OEHHA Findings on DPR's Draft TAC Document for Chlorpyrifos

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OEHHA Findings

- OEHHA, under Food and Agriculture Code Sections 14022 and 14023
  - Provides consultation and technical assistance to the Department of Pesticide Regulation on the evaluation of health effects of pesticides that are candidate toxic air contaminants

- Findings are posted at:
  - https://oehha.ca.gov/pesticides/report/tac-findings-chlorpyrifos
  - http://www.cdpr.ca.gov/docs/whs/pdf/chlorpyrifos_oehha_findings.pdf

OEHHA Findings for Chlorpyrifos

1) Toxicity Endpoints
2) Points of Departure
3) Exposure Assessment
4) Uncertainty Factors

Finding 8 - RBC Acetylcholinesterase (AChE) Inhibition

- RBC AChE is a sensitive marker of systemic AChE inhibition
- It is often used as a surrogate for nervous system AChE activity
- It is more sensitive than brain AChE to chlorpyrifos (CPF) (Table 1)

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). Both pups and adults were exposed to CPF. PND=postnatal day and N = 8 animals/group.
* Significantly different from control at 0.05.

Finding 9 - Developmental Neurotoxicity (DNT)

- There are epidemiological and animal data showing DNT
- Animal studies
  - Some showed DNT effects at doses with minimal or no brain AChE inhibition
  - Studies conducted with low doses can provide the basis for dose-response relationship analysis (Table 2)

Finding 9 Table 2. Selected developmental neurotoxicity studies in animals with multiple doses of CPF.

Study	Species Exposure period	Admin-istered Doses mg/kg-day	Dose for Observed Effects mg/kg-day	Observed Effect at Low Dose in Offspring
Hoberman, 1998 (Guideline study)	Rat Dam: GD6-LD11	0, 0.3, 1.0, 5.0	[1.0]	↓ Parietal cortex thickness in PND66 females [no data for 0.3 mg/kg-day]
Silva et al., 2017	Rat Dam: GD14-20	0, 0.01, 0.1, 1	0.1	↑ Anxiety and ↑ locomotor activity in PND21 males
Gómez-Giménez et al., 2017a	Rat Dam: GD7-PND21	0, 0.1, 0.3, 1	0.1	↓ Spatial learning in Morris Water maze in adult males
Gómez-Giménez et al., 2017b	Rat Dam: GD7-PND21	0, 0.1, 0.3, 1	0.1	↑ Locomotor activity in 2-3 month old males and females
Lee et al., 2015	Mouse PND10 male	0, 0.1, 1.0, 5	0.1	↑ Total activity in PND60 males
Carr et al., 2017	Rat PND10-16	0, 0.5, 0.75, 1.0	0.5	↓ Time to emergence into novel environment in PND25 males and females

- Oral route
- Exposure during gestation and/or postnatal, but tested later
- Lowest effective dose at 0.1 mg/kg-day from 4 studies
- Effects on anxiety, motor activity, and spatial learning

Finding 9 - DNT (continued)

- Epidemiological studies
  - Associations between organophosphate exposure during pregnancy and adverse neurodevelopmental outcomes
  - Data pose challenges for dose-response assessment
    - Single time point measurement
- *In vitro* zebrafish: abnormal behavior and AChE inhibition
- Mode of action for DNT: many possible, no definitive conclusion

Finding 13 - Toxicity Endpoints

- Draft TAC risk assessment critical toxicity endpoint is RBC AChE inhibition
- Data indicate that other endpoints such as DNT and respiratory toxicity endpoints may be more sensitive and toxicologically more relevant

Finding 14 - Steady-state POD for Acute Exposure

- DPR's use of steady-state PODs for acute exposure is a conservative approach for the RBC AChE inhibition endpoint
  - The approach was used to compensate for background exposure and cumulative RBC AChE inhibition

- However, it may add uncertainty to the risk estimate for this endpoint

Finding 14 - Steady-state POD (continued)

- An explanation for the age difference in PODs is needed
  - Inhalation PODs: children and adult females are similar.
  - Dermal PODs: children's is 5-fold higher than that for adult females.

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

Exposure routes	Children 1-2 years old[a]	Females 13-49 years old[a]
Inhalation (CPF)	2,370 µg/m^3 [1,232 µg/kg-day[b]]	6,150 µg/m^3 [1,722 µg/kg-day[b]]
Dermal (CPF)	**134,250 µg/kg-day**	**23,600 µg/kg-day**

[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.

Finding 15 – Uncertainty in Steady-state POD

- There is uncertainty in the steady-state inhalation PODs derived from the model
  - CPF was modeled as dry particles and bystanders are exposed to liquid aerosols
    - Pharmacokinetics of CPF could be different at different deposition sites
  - Steady-state outputs of the inhalation component of the model have not been validated
    - There are no suitable subchronic inhalation animal or human toxicity data
    - The only human inhalation study was an acute combined dermal and inhalation exposure study and RBC AChE inhibition was not measured. (Vaccaro et al., 1993)

Finding 16 - Residential Bystander Exposure Routes

- Exposure for 1 to 1.5 hours per day
- Spray drift and dietary aggregate exposure scenario was not assessed for the female group- risk is unclear for this scenario

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[b]	Inhalation, dermal[a]
Spray drift and dietary aggregate exposure	All routes for spray drift plus CPF in food and 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.

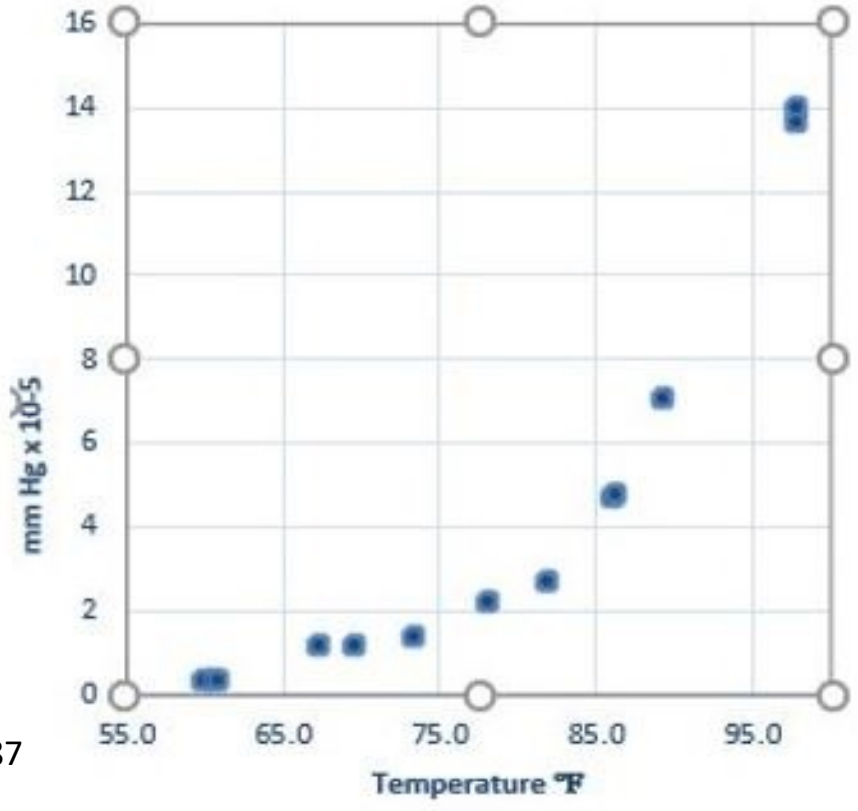
Finding 17 - Surrogate Air Concentration

- AGDISP aerial application modeling to derive surrogate air concentrations for ground boom and orchard air blast applications is a conservative approach

  - Best available method to estimate air concentration
  - Surrogate air concentrations are similar to air monitoring data from air blast application
  - However, the approach may underestimate concentration from air blast when there is little or no foliage

Finding 19 - Exposure to CPF Vapor

- Potential for residential bystander exposure to CPF vapor and CPF aerosol
  - Aggregate exposure when residential bystander also lives near the application field
  - CPF vapor level in the air
    - Increases with temperature
    - May last many hours after the application
    - US EPA incorporated vapor exposure estimate in the 2016 risk assessment



Chakrabarti and Gennrich, 1987

Finding 22 - Interspecies UF

- OEHHA recommends an interspecies UF of 3, instead of 1
- This factor is needed to address model uncertainty
  - PBPK-PD model is not equivalent to a well-conducted human study
  - Some parameters were derived from animal studies
  - Limited data for model validation
    - Model validated with acute oral and dermal human data (see next slide)
    - Model not adequately validated for human steady state exposures for any route

Finding 22 - Human studies used in model validation

- Few subjects, all adults
- Mostly single dose, one-time exposure
- RBC AChE inhibition observed only in one subject

	Nolan et al., 1982, 1984	Nolan et al., 1982, 1984	Kisicki et al., 1999	Vaccaro et al., 1993
Exposure Route	Oral	Dermal	Oral	Dermal and inhalation combined
Number of subjects	6 males	6 males	6 males and 6 females	7 males and females
Dose one time	0.5 mg/kg (tablet)	5.0 mg/kg (CPF in methylene chloride, on forearm)	0.5, 1, or 2 mg/kg (capsule)	Encapsulated CPF formulation applied to carpet
RBC AChE inhibition	None	None	One female (2 mg/kg with high absorption rate, ~3 times average)	Not measured

Finding 23 - Intraspecies UF (variation in human response)

- OEHHA recommends an intraspecies UF of 30, instead of 10
  - Model did not fully account for differences in physiological, anatomical and biochemical factors during pregnancy and within different age groups
- **Pharmacokinetic considerations**
  - Key metabolism parameters were based on *in vitro* study with few samples and from post-mortem tissues

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

Tissues	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).

Finding 23 - Intraspecies UF (continued)

- **Pharmacodynamic considerations**
  - Question about the representativeness of the RBC AChE parameters (e.g., inhibition rate, reactivation rate)
    - Small sample size or limited age group
  - RBC AChE activity varies with age, pregnancy, and even between healthy adults

- Applicability of intraspecies UF for RBC AChE inhibition to DNT?
  - Many factors can influence an individual's susceptibility to neurotoxicants

Finding 24 - Additional UF

- This UF was applied because RBC AChE inhibition is used to address DNT concern
  - Food Quality Protection Act requires US EPA to apply an additional UF of 10-fold when there is:
    - Potential pre- and postnatal toxicity
    - Incomplete exposure and toxicity data for infants and children
- The approach adds uncertainty to the risk characterization
- OEHHA recommends thorough evaluation of DNT studies to see if a POD for DNT can be directly determined, instead of using RBC AChE inhibition as a surrogate, and this additional UF

Questions?