Chlorpyrifos: Developmental Toxicity
DARTIC Meeting

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Disclosure

No Financial Interest in the Topic of these Comments
Outline

• Public Health Significance
• Criteria for Listing as a Developmental Toxicant under Prop 65
• Expert Review of Developmental Toxicity Since 2008
• Discussion of Registrant Studies
• Biological Plausibility
Widespread Exposure During the Prenatal Period

• Over 1 million pounds/year in CA fields (DPR)
• Air Monitoring:
  – Routinely found in the air in agricultural communities (DPR 2016, Harnly et al. 2005)
• House Dust (Harnley 2009)
• Residues on Food (USDA)
• Drinking Water (DPR 2017)
• Biomonitoring (Castorina et al. 2010)
Prop65 Criteria

One of the following:

A. Sufficient evidence in humans

B. Limited evidence or suggestive evidence in humans, supported by sufficient experimental animal (mammalian) data

C. Sufficient evidence in experimental animals (mammals), such that extrapolation to humans is appropriate.
USEPA Science Advisory Panel Reviews

2008: “maternal chlorpyrifos exposure would likely be associated with adverse neurodevelopmental outcomes in humans.”

2012: “developmental neurobehavioral studies [in laboratory animals] demonstrate adverse effects from chlorpyrifos exposure.”

“chlorpyrifos likely plays a role in impacting the neurodevelopmental outcomes examined in the three cohort studies.”

2016: “CCCEH [Columbia] study is a well-designed longitudinal birth cohort research investigation that provides some of the strongest epidemiological data linking prenatal exposures to chlorpyrifos to developmental impairments later in childhood.”
US EPA Assessments

2015: Literature Review of Neurodevelopmental Effects OP pesticides
Combined evidence from animal and human studies finds neurodevelopmental effects for OP pesticides including, but not limited to, chlorpyrifos.

2014 & 2016: USEPA Revised Human Health Risk Assessments
“The agency agrees with the 2016 FIFRA SAP (and previous SAPs) that there is a potential for neurodevelopmental effects associated with chlorpyrifos exposure to occur at levels below 10% RBC AChE inhibition”
“Multiple epidemiological and toxicological studies indicate that children who have had an exposure to organophosphate pesticides such as chlorpyrifos in both urban and agricultural settings are at increased risk for abnormal neurodevelopment with persistent loss of intelligence and abnormalities of behavior.”
Scientific Reviews

• **Burke et al 2017:** Developmental neurotoxicity of the organophosphorus insecticide chlorpyrifos: from clinical findings to preclinical models and potential mechanisms.
  
  – Various preclinical research groups throughout the world have consistently demonstrated that CPF is a developmental neurotoxicant.”

• Two systematic reviews of neurodevelopmental effects of prenatal and postnatal organophosphate pesticide exposure. (*González-Alzaga et al 2014 and Muñoz-Quezada et al 2013*)
  
  – The evidence obtained from this systematic review of studies points to the adverse neurodevelopmental effects of OP pesticide exposure in children, especially for cognitive, behavioral (mainly related to attention problems), and motor outcomes.
Registrant Animal Studies

1970-1990

4 animal studies cited in Dow’s comments:
- Ouelette et al, 1983 (rat)
- Rubin et al 1987a (rat)
- Rubin et al 1987b (rabbit)
- Deacon et al 1979 (mouse)

NONE conducted according to EPA’s (1996) DNT protocol

1998

DNT study cited in Dow’s comments
Hoberman 1998 (rat)

EPA classified (1999): UNACCEPTABLE
Low-dose effects not properly quantified

2008

DARTIC review of chlorpyrifos
Biological Plausibility

• Specific Mode of Action not a criteria for listing
• USEPA (2015): “The lack of established MOA/AOP pathway does not undermine or reduce the confidence in the findings of the epidemiology studies.”
• Evidence for Biological Plausibility
  – Multiple mechanisms identified (EPA 2014, Burke et al 2017)
  – Known neurotoxicity
THANK YOU