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MEMORANDUM

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DATE: August 15, 2017

SUBJECT: Response to Comments from the Office of Environmental Health Hazard Assessment on the DPR Draft Chlorpyrifos Risk Characterization Document (dated December 31, 2015)

INTRODUCTORY COMMENTS:

During the time in which the Office of Environmental Health Hazard Assessment (OEHHA) was reviewing the December 2015 draft Risk Characterization Document (RCD), the Human Health Assessment (HHA) Branch of the Department of Pesticide Regulation (DPR) made several changes and updates to the document, including a review of recent findings of chlorpyrifos (CPF) effects on the endocannabinoid system in rats and a revised discussion of epidemiological findings. ToxCast and zebrafish data were also updated and a summary table of all critical epidemiological and animal studies with endpoints was added. During the same time, US EPA revised their assessment of chlorpyrifos, which included a presentation of the modified pharmacokinetic-pharmacodynamic (PBPK-PD) model to the FIFRA Scientific Advisory Panel (SAP) on April 19-21, 2016[1] and the release of a revised risk assessment in November 2016, titled "Revised Human Health Risk Assessment for Registration Review"[2]. The SAP presentation predicted CPF blood concentrations in women for comparison with the measured values in the Columbia Center for Children's Environmental Health (CCCEH) cohort[3]. The revised US EPA risk assessment included predictions of exposures in adults, infants, and children using reverse dosimetry based on a simulated time-weighted average (TWA) concentration of CPF in blood. The revised DPR risk assessment extends the discussion to these new findings and has incorporated comments from the OEHHA review.

[1] FIFRA Scientific Advisory Panel Meeting, April 19-21, 2016, http://www.epa.gov/scipoly/sap/; Docket #: EPA–HQ–OPP–2016–0062; U.S.EPA 2016a. Chlorpyrifos Issue Paper: Evaluation of Biomonitoring Data from Epidemiology Studies *Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington, DC.* EPA-HQ-OPP-2016-0062-0005:https://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2016-0062-0005.

[2] The US EPA Revised Human Health Risk Assessment for Registration Review, November 3, 2016, available at https://www.epa.gov/ingredients-used-pesticide-products/revised-human-health-risk-assessment-chlorpyrifos.

[3] The Mothers and Newborn Study of North Manhattan and South Bronx performed by the Columbia Center for Children's Environmental Health (CCCEH) at Columbia University (http://ccceh.org/our-research/featured-nyc-research-findings).

I. SUMMARY OF REVIEW

The following response is to comments that OEHHA provided DPR on June 1, 2016 following their review of the December 2015 draft Risk Characterization Document (RCD) for Chlorpyrifos. Additional discussion was added to this response based on meetings with OEHHA on January 26, 2017, April 27, 2017, May 1, 2017, May 8, 2017, and June 5, 2017.

The Exposure Assessment summary comments are responded to immediately below. The remaining Summary Comments are addressed with the Responses to Charge Questions and in the Responses to Detailed Comments later in this document.

II. RESPONSE TO OEHHA SUMMARY COMMENTS

OEHHA Comments on Spray Drift Bystander Exposure Assessment: DPR did not evaluate inhalation exposure from ground boom 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.

> **HHA Response:** At the time of this assessment, acceptable methods for estimating inhalation exposure from ground boom and airblast applications were unavailable, as is the case today. However, HHA will take OEHHA's comments under consideration and evaluate other potential estimation methods in the future. As a preliminary method to address this data gap the AGDISP fixed-wing estimated air concentrations, adjusted for inhalable fraction, will be used to provide initial estimates of inhalation exposure associated with orchard airblast and ground boom applications.

OEHHA Comments on Spray Drift Bystander Exposure Assessment, continued: The draft exposure assessment did not evaluate exposure associated with volatilization of CPF or dust contaminated with CPF.

> **HHA Response:** Volatilization was not evaluated for two reasons:
>
> 1) A review of the air dispersion modeling presented in US EPA (2013) found that its estimates of the air concentrations of CPF were higher than the theoretical saturated air concentration (Reiss *et al.*, 2013). Air concentrations higher than the saturated air concentration of CPF cannot occur in the environment.
>
> 2) New toxicological studies submitted to US EPA show that saturated air concentration of CPF did not result in more than 10% acetylcholinesterase inhibition (U.S. EPA, 2014a; U.S. EPA, 2014b; U.S. EPA, 2014c).
>
> Considering 1) and 2) above, in the document entitled "Chlorpyrifos: Reevaluation of the potential risks from volatilization in consideration of chlorpyrifos parent and oxon inhalation toxicity studies" US EPA (2014d) reevaluated risks due to volatilization and stated: "Based on

the new data, there are no human health risks of concern anticipated for volatilization exposure to either chlorpyrifos or chlorpyrifos-oxon."

However, HHAB will further examine this issue if new information becomes available in the future.

In response to OEHHA's comment on the exposure to house dust, we conducted the following analysis. In the study by Bradman et al. (2007), organophosphate pesticides including CPF were measured in house dust samples collected from 20 farmworker families in 2002 at Salinas Valley, CA. For evaluating children's exposure to CPF via house dust, we combined the highest measured CPF house dust concentration (i.e., 1200 ng/g) with a daily dust ingestion rate of children 0<2 years old (i.e., 304 mg/day [at the 95th percentile]) (OEHHA, 2012). Assuming an infant body (i.e., < 1yr old) weight of 7.6 kg (Andrews and Patterson, 2000) and 100% oral absorption, a short term absorbed daily dose can be estimated as 0.048 μg/kg/day; compared the estimated dose to an acute oral PoD (steady state) of 103 μg/kg/day from infants, the MOE of CPF exposure due to house dust is 2146. It is noteworthy that the study by Bradman was conducted after the cancellation of CPF home-use in 2000; hence, CPF found in the house dust may be considered as "take-home" by the farmworkers from their works. Based on the results presented, CPF exposure from house dust would not constitute more than 10% acetylcholinesterase inhibition in infants.

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

HHA Response: Chlorpyrifos is now entering the formal Toxic Air Contaminant evaluation process with the Scientific Review Panel as per California Health and Safety Code sections 39660-39661, 39669.5 and 44360 and California Food and Agricultural Code sections 14022-14023.

III. OEHHA 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

HHA 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."*

OEHHA 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.

HHA Response: No response necessary.

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

OEHHA 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.

HHA Response: No response necessary.

B. Spray Drift Exposure Assessment

HHA Statement 1: Due to the limitation of AgDRIFT model, air concentrations of CPF from orchard airblast and ground boom applications can't be estimated.

OEHHA 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 (CARB, 1998; U.S. EPA, 2013a; Nsibande *et al.*, 2015).

HHA Response: Field data is only a snapshot of air concentrations associated with a particular type of pesticide application captured at that specific time and location. Without a sufficiently large number of independent studies it is difficult to evaluate the representativeness of field data. There are not enough available field studies to place confidence in how well the measured air concentrations represent the true population of air concentrations associated with a particular type of pesticide application (e.g., mean, 95th percentile, etc.). In addition, field data from a single study cannot be extended to other conditions, such as a different field size or application rate. For these reasons, HHA decided not to use field data to estimate air concentrations associated with ground boom or orchard airblast applications.

HHA has been cautious about using the AGDISP ground boom model because it has not been fully vetted. The comparison of AGDISP ground boom model outputs with field data have shown various discrepancies, including significantly over- or under predicting horizontal deposition depending upon the distance downwind (Woodward *et al.*, 2008; Teske *et al.*, 2009) and an inability to reasonably estimate vertical flux when compared to measured values (Connell *et al.*, 2012). The most recent AGDISP ground boom paper (Nsibande *et al.*, 2015) only modeled air concentrations for a ground application made to a 7.6 ha sorghum field with a height of 0.9m. The study did not model or measure actual deposition. The AGDISP ground model initially did not include a canopy effect algorithm (Teske *et al.*, 2009). The most recent version of the model

includes the ability to model the presence of a crop canopy. However, there are known deficiencies with the algorithm, including overestimation of the fraction of spray retained by the canopy (Forster *et al.*, 2012). Figure 2 of Nsibande et al. (2015) indicates a linear relationship between modeled and measured air concentrations. From the same figure, one can also see that the fit of the modeled air concentrations to measured air concentrations is sensitive to the fraction of the nozzle droplet spectrum less than 141 µm (the driftable fines) and the height at which the air concentrations are measured. This is evident from the non-parallel regression lines for nozzle types and the slopes values at different heights within nozzle type. Results from Nsibande et al. (2015) show that the model performance is highly dependent upon which nozzle is simulated and at what height the air concentration is estimated. In statistical terms, this is an interaction between nozzle and measurement height. Therefore, at this time we feel we cannot use the AGDISP ground boom algorithm to estimate air concentrations associated with ground boom applications.

C. Dietary Exposure Assessment

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

OEHHA 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.

HHA Response: See HHA response to OEHHA's comment on page 40 under a.1 "Residue Data" of this document.

HHA Statement 2: *"HHA 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."*

OEHHA 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.

HHA Response: The uncertainties associated with the use of residue data based on PDP or residues in surface and ground water in California to evaluate the acute and steady-state exposures in drinking water are discussed in the draft RCD (see sections III.B. and III.B.4.in Appendix 2; also see pp. 43 under "c. Exposure" in this document). The exposure from food and water for formula-fed infants is addressed in the HHA response to OEHHA's comment on pages 40-41 of this document in a3, under "Consumption Rate" and on page 43 under "c. Exposure."

D. Risk Characterization

HHA 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."*

OEHHA 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).

HHA Response: HHA prefers to use data from human studies if available. The PBPK-PD model employs data derived from human studies (Nolan *et al.*, 1984; Kisicki *et al.*, 1999). Allometric scaling approach was used for establishing those physiological parameters having no equivalent human data. This model has undergone extensive peer review including by the FIFRA Scientific Advisory Panel (see the 2014 US EPA Revised Human Health Risk Assessment (US EPA 2014a) for complete references). HHA reviewed the US EPA's 2014 Revised Human Health Risk Assessment and adopted the PBPK-derived human equivalent doses for establishing critical PoDs. HHA concurs with US EPA that, with respect to RBC AChE inhibition, the model accounted for the interspecies variation. Therefore the interspecies uncertainty factor can be reduced from 10-fold to 1. Table 1 shows that the critical PK biomarkers of CPF elimination and activation were concordant between humans and rats. Table 2 shows PoDs from US EPA and OEHHA's recommendations.

Table 1. Data Concordance and Completeness for PBPK-PD Model Validation

Data Source	Pharmacokinetic (PK) Biomarkers					Cholinesterase Biomarkers			
	Blood CPF	Blood Oxon	TCPy	Urine TCPy		Plasma	RBC	Diaphragm/ lung	Brain
ORAL						**ORAL**			
Rat	X	X	X	X		X	X	X	X
Human	X	X	X	X		X	X	X	X
INHALATION						**INHALATION**			
Rat	X	X	X	X		X	X	X	X
Human	X	X	X	X		X	X	X	X
DERMAL						**DERMAL**			
Rat	X	X	X	X		X	X	X	X
Human	X	X	X	X		X	X	X	X

Note: Replicated from Table 5, December 2015 Draft Chlorpyrifos Risk Characterization Document. Yellow highlighted areas indicate measured data used for the PBPK-PD model validation that was the most complete and showed the best concordance for RBC AChE and BuChE inhibition and TCPy biomarkers for oral, dermal, and inhalation routes of exposure (Timchalk and Poet, 2008; Smith *et al.*, 2011; Poet *et al.*, 2014; Poet *et al.*, 2017).

Table 2. Comparison between PoDs established by US EPA in the 2006, 2011, and 2014 Risk Assessments and OEHHA's Recommended PoDs

	US EPA 2006 (IRED)		**US EPA 2011 (Preliminary HHRA for Reregistration)[c]**		**US EPA 2014 (Revised HHRA for Reregistration)**		**OEHHA Recommendation**	
Oral Route	**PoD**	**PAD**	**PoD**	**PAD**	**PoD**	**PAD**	**PoD**	**PAD**
Acute (mg/kg/day)	**0.5** Rat NOEL for plasma and RBC AChEI 1 dose[a]	0.0005 ***UF=1000*** 10 inter 10 intra 10 FQPA	**0.36** Rat $BMDL_{10}$ for RBC AChEI pups (PND11) 1 dose[b]	0.0036 ***UF= 100*** 10 inter 10 intra 1 FQPA	**0.5-0.6** Human PBPK-PD for 10% RBC AChEI	0.005 ***UF=100*** 1 inter 10 intra 10 FQPA	**0.04** Rat $BMDL_{10}$ for RBC AChEI in dams at LD1 (16 doses)	**0.00004** **UF=1000** **3 inter** **30 intra** **10 FQPA**
Steady-state (21 d) or subchronic					**0.08-0.1** Human PBPK-PD for 10% RBC AChEI	0.0008 ***UF=100*** 1 inter 10 intra 10 FQPA	**0.05** **Rat BMDL10 for RBC AChEI adult F (4 wks)[d]**	**0.00005** **UF=1000** **3 inter** **30 intra** **10 FQPA**
Chronic (mg/kg/day)	**0.03** **Rat WOE from 5 Studies: NOEL for plasma & RBC AChEI[e] (16d—2 yrs)**	**0.00003** **UF=1000** **10 inter** **10 intra** **10 FQPA**	**0.03** **Rat BMDL10 for RBC AChEI in pregnant (GD6-20) rats, DNT (16d)[f]**	**0.0003** **UF=100** **10 inter** **10 intra** **1 FQPA**	ND	ND	ND	ND

[a] Mendrala and Brzak 1998 (adult Male NOEL=0.5 mg/kg/d; Zheng et al. 2000 (adult & pup NOEL=0.75 mg/kg/d for RBC AChE)

[b] Marty and Andrus, 2010 (pup & adult female NOEL=0.5 mg/kg/d; pup $BMDL_{10}$ 0.36 mg/kg/d)

[c] Subsequent to 2008 SAP Meeting.

[d] Maurissen, 1996

[e] Weight of evidence from 5 studies: 2 year dog (McCollister et al. 1971); 90 day dog (McCollister, 1964); 2 year rat (Young & Grandjean, 1988); 90 day rat (Szabo et al. 1988); developmental neurotoxicity (DNT) rat study (at 2 weeks; Hoberman, 1998)

[f] Weight of evidence for RBC AChEI in rat dams: 0.3 mg/kg/d; GD 6 – 20, 15d; Hoberman, 1998 and Gavage study in pregnant rats: 0.35 mg/kg/d; GD 6 –20, Marty & Andrus, 2010.

Note: After the release of the DPR draft RCD dated December 31, U.S. EPA proposed PoDs for CPF that were not for RBC AChE inhibition, but were for predicting risk from neurodevelopmental outcomes. These PODs were based on either (1) cord blood data from the prospective birth cohort study "Mothers and Newborn Study of North Manhattan and South Bronx conducted by Columbia University (CCCEH) (U.S. EPA 2016a) or (2) time weighted average (TWA) blood concentrations of CPF predicted for the CCCEH cohort (U.S. EPA 2016c).

OEHHA Response, continued: OEHHA suggests increasing the intraspecies UF to *at least* [emphasis OEHHA] 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.

HHA Response: We agree with OEHHA that the existing PBPK-PD model does not have the ability to account for physiological and biochemical changes during pregnancy. Consequently HHA addressed this uncertainty by applying a default 10X intraspecies factor. The variations due to genetic polymorphism, metabolism, age and environmental factors are addressed later in this document. It should be noted that the model has a built-in variability of up to 10-fold for intraspecies variability in metabolism and cholinesterase activities associated with age (from infant through adulthood). Table 3 illustrates the range of overall variability for the critical metabolic pathways incorporated in the model.

Table 3. Ratios of the maximum to minimum value in the raw data, parametrically distributed, and bootstrap model simulations for the critical enzymatic pathways

Parameter	**CYP450 to TCPy**	**CYP450 to Oxon**	**Hepatic PON1[a]**	**Plasma PON1[a]**
Range in raw *in vitro* data (Smith *et al.*, 2011)	12	28	11	6
Range in parametric distribution	26	34	33	33
Range used in PBPK model for DDEF calculations (from 20 parametric bootstraps [b] (Smith *et al.*, 2014)	**74**	**98**	**58**	**58**
Ratios (raw data to data used in PBPK model)	1:6.1	1:3.5	1:5.2	1:9.6

[a] Values for PON1 in liver & plasma assumed to be correlated & thus have the same variation (U.S. EPA, 2014a). Red text indicates data used in the PBPK-PD model (US EPA, 2014a).
[b] Data reported in US EPA 2014a and subsequently published in Poet et al., 2017.

OEHHA Response, continued: 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 (U.S.EPA, 2015). Thus, OEHHA recommends a target margin of exposure (MOE) of at least 1,000, instead of 100 as proposed in the draft RCD.

HHA Response: HHA applied a 10-fold uncertainty factor to account for the intraspecies variability with respect to inhibition of RBC AChE activity and an additional 10-fold UF to address potential neurodevelopmental/neurobehavioral effects. Therefore, the total UF used by DPR is 100. However, because of the 10-fold built-in variability in the PBPK-PD model, the effective total uncertainty factor is 1000. Further discussion on PoD derivation using PBPK-PD modeling can be found starting on page 14 of this document and additional explanation of intraspecies and metabolic variability on pages 16 and 19-24 of this document. Table 4 shows a side-by-side comparison of factors compiling the total uncertainty factors used by DPR and suggested by OEHHA.

Table 4. Comparison of Uncertainty Factors Used by DPR and OEHHA

Uncertainty Factors	DPR	UF Basis (Deficiencies)	OEHHA	UF Basis (Deficiencies)
Interspecies	1	Human equivalent doses derived from the PBPK-PD model	3	Animal model; data from human post-mortem tissues; limited validation (1 acute oral human study)
Intraspecies	10	PBPK-PD Model: PBPK-PD model did not account for all physiological, anatomical, & biochemical pregnancy changes Metabolic parameters (variability of PON1 & CYP450) were based on cryopreserved tissues from a small sample sizes; not representative of general population	30	PBPK-PD Model: Pregnancy (did not fully account for physiological, anatomical, biochemical changes associated with pregnancy, did not include fetal metabolism related to RBC AChE inhibition); genetic polymorphism (PON1, CYPs); metabolic variation; AChE activities based on age, environmental factors
Neuro-developmental	10	Neurodevelopmental toxicity	10	Neurodevelopmental toxicity
Combined UF	**100**		**900**	

HHA 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.

OEHHA 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.

HHA Response: No response is necessary.

HHA 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."

OEHHA 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 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.

> **HHA Response:** Besides AChE, other CPF targets and potentially more sensitive non-cholinergic pathways are discussed in the RCD, along with the data limitations for defining quantitative dose-response relationships based on these mechanisms. Therefore, the aggregate exposures in the RCD were evaluated for the potentially most sensitive populations (females of childbearing age and children 1-2 years old) using acute and steady- state PoDs based on AChE inhibition. The use of steady-state PODs for routes other than dietary was detailed in the RCD. Please refer to Section IV.A.2. *Exposure Scenarios Development* in the revised RCD for further explanation.

IV. OEHHA DETAILED COMMENTS

1. OEHHA Comments on 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.

> **HHA Response:** As OEHHA correctly pointed out, factors such as temperature affect the environmental fate of CPF. That is why the spray drift modeling uses the reasonable worst case meteorological conditions that were chosen based upon procedures stated in (Barry, 2015). Updated environmental fate information on chlorpyrifos the DPR Environmental Monitoring branch can be found here: http://www.cdpr.ca.gov/docs/emon/airinit/2560_chlorpyrifos_final.pdf and http://www.cdpr.ca.gov/docs/emon/pubs/tac/tacpdfs/chlrpfs/append_a_chlorpyrifos_use_information.pdf. For a more complete description of the environmental fate of CPF, please refer to the Physico-Chemical Properties and Environmental Fate of Pesticides (1994) available at http://www.cdpr.ca.gov/docs/emon/pubs/ehapreps/eh9403.pdf

2. OEHHA Comments on Pesticide Use and Sales:

The draft 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 (U.S. EPA, 2015; CDPR, 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.

> **HHA Response:** Based on the information presented in RCD, inhalation exposure to CPF was identified as the exposure route of greatest concern. The aerial application scenario is the worst case exposure scenario due to both the ground speed of the aircraft relative to ground boom applications and the release height of 10 ft above the target for aerial versus a maximum of 50 in for high boom ground. For the same application equipment, spray drift increases with increased speed and increased release height (Bird *et al.*, 2002; CSIRO, 2002). Thus, the spray drift associated with aerial applications can be expected to be much higher than ground application methods with respect to the bystander exposure of CPF. The risk assessment seeks to characterize the maximum exposed individual. However as a preliminary method to address the data gap on characterizing airblast and ground boom applications, the AGDISP fixed-wing estimated air concentrations adjusted for inhalable fraction will be used to provide initial estimates of inhalation exposure associated with both application types.

3. OEHHA Comment on 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.

> **HHA Response:** The revised risk assessment includes updated pesticide illness data from DPR's Pesticide Illness Surveillance Program. For the comments regarding contaminated dust, please see our response on page 3 of this document.

OEHHA Comments on 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.

> **HHA Response:** The PBPK-derived dermal PoD employed in this risk assessment already integrates a dermal absorption of CPF in humans into its derivation (Poet et al., 2014). Hence, the use of a dermal absorption factor for computing an internal dose in the draft assessment is not necessary. Similarly, the PBPK-derived inhalation PoDs are age- and gender-specific (US EPA, 2014a). In other words, the use of age- or gender-specific breathing rate for computing an internal dose in the draft assessment is not needed. Inhalation exposure was based on an acute rat CPF aerosol inhalation study (Hotchkiss, 2010) and a human volunteer study (Vaccaro, 1993). Data from these studies were incorporated into the PBPK-PD multi-route exposure model used in the 2014 US EPA Risk Assessment and later reported by Poet et al., 2015. The article provides the code and calculations for deriving inhalation exposures.

OEHHA Comments on Pharmacokinetics, continued:

The draft RCD described in detail studies on the oral pharmacokinetics of CPF in the rat (Nolan et al., 1987) and the oral (Nolan et al., 1984; Griffin et al., 1999; Kisicki 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; Hotchkiss et al., 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.

HHA Response: The above mentioned articles were included in the RCD, however not in the Pharmacokinetics section. The RCD has been revised to include review and discussion of these articles in the Pharmacokinetic Section (II.B.1. Metabolism and Pharmacokinetics in Rat). Mattsson *et al*. indicate that fetuses and pups are exposed in milk and through blood, but the AChE inhibition values in all tissues are less than those of the dams (Mattsson *et al.*, 1998; Mattsson *et al.*, 2000).

OEHHA Comments on POD Determination Using PBPK-PD Model:

DPR chose to adopt the PBPK-PD model-derived PODs established by U.S. 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).

HHA Response: OEHHA's comment on the utilization of the PBPK-PD model is noted.

OEHHA Comments on POD Determination Using PBPK-PD Model, continued:

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).*

HHA Response: In relation to CPF levels in infants versus adults, CPF-oxon levels, and metabolism/distribution, please refer to the following from (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."

*"*After equivalent oral doses of CPF, the life-stage model predicts marginally lower systemic levels of CPF and, at doses ≥0.6 mg/kg CPF, higher levels of CPF-oxon in children compared to adults. These age-dependent discrepancies resulted from differences in overall CPF and CPF-oxon metabolism and, to a lesser extent, CPF distribution (see Fig. 13 below from Smith *et al.* (2014). Since levels of hepatic CPF and CPF-oxon metabolism on a microsomal basis and the level of hepatic microsomal protein are constant as a function of age in the model, increased hepatic CPF and CPF-oxon metabolism in children is driven by a larger liver fraction per body weight compared to adults. At doses ≥0.6 mg/kg…predicted increases in CPF-oxon in children are a result of CPF-oxon levels overwhelming CPF-oxon metabolism capacity in plasma, which is lower in children than in adults (Smith *et al.* (2011). At doses <0.6 mg/kg, increased CPF-oxon metabolism in children is enough to cause marginally lower CPF-oxon levels compared to adults. The model predicts that plasma ChE inhibition is slightly higher in adults than in children, because the dynamic range for ChEI in plasma occurs at doses lower than 0.6 mg/kg CPF, and thus, CPF-oxon levels are slightly higher in adults. These simulations (<0.6 mg/kg CPF) are comparable to predictions made previously, suggesting that 19-year old humans are more sensitive to plasma and RBC ChE inhibition than 1-year olds from equivalent oral doses of CPF (Foxenberg *et al.*, 2011). Besides metabolism, distribution also plays a role in age-dependent differences in CPF pharmacokinetics. Adults have more fat content than children, and since CPF is lipophilic ($\log K_{ow}$ 4.82;(McCall *et al.*, 1980)), fat can act as a CPF depot. Following an oral dose of CPF, adults have a larger fraction of the dose in fat depots compared to 6 months infants (~2-fold), which alters the distribution of CPF. Lower overall CPF metabolism and, at a lesser extent, altered distribution increases the half-life of CPF in blood to nearly double in adults compared to 6 months old neonates."

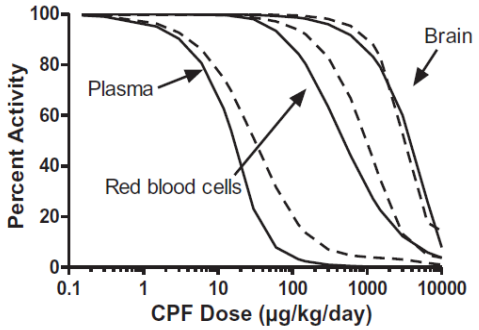

Fig. 13. Comparison of cholinesterase inhibition in plasma and acetylcholinesterase inhibition in red blood cells and brain between the life-stage physiologically based pharmacokinetic and pharmacodynamic (PBPK/PD) model (solid lines) and a previously published PBPK/PD model (dashed lines) for chlorpyrifos (CPF) in adults. Single doses were administered as zero order constant rates of uptake for both simulations.

HHA Response, continued: In relation to a comparison of the metabolic capacity of infants versus adults it is important to note that Smith et al (2011) characterized the metabolism of CPF and CPF-oxon in hepatic microsomes and plasma acquired from human tissues spanning a broad age-range. They showed that the metabolic rates of CPF and CPF-oxon did not change across age groups on a microsomal protein basis. However, variability was generated by physiological changes that affect age-dependent pharmacokinetics (e.g., age-dependent changes in liver volume; (Young *et al.*, 2009). This is shown in the graph below:

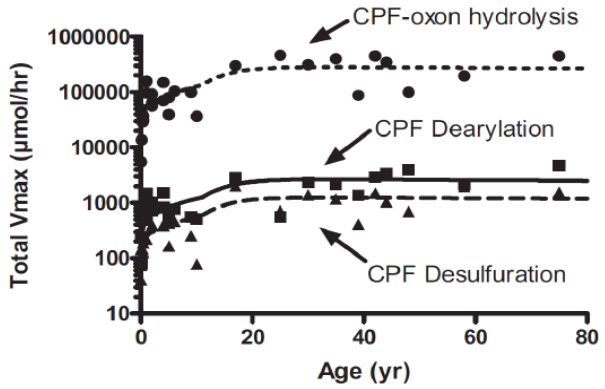

Figure 7 from Smith et al. (2011). Total *V*max values of human enzymatic metabolism of CPF dearylation, CPF desulfuration, and CPF-oxon hydrolysis in liver over various ages. *V*max values are scaled to age-dependent volume of the liver and a constant

OEHHA Comment on POD Determination Using PBPK-PD Model, continued:

There is a "constant" amount of microsomal protein per gram liver (33 mg/g) across all ages (Smith et al., 2014).

HHA Response: Based on findings from Wilson et al. (2003), Smith and colleagues used a constant of 33 mg human microsomal protein/gram liver tissue (MPPGL) to scale the in vitro-derived human metabolic rate constants to predictions of in vivo metabolism (Smith *et al.*, 2014). By way of background, several researchers measured MPPGL in adult, pediatric, and fetal samples. In order to examine human inter-individual variability, Wilson et al. (2003) estimated the MPPGL ratio from 20 samples as well as the hepato-cellularity (HPGL n = 7))/g human liver. Their results showed that in samples from adults aged 37 to 76, the MPPGL ranged from 26 to 54 mg/human adult liver with a geometric mean of 33 mg/g. In the same samples, HPGL ranged from 65-185 x 106 cells/g human livers (Wilson *et al.*, 2003). Then in 2007, Barter et al. used a meta-analysis to further elucidate the variability of MPPGL in human livers from samples from adults aged 11-80 (n ≈ 200) (Barter *et al.*, 2007). In 2008, Barter *et al*. went on to show that MPPGL ratios change with age. Their results indicated that samples from children aged 2-13 (n = 4) had MPPGL ratios of 23-30 mg/g liver while a fetal sample (n = 1) had a MPPGL ratio of 26 mg/g. MPPGL values peak at age 28-30 (37-43 mg/g n ≈ 170) then start to decline with age (65 years old = 27-32 mg/kg) (Barter *et al.*, 2008). Therefore, the selection of a MPPGL constant

of 33 mg/g fits the average ratio in adults prior to age-related decreases and it is also close to the MPPGL range found from both fetal and pediatric samples.

OEHHA Comments on POD Determination Using PBPK-PD Model, continued:

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 hyper-variability 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).

HHA Response: Age-related CYP levels and how their variability is accounted for in the model are discussed in the responses on pages 15 and 23-24 in this document.

OEHHA Comments on POD Determination Using PBPK-PD Model, continued:

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.

HHA Response: No response is necessary.

OEHHA Comments on the 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.

HHA Response: No response is necessary.

OEHHA Comments on the 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., 2002a). It underwent numerous modifications culminating in the current multi-route life-stage PBPK-PD model (Poet et al., 2014; Smith 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 (U.S. EPA, 2016a). 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).

HHA Response: The PBPK-PD model that generated the critical PoDs values used in our draft risk assessment had been described in numerous publications and in the 2014 US EPA Revised Human Health Risk Assessment. All of these publications were cited in the draft document. In the revised draft, we extended the model description to include a recently updated PBPK-PD model aiming to predict the systemic exposure and AChE inhibition in pregnant woman.

OEHHA Comments on the 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.

HHA Response: Many of the concerns mentioned above are discussed in the "Risk Characterization" section starting on page 6 of this document. HHA agrees that the sample sizes may not be representative of the variation within the general population. However, the model incorporates life-stage parameters based on tissues from newborns to adults (Smith et al., 2011) including the liver metabolism pathways documented in the 30 cryopreserved human microsomal samples. This series of pathways is as follows:

1. Activation of CPF → CPF-oxon by CYP2B6 and CYP3A4/5
2. Detoxification of CPF → TCPy by CYP2C19 and CYP3A4/5
3. Detoxification of CPF-oxon → TCPy by PON1 and AChE

The age-related subpopulations from which the tissues were obtained are listed in Table 1 below, originally published in Smith et al., 2011.

TABLE 1

Demographic data for liver samples in this study

Data were supplied by XenoTech, LLC (http://www.xenotechllc.com).

Sample	Gender	Age	Race	COD	Smoker/Drinker
		years			
H0354	F	0.04	W	CVA	N/N
H0845	M	0.08	W	HT	N/N
H0282	M	0.17	H	Anoxia	N/N
H0671	M	0.25	H	Anoxia	N/N
H0268	M	0.33	W	SIDS	N/N
H0270	M	0.42	W	Anoxia	N/N
H0395	M	0.42	W	HT	N/N
H0825	M	0.92	W	Anoxia	N/N
H0322	M	1	H	Anoxia	N/N
H0346	M	1	W	CVA	N/N
H0057	F	2	W	Anoxia	N/N
H0551	M	2	W	HT	N/N
H0852	M	2	H	HT	N/N
H0776	F	4	AA	CVA	N/N
H0792	M	4	AI	HT	N/N
H0675	M	5	W	Anoxia	N/N
H0689	F	5	W	HT	N/N
H0215	M	6	W	HT	N/N
H0059	M	9	W	HT	N/N
H0485	M	10	W	Anoxia	N/N
H0133	M	17	W	HT	Y/Y
H0459	F	25	W	HT	N/Y
H0025	F	30	W	CVA	Y/Y
H0743	M	35	W	CVA	Y/Y
H0424	F	39	W	CVA	Y/Y
H0251	F	42	W	Anoxia	Y/Y
H0752	M	44	W	Anoxia	N/Y
H0115	F	48	W	CVA	N/N
H0201	M	58	H	CVA	N/Y
H0203	M	75	W	CVA	Y/N

AA, African American; W, white; H, Hispanic; AI, American Indian; COD, cause of death; SIDS, sudden infant death syndrome; CVA, cerebrovascular aneurysm; HT, head trauma; F, female; M, male; N, no; Y, yes.

The PBPK-PD model for chlorpyrifos incorporates data from two human acute oral studies and one acute dermal dosing study (Nolan *et al.*, 1984; Kisicki *et al.*, 1999), including metabolic data derived from plasma metabolism studies in 20 cryopreserved human plasma samples. There may be some concern in using metabolic data derived from cryopreserved human tissues because enzymatic activity may have changed from the time of tissue acquisition to the time of microsomal preparation. It is noteworthy that XenoTech, LLC uses the same standardized protocols for tissue donation, tissues collection, procurement, and preparation of human microsomes.[4] Once the human livers are obtained, they are cooled and filled with cryopreservation solution. The stability of the human liver microsomes has been documented with little effect in metabolic activity over multiple freeze-thaw cycles.[5] In addition, the human livers used as a source for microsomes are prepared in a similar fashion to those used for organ transplantation. Utilization of microsomes derived from human tissues is recommended by the federal Food and Drug Administration in its Guidance for Industry Drug Interaction Studies.[6]

The results of the reaction of CPF-oxon → TCPy by esterases is shown in Table 2 below, originally published in (Smith *et al.*, 2011).

TABLE 2

Demographic and metabolism data for plasma samples in this study

Sample	Gender	Age	Protein Concentration	CPF-oxon Hydrolysis V_{max}	CPF-oxon Hydrolysis K_m	CPF-Oxon Hydrolysis Cl_i
		years	*mg/ml*	*nmol · min^{-1} · ml^{-1}*	*μM*	*μl · min^{-1} · mg microsomal protein^{-1}*
BRH338829	F	0.01	49.44	802	118.46	6771
BRH338830	F	0.02	48.13	2410	283.13	8513
BRH338828	F	0.06	53.91	1938	114.32	16950
BRH338832	F	0.17	56.74	1919	132.53	14482
BRH338831	M	0.42	49.73	2438	146.15	16679
BRH338837	M	0.58	66.87	4873	175.21	27814
BRH338833	F	0.67	46.20	1241	527.12	2354
BRH338836	M	0.67	69.01	4900	205.94	23793
BRH338834	M	0.83	69.30	4027	136.12	29585
BRH338835	M	0.83	75.05	2460	192.25	12795
BRH338841	M	2	77.95	3082	169.61	18169
BRH338839	M	4	80.77	598	230.75	2591
BRH338842	M	9	72.75	6624	191.70	34555
BRH338840	M	10	71.51	4914	217.85	22556
BRH338838	M	12	95.95	9643	264.73	36428
BRH338843	F	16	90.69	7531	202.66	37162
BRH338844	F	17	84.75	6650	174.87	38031
BRH338847	M	30	97.68	8849	203.27	43533
BRH338846	F	43	75.47	6691	200.59	33358
BRH338845	F	46	86.55	4423	176.51	25056
Adult mean ± S.D.			87 ± 8	6829 ± 1614	192 ± 15	35428 ± 6843

F, female; M, male; Cl_i, intrinsic clearance.

In Smith *et al*. (2014), an even broader range of variability was incorporated into the model by use of a bootstrap method whereby 20 bootstraps were used from over 20,000 iterations of the model. Although not specifically accounting for genetic or ethnic variability, the fold-difference generated by the bootstrap method resulted in a 58-fold variability for PON1 in liver and plasma. According to Ginsberg *et al.* (2009), the intra-genotypic variability in activity due to the PON1 192 polymorphism was 15-fold for CPF. Therefore, the PBPK-PD model exceeds the range of CPF allotype variability by at least 4-fold beyond the projected (measured) range for PON1

[4] XenoTech LLC, https://www.xenotech.com/company. Protocols available at https://www.xenotech.com/products/subcellular-fractions/human/liver/microsomes

[5] Ibid.

[6] Federal Food and Drug Administration Guidance for Industry Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations specifically for use in PBPK modeling. Draft Guidance, February 2012. Available at https://www.fda.gov/downloads/Drugs/Guidances/ucm292362.pdf.

based on Ginsberg *et al*. (2009). The variability also exceeds the measured PON1 activity by about 10-fold when compared to the measured values from Smith *et al*. (2011). The four metabolism-related parameters (shown above on page 18 of this document and in US EPA 2014d) were found to drive more than 80% of the total variation in RBC AChE inhibition.

OEHHA remarks that acute dosing studies were used to derive steady-state PODs for 10% RBC AChE inhibition. However, the model is capable of deriving acute and steady-state values depending on the input parameters.

In summary, the PBPK-PD model has incorporated 60-100-fold differences for the 4 critical pathways and the enzymes involved in the CPF metabolism.

OEHHA Comments on 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).*
- *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 ((U.S. EPA, 2016b): 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.*

HHA Response: The utilization of the PBPK model by US EPA has changed since we completed our draft RCD and these comments have been addressed in the updated risk assessment.

OEHHA Comments on the PBPK-PD Model-Derived PODs – 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.

HHA Response: The issue of interspecies UF can be found on pp. 6 and 18-20 of this document.

OEHHA Comments on the PBPK-PD Model-Derived PODs – Intraspecies Extrapolation:

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. 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.

HHA Response: Data have shown that in human liver microsomal samples there is variation of: 1) activity among CYPs, 2) CYP phenotypes/microsomal sample; 3) gram microsome/liver, and 4) overall activity per individual (Boobis *et al.*, 1998; Sams *et al.*, 2004). The overall activity per individual (hence variability) is highly dependent on substrate. However, other considerable variables involve consistent testing procedures across laboratories as well as experimental protocol factors such as substrate concentration, length of incubation, and the amount of protein used to assess activity of CYPs involved with CPF metabolism (CYP1A2, CYP2C9, CYP2D6, CYP2E1 and CYP3A4). These factors have been largely accounted for in the PBPK-PD model.

The modeled metabolic rate parameters for CYP-based activation (desulfuration) and detoxification (dearylation) are set as constants across different age groups based on laboratory determinations discussed previously and in Smith et al., 2011. In addition to the CYP variability incorporated (3.5-9.6x) into the model, HHA added an additional10-fold UF for intraspecies differences in genetics, ethnicity, range of sensitivity, for lack of physiological changes during pregnancy, for uncertainty relating to cryopreserved samples analysis, and for the small sample sizes.

OEHHA's recommendation to apply a larger intra-species uncertainty factor is based on the reported differences in activities of metabolic enzymes that can exceed 10-fold. Such differences can be due to age, genetic polymorphisms, and environmental factors. Citing Ginsberg *et al*., 2009, OEHHA states that the PON1 genetic polymorphisms can generate up to a 100-fold difference between the extreme minimum and maximum enzyme activity. This was based on results from Monte Carlo modeling of PON1 function related to polymorphisms. By way of clarification, Ginsberg *et al*. (2009) did not report Monte Carlo analysis results for CPF or CPF-oxon. We were unable to confirm OEHHA's calculation of the 100-fold difference between the extreme minimum and maximum enzyme activities for either paraoxon or Sarin in Ginsberg et al. (2009). The authors, however, did report the widest range in PON1 enzymatic activity for paraoxon and Sarin as substrates. The study reported the individual human variation in serum PON1 activity to be 15-fold for chlorpyrifos, and this is compared to a 56-fold variation for paraoxon. It should be noted that PON1 activity does not necessarily equate to differences in toxicity. For example, PON1-knockout mice lacking PON1 activity in liver or plasma were not more sensitive to paraoxon toxicity (Li *et al.*, 2000b; Ginsberg *et al.*, 2009).

Thus, while differences in PON1 activity may partially account for differences in sensitivity to OPs, the range of sensitivity in human populations depends on more than just the activity of this enzyme alone. Other factors impacting the activity of the enzyme include the substrate specificity and binding efficiencies, the rate of oxon formation via phase I metabolism, competing pathways for the removal of the parent compound, metabolic interactions with endogenous compounds and therapeutic drugs that compete for CYPs, as well as certain lifestyle or environmental factors. All of the factors that may contribute to OP sensitivity are not known. Nor have their quantitative contribution to sensitivity been elucidated. But based on current knowledge, we have concluded that a default intra-human variability factor of 10 will adequately protect human populations. Nonetheless, we accept that further research directed toward a quantitative appreciation of the range of chlorpyrifos sensitivity among humans is both necessary and needed. Discussion of the results of Ginsberg *et al*. (2009) is included in the revised RCD.

OEHHA Comments on the 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 (U.S. 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.

HHA Response: No response necessary.

OEHHA Comment on the 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 (U.S. EPA and /SAP, 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.

> **HHA Response:** In 2012, the SAP[7] suggested using a PBPK-PD model for CPF risk assessment. With respect to using animal data to "bound" the PoDs derived from the PBPK-PD model, HHA notes that the human PoDs are similar to the PoDs derived from animal studies based on the same endpoint (RBC AChE inhibition) for either acute or subchronic duration (see Table 2 on p. 7 of this document). Therefore, "bounding" the human PoDs with animal data does not provide a basis for increasing the total uncertainty factor by 10-fold. The PBPK-PD model, on the other hand, accounts for pharmacokinetic and pharmacodynamic differences between animals and humans and provides scientific support to reduce the interspecies factor to 1x.

OEHHA Comment on the Comparative Analysis Using Animal Toxicity Data, continued:

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.

> **HHA Response:** HHA concurs with US EPA that the neurodevelopmental/ neurobehavioral effects in animals and humans are qualitatively similar. OEHHA's selection of animal studies for use in developing the bounding estimate is discussed earlier in this document.

OEHHA Comment on 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

[7] SAP Minutes No. 2012-04. A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding Chlorpyrifos Health Effects. April 10 – 12, 2012 FIFRA Scientific Advisory Panel Meeting. Available at https://www.epa.gov/sites/production/files/2015-06/documents/041012minutes.pdf

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 BMDL10 (10% benchmark response3) of 0.04 mg/kg-day for the inhibition of RBC AChE in the rat dam on LD1.

> **HHA Response:** Mattsson *et al*. (1998) used a repeated dose protocol treating pregnant rats during the gestation with exposure continuing through the lactation period. The first measurement of ChE activity was conducted after dosing pregnant dams for 2 weeks. Given the fact that the time needed for achieving pre-dose ChE activity is much longer than one day (Nolan *et al*., 1984), the repeated doses received by the pregnant rats in Mattsson *et al*. (1998) would be expected to cause accumulated ChE inhibition prior to the first measurement at week 2. Accordingly, OP-induced ChE inhibition measured after 2 or more weeks of treatment would approach a steady-state level of inhibition, and should not be used as an endpoint to derive the acute risk evaluation. Comparison between the OEHHA's $BMDL_{10}$ of 0.04 mg/kg/day from the Mattsson study to the PoDs for various exposure duration supports that this value is in the range of the steady state or chronic PoDs.

OEHHA Comments on 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 BMDL10 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 BMDL10 values of around 0.05 mg/kg-day for RBC AChE inhibition. These BMDL10 values and source studies are: (1) BMDL10 of 0.06 mg/kg-day from male rats at 6 months of treatment in a chronic rat study (Young and Grandjean, 1988), (2) BMDL10 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) BMDL10 of 0.06 mg/kg-day from male dogs after 6 weeks of exposure (Marable et al., 2001), and (4) BMDL10 of 0.05 mg/kg-from female rats following 4 weeks of exposure (Maurissen, 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.

> **HHA Response:** The error in the labeling of our tables is corrected in the revised risk assessment draft. Please see previous discussions in this document regarding adopting the 2014 US EPA's human PoDs for CPF versus PoDs derived from animal studies.

OEHHA Comment on 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.

HHA Response: Please see previous discussions in this document regarding use of interspecies UF.

OEHHA Comments on 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 activities 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.

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.

HHA Response: HHA has updated the ToxCast information to include the latest available data (dashboard 2; version 2).

OEHHA Comments on the 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" (U.S. EPA, 2011) (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.

> **HHA Response:** This comment is valid and we included a section in the revised RCD discussing the recent IARC reports and the findings from the Agricultural Health Study (Lee *et al.*, 2004; Lee *et al.*, 2007).

OEHHA Comments on 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 (Rahman et al., 2002; Mehta et al., 2008). OEHHA suggests that DPR discuss whether or not the positive studies provide evidence of genotoxicity.

> **HHA Response:** FIFRA guideline and non-guideline genotoxicity studies yielded mixed results. In the absence of evidence for CPF-induced tumors in the rodent cancer bioassays, the weight of evidence for carcinogenicity is not compelling. In recognition of the issues raised by OEHHA, HHA has added additional discussion in the revised RCD addressing cancer epidemiology studies and positive genotoxicity assays.

OEHHA Comments on 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; Alavanja et al., 2004; Lee et al., 2004; Engel et al., 2005; Lee et al., 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.

> **HHA Response:** The mutagenicity and animal bioassays for carcinogenicity of CPF were mostly negative. However, several epidemiological studies of pesticide applicators and farmers reported associations between CPF use and non-Hodgkin lymphoma, lung and rectal cancer. These positive associations were based on small numbers of cases and concomitant exposure to other chemicals was a common confounder in these studies. Therefore, the available data are inadequate for carcinogenicity evidence in humans. A summary of the human epidemiological studies was added to the revised RCD.

OEHHA Comments on 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 (U.S. EPA, 2014b). However, a worker exposure assessment was not conducted in this draft RCD and no rationale was provided for this limited scope.

> **HHA Response:** The scope of the RCD was limited to non-occupational bystander exposure to CPF due to off-site movement, such as spray drift from agricultural applications in California.

OEHHA Comments on Exposure Assessment, continued:

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.

> **HHA Response:** We have updated the text to indicate that children 1-2 years old and women of childbearing age are the population subgroups of interest in evaluating spray drift exposure CPF.

OEHHA Comments on Residential Bystander Spray Drift Exposure Assessment (Environmental Concentrations – 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.

> **HHA Response:** HHA is in the process of evaluating alternative methods to estimate potential inhalation exposure associated with orchard airblast and ground boom application methods. HHA is evaluating both air monitoring studies provided by OEHHA (CARB, 1998; Fenske *et al.*, 2009) for determining off-site airborne pesticide concentrations. New studies available in the public domain will also be reviewed and, as appropriate, be incorporated into the revised RCD. If the 2014 and 2015 CARB air monitoring studies become publically available, those data will also be considered. However, for any air monitoring study, we need to be cautious in evaluating the data and determining the appropriateness of including in the revised risk assessment. Our primary concern is the comparability of the model estimated air concentrations to empirical data. The data need to be directly comparable on several levels including: 1) similarity in the duration of the sampling period and the duration of the application period; 2) the appropriateness of sampling methods for aerosols; and, 3) consistency in the meteorology data used, including whether the predominant wind direction was determined according to the wind rose. Given these potential complications in comparing measured air concentrations to modeled air concentrations, we will review available data and revise the RCD as appropriate.

OEHHA Comments on Residential Bystander Spray Drift Exposure Assessment (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.

> **HHA Response:** Please see response starting on page 2 of this document.

OEHHA Comments on Residential Bystander Spray Drift Exposure Assessment (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).

HHA Response: HHA will evaluate additional information on air concentrations for ground boom and orchard blast and will examine the data for quantifying the additional pathways proposed by OEHHA. However, it is important to note that direct exposures (via inhalation or dermal contact) are prohibited by the product labels. Because the RCD only addresses legal application scenarios, the direct pathways suggested by OEHHA cannot be included.

As mentioned earlier in this document, two index life stages were considered when evaluating impacts from indirect chlorpyrifos exposure: children of 1-2 years old and women of childbearing age. These life stages were selected as the most at-risk subpopulations because of data limitations on behavioral characteristics of children and adults of other age groups as explained in the US EPA Standard Operating Procedures for Residential Pesticide Exposure Assessment (U.S. EPA, 2012). Also, women of childbearing age were selected as a sensitive life stage in the draft exposure assessment because of the increased concern of the developmental neurotoxic effect of CPF on fetuses. With respect to exposure pathways, inhalation, dermal, and incidental oral exposures associated with the aerial application and potential resulting drift of CPF were evaluated for children 1-2 years old. HHA is in the process of evaluating alternative methods to estimate potential inhalation exposure associated with orchard airblast and ground boom application methods.

OEHHA Comments on Residential Bystander Spray Drift Exposure Assessment (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 (CDPR, 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.

HHA Response: HHA will evaluate additional information on air concentrations for ground boom and orchard blast and will examine the data for quantifying the additional pathways proposed by OEHHA. However, it is important to note that direct exposures (via inhalation or dermal contact) are prohibited by the product labels[8]. Additionally, DPR's regulation CCR 6614 also makes any direct exposure to human a violation that may result in legal actions by the county or the State. DPR's risk assessments only address legal application scenarios. Therefore, the direct pathways suggested by OEHHA are not included.

As mentioned earlier in this document, two index life stages were considered when evaluating impacts from indirect chlorpyrifos exposure: children of 1-2 years old and women of childbearing age. These life stages were selected as the most at-risk subpopulations because of data limitations on behavioral characteristics of children and adults of other age groups as explained in the US EPA Standard Operating Procedures for Residential Pesticide Exposure Assessment (U.S. EPA, 2012). Also, women of childbearing age were selected as a sensitive life stage in the draft exposure assessment because of the increased concern of the developmental neurotoxic effect of CPF on fetuses. With respect to exposure pathways, inhalation, dermal, and incidental oral exposures associated with the aerial application and potential resulting drift of CPF were evaluated for children 1-2 years old. HHA is in the process of evaluating alternative methods to estimate potential inhalation exposure associated with orchard airblast and ground boom application methods.

OEHHA Comments on 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.

[8] For example, the label for Lorsban Advanced states in the Directions for Use under Restricted Use Pesticide, "Do not apply this product in a way that will contact workers or other persons, either directly or through drift. Only protected handlers may be in the area during application."

Use of US EPA SOP to estimate the exposure.

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

HHA Response: No response necessary.

OEHHA Comments on Methods Used to Estimate CPF Exposure (Spray Drift Exposure Estimates from Aerial Applications):

Instead of applying the AgDRIFT model to all scenarios as was done by US EPA (U.S. EPA, 2013a; U.S. EPA, 2014a; U.S. 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 (Teske et al., 2009; U.S. EPA, 2014b). 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.

HHA Response: The 0.35 percent was an initial deposition "screening level" chosen by the original risk assessor and was used only to rank aircraft according to the distance downwind to that deposition level. The final aircraft selected were those that showed the furthest distance downwind to that benchmark (one fixed-wing and one rotary aircraft). The 0.35% fraction is small enough to provide an assessment of deposition in the far field for all the candidate aircraft. Fixed wing (non-biplane) and helicopter distances are relatively similar across aircraft models (Barry, 2015).

OEHHA Comments on Methods Used to Estimate CPF Exposure (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 (U.S. 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.

> **HHA Response:** In 2012, US EPA issued the agency's nationwide spray drift mitigation decision for CPF (Keigwin, 2012). This decision maintains that the smallest nozzle droplet type allowed, regardless of spray-application method, is "medium." To match the US EPA mitigation decision and the label requirements for agricultural uses, ground boom inputs in the DPR exposure assessment were based on "medium" nozzle droplet size. No "fine" or "very fine" droplet size distributions were analyzed. The discussion of use of the 50^{th} versus 90^{th} percentile is found below.

OEHHA Comments on Methods Used to Estimate CPF Exposure (Spray Drift Deposition Estimates from Groundboom and Airblast Applications) continued:

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.

> **HHA Response:** The orchard airblast are 50^{th} percentile estimates and the aerial deposition estimates are ensemble mean estimates. The AgDRIFT model does not include 90^{th} percentile estimates for any orchard airblast scenarios. The AGDISP model in a first principles physics based model that does not produce 90^{th} percentile estimates. The AGDISP inputs used to estimate the downwind horizontal deposition and air concentrations were selected to be reasonable worst case, as described in Barry (2015). Therefore, in the context of the AGDISP inputs, the estimated horizontal deposition and air concentrations are the ensemble mean of a *reasonable worst case application*, not a mean, 50^{th} percentile or usual aerial application. The ground boom should be evaluated on the same basis.
>
> As OEHHA stated, the deposition curves were based on the measured values. However, according to the methods given in the AgDRIFT user manual (Teske *et al.*, 2003), it appears that

the function labeled as the 90th percentile function for ground boom was derived by fitting a function only through the 90th percentile rank deposition observed at each distance in each scenario (assuming the "bounding value" mentioned in the text means the 90th percentile rank value). If this is true, then the 90th percentile value returned by the function in AgDRIFT will never be larger than what was measured in the field. Unfortunately, it is not known whether any of the measured values in the field studies actually represent the true 90th percentile deposition. Thus, it is impossible to conclude that the function represents the true 90th percentile deposition at a particular downwind distance. The actual data and process of how the curves were developed is not given in the AgDRIFT user manual and a detailing of Dr. Teske's analysis is not published. As a result, the reader cannot verify the results by repeating the Teske analysis. Thus, the uncertainty associated with the 90th percentile function is unknown. In addition, since the 90th percentile function in AgDRIFT was not developed using the 50th percentile function as a basis, there is no ability to give a statistical confidence with which the 90th percentile deposition value was captured.

Unlike fitting a function through the 90th percentile rank values at each downwind distance, tolerance bounds on the 50th percentile function captures a percentile value (e.g. 90th percentile) with a known confidence. The width of the tolerance bound depends upon the sample size, variance, and selected confidence level. The tolerance bound may exceed values observed in the measured values if the variance is high. Barry et al. (Barry *et al.*, 1999) presented tolerance bounds for the ground boom deposition curves. In addition, Barry (Barry, 1999b; Barry, 1999a) together with OPP staff (U.S. EPA, 1999) developed tolerance bounds on the ground boom deposition curves using different functions than those selected by Teske. Those tolerance bounds had known confidence levels. However, those deposition curves and the associated tolerance bounds were not implemented in the AgDRIFT model. Thus, the 50th percentile ground boom deposition estimate was used because: 1) the orchard airblast and aerial estimates are 50th percentile estimate (or ensemble means) and ground boom should be evaluated on the same basis; 2) Dr. Teske's analysis methods cannot be examined; and, 3) the confidence (representing the likelihood that the true 90th percentile was captured) associated with the 90th percentile deposition for ground boom as represented by the function in AgDRIFT is unknown.

OEHHA Comments on 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/m3) during an airblast application (CARB, 1998) were similar in magnitude to AGDISP simulated values (19-34 µg/m3) 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., it was shown that spray drift estimates predicted by AGDISP for groundboom application were similar to the

high volume air sampling results (Nsibande et al., 2015). 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.

HHA Response: Aerial, ground boom, and orchard airblast are significantly different methods of delivering pesticide liquid spray to crops. The amount of spray drift and the partitioning between aloft and deposited material at distances downwind of an application are directly related to the application method (aerial, ground boom or orchard airblast). In addition to the spray quality (e.g. very fine, fine, medium, or coarse droplet size classification), there are three important factors in spray drift determination: 1) ground or air speed of the release; 2) the height of the release above the target; and, 3) the direction of the nozzles during the release. Aerial application has the following features important to spray drift: 1) release of the liquid spray occurs at high air speed – from approximately 50 mph for slower helicopters to over 200 mph for the fastest fixed wing aircraft (from the AgDRIFT V 2.1.1 aircraft library); 2) the spray can be directed at various angles relative to the line of travel and nozzles directed straight back relative to the slipstream of air generated by the aircraft minimizes changes to the desired droplet spectra; and, 3) the aerial application release height is typically greater than or equal to 10 ft from the target surface. Orchard air blast characteristics important to spray drift are: 1) air blast directs spray up at very high velocity towards tree/crop canopies, since it is directed upward, a large proportion of mass may remain airborne close to the release point; and, 2) the spray consists of fine to very fine spray quality. Thus, it could be argued that aerial and orchard airblast might show somewhat similar air concentrations at comparable distances close to the application block. In contrast, ground boom characteristics related to spray drift are: 1) releases occur at much slower ground speeds (ground speeds of 5 – 15 mph; SDTF, 1997); 2) the release height is less than or equal to 4 ft; and, 3) the spray is directed down towards the ground. So, the characteristics of ground boom applications are dissimilar enough to aerial applications to make it difficult to conclude that a similar level of inhalation exposure would occur. As a preliminary method to address this data gap, the AGDISP fixed-wing estimated air concentrations, adjusted for inhalable fraction, will be used to provide initial estimates of inhalation exposure associated with orchard airblast and ground boom applications.

For response to AGDISP ground boom model comments, please see the response starting on page 4 of this document.

OEHHA Comments on 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 (U.S. 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; U.S. 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.

> **HHA Response:** US EPA (2014a, 2014b) reviewed newly submitted toxicology studies submitted together with the revised analysis of the volatilization data based on public comments (Reiss *et al.*, 2013). Based on those evaluations, US EPA concluded that "…volatilization of chlorpyrifos does not present a risk of ChE inhibition from inhalation of CPF vapor…" (U.S. EPA, 2014a). In addition, in the volume entitled "Chlorpyrifos: Reevaluation of the potential risks from volatilization in consideration of chlorpyrifos parent and oxon inhalation toxicity studies" US EPA reevaluated risks due to volatilization exposure to CPR or CPR-oxon and concluded that based on new data, there are no human health risks of concern anticipated for volatilization exposure (US EPA, 2014d). Thus, this route of exposure presents a very minor risk when compared to all other risks or the risks from aggregate exposures. However, HHAB will further examine this issue if new information becomes available in the future.

OEHHA Comments on 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, (CDPR, 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.

> **HHA Response:** Please see our previous comment. As mentioned earlier, chlorpyrifos is now entering the formal TAC evaluation process.

OEHHA Comments on "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.

HHA Response: Please see response starting on page 2 of this document.

OEHHA Comments on the Food Exposure Assessment – Residue Data:

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

In US EPA (2014b, 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.

HHA Response: Like OEHHA, HHA also noticed that US EPA listed both soybeans and soybean oil as blended in their residue tables in the 2011 and 2014 risk assessments. While HHA did not find an explanation from US EPA of how the commodities were treated, we deduced from the residue table in the 2104 dietary (food only) assessment that US EPA treated only soybean oil as a blended commodity and used the 2001 PDP residue data on soybeans to generate an average value for a point estimate. In their analysis, US EPA treated soybeans as a non-blended commodity creating a distribution of residues and applying a 10% of crop treated (PCT) adjustment that resulted in 270 samples at 0 ppm residue and 22 samples at the LOD.

Blended foods are defined as foods mixed over a wide geographic region prior to consumption (CDPR, 2009). According to this definition, HHA will consider soybeans as blended. However, "blended food" is also a relative term used when comparing the food form being evaluated (i.e., soybean oil) to the food form from which residue data are available (i.e., soybeans; (CDPR, 2009)).

In the case of the blended food soybean oil for which residue data are not available, HHA will use the average residue value for the food soybean as in the US EPA acute dietary analysis. However for soybeans that HHA defines as a blended food, we will not apply PCT adjustment since the data are assumed to derive from both treated and non-treated batches of the commodity. Therefore in the distribution of residues for soybeans, HHA will assume that non-detect samples are at the LOD and will not replace them with zeroes (0). Applying PCT adjustment to a residue distribution for a blended commodity may result in an underestimation of the acute dietary exposure. Nevertheless, the dietary exposure had a minimal contribution to the overall exposure to CPF.

OEHHA Comments on the Food Exposure Assessment – Residue Data, continued:

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.

HHA Response: US EPA selected PCT values for CPF based on the Biological and Economic Analysis Division (BEAD) 2014 Screening Level Usage Analysis (SLUA). SLUA data are from: 1) USDA-NASS (United States Department of Agriculture's National Agricultural Statistics Service); 2) private pesticide market research; and, 3) California Department of Pesticide Regulation. BEAD uses California PUR data when 80% or more of domestic production is from California (see page 36 in the 2014 US EPA Chlorpyrifos Dietary Exposure food-only assessment). When there are differences in the estimates from each of the 3 sources, BEAD uses the source that has the highest PCT (personal communication; Cynthia Doucoure, OCSPP/OPP/BEAD on July 27, 2016; see also page 36 in US EPA 2014b). Therefore, the PCT values for strawberries, grapes, broccoli, peaches, and walnuts included in the 2014 US EPA dietary exposure assessment are either based on CPF usage in California or represent the highest PCT from the three SLUA sources.

OEHHA Comments on Consumption Rate:

US EPA used per capita consumption rates to calculate both acute and steady-state food exposures (Draft RCD: p. 135; US EPA, 2014b: pp. 50-51). DPR (p. 135) noted 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 (U.S. EPA, 2011). Thus, OEHHA recommends that DPR only include consumer-only, non-nursing infants in the <1 year food exposure estimation.

HHA Response: Infant formulas are prepared with heat treatments and purification procedures designed to reduce potential pesticide residues that may have occurred from applications to crops used as formula ingredients. Infant formulas are mainly based on cow's milk or soy protein and soy oil derived from soybeans. Monitoring studies over the years have confirmed that pesticides are rarely detected in infant formulas (NRC, 1993). In 2013-14, PDP analyzed 705 samples of cow milk and 706 samples of soy-based infant formula and found no detectable resides of CPF or CPF-oxon (LOD ranged from 0.001 and 0.01 ppm). PDP monitoring of cow's milk in 2012 resulted in 3 chlorpyrifos detects out of 792 samples, with a LOD of 0.5 ppb.

We conducted a sensitivity analysis of food consumption by the various infant population subgroups in DEEM-FCID v3.16 to determine if their consumption was significantly different. To do this analysis we set the residue levels for all commodities, excluding water, at a point estimate of 1 ppm. Table 1 shows the number of users compared to number of persons surveyed in each population subgroup. Because so many commodities were included, most persons surveyed were users. The exposure estimates at the 95th percentile were slightly higher for non-

nursing infants compared to all infants. At the 99.9th percentile, the exposure estimates for non-nursing infants and all infants were essentially the same. Nevertheless, we recognize that non-nursing infants that are on formula can have higher exposures to CPF on average, but at the higher exposure levels the difference in exposure estimates between non-nursing infants and all infants is small (Table 5). See response on pg. 42 and Table 6 of this document for a discussion concerning resulting residues from both infant formula and drinking water.

Table 5. Comparison of Consumption of Food Commodities for Infant Population Subgroups

Population Subgroup	Persons Surveyed	Users Surveyed	Exposure (mg/kg/day) per capita		
			Mean	95th percentile	99.9th percentile
Nursing infants	792	604	0.019639	0.069205	0.181581
Non-nursing infants	1708	1707	0.046784	0.125402	0.222562
All infants	2500	2311	0.038403	0.111445	0.221506

OEHHA Comments on 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; Mattsson et al., 2000) and humans (Vaccaro et al., 1993; Sanghi et al., 2003; Casey, 2005; Srivastava et al., 2011) 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.

HHA Response: Presently, there are very few studies that have measured CPF concentrations in breast milk of mothers in the US. A pilot study conducted in 2011 measured CPF concentrations in the milk of women residing in urban and agricultural regions in CA (Weldon *et al.*, 2011). While this study detected CPF residues in breast milk, the number of subjects was small (21 urban women and 13 agricultural women). Residues ranged from 13 to 1,000 pg/g milk (or ppt), although the median values between urban and agricultural women were similar (24.5 and 28.0 pg/g, respectively). The limits of detection (LOD) were very low, ranging from 0.1 to 0.5 pg/g. Casey reported approximately 40x higher levels of CPF in breast milk than Weldon *et al*., however, this study was not peer-reviewed and used ELISA to detect residues rather than other verified analytical methods (Casey, 2005). Additionally, studies outside of the US also reported detections in breast milk. Bedi et al., (2013) reported residues in breast milk in a small number of female participants (34 primiparate and 19 multipararate women), although the LOD was not reported. Other studies have postulated that the concentrations of CPF in breast milk may be associated with occupational practices, including non-compliance of re-entry intervals following CPF applications ((Sanghi *et al.*, 2003; Weldon *et al.*, 2011)).

Each of these studies has its limitations. However, we consider the results from Weldon *et al*. (2011) to be the most reliable estimate of breast milk residues for US women. These data can be used to evaluate exposure to CPF from human breast milk to nursing infants when consumption data from NHANES or other sources become available. HHA will continue to follow the

literature on pesticide residues in human milk and consumption to address pesticide exposure via the lactational pathway.

OEHHA Comment on 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.

HHA Response: Since the completion of the 2015 draft RCD, DPR changed its practice and no longer evaluates the health-protectiveness of pesticide tolerances on a commodity by commodity basis (CDPR, 2017). Accordingly, our dietary exposure assessment for CPF was revised to remove this section However, DPR will continue to conduct tiered dietary evaluations, including estimating exposures resulting from pesticide residues at tolerance levels on all commodities combined. DPR's tier approach is described in our dietary exposure guidance (CDPR, 2009).

OEHHA Comments on the 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.

HHA Response: No response necessary

OEHHA Comments on the Drinking Water Exposure Assessment – 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.

HHA Response: No response necessary

OEHHA Comments on the Drinking Water Exposure Assessment – 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.

HHA Response: No response necessary

OEHHA Comments on the Drinking Water Exposure Assessment – 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 (U.S. 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.

HHA Response: HHA recognizes this issue and is in a process of updating its own risk assessment guidance, including partnering with the SWRCB Division of Drinking Water to analyze California-wide drinking water data for inclusion in our future dietary risk analyses.

Regarding summing together the food and water exposure estimates of formula-fed infants, HHA performed a sensitivity analysis described above for consumption of all food, this time including water commodities by the various infant population subgroups in DEEM-FCID. Similar differences in infant population subgroups were seen when drinking water was included. That is, non-nursing infants had a higher exposure on average, but the exposures were similar between non-nursing infants and all infants at the higher percentiles. See Table 6 below for food and water consumption values.

Table 6. Comparison of Consumption of Food and Water Commodities for Infant Population Subgroups

Population Subgroup	Persons Surveyed	Users Surveyed	Exposure (mg/kg/day) per capita		
			Mean	95th percentile	99.9th percentile
Nursing infants	792	615	0.038583	0.135306	0.272393
Non-nursing infants	1706	1705	0.116474	0.224447	0.384398
All infants	2498	2320	0.092418	0.215336	0.383182

OEHHA Comments on 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.

HHA Response: We consider children1-2 years old as a sentinel subpopulation for reasons including increased time spent outside and contact with indoor and outdoor surfaces. In addition, the probabilistic

food-only exposure analysis for CPF identified children 1-2 years old as the highest exposed population subgroup at the high end percentiles. Accordingly, we chose this group for the aggregate exposure assessment to combine exposures from food, drinking water, inhalation and mouthing activities. We note that our probabilistic drinking water assessment showed infants <1 year old as receiving the highest exposure from drinking water (0.2 µg/kg/day compared to 0.1 µg/kg/day for children 1-2 years old; Table 12 in Appendix 2 "Dietary and Drinking Water Exposure Assessment"). However, we used the drinking water exposure for children 1-2 years old in the aggregate MOE calculations to match the age of the evaluated subgroup from other exposure routes. Our draft RCD included a discussion that the drinking water MOEs would be about 2-fold lower had the exposure estimates for infants <1 year old been used instead (see p. 22, "The main uncertainties in the risk characterization"). Nevertheless, the aggregate MOEs would not be significantly reduced (< 5%) at distances up to 50 feet to the field had they been calculated based on drinking water exposure for infants <1 year old. At distances up to 1000 feet, the aggregate will be reduced by less than 20%. This is because the main driver of the aggregate MOEs was inhalation exposure to chlorpyrifos in the form of aerosols as a result of spray drift.

OEHHA Comments on Aggregate Exposure Assessment, continued:

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.

> **HHA Response:** OEHHA's suggestions are noted. Our current aggregate exposure accounts for the cumulative nature of AChE inhibition. Because the enzyme inhibition reaches its maximum level in ~21 days, the steady state PoDs employed in our assessment should be protective for the exposure of a longer term.

OEHHA Comments on the Risk Characterization – 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.

> **HHA Response:** HHA assumed that the inhibitory effect of CPF on RBC AChE is cumulative, and therefore, the acute PoDs may not be sufficient for characterizing the AChE inhibition from spray drift subsequent to the dietary exposure in one day. The basis for this assumption is that studies in humans (Nolan et al., 1984) showed that CPF inhibits RBC AChE after a single dose, but the enzyme activity does not recover to 100% even after 10 days. Therefore, the 21-day steady state PoD values were used to evaluate the risk associated with dermal, inhalation, and non-dietary oral exposures from spray drift. Had acute PoDs been used instead, the resultant

MOEs would have been higher, and the cumulative nature of AChE inhibition would not be accounted for.

OEHHA Comments on the Risk Characterization – 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.

HHA Response: See earlier discussion regarding comparison of the PBPK-PD derived PoDs and those derived by OEHHA from animal studies. With respect to the data from the Columbia study, the revised RCD includes a discussion of the US EPA approaches to using the PBPK model to derive PoDs based on neurodevelopmental effects. The intraspecies variability of enzymes involved in the metabolism of CPF is discussed throughout this document.

OEHHA Comments on the Risk Characterization – 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.

HHA Response: See response on page 40 of this document.

V. 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/m3 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.

HHA Response: Thank you for the careful review of our work. The corrections will appear in the final draft where necessary.

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