Comments of Dow AgroSciences LLC

Chlorpyrifos Should Not Be Prioritized for Consideration as a Developmental and Reproductive Toxicant

Christian Volz
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Dow AgroSciences LLC Comments

Speakers

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Overview

- Authoritative and expert agencies have recently examined chlorpyrifos and have concluded that it is not a DART
- Epidemiology studies do not support a conclusion that chlorpyrifos is a DART (Dr. Burns)
- Animal toxicology data that meet the Proposition 65 criteria do not demonstrate that chlorpyrifos is a DART (Dr. Juberg)

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Recent Evaluations by Expert Agencies

- OEHHA Prioritization Process (2004)
  - "[I]t is unlikely that chemicals will be proposed for CIC or DARTIC review that have recently been reviewed by an authoritative body and found to have insufficient evidence of carcinogenicity or reproductive toxicity, respectively."

- USEPA (Office of Pesticide Programs) – 2002, 2006
- European Commission on Classification & Labeling - 2002
- Australia National Registration Authority - 2000
- California Department of Pesticide Regulation - 2001

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Epidemiology Studies

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Presented Before OEHHA DARTIC
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Epidemiology timeline

- 1920: Founding of American Journal of Hygiene (renamed Amer J Epidemiol)
- 1938: March of Dimes founded
- 1965: *Chlorpyrifos registered*
- 1982: First meeting of American College of Epidemiology
- 1966-2002: 8724 publications on birth weight
- 2003: Perera et al report decreased birth weight associated with chlorpyrifos

Studies of Infants
2 Negative, 1 "Positive"

Eskanazi 2007: N = 396, negative
(Salinas Valley mothers)

Perera, Whyatt 2003-6: N ~ 254, positive
(Columbia – Mothers & Newborns)

Berkowitz 2004: N = 404, negative
(Mt. Sinai Children's Env. Cohort)

Columbia University New York City Mothers and Newborns Study

- One study – multiple reports
- Many confounders
  - Low income, multi-disadvantaged cohort
  - Chlorpyrifos levels correlated to many other chemicals
- Exposure misclassification
  - Chlorpyrifos levels not adjusted for blood lipids
- Plausiblility
  - Effects on birth weight not observed in other studies
  - Effects within expected variability
  - Effects of no developmental significance
  - Mischaracterized support from animal studies

Studies of Children
2 Negative

Eskanazi 2007: N = 396, negative

Rauh 2006: N = 254, negative at 12, 24 months

No results on neurodevelopment

Epidemiology Data Summary

- Epidemiology studies do not support a conclusion that chlorpyrifos is a DART

Animal Studies

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Importance of Study Design

- OEHHA Prop 65 Prioritization Process, 2004:
  - "factors considered in weighing evidence from animal studies include...routes of administration...dose-response."
- Society of Toxicology:
  - "the relevance of experiments using doses that are many multiples of conceivable human exposure and unrealistic routes of exposure is, at most, quite dubious."
  - "use of routes of exposure and high-dose levels, set primarily for purposes of experimental convenience, should be avoided."

Chlorpyrifos and DART: Studies Included in OEHHA Survey

- 21 citations listed as evidence of DART
- Most had major deficiencies in study design
  - 2 included coexposure to other chemicals
  - 6 had no information included on route of exposure
  - 4 had no information on dosing regimen
  - 12 used routes not relevant for evaluation of DART
    - subcutaneous or intraperitoneal
- Only 5 used appropriate design

Appropriately Designed Studies Demonstrate Chlorpyrifos Is Not a DART

- Akhtar (2006) – Oral gavage
  - *No evidence of teratogenicity*
- Farag (2003) – Oral gavage
  - *Fetotoxicity and teratogenicity only at maternally toxic doses*
- Breslin (1996) – Oral gavage and dietary
  - *Chlorpyrifos was not embryolethal, embryo/fetotoxic or teratogenic and did not adversely affect fertility or the function or structure of the reproductive organs*
- Rubin (1987) – Oral gavage
  - *Chlorpyrifos is not teratogenic and is not fetotoxic in the absence of maternal toxicity*
- Thompson (1971) – Oral gavage
  - *Equivocal developmental effects that were not replicated in later studies at higher doses*

Animal Studies Summary

- Animal toxicology studies included in OEHHA survey do not support conclusion that chlorpyrifos is a DART
- Most studies cited use inappropriate routes of administration and/or have confounding issues
- Appropriately designed studies do not indicate DART
- Regulatory authorities and expert panels worldwide do not consider chlorpyrifos to be a DART

Conclusion

- Neither epidemiology nor animal data support prioritization of chlorpyrifos for consideration as a DART