U.S. EPA Activities in the Field of Epidemiology:
Integrating Epidemiology into the Regulatory Process of Pesticide Risk Assessment

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EFSA EPIDEMIOLOGY STAKEHOLDER WORKSHOP
HOLIDAY INN PORT – CLICHY
PARIS
Outline

I. EPA’s Office of Pesticide Programs Structure

II. Epidemiology Draft Framework document (2010)

III. Epidemiology Review in OPP

IV. Epidemiology Review in OPP: anticipated future

V. Conclusion
EPA’s Office of Pesticide Programs

- Registers pesticides for agricultural, residential, and public health applications
- Evaluates safety of pesticides by assessing exposure and associated risks
- Establishes legal limits (aka “tolerances”) for residues of pesticides in/on agricultural commodities
Epidemiology Review in OPP

- Information on the toxic effects of pesticides is generally derived from studies with laboratory animals.
- In the past, information from well designed epidemiology studies on pesticides has not been typically available to inform evaluations of potential risks.
  - This is changing, in large part due to increased availability of studies:
    - Agricultural Health Study
    - National Children’s Study
- OPP intends to focus on these epidemiology studies to a greater extent -- along with other sources of human effects information -- in its human health risk assessments.
Epidemiology Draft Framework

- In 2010, OPP proposed a “framework” to describe the scientific considerations necessary to evaluate epidemiological studies for integration into the risk assessments of pesticide chemicals

*DRAFT Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment*
Epidemiology Draft Framework

- Concepts in the Draft Framework are based on peer-reviewed, robust principles & tools:
  - Standard practices in epidemiology, toxicology & risk assessment
  - Uses Bradford Hill Criteria as modified by Mode-of-Action framework as organizational tool for describing/organizing data
  - Flexibility to incorporate information from different sources
  - Transparent tool for organizing, reviewing & interpreting complex information
  - Incorporates a number of epidemiological case studies
Epidemiology Draft Framework

- Improvements based on recommendations from
  - NRC 2009: *Science & Decisions: Advancing Risk Assessment*
  - NRC 2007: *Toxicity Testing in the 21st Century*
    - “Mechanism of Action” (MOA): a biologically plausible sequence of key events that are obligatory and quantifiable steps to an adverse outcome
    - “Source to Effect Pathway”
Epidemiology Draft Framework: Feedback from the SAP, 2010

Science Advisory Panel held in February 2010 to review document

The Panel & the stakeholders supported the overall approach:
- Begin with transparent problem formulation followed by use of MOA Framework & AOP construct

The Panel issued a report and suggested some improvements:
- A broader evaluation of epidemiology in risk assessment beyond pesticide chemicals may provide a source of information for risk assessment approaches & interpretation
- Include a discussion of the value of a Framework analysis to aid in encouraging research focused on areas of uncertainties
- Consider ‘bounding’ analyses using epidemiologic exposure assessments to aid in characterizing effects in animals

http://www.epa.gov/scipoly/sap/meetings/2010/020210meeting.html
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Additional suggested improvements from the Panel report:
- Provide a clear definition of ‘biological plausibility’
- Consider establishing some criteria for epidemiology study quality
  - Possibly a combination of quantitative criteria & scientific judgment
- Improved discussion of some aspects of epidemiology characteristics

http://www.epa.gov/scipoly/sap/meetings/2010/020210meeting.html
Epidemiology Review in OPP

Human Incident/Epidemiology reviews done using Tiered Process

- Tier I incident/epi reviews (scoping) -
  - Incorporate epi only if AHS study or “significant interest/concern”
  - Summarize facts

- Tier II analysis of epidemiology and incident data — for Draft Risk Assessment
  - More complete review of epi data if Tier I shows concern
  - Standardized literature search
  - Narrative descriptions, with synthesis and conclusions
  - Examples: glyphosate; malathion; acephate
Epidemiology Review in OPP

Additional Epidemiological Activities in OPP

- Desk Statements/Rapid Response
- Various unscheduled literature reviews
- Table of Contents Alerts
- Meetings/Symposia
Epidemiology Review in OPP: anticipated future

Anticipate increasing number, quality, and diversity of pesticide epidemiology studies

- AHS – 20+ years on study
- Pooling of agricultural cohorts
  - E.g., International Agricultural Cohort Consortium to take advantage of multiple studies
- Children’s Environmental Health cohorts, Parkinson’s studies, other studies
- International cooperation

Planned [March 2015/June 2015 IARC review](#) of certain pesticides

- Based on strength of human studies, in part
Epidemiology Review in OPP: anticipated future

Systematic Review/Meta-analysis

- Consistent and coordinated process to identify, evaluate, synthesize and integrate data to inform decisions, reach conclusions, identify research needs
  - Objective, transparent, reproducible process
  - Criteria may be developed that will be used to include or exclude studies
  - May assess the quality of study and potential for bias
  - Process guides the content of research evaluation and conclusions

  - Encourages systematic review principles in review of relevant experimental and observational data
  - See [http://www.epa.gov/pesticides/science/literature-studies.html](http://www.epa.gov/pesticides/science/literature-studies.html)
  - OPP developing website that contains additional info on systematic review
Epidemiology Review in OPP: anticipated future

Systematic Review/Meta-analysis

- “A Federal Summit on Evaluating and Synthesizing Evidence” (NAS Formaldehyde) -- Feb 2013
  - EPA, OSHA, NIOSH, ATSDR, NTP
- Not “one thing”
  - Various approaches and flavors
  - Scope will vary by research question
- Several Frameworks developed – little consensus
  - NTP OHAT
  - Navigation Guide
  - Modified IRIS review (workshop held August 2013)
- Prioritization and resource issues need to be considered
Epidemiology Review in OPP: anticipated future

Additional Issues/Considerations:

- Role of Systematic Review/Meta-analysis – resource issues
- Interpretation of standard epidemiological effect sizes (e.g., OR, RR) in classic risk assessment
- Consideration of (unmeasured) confounders
- False positives/inflated p-values and multiple comparisons
- Ecologic studies and the increasing use of GIS (Geographic Information Systems) to evaluate exposure
- How to evaluate and interpret “discrepancies” between epidemiological and animal findings
- Molecular/genetic epidemiology
- Raw data availability/alternative analyses
- International Collaboration/Cohorts
Conclusions

- Epidemiology is increasing in relevance, importance, interest, and capability

- EPA/Pesticides has developed a draft framework for incorporating epidemiological studies into risk assessments

- EPA/Pesticides is currently using a tiered process for evaluation of epidemiological literature

- Systematic review/meta-analysis is an approach which EPA/Pesticides is exploring
  - Many advantages
  - Prioritization and Resource issues

- Many challenging additional issues to be considered
Contact Information

For further questions, contact:

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Web Links for References from Slides

1. Agricultural Health Study [slide 4]: http://aghealth.nih.gov/
2. National Children’s Study [slide 5]:
   https://www.nationalchildrensstudy.gov/Pages/default.aspx
3. DRAFT Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment [slide 4]:
   http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0851-0004
   http://www.nap.edu/catalog/12209/science-and-decisions-advancing-risk-assessment
5. NRC 2007: Toxicity Testing in the 21st Century [slide 7]:
   http://www.nap.edu/catalog/11970/toxicity-testing-in-the-21st-century-a-vision-and-a
Web Links for References from Slides

6. SAP meeting website [slide 9] :
   http://www.epa.gov/scipoly/sap/meetings/2010/020210meeting.html#materials

7. SAP Panel Report [slide 9] :

8. IRAC upcoming meeting [slide 13] :
   http://monographs.iarc.fr/ENG/Meetings/index.php

   http://www.epa.gov/pesticides/science/literature-studies.html
   http://www.epa.gov/pesticides/science/lit-studies.pdf
Web Links for References from Slides

10. NTP OHAT [slide 15]:


12. Modified IRIS review [slide 15]:
    http://www.epa.gov/IRIS/irisworkshops/systematicreview/wrk_agenda.htm