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Pesticide Regulation amid the Influence of Industry

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Pesticide use results in the widespread distribution of chemical contaminants, which necessitates regulatory agencies to assess the risks to environmental and human health. However, risk assessment is compromised when relatively few studies are used to determine impacts, particularly if most of the data used in an assessment are produced by a pesticide's manufacturer, which constitutes a conflict of interest. Here, we present the shortcomings of the US Environmental Protection Agency's pesticide risk assessment process, using the recent reassessment of atrazine's impacts on amphibians as an example. We then offer solutions to improve the risk assessment process, which would reduce the potential for and perception of bias in a process that is crucial for environmental and human health.

Keywords: amphibian, atrazine, conflicts of interest, Environmental Protection Agency, risk assessment

Shortly after the publication of Silent Spring (Carson 1962), approximately 245,000,000 kilograms (kg) of active ingredients of pesticides were applied in the United States in 1964, a value that steadily increased and leveled off to approximately 500,000,000 kg (Waxman 1998, Grube et al. 2011), or about 1.5 kg of active ingredient per US citizen per year today. Although pesticides are applied at particular locations, they are distributed widely by atmospheric drift, runoff, and movement through food webs, creating the potential for health and environmental risks that are managed, mitigated, and regulated by the US Environmental Protection Agency (USEPA). Pesticides undergo a series of toxicity tests to assess risks; these tests are typically conducted or funded by a pesticide's manufacturer (i.e., industry-supplied studies; USEPA 2008). The USEPA evaluates the risks indicated by industry-supplied studies and by studies funded through other means from independent laboratories to determine whether a pesticide can be used and the conditions under which it can be applied. The USEPA's decisionmaking process for registration and reregistration of a pesticide is a complex balancing act in which the benefits of use are weighed against the risks to human and environmental health. As experienced researchers working in the field of ecotoxicology, we are concerned that the USEPA's risk assessment process can proceed using a narrow portion of the available data and can be based exclusively on industry-supplied studies. The ongoing reassessment of atrazine's impact on amphibians underscores some of the pitfalls of the USEPA's current approach and illustrates how the USEPA's directive to protect human and environmental health may be undermined.

Concerns with the USEPA's risk assessment process

A major weakness of the USEPA's pesticide risk assessment is the use of industry-supplied data, which has inherent conflicts of interest (COIs). The risks of COIs within the federal regulatory system have been discussed in recent years, largely with respect to the regulation of drugs (Cheng 2009, Irwin 2009). Similar problems exist in the regulation of chemicals that fall under the purview of the USEPA, but the discussion regarding COIs in this context are limited. COIs occur when professional judgment or decisionmaking has the potential to be influenced by personal or financial gain (Rohr and McCoy 2010a). COIs do not signify that misconduct has or will occur, but they do create the risk that professional judgment could be compromised, whether that is intentional or not. The perception of COIs in research undercuts confidence in results, which leads to skepticism from both the public and the scientific community. Because of this, the National Institutes of Health now requires the disclosure of personal financial COIs when applying for or receiving federal grants (*http://grants.nih.gov/grants/policy/coi*). The USEPA also prohibits any scientist from serving on its Scientific Advisory Panels (SAP; independent bodies of expert scientists who are selected by the USEPA to evaluate their risk assessments) if the panel member's

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recommendation could have "direct and predictable effects on [his or her] financial interests" because it could result in "the appearance of [a] loss of impartiality."

Despite the USEPA's recognition of COIs in certain aspects of risk assessment, COIs are currently ingrained in the process, because the companies registering chemicals are required to supply data involved in risk review (USEPA 2008). Furthermore, the USEPA works with industry to establish the methodology and experimental design for studies. The complexity and logistics of these designs can make them prohibitively expensive for researchers outside of industry, often leaving industry as the only entity that can afford to conduct the research to the USEPA's specifications or that is knowledgeable of the requirements. Therefore, all or most of the data used in risk assessments may come from industry-supplied research, despite clear COIs.

In many studies, the effects of funding source on research outcomes have been quantified, and it has been shown that industry-supplied studies are more likely to support effects favorable to industry. For instance, the best predictor of whether the herbicide atrazine had significant biological effects in a study was the funding source, with manufacturer-funded research having a greater likelihood of finding no effect or only small effects (Hayes 2004). A comparable conclusion was reached in the pharmaceutical industry, with industry-supplied studies significantly more likely to find outcomes favorable to the company (Lexchin et al. 2003). Similarly, in research on bisphenol-A, in 95 out of 115 published *in vivo* studies, significant effects were reported, whereas industry-supplied studies did not show significant effects (vom Saal and Hughes 2005). Because of potential or real biases, industry-supplied studies can obscure the real impact of a pesticide, which may result in a sluggish regulatory process most advantageous to manufacturers (Michaels 2008, Rohr and McCoy 2010a).

For these reasons, it is essential to consider that industry-supplied studies suffer from COIs, which must be mitigated. A USEPA risk assessment, however, does not mitigate COIs. In fact, the system in place increases the likelihood that only industry-supplied data will be used in the risk assessments, as we demonstrate below, which potentially obscures the impact of a pesticide so that risks cannot be responsibly managed.

Rigid criteria for the inclusion of studies in risk assessments. Pesticide risk assessments can be constrained to a narrow subset, with the inclusion of few or no studies independent of pesticide manufacturers, because the USEPA has rigid criteria for study inclusion in these risk assessments. For instance, the USEPA's reassessment of atrazine on amphibians was based solely on a single study funded directly by the manufacturer (Kloas et al. 2009), excluding a large body of literature. Such outcomes transpire when most published studies do not meet specific criteria, even when the inclusion of this data would result in different conclusions.

Although the criteria are meant to establish that the data quality is sufficient for regulation and minimizes ambiguities in cause–effect relationships, which are important for regulation and potential litigation, strict criteria can result in basing regulatory decisions on only a handful of studies (as with the assessment of bisphenol-A; Myers et al. 2009). In the 2007 and 2012 USEPA assessments on the effects of atrazine on amphibians (USEPA 2007, 2012), only one of 75 published laboratory studies (Kloas et al. 2009; field studies were evaluated but excluded from consideration) met the USEPA's criteria for *quantitative* assessment (i.e., useful for risk assessment; the test criteria are detailed in USEPA 2012). In this study, Kloas and colleagues (2009) conducted two parallel experiments in different laboratories to examine the effects of atrazine on growth, survival, and reproductive endpoints in African clawed frogs (*Xenopus laevis*) and found that atrazine exposure had no effect on reproductive endpoints and small or no effects on other responses at concentrations from 0.1 to 100 milligrams per liter (mg/L).

The remaining published laboratory studies did not meet all of the USEPA criteria and were categorized as either *invalid* (i.e., not useful for risk assessment) or *qualitative* (i.e., useful for examining whether atrazine has effects but not for determining the concentrations of concern; USEPA 2012). The *invalid* studies failed to meet many basic and appropriate requirements of good experimental design, such as replication, randomization of treatments, the use of proper controls, and pesticide screening (USEPA 2012). The *qualitative* studies failed to meet one or more of many additional criteria (e.g., the use of glass containers, loading densities lower than 1 tadpole per liter, measured pesticide or ammonia concentrations in treatments and controls throughout the study, the use of a flow-through design apparatus; USEPA 2012). Although many of the additional criteria may be ideal, a failure to meet one or more of the criteria does not preclude the determination of cause–effect relationships. Therefore, eliminating such studies from a risk assessment is questionable—a viewpoint that was stressed in the 2007 and 2012 SAP reviews (FIFRA SAP 2007, 2012). When the USEPA develops criteria for a manufacturer's future regulatory studies and then applies them retroactively to the literature, which happened in the reassessment of atrazine (USEPA 2012), it is improbable that many studies will meet all of the criteria—and none did, except for a single industry-supplied study (Kloas et al. 2009). Although numerous studies ranked as *qualitative* demonstrated effects of atrazine at environmental concentrations (USEPA 2012), they did not appear to affect the USEPA's ultimate conclusions that atrazine did not have an effect on amphibians.

The USEPA sacrificed independent replication, the hallmark of the scientific process, for a long list of test criteria, resulting in the use of a single study in evaluating the risk of atrazine to amphibians. Therefore, they are showing greater tolerance of making type II errors (i.e., not finding an effect when one exists) over type I errors (i.e., finding effects when they do not exist), which indicates a lack of adequate

precaution. All studies with sound experimental designs that do not suffer from COIs should be included in risk assessments and decisionmaking.

Inconsistent application of criteria among taxonomic groups. The inconsistent application of standard criteria across taxonomic groups can also be problematic in risk assessments. For instance, to assess the toxicity of atrazine to aquatic plant communities (predominantly phytoplankton), the USEPA (2012) showed that 46 of 73 mesocosm studies met their acceptance criteria. Despite a similar number of studies in the amphibian and plant community literature before screening, only about 1.3% of the amphibian studies were acceptable after screening. The difference in acceptance rate appears to be related to the specific criteria, which were good experimental design for aquatic plants and additional criteria for amphibians (listed in USEPA 2012; examples above). Although species-specific differences may increase the relative importance of some criteria over others, there appears to be a lack of consistency in the application of criteria among taxonomic groups, which can further increase the public and scientific suspicion of bias.

The expectation of a uniform response among lab strains, populations, or species. Assessing pesticide effects is a challenge, because organisms vary in their responses to stressors. In some cases, the USEPA appears to have an expectation of a uniform response among populations or species. For instance, the USEPA (2012) concluded there were insufficient data to confirm or reject the hypothesis that atrazine affected gonadal development in amphibians "because of the inconsistency and lack of reproducibility across studies and uncertainties in the nature of any dose–response relationship in the current data."

Ecological studies have taught us that individuals, populations, and species differ in their responses to natural and environmental variables, including pH, predators, competitors, and environmental contaminants (for a review, see Duellman and Trueb 1994, Sparling et al. 2010, Hammond et al. 2012). Even laboratory-reared animals (or, perhaps, *especially* laboratory-reared animals) can vary in their responses, because different laboratory strains or lineages can have genetic differences. Variation in the laboratory lineages of African clawed frogs (*X. laevis*) could explain their strong (e.g., Hayes et al. 2002) or weak (e.g., Kloas et al. 2009) responses to atrazine—a hypothesis that could be tested. Because of the inherent variation in living organisms, meaningful regulatory testing necessitates the evaluation of population- and species-level variation. A single species or population is unlikely to reveal a single answer for an entire taxonomic group.

Although the available studies indicate that atrazine can act as an endocrine-disrupting chemical by influencing the reproductive development and mating behavior of some species of amphibians and fish and through other effects (Hayes et al. 2011, Rohr and McCoy 2010b), the concentrations that will cause biologically significant impacts in the field are not clear, and this is the crucial information the USEPA needs to make a valid assessment of atrazine's impacts on nontarget organisms, including humans.

The importance of ecological context. Although the strengths and weakness of laboratory, field, and natural studies have been enumerated by others, examining pesticide effects exclusively in the laboratory is problematic and can lead to incomplete conclusions. Laboratory studies offer opportunities to control environmental conditions but suffer from inherent limitations in external validity and generalizability; therefore, they must be complemented by relevant field studies. Organisms exist in food webs, and if a pesticide influences the food web or an organism's response to it, its impacts can be profound but are often not detectable in the laboratory. However, the tiered approach used by the USEPA is based on the assumption that field effects will be weaker than those found in the laboratory; therefore, if effects are not detected in the laboratory, field studies are not necessary. However, this assumption is not necessarily accurate (e.g., Relyea and Diecks 2008).

There are many studies that demonstrate the value of field studies in risk assessments. For instance, in a field study, Rohr and colleagues (2008) found that atrazine and one of its metabolites accounted for a significant portion of the variation in larval trematode abundance in natural populations of the northern leopard frog (*Lithobates* [formerly *Rana*] *pipiens*) from ponds in Minnesota. On the basis of the field results, Rohr and colleagues (2008) then conducted a mesocosm study to experimentally test how atrazine affected the infection load of amphibians. Atrazine exposure led to an increased parasite load in tadpoles both directly, by suppressing the amphibians' immune function, and indirectly, by stimulating snail population growth (the intermediate hosts of trematodes), which supported patterns observed in the field. Comparing animals exposed to atrazine with controls under more natural conditions allows for the determination of cause–effect relationships and clarifies the importance of the food web in driving responses—links that could be easily missed or underestimated in laboratory studies.

Addressing the recommendations of SAPs. SAPs were created to offer a scientific assessment of the USEPA's risk assessment evaluation, as well as advice on whether more studies are needed to determine that risk. However, the USEPA does not have to accept a panel's advice or to clarify explicitly why the advice was accepted or rejected. Three SAPs (FIFRA SAP 2003, 2007, 2012) were brought together specifically to evaluate the USEPA's assessment of the effects of atrazine on amphibians, and each panel offered similar advice, such as including data from North American amphibians and field studies to evaluate the potential for atrazine to affect reproductive systems (FIFRA SAP 2003, 2007, 2012). It is unclear how or why the USEPA may elect to ignore the consistent advice of multiple panels.

Solutions for an improved registration and reregistration process

As scientists, we are trained to discern the strengths and weaknesses of any given study, to use a weight-of-evidence approach to reach a conclusion that is up to date, and to be open to changing a given conclusion in light of new information; however, to do this effectively, we have to evaluate the scientific literature and the available data. Formulating a rigid list of criteria that eliminates a large portion of the information and then arriving at a conclusion with one or a handful of studies lacks balance and perspective—the antithesis of evidence-based science and policy. The risk assessment of the impacts of atrazine on amphibians demonstrates that adhering to rigid criteria can seriously limit perspective, that industry-funded research may be the only source of data used to make decisions regarding the impacts on a given taxonomic group, and that outside input from the scientific community through SAPs may have little impact on the data collected or the standards applied. As a result, the agency responsible for pesticide regulation in the United States cannot fully realize its mandate to protect human health and the environment. We, the authors, do not have a personal investment in decisions regarding the use and regulation of any particular pesticide, including atrazine, but the risk assessment process can and should be improved so that decisions are made with the best available data with an evidence-based approach. We offer four measures to improve the reliability of this process.

(1) Eliminate the use of studies with COIs and separate industry influence from research. Although manufacturers who directly profit from chemical sales should continue to bear the costs of testing, this can be accomplished without COIs by an independent party with no potential for financial gain from the outcome and with no direct ties to the manufacturer. Such a change would minimize the potential for industry's influence on science and would restore confidence in the USEPA's review process. The National Fish and Wildlife Foundation is a nonprofit created by the US Congress that acts as a neutral third party to distribute grants for specific regulatory issues. This model is being used to evaluate the impacts of the *Deepwater Horizon* oil spill, with research funding from BP being filtered through the independent Gulf of Mexico Research Initiative. Through a third-party wall, the essential separation between the manufacturer and the research can be achieved, thus mitigating COIs. At a minimum, reassessments could evaluate all of the available literature, while considering how or whether the inclusion of data from the manufacturer affects the conclusions drawn.

(2) Weight-of-evidence approaches using the available research. Rohr and McCoy (2010b) used a range of studies to evaluate whether there was enough weight of evidence supporting the hypothesis that atrazine affects specific endpoints for amphibians. Using a qualitative meta-analysis, they examined the effects of atrazine across numerous amphibian and fish species in more than 125 studies and concluded that atrazine can alter the timing of metamorphosis, reduce the size at metamorphosis, alter antipredator behaviors, reduce immune function, increase infection, alter gonadal morphology, and affect gonadal function. They also compared their analysis based on studies that met their study criteria with an analysis including all of the studies and reached similar conclusions; in this way, Rohr and McCoy (2010b) were able to evaluate whether and how their conclusions would be altered by their design criteria, something the USEPA or an industry-supplied analysis (Solomon et al. 2008) has not done. However, despite many studies' showing significant effects of atrazine, the USEPA concluded that 0.1 to 100 mg/L of atrazine "does not consistently affect amphibian gonadal development" of *X. laevis* and that "no further testing was needed" on amphibians (USEPA 2012, p. 9, 62). Such a conclusion indicates that studies judged to be of qualitative value did not influence the USEPA's conclusion. An approach similar to that of Rohr and McCoy (2010b) allows for the evaluation of how one's conclusions are affected by criteria for study inclusion, which can then be compared and assessed, and also permits general conclusions to be made regarding the potential for effects of a pesticide and areas in which more information is needed. Such methodologies would be superior to the current process.

(3) Include both laboratory and field studies in regulatory decisions. Predicting impacts in nature from laboratory studies is difficult without incorporating natural factors into experimental designs, which often necessitates conducting studies in outdoor mesocosms or in the field to gain insights. Because the USEPA (2012) used only a single study, in which no effect of atrazine was found on amphibians, in its risk assessment, it did not find sufficient justification to move to field testing (although it likely would have if it had used a greater portion of the available research). Although the value of industry-supplied field studies is questionable because of COIs, there are published field studies that were excluded from consideration and that suggest important consequences from environmental exposure to atrazine. For instance, Rohr and colleagues (2008) linked atrazine exposure to variation in larval trematode abundance in northern leopard frogs in the field, which was supported by an experimental mesocosm study that provided a mechanism for that variation. Furthermore, Hayes and colleagues (2003) found hermaphroditic northern leopard frogs in areas where atrazine was detected in the water, which matched the responses observed in controlled laboratory experiments. Pairing mechanistic mesocosm or laboratory studies with observations from the field offers powerful insights to the potential effects of a given pesticide on natural populations, which are the target for protection in regulatory risk assessment.

(4) Explicitly addressing a SAP's recommendations. Although similar advice was given to the USEPA by multiple SAPs (FIFRA SAP 2003, 2007, 2012) regarding the inclusion of data on

North American amphibians, the use of field studies, and the insufficiency of basing a conclusion on a single study, the USEPA has failed to act on SAPs' past advice, and the reason remains unclear. When researchers submit grant revisions to funding agencies or revised manuscripts to journals, it is not required that the researchers accept all of the advice, but they must detail the suggestions that were accepted or rejected. The risk assessment process could benefit from similar transparency.

Conclusions

The presumption of innocence until guilt is proven (i.e., of no effect until one is proven) weighs heavily on the US regulatory system when precaution may be more appropriate. The current regulatory system in the United States cannot embrace precaution when it primarily uses industry-supplied and -funded data to draw its conclusions. Furthermore, it is more difficult to assess the innocence or guilt—or the degree of guilt—of a pesticide when most of the data are eliminated from review. Atrazine serves as a case in point. Although the USEPA evaluated 75 laboratory studies in the assessment of the effects of atrazine on amphibians, none of the data labeled *qualitative* had an influence on their ultimate conclusion, which led the USEPA to state that "Based on previous analyses of the available ecotoxicity data, USEPA (2012) concluded for atrazine that the level of concern for effects on aquatic plant communities… was lower than the atrazine concentrations observed to produce significant direct or indirect effects on invertebrates, fish, and amphibians" (p. 97), with an apparent attempt to remove the need for future studies or assessments on amphibians. The scientific literature indicates that atrazine can have an impact at environmentally relevant concentrations on the growth, immunity, and reproductive development and behaviors of some species. It is time for the USEPA to lead an effort to determine the pervasiveness of these effects and the concentrations of concern so that meaningful management and regulatory decisions can be made.

Carson (1962) wrote, "As man proceeds toward his announced goal of the conquest of nature, he has written a depressing record of destruction, directed not only against the Earth he inhabits but against the life that shares it with him" (p. 85). The USEPA was established, in part, to stem the tide of this destruction. However, when the risk assessment process is fraught with problems that impede appropriate evaluation of the available data, the USEPA places human health and the environment at the mercy of industry. In principle, the necessary changes to improve the regulatory process are simple and start with removing the overwhelming influence of industry. In practice, such changes will be difficult and will likely require legislative action, because industry will be reluctant to relinquish its influence. Risk assessments should be made on the basis of a sound body of research, and decisions should be made with precaution and objectivity regarding the risks and benefits of a pesticide's use. The USEPA's assessment of the effects of atrazine on amphibians demonstrates that this is not always the case.

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