United States Environmental Protection Agency

US EPA OPP's Approach to Pesticide Epidemiology

Update and Current Activities

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CLA/RISE Regulatory Conference, Spring 2018
Session on: Application of Environmental Epidemiology in Risk Assessment and Decision-Making
Renaissance Hotel, Arlington VA

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Outline

- EPA/OPP Regulatory Mandate
- Epidemiological Studies in EPA/OPP
- EPA/OPP Epidemiological Framework document
- EPA/OPP Approach : Tiered Process
- Study Quality
- Other or Ongoing Epidemiological Projects/ Activities

EPA Regulatory Mandate

- US EPA's Office of Pesticide Programs (OPP) is the US governmental agency responsible for registering and regulating pesticide products in the USA.
  - As part of this activity, OPP evaluates the effects of pesticides on human health and the environment.
- Under FIFRA and FQPA, EPA has a regulatory mandate to determine if pesticides cause unreasonable adverse effects on human health.
  - OPP receives extensive hazard and exposure information through FIFRA and FFDCA.
  - Information on hazard generally derived from laboratory animal studies.
  - high quality, pesticide-specific epidemiological information not traditionally been widely available.

Epidemiological Studies in OPP

- An increasing number of epidemiology studies are entering literature, particularly from the Agricultural Health Study (AHS) and its publications.
- OPP is putting increasing emphasis and use of these epidemiology studies in its Human Health Risk Assessments.
  - Goal of using this information in a scientifically robust and transparent way.
- Epidemiology review is an important component of the risk assessment process and complements other information available to the Agency.

Advantages of Epidemiological Studies

- **Relevance:** Health risks in human populations.
- **Real-World Evidence:** Real-world exposure conditions.
- **Vulnerable Populations:** Subpopulations with elevated exposure and/or susceptibility to disease
  - e.g., farmworkers, children, pregnant women, etc.

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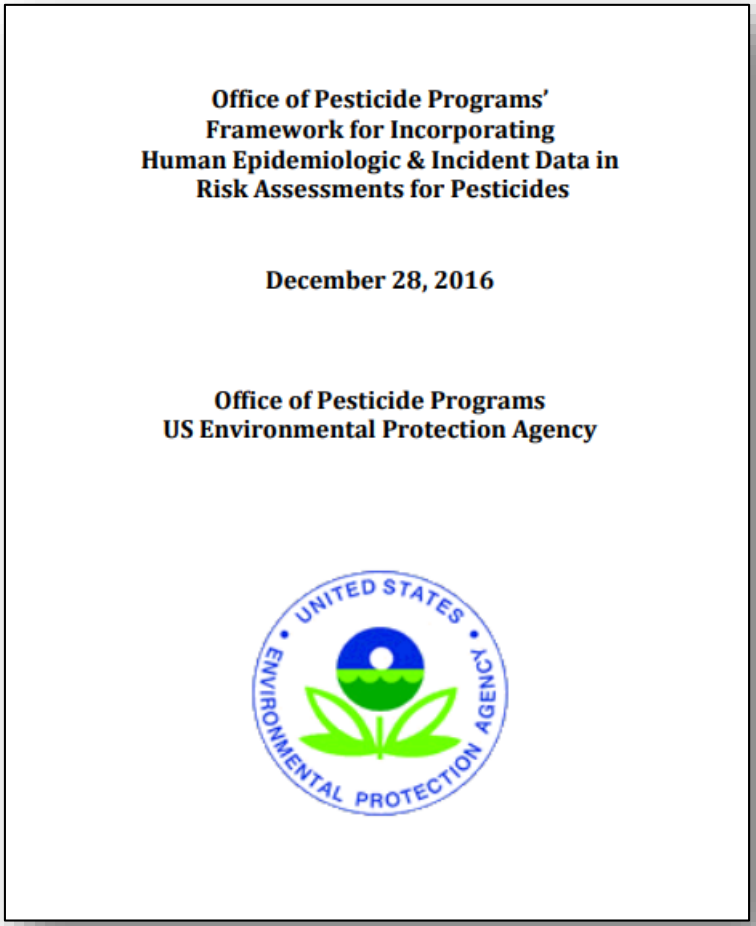
However, epidemiological studies are observational -- and not controlled -- studies. As such, they can be difficult to evaluate and judge and to interpret and characterize.

OPP Framework: Timeline

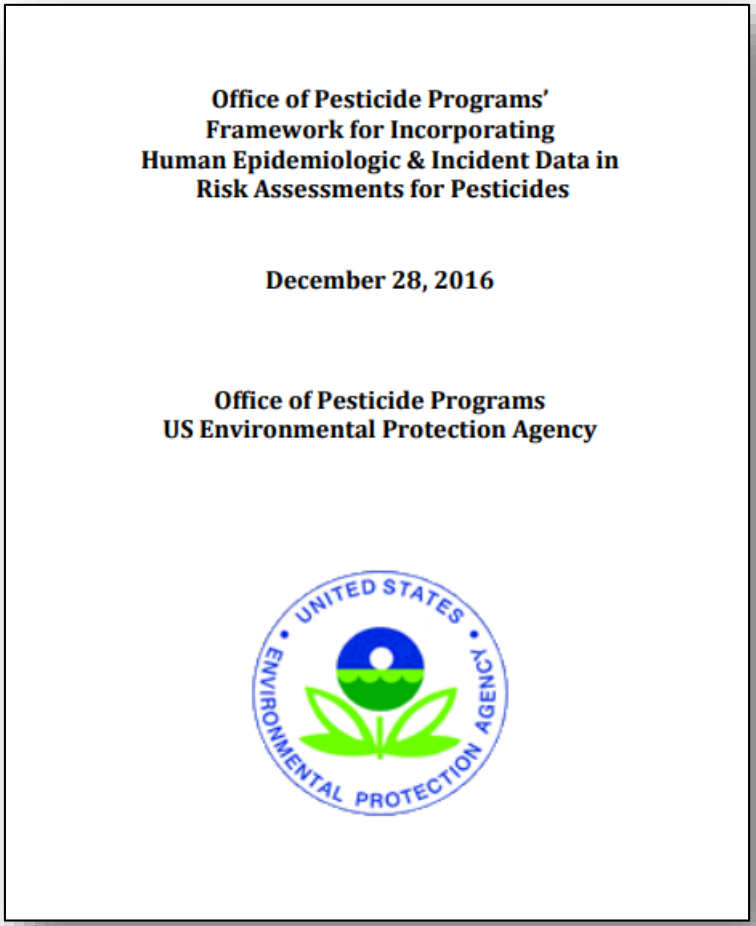
- In 2010, OPP developed a draft framework for incorporating epidemiology and incident data
- Favorably reviewed by 2010 FIFRA Scientific Advisory Panel
- Final version published in December 2016



OPP Framework Report Link

OPP Framework: Key Points

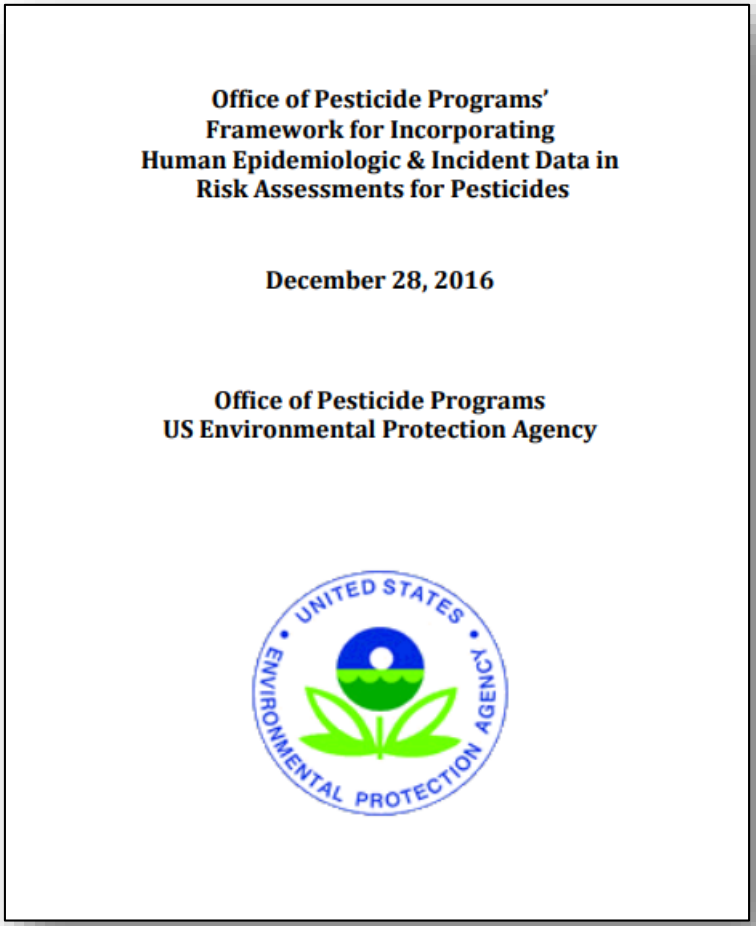
- Acknowledges limitations of epidemiology data in regulatory decision-making, but highlights increased publication of data
  - Agricultural Health Study
  - NIEHS/EPA Children's Centers
  - Other cohorts/study populations
- Aims to improve transparency of scientific considerations
- Not a formal regulatory guideline or manual of OPP standard operating procedures



OPP Framework Report Link

OPP Framework: Key Points

- Epidemiological and toxicological data can together provide insight into possible effects caused by pesticide exposures
- Consistent with WHO/IPCS MOA/human relevance framework and 2009 National Research Council's "Science and Decisions" publication

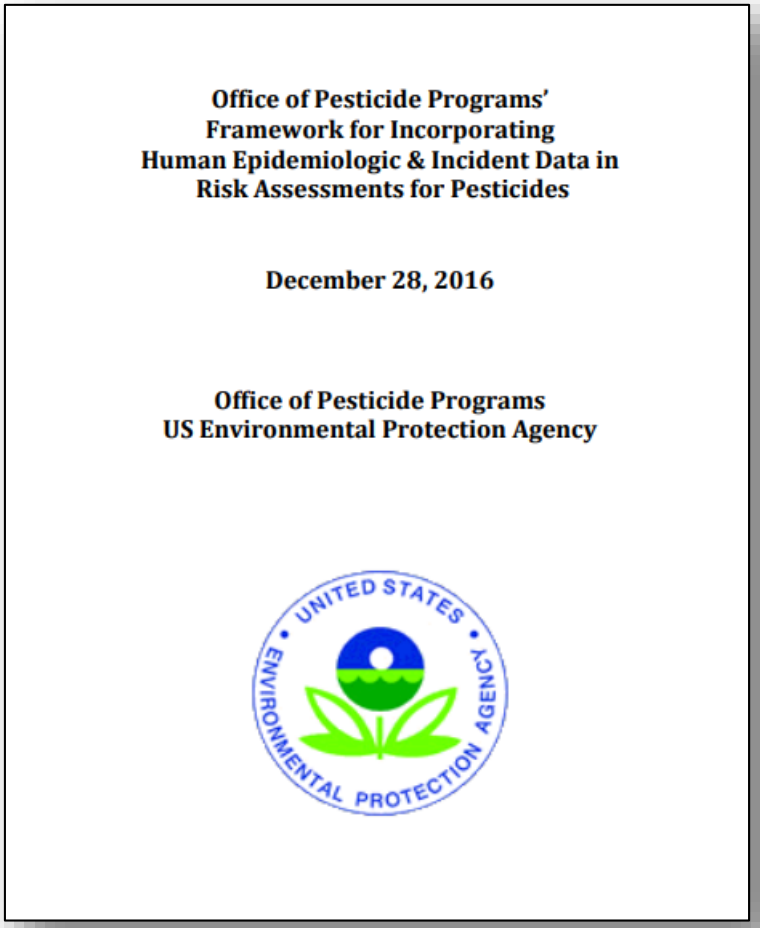


OPP Framework Report Link

OPP Framework: Key Points

Key Issues:

- Exposure
- Outcome
- Confounding
- Statistical Analysis
- Risk of Bias

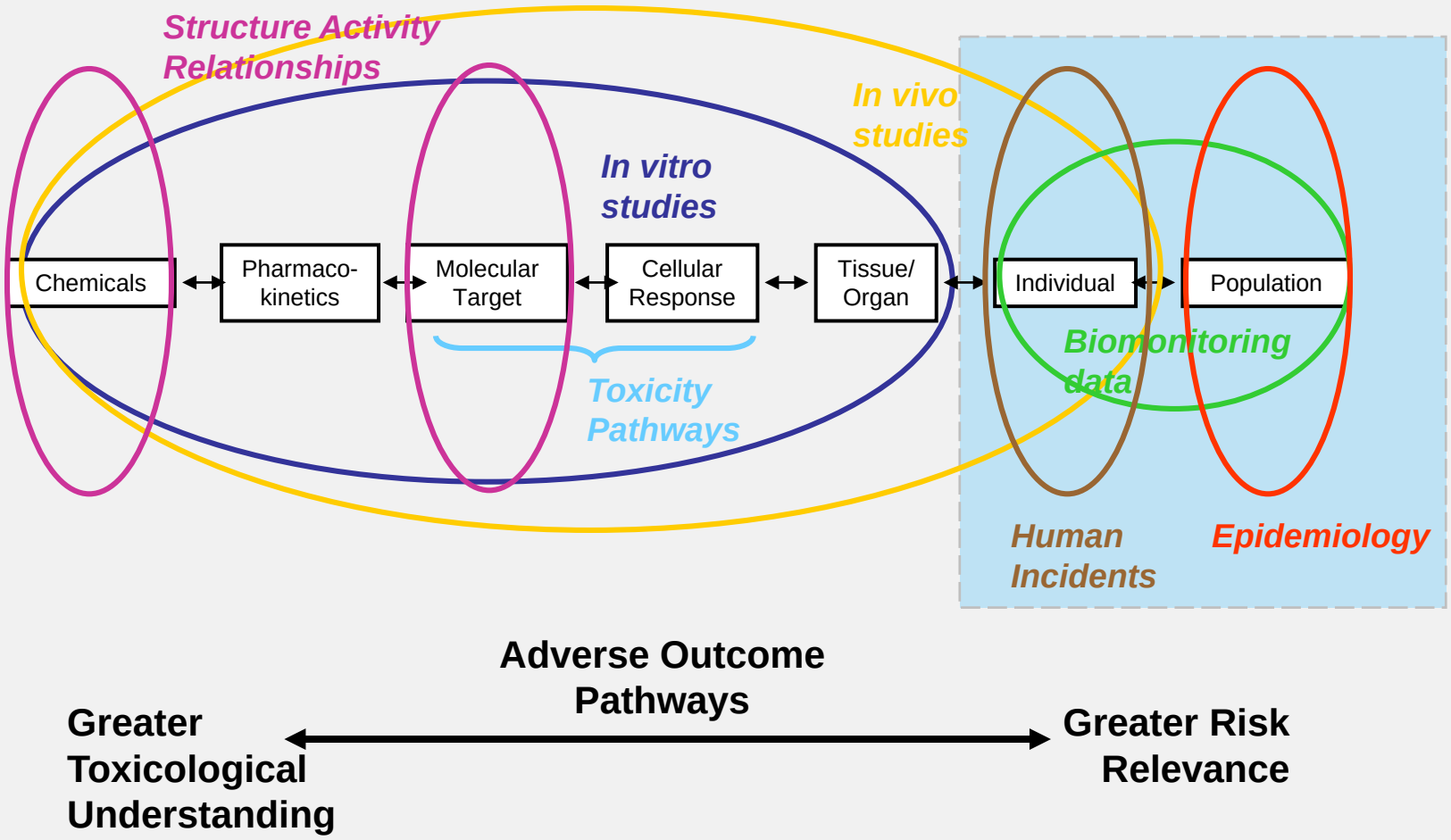


OPP Framework Report Link

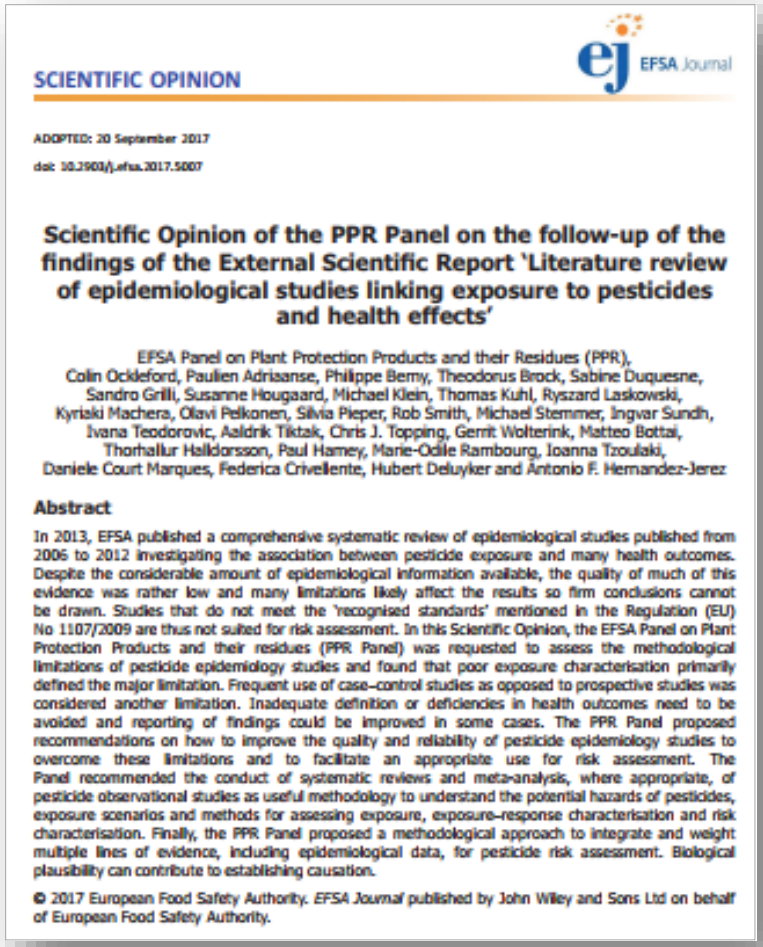
OPP Framework: Guiding Principles

- **Problem Formulation**
  - Scope and complexity of systematic reviews should address major factors that will inform risk assessment.
- **Mode of Action/Adverse Outcome Pathway Framework**
  - Identify key events along a causal path
  - Organize and integrate different sources of information from both experimental and observational studies

Source to Effects Pathway, Adapted from NRC, 2007



EFSA "Scientific Opinion…." (2017)



SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 20 September 2017

doi: 10.2903/j.efsa.2017.5007

Scientific Opinion of the PPR Panel on the follow-up of the findings of the External Scientific Report 'Literature review of epidemiological studies linking exposure to pesticides and health effects'

EFSA Panel on Plant Protection Products and their Residues (PPR), Colin Ockleford, Paulien Adriaanse, Philippe Berny, Theodorus Brock, Sabine Duquesne, Sandro Grilli, Susanne Hougaard, Michael Klein, Thomas Kuhl, Ryszard Laskowski, Kyriaki Machera, Olavi Pelkonen, Silvia Pieper, Rob Smith, Michael Stemmer, Ingvar Sundh, Ivana Teodorovic, Aaldrik Tiktak, Chris J. Topping, Gerrit Wolterink, Matteo Bottai, Thorhallur Halldorsson, Paul Harney, Marie-Odile Rambourg, Ioanna Tzoulaki, Daniele Court Marques, Federica Crivellente, Hubert Deluyker and Antonio F. Hernandez-Jerez

Abstract

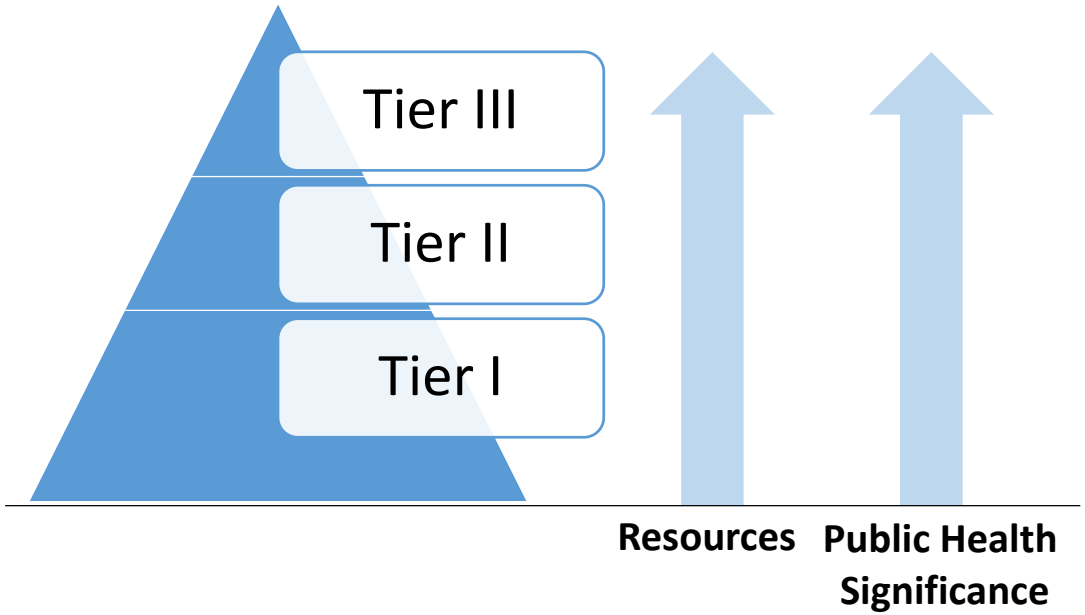
In 2013, EFSA published a comprehensive systematic review of epidemiological studies published from 2006 to 2012 investigating the association between pesticide exposure and many health outcomes. Despite the considerable amount of epidemiological information available, the quality of much of this evidence was rather low and many limitations likely affect the results so firm conclusions cannot be drawn. Studies that do not meet the 'recognised standards' mentioned in the Regulation (EU) No 1107/2009 are thus not suited for risk assessment. In this Scientific Opinion, the EFSA Panel on Plant Protection Products and their residues (PPR Panel) was requested to assess the methodological limitations of pesticide epidemiology studies and found that poor exposure characterisation primarily defined the major limitation. Frequent use of case–control studies as opposed to prospective studies was considered another limitation. Inadequate definition or deficiencies in health outcomes need to be avoided and reporting of findings could be improved in some cases. The PPR Panel proposed recommendations on how to improve the quality and reliability of pesticide epidemiology studies to overcome these limitations and to facilitate an appropriate use for risk assessment. The Panel recommended the conduct of systematic reviews and meta-analysis, where appropriate, of pesticide observational studies as useful methodology to understand the potential hazards of pesticides, exposure scenarios and methods for assessing exposure, exposure–response characterisation and risk characterisation. Finally, the PPR Panel proposed a methodological approach to integrate and weight multiple lines of evidence, including epidemiological data, for pesticide risk assessment. Biological plausibility can contribute to establishing causation.

https://www.efsa.europa.eu/en/efsajournal/pub/5007

- Both EFSA and EPA attempt to integrate epidemiology with AOP/MOA and animal toxicology data, and both organizations follow a WoE approach that make extensive use of Bradford Hill criteria
- Both EFSA and EPA list similar generic "quality" criteria that they use for rating the reliability of epidemiological studies
- Both EFSA and EPA have guidance on literature retrieval and encourage a systematic approach

Tiered Review Approach

- EPA's Office of Pesticide Programs has adopted a tiered assessment approach to fulfill its regulatory mandate and respond to emerging public health issues.
  - Manage program workload
  - Prioritize potential risk issues that warrant systematic investigation



Epidemiology Assessment Approach

- Tiered reviews are guided by OPP's published 2016 Epidemiological Framework
- Emphasizes study quality and weight of evidence
- "Fit for purpose"
  - Required resources are "matched" or balanced against any anticipated or expected information gain from further, more in-depth research
  - Can include formal systematic review, when appropriate

Epidemiology Assessment Approach

- In recent years, NAS has encouraged the EPA to move towards **systematic review** processes to enhance transparency of scientific literature reviews that support chemical-specific risk assessments.

  - systematic review : *"a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies*"

- Other organizations offering guidance on Systematic Review:
  - US EPA IRIS
  - NTP/OHAT
  - Cochran Collaboration
  - Campbell Collaboration
  - "Navigation Guide" (EHP series)

Epidemiology Literature Search/Retrieval

Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment (2012)

Special Notes on Epidemiologic Data (§3.2.3)

Tier I, Tier II, & Tier III Epidemiology Reviews

- **Tier I: Update to scoping exercise**
  - Research and evaluation generally limited to Agriculture Health Study (AHS)-related publications
- **Tier II: Systematic review**
  - broader search of epidemiologic literature including comprehensive data collection and systematic literature review
  - generally limited in scope to epidemiology
  - integration by risk assessors occurs as part of Draft Risk Assessment
- **Tier III: Systematic review + multi-disciplinary integration**
  - can involve more comprehensive epidemiologic methods

Tier I, Tier II, & Tier III Epidemiology Reviews

Links to Tier I Epi/incident reviews available in the chemical dockets:

- Carbaryl https://www.regulations.gov/document?D=EPA-HQ-OPP-2010-0230-0035
- EPTC https://www.regulations.gov/document?D=EPA-HQ-OPP-2012-0720-0017
- Metribuzin https://www.regulations.gov/document?D=EPA-HQ-OPP-2012-0487-0021
- Aldicarb https://www.regulations.gov/document?D=EPA-HQ-OPP-2012-0161-0024

Links to Tier II Epi/incident reviews available in the chemical dockets:

- Diazinon https://www.regulations.gov/document?D=EPA-HQ-OPP-2008-0351-0091
- Permethrin https://www.regulations.gov/document?D=EPA-HQ-OPP-2011-0039-0084
- 2,4-D https://www.regulations.gov/document?D=EPA-HQ-OPP-2012-0330-0084 for carcinogenic effects and https://www.regulations.gov/document?D=EPA-HQ-OPP-2012-0330-0087 for non-carcinogenic effects.

Tier III Epidemiology Literature Review

- Most extensive literature search of epi data + comprehensive and integrated epidemiological review
  - Meta-analysis
  - Design calculations/power issues
  - Publication Bias/Egger (Funnel) Plots
  - Multiple Comparisons/False Discovery Rate
  - GLS Trend Estimation (dose-response)
  - Heterogeneity/ I^2
  - Meta-regression
  - Sensitivity analysis/quantitative bias analysis
  - Fractional polynomials (vs. categorical classification)
  - Causal analyses/DAGs
  - Propensity scores
- Focus may be on a targeted specific association or a more general multi-disciplinary integrative review
  - Previous SAPs for glyphosate, chlorpyrifos, atrazine
- Can be more forward looking ("what do we need to see in studies to conclude that….")

Study Quality ("Grading") Considerations

Learning Process/Ongoing Development ….

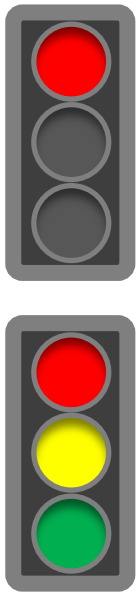
- Lakind, J, *et al.* A proposal for assessing study quality: Biomonitoring, Environmental Epidemiology, and Short-Lived Chemical (BEES-C) instrument *Environ. Intl.* (2014).
- Goodman, M. et al., Atrazine and Pregnancy Outcomes: A Systematic Review of Epidemiologic Evidence. *Birth Defects Research (Part B)* (2014)
- Von Elm, E. et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J. Clin. Epid.* (2008).
- Office of Health Assessment and Translation, OHAT. Handbook for conducting a literature-based health assessment using OHAT approach for systematic review and evidence integration. edited by Division of the National Toxicology Program. 2015.
- Burns, C. and T. Pastoor. Pyrethroid epidemiology: a quality based review. *Crit. Rev. Toxicol.* (2018).
- EFSA. Scientific Opinion of the PPR Panel on the …. Epidemiological studies linking exposure to pesticides and health effects (2017)
- Adami, H-O, *et al.* Toxicology and Epidemiology: Improving the Science with a Framework for Combining Toxicological and Epidemiological Evidence to Establish Causal Inference, *Toxicol. Sci.* (2011)

Study Quality

Parameter	High	Moderate	Low
Exposure Assessment	Accurate and precise quantitative relationship with external exposure, internal dose, or target dose, possibly associated with an MOA/AOP. If questionnaire utilized, questionnaire and/or interview answered by subjects for chemical-specific exposure	Evidence exists for a relationship between biomarker in a specified matrix and external exposure, internal dose, or target dose. Questionnaire and/or interview for chemical-specific exposure answered by subjects or proxy individuals	Poor surrogate Low-quality questionnaire and/or interview; information collected for groups of chemicals rather than chemical-specific; no chemical-specific exposure information collected; ever/never use of pesticides in general evaluated
Outcome Assessment	Standardized tool, validated in study population; medical record review/diagnosis confirmation by trained staff; appropriate consideration of prevalence/incidence of cases	Standardized tool, not validated in population, or screening tool; or, medical record review, methods unstated	Selected sections of test, or maternal report, other; or, maternal/paternal self-report; unclear/no consideration for whether prevalent or incident cases are appropriate
Confounder Control	Good control for important confounders relevant to scientific question, and standard confounders	Moderately good control confounders, standard variables, not all variables relevant for scientific question	Multi-variable analysis not performed no adjustments; no stratification, restriction, or matching
Statistical Analysis	Appropriate to study question and design, supported by adequate sample size, maximizing use of data, reported well (not selective)	Acceptable methods, questionable study power (especially sub-analyses), analytic choices that lose information, not reported clearly	Minimal attention to statistical analyses, comparisons not performed or described clearly
Risk of (other) bias (selection, differential misclassification, effect size magnification, other)	Major sources of other potential biases not likely present, present but analyzed, unlikely to influence magnitude and direction of the risk estimate	Other sources of bias present, acknowledged but not addressed in study, may influence magnitude but not direction of estimate	Major study biases present, unacknowledged or unaddressed in study, cannot exclude other explanations for study finding

Evaluating Study Quality… ongoing process

Risk Assessment Relevance	Observational Study Type	General Agency Evaluation
"Inadequate"	Ecologic	**Evaluation (generally) not warranted**
"Supplemental"	Semi-Ecologic Cross-Sectional	**Proceed to Evaluation**
"Acceptable"	Case-Control Cohort	**Proceed to Evaluation**



- ❑ Study Design
- ❑ Exposure Assessment
- ❑ Outcome Ascertainment
- ❑ Statistical Methods/Confounding
- ❑ Risk of Bias

Study Quality

- Low
- Medium
- High

Other Epidemiological Projects/Activities

- HESI (Health and Environmental Sciences Institute)

  "Application of Environmental Epidemiology for Risk Assessment and Decision Making"

- IRAC (Interagency Risk Assessment Consortium)

  "Reproducibility and Replication Issues in Science: Quantitative analysis of biases in epidemiology and its role in risk assessment"

- EFSA (European Food Safety Agency)

  "Scientific Opinion of the PPR Panel on the follow-up of the findings of the External Scientific Report 'Literature review of epidemiological studies linking exposure to pesticides and health effects'" [link]

Summary

- OPP has placed increased emphasis on incorporating high quality epidemiology studies, when available, in its Human Health Risk Assessments, with the goal of using this information in a scientifically robust and transparent way.
- Review of epidemiologic research is an important component of the EPA OPP risk assessment process mandated under FIFRA and FQPA.
- In order to support regulatory risk assessment and public interest needs, OPP has adopted a tiered review approach to manage workload and prioritize potential risk issues that warrant systematic investigation
- OPP has developed a framework document for incorporating epidemiological studies into risk assessments
- Evaluating study quality is an ongoing process
- OPP is involved in variety of other collaborative epidemiological activities

Thank you

Contact Information

For further questions, contact:

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Visit www.epa.gov/pesticides

Additional Material

Web Links for References from Slides

1. Agricultural Health Study [slide 4] : http://aghealth.nih.gov/
2. Agricultural Health Study Publications [slide 4] : https://aghealth.nih.gov/news/publications.html
3. Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment [slides 6-10] : https://www3.epa.gov/pesticides/EPA-HQ-OPP-2008-0316-DRAFT-0075.pdf
4. WHO/IPCS Mode of Action Framework [slide 8] : http://www.who.int/ipcs/methods/harmonization/areas/cancer/en/
5. NRC 2009: Science & Decisions: Advancing Risk Assessment [slide 8] : https://www.nap.edu/read/12209/chapter/1
6. US EPA's Integrated Risk Information System (IRIS) [slide 15] : https://www.epa.gov/iris/advancing-systematic-review-workshop-december-2015
7. NTP/OHAT [slide 15] : https://ntp.niehs.nih.gov/pubhealth/hat/review/index-2.html
8. Navigation Guide [slide 15] : http://ehp.niehs.nih.gov/1307175/
9. Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment [slide 16]: https://www.epa.gov/sites/production/files/2015-07/documents/lit-studies.pdf

Web Links for References from Slides

10. Journal Articles [slide 19] :

- S. Greenland and M. Longnecker, Methods for Trend Estimation from Summarized Dose-Response Data, with Applications to Meta-Analysis. *American Journal of Epidemiology* Volume 135, Issue 11, 1 June 1992, Pages 1301–1309. https://doi.org/10.1093/oxfordjournals.aje.a116237
- M.Madure and S. Greenland, Tests for Trend and Dose Response: Misinterpretations and Alternatives. *American Journal of Epidemiology* Volume 135, Issue 1, 1 January 1992, Pages 96–104. https://doi.org/10.1093/oxfordjournals.aje.a116206
- T. Lash et al., Good Practices for quantitative bias analysis. *International Journal of Epidemiology* Volume 43, Issue 6, 1 December 2014, Pages 1969–198., https://doi.org/10.1093/ije/dyu149
- P. Royston, et al., The use of fractional polynomials to model continuous risk variables in epidemiology. *International Journal of Epidemiology* Volume 28, Issue 5, 1 October 1999, Pages 964–974. https://doi.org/10.1093/ije/28.5.964
- T. Lash et al., Quantitative Bias Analysis in Regulatory Settings. *American Journal of Public Health* 106, no. 7 (July 1, 2016): pp. 1227-1230.
- Y. Benjamini and Y. Hochberg, Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society. Series B (Methodological)* Vol. 57, No. 1 (1995), pp. 289-300. http://www.jstor.org/stable/2346101