

Chlorpyrifos Status Update



Pesticide Program Dialogue Committee

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Outline

- Chlorpyrifos
 - Background and Regulatory History
 - 2016 Scientific Advisory Panel
 - Next Steps

EPA Background – Use Pattern

- Chlorpyrifos – An OP insecticide, most used conventional insecticide with ~6 million pounds used on ~10 million total acres (2009-2013)
- Used in over 40 States
 - Top 5 states in terms of pounds applied are California, North Dakota, Minnesota, Iowa, and Texas
- Top Crops (used on nearly 50 crops) in pounds applied and percent crop treated
 - Top 5 crops in terms of pounds applied are soybeans, corn, alfalfa, oranges, and almonds
 - Crops with greater than 30% crop treated (PCT) (ratio of acres treated to acres grown)
 - Apples, asparagus, walnuts, onions, grapes (table), broccoli, cherries and cauliflower

Background – Regulatory History

- 2000 –all homeowner residential uses eliminated except for roach baits (child-resistant packaging) and ant mound treatments
- 2006 – organophosphate (OP) cumulative assessment, after significant risk mitigation associated with individual OPs, EPA determined the cumulative risks from the OP pesticides do not exceed EPA's level of concern
- 2009 - began registration review, moved chlorpyrifos (and other OPs) up in the schedule because of complex and cutting edge scientific issues
 - Hazard determination, endangered species, and drinking water (chlorpyrifos-oxon more toxic than parent & not included in earlier assessment)



Background - Peer Review & Process

- **2008:** New science on infants, children, & pregnant women from experimental laboratory toxicology & epidemiology studies
 - http://www.epa.gov/scipoly/sap/meetings/2008/091608_mtg.htm
- **2009:** Approach for risk assessment of semi-volatile pesticides
 - <http://www.epa.gov/scipoly/sap/meetings/2009/120109meeting.html>
- **2010:** Development of the draft “Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment”
 - <http://www.epa.gov/scipoly/sap/meetings/2010/020210meeting.html>
- **2011:** Chlorpyrifos Physiologically-Based Pharmacokinetic/Pharmacodynamic (PBPK/PD) Modeling linked to the Cumulative and Aggregate Risk Evaluation System (CARES)
 - <http://www.epa.gov/scipoly/sap/meetings/2011/021511meeting.html>
- **2012:** Scientific Issues Concerning Health Effects of Chlorpyrifos
 - <http://www.epa.gov/scipoly/sap/meetings/2012/041012meeting.html>
- **2013:** Federal review panel on MRI findings from Columbia U.

EPA NRDC/PANNA Petition

- 2007 – NRDC & PANNA petitioned EPA to revoke all chlorpyrifos FFDCAs tolerances and cancel all FIFRA registrations to address neurotoxicity and neurodevelopmental risks, including risks to the children of farmworkers from spray drift and volatilization
 - Petition identified cutting edge scientific issues (potential for long-term neurodevelopmental effects, integrating the results of toxicity studies with epidemiological research, assessing risk from volatilization)
 - Between 2008 – 2012 EPA took these issues to the Scientific Advisory Panel (SAP) for peer reviewed feedback (5 SAP meetings were held)

EPA NRDC/PANNA Petition

- Petitioners brought the most recent suit in 2014 in the 9th Circuit, seeking to compel either a denial or a proposed or final tolerance revocation (or cancellation)
- On June 10, 2015, the 9th Circuit ordered EPA to inform the Court of its planned response to the petition
- On June 30, 2015, EPA reversed its provisional response, indicating its intention to issue a proposed rule revoking tolerances by April 15, 2016, to address the previously identified drinking water concerns.
 - The proposed revocation would be informed by completing additional scientific analysis, including a refined drinking water assessment by the end of 2015 and any mitigation reached with registrants

EPA NRDC/PANNA Petition

- On August 10, the 9th Circuit rejected EPA's time line, ordering EPA to either deny the petition or issue a proposed or final revocation rule by October 31, 2015.
 - EPA Issued a Proposal To Revoke All Chlorpyrifos Tolerances on 10/30/15
 - EPA Also Informed The Court It Expects To Issue A Final Rule By December 2016

EPA Background - Risk Assessments

- June 2011 - Preliminary Human Health Risk Assessment was completed, FQPA Safety Factor (SF) was 1x
- June 2012 - Spray drift assessment and corresponding label mitigation addressing risk concerns
- January 2013 - Draft volatilization assessment; no risks identified
- December 2014 Revised Human Health Risk Assessment
 - FQPA SF of 10x was retained because of neurodevelopmental concerns (Columbia et al studies), pertains to females and children
 - Risks to workers who mix, load, and apply pesticide products
 - Individuals of concern are women workers of child bearing age
 - The potential to pose risks in limited geographic areas when drinking water from small watersheds that are heavily cropped
 - No new risks identified from exposures in food or to bystanders from either spray drift or volatilization

2014 Risk Assessment - Overview

- Approach Considers Key Guidance Documents
 - NRC Report: Science and Decisions
 - Revise default factors when science suggests
 - 2014 EPA - Data Derived Extrapolation Factors
 - Defining a mode of action to inform DDEFs
 - 2006 EPA – Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment
 - Peer reviewed (3 SAPs) and numerous publications, used to consider multiple exposure routes & pathways related to use of PBPK for chlorpyrifos

2014 Risk Assessment - Overview

- December, 2014 Revised Risk Assessment
 - RBC AChE inhibition as the critical effect for deriving the POD
 - PBPK/PD model used to derive human specific PODs for various age groups, routes, and durations
 - PBPK/PD model used to derive intra-species factor for some lifestages (not women of childbearing age)
 - Retained FQPA 10X Safety Factor: uncertainty in the human dose-response relationship for neurodevelopmental effects

Epidemiology Data

- Three prospective birth cohorts to examine environmental exposures and adverse health outcomes
 - Columbia cohort (1998-2002)
 - NYC, multi-ethnic, Cord Blood Chlorpyrifos
 - Mt. Sinai cohort (1998-2001)
 - NYC, multi-ethnic, TPCy (fetal growth only), DAPs, PON1
 - U of CA Berkeley Cohort (CHAMACOS) (1999-2002)
 - CA-Ag region, Mexican-American, ag worker, TCPy/DAPs, PON1
- Children's Environmental Health and Disease Prevention Research Centers (funded by EPA and NIEHS)

Epidemiology Data

- Over the time course of the project, EPA identified several supplemental analyses that may inform regulatory information needs
- Met with CCCEH (Columbia U.) researchers April 2013 to discuss specific information needs
 - Additional biomonitoring data
 - Pesticide Use information from NYC, application rates, etc.
 - Other pesticide characterization
- Information EPA hoped to obtain either unavailable (not collected), or not useful for the intended purpose
- HED documented pursuit of “raw data” in RHHRA



Weight of Evidence: Biological Plausibility

- No clear MOA/AOP for CPF influence on neurodevelopment
- Data suggest chlorpyrifos and/or its oxon are biologically active on a number of processes that affect the developing brain
- Uncertainties remain, but are diminished in the context of the qualitative similarity between the (tox+epi) databases
 - *Concern for long-term neurodevelopmental effects as a result of prenatal, perinatal and possibly early life exposure.*



2012 SAP Review of Epidemiological Literature

- “The Panel considers the Agency’s epidemiology review to be very clearly written, accurate, and to generally provide a very thorough review of the epidemiology literature.”
- “Overall, the Panel concurs with the 2008 SAP and the Agency in concluding that chlorpyrifos likely plays a role in impacting the neurodevelopmental outcomes examined in the three cohort studies.”
- “The strengths of the three studies support the Panel’s conclusion. There are nine strengths identified by the Panel which are discussed in the detailed response section of this report.”

EPA 2012 FIFRA SAP Report

- From the 2012 SAP Report, pp. 49-50:
 - The Panel acknowledged the limitations in the three longitudinal children's cohort studies of estimating chlorpyrifos exposures (i.e., the Columbia study, the Mt. Sinai study, and the CHAMACOS study), based on the exposure measures collected, and was in general agreement that the data from these studies alone were not sufficient to derive a point of departure (POD) for purposes of quantitative risk assessment.



2012 FIFRA SAP Report

- Per the 2012 SAP report, the agency was urged to find ways to use the epidemiology studies, in particular the CCCEH study, to inform the chlorpyrifos assessment (emphasis added):
 - "...if one assumes that cord blood measurements reflect exposure levels during the critical prenatal period for induction of neurodevelopmental effects, then in theory, these would be the ideal data from which to derive the POD for chlorpyrifos in humans"
- In doing so, the agency was encouraged to make use of the PBPK model to further characterize CCCEH dose estimates
 - "...a [PBPK] model could be used to further characterize the dose estimates in the epidemiology studies, for additional dose response analyses. Such a PBPK model will become even more important in the event that the agency might, at some point in the future, decide to move from using AChE inhibition to another outcome."



Science Topics Taken to 2016 SAP

- Used PBPK model & EPA-OPP's exposure assessment approaches in an attempt to more fully characterize exposure profile to women in the CCCEH cohort.
 - Exposure approaches have been previously reviewed by SAP and have used extensively in risk assessments.
 - Results provide support for using cord blood data for POD.
- Case studies developed to illustrate how the PBPK model would be used to predict internal doses from existing exposures to chlorpyrifos.

EPA Scientific Advisory Panel (SAP)

- April 2016 SAP meeting:
 - Represented expertise in a variety of scientific disciplines: epidemiology, laboratory animal toxicology, in vitro & mechanistic toxicology, biomonitoring, PBPK modelling
 - Expressed diversity of opinions on multiple issues
 - Acknowledged scientific challenge faced by the EPA
- Meeting transcript is available:
https://www.epa.gov/sites/production/files/2016-05/documents/fifra_sap_04_19_16_to_04_21_16_final_transcript.pdf
- SAP report expected by mid July



Next Steps

- Wait for SAP written report
- Letter sent to Columbia University to request raw data
- Contact with CDC to request raw data
- Check-in on progress to the 9th Circuit Court in June

Federal Register Links

- Proposed Tolerance Revocation

<https://www.federalregister.gov/articles/2015/11/06/2015-28083/chlorpyrifos-tolerance-revocations>

- Revised Human Health Risk Assessment

<http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0195>

- Literature Review for OP FQPA Safety Factor

<http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2010-0119-0023>



EPA Web Links

- Chlorpyrifos Fact Sheet

<http://www2.epa.gov/ingredients-used-pesticide-products/chlorpyrifos>

- Revised Human Health Risk Assessment Summary

<http://www2.epa.gov/ingredients-used-pesticide-products/revised-human-health-risk-assessment-chlorpyrifos>

- Proposed Tolerance Revocation Summary

<http://www2.epa.gov/ingredients-used-pesticide-products/proposal-revoke-chlorpyrifos-food-residue-tolerances>



Questions?