: Tables 54 and 55), but no values were given for this route alone.

The application of CPF can result in direct or indirect exposure. Direct exposure is due to inhalation or dermal contact with spray drift aerosol during or immediately after the pesticide application. Indirect exposure is caused by deposited CPF residue that is subsequently transferred to: 1) the skin, 2) the surface of the hand or another object and then ingested, 3) incidental ingestion of soil, or 4) when vaporized CPF is inhaled. In marked contrast to recent US EPA spray drift policy (US EPA, 2013a), DPR has stated that direct contact with spray drift can occur via dermal and inhalation routes during compliant applications (DPR, 2014) and estimated resident exposures to spray drift from some direct and indirect routes. OEHHA supports DPR's position considering both direct and indirect exposure to spray drift; however OEHHA suggests additional pathways as indicated in Table 3 to be included in the draft RCD.

b2. Methods Used to Estimate CPF Exposure

AgDRIFT and AGDISP models

DPR used the AGDISP model to estimate air concentrations and surface deposition from spray drift. California-specific model inputs included meteorological conditions, field size, and aircraft type for the aerial application scenarios. DPR also calculated

composite deposition curves when necessary to estimate deposition for application sites whose size could not otherwise be calculated with AGDISP.

The AgDRIFT model was used to estimate surface deposition for both groundboom and airblast operations. OEHHA agrees with these approaches.

Use of US EPA SOP to estimate the exposure.

DPR employed the modified US EPA Standard Operating Procedure (SOP) for Residential Pesticide Exposure Assessment (US EPA, 2013b) in estimating the residential exposure (incidental oral and dermal contact) to spray drift.

b3. Spray Drift Exposure Estimates from Aerial Applications

Instead of applying the AgDRIFT model to all scenarios as was done by US EPA (US EPA, 2013a; US EPA, 2014a; US EPA, 2014b), DPR used the related AGDISP model to calculate air concentrations and surface deposition for aerial application scenarios. Estimates were generated for two application rates and two types of aircraft. DPR and US EPA applied similar input parameters to these models. By using AGDISP, which better predicts small droplet deposition, DPR was able to improve the accuracy of the estimated exposure (US EPA, 2014b; Teske et al., 2009). OEHHA concurs with DPR's aerial spray drift model selection, input parameters and the resulting exposure estimates.

In the development of the exposure scenarios, the draft RCD indicates that 0.35% of the application rate was used as a "preliminary deposition limit" in initial drift model scoping. As the draft RCD appendix did not explain how setting a default deposition limit might affect the scenario selection or amounts of surface deposition in the final analysis, OEHHA suggests that DPR explain how this value was selected and how it was used in the initial screening process.

b4. Spray Drift Deposition Estimates from Groundboom and Airblast Applications

DPR used the AgDRIFT groundboom module to estimate surface deposition in the vicinity of the applications. Since this module is based entirely on field study data to predict spray drift deposition on the ground, it is not able to estimate air concentrations (Teske et al., 2002). For this reason, inhalation exposure of residential bystanders were not considered and only indirect dermal and oral exposures to CPF from ground spray applications were evaluated in the draft RCD.

As described in the draft RCD, DPR used two boom heights, a fine-to-medium/coarse droplet spectrum distribution and the 50th percentile options in estimating exposure (Draft RCD: p. 83). The rationale stated by DPR for choosing the 50th percentile was to "maintain uniformity with orchard airblast" and that the "derivation of the 90th percentile

is not clear" insofar as the AgDRIFT documentation provided insufficient mathematical detail.

OEHHA disagrees with the choice of input parameters for estimating groundboom-related spray drift deposition. The US EPA chose more conservative options (fine to very fine droplet size distribution and outputs based on the 90th percentile deposition curve) in their exposure assessment (US EPA, 2014c) that resulted in significant exposure for children at distances out to 50 feet, while the DPR analysis found only unacceptable exposure risk 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, 1999). OEHHA verified this information by personal communication with US EPA staff. OEHHA recommends that DPR use the more conservative and health-protective 90th percentile output option for the groundboom application deposition algorithms.

The AgDRIFT airblast module, like the groundboom module, is based on empirical data. DPR conducted the AgDRIFT simulation for airblast applications using sparse orchard, dormant apples, and grapevine scenarios, and compared deposition levels near and far field. OEHHA concurs with these choices.

b5. Estimation of Air Concentrations from Groundboom and Airblast Applications

The draft RCD did not evaluate inhalation exposure of residential bystanders due to the lack of an approved methodology for estimating air concentrations for nearby CPF ground spray applications. The draft RCD indicated that the CPF air concentrations measured (up to 47 µg/m^3) during an airblast application (CARB, 1998) were similar in magnitude to AGDISP simulated values (19-34 µg/m^3) during aerial applications. OEHHA noted that if air concentration of CPF after airblast application is roughly equal to the air concentration after aerial application, then inhalation is likely to be equally important for ground application exposure scenarios.

As shown in Table 4 below, OEHHA suggests DPR consider using air dispersion models, field studies or other methods to estimate air concentrations in the vicinity of groundboom and airblast applications. One possibility is to apply AGDISP for ground spray applications. In a study by Nsibande et al., (2015), it was shown that spray drift estimates predicted by AGDISP for groundboom application were similar to the high volume air sampling results. Another possibility is to use existing air sampling data from groundboom and airblast applications of CPF for estimating air concentrations in the

vicinity of the applications (CARB, 1998; Fenske et al., 2009; Rotondaro and Havens, 2012).

Table 4. Air Concentration and Surface Deposition Models for Residential Bystanders as Evaluated in the draft RCD and Proposed by OEHHA (in parentheses)[a].

Application Method	Groundboom	Airblast	Aerial
Air Concentration Model	*(AGDISP, field studies, or other methods)*[a]	*(AGDISP, field studies, or other methods)*[a]	AGDISP
Surface Deposition Model	AgDRIFT	AgDRIFT	AGDISP

[a]Additional approaches proposed by OEHHA are in italics inside parenthesis
Abbreviations:
AGDISP= AGricultural DISPersal model 8.28,
AgDRIFT=model developed by US EPA and the Spray Drift Task Force for estimating surface deposition from aerial and ground spray applications.

b6. Post-application Volatilization of CPF

The draft RCD did not address the potential contribution of CPF vapors to exposure either alone or as a part of the aggregate exposure. US EPA estimated that 30% of the chlorpyrifos applied to alfalfa volatilized within the first 24 hours (US EPA, 2013a).

Although US EPA concluded that bystander exposure to volatilized CPF is unlikely to pose a significant health risk by itself, OEHHA believes the contribution of this additional pathway should be considered in the aggregate exposure for residential bystanders, particularly since CPF use will occur most frequently during the warmest months of the year in California. Recently, US EPA applied CPF flux data and the PERFUM (Probabilistic Exposure and Risk Model for FUMigants) model to a citrus orchard monitoring study and found “good agreement” between measured and estimated air concentrations (Rotondaro and Havens, 2012; CARB, 1998; US EPA, 2013a). This suggests that this approach can be used to provide reasonably accurate estimates of air concentrations resulting from volatilization of CPF from treated fields.

OEHHA recommends that DPR discuss whether inhalation of volatilized chlorpyrifos would contribute to CPF exposure.

b7. Ambient Air Exposure

DPR ambient air monitoring data showed that residents in high use areas such as Kern, San Joaquin, and Monterey are exposed to chlorpyrifos and its oxon at quantifiable concentrations and at frequencies ranging from 2% to 75% at the three monitoring locations (DPR, 2015b, 2016). These results are similar in magnitude to an earlier

seasonal ambient air monitoring study in Tulare (CARB, 1998). However, potential acute or seasonal exposure to CPF in the ambient air was not considered in the draft RCD. OEHHA suggests the inclusion of ambient air exposure assessment for the consideration of CPF as a potential candidate TAC and for aggregate exposure assessment.

b8. "Take-home" Dust

The draft RCD did not address exposure of residential bystanders to contaminated "take home" dust as a consequence of spray drift. In a study of residential exposure near orchards (Fenske et al., 2002), house dust from homes within 200 feet of pesticide-treated farmland contained significantly more CPF (0.59 ± 0.59 microgram/gram, µg/g, n= 46) when compared to more distant homes (0.22 ± 0.18 µg/g, n= 15). Additional 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 RCD.

2. Food Exposure Assessment

a. Estimated Exposure

DPR adopted US EPA's (2014a) CPF food exposure estimates for the exposure of CPF in the diet. Therefore, the comments below are based on OEHHA's review of US EPA's food exposure assessment and the applicability of the assessment to California.

a1. Residue Data

US EPA states that the only residue of concern in/on plants and livestock is the parent compound CPF (US EPA, 2014d). OEHHA concurs.

In US EPA (2014d, Table A.1.a. on page 13/53), both soybean and soybean oil commodities are listed as blended. For the commodity "soybean", the table reports "RDF" (residue distribution file). OEHHA suggests that DPR explain why US EPA used a residue distribution for a blended commodity (soybean), and discuss the effect this may have on the risk assessment results.

California grows much of US-consumed produce including 88% of US strawberries 99% of grapes, 65% of peaches, 90% of broccoli, and 99% of walnuts. In Attachment 3 of US EPA's risk assessment (US EPA, 2014d), only one commodity (brussels sprouts) is listed as having a PCT value derived from California DPR PUR data. The geographic source for the other PCT values is not reported. OEHHA recommends that DPR clarify the use of the PCT and consider using California-specific PCT values.

a2. Consumption Rate

US EPA used per capita consumption rates to calculate both acute and steady-state food exposures (Draft RCD: p. 135; US EPA, 2014d: pp. 50-51). DPR (p. 135) noted that since CPF is used on a wide variety of crops that the level of per capita exposure is likely to be similar to per consumer exposure. OEHHA reviewed the commodities to which CPF is applied and agrees with DPR's conclusion for all subpopulations except infants. Including nursing infants and using per capita rates can significantly underestimate exposures of non-nursing infant, especially those on formula. About 95% of formula is made from cow's milk or soy milk, commodities in which CPF has been detected and soy milk has been determined to be a driver of acute exposure (US EPA, 2011a). Thus, OEHHA recommends that DPR only include consumer-only, non-nursing infants in the <1 year food exposure estimation.

b. Exposures via Breast Milk

Assessing exposures via the lactational pathway is supported by growing evidence for DNT associated with CPF exposures, and by findings of CPF in milk from rats (Mattsson et al, 1998, 2000) and humans (Srivastava et al., 2011; Sanghi et al, 2003; Casey, 2005; Wagner et al, 1990), including at levels higher than in maternal plasma, as well as the documented transfer of CPF to nursing rat pups via milk (Marty and Andrus, 2010). OEHHA therefore recommends that exposures via the lactational pathway be assessed or that DPR provide reasons for not assessing the pathway in the risk assessment.

c. Tolerance Assessment

For the tolerance assessment, the draft RCD evaluated the exposure to CPF from selected individual commodities at their respective tolerance levels, the maximal residue legally allowed on a commodity. However, the methodology for the tolerance assessment was not clearly described. It seemed that the commodities were selected based on high consumption rates or their high contributions to exposure in US EPA's (2011a) CPF dietary exposure assessment (Draft RCD: p. 114 and Appendix 2). However, the legend of Table 52 indicated that they were chosen based on consumption frequency only. In addition, some commodities (grape juice, soy milk, and cranberry juice) with high contribution in US EPA's CPF acute dietary exposure were not included. OEHHA suggests that DPR provide more explanation of the tolerance assessment methodology.

3. Drinking Water Exposure Assessment

DPR's acute drinking water assessment assumes 100% conversion of CPF to the more toxic CPF-oxon (the predominant CPF transformation product formed during drinking water treatment, i.e. chlorination). OEHHA concurs that this is a reasonable assumption and approach in general.

a. Residue Data

For estimating CPF-oxon exposures, DPR used three sources of CPF or CPF-oxon residues, with all samples from California. The three sources are: USDA's PDP data specific to California as well as DPR's surface and ground water databases. OEHHA concurs that using California specific samples is appropriate for assessing exposures to California residents.

b. Ingestion Rate

DPR estimated drinking water probabilistic exposures using drinking water consumption rates in the Dietary Exposure Evaluation Model Food Commodity Ingredient Database (DEEM-FCID™, version 2.036) for acute exposure. DEEM-FCID uses consumer-only consumption rates for acute exposure estimates. OEHHA concurs that a probabilistic assessment which uses consumer-only consumption rates is appropriate.

c. Exposure

The draft RCD (p. 243/298) states that "monitoring and modeling data were not available to estimate the steady-state (21-day) exposure to CPF-oxon in drinking water ... lack of residue data precludes a steady-state drinking water assessment at this time." OEHHA recommends that DPR seek an appropriate approach to estimate steady-state drinking water exposures. Excluding steady-state exposure is in contrast to US EPA's draft HHRA (US EPA, 2014a) which concluded that steady-state assessments were protective of acute assessments. In addition, OEHHA recommends that the food and water exposure estimates of formula-fed infants be summed together to give a dietary exposure estimate specific to this potentially highly exposed group.

4. Aggregate Exposure Assessment

In the draft RCD, acute aggregate exposure was only estimated for children 1-2 years old. OEHHA assumes this was due to the significant hand-to-mouth, object-to-mouth, and soil ingestion activity among this age group. However, other sensitive subpopulations (e.g., infants <1 year old) who have high inhalation rates adjusted for body weight were not included in the aggregate assessment and rationale for their exclusion should be provided.

OEHHA suggests that DPR conduct a screening-level assessment to prioritize the most important exposure pathways and identify susceptible populations. Dermal, inhalation, and incidental oral exposures to contaminated household dust as well as inhalation exposure to vapor should be considered as additional residential bystander exposure pathways.

In addition to the acute aggregate assessment, OEHHA suggests the inclusion of a steady-state aggregate assessment for susceptible populations due to the persistence of CPF in soil as well as its widespread use in food commodities and presence in ambient air and drinking water.

H. Risk Characterization

1. POD for Aggregate Exposure

For the acute aggregate MOE calculation, OEHHA agrees that CPF-induced inhibition of RBC AChE is cumulative. However, the rationale for using an acute oral POD for acute dietary exposures and steady-state PODs for acute dermal, inhalation, and non-dietary oral exposures is unclear. Intuitively, the acute PODs for all routes should be applied because the duration is acute. OEHHA suggests that DPR provide a clear explanation.

2. Target MOE

DPR considered a target MOE of 100 (which is the same as the total UF) as health protective for all exposure groups, durations, and routes (both single-route and aggregate exposures). This was based on a 1-fold UF for interspecies extrapolation, 10-fold for intraspecies variability, and 10-fold for DNT effects. As previously discussed (Section III.D), OEHHA recommends a target MOE of at least 1,000 when using PODs associated with RBC AChE inhibition derived from the PBPK-PD model for single-route and aggregate exposures. This is justified by (a) comparison of the PODs derived from the model to those OEHHA derived from the animal studies (Section III.D.2), (b) comparison of the PODs derived from the model to those suggested by the cord blood data and DNT effects reported in the Columbia study, and (c) large intraspecies variability of some key enzymes involved in the metabolism of CPF.

3. Tolerance Assessment

The draft RCD concluded that the MOEs of several commodities at their respective tolerance levels were below DPR's target MOEs of 100 (Draft RCD: p. 114-115). These included many commonly eaten fruits and vegetables: banana, broccoli, cabbage, grapefruit, and orange. DPR indicated that "when the risk is considered deleterious to human health, DPR can promulgate regulations to mitigate the exposure." OEHHA recommends that DPR mitigate situations where exposures are estimated to be higher than their respective tolerances. In addition, if the target MOE is increased to at least 1,000, there could be many more cases of tolerance exceedance.

IV. MINOR COMMENTS

The draft RCD needs careful proof-reading and revision for clarification and to correct errors. The following is not a comprehensive list and page numbers refer to the draft RCD.

Clarification

- PODs from the PBPK-PD model should not be referred to as “critical NOELs” or “critical human equivalent NOEL” (e.g., Draft RCD: p. 99).
- Pages 12-13, 30-32: The information related to pesticide illness in these two places is not consistent. OEHHA suggests checking the information.
- Page 16. Summary Table 1, footnote c refers to Table 20 for conversion data but Table 20 does not give the conversion data and these data could not be readily found in the RCD. Please provide the drinking water and body weight conversion data.
- Pages 17 and 83: The term “swath percentiles” is not defined within the draft RCD or appendices.
- Page 18: The version of DEEM used for DPR’s drinking water exposure assessment should be verified. DEEM 2.036 is a very old version.
- Pages 19 and 99: The minimum buffer zone distance is indicated as 25 feet, but the minimum federal label buffer zone is 10 feet and was used in the exposure assessment (pages 24-25 of Appendix 3).
- Page 30: Table 2 should indicate the extensive use of CPF, not just highlight the top 5 crops used.
- Page 82: OEHHA suggests providing the equation(s) or process for calculating inhalation exposure via AGDISP.
- Page 96: The number of water samples is inconsistent between the text under IV.B.2.d, Table 36 footnote b, and text on page 96.
- Page 97: In Table 35, for year 2009, the CPF residue of 0.000572 ppb seems low compared to the average limit of detection (LOD).
- Page 115, Table 52: Infant consumption of broccoli, cabbage, and grapefruit is greater than that of one or more of the other age groups. Children 1-2 years have a greater consumption rate of bell peppers than the older age groups. It is suggested that these values be double checked.
- Page 115: The text states that MOEs were lower than 100 for banana and grapefruit, yet Table 52 shows MOEs greater than 100.
- Page 132: DPR stated that the ambient air concentrations of CPF measured after a ground-based application (CARB, 1998) is similar to the simulated values from an aerial application obtained using AGDISP, but did not provide calculated values to support this statement. OEHHA suggests DPR include the calculation of the values when comparing simulated to field data.
- Page 132-133: Tables 57 and 58 need data source (Mississippi or California).
- Page 132-133: Table 57 (footnote b) states that the aggregate deposition “CD” risk estimates do not include inhalation exposure. However, the MOEs for CD

and Inhalation alone are nearly the same. This suggests that the inhalation exposures were included in the aggregate (CD) risk estimates and the footnote should be corrected.
- Page 132-134: Table 58 should cite the source for the TTR data (California).
- Appendix 2, Table 6, Pages 5-9: LOD values should be converted to ppb for consistency.
- Appendix 2, Tables 8 and 10, Pages 16-17: The minimum and maximum LOD values should be reported along with the average for each year.

Errors and Proofreading

- Page 19: Some text in the first paragraph is duplicated.
- Page 29: In the table of chemical and physical properties, the conversion factor appears to have several typos and should probably read as:
    - **Conversion Factor:** 1 ppm = 14.31 ± 3 mg/m^3 at 25°C
    - The units for the Henry's Law constant and density are not clear. Values for the Henry's Law constant and vapor pressure would be more clearly expressed in scientific notation (e.g., 2 x 10^{-5} mm Hg instead of 0.00002 mm Hg)
- Pages 44-45: Table 8 and Table 9 appear to be the same.
- Page 45: The footnotes from Table 7 are improperly replicated under Table 8.
- Page 81: Table 23 does not specify the application rate for Nufos 4E.
- Page 82: It is unclear why the Andrews and Patterson citation for inhalation rates is referenced (on top of this page) in the middle of the dermal exposure calculations.
- Page 83 (2nd paragraph): Table 27, instead of Table 26, should be cited for the drift exposure estimates for females exposed to CPF via groundboom or airblast
- Page 114: The table that lists tolerances for various commodities is Table 52, not Table 54.
- Page 132 (2nd paragraph): Table 24, not Table 23, should be cited for the simulated values.
- Page 133-134: Table 58 footnote c: the drinking water POD of 0.159 mg/kg-day is the same regardless of the source of exposure data so the term "from DW_EMON or DW_PDP" should be deleted.
- Table 58 is missing definitions for acronyms DW_EMON and DW_PDP.
- Page 137-138 (last paragraph): The text refers to Table 60 for the aggregate MOE combined scenarios. There is no Table 60.
- Appendices 2 and 3: Pagination needs to be changed so the page numbers for these two appendices continue from the last page of Appendix 1. Page numbers in the Table of Contents for Appendix 2 should be consistent with the newly assigned page numbers.
- Appendix 3, Page 2 (second paragraph): The text should read AGDISP 8.28, not AGDISP 2.28.

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