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**Pesticides**

**Risk Assessment**

As EPA experiments with more reliance on epidemiology in pesticide assessments, risk assessors weigh the pros and cons of this new science policy emphasis. In this BNA Insights, expert consultant Rick Reiss explores the challenges and opportunities inherent in animal toxicology studies versus epidemiological approaches.

# Epidemiology and Its Place in Risk Assessment

BY RICK REISS

*Dr. Reiss is an environmental health scientist with expertise in risk assessment, exposure assessment, environmental chemistry and fate, mathematical modeling, and applied statistics. He provides consulting services related to scientific issues associated with numerous environmental statutes and has expertise in both air quality and chemical risk assessment. He has conducted risk assessments, data analyses, probabilistic exposure modeling, and environmental exposure modeling for environmental agents, such as pesticides, industrial chemicals, and consumer product chemicals. His is a past-President and Fellow of the Society for Risk Analysis.*

## Introduction

Epidemiology has always played a role in risk assessment, both quantitatively and qualitatively. It was most easily implemented into cancer risk assessment by estimating cancer unit risk values from occupational cohorts where workers were exposed to gaseous contaminants. These occupational cohorts typically had high exposures—making elevated cancer rates from exposure clear—and a plethora of industrial hygiene measurements of air concentrations to quantify exposures. In some cases, non-occupational cohorts have been used for non-cancer risk assessment, but particularly for persistent contaminants where exposure assessment is easier.

The field of environmental epidemiology has expanded in recent times and there is now a large set of epidemiologic studies on a variety of contaminants, including some short-lived chemicals that present expo-

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sure classification challenges. Often these studies report associations for outcomes that are not found in animal toxicology studies. For many of the contaminants, risk assessments have traditionally used animal toxicology studies for dose-response assessment. The emergence of new epidemiologic data showing associations at potentially lower doses sets up a challenge for risk assessors.

In this article, I'll discuss some of the challenges in using epidemiologic studies in risk assessment, including its advantages and disadvantages relative to animal toxicology data. I will also present a case study on organophosphorus pesticides, where the U.S. EPA is currently struggling to grapple with emerging epidemiological studies that report neurodevelopmental associations at doses far below current regulatory standards based on animal toxicology data.

## Challenges in Using Epidemiology for Risk Assessment

There are many issues associated with using epidemiology in risk assessment, but in this short article, I want to focus on a few major topics. At regulatory agencies, many non-epidemiologists are in a position of interpreting epidemiologic studies to be used in regulation. Non-epidemiologists are certainly aware that the studies are conducted in humans, and view that as a positive attribute, but many are not aware of the uncertainties associated with epidemiologic studies that complicate their use in risk assessment.

### *Are Humans Always Better than Animals?*

As regulators confront divergent results from animal toxicology and human epidemiology results, it is important to bear in mind that both fields have important limits for risk assessment. The limitations in animal toxicology are obvious and frequently discussed. Of course, any result in an animal test may not be relevant for humans, who could be more- or less-sensitive to a contaminant than an animal model. Also, there are limitations in the outcomes that can be measured in animal studies. For example, a small change in intelligence would be difficult to detect in an animal model.

However, epidemiology also has its limits, many of which are not apparent to non-epidemiologists. In contrast to animal toxicology, there are potentially significant errors in exposure and outcome assessment. In epidemiology studies, the true exposure of any given subject may be uncertain. Worse still, the rank-ordering of exposure (i.e., which subjects have truly higher exposures than other subjects) can be uncertain. By contrast, in an animal toxicology study, one can be reasonably sure that animals in a dose group at 5 milligrams per kilogram of body weight per day were exposed at that level and that they were exposed at 5 milligrams per kilogram of body weight more than the animals in the unexposed control group. Similarly, outcome assessment is often easier and more accurate in animal toxicology studies compared to epidemiologic studies. Other limitations of epidemiologic studies include several potential sources of bias (e.g., from incomplete participation or selective reporting or recording of information), confounding (i.e., failure to control for alternative risk factors that may explain apparent associations), and chance, which can never completely be ruled out as an explanation for any given finding.

There is a growing literature critical of current epidemiologic methods. Essentially, this criticism boils down to the notion that the myriad of epidemiologic associations that are reported in the literature (and many subsequently in the popular press) cannot all be true, and in fact may mostly be false. John Ioannidis, a professor of medicine and epidemiology currently at Stanford, caused a stir in 2005 with the publication of his seminal article ''Why Most Published Research Findings are False.'' Ioannidis's article was motivated by the frequent lack of replication of published research findings. Too often, published findings are not replicated by subsequent studies. Ioannidis developed a mathematical model to quantify the potential errors associated with prevailing research methods and ultimately concluded that ''for most study designs and settings, it is more likely for a research claim to be false than true.''

The public is aware of the problem of inconsistent findings in epidemiologic studies, particularly through popular press reports on food and nutrition, though the public does not always understand that similar methods are used for food and nutrition studies as in environmental epidemiology studies. Coffee is a prominent example. Over the years, coffee has been reported to be associated with any number of adverse or beneficial health effects. The harmful effects touted as resulting from coffee consumption have included early death, elevated blood pressure, heart attacks and many others. Yet recently, the U.S. Dietary Guidelines Advisory Committee said drinking three to five cups of coffee a day is fine and not associated with any long-term health problems. Nutritional epidemiology is increasingly an example of a field where a wide variety of published findings are inconsistent and many are probably false. In fact, for years, one of the central recommendations for weight loss has been a low-fat diet, resulting in food suppliers' redesigning many of their products. Yet in recent years, this concept has been called into question, with research suggesting that a low-carbohydrate diet may be more effective for weight loss.

One of the central problems in nutritional epidemiology studies is accurately assessing the diets of the subjects in the studies. Mostly, this is done through dietary surveys. At first blush, one might think asking people about their diet would be an accurate measurement method, but there are many problems with dietary surveys. People do not always accurately recall their diets, even in the short-term, and do not always tell the truth. Perhaps more importantly, diets change over time, and the health effects of diet may reflect distant past or long-term dietary patterns, which are particularly hard to accurately quantify. Most environmental epidemiologic studies face similar, or even more daunting, exposure assessment challenges.

Ioannidis published another thought-provoking study in 2013, titled ''Is everything we eat associated with cancer? A systematic cookbook review'' (Schoenfeld and Ioannidis, 2013). The study illustrates the frequently inconsistent findings of nutritional epidemiology. The authors searched for epidemiology studies that examined associations with cancer for 50 common ingredients in food and found studies on 40 of the 50 ingredients. Of 264 single-study assessments, 72 percent reported associations showing that an ingredient caused or prevented cancer. Things got really interesting when these results were compared. Of 20 ingredients with 10 or more reported results, all but four (pork,

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bacon, salt, and olives) had reported relative risks both above 1 (showing an increased risk of cancer) *and* below 1 (showing a decreased risk of cancer). Many ingredients had studies with relative risks both above 2 (showing a doubling of risk) *and* below 0.5 (showing a protective effect of a similar magnitude). These results clearly show the potential for inconsistent results in epidemiology studies and the need for caution when translating these results to a regulatory context.

### *Misclassification as a Get out of Jail Free Card*

At the heart of the uncertainties in environmental epidemiology studies is the potential for misclassification (that is, measurement error) in exposures, outcomes, or potential confounders. The common comeback to that criticism is that any misclassification is likely to be non-differential (i.e., random), resulting in underestimated associations, such that the true effect is actually likely larger than reported (i.e., the bias is towards the null). In the extreme, the claim of non-differential misclassification is used as a ''get out of jail free card'' against any study flaws. However, many of these claims are incorrect.

First, in most observational epidemiology studies, establishing that misclassification is completely non-differential is virtually impossible. Many researchers will state something like ''we have no reason to believe that misclassification is differential,'' but that is a weak assurance; the fact is that they almost never know for sure. Even slightly differential misclassification can result in predictable bias away from the null (i.e., overestimated associations). Therefore, the direction of bias in risk estimates can virtually never be known with certainty. Even if misclassification is completely non-differential, it does not necessarily mean that a positive association is truly stronger than estimated. Rothman et al. (2012), in their influential textbook *Modern Epidemiology*, discuss the numerous misunderstandings in the literature regarding misclassification and detail the reasons why even non-differentiality on its own does not guarantee bias toward the null. Clearly, the issue of misclassification is complicated and it cannot easily be used to absolve study flaws.

## Organophosphorus Pesticides

### *The Long-Standing Paradigm for Risk Assessment*

Organophosphorus (OP) pesticides are a common class of pesticides that are widely used in U.S. agriculture, mostly as insecticides. For more than half a century, the mode-of-action for toxic effects of OP pesticides has been understood to be inhibition of acetylcholinesterase, an enzyme that catalyzes the breakdown of acetylcholine. OP inhibition of acetylcholinesterase causes neurotoxicity from excessive accumulation of acetylcholine in cholinergic synapses. Quantifying doses that cause acetylcholinesterase inhibition is relatively straightforward to do in animal studies; thus, most OPs registered in the U.S. have a toxicology database that allows dose-response analysis for acetylcholinesterase inhibition. Most toxicology studies are in animals, but there are some human toxicology studies for OPs. U.S. EPA has typically set a point-of-departure (POD) for risk assessment based on 10% inhibition of acetylcholinesterase in red blood cells or in the brain.

### *Epidemiology Challenges the Paradigm*

During the past decade or so, a number of epidemiologic studies have been published that have detected apparent neurodevelopmental effects of OPs at doses far lower than those that would cause meaningful acetylcholinesterase inhibition. We found that the vast majority of subjects in these studies have OP exposures that would cause less than 0.1 percent acetylcholinesterase inhibition, which generally has been considered biologically irrelevant. The basic design of most of the epidemiologic studies includes the measurement of OP exposure (with limitations discussed below) in pregnant women and a subsequent assessment of neurodevelopment in their offspring. A variety of studies have been conducted in North America, Europe, and China. Most, but not all, of the studies report some statistical associations between OP exposure and neurodevelopment. In my opinion, however, there is not a consistent picture of neurodevelopmental effects of OP exposure across the studies, though others disagree.

The study conducted by the Columbia Center for Children's Environment and Health (CCCEH) has perhaps received the most scientific and regulatory attention because the U.S. EPA is using it to regulate the widely used OP insecticide chlorpyrifos. The CCCEH study measured chlorpyrifos in cord blood and associated those measurements with neurodevelopment through 7 years of age. The U.S. EPA recently proposed setting a Point of Departure based on findings in the CCCEH study and asked the FIFRA Scientific Advisory Panel (SAP) to evaluate its methods.

EPA faced several challenges. First, the cord blood measurements occurred after prenatal chlorpyrifos exposure, and the gap between exposure and measurement was unknown. Second, the CCCEH represents only one study and, given the uncertainties associated with individual epidemiology studies, including the potential for any given result to be due to bias, confounding, or chance, it is preferable that multiple studies are available with consistent results. The SAP concluded that the CCCEH data are insufficient to establish a POD.

Another set of OP epidemiology studies estimates exposure with urinary levels of six dialkylphosphates (DAPs). These studies were instrumental to EPA's concluding that all OPs require an additional 10x safety factor under the Food Quality Protection Act. Many, but not all, OPs metabolize to one or more of the six DAPs, though no DAP is specific to any one OP, which vary in toxicity. Thus, DAPs represent a non-specific and incomplete marker of OP exposure. Exposure assessment in epidemiology studies is further complicated because plants similarly metabolize OP pesticides to DAPs, which are considered to be non-toxic (Zhang et al., 2008). Thus, food items include pre-formed DAPs, resulting in exposure to DAPs that is not directly related to OP exposure. For all of these reasons, accurate dose-response analysis is out of the question.

Unlike the CCCEH study with chlorpyrifos, multiple epidemiologic studies are available with DAPs and, in a few cases, comparisons in risk estimates can be made for the same outcome at the same child age. My colleagues and I performed a consistency analysis in a review paper last year (Reiss et al., 2015). While we found

some suggestive results, we concluded that the body of studies did not show consistency in neurodevelopmental effects associated with DAPs. There were only a handful of cases where the same outcome was measured at the same child age, and there were never more than two studies to compare. In one example, we compared results from two studies that measured the Bayley Mental Development Index (MDI) at two years of age. One study found a positive association (Bouchard et al., 2011), while another did not (Engel et al., 2011).

Interestingly, after we published our paper, Engel et al. (2016) published a pooled analysis that reported associations of DAPs with MDI at two years of age. Instead of two studies, Engel et al. (2016) had access to data for four studies. The data from the other two cohorts were unpublished, though data from these cohorts had previously been published for other exposure-outcome combinations. This raises questions about publication bias, given that the two additional cohorts did not show statistically significant results. Moreover, the null results in the two additional cohorts diminish the argument for consistency of any association between OP exposure and neurodevelopmental outcomes.

Overall, EPA has to grapple with inconsistent epidemiologic results that lack a plausible mode-of-action. However, EPA has a public-health-protective mandate and it must carefully consider any scientific study that alleges neurodevelopmental effects in the population associated with chemicals that it regulates.

## Summary

Regulators are confronted with challenging decisions when epidemiologic studies report results that conflict with animal studies, particularly when the epidemiology studies show associations at lower doses than have been established to result in toxicity in animal toxicology studies. On one hand, epidemiology studies are conducted in human populations, an obvious advantage over animal toxicology. On the other hand, animal toxicology studies are conducted in controlled conditions that have less chance for error. Some scientists have called for regulators to work on integrating lines of evidence from epidemiology and toxicology. However, many of those calling for integration usually stop short of saying exactly how to do it. For OP pesticides, the epidemiology and toxicology are simply inconsistent. While I do not agree with EPA's approach of adding an additional safety factor to account for epidemiologic results, it is not clear what other options there are for integrating epidemiology into risk assessment.

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