Chlorpyrifos Does Not Meet the Criteria for Listing as a Developmental Toxicant

OEHHA DART Identification Committee Hearing
November 29, 2017

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The Criteria for Listing

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The Statute

(a) “. . . the Governor shall cause to be published a list of those chemicals known to the state to cause . . . reproductive toxicity within the meaning of this chapter . . . .”

(b) A “chemical is known to the state to cause . . . reproductive toxicity if in the opinion of the state’s qualified experts it has been clearly shown through scientifically valid testing according to generally accepted principles to cause . . . reproductive toxicity . . . .”

California Health & Safety Code § 25249.8(a), (b) (emphasis added).

The Regulation

“. . . the DART Identification Committee may . . . :”

“(1) Render an opinion pursuant to subdivision (b) of Section 25249.8 of the Act, as to whether chemicals have been clearly shown through scientifically valid testing according to generally accepted principals, to cause reproductive toxicity . . . .”
DART IC Guidance Criteria for Identifying Chemicals for Listing as “Known to the State to Cause Reproductive Toxicity” (November, 1993)

“criteria included herein shall be utilized by the [DART IC] to identify chemicals which are to be recommended for listing as known to the State to cause reproductive toxicity.”

* * *

“In evaluating the sufficiency of data, a “weight of evidence” approach shall be used to evaluate the body of information for a given chemical.”

* * *

(Emphasis added.)
The Criteria for Listing (cont’d)

What Does “Clearly Shown” Mean?

Roget’s Thesaurus (2013)

• “show clearly” = “prove”

What Does “Clearly Shown” Not Mean?

• “Data suggest that . . . .”
• “Likely to be . . . .”
• “I have concerns . . . .”
• “Err on the side of health or safety”
• Precautionary Principle
# Chlorpyrifos Registration Review Timeline

<table>
<thead>
<tr>
<th>Year</th>
<th>2009</th>
<th>2011</th>
<th>2014</th>
<th>2016 (April)</th>
<th>2016 (Nov.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event</td>
<td>EPA initiates Registration Review</td>
<td>EPA Preliminary Human Health Assessment</td>
<td>EPA Revised Human Health Risk Assessment</td>
<td>SAP rejects EPA proposed reliance on Columbia study for Risk Assmt.</td>
<td>EPA Revised Human Health Risk Assessment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>2017</th>
<th>2017 (April)</th>
<th>2017 (Sept.)</th>
</tr>
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<tbody>
<tr>
<td>USDA</td>
<td>USDA Comments on Chlorpyrifos Risk Assessment</td>
<td>EPA Federal Register Notice denying petition to revoke</td>
<td>EPA statement on status of chlorpyrifos registration</td>
</tr>
</tbody>
</table>

None of the EPA documents since 2006 represents final decision.
2017 USDA Comments on US 2016 EPA Risk Assessment

“USDA has both grave concerns about the EPA process that has led to Agency publishing three wildly different human health risk assessments for chlorpyrifos within two years and has doubts about the validity of the scientific conclusions underpinning EPA’s latest chlorpyrifos risk assessment. Even though use of the Columbia Center for Children’s Environmental Health (CCCEH) study to derive a point of departure was criticized by the FIFRA Scientific Advisory Panel, EPA continues to rely on this study and has now paired it with an inadequate dose reconstruction.”

“…the latest risk assessment fails to show either a causal or a dose response relationship between chlorpyrifos exposure and a change in working memory among the…cohort, even though causality and the existence of a dose response relationship are two fundamental pillars of regulatory toxicology and risk assessment.”

(emphasis added)
2017 US EPA statement on status of chlorpyrifos registration

“Following a review of public comments on both the November 2015 proposal to revoke tolerances and the November 2015 notice of data availability, the EPA concluded, despite several years of study, the science addressing neurodevelopmental effects remain unresolved. Further evaluation of the science during the remaining time for completion of registration review is warranted to achieve greater certainty as to whether the potential exists for adverse neurodevelopmental effects to occur from current human exposures to chlorpyrifos.”

(emphasis added)
Epidemiology studies

2008: Evidence is not sufficient to establish chlorpyrifos as a developmental toxicant.

2017: Same as 2008

- Epidemiology results are inconsistent and do not clearly show an effect.
Evidence since 2008 OEHHA review

- NEW epidemiology publications
- NEW Interpretation
  - Risk of bias
  - Quality for public health decisions
New Interpretations:  
Best practices for exposure assessments

• Proximity to application incorporates validation
• Biomonitoring (of a short-lived chemical) uses multiple samples and estimates error
• Specificity (metabolite of chlorpyrifos)
“Other variables independently associated with dust levels included temperature and rainfall, farmworkers storing work shoes in the home, storing a … product in the home, housing density, having a home less clean, and having an air conditioner.”

Harnly et al., 2009 (part of CHAMACOS study)
Proximity is not the sole determinant of exposure

“no evidence of increased pesticide biomarker excretion in rural residents following a spray event within 100 m of their home”

Galea et al., 2015
Biomonitoring best practices use multiple samples - Urinary metabolite levels vary widely

3 urine samples (TCPy metabolite) collected in 21 pregnant women in Mexico City
(Fortenberry, et al. 2014)

Fig. 2. TCPY concentrations in maternal spot urine samples collected in each trimester of pregnancy (N=21). Each color represents repeated samples collected from the same woman.
Biomonitoring best practices use multiple samples - Urinary metabolite levels vary widely

3 urine samples (TCPy metabolite) collected in 21 pregnant women in Mexico City
(Fortenberry, et al. 2014)

Exposure estimated late in pregnancy does not reflect levels early in pregnancy.
New interpretation of 3 cohort studies

CHAMACOS study exposure strengthened
- 2 urine samples collected during pregnancy
- Blood sample near/at delivery
- QA/QC methods in place

CCCEH (Columbia study) exposure limited
- Single blood sample near/at delivery,
- No control for lipids
- QA/QC methods not reported

Mt. Sinai study exposure limited
- Single urine sample near/at delivery
New studies show no consistent adverse association

- **Infant health**
  - ✓ 7 studies published 2010 – 2015 on birth weight, birth length, head circumference, or gestational age

- **Bayley Scales of Infant Development (BSID)**
  - ✓ 4 studies published 2011 – 2016 on BSID MDI or PDI

- **Other Outcomes in neonates and children**
  - ✓ 3 studies published 2013 – 2017 on children ages 3 d, 5 w, and 9 m using different tests
  - ✓ 6 studies published 2010 – 2015 on children ages 3.5 y to 14 y, using different tests and diagnoses for ADHD, autism spectrum disorder, social responsiveness, tremor, etc.
### NEW STUDIES:
Intelligence Testing (Full Scale IQ and Working Memory)

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Exposure</th>
<th>Study (area) IQ test</th>
<th>FS IQ P &lt; 0.05?</th>
<th>Working Memory P &lt; 0.05?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouchard, 2011</td>
<td>DEP**</td>
<td>CHAMACOS, (CA) - WISC-IV</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Mean of 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donauer, 2016</td>
<td>DEP</td>
<td>HOME, (OH) - WPPSI-III</td>
<td>No</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Mean of 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rauh, 2011*</td>
<td>Chlorpyrifos in blood</td>
<td>Columbia, (NYC) - WISC-IV</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Engel, 2011</td>
<td>DEP**</td>
<td>Mt. Sinai (NYC) - WPPSI-III</td>
<td>No</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- WISC-IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cartier, 2016</td>
<td>DEP</td>
<td>PELAGIE, (France) - WISC-IV</td>
<td>NR</td>
<td>No</td>
</tr>
</tbody>
</table>

*Studies with 1 sample

*Also Horton, et al. 2012; NR: Not reported. **TCPy data not reported.
Epidemiology Conclusion

The epidemiology data do not meet the criteria for sufficient evidence in humans.

- Risk of bias limits the interpretation of individual studies.
  - Causal inference cannot rely upon weak exposure assessment
- Data from multiple studies do not consistently show similar adverse association with chlorpyrifos.
- The CHAMACOS study does not show clear relationship with exposure (urinary TCPy, DEP) and adverse effects.
  - ✓ collection of 2 biological samples during pregnancy,
  - ✓ strong QA/QC
  - ✓ reported for urinary TCPy and DEP.
2008: DARTIC: Evidence is not sufficient to establish chlorpyrifos as a developmental or reproductive toxicant

2017: Evidence has not changed

- New *in vivo* animal studies do not clearly show developmental toxicity
- Studies report multiple outcomes, many implicating non-cholinergic pathways, but are not supported by an identified or confirmed mode of action
- Alternative non-animal approaches can be useful screening tools but do not provide ‘clearly shown through scientifically valid testing’ evidence of effects in mammals
Chlorpyrifos Developmental Toxicity Studies

- 4 studies in 3 animal species (rat, mouse, rabbit)
  - Testing according to USEPA Guidelines
    (OPPTS 870.3700 Prenatal Developmental Toxicity Study)

- Study Conclusions
  - No developmental toxicity in the absence of maternal toxicity
  - Cholinesterase inhibition (ChEI) was the most sensitive endpoint in all studies
  - Significance of this is that protection against ChEI is protective against other potential toxicities
New Studies Provided to DARTIC

• USEPA 2014, 2016 RHHRA; OEHHA September 1 and 8 lists
  ▪ Many studies do not meet ‘sufficient’ relative to animal testing
    – Numerous studies did not use chlorpyrifos as test material
    – Postnatal exposure
    – Non-developmental endpoints
  ▪ Included for review were those involving gestational exposure

• For many studies, experimental elements conflict with criteria for what would be considered sufficient animal evidence and scientifically valid testing
Experimental Design Challenges

- Non-relevant route of administration for humans (e.g., subcutaneous injection)

- Use of DMSO as solvent vehicle – has neurotoxic effects

- Use of single dose or high doses which exert frank toxicity (e.g., brain ChEI, clinical effects); Dose-response evaluation not possible

- Effects reported on offspring below threshold for ChEI, but ChEI often not measured
<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Test Syst.</th>
<th>Route of Admin</th>
<th>Vehicle</th>
<th>Dose (mkd)</th>
<th>Exposure Period</th>
<th>Dose Response</th>
<th>ChE Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chanda, 1995</td>
<td>Rat</td>
<td>SC</td>
<td>Peanut oil</td>
<td>200</td>
<td>GD12</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Qiao, 2002</td>
<td>Rat</td>
<td>SC</td>
<td>DMSO</td>
<td>1,2,5, 10,20, 40</td>
<td>GD 9-12, GD 17-20</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Slotkin, 2007</td>
<td>Rat</td>
<td>SC</td>
<td>DMSO</td>
<td>1 or 5</td>
<td>GD 9-12 or GD 17-20</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Venerosi, 2009</td>
<td>Mouse</td>
<td>Gavage</td>
<td>Peanut oil</td>
<td>6</td>
<td>GD 15-18</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Chen, 2010</td>
<td>Rat</td>
<td>SC</td>
<td>DMSO</td>
<td>5</td>
<td>GD 7.5 to 11.5 or GD 13-17</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Turgeman 2011</td>
<td>Mouse</td>
<td>SC</td>
<td>DMSO</td>
<td>3</td>
<td>GD 9-18</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
• “... in keeping with the 2008 SAP, this Panel expresses concern about the use of Dimethyl Sulfoxide (DMSO) as a vehicle because of its intrinsic toxicity, its potential influence on absorption and interaction with chlorpyrifos, and the impact of this interaction on the developing organism.” (p. 12)

• “The Panel recommends these experimental outcomes be regarded as exploratory, and hypothesis-generating, as opposed to being evidence of toxicity. The lack of specificity in the direction of the neurobehavioral dose response findings is a problematic issue.” (p. 15)
2000 Developmental Neurotoxicity Study

- The definitive animal study, **required by USEPA** to evaluate potential for developmental neurotoxicity and neurobehavioral/neuropathological observations in offspring
- Study is specifically **required to address**, in an appropriate animal model, the types of observations and outcomes that are reported in epidemiological studies
- **Dose range 0.3, 1, or 5 mg/kg/day** for 24 days
- Outcome: **Normal learning & memory** (T-maze spatial delayed-alternation) and **Habituation** (motor activity and auditory startle)
- **No effects** on brain weight, histopathology, and morphometrics covering **9 brain regions**: length of cerebrum and cerebellum, height of cerebellum, thickness of corpus callosum, frontal cortex, parietal cortex, caudate-putamen, hippocampus and external germinal layer of the cerebellum (pups only)
- **No evidence of selective neurodevelopmental toxicity in absence of maternal toxicity**

2012 Comparative Cholinesterase Assay (CCA)

• Required by USEPA to examine life stage sensitivity to ChEI over lower portions (10X lower than 1 mkd) of the dose-response curve.

• Following acute and repeat dosing, (chlorpyrifos & chlorpyrifos-oxon) no-observed-effect-levels were the same across age groups for both brain and RBC ChEI.

Consistent evidence across studies (developmental, DNT, CCA) demonstrates fetuses/young less sensitive than dams.

Conclusions

• Results from “scientifically valid testing according to generally accepted principles” do not indicate developmental or neurodevelopmental toxicity in absence of maternal toxicity.

• Many experimental studies do not meet the criteria for “sufficient evidence in experimental animals (mammals) such that extrapolation to humans is appropriate”

In conclusion, no new animal data justify listing chlorpyrifos as a developmental toxicant
Conclusions

None of the three criteria are met for the DART IC to recommend listing chlorpyrifos to cause developmental toxicity

- The epidemiology studies do not provide “sufficient evidence in humans” that chlorpyrifos causes developmental toxicity
- Neither the epidemiology studies nor the animal studies provide “limited evidence or suggestive evidence in humans” that chlorpyrifos causes developmental toxicity
- The animal studies do not provide “sufficient evidence in experimental animals (mammals)” that chlorpyrifos causes developmental toxicity