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MEMORANDUM

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FROM: David Ting, Ph.D., M.P.H.
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DATE: December 12, 2017

SUBJECT: FINDINGS ON THE HEALTH EFFECTS OF THE ACTIVE INGREDIENT CHLORPYRIFOS AS A CANDIDATE TOXIC AIR CONTAMINANT

Enclosed please find a copy of the Office of Environmental Health Hazard Assessment's (OEHHA) findings on the health effects of the active ingredient chlorpyrifos relevant to its review as a candidate toxic air contaminant (TAC). OEHHA is submitting these findings for inclusion as part of the Department of Pesticide Regulation's submission to the Scientific Review Panel as required by statute.

In developing these findings, OEHHA used as its main reference the department's draft document titled: Evaluation of Chlorpyrifos as a Toxic Air Contaminant: Risk Characterization of Spray Drift, Dietary, and Aggregate Exposures to Residential Bystanders. OEHHA's analysis finds that the margin between modeled air concentrations of chlorpyrifos and the levels of chlorpyrifos exposure associated with health effects is not sufficiently protective. As is the case with the department's analysis, OEHHA's findings support the identification of chlorpyrifos as a TAC.

For any questions regarding OEHHA's findings on chlorpyrifos, please contact Dr. David Ting at (510) 622-3226.

Enclosure

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Findings on the Health Effects of Chlorpyrifos Relevant to Its Identification as a Toxic Air Contaminant

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

December 2017

Pursuant to Food and Agriculture Code Sections 14022 and 14023, the Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency (CalEPA) provides consultation and technical assistance to the Department of Pesticide Regulation (DPR) on the evaluation of health effects of pesticides that are candidate toxic air contaminants (TAC). DPR has developed the following document, currently in draft form, for use in considering whether to identify chlorpyrifos as a TAC:

> DPR, 2017a. Evaluation of Chlorpyrifos as a Toxic Air Contaminant: Risk Characterization of Spray Drift, Dietary, and Aggregate Exposures to Residential Bystanders. Hereafter this document is referred to as the "draft TAC document."

Food and Agricultural Code Section 14023 also requires that OEHHA prepare its own findings on the health effects of chlorpyrifos, the availability and quality of health-effects data, and levels of exposure that may result in adverse health effects. This document contains OEHHA's findings and is part of DPR's submission to the Scientific Review Panel for its evaluation. OEHHA used the draft TAC document as its primary reference and has included commentary on it. Additional documents and studies cited in these findings are listed in the References Section.

Under the Toxic Air Contaminant Identification and Control Act (AB 1807, Chapter 1047, Statutes of 1983) and its implementing regulations (Title 3, California Code of Regulations, Section 6864), one of the criteria for identifying a pesticide as a TAC is if its concentration in the air exceeds one-tenth of the level that has been determined to be adequately protective of human health. The draft TAC document shows that bystanders can be exposed to modeled air concentrations of chlorpyrifos that exceed one-tenth the protective level, and thus meet the criteria for TAC identification. OEHHA's findings below serve to reinforce this overall conclusion, and further support the identification of chlorpyrifos as a TAC.

Chemical Identification

1. Chlorpyrifos (CPF; O,O-diethyl O-3,5,6-trichloro-2-pyridyl phosphorothioate) is a broad-spectrum, chlorinated, organophosphate (OP) insecticide, acaricide, and miticide. It is used to control targeted pests in food commodities (e.g., nut trees, fruits, vegetables, and grain crops), as well as in non-food crops.

Usage and Environmental Fate

2. CPF use in California has been approximately 1.1 to 1.5 million pounds per year in recent years. CPF use is greater in the summer months, and applications to almonds, alfalfa, walnuts, oranges, and cotton account for more than two-thirds of the total poundage applied (DPR, 2016, 2017a).

3. After application, CPF dissipates by volatilization, photolysis, abiotic hydrolysis, and microbial degradation. CPF in air and on foliar surfaces can be degraded to the toxicologically active form, chlorpyrifos-oxon (CPFO), by photolysis and oxidation within hours. In field studies, CPF post-application volatilization losses were highly variable, ranging from 4.5-71% during the first 24 hours (US Environmental Protection Agency, US EPA, 2013a). The extent of spray drift that potentially exposes bystanders (not those involved in the application of the pesticide, but in the vicinity of the application site) depends on application methods, equipment settings and conditions, and wind velocity.

Reported Illnesses

4. The most commonly reported symptoms for CPF-associated pesticide illness cases during 2004-2014 were systemic symptoms (including headache, nausea and dizziness), eye irritation, and respiratory complaints (breathing difficulties, cough, and irritation of throat) (DPR, 2017b). Nearly 90% of these cases were for bystanders (workers or residents near the application site).

Metabolism and Pharmacokinetics

5. CPF is almost completely absorbed through the oral route in rats and humans. The extent of dermal and inhalation absorption is estimated from inhibition of acetylcholinesterase (AChE) activities and urinary recovery of metabolites. In both animals and humans, CPF is extensively metabolized by cytochrome P450 enzymes (CYP), including to its active oxon metabolite CPFO and urinary metabolite 3,5,6-trichloro-2-pyridinol (TCPy). The key reactions are:

    a. Activation of CPF → CPFO by CYP2B6 and CYP3A4/5
    b. Detoxification of CPF → TCPy by CYP2C19 and CYP3A4/5
    c. Detoxification of CPFO → TCPy by paraoxonase 1 (PON1) and β-esterases
    (butyrylcholinesterase and carboxylesterases)

The balance between CPF activation and detoxification is influenced by factors such as species, gender, age, and polymorphism of key metabolic enzymes (e.g., CYP and PON1) (Ma and Chambers, 1994; Ginsberg et al., 2009; Wason et al., 2012). The variation of these factors across a population contributes to the inter-individual variability in response to CPF exposures.

6. CPF has been detected in rat and human milk. In pregnant rats, CPF crosses the placenta as evidenced by the detection of CPF in fetal liver, brain, blood, placenta, umbilical cord, and amniotic fluid, and the inhibition of fetal plasma, red blood cell (RBC), brain, and heart cholinesterase (ChE). In rats, low levels of CPFO was detected in the blood samples of fetuses on a day of maternal exposure to CPF.

Toxicological Effects of CPF and Critical Endpoints for Risk Assessment

7. AChE is found at the synaptic clefts in the central and peripheral nervous systems, at neuromuscular junctions, and in some non-neuronal cells such as RBCs. When CPFO covalently binds the active site of AChE, it prevents AChE from hydrolyzing the neurotransmitter acetylcholine (ACh). The accumulation of ACh in synaptic clefts results in excessive stimulation of the peripheral and central nervous systems. The reduction of AChE hydrolysis activity is an early indicator of toxicity. At higher doses, acute signs of poisoning are salivation, lacrimation, urination, defecation, slurred speech, tremors, ataxia, convulsion, as well as depression of respiratory and circulatory centers.

8. Since blood is more readily available than brain tissue and RBC AChE activity is a sensitive marker of systemic AChE inhibition, RBC AChE activity is often used as a surrogate for inhibition of AChE activity in the nervous system.

   Following an acute oral exposure in three groups of rats, RBC AChE was found to be more sensitive to CPF than brain AChE, and the postnatal day (PND)11 pups appeared more sensitive than the adult to RBC AChE inhibition (Marty et al., 2012; Table 1). The study did not find an age difference for brain AChE inhibition.

   Table 1. Percent change of RBC and brain AChE activities following acute oral gavage exposure of PND11 pups and adults to CPF.

Compartment	Dose[a]	Male PND11 pup	Female PND11 pup	Adult female
RBC	0.5 mg/kg	-5%	-1%	+10%
	2 mg/kg	-36%*	-31%*	-19%*
Brain	0.5 mg/kg	+11%	+3%	-5%
	2 mg/kg	-2%	-7%	-5%

[a] From Marty et al. (2012) for CPF given in corn oil. Doses shown are those that were tested in both pups and adults and which induced ≥1% inhibition in at least one group.

* Significantly different from control at alpha = 0.05 using Dunnett's test of raw ChE data. N = 8 animals/group

9. There are numerous animal and human studies showing exposure to CPF is associated with developmental neurotoxicity (DNT). In some rat and mouse studies, CPF exposure during gestation and postnatal periods was found to cause DNT effects on cognition, anxiety, social behavior, and motor activity. OEHHA's review of the DNT observations from a registrant study (Hoberman, 1998) and those in recent literature are presented in Table 2. In some studies, these DNT effects were observed at doses that elicit minimal or no brain AChE inhibition. The recent animal studies incorporated low doses in the study design, which provide the basis for improved dose-response relationship analysis.

Table 2. Selected developmental neurotoxicity studies in animals with multiple doses of CPF.

Study	Species Exposure period	Administered Doses[a]	Dose for Observed Effects	Observed Effect at Low Dose in Offspring
Hoberman, 1998	Rat Dam: GD6-LD11	0, 0.3, 1.0, 5.0 mg/kg-day	1 mg/kg-day	↓ Parietal cortex thickness in PND66 females
Silva et al., 2017	Rat Dam: GD14-20 (only male pups)	0, 0.01, 0.1, 1, 10 mg/kg-day	0.1 mg/kg-day	↑ Anxiety and ↑ locomotor activity at PND21 males
Gómez-Giménez et al., 2017a	Rat Dam: GD7-PND21	0, 0.1, 0.3, 1 mg/kg-day	0.1 mg/kg-day	↓ Spatial learning in Morris Water Maze in adult males
Gómez-Giménez et al., 2017b	Rat Dam: GD7-PND21	0, 0.1, 0.3, 1 mg/kg-day	0.1 mg/kg-day	↑ Locomotor activity in 2-3 month old males and females
Lee et al., 2015	Mouse PND10 male	0, 0.1, 1.0, 5 mg/kg	0.1 mg/kg-day	↑ Total activity at PND60 males
Carr et al., 2017	Rat PND10-16	0, 0.5, 0.75, 1.0 mg/kg-day	0.5 mg/kg-day	↓ Time to emergence into novel environment in PND25 males and females

[a] All studies conducted via oral gavage with corn oil except for Gómez-Giménez et al. (2017a and b), which administered CPF in corn oil mixed in a sweet jelly.
Abbreviations: GD, gestation day; LD, lactation day; PND, postnatal day.

With regard to humans, there are three major prospective birth cohort studies conducted by: Columbia University, Mount Sinai Hospital (in New York City), and University of California, Berkeley. All three studies showed an association between exposure to OP pesticides during pregnancy and adverse neurodevelopmental outcomes such as changes in brain morphology, delays in cognitive (working memory) and motor functions, problems with attention, and tremors.

Many *in vitro* studies with zebrafish show that exposure to CPF resulted in abnormal behavior and inhibition of AChE activity. Zebrafish requires a certain level of AChE for normal neurodevelopment, and is often used as a model for DNT studies.

Many plausible mode of actions or adverse outcome pathways for CPF-induced DNT effects have been suggested, as outlined in US EPA (2014), but there is no definitive conclusion.

On November 29, 2017, the state's Proposition 65 Developmental and Reproductive Toxicant Identification Committee determined that CPF has been clearly shown to cause developmental toxicity, after considering the human studies and many animal studies showing DNT subsequent to CPF exposure. As a result of the committee's determination, chlorpyrifos will be added to the Proposition 65 list effective December 15, 2017.

Taken together the human and animal studies show that CPF causes DNT, although the human data pose challenges for dose-response assessment because of uncertainty in the exposure assessment in the studies. A thorough analysis of the DNT literature for CPF is needed to determine if it can be used directly for dose-response characterization in the risk assessment of CPF.

Outcomes of developmental toxicity of CPF besides DNT have been observed in rats, mice, and rabbits. When exposed during gestation by the oral route, CPF caused fetal effects such as increased post-implantation loss, decreased crown-rump length, delayed ossification, and reduced fetal body weight. Most of these effects were observed at the same or higher doses than those causing maternal toxicity. The lowest No-Observed-Adverse-Effect Level (NOAEL) for these effects was 2.5 mg/kg-day in fetal rats (Rubin, 1987). The maternal toxicity included inhibition of plasma and RBC AChE, cholinergic signs, reduction of food consumption, and decreased body weight. In a two-generation reproductive toxicity study in rats, CPF did not cause adverse reproductive effects in the offspring. Slightly reduced pup weights and pup survival were observed at the highest dose tested, a dose (5 mg/kg-day) which was higher than that causing RBC AChE inhibition (1 mg/kg-day) in the parental rats.

DNT endpoints appear to be more sensitive than the other developmental endpoints that have been observed in these guideline developmental and two-generation reproductive toxicity studies.

10. The respiratory effects of CPF may provide potential critical toxicity endpoints, and should be considered as such in the DPR analysis. Respiratory effects are the most commonly reported symptoms in bystanders in DPR's pesticide illness report (DPR, 2017b). There is additional evidence of CPF-induced respiratory effects in agricultural workers. Among farmers in an epidemiological study evaluating the impact of pesticide exposure - the Agricultural Health Study - the OP insecticides (CPF, malathion, and parathion) were positively associated with wheeze; for the

commercial applicators, the OP insecticides (CPF, dichlorvos, and phorate) were positively associated with wheeze (Hoppin et al., 2006). Exposure to CPF was strongly associated with wheeze in a dose-dependent manner in both groups.

Bystanders may be children, and the developing lungs of young children and those with respiratory problems can be more sensitive to CPF exposure due to various factors, including lung structure and limited detoxification capacity. The respiratory architecture of the developing lung is characterized by a much lower surface area compared with adults, resulting in an approximately 2-fold increase in respiratory tract exposure (per unit surface area) to particulates (Ginsberg et al., 2004; de Zwart et al., 2004; Sarangapani et al., 2003).

The metabolic capacity of the developing lung is also much lower than that of the adult. The majority of differentiation activity of pulmonary xenobiotic metabolizing enzyme systems occurs for an extended period of time after birth (Fanucchi, 2014). For example, CYP gene expression was found to be much greater in the adult versus fetal human lung (Choudhary et al., 2005). Lung carboxylesterase activity in neonatal (PND7) and juvenile (PND21) rats was estimated to be 27% and 64% that of the adult (PND90) (Karanth and Pope 2000). CPFOase (PON1 activity using CPFO as the substrate) in the neonatal (PND7) and juvenile (PND21) rat lung was about 8-fold and 1- to 1.8-fold lower than adult (PND90) levels, respectively (Karanth and Pope, 2000). These differences may lead to higher CPFO in the lungs of infants and children compared with adults.

11. In the review of genotoxicity assays in the draft TAC document, CPF was found to be largely negative, with some positive effects found in yeast and bacteria. OEHHA notes that there are additional studies in the literature and should be considered in the overall evaluation of genotoxic potential of CPF, not only for oncogenicity concern, but also for other effects such as neurotoxicity (Muller et al., 2014).

12. CPF was reported not to cause cancer in two pesticide registration studies in rats and one in mice. One study in dogs was of too short duration (2 years compared to an average lifetime of 14 years) to be considered an adequate test of carcinogenicity. The carcinogenicity of CPF has not been well studied in epidemiological studies. Currently, CPF is not considered a carcinogen by the US EPA and DPR, and has not been evaluated for carcinogenicity by the International Agency for Research on Cancer (IARC) or California's Proposition 65 Carcinogen Identification Committee. OEHHA concurs with the approach of using non-cancer endpoints as the basis for the risk assessment of CPF at this time.

Dose-Response: Derivation of Points of Departure

13. For all exposure scenarios evaluated in the draft TAC document, the critical toxicity endpoint used is 10% inhibition of RBC AChE. While AChE inhibition is a sensitive toxicity endpoint, other endpoints such as DNT and respiratory toxicity endpoints may be more sensitive, as discussed in Findings 9 and 10 above.

14. The point of departure (POD) is the starting point of a low-dose extrapolation and is used to determine the health risk associated with a certain exposure level. The PODs for all exposure routes and durations and sensitive populations were developed by DPR using a physiologically-based pharmacokinetic and pharmacodynamic (PBPK-PD) model. This model was developed by the registrant and used by US EPA for deriving the PODs for RBC AChE inhibition in its 2014 Human Health Risk Assessment (US EPA, 2014).

    The PBPK-PD model estimated the air concentration or dose (dermal and oral) for 10% RBC AChE inhibition. For the residential bystander exposure scenarios, the PODs used to evaluate the risks are listed in Table 3. For inhalation, dermal, and incidental oral exposures, the steady state PODs were used in risk characterization. The use of the lower PODs in the draft TAC document, compared to the higher acute PODs, was said to compensate for background exposure to CPF. OEHHA finds that this is a conservative approach, but notes that it may add uncertainty to the risk estimate.

    OEHHA notes that for inhalation exposure, the exposure expressed as air concentration is lower for children than females (13-49 years old). However, the exposures in terms of dose (mg/kg-day) are similar, when the DPR's default breathing rates are used for the conversion. On the other hand, the dermal POD for children is more than 5-fold higher than that for females (13-49 years old). An explanation for the biological basis for the differences in the magnitude of PODs would be helpful to support their use in the risk characterization.

Table 3. PODs used for the risk characterization of residential bystander exposures

Exposure routes	Duration	Children 1-2 years old[a]	Females 13-49 years old[a]
Inhalation (CPF)	Steady state	2370 µg/m^3 1232 µg/kg-day[b]	6150 µg/m^3 1722 µg/kg-day[b]
Dermal (CPF)	Steady state	134250 µg/kg-day	23600 µg/kg-day
Incidental Oral (CPF)	Steady state	101 µg/kg-day	NA
Food (CPF)	Acute	581 µg/kg-day	467 µg/kg-day[c]
Water (CPFO)	Acute	159 µg/kg-day[c]	129 µg/kg-day[c]

[a] Values are from Summary Table 1 of draft TAC document.

[b] OEHHA's conversion to dose using DPR's default breathing rates of 0.52 m^3/kg-day and 0.28 m^3/kg-day for children and adults, respectively, for comparison purpose.

[c] Converted from ppb unit as shown in Table 54 of draft TAC document.

Abbreviations: NA=not applicable

Inhalation component of the PBPK-PD model

15. Overall PBPK-PD model application, construction and validation as well as the uncertainty and variability of the outputs are discussed in Findings 22 and 23 below.

    There is uncertainty associated with the steady state inhalation PODs derived due in part to the difference in the physical characteristics of CPF between the inhalation model and the bystander exposure and the lack of model validation.

    Inhalation exposure is the primary route of exposure from spray drift due to aerial, ground boom, and air blast applications, as noted below (Finding 16). In both the rat inhalation and human inhalation models, CPF was modeled as dry particles with relatively small sizes and assumed to be mostly (>90%) absorbed in the gastrointestinal tract following deposition in the respiratory tract and mucociliary clearance. The inhalation PK data of the PBPK-PD model were derived from an acute inhalation study in rats using dry particles in the respirable range (<10 µm) (Hotchkiss et al., 2010).

    In contrast, the bystander's inhalation exposure to CPF, as predicted by the AGricultural DISPersal (AGDISP™) model, is a spray drift cloud comprised of aerosol droplets of varying sizes that continually change as the cloud travels away from the application target. As larger droplets drop out, the cloud would have a greater portion of smaller droplets. The bystander at less than 25 feet from the application was estimated to be exposed to mostly "medium" and "coarse" spray droplets (Grisso et al., 2013). "Medium" and "coarse" are defined as droplets with diameters of 240 µm and 400 µm, respectively. Due to their large sizes, most of these droplets are expected to be deposited in the upper respiratory tract and absorbed in situ. Even if some of the smaller droplets reach the lower respiratory tract, they are likely to be absorbed in situ and not likely to be moved by the mucociliary mechanism and enter the gastrointestinal tract. In both cases, local effects of CPF on the upper and lower respiratory tracts would be a concern.

    Finally, the steady state outputs of the inhalation component of the PBPK-PD model have not been validated. There are no subchronic inhalation animal or human toxicity data suitable for this purpose. Although there are three subchronic inhalation toxicity studies conducted in rats (Newton, 1988; Corley et al., 1986; Landry et al., 1986), they cannot be used because the main reported effect was inhibition of plasma ChE; RBC and brain AChE were not inhibited.

Residential Bystander Exposure Assessment

16. Residential bystanders who are adjacent to a pesticide application are exposed to airborne CPF due to drift during or after the application. The draft TAC document assumed this was for 1 to 1.5 hours per day for 21 days. The scenarios evaluated in the draft TAC document are summarized in Table 4. The draft TAC document found that inhalation exposure contributed up to 95% of the total aggregate risk and

contributions from exposures via diet and drinking water were minor. The spray drift and dietary aggregate exposure assessment was conducted only for children 1-2 years old, but not females (13-49 years old). While children often have the higher intake on a body weight basis, it is not clear from the draft TAC document whether the children group is the more sensitive group.

Table 4. Bystander exposure scenarios from spray drift of CPF.

Exposure Scenarios	Children 1-2 Years Old	Females 13-49 Years Old
Spray drift only Individual routes and all routes (Aggregate exposure)	Inhalation, dermal[a], incidental oral	Inhalation, dermal[a]
Spray drift and dietary aggregate exposure	All routes for spray drift plus CPF in food and to CPFO in the drinking water.	Not assessed

[a] Dermal- skin contact with airborne deposits on lawns or other outdoor surfaces.

[b] Incidental oral- transfer of residues from object (ie. a toy) to mouth, from hand to mouth, and from ingestion of soil.

17. Three application methods were considered in the draft TAC document: aerial, ground boom, and air blast. A bystander can be exposed to CPF in air and after it has deposited on soil or vegetation surfaces.

    a. For aerial applications, DPR used the AGDISP™ model for predicting downwind deposition of CPF residues. The model was also used to estimate one-hour time-weighted average (1-hour TWA) aerosol concentrations at specific downwind distances and receptor heights.

    b. For ground boom and air blast applications, DPR used the AgDRIFT® model to predict downwind deposition of CPF residues. This model uses empirical data from a limited number of field trials to estimate droplet deposition. The AgDRIFT® model cannot predict aerosol concentrations in air. Instead, DPR applied "reasonable worst-case" inputs for AGDISP™ to generate air concentrations to predict aerosol concentrations from aerial application and used them as "surrogate" aerosol concentrations for ground boom and air blast applications in the evaluation of inhalation exposure (DPR, 2017a).

OEHHA agrees that use of the surrogate aerosol concentrations (62-101 µg/m^3) are appropriate because they are similar to air monitoring data by the California Air Resources Board (60-81 µg/m^3) when adjusted for distance from the field. These concentrations are likely conservative estimates for ground boom applications. However, they could be underestimates from air blast applications under some scenarios as more spray drift (higher concentration) may occur when little or no foliage is present.

18. The exposure estimates in the draft TAC document were determined for bystanders at various distances from the application site. Examples of dermal doses and predicted air concentrations for the application methods and receptors used in risk characterization are shown in Table 5. At a fixed distance and application method, children's dermal and inhalation exposure estimates are higher than those of females (13-49 years old).

Table 5. Comparison of dermal and inhalation exposures for bystanders.

Receptors	Exposure Route	Exposure at a Downwind Distance of 25 feet from the Treated Field		
		Aerial	Air Blast	Ground Boom
		Exposure (µg/kg/day)		
Children 1-2 years old	Dermal	69.55[a]	61.27[b,c]	10.52[b,d]
Females 13-49 years old	Dermal	47.45[a]	41.80[b,c]	7.17[b,d]
		Maximum 1-Hour Air Concentration (µg/m^3)		
Children 1-2 years old	Inhalation	52.6[a]	104.2[e]	104.2[e]
Females 13-49 years old	Inhalation	39.4[a]	78.1[e]	78.1[e]

All values are from the cited tables in the Draft TAC document.
[a] AGDISP™ model, AT802, 2 gallons/acre, 2.3 lbs/acre (Tables 27 and 28)
[b] AgDRIFT® empirical model, 6 lbs/acre (Tables 29-32)
[c] 60 swath, dormant apples, 6 lbs/acre (Tables 29 and 32)
[d] 40 swath, 50th percentile deposition, high boom, 6 lbs/acre (Tables 29 and 30)
[e] Surrogate air concentrations from AGDISP™ (Table 33 for 6 lbs/acre)

For evaluating child exposures to deposited residues, dermal and incidental oral ingestion exposure estimates were appropriately calculated from predicted surface deposition using standard assumptions and algorithms developed for contact with pesticide residues on turf (US EPA, 2012; US EPA, 2013b; DPR, 2017a).

19. There is a potential residential bystander exposure to CPF vapor produced by the deposited CPF aerosols. CPF is considered to be semi-volatile and has a relatively low vapor pressure at 25°C. In some regions of California where CPF use is high, summer daytime temperatures routinely reach or exceed 100ºF and this could turn the deposited aerosol material to a source of CPF vapor. For bystanders close to the application site, the concentration of CPF vapor is likely to be much lower than that of CPF aerosol in the first hour following application. However, compared to the exposure to aerosol, the exposure duration to the vapor can last many hours after the application has ended.

20. Another potential exposure pathway for CPF is take-home dust (dust from an outside source). DPR used the highest reported CPF residue level in house dust sampled in farming communities in the Salinas Valley after the residential use ban

(Bradman et al., 2007) and chose children 0 < 2 years of age as the most vulnerable life stage for inadvertent ingestion due to hand-to-mouth activity. The evaluation assumed an ingestion rate of 40 mg/kg-day (OEHHA, 2012) and an absorption rate of 100%, and showed such exposure would not induce more than 10% RBC AChE inhibition. However, OEHHA notes that DNT appears to be a more sensitive endpoint, as discussed above. OEHHA concurs with the conclusion that the exposures associated with this scenario are relatively low.

Risk Characterization

21. For non-cancer effects, the risk expressed as margin of exposure (MOE) is the appropriate approach. It is the ratio of the POD to the estimated human exposure level. For aggregate exposure, the overall MOE was determined by combining the MOEs of the individual routes. DPR selected a value of 100 as the target MOE; exposure with an MOE at or above this level is considered protective against CPF toxicity. This value was determined using three uncertainty factors (UF): 1 for interspecies extrapolation, 10 for intraspecies variability, and 10 for potential DNT effects. The interspecies and intraspecies UFs each consist of pharmacokinetic (PK) and pharmacokinetic (PD) components.

    OEHHA recommends a higher target MOE of 1,000: 3 for interspecies extrapolation, 30 for intraspecies variability, and 10 for potential DNT effects. The basis of this recommendation is discussed in Findings 22-24 below.

22. An interspecies UF of 3-fold should be applied because there are uncertainties in the output of the PBPK-PD model: not all model parameters were derived from human studies, differences between the nature and location of absorption of particles in the model and the residential bystanders, and the model has not been adequately validated for human steady state exposures.

    Limited human subject data are available for model development and validation. Between the Nolan et al. (1982, 1984) and Kisicki et al. (1999) studies, only one subject exhibited significant RBC AChE inhibition. The following is a summary of the studies.

    Nolan et al. (1982,1984[1])
    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 ChE activities in plasma and RBC 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 model parameters were sourced directly from the Nolan study: intestinal absorption of CPF to the liver, dermal absorption rate, elimination rate for TCPy, and transfer rate of CPF from stomach to intestine. Plasma ChE was inhibited only after oral exposure, but RBC AChE was not inhibited by either route by any individual.

[1] Nolan et al., 1984 is the published version of Nolan et al., 1982.

Kisicki et al. (1999)
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, CPFO, and TCPy levels, and RBC AChE activity were measured. The transfer rate of CPF from stomach to intestine from the Nolan et al. (1982, 1984) study was adjusted using the Kisicki data due to differences in the dosing formulations. Only one subject (female) at 2 mg/kg-day had RBC AChE inhibition, but she showed unusually high absorption of CPF (87.9% versus a mean of 29.5%).

The lack of AChE inhibition in these two studies brings into question the suitability of these studies for parameterization and validation of a PBPK-PD model in which RBC AChE inhibition is the critical endpoint. The model results for oral exposure were largely validated with one acute oral *in vivo* human study conducted in adults (Kisicki et al., 1999). For the dermal component of the model, the acute Nolan et al. (1982, 1984) study was used in part to parameterize the model for dermal exposures, and was used in addition to the acute Vaccaro et al. study (1993) to validate the model.

Vaccaro et al. (1993)
Adult subjects - males and non-pregnant females (n=7; ages 21-55) were exposed to CPF after Empire^{TM} 20 insecticide (encapsulated CPF in water) was applied to the carpet in two apartments. After application, four subjects were assigned to apartment #1 and three different subjects were assigned to apartment #2. Each volunteer (dressed in T-shirt and shorts) was asked to crawl, roll, or lie on the carpet for 4 hours to simulate a child's activity on the carpet. Air samples near the volunteers showed TWA of 11.4 mg/m^3 in Apartment #1 and 5.53 mg/m^3 in Apartment #2. It should be noted that the Empire^{TM} 20 insecticide formulation is special in that CPF was encapsulated in a polyurea shell and is intended to be a slow release formulation. When compared to non-encapsulated CPF, the EMPIRE^{TM} 20 formulation exhibits lower peak air concentrations (by ~4-fold) and much higher oral and dermal LD_{50} values.

The Vaccaro et al. study also provided human inhalation PK data to validate the model. As noted above, there is uncertainty in the data because of the formulation used and because the volunteers were exposed to CPF by both dermal and inhalation routes.

23. An intraspecies UF of 30 is needed to fully account for the potential variability in both PK and PD in the human population. An UF of 10 is not sufficient as the PBPK-PD model did not fully account for physiological, anatomical, and biochemical changes during pregnancy and among different age groups. As DPR noted, sensitive parameters related to metabolic clearance of CPF and CPFO were based on data from a small number of plasma and liver postmortem tissues (Smith et al., 2011) (Table 6), and metabolic activities between live and preserved human microsomes may not be concordant.

Table 6. Number of *in vitro* samples used in deriving model input parameters, by age groups.

Tissues[a]	Infants < 1 year old	Children 1-2 years old	Children 3-17 years old	Adult ≥ 18 years
Plasma	10	1	6	3
Liver	8	5	8	9

[a] From Smith et al. (2011). Total of 20 plasma samples from 0.01 to 46 years old and total of 30 liver samples from 0.04 to 75 years old.

The draft TAC document described the derivation of Data Derived Extrapolation Factors (DDEF) for acute oral exposure in humans by Poet et al. (2017). The DDEF in this case was defined as the ratio between the oral doses for 10% RBC AChE inhibition for the median individual (50th percentile) and the sensitive individual (e.g.,1st percentile). The different percentiles were calculated by varying pharmacokinetic variables in the PBPK-PD model, as described below. Poet el al. found the calculated DDEFs are not large for different age groups: adult (3.4), infants (3.6), non-pregnant female (3.4), and pregnant female (2.9). These DDEF estimates are used to justify the intraspecies UF of 10 in the draft TAC document.

OEHHA is concerned about the small sample size in the raw data and the reliability of the method that was used to extend the variability range of the parameters. Using sensitivity analysis, Poet et al. determined that four key metabolic enzymes contributed over 80% of the variability in the model output. The four enzymes are CYP450 to TCPy, CYP450 to CPFO, hepatic PON1, and plasma PON1. Because there are very few age-specific *in vitro* tissue samples for these enzymes (Table 6), Poet et al. extended their ranges by using a boot strap method, assuming the four parameters are log-normally distributed, and conducting Monte Carlo simulations. However, OEHHA notes that it is unlikely that the few samples of a given enzyme in Smith et al. (2011) can cover the full range of values within a given age group, especially at the tail ends of a distribution. For this reason, there are uncertainties in the mean and range estimated for the log-normal distributions. It is not clear that by extending the ranges of these four sensitive enzymes, to what extent was Poet et al. able to address the limitation of the dataset in Smith et al. (2011).

In addition, there is a need to account for the variability in the PD aspect of the PBPK-PD model for RBC AChE inhibition. The reported coefficient of variation (CVs) for the parameters (i.e., inhibition rate, degradation rate, reactivation rate) describing RBC AChE inhibition are relatively small, between 0.14 and 0.36 (Poet et al., 2017). For example, the inhibition rate was derived from Dimitriadis and Syrmos (2011). While the sample size was large (n=306), it consisted of only adult male hazardous material team workers and support staff. It is unclear how representative these mean and CV values are for the general population.

RBC AChE activity varies with age, pregnancy, and even between healthy adults. Newborn infant RBC ChE activity was reported to be only half that of adult activity

(Miyazono et al., 1999; Vlachos et al., 2010). Adult activity was only reached by 4 months to 1 year of age (Karlsen et al., 1981; Ecobichon and Stephens, 1973). Hematocrit was reported to decrease over pregnancy (Cunningham, 2010; Abduljalil et al., 2012), with a concomitant decrease in RBC AChE specific activity.

Thus, OEHHA believes the intraspecies UF of 10-fold should be at least 30-fold to capture the full range of PK and PD variability for RBC AChE inhibition in the population, especially when this endpoint is used as a surrogate for DNT (See Finding 24). Many factors can influence an individual's susceptibility to developmental neurotoxicants, potentially resulting in a large inter-individual variability (Bellinger, 2009). These factors include: maternal stress and low socioeconomic status, sex, coexposures to other neurotoxicants and health co-morbidities, and genetic polymorphisms (Cowell and Wright, 2017; Dipietro and Voegtline 2017; Bellinger, 2009; De Felice et al., 2015).

24. An additional factor is needed to address endpoints potentially more sensitive than RBC AChE inhibition. For DNT, the default UF is 10-fold; however, the use of this factor adds uncertainty to the risk characterization. There are several animal studies showing DNT effects at low doses (Table 2), and there are epidemiological data showing relationships between DNT and CPF exposure. OEHHA recommends a thorough evaluation of the studies to see if a POD for DNT can be directly determined.

25. Under the implementing regulations[2] for the Toxic Air Contaminant Identification and Control Act, one of the criteria for identifying a pesticide as a TAC is that the air concentration should be 10-fold lower than that which has been determined to be adequately protective (i.e., the target MOE). In the case of chlorpyrifos, this TAC target MOE would be 1000 based on DPR's analysis.

    The consideration of OEHHA's above findings on the UFs could result in a higher TAC target MOE (of at least 10,000). Many of the exposure scenarios in the draft TAC document for a residential bystander's drift exposure showed air concentrations resulting in MOEs of 1000 or lower values. Thus, the OEHHA analysis also supports the identification of chlorpyrifos at a TAC.

[2] Title 3, California Code of Regulations, Section 6864

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