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Lauren Zeise, Ph.D.
Deputy Director
Office of Environmental Health Hazard Assessment (OEHHA)
1001 I Street
Sacramento CA
95812-4010

Re: Comments of Gary Burin, Ph.D., MPH, DABT in Opposition to Potential Listing of Atrazine as a Reproductive or Developmental Toxicant under Proposition 65's Authoritative Body Listing Mechanism

Dear Dr. Zeise,

OEHHA proposes to list atrazine as a developmental and reproductive toxicant because it concludes that the US Environmental Protection Agency (US EPA), an authoritative body for purposes of Proposition 65, has formally identified atrazine as causing reproductive toxicity under the California Code of Regulations Title 27, Section 25306(d). There are compelling reasons why this listing should not occur at the present time and I discuss these reasons below.

By way of background I am familiar with the US Environmental Protection Agency evaluation of reproductive and developmental toxicity because I worked at the US EPA for 13 years and during my employment I served as the Chairman of the Developmental and Reproductive Toxicity Peer Review Committee for the US EPA Office of Pesticide Programs. I also served as a member of the US EPA working groups that authored the 1991 Guidelines for Developmental Toxicity Risk Assessment (Federal Register 56(234): 63798-63826) and the 1996 Guidelines for Reproductive Toxicity Risk Assessment (Federal Register 61(212): 56274-56322).

First, it should be recognized that the US EPA Office of Pesticide Programs does not formally identify a chemical as a developmental or reproductive toxicant. Many natural and synthetic chemicals induce manifestations of developmental or reproductive toxicity at sufficiently high dose levels in sensitive species of laboratory animals and test guidelines for developmental and reproductive toxicity require that the highest dose level induce toxicity (or that the chemical be tested at a limit dose of 1,000 mg/kg/day). Recognizing this, the US EPA guidelines require the US EPA to identify the most sensitive endpoints of developmental or reproductive toxicity to compare the dose-response patterns for the endpoints with the expected human exposure to determine the acceptability of these exposures. Neither of these EPA guidelines contains a definition for “developmental toxicant” or “reproductive toxicant” because such classification of chemicals is discouraged by the EPA guidelines and is unnecessary in the risk assessment process used by the US EPA.

The 2002-2006 statements regarding atrazine cited by OEHHA in the Notice of Intent to List are consistent with these EPA guidelines. The EPA notes reproductive and developmental effects that were observed under certain conditions in laboratory animals but the Agency does not go so far as to classify the pesticide as a developmental or reproductive toxicant. This distinction follows the admonition of the US EPA developmental toxicity guidelines: “Judging that the health-related database is sufficient to indicate a potential developmental hazard does not mean that the agent will be a hazard at every exposure level (because the assumption of a threshold) or in every situation (e.g., hazard may vary significantly depending on the route and timing of exposure).” (emphasis added). The US EPA Office of Pesticide Programs evaluations of developmental and reproductive toxicity data therefore must be used with caution for purposes of Proposition 65.

The second reason that atrazine should not be identified as a developmental or reproductive toxicant under Proposition 65 is that the EPA position documents that are cited as the basis for the authoritative body determination are outdated and no longer reflect the knowledge that is available regarding the reproductive and developmental toxicity of atrazine. Of critical importance is recent research which casts doubt upon the human relevance of atrazine-associated perturbations of the hypothalamic-pituitary ovarian axis in rats. The route of administration for the atrazine studies showing the suppression of the Luteinizing Hormone (LH) surge is bolus dosing by oral gavage. This dosing method results in artificially high atrazine plasma concentrations (C_{max}) which have been demonstrated to result in developmental and reproductive effects that are not observed using more relevant dosing methods.¹ It is clear that the C_{max} rather than Area Under the Curve (AUC) is critical in the case of an effect such as the suppression of the LH surge following the dosing of rats

¹ See Coder et al., (2011). Atrazine: An oral (gavage and dietary) study of the effects of atrazine on the spontaneous luteinizing hormone surge in female Sprague-Dawley rats. WIL Laboratories, April 7, 2011.

with atrazine. 27 CCR Section 25306(G) requires OEHHA to determine whether animal studies cited by the authoritative body constitute sufficient evidence taking into account a number of factors including the route of administration. It appears that recent research shows that the bolus route of administration in the studies supporting a listing is less relevant than dietary administration studies which show no evidence of developmental or reproductive toxicity.

Finally, consideration should be given to the fact that the authoritative body for atrazine, the US EPA, is actively re-evaluating this herbicide and their conclusions regarding the developmental and reproductive toxicity of atrazine will be issued in the near future (the Registration Review of atrazine began in mid-2013). The body of knowledge concerning mechanism of action and the human relevance of atrazine-related toxicity has grown significantly since the US EPA evaluated atrazine in the period of 2002 to 2006. In fact, atrazine has since become one of the most thoroughly researched pesticides. The US EPA is carefully reviewing this new evidence and weighing the advice and conclusions of several FIFRA Scientific Advisory Panel meetings that have evaluated new atrazine research. It would be prudent to allow the authoritative body to complete the review which is now taking place before a decision whether to list atrazine as a developmental or reproductive toxicant is made by the State of California.

Sincerely,



Gary Burin, Ph.D., MPH, DABT