

Q&As from the U.S. EPA on The Recognition and Management of Pesticide Poisonings Chapter 21: Chronic Effects

The following information represents the views of the U.S. EPA and not necessarily the opinions of the authors of the 6th Edition of *Recognition and Management of Pesticide Poisonings* or of the Medical University of South Carolina.

General Q&As

1. What is the purpose of this manual?

The *Recognition and Management* series is an important resource for doctors and nurses to treat patients made ill from acute pesticide exposure. The EPA has sponsored this series since 1973. EPA conducted a competitive grant process to ensure the new 6th edition would continue to be a high-quality product available to assist healthcare providers in protecting human health.

The Medical University of South Carolina and two of their professors are the authors of this document.

2. Why was information on chronic effects included in the new edition?

This chapter was included to inform clinicians of the state of scientific literature regarding the potential chronic effects of pesticide exposures. Following the publication of the 5th edition, clinicians and other users of the manual asked that future editions describe well-known epidemiological literature, which they thought could be useful in treating patients. For instance, longer term chronic symptoms may occur after only 1-2 acute exposures. While the new edition includes such information, it also documents the weaknesses and limitations of epidemiological studies.

3. What does the Chronic Effects chapter say?

This chapter is a compilation / synopsis of existing epidemiological literature. The authors describe a variety of studies showing the association – from none to weak to strong -- between pesticides and health effects, and offer their own judgments on the importance of the studies.

Epidemiology is the study of disease(s) in a population, specifically how, when and where they occur. The studies are aimed at determining what factors are associated with diseases (risk factors), and what factors may protect people against disease. Individual epidemiology studies cannot generally establish cause and effect relationships because of the uncontrolled, observational nature of epidemiology studies and challenge of accurately measuring disease/exposure. As such, determination of cause and effect requires careful evaluation of several well designed epidemiology studies and consideration of biological plausibility based on toxicity testing and experimental evidence. Specific to pesticides, most epidemiology studies are generic in nature or focus on associations across classes of chemicals including the organophosphates, pyrethroids and triazines.

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4. Does the EPA agree with the content in the chronic effects chapter?

The publication does not present either the EPA's scientific conclusions or state EPA policy. On the first page of the manual is the following disclaimer statement: "The information in this publication does not in any way replace or supersede the restrictions, precautions, directions or other information on the pesticide label or any other regulatory requirements, nor does it necessarily reflect the position of the EPA".

The EPA, however, does consider epidemiological data valuable information when assessing the potential risks of pesticides and routinely uses epidemiology studies in conjunction with the required animal toxicity studies and other relevant literature findings during the registration review process. The agency has included many of the studies cited in Chapter 21 in its own risk assessments.

5. What is the EPA doing about the issues highlighted by the epidemiological studies?

EPA science policy considers epidemiological data as one component of a comprehensive, peer-reviewed scientific analysis process. As stated by the manual authors, epidemiological data alone does not provide cause and effect. The EPA systematically considers epidemiological studies as part of scientific risk assessments that the Office of Pesticide Programs conducts for individual chemicals (active ingredient risk assessments). The EPA considers these studies in risk assessments in conjunction with animal toxicological data, exposure monitoring data, incident data, and modeling data.

6. Has EPA taken steps to address the potential for pesticide risk cited in Chapter 21?

Yes, through reregistration and tolerance reassessment, the EPA made significant decisions about the future use of older pesticides. Although not based on the epidemiological studies highlighted in chapter 21, to mitigate risks of concern, EPA canceled pesticides, terminated uses, or imposed new use restrictions, as needed through reregistration and tolerance reassessment.

For example, many organophosphate (OP) pesticides and others posing risk concerns were voluntarily canceled, and some uses were phased out over several years. Examples include azinphos-methyl, benomyl, cyanazine, ethion, ethyl parathion, fenamiphos, fenthion, lindane, mevinphos, molinate, and zineb. In addition, the EPA eliminated pesticide uses or imposed new use restrictions to address residential risks, especially to children. For example, all indoor and outdoor residential uses were cancelled for the OPs chlorpyrifos, diazinon, dimethoate, fenthion, naled, phosmet and propetamphos. Cancellation of most residential uses and mitigation of other uses was required for the OPs acephate, bensulide, disulfoton, DDVP, ODM, tetrachlorvinphos and trichlorfon.

To support the EPA's efforts and to seek guidance on a draft framework on how to best integrate epidemiology and human incident data into its human health risk assessments, the EPA convened a FIFRA Scientific Advisory Panel (SAP). Atrazine was used as a case study for this meeting.

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Additionally, the agency has sought the SAP's advice on how to best consider epidemiology studies in several of its chemical assessments including atrazine in 2011 and in chlorpyrifos in 2008 and 2012.

Specific Questions on Chapter 21 Statements:

[Page 214] Evidence of neurodevelopmental toxicity arising from chronic, low-level exposure in gestational or early life is accumulating.

- **What does the statement mean?** This is a generic statement that there is suggestive evidence that low-level exposure to environmental chemicals during gestation may be associated with neurodevelopmental toxicity.
- **What does it not mean?** It does not mean that low-level, environmental exposure to pesticides causes adverse neurodevelopmental health outcomes in infants and children. Rather, it suggests that further research is warranted to determine if low-level exposure to particular pesticides can cause adverse neurodevelopmental health outcomes.
- **What is the EPA doing about it?** The EPA is responsible for evaluating the human health effects of pesticides and requires extensive toxicity testing, including acute, subchronic, and chronic toxicity tests, and tests to assess mutagenicity. The EPA is also required to evaluate the special vulnerability of infants and children under the Food Quality Protection Act when assessing health risks. With regard to neurodevelopmental toxicity, the EPA requires developmental neurotoxicity testing and has recently convened a number of Scientific Advisory Panel meetings to obtain scientific guidance on potential neurodevelopmental health outcomes. Additionally, the EPA and the National Institute of Environmental Health Services jointly fund several Children's Environmental Health and Disease Prevention Research Centers located throughout the U.S., which have the long-range goal of understanding how environmental factors affect children's health.

[Page 216] A body of research associates pesticide exposure with ADHD and autism.

- **What does the statement mean?** Some epidemiology studies that have observed associations between pesticides and ADHD/autism.
- **What does it not mean?** It does not mean that a causal link has been established between pesticide exposure and ADHD/autism. Rather, it suggests that further research is warranted to evaluate if causal associations exist between exposure to particular pesticides and ADHD/autism.
- **What is the EPA doing about it?** The EPA is responsible for evaluating the human health effects of pesticides and requires extensive toxicity testing, including acute, subchronic, and chronic toxicity tests, and tests to assess mutagenicity. The EPA closely follows the emerging research on pesticide exposure and ADHD/autism. The EPA has also recently held a number of Scientific Advisory Panel meetings to obtain scientific guidance on pesticide exposure and neurodevelopmental health outcomes, such as ADHD. Through this guidance, the EPA has received external peer-review of its assessment of the relationship between pesticide exposure and adverse neurodevelopmental outcomes.

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[Page 217] Studies of school-age children with prenatal exposure suggest adverse neurodevelopmental outcomes in both urban and agricultural environments.

- **What does the statement mean?** Some epidemiology studies have suggested that pesticide exposure in agricultural and urban environments may be associated with adverse neurodevelopmental health outcomes.
- **What does it not mean?** It does not mean that a causal link has been established between pesticide exposure and adverse neurodevelopmental outcomes. Rather, it suggests that further research is warranted to evaluate if causal associations exist between exposure to particular pesticides and adverse neurodevelopmental outcomes.
- **What is EPA doing about it?** The EPA is responsible for evaluating the human health effects of pesticides and requires extensive toxicity testing, including acute, subchronic, and chronic toxicity tests, and tests to assess mutagenicity. As stated above, the EPA closely follows the emerging research on pesticide exposure and adverse neurodevelopmental outcomes. The EPA has also recently held a number of Scientific Advisory Panel meetings to obtain scientific guidance on pesticide exposure and neurodevelopmental health outcomes. Through this guidance, the EPA has received external peer-review of its assessment of the relationship between pesticide exposure and adverse neurodevelopmental outcomes.

[Page 219] Data support associations between occupational pesticide exposure and cancers in both adults and children.

- **What does the statement mean?** Several epidemiology studies that have observed an association between occupational pesticide exposure and cancer. Many of these epidemiology studies, however, have limitations that make it difficult to draw conclusions about the strength of the associations, for example because the researchers did not determine the level of pesticide exposure actually experienced by individuals who developed cancer.

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[Page 220] The pediatric cancer types with the most compelling evidence for an association with pesticides are leukemia and brain tumors.

- **What does the statement mean?** A recent review article in the scientific literature suggests that there is more evidence that pesticides may be associated with leukemia and brain cancer. Many of these studies, however, have limitations that make it difficult to determine if pesticide exposure actually caused individuals to develop cancer.

[Page 221] There is evidence for increased risk of developing some types of childhood cancers following preconception and/or prenatal exposure to pesticides.

- **What does the statement mean?** There have been several published epidemiology studies that observed an association between pesticide exposure and childhood cancers.

[Page 222] Tumors of the prostate, pancreas, kidney, and breast have been among the more consistently reported findings.

- **What does the statement mean?** Reviews have reported that epidemiology studies have more consistently observed an association between adult pesticide exposure and prostate, pancreas, kidney, and breast.

[For Pages 219-221] – Common Responses:

- **What does it not mean?** Given limitations of epidemiologic research, the statement does not mean that pesticide exposure causes cancer. Likewise, it does not suggest that EPA testing requirements and guidelines for evaluating carcinogenicity are incapable of detecting if pesticides may cause cancer.
- **What is the EPA doing about it?** The EPA is responsible for evaluating the human health effects of pesticides and requires extensive toxicity testing, including acute, subchronic, and chronic toxicity tests, and tests to assess mutagenicity. As stated above, the EPA performs detailed assessments of the carcinogenicity of pesticides that consider findings from epidemiology and toxicology studies. The EPA is also actively engaged with the research community and is a co-sponsor of the Agricultural Health Study, a large prospective study that is actively examining the association between occupational pesticide exposure and cancer.

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[Page 224] Data relating human endocrine disruption has become progressively stronger in supporting a role of pesticides. Extensive research continues in this area of investigation.

- **What does it mean?** Epidemiological studies have been published that associate reproductive effects in humans and wildlife with exposure to a variety of chemicals including some pesticides. As the authors note, epidemiological studies do not establish cause and effect, that is, these studies do not establish that these chemicals actually disrupt endocrine systems at environmentally relevant exposures.
- **What does it not mean?** It does not mean that pesticides, generally, cause endocrine effects. It does not mean pesticides are unsafe and it does not mean that the extensive toxicity testing of pesticides that is required for safety evaluations are incapable of detecting potential reproduction and development effects.
- **What is the EPA doing?** The EPA is responsible for evaluating the human health effects of pesticides and requires extensive toxicity testing, including acute, subchronic, and chronic toxicity tests, and tests to assess mutagenicity. Based, in part, on some of the studies cited in the RMPP, and similar studies not cited, Congress tasked the EPA through passage of the Food Quality Protection Act to screen all pesticide ingredients for their potential to disrupt endocrine systems in humans and wildlife and to ensure their safety. Using externally-peer reviewed methods the EPA has initiated the systematic screening.

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Pesticides Mentioned in Chapter 21: Registration Review Scheduling Information

Organophosphates

--began registration review in 2008 and 2009

--decisions anticipated in 2014/2015

Carbamates

--began registration review in 2010 thru 2012

--decisions anticipated in 2016/2017

Pyrethroids

--began registration review in 2010 thru 2012

--decisions anticipated in 2012/2018

Triazines (atrazine and simazine)

-- registration review docket open June of 2013

-- decisions anticipated in 2017/2018