United States Environmental Protection Agency

US EPA's Approach to Pesticide Epidemiology: Similarities and Differences with the EFSA Proposal

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Scientific Conference on the "Use of Epidemiological Findings in Regulatory Pesticide Risk Assessment"
European Food Safety Authority
NH Hotel
Parma, Italy
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Outline

- EPA/OPP Regulatory Mandate
- Epidemiological Studies in EPA/OPP
- EPA/OPP Epidemiological Framework document
- EPA/OPP Approach : Tiered Process
- EPA/OPP Incident Data
- Epidemiology in EFSA and EPA: comparison and contrast

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

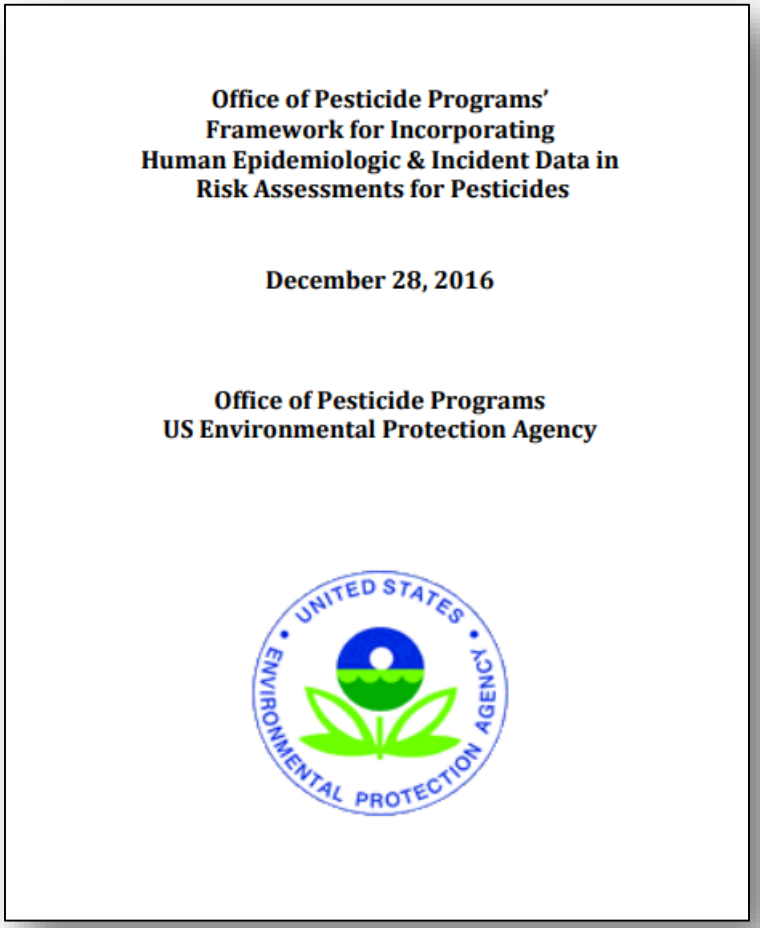
- An increasing number of epidemiology studies are entering literature, particularly from the Agricultural Health Study (AHS) and its publications.
- OPP is putting increasing emphasis and use of these epidemiology studies in its Human Health Risk Assessments.
  - Goal of using this information in the most 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.

OPP Framework: Timeline

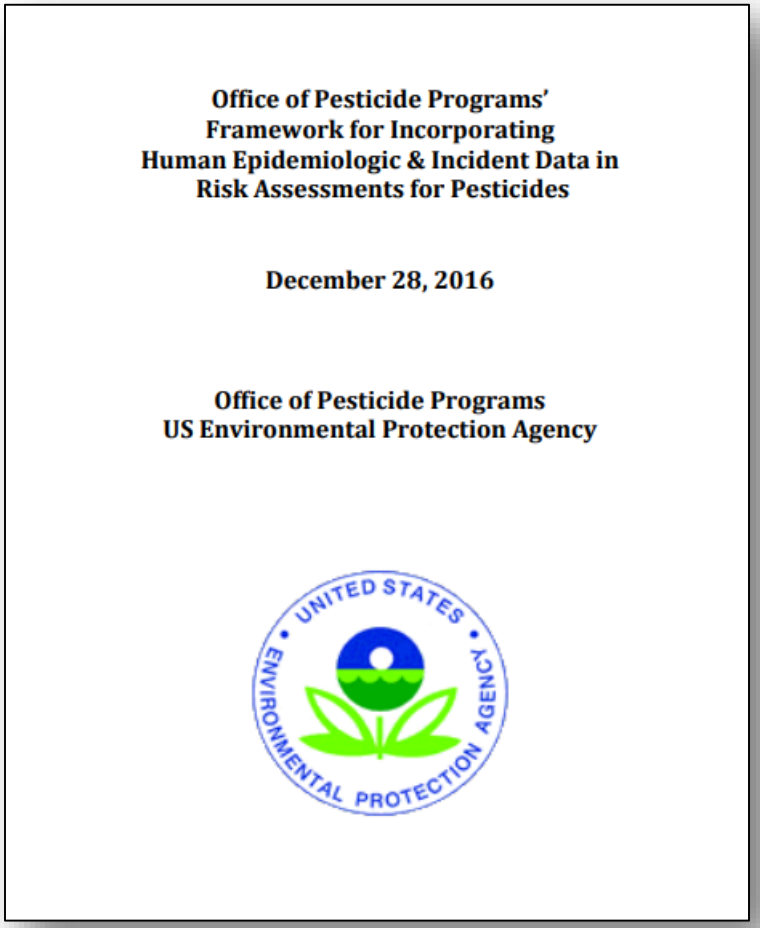
- In 2010, OPP developed a draft framework for incorporating epidemiology and incident data
- Favorably reviewed by 2010 FIFRA Scientific Advisory Panel
- Final version published in December 2016



OPP Framework Report Link

OPP Framework: Key Points

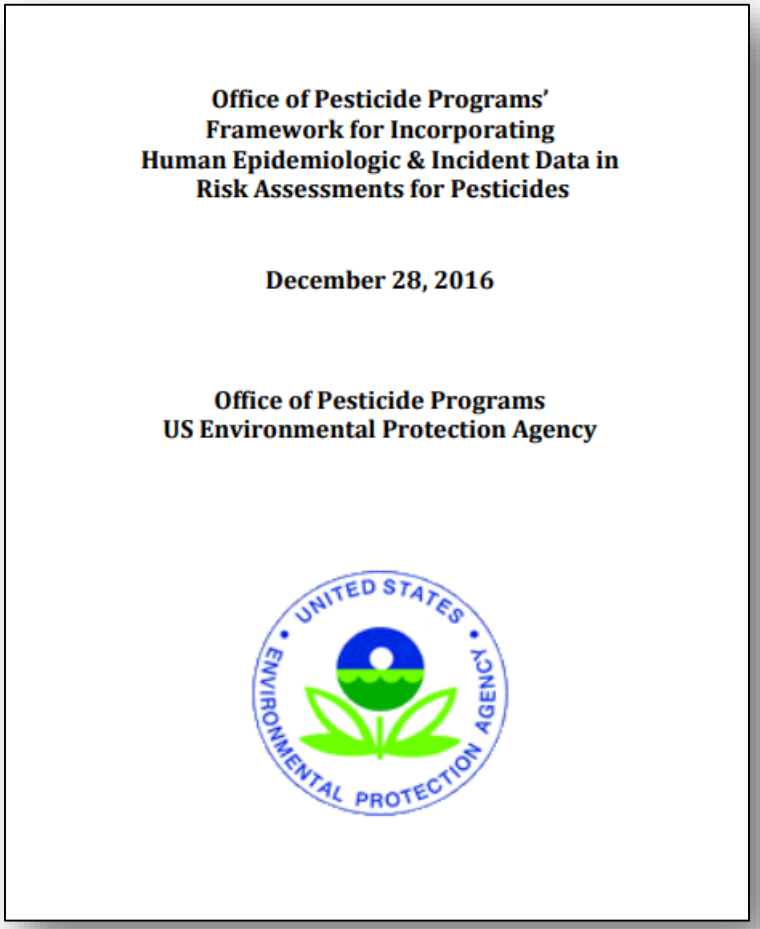
- Acknowledges limitations of epidemiology data in regulatory decision-making, but highlights increased publication of data
  - Agricultural Health Study
  - NIEHS/EPA Children's Centers
  - Other cohorts/study populations
- Aims to improve transparency of scientific considerations
- Not a formal regulatory 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
- Framework has guided evaluation of atrazine and chlorpyrifos
- Consistent with WHO/IPCS MOA/human relevance framework and 2009 National Research Council's "Science and Decisions" publication


Office of Pesticide Programs'
Framework for Incorporating
Human Epidemiologic & Incident Data in
Risk Assessments for Pesticides

December 28, 2016

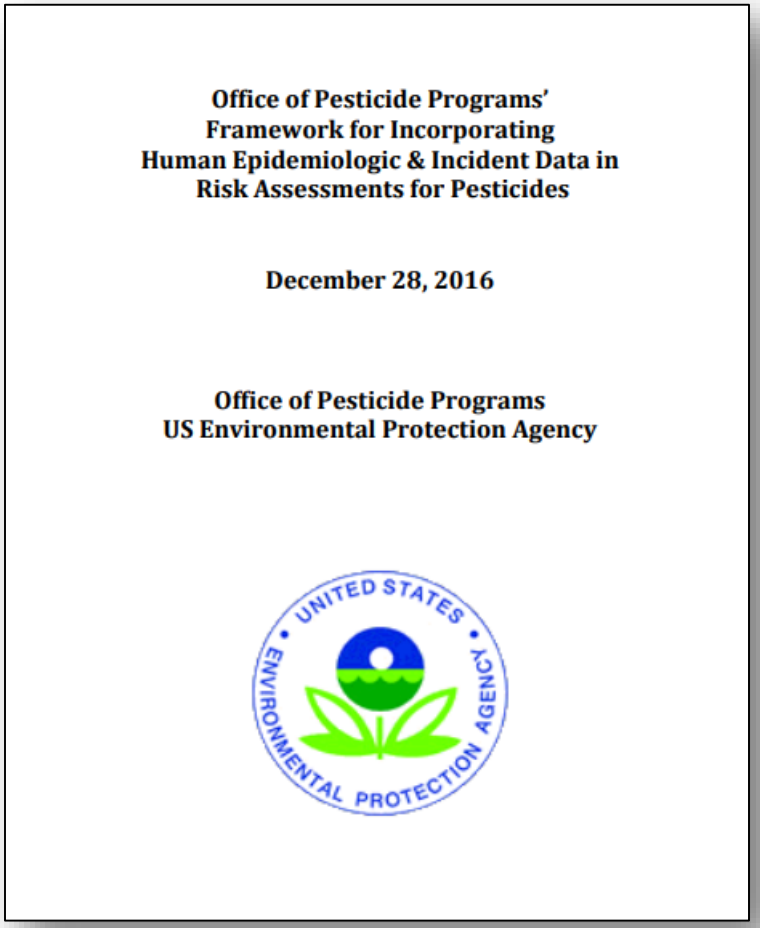
Office of Pesticide Programs
US Environmental Protection Agency

OPP Framework Report Link

OPP Framework: Key Points

Key Issues:

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

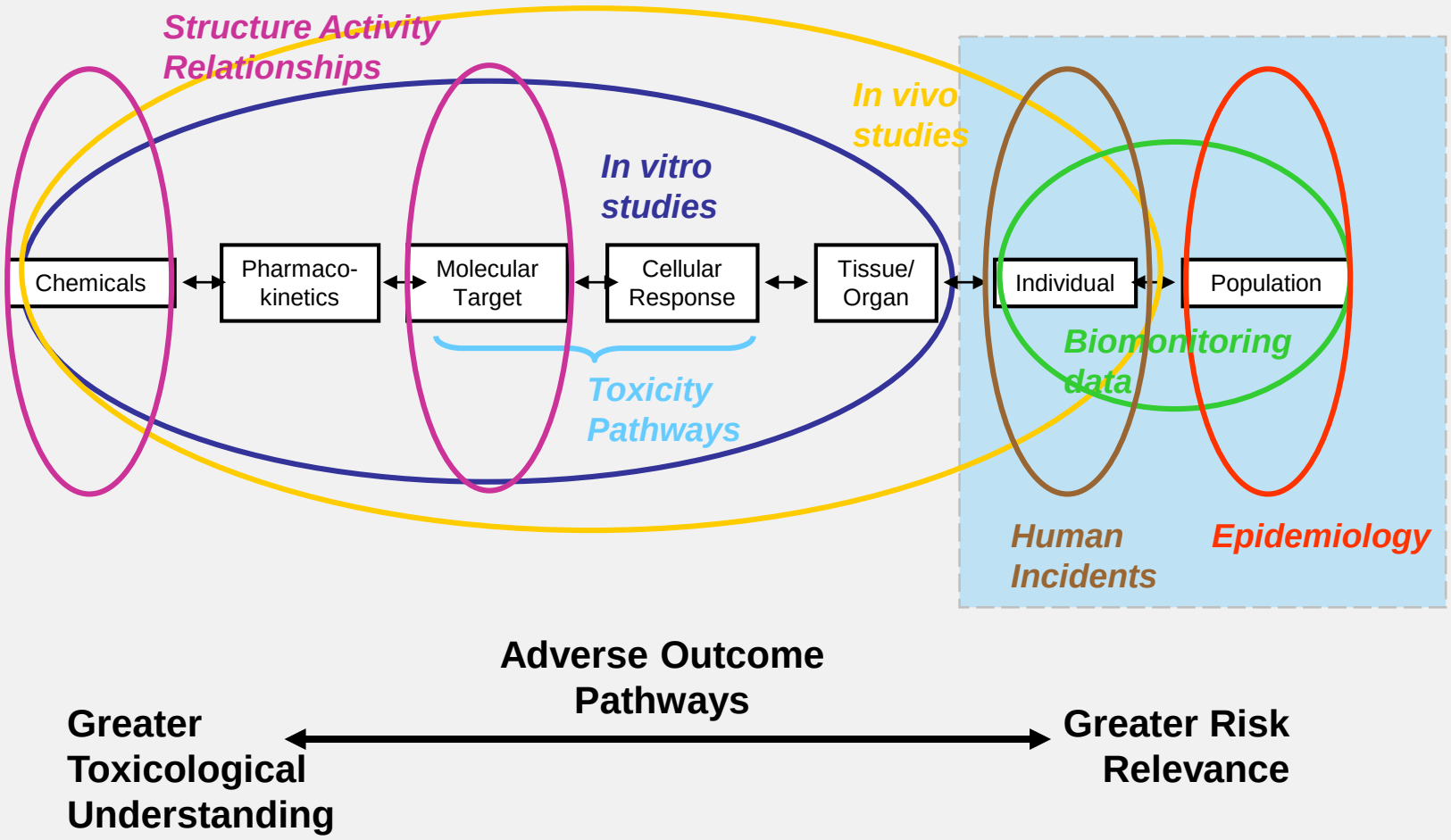


OPP Framework Report Link

OPP Framework: Guiding Principles

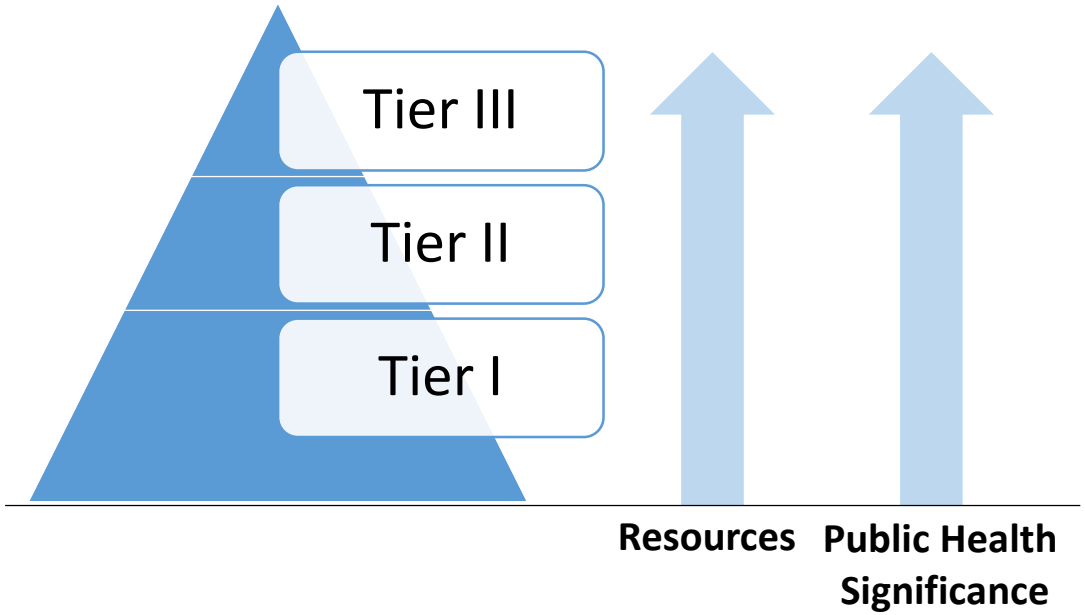
- **Problem Formulation**
  - Scope and complexity of systematic reviews should address major factors that will inform risk assessment.
- **Mode of Action/Adverse Outcome Pathway Framework**
  - Identify key events along a causal path
  - Organize and integrate different sources of information from both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

Source to Effects Pathway, Adapted from NRC, 2007



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)

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 III Epidemiology Literature Review

- Most extensive literature search of epi data + comprehensive and integrated epidemiological review
  - Meta-analysis
  - Design calculations/power issues
  - Publication Bias
  - 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….")

OPP Incident Data

- In addition to performing epidemiologic reviews, the Agency also monitors adverse incident reports.
  - EPA receives ~ 20,000 human incidents per year
    - ~ 90% of these human incidents per year are minor severity
- EPA defines a pesticide incident as any exposure or effect from a pesticide's use that is not expected or intended.
- FIFRA 6(a)(2) mandates registrants to submit information about adverse outcomes resulting from exposure to a pesticide for which they hold a registration.
  - Mandatory registrant reporting accounts for ~ 95% of incidents reported to IDS
  - Other reporters include:
    - Federal and state health and environmental agencies
    - Individual consumers

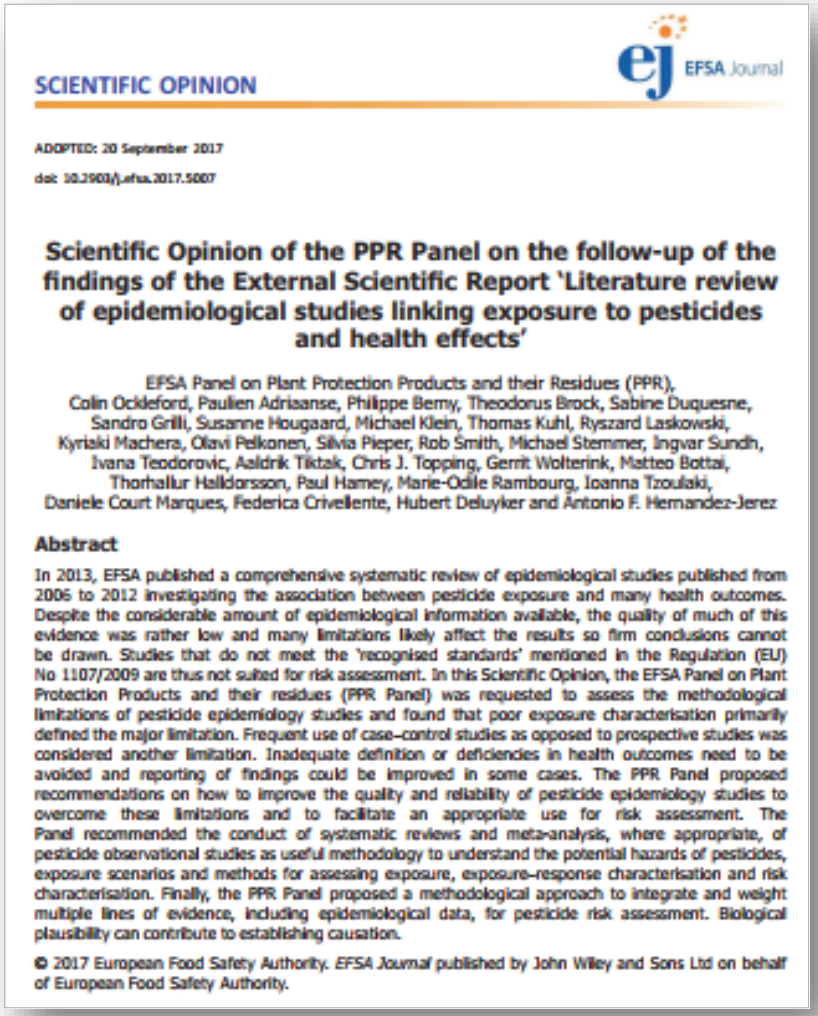
Data Sources on Pesticide Exposure Incidents

Data Sources on Pesticide Exposure Incidents	
EPA's FIFRA 6(a)(2) Incident Data System	FIFRA 6(a)(2) mandates registrants submit information about adverse outcomes resulting from exposure to a pesticide for which they hold a registration. This data is managed centrally by EPA/OPP.
Sentinel Event Notification System for Occupational Risk (SENSOR)- Pesticides Program	NIOSH has built the capacity to perform occupational injury surveillance state health departments. The SENSOR Pesticides program includes 13 states that collect standardized data on acute-pesticide-related incidents.
National Pesticide Information Center	NPIC is a pesticide public health information service funded through an EPA grant with Oregon State University. NPIC's primary purpose is to provide information to the public on pesticides, but NPIC collects information about incidents.
California Pesticide Illness Surveillance Program	California's Department of Pesticide Regulation runs the Pesticide Illness Surveillance Program (PISP) and maintains a database of pesticide-related illnesses and injuries.

OPP Incident Data

- Incident data also complement primary data sources and provide feedback on use of pesticide products in real-world conditions.
  - Patterns in the severity and frequency of pesticide over-exposure
    - may signal the need for further investigation of a particular pesticide a.s. or product
  - Trend following risk mitigation action
  - Information on real-world use practices related to application and use of personal protective equipment

Epidemiology in EFSA and EPA: comparison and contrast



SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 20 September 2017

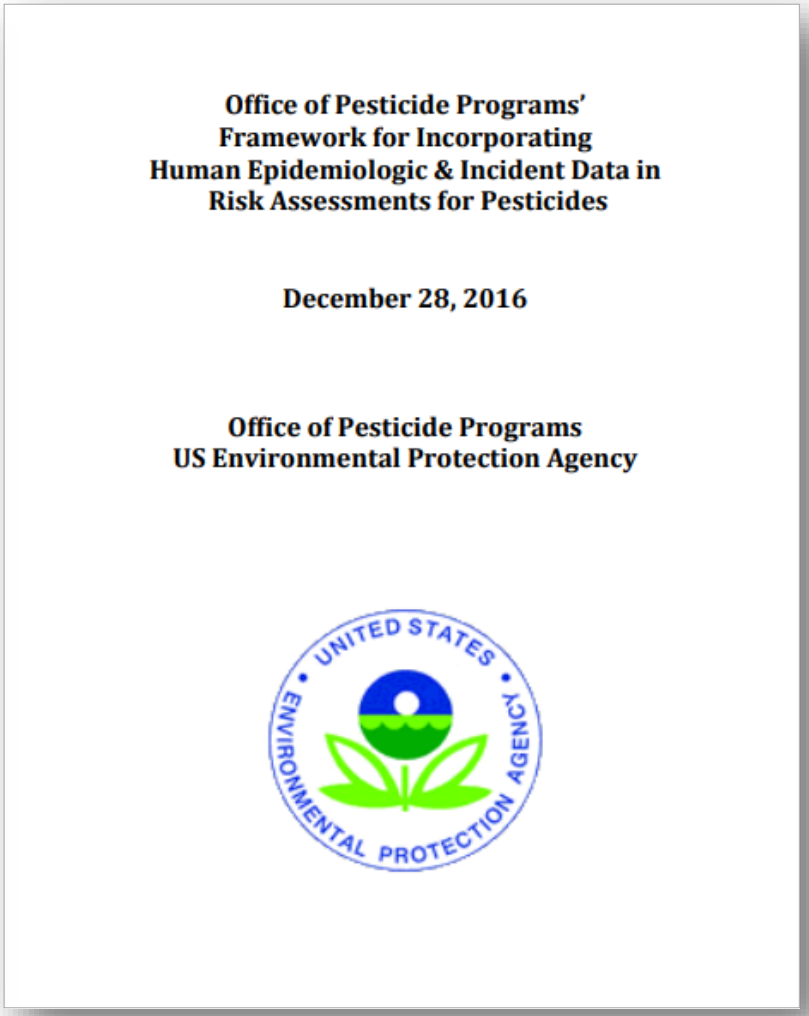
doi: 10.2903/j.efsa.2017.5007

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 Hamey, 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.



Office of Pesticide Programs' Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides

December 28, 2016

Office of Pesticide Programs
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Epidemiology in EFSA and EPA: comparisons and contrasts

- Epidemiological data review is relatively new to both EFSA and EPA with respect to routinely incorporating this information into pesticide risk assessments
- Both EFSA and EPA attempt to integrate epidemiology with AOP/MOA and animal toxicology data, and both organizations follow a WoE approach (framework documents) 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
- Both EFSA and EPA are affected by an asynchrony between the processes associated with the renewal of a.s. and the output/release of epidemiological studies
- EPA has a more formalized tiered process and emphasizes "fit-for-purpose" criteria
- EPA has begun to routinely incorporate epidemiology studies into its HHRA
  - Tier I and II assessments
  - Scientific Advisory Panels/Tier III

Epidemiology in EFSA and EPA: comparisons and contrasts

- Formal submission of "medical data" for regulatory review in EU DARs, per Regulation EC No. 1107/2009 including data on:
  - Medical surveillance on manufacturing plant personnel (**§**5.9.1)
  - Direct observation (**§**5.9.3)
  - Epidemiological studies (**§**5.9.4)
  - Diagnosis of poisoning (**§**5.9.5)
  - Proposed treatment/first aid/antidotes (**§**5.9.6)
  - Expected effects of poisoning (**§**5.9.7)

- FIFRA Adverse event data for incidents (6(a)(2) requirement)
  - To include other data incident data sources
- EPA publication "Recognition and Management of Pesticide Poisonings" (6th ed.)
- No requirement for submission of epidemiological studies/literature
  - EPA OPP collects and reviews these itself

Summary

- Epidemiology is increasing in relevance, importance, interest, and capability
- Review of epidemiologic research is an important component of the EPA/Pesticides risk assessment process mandated under FIFRA and FQPA.
- In order to support regulatory risk assessment and public interest needs, EPA's Office of Pesticide Programs has adopted a tiered review approach to manage workload and prioritize potential risk issues that warrant systematic investigation
- EPA/Pesticides has developed a framework document for incorporating epidemiological studies into risk assessments
  - Concepts in EPA framework is similar in many ways to EFSA's proposed framework

Thank you

Contact Information

For further questions, contact:

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Visit www.epa.gov/pesticides

Additional Material

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

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] : http://www.nap.edu/catalog/12209/science-and-decisions-advancing-risk-assessment
6. US EPA's Integrated Risk Information System (IRIS) [slide 14] : https://www.epa.gov/iris/advancing-systematic-review-workshop-december-2015
7. NTP/OHAT [slide 14] : https://ntp.niehs.nih.gov/pubhealth/hat/review/index-2.html
8. Navigation Guide [slide 14] : http://ehp.niehs.nih.gov/1307175/

Web Links for References from Slides

9. Journal Articles [slide 16] :

- Sander Greenland and Matthew P. 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
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- 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
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Web Links for References from Slides

10. Sentinel Event Notification System for Occupational Risk (SENSOR)-Pesticides Program [slide 18] : https://www.cdc.gov/niosh/topics/pesticides/overview.html
11. National Pesticide Information Center (NPIC) [slide 19] : http://npic.orst.edu/
12. Recognition and Management of Pesticide Poisonings: 6th Edition [slide 22] : https://www.epa.gov/pesticide-worker-safety/recognition-and-management-pesticide-poisonings