Draft Evaluation of Chlorpyrifos as a Toxic Air Contaminant

Department of Pesticide Regulation
Human Health Assessment Branch

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Presenting today from DPR’s Human Health Assessment Branch

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Introduction

- Chlorinated organophosphorus (OP) ester
- O,O-Diethyl 0-3,5,6-trichloropyridin-2-yl phosphorothioate
- Synonyms: Brodan, Dowco 179, Dursban, Empire, Lorsban
- Manufactured by Dow AgroSciences as an insecticide, acaricide, and miticide
Uses

• First registered in the US in 1965

• Concerns regarding effects on the developing nervous system have limited its use
  ▪ All US home uses banned in 2001
  ▪ Globally phase-out of non-agricultural uses in US and EU in 2006

• Currently registered for many fruits, vegetables, tree nuts, and grain crops in the US

• Some of the non-agricultural uses in the US are for mosquito control for public health protection and insect control on golf courses
Uses in California

• 48 products with an active registration in the California Product/Label Database

• Total yearly use of 1.1 million pounds (2015)

• Highest usage is on almonds; other major uses include orange, walnut, alfalfa, cotton

• Major use areas in California include the Central Valley, the Central Coast, and Imperial County

• Year-round use, with peak use in the summer

• Allowed methods of application include aerial, airblast, ground boom, chemigation, and others
Human Illness and Exposure Reports

• 246 cases of pesticide exposure from 84 episodes involving chlorpyrifos (2004 – 2014)

• Majority of cases:
  ▪ Due to drift (66%)
  ▪ Residue exposure (17%)
  ▪ Ingestion (5%, largely accidental)

• Bystanders accounted for majority of cases (> 88%), most of whom were engaged in routine activities at the time of exposure
Symptomology

**Acute Poisoning**

- Human deaths reported due to accidental exposure or intentional ingestion
- Doses > 300 mg/kg in humans resulted in unconsciousness, convulsions, cyanosis, and uncontrolled urination
- Lower doses can cause hypersalivation, respiratory distress, muscle tremors, ataxia, diarrhea, vomiting

**Chronic Toxicity**

- Workers with higher exposures report impaired memory, speech difficulties
- Workers with lower exposures reported no consistent effects
California Risk Assessment History

- May 1992 – Risk Characterization Document based on Dietary Exposure
- June 1993 – Exposure Assessment Document focused on Occupational and Indoor Residential Exposures
- High priority status due to:
  - Potential neurodevelopmental/ neurobehavioral effects
  - Results from genotoxicity and reproductive toxicity studies in rats
  - Potential exposure due to spray drift, infant hand-to-mouth activity, food & drinking water
- Chlorpyrifos entered the comprehensive human health risk assessment process in 2011
- DPR released draft risk characterization document for external scientific review in December 2015
- Revised risk assessment released August 2017
Toxicology Profile
Mode of Action

Classical Target:

• Toxicity associated with binding and inhibition of the enzyme acetylcholinesterase (AChE) in insects and mammals
  ▪ accumulation of neurotransmitter acetylcholine (ACh)
  ▪ results in excessive stimulation of the cholinergic pathways in central and peripheral nervous systems

• Requires metabolic activation to chlorpyrifos oxon to inhibit cholinesterase activity
Red Blood Cell Cholinesterase Inhibition

- AChE hydrolyzes acetylcholine in some non-neuronal cells such as red blood cells (RBCs)
- RBC AChE inhibition is commonly used as a surrogate of the inhibition in target tissues
- Threshold dose for RBC AChE inhibition is approximately 1 mg/kg/day, including for immature organisms
Toxicokinetics (Mammalian)

Absorption:
- Oral absorption is complete (~ 70-99% in rats, humans)
- Dermal absorption is ~ 3-10% based on urinary metabolites
- Evidence of inhalation absorption shown by ChE inhibition

Distribution:
- Highest levels found in fat
- Binds to plasma proteins (e.g., albumin)
- Detected in rat and human milk
- Evidence of transplacental transfer (liver, brain, placenta, umbilical cord, amniotic fluid)
Toxicokinetics, continued

**Metabolism:**
- Extensively metabolized by liver cytochrome P450 enzymes
- Oxidative desulfuration results in chlorpyrifos oxon
- Dearylated into 3,5,6-trichloro-2-pyridinol (TCPy) and diethyl thiophosphate (DETP)
- Hydrolyzed into TCPy and diethylphosphate (DEP)

**Elimination:**
- Biological half-life is 10-27 hrs
- Urine is the main route of elimination; TCPy, DEP, DETP, and glucuronide and sulfate conjugates are major metabolites
- Urinary TCPy commonly used in human biomonitoring studies
Targets of Toxicity

Developmental and Reproductive Toxicity
✓ No evidence that chlorpyrifos is a teratogen or affects reproduction
✓ Fetal toxicity was only observed in the presence of maternal toxicity

Immunotoxicity
✓ Doses that cause cholinesterase inhibition did not result in immune system effects

Genotoxicity
✓ Studies for genotoxic effects were mostly negative, however DNA damage assays were positive in yeast, bacteria, and in cells from treated laboratory animals
Carcinogenicity

**Animals:**
Chlorpyrifos did not cause tumors in chronic feeding studies in rats & mice

**Humans:**
Associations are reported between chlorpyrifos use and non-Hodgkin's lymphoma, and lung and rectal cancer in pesticide applicators and farmers

- Associations based on small numbers of cases and concomitant exposure to other chemicals
- Exposure based on recall, questionnaires with family members

According to US EPA, chlorpyrifos is not likely to be carcinogenic to humans, based on the lack of evidence of carcinogenicity in animals studies and the absence of mutagenicity
Neurodevelopmental Toxicity in Animals

Females dosed throughout pregnancy and lactation or pups dosed after weaning (repeated dosing); Evaluated motor activity, auditory startle response, spatial orientation, social behavior, cognition, anxiety in young pups and as they matured

Results:

- Developmental neurotoxicity occurs at doses that do not alter pregnancy or general health of offspring
- Evidence of long-lasting impairment of locomotor activity, deficits in cognitive function, and social interaction at doses equivalent to the threshold for ChE inhibition (i.e., 1 mg/kg/day)
- Evidence of a decline in anxiety shortly after weaning associated with doses below those that inhibit brain ChE (0.5 mg/kg/day)
- Inhibits neuronal growth in tissue culture (in vitro) at concentrations well below those that cause AChE inhibition
Neurodevelopmental Epidemiology

- Ongoing prospective cohort studies and multiple observational studies investigated associations between markers of fetal or early life exposure to chlorpyrifos and effects on neurodevelopment, learning, and behavior.

- Exposure, if quantified, was measured as chlorpyrifos in cord blood, TCPy, or non-specific OP metabolites in maternal or child urine.

- Columbia Center for Children's Environmental Health study was one of the many cohorts we considered:
  - Only study that specifically quantified chlorpyrifos in blood at birth.
  - Quantified ambient air and personal monitoring.
  - Statistically significant associations between chlorpyrifos blood concentrations and decreased birthweight, attention problems, attention-deficit/hyperactivity disorders, pervasive developmental disorder, working memory, and Full Scale IQ.
Neurodevelopmental Epidemiology, continued

- Difficult to quantify associations between chlorpyrifos exposure and neurodevelopmental effects
- Complicated by:
  - Potential exposure to multiple OPs in the environment
  - Several OPs have the same urinary metabolites (dialkyl phosphate metabolites DEP, DMP, DETP, DMTP, etc.)
  - Measurement of chlorpyrifos or its metabolites at birth does not indicate what exposure may have occurred throughout pregnancy
  - Critical window(s) of susceptibility for these neurodevelopment effects not known

Compelling evidence that developmental neurotoxicity may occur in humans potentially at exposures below those that cause overt toxicity or inhibit AChE
Neurodevelopment may be affected by:

**Metabolic mechanisms:**
- Butyrylcholinesterase
- Carboxylesterases
- Neuropathy target esterase
- Monoacylglycerol lipase
- Fatty acid amide hydrolase

**Other mechanisms:**
- Oxidative stress
- Disruption of neurogenesis
- Cytotoxicity
- Disruptions in cell signaling
- Altered nuclear transcription factors
- Altered neuronal-glial cell interactions

**Environmental Stressors:**
- Combined chemical exposures
- Health status of mother
- Infectious diseases
- Heavy metal exposures
- Social determinants

Human development is multifactorial and evidence of the specific mode of action for chlorpyrifos is not known at this time.
Hazard Identification
Risk assessment addresses potential bystander effects arising from:

- Food and drinking water exposure
- Air and skin contact
- Incidental ingestion
- Aggregate exposures from various combined sources

Risk assessment focused on two at-risk groups:

1. Women of childbearing years due to potential pregnancy status
2. Children 1-2 yrs old because of the time spent outdoors and their potential for oral exposure due to mouthing objects and eating dirt
2017 Draft Points of Departure (PoDs)

Point of Departure Definition: A dose not associated with adverse effects or that causes a low level of response

PoDs are used as starting point for determining risk

- PoDs based on 10% RBC AChE inhibition
- DPR risk assessment adopted the 2014 US EPA PoDs
- Human equivalent doses estimated by PBPK-PD modeling
  - Model-derived acute PoDs for oral exposure
  - Model-derived 21-day (steady-state) PoDs for inhalation, dermal, and oral exposures
PBPK-PD Model

• Predicts a time-course of chlorpyrifos metabolism in humans

• Incorporates RBC AChE inhibition, reactivation, and regeneration after exposure to chlorpyrifos

• Pharmacokinetic data derived from human studies
  - Human liver microsomes and plasma were used to represent metabolic variability across a broad range of ages
  - Life-stages for infants, children, and adults

• Multi-route human exposure parameters (oral, dermal, inhalation)

• PBPK-PD model has undergone numerous scientific evaluations
## Points of Departure for Calculating Risks from Exposure

<table>
<thead>
<tr>
<th>Routes and Duration</th>
<th>Exposure Scenarios</th>
<th>DPR 2017 (10% RBC AChE inhibition)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Point of Departure</td>
</tr>
<tr>
<td><strong>Acute Oral [µg/kg/day]</strong></td>
<td>Dietary; Spray-Drift; Aggregate Dietary &amp; Spray-Drift</td>
<td>581 467</td>
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<tr>
<td>Children 1-2</td>
<td></td>
<td></td>
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<tr>
<td>Females 13-49</td>
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<tr>
<td><strong>Steady State Oral [µg/kg/day]</strong></td>
<td>Dietary; Spray-Drift; Aggregate Dietary &amp; Spray-Drift</td>
<td>99 78</td>
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<tr>
<td>Children 1-2</td>
<td></td>
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<td>Females 13-49</td>
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<tr>
<td><strong>Steady State Dermal [µg/kg/day]</strong></td>
<td>Spray-Drift; Aggregate Spray-Drift</td>
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<td>Children 1-2</td>
<td></td>
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<td>Females 13-49</td>
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<tr>
<td><strong>Steady State Inhalation [µg/m³]</strong></td>
<td>Spray-Drift; Aggregate Spray-Drift</td>
<td>2370 6150</td>
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<tr>
<td>Children 1-2</td>
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</table>
Exposure Assessment
Exposure Assessment

Non-Occupational Bystanders
- Short-term exposure (≤ 24 hr exposure from a single application)
- Two populations of concern:
  - Women of childbearing years
  - Children 1-2 yrs old

Indirect Exposure Associated with Primary Spray Drift
- Ground boom
- Orchard airblast
- Aerial

Routes of Exposure
- Dermal
- Oral (non-dietary incidental ingestion; children 1-2 yrs old)
- Inhalation
- Food
- Drinking water
- Aggregate exposures
Exposure Assessment, continued

The exposure assessment approach adopted:

- US EPA spray drift methods (Dawson et al, 2012)
  - To determine expected environmental concentrations
- US EPA SOP (2013) for Residential Exposure Assessment
  - For exposure calculations

Computer simulation modeling used to estimate spray drift:

- Horizontal deposition (ug/cm²)
- 1-hr time-weighted average (TWA) air concentrations (ng/L)
Exposure Assessment, continued

Spray drift models used:

• AgDRIFT V2.0.5/V2.1.1 empirical (curve fit) model
  ▪ Deposition only (dermal/oral)
  ▪ Application methods (ground boom, orchard airblast)

• AGDISP V8.28 Lagrangian First Principles model
  ▪ Deposition (dermal/oral) and air concentrations (inhalation)
  ▪ Application methods included fixed wing aircraft and rotary aircraft

Reasonable worst case model inputs:

• Ground boom and orchard airblast worst case application method scenarios
  ▪ High boom ground boom
  ▪ Dormant apple application

• Aerial
  ▪ Reasonable worst case California agricultural aircraft types based on a DPR Enforcement county survey
  ▪ Real world (CIMIS) meteorological conditions for the San Joaquin Valley chosen to produce the highest modeled downwind deposition
Risk Calculations

- Risks were calculated as margins of exposure (MOE)
  - Ratio of the PoD to the estimated human exposure level
- A target MOE of 100 is generally considered protective
- The target takes into account the following uncertainty factors:
  - 1 for interspecies sensitivity
  - 10 for intraspecies variability
  - 10 for potential neurodevelopmental effects

- MOEs were calculated from route-specific PoDs
- Aggregate (combined) MOEs were calculated for exposure through skin contact, mouthing, breathing, eating and drinking
Exposure scenarios with no health risks (MOE > 100)

No risk to children and women in childbearing age from:

- Dietary exposure (residue in food and drinking water)
- Dermal exposures resulting from spray drift
Exposure scenarios with potential health risks (MOE<100)

- Hand-to-mouth exposure to children
- Inhalation exposure to children and women of childbearing age
- Various aggregate exposures from combined media (food, drinking water, deposition from spray-drift)
  - Exposure to aerosols in the air near application sites was the main driver when the aggregate MOEs < 100
Discussion and Uncertainties
Uncertainties Associated with Toxicity

• Selection of 10% RBC AChE inhibition as critical toxicity endpoint to protect human populations from other endpoints that were not as easily measured

• PBPK-PD model version used in this risk assessment lacked critical data, including certain physiological changes during pregnancy
Uncertainties Associated with Exposure

- Default physiology assumptions and conventions, as well as modeling parameters used to estimate bystander exposures

- No incorporation of illegal pesticide residue data into the dietary exposure assessment (from the California Pesticide Residue Monitoring Program)

- Estimates of chlorpyrifos contaminated drinking water based on DPR surface water monitoring program data, (irrigation ponds, sloughs, and agricultural drains monitoring data; may not be used for drinking water)
Uncertainty Factors (UF) used in Risk Characterization

- UF of 10 due to database deficiencies
  - Example: PBPK-PD model may not have captured the range of human sensitivities
- UF of 10 was used to protect against potential neurodevelopmental effects in humans
  - Sufficient data are not available at this time to establish a quantitative dose-response relationship for assessing the neurodevelopmental effects in humans
Key Conclusions

- Established a dose that will protect humans from toxicity resulting for cholinesterase inhibition
- Reduced the dose by 10-fold to protect sensitive human subpopulations
- Reduced the dose by a further 10-fold factor to account for the possibility of neurodevelopmental effects

DPR has confidence that this risk assessment reflects the most current scientific understanding of chlorpyrifos’s potential for toxicity to humans
Extra Slides
Risk Assessment History US EPA

**2006:** Reregistration Eligibility Decision (RED)
- Critical endpoints based on 10% RBC and plasma ChE inhibition in adult rats.

**2011:** Preliminary Human Health Risk Assessment
- Critical endpoints were BMDLs for 10% RBC AChE inhibition in pups (PND 11 pups) or pregnant dams.

**2014:** Revised Human Health Risk Assessment
- Critical endpoints are PBPK-PD-estimated human equivalent doses based on 10% RBC AChE inhibition.
- Human PoDs are similar to the animal PoD values in the 2006 and 2011 US EPA risk assessments.
- Much objection from public and other groups for the continued use of AChE inhibition basis for regulatory standards.
April 2016: Chlorpyrifos Issue Paper: Evaluation of Biomonitoring Data from Epidemiology Studies

- PBPK portion of the PBPK-PD model was used to predict blood levels in women for comparison with the cord blood levels measured in the Columbia CCCEH study cohort.
- For the first time proposed PoDs were not based on RBC AChE inhibition.
- PoDs were for predicting risk of neurodevelopmental outcomes.
- PoDs were drastically lower (approximately 1000-6400-fold) than the PoDs for AChE inhibition.
- SAP (April 2016) did not support the approach of using the Columbia CCCEH cohort cord blood data for deriving PoDs.
- SAP supported use of the PBPK model for predicting internal dosimetry.
Risk Assessment History US EPA

November 2016: Revised Human Health Risk Assessment for Registration Review

- Used the PBPK model to estimate time-weighted average (TWA) chlorpyrifos concentrations in human blood
- Exposure based on residential use of chlorpyrifos on crack and crevice/hard surfaces.
- External doses estimated as points of departure (PoDs) for infants, children, and adults.
- PoDs approximately 150-9000-fold lower than the PoDs based on 10% RBC AChE inhibition
- US EPA is still working through the scientific and regulatory basis. Risk assessment is not finalized.