U.S. EPA Activities in the Field of Epidemiology:

Integrating Epidemiology into the Regulatory Process of Pesticide Risk Assessment

David J. Miller
U.S. Environmental Protection Agency

FEBRUARY 18, 2015

EFSA EPIDEMIOLOGY STAKEHOLDER WORKSHOP

HOLIDAY INN PORT –CLICHY

PARIS

Outline

I. EPA's Office of Pesticide Programs Structure

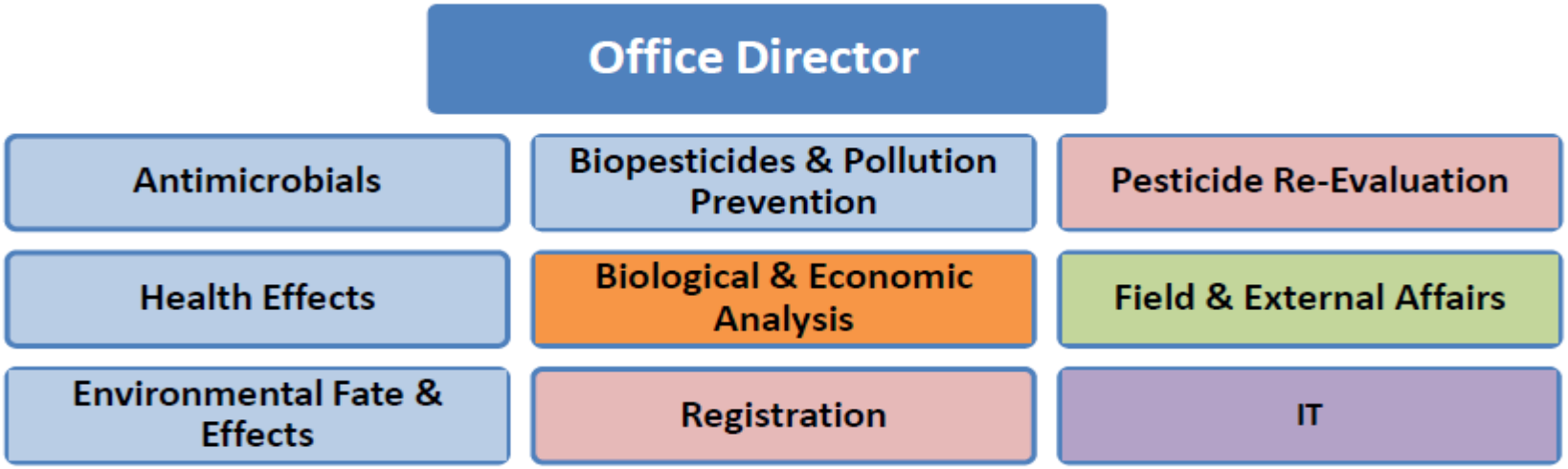
II. Epidemiology Draft Framework document (2010)

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

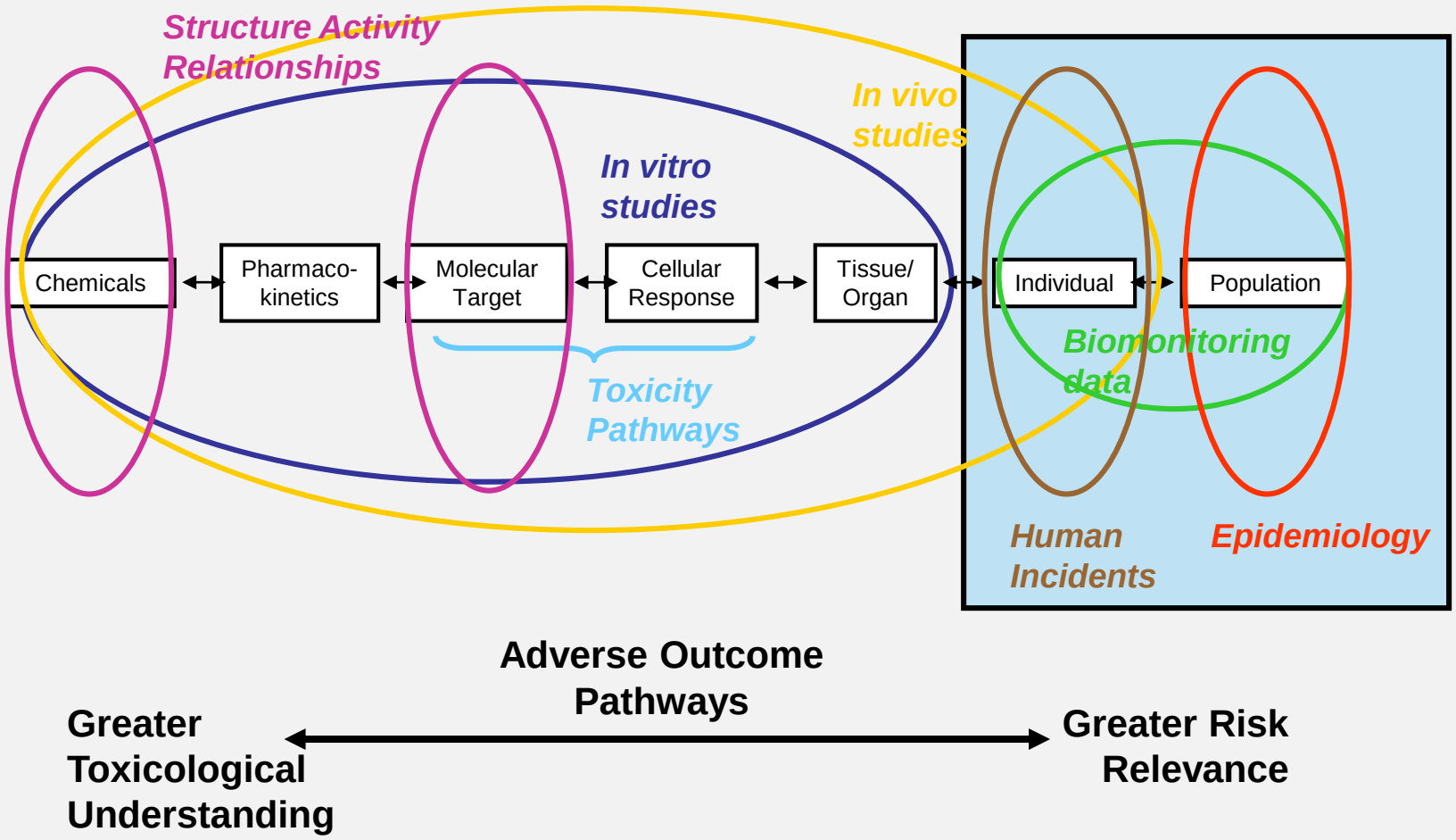
Epidemiology Draft Framework

- 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"

Source to Effects Pathway, Adapted from NRC, 2007



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

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

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 <u>if Tier I shows concern</u>
  - Standardized literature search
  - Narrative descriptions, with synthesis and conclusions
  - <u>Examples:</u> 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

- EPA OPP's Guidance for Review of Open Literature Studies (2012)
  - Encourages systematic review principles in review of relevant experimental and observational data
    - See http://www.epa.gov/pesticides/science/literature-studies.html
    - See http://www.epa.gov/pesticides/science/lit-studies.pdf
  - 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:

David J. Miller CAPT | US Public Health Service

Chief, Chemistry & Exposure Branch
and Acting Chief, Toxicology & Epidemiology Branch
Health Effects Division
Office of Pesticide Programs
email: miller.davidj@epa.gov

Visit www.epa.gov/pesticides

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

4. NRC 2009: Science & Decisions: Advancing Risk Assessment [slide 7]:

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] :

http://www.epa.gov/scipoly/sap/meetings/2010/020210minutes.pdf

8. IRAC upcoming meeting [slide 13]:
   http://monographs.iarc.fr/ENG/Meetings/index.php
9. EPA OPP's Guidance for Review of Open Literature Studies (2012) [slide 14] :

   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] :
    http://ntp.niehs.nih.gov/pubhealth/hat/noms/index-2.html
11. Navigation Guide [slide 15] : http://ehp.niehs.nih.gov/1307175/
12. Modified IRIS review [slide 15]:
    http://www.epa.gov/IRIS/irisworkshops/systematicreview/wrk_agenda.htm