

March 21, 2014

Lauren Zeise, Ph.D.  
Deputy Director  
Office of Environmental Health Hazard Assessment  
1001 I Street  
Sacramento, California 95814

**Re:** *Notice of Intent to List Chlorotriazines as Reproductive Toxicants  
for Purposes of Proposition 65*

Dear Dr. Zeise:

This responds to a Notice of Intent to List (NOIL or Notice) atrazine, simazine, propazine and certain of their chlorometabolites (triazine compounds) as developmental and reproductive toxicants for purposes of Proposition 65, issued by OEHHA on February 7, 2014. According to the Notice, OEHHA has concluded that the United States Environmental Protection Agency (EPA), an authoritative body for purposes of Proposition 65, has “formally identified” these compounds as causing developmental and reproductive toxicity. The basis for this conclusion is several statements in certain EPA documents dated from 2002 to 2006, quoted in the NOIL. As explained below, I do not believe EPA has concluded that these compounds cause developmental or reproductive effects in humans. Rather, EPA scientists have taken certain dose-related effects noted in laboratory animal studies into account in developing precautionary and protective risk assessments for these pesticide active ingredients.

To provide context for my comments, I will provide a brief history of my professional background and experience. From 2007 to 2010 I was the Director of the Office of Pesticide Programs (OPP) at EPA. In that role, I supervised over 800 employees within Divisions with responsibility for assessing human and ecological risks and for making risk management decisions related to pesticide product registration, reregistration and compliance with the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) as well as the Federal Food, Drug and Cosmetic Act (FFDCA), both of which were amended in 1996 by the Food Quality Protection Act (FQPA).

I joined EPA’s Office of Pesticide Programs in 1985 and was employed there for over 24 years, where I held several other senior level management and executive positions, including Director of the Risk Characterization and Analysis Branch, Associate Director of the Health Effects Division, Associate Director of the Antimicrobial Division, Director of the Registration Division and Director of the Special Review and Reregistration Division. Thus, I believe I am well-qualified to speak with authority on the subject of how EPA approaches the evaluation and regulation of pesticides.

As the basis for the opinions expressed in this letter, I have reviewed the NOIL and the EPA statements and documents referred to in the NOIL. I also have reviewed pertinent portions of the Proposition 65 regulations at Title 27 of the California Code of Regulations, in particular Section 25306, which provides for listing chemicals as

reproductive toxicants on the basis of their “formal identification” by authoritative bodies, such as EPA.

In the NOIL, OEHHA lists a number of OPP documents dated 2002 to 2006 that relate to tolerance reassessment and reregistration of the triazine compounds. OEHHA quotes statements from these documents, describing adverse reproductive and developmental effects observed in animals dosed with triazines, and notes that EPA has calculated reference doses on the basis of the animal studies in which these effects were observed. OEHHA appears to conclude from these statements and the fact that EPA calculated reference doses based on these observations that EPA “formally identified” the triazines as causing developmental and reproductive toxicity in humans.

OEHHA’s conclusion that EPA has identified triazine pesticides as causing developmental and reproductive toxicity in humans is inaccurate and appears to be based on a fundamental misunderstanding of EPA/OPP’s role and approach to the regulation of pesticides. To explain, EPA does not follow a strictly hazard-based approach to regulation, but rather uses the National Research Council’s four-step *risk assessment* process, as follows:

- **Step 1 - Hazard Identification**  
Examination as to whether a substance has the *potential* to cause harm to humans and/or ecological systems and, if so, under what circumstances.
- **Step 2 - Dose Response Assessment**  
Examination of the numerical relationship between exposure and effects.
- **Step 3 - Exposure Assessment**  
Examination of what is known about the frequency, timing, and levels of contact with a substance.
- **Step 4 - Risk Characterization**  
Examination of how well the data support conclusions about the nature and extent of the risk from exposure to pesticides.

EPA’s approach to risk assessment is highly protective. In fact, I can think of virtually no currently EPA-registered pesticide product for which it can be said that harm to humans is expected to occur. Simply put, EPA’s routine risk assessment and regulatory process is intended to preclude any such outcome by extrapolating from levels and routes of exposure where adverse effects were observed in animals and restricting conditions of use by law to levels where exposure to humans will be far lower, *i.e.*, orders of magnitude lower, than the levels to which the test animals were dosed. Thus, barring gross negligence or illegal use, no harm to humans should occur.

It is important to emphasize that the first step of EPA’s four-step risk assessment process is *not* the equivalent of the “hazard identification” process contemplated by Proposition 65. The Prop 65 hazard identification process is focused on reaching a conclusion whether the chemical in question is “known,” or “clearly shown” to cause cancer or reproductive harm in humans, based on the weight of all available scientific evidence. Chemicals that meet that standard are published on a list as “known” to cause

the harm in question. Where such a potential listing is based solely on animal data, the animal data are to be carefully scrutinized to determine whether the effects seen in animals are sufficient evidence to conclude that the chemical would cause the same effects in humans. The factors to be considered in scrutinizing the animal data are summarized in Title 27 CCR Section 25306(g), which, I understand from reviewing the “Statement of Reasons” explaining the intent of the regulations, is intended to ensure that chemicals listed by the “authoritative bodies” mechanism meet the same standards of sufficiency of evidence that are applied by the “state’s qualified experts” when they review chemicals for potential listing.

The “hazard identification” step of the EPA risk assessment process, as the first of four steps in risk assessment, is not intended to involve such a careful weighing of the animal data to determine whether the data support “listing” or “formally identifying” a chemical as causing reproductive harm in humans. It simply identifies adverse effects, observed in laboratory animals, which may have the *potential* to cause harm in humans and for which the risk of harm is to be assessed and mitigated by regulatory measures. In step two, EPA scientists examine the relationships between dosing levels, *i.e.*, exposure, and adverse effects observed. EPA then applies additional uncertainty factors to appropriately selected “No Observable Adverse Effects Levels” (NOAELs) in establishing benchmark values for risk assessment purposes. These uncertainty factors, intended to account protectively for potential increased sensitivity in humans and/or within a population, generally yield “acceptable” exposure values that are 2-3 orders of magnitude lower than the NOAELs selected for use in assessing risk. Step 3 then involves estimation of potential high-end, real-world exposures to the chemical for comparison to the acceptable levels identified in step 2. A characterization of risk then occurs in step 4, taking into account a number of factors including data quality, uncertainties, populations exposed, etc.

The objective of this entire process is to ensure that humans will experience *no harm* from use of the chemical. That end result of the four-step process, protection of humans based on multiple conservative assumptions, is EPA’s focus.

My review of the EPA documents OEHHA has cited in the NOIL shows that they are consistent with the foregoing general discussion. The documents contain various statements indicating that the effects have been observed in animals, and that EPA is regulating the triazines on the basis of such effects on the assumption that similar effects in humans are possible. The documents nowhere state that EPA has concluded that the triazines *will* cause such effects in humans, only that EPA believes such effects are *possible* and as long as the possibility exists, EPA will ensure that human exposures are below the levels at which adverse effects are even possible. In taking such a conservative, protective approach, EPA has not “formally identified” the triazines as reproductive toxicants.

The EPA documents cited by OEHHA all were generated in the course of EPA’s reregistration and tolerance reassessment programs, which were mandated by the FQPA in 1996 and essentially completed in 2006. The passages quoted from these EPA documents are taken out of context, as they relate solely to the first step of EPA’s risk assessment process (Step 1) and are simply consistent with the fact that EPA considers

and evaluates pesticides and candidate pesticides for all *potential* adverse effects observed at doses tested in animal studies. It is a virtual truism that adverse effects will be observed in these studies, because EPA test guidelines specify that dosing regimens must elicit an adverse effect (or a “limit dose,” in the absence of achieving a maximum tolerated dose). Thus, when adverse effects are observed, EPA does not then conclude that exposure to the chemical will “cause” adverse effects in humans, but rather completes the remaining steps of the routine risk assessment process and regulates accordingly to avoid any adverse effects or “harm.” In the case at hand, to my knowledge, EPA has never stated that it expects reproductive or developmental effects to occur in humans under actual conditions of legal sale and use of triazine pesticide products.

In 2006, EPA completed decision-making processes for reassessing tolerance and reregistration decisions for all of the triazine pesticide active ingredients, based upon safety standards under both FIFRA and the FQPA. The FQPA is indisputably one of the most protective/precautionary environmental statutes in existence. The standard for safety is “reasonable certainty of no harm” and, in effect, does not even include a provision for balancing risks against benefits, as does FIFRA. In 2006, EPA concluded that for purposes of the FQPA, taking into account the estimated cumulative exposures of *all* triazine pesticides through diet, drinking water and any residential use, there existed a reasonable certainty of *no harm*.

In my opinion, EPA/OPP’s scientifically rigorous and highly protective risk-based approach to regulating pesticides runs counter to the simplistic approach of labeling chemicals as “known to cause cancer” or “known to cause reproductive toxicity” under Proposition 65. The two approaches are so dissimilar that it is inappropriate to use isolated statements from evaluations of animal studies in the absence of a firmly stated conclusion, as the basis for designating a chemical as a reproductive toxicant for purposes of Proposition 65.

Finally, I believe there is a compelling policy reason why EPA’s statements and actions in 2006 should not be used as the basis for an “authoritative body” listing. Though a comprehensive reevaluation process for the triazines was concluded successfully in 2006, EPA has recently initiated its “Registration Review” process for the triazines. Registration Review is EPA’s newest reevaluation program for pesticides and requires periodic reevaluation of the risks and risk management needs associated with all pesticide products. The legal mandate is for reevaluation at least every 15 years. For example, in December of 2013, EPA published its Final Work Plan for the Registration Review of atrazine. This work plan indicates that EPA intends to fully *re*assess the human and ecological risks associated with *all* uses of these chemicals as active ingredients pesticides and will make those risk assessments available for public comment as early as June of 2015, *i.e.*, little more than one year from now.

This comprehensive reevaluation of the triazines, currently ongoing, also provides a compelling reason not to pursue any determination of whether these chemicals should be listed as reproductive toxicants for purposes of Proposition 65, on the basis of evaluations conducted in 2006. In my view, it would be highly prudent to carefully consider EPA’s more recent risk assessments, based in current science, prior to assuming

any “known” or “causal” relationship between human exposure to triazines and reproductive or developmental effects. If EPA’s new risk assessments indicate *any* concern whatsoever that these compounds might result in adverse effects in humans, the Agency will certainly require changes in the registered use patterns to preclude that possibility.

Sincerely yours,

A handwritten signature in cursive script that reads "Debra Edwards". The signature is written in black ink and is positioned to the right of the typed name.

Debra Edwards, Ph.D.  
Pesticide Regulatory Consultant  
Former Director, Office of Pesticide Programs/EPA