Application of a Source-to-Outcome Model to Quantitatively Assess Variability in Dose and Sensitivity in Humans

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Introduction

• Project description
• Key findings
• Project findings and the goals of “Science and Decisions”
  – Modeling variation in exposure and response
  – Assessing the impact of background exposures and disease processes on dose response for apical effects
Background

- ACC/LRI request for proposals to use science to advance risk assessment (2007)
  - Goal: replace safety factors with quantitative predictions of adverse effects
  - Leverage extensive knowledge on chlorpyrifos
  - Two publications (Price et al., 2011; Hinderliter et al., 2011)
- Project was expanded in 2010 to address new data on variation in human metabolism
- Subject of EPA Science Advisory Panel meeting February 2011
Chlorpyrifos

- Widely used active ingredient in insect control products for agriculture (registered in 1965; 100 countries globally)
- Extensive toxicological database including:
  - Full toxicological database for global registrations
  - Occupational exposure and health monitoring data
  - Epidemiology studies
- Toxicological mode of action and endpoint upon which human exposure limits are based is cholinesterase inhibition (ChEI)
What was done?

• Created a source-to-outcome model that evaluates the relationship between dietary residues in food and impact on ChEI in exposed populations. Based on combined models:
  – Dietary model estimates daily dose from dietary residues
  – PBPK/PD model measures changes in ChEI from oral exposure

• The focus on ChEI is an example of the upstream ‘obligatory perturbation’ concept described in the NAS Toxicity Testing in the 21st Century (2007)
Description of modeling

**Exposure Modeling**
- Chlorpyrifos use on crops
  - Chlorpyrifos Residues in diet
    - Dietary Exposures

**PBPK Modeling**
- Chlorpyrifos absorption and transport to tissues and conversion to oxon

**PBPD Modeling**
- Inhibition of AChE
  - Biomarker: AChE in RBC and BuChE in Plasma
  - Brain
    - Smooth Muscles
    - Other tissues
    - Build up of acetylcholine in nervous tissue
      - Apical Effects
Advancements in risk assessment

• Assessed variability in both
  – exposure (variation of residue levels across foods and variation in individual’s dietary consumptions) and
  – response (variation in physiology and metabolism)

• Evaluated response to the range of actual human exposures

• Assessed human sensitivity in multiple age groups (infants, children, adults)

• Modeling was made more tractable by focusing on “key event” AChE inhibition
Results

Focus on Red Blood Cell Acetyl Cholinesterase Inhibition (RBC AChEI)
Prediction of RBC AChEi in populations of adults and infants (age 6 months)
Distributions of daily dietary doses in three age groups
Predicted impact on RBC AChE

Dietary Dose on the 5th day (mg/kg)

Percent Inhibition of RBC AChE

Adults
Predicted impact on RBC AChE

Dietary Dose on the 5th day (mg/kg)

Percent Inhibition of RBC AChE

△ Adults

□ Children
Predicted impact on RBC AChE

Dietary Dose on the 5th day (mg/kg)

Percent Inhibition of RBC AChE

Adults
Children
Infants
Implications for the occurrence of apical effects

- RBC AChEI is a conservative marker for CNS AChEI
- Short-term fluctuations of individuals’ AChEI levels are more than ±10% in the general population
- AChEI inhibition levels of 35%-90% are required before apical effects are observed (Nigg and Knaak, 2000)
- A level of 30% AChEI is regarded as protective for workers (States of California and Washington)
- Predicted impacts on AChEI from dietary exposures are more than three orders of magnitude lower than the above values (maximum individual < 0.01% inhibition)

Conclusion: AChEI-mediated effects are unlikely to occur in any individual from dietary exposures to chlorpyrifos
Research findings and “Science and Decisions”

- The assessment of the impacts of the dietary exposure meet many of the goals of “Science and Decisions”
  - Addressed variation in dose
  - Addressed variation in response due to age, gender, and genetic variation
  - Produced quantitative predictions of impacts on a key event and the occurrence of apical effects
- The question that now needs to be addressed
  - How to use these data to assess the impact of background exposures and underlying disease processes?
Statements in “Science and Decisions”

“The assessment of ‘background exposure’ and ‘background disease processes’ would involve characterization of other chemicals or nonchemical stressors that influence the same general pathologic processes as the chemical under evaluation.”

“Effects of exposures that add to background processes and background endogenous and exogenous exposures can lack a threshold if a baseline level of dysfunction occurs without the toxicant and the toxicant adds to or augments the background process. Thus, even small doses may have a relevant biologic effect.”
Individual dose-response relationships lead to a population dose-response relationship, where the fraction of the population affected is plotted against dose.
Apical Effects of Cholinesterase Inhibition

- Accumulation of Acetylcholine in tissues results in a range of effects (DUMBBELSS)
  - Diarrhea, Urination, Miosis/muscle weakness, Bronchorrhea, Bradycardia, Emesis, Lacrimation, and increased Salivation/Sweating

- A background frequency of occurrence of many of these effects exist at any point in time in the general population
  - Due to a wide range of stressors (diet, pathogens, etc.)

- Key Question:

  Do these background rates of apical effects indicate a linear dose-response for chlorpyrifos and the occurrence of effects from current dietary exposures?
Findings from source-to-outcome models

Source-to-outcome models provide information on both the occurrence of apical effects and the occurrence of obligatory precursor effects.

- No change in the frequency of apical effects will occur unless AChE inhibition exceeds 35%.
- Predicted AChEI < 0.01%
Summary and conclusions

- A source-to-outcome model has successfully been created for chlorpyrifos and ChEI-mediated effects.

- The findings indicate changes in AChE will be >1000-fold below changes associated with apical effects.

- A finding of a threshold in an early key event “accumulation of acetylcholine” negates the impact of “background exposures and underlying disease states” that are relevant to the apical effects.

- Therefore: a population threshold is expected for the compound.