

Draft Evaluation of Chlorpyrifos as a Toxic Air Contaminant

Department of Pesticide Regulation
Human Health Assessment Branch

Scientific Review Panel Meeting
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Presenting today from
DPR's Human Health Assessment Branch

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Today's Presentation

- Background on Pesticide TACs
- Steps in Evaluating Chlorpyrifos as a TAC
- Overview of DPR's evaluation
- Discussion of Charge Questions #1 and #2

Background on Pesticide TACs

- DPR Authority cited in Food and Agricultural Code Sections 11456 and 14026
- Requirements for evaluation of pesticide toxic air contaminants (TACs) cited in Food & Agricultural Code Sections 14021-14027
- Pesticide TAC - air pollutant that may cause or contribute to an increase in mortality or an increase in serious illness, or which may pose a present or potential hazard to human health

Background on Pesticide TACs, *continued*

- 14022(a) – in consultation with OEHHA and ARB, DPR shall evaluate the potential hazards and health effects of pesticides that may be determined to be a TAC
- 14023(a) – in consultation with OEHHA, DPR prepares a report on the health effects of the pesticide; the report shall assess:
 - availability and quality of data on health effects
 - potency, mode of action, and other relevant biological factors
 - an estimate of the levels of exposure that may cause or contribute to adverse health effects
 - the range of risk to humans resulting from current or anticipated exposure.

Chlorpyrifos TAC Evaluation to Date

- December 2015 – DPR released draft *Chlorpyrifos Risk Characterization Document* (RCD)
- Receipt of technical comments from OEHHA, ARB, Dow AgroSciences LLC
- Evaluation/assessment of chlorpyrifos as a TAC
 - Based on Dec 2015 RCD draft
 - Incorporated pertinent technical comments
 - Included expanded analysis of new/additional data: developmental and cancer epidemiology, in vitro and in vivo, human exposure and illness, pesticide use, mechanism, PBPK-PD modeling, air drift modeling, dietary, drinking water, and aggregate exposures
- August 2017 – DPR released draft *Evaluation of Chlorpyrifos as a Toxic Air Contaminant* and formal responses to technical comments from OEHHA, ARB, and Dow AgroSciences LLC

Chlorpyrifos TAC Evaluation to Date, *continued*

- September 2017 – Presented draft evaluation to Pesticide Registration and Evaluation Committee; opening of 45-day public comment period
- December 2017 – DPR released revised draft *Evaluation of Chlorpyrifos as a Toxic Air Contaminant*
 - Incorporated pertinent technical comments received during public comment period
 - Included expanded analysis of new/additional data, including new animal developmental neurotoxicity (in vivo) results
- December 2017 – DPR released response to technical public comments and additional comments from Dow AgroSciences LLC
- Distributed latest draft evaluation along with previously mentioned documents to Scientific Review Panel

Chlorpyrifos TAC Evaluation to Date, *continued*

- December 12, 2017 – SRP and DPR received OEHHA's findings
- December 13, 2017 – orientation presentation to SRP; follow up with additional supporting materials
- January 17, 2018 – DPR released response to OEHHA findings

All documents are available at

http://www.cdpr.ca.gov/docs/whs/active_ingredient/chlorpyrifos.htm

Chlorpyrifos TAC Evaluation to Date, *continued*

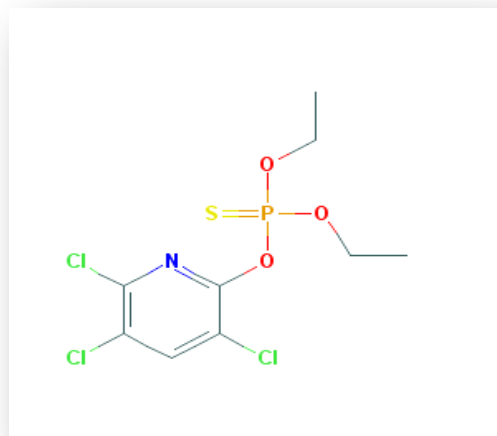
- January 23, 2018 – first SPR meeting to review the data presented by DPR
- By law, the Panel shall review “the scientific data on which the report is based, the scientific procedures and methods used to support the data, and the conclusions and assessments on which the report is based.”
- If SRP determines “the health effects report is seriously deficient,” it returns the report to the DPR director who shall revise and resubmit it within 30 days of receiving the SRP’s determination of deficiency, and prior to developing control measures or other regulations

Reference: Food and Agricultural Code Section 14023(b)-(c)

Evaluation of Chlorpyrifos as a Toxic Air Contaminant

Introduction

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



Chlorpyrifos Uses - United States

- First registered in the US in 1965
- December 2000 – EPA reached agreement to halt manufacture of chlorpyrifos for nearly all residential uses
- March 2001 – Registration cancelled for indoor residential products except containerized baits in child resistant packaging
- Outdoor residential products were cancelled except fire ant mound treatment by licensed applicators or mosquito control by public health agencies
- December 2002 - All retail sales were stopped
- Currently agricultural uses include fruits, vegetables, tree nuts, and grain crops

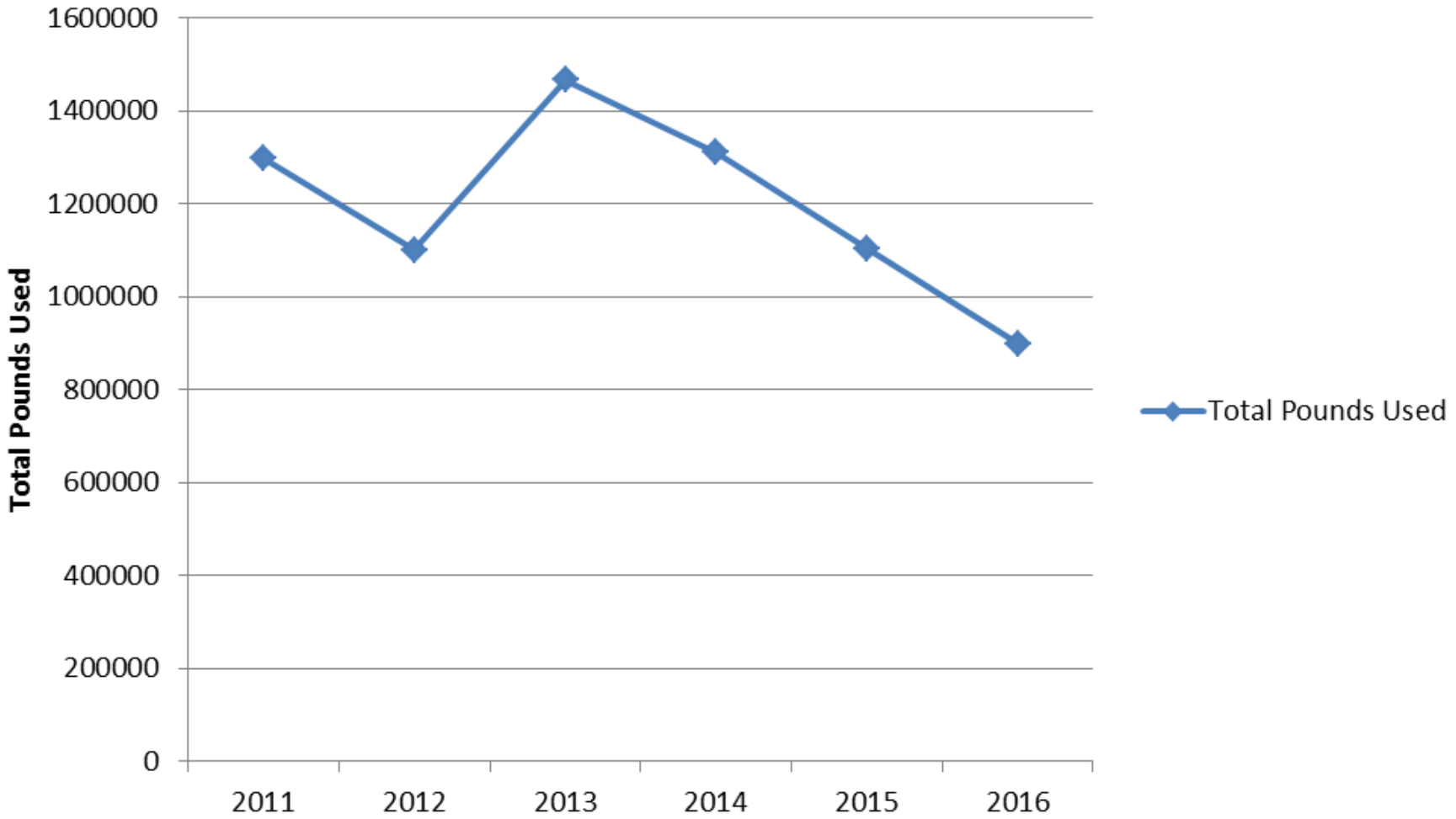
Chlorpyrifos Uses - California

- 48 products with an active registration in the California Product/Label Database
- Major CA agricultural uses include nut trees, fruit, vegetable, and grain crops
- Several registered non-production agricultural uses including golf course turf, industrial sites, greenhouse and nursery production, seed treatments, sod farms, and wood products
- Additional uses include cattle ear tags, roach bait (childproof) for use in homes and sewer manholes, fire ant control, and public health control of mosquitos
- California is the only state that regulates chlorpyrifos as a restricted use material (http://www.cdpr.ca.gov/docs/legbills/rulepkgs/14-002/final_text.pdf)

Chlorpyrifos Uses - California, *continued*

- 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 application methods include aerial, airblast, ground boom, chemigation, and others

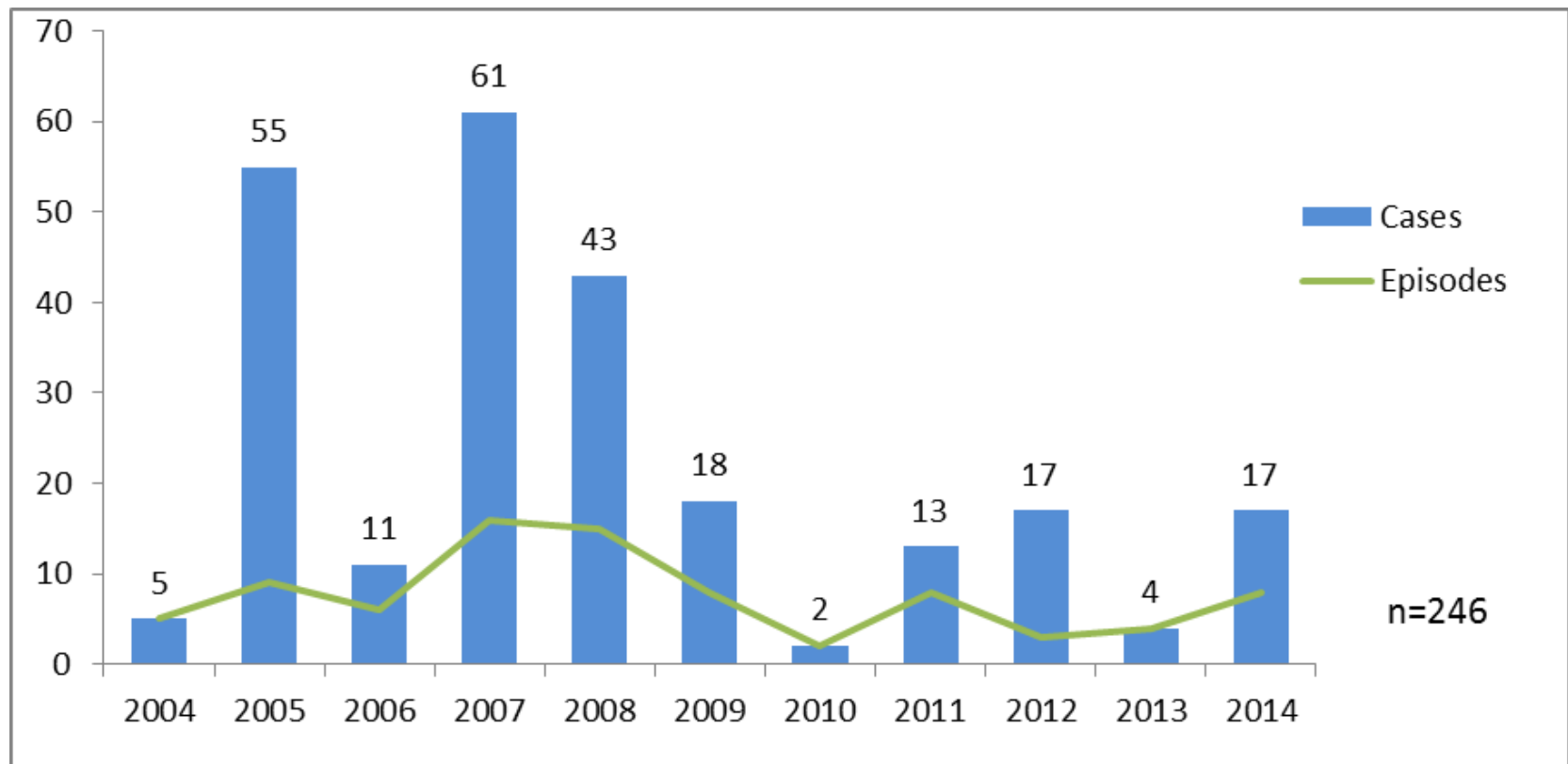
Total Pounds of Chlorpyrifos used in CA Agricultural Production



Human Illness and Exposure Reports

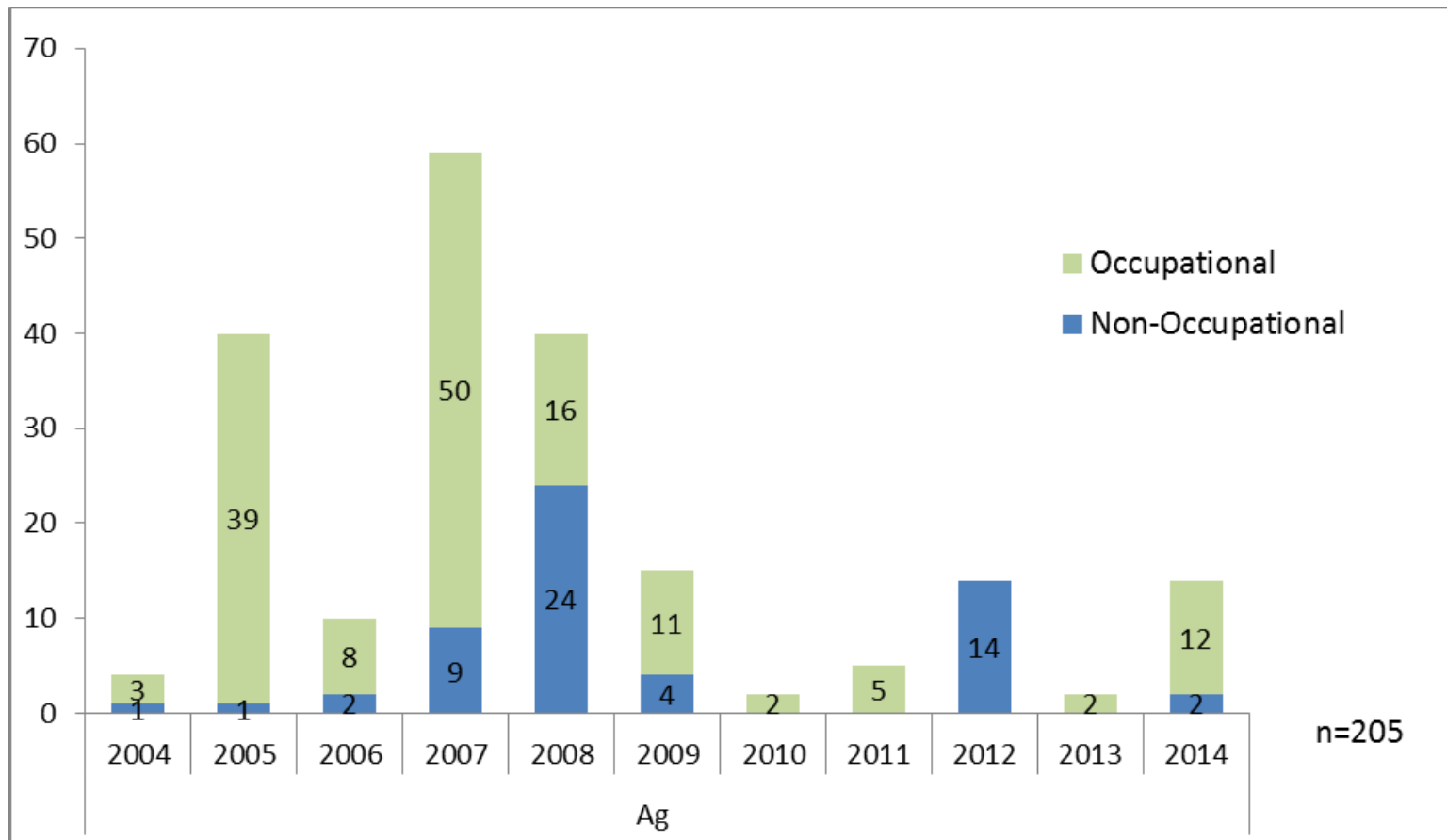
- 246 cases of pesticide exposure from 84 episodes involving chlorpyrifos (2004 – 2014)
- Majority of cases:
 - Due to drift (66%)
 - Residue exposure (17%)
 - Ingestion (5%, largely accidental)
- Bystanders accounted for majority of cases (> 88%), most of whom were engaged in routine activities at the time of exposure

Cases and Episodes of Illness Due to Chlorpyrifos Exposure, 2004-2014



Source: Cases Reported to the Pesticide Illness Surveillance Program and Evaluated as Associated With Exposure to Chlorpyrifos, Alone or in Combination with Other Products, 2004-2014. California Department of Pesticide Regulation, Worker Health & Safety Branch.

Chlorpyrifos Illnesses Caused by Agricultural Use, 2004-2014



Source: Cases Reported to the Pesticide Illness Surveillance Program and Evaluated as Associated With Exposure to Chlorpyrifos, Alone or in Combination with Other Products, 2004-2014. California Department of Pesticide Regulation, Worker Health & Safety Branch.

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

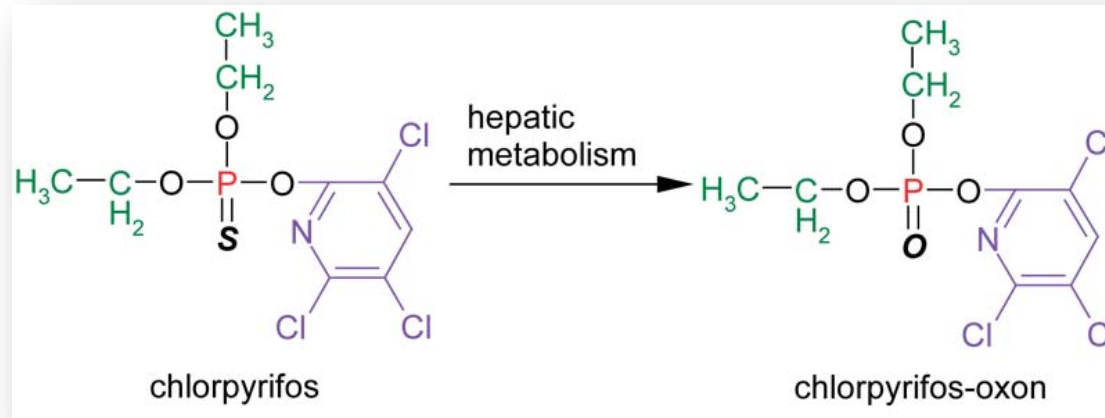
- Workers with higher exposures report impaired memory, speech difficulties
- There were no consistent reports of effects by workers exposed to lower levels

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 (Dec. 2015 and Aug. 2017 draft assessments)

- ✓ 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 Toxicity in Animals, *continued*

Results (Dec 2017 and subsequent drafts)

Abstracts, published papers from 2014-2017 reporting developmental neurotoxicity or neurotoxicity in adults at LOEL of 0.1 –0.5 mg/kg/day

- ✓ Three domains affected: Cognitive, Behavioral and Motor Activity
- ✓ Two rodent species (rats and mice)
- ✓ Treatment: gavage (dams or pups), indirect (pups in utero and through milk), subcutaneous (adults)
- ✓ Exposure: gestational, post-natal , both; single or repeated doses

Neurotoxic and Neurobehavioral Effects after Pre-, Postnatal and Adult Exposure to Chlorpyrifos

Test Age	Behavioral/Neurotoxic Effects	LOEL Beh/ NTX	LOEL AChE	Reference
Sprague-Dawley Rat Developmental Neurotoxicity : Dam Treated GD6-LD 11; Pups Tested PND				
PND 12-71	↓ Parietal cortex thickness	1.0	Brain 5.0	Hoberman et al. 1998
Sprague-Dawley M/F Rat Pups PND 11-16 at 0.5, 0.75 & 1.0 mg/kg/d (period following birth in humans for brain development maturation)				
PND 25	↑ time in open arm of + maze; ↑ number of + maze entries; ↑ motor activity, ↑ sociability (chasing, playing)	0.5	Not tested	Carr et al. 2015a
PND 25	↓ anxiety: ↓ time to emergence from dark container to a novel aversive environment)	0.5	Brain: 0.75	Carr et al. 2015b
PND 25	↑ anxiety (↑ time of emergence to light)	0.5	Not tested	Mohammed et al. 2015
PND 16	NA	Not tested	Brain: 0.75	Carr et al. 2017
Wistar Rats Treated GD 14-20 at 0.01, 0.1, 1.0, 10 mg/kg/d				
PND 21 & 70 M pups	↑ cognition (↓ % time in open-arm elevated + maze); ↑ motor activity; ↑ anxiety	0.1	Not tested	Silva et al. 2017
Wistar Rats Treated from Gestation Day 7 Through Post Natal Day 21 at 0.1, 0.3, 1.0 mg/kg/d				
2-3 months	↓ Spatial learning Morris Water Maze (M)	0.1	Not tested	Gomez-Gimenez et al. 2017a
2-3 months	↑ Spontaneous motor activity (M/F)	0.1	Not tested	Gomez-Gimenez et al. 2017b
NMRI Male Mice Treated at 5.0 mg/kg/d for Brain AChE PND 10 (3 hr post-dose) or 0.1, 1.0 and 5 mg/kg				
PND 60 or 120	↓ Spontaneous movement in a novel home environment (↓ motor activity; ↑ rearing)	1.0	Brain 5.0 1 dose	Lee et al. 2015
Sprague-Dawley Male Adult Male Rats Treated for 7 Days at 0.1, 1.0, 10 mg/kg/d				
Post-terminal dose day 8	↓ acoustic startle when a pre-pulse was sounded before the acoustic pulse; ↑ amplitude of N1 wave in SEP	0.1 (S.C.)	Not tested	Muller et al. 2014

Neurodevelopmental Toxicity in Animals, *continued*

Behavior and cognition are difficult to assess and quantify in animal models

Complicated by:

- Some effects showed a dose-response and others did not
- The many neural pathways involved in regulation of complex behaviors are not known
- ChE activity or inhibition was not concurrently measured in most studies
- Individual data were not available to perform further analyses

Neurodevelopmental Epidemiology

- Several ongoing prospective cohort studies and multiple observational studies investigated associations between markers of chlorpyrifos exposure and effects on neurodevelopment, learning, and behavior
- Some studies included biomarkers of exposure (chlorpyrifos in plasma, TCPy, or non-specific OP metabolites in maternal or child urine)
- Columbia Center for Children's Environmental Health (CCCEH) cohort
 - Quantified chlorpyrifos in maternal or cord blood plasma around birth
 - Personal air sampling for mothers \pm 1 month prior to birth
 - Evaluated associations between plasma concentrations at birth and attention problems, attention-deficit/hyperactivity disorders, pervasive developmental disorder, working memory, and Full Scale IQ in offspring

Neurodevelopmental Epidemiology, *continued*

Detection of Chlorpyrifos in maternal plasma or cord blood plasma samples around the time of birth					
Study (location)	No. samples	No. samples > LOD or LOQ (%)	LOD or LOQ	Median (Range)	Methodology
Wyhatt et al., 2003 (CCCEH)	211	150 (68%)	0.001 ppb	0.0026 ppb (ND – 0.035 mat; ND – 0.063 cord)	Barr et al., 2002 Recovery 18-21% Standard curve = 21 – 6400 ppb Standards in water
Neta et al., 2010 (Baltimore MD)	183	3 (1.6%)	21 ppb	NR (ND – 14 ppb)	In-house
Barr et al., 2010 (New Jersey)	138	NR	0.021 ppb	0.09 ppb (0.0007 – 10 ppb)	Perez et al., 2010 Recovery 73-87% Standard curve = 21 – 6400 ppb
Huen et al., 2012 (CHAMACOS)	234	42 (17.9%)	0.021 ppb	0.006 ppb (cord) 0.004 ppb (mat) (ND – 0.4 ppb)	Perez et al., 2010
Silver et al., 2015, 2017 (Zhejiang Province)	336	136 (40.5%)	0.675 ppb	NR (ND – 11.40 ppb)	Modified from Perez et al., 2010
Wickerman et al., 2012 (Zhejiang Province)	116	27 (23.3%)	0.05 ppb	NR (ND – 0.26 ppb)	In house

NR = not reported; ND = non-detect; LOQ = limit of quantitation; LOD = limit of detection; ppb = parts per billion

Neurodevelopmental Epidemiology, *continued*

- Difficult to quantify associations between chlorpyrifos exposure and neurodevelopmental effects in humans
- 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
 - Inconsistencies with analytical methods
- As stated in our Aug 2017 and Dec 2017 risk assessments, we conclude that the epidemiological data, alone, are not sufficient to derive a PoD for chlorpyrifos as a toxic air contaminant

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. Females 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
- 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, most recent update was September 2017

Points of Departure for Calculating Risks from Exposure

Routes and Duration	Exposure Scenarios	DPR 2017 (10% RBC AChE inhibition)	
		Point of Departure	RfD or RfC (= PoD/UF of 100)
Acute Oral [$\mu\text{g}/\text{kg}/\text{day}$] Children 1-2 Females 13-49	Dietary; Spray-Drift; Aggregate Dietary & Spray-Drift	581	5.81
		467	4.67
Steady State Oral [$\mu\text{g}/\text{kg}/\text{day}$] Children 1-2 Females 13-49	Dietary; Spray-Drift; Aggregate Dietary & Spray-Drift	99	0.99
		78	0.78
Steady State Dermal [$\mu\text{g}/\text{kg}/\text{day}$] Children 1-2 Females 13-49	Spray-Drift; Aggregate Spray-Drift	1342500	13425
		23600	236
Steady State Inhalation [$\mu\text{g}/\text{m}^3$] Children 1-2 Females 13-49	Spray-Drift; Aggregate Spray-Drift	2370	23.7
		6150	61.50

Points of Departure for Calculating Risks from Exposure, *continued*

- Dow AgroSciences LLC commented that the steady state (21 day) inhalation PoD of departure for children of 1-2 years old (2370 ug/m³) presented in the US EPA 2014 revised chlorpyrifos risk assessment would not achieve a 10% inhibition of RBC AChE
- In a separate analysis requested by DPR, Dow used the DPR default physiological parameters for children 1-2 years old to estimate an air concentration of 3000 ug/m³ that will result in 10% RBC AChE inhibition at 1 hour per day for 21 days
- Conducting an independent analysis, DPR estimated a 1 hour per day 21-day (steady state) PoD value for inhalation using the latest version of the PBPK-PD model and the model input parameters as specified in the US EPA 2014 chlorpyrifos risk assessment

The resulting PoD was 2850 ug/m³

Comparison of PBPK Modeled 21-Day PoDs for Inhalation Exposure of Children (1-2 yrs old)

Inhalation Concentration (ug/m ³)	Exposure Hours per Day for 21 Days	Percent Control RBC AChE Activity	Source
2370	1	<<10%	US EPA*
3000	1	~10%	Dow
2850	1	~10%	DPR**

* Also used by DPR in Dec 2015 and Aug 2017 risk assessments

** New 21-day steady state PoD to be used by DPR for finalization of chlorpyrifos TAC evaluation

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 ($\mu\text{g}/\text{cm}^2$)
- 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
 - Well vetted Lagrangian First Principles model that follows the behavior of droplets after they are released from aircraft nozzles
 - Comparisons of AGDISP output with measured field data have shown that the model tends to overestimate the field measurement, so will likely overestimate residential bystander exposure estimates
 - Deposition (dermal/oral) and air concentrations (inhalation)
 - Application methods included fixed wing aircraft and rotary aircraft

Exposure Assessment, continued

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 and Conclusions

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 females 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

Key Conclusions

- ✓ Database on chlorpyrifos inhibition of AChE is extensive
- ✓ Supports the establishment of dose-response that can be re-created at a specific dose level in animals
- ✓ At this time, it is not possible to determine a quantitative dose-response or dose-effect relationship based on any human endpoint; therefore these studies cannot be used as the scientific basis for a regulatory target
- ✓ The lack of dose-response and a clear mechanism of action does not negate results showing potential associations between in utero exposure and altered human development; new data will be evaluated as they become available
- ✓ Basis for a 10-fold UF for neurodevelopmental toxicity
- ✓ New animal identifying developmental neurotoxicity (DNT) at doses lower than AChE inhibition; DPR will consider the suitability of deriving a PoD specific to DNT in the final TAC evaluation document

Thank you