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

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, in-

sure classification challenges. Often these studies report associations for outcomes that are not found in animal toxicology studies. For many of the contaminants,

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.

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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

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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.

[illegible]

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 atten-

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.

  DEN ISSN 1060-2976