



Submitted via E-mail

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RE: Comments on Proposed Maximum Allowable Dosage Levels for Atrazine, Propazine, Simazine, 2, 3-Diamino-6-Chloro-S-Triazine, Des-Ethyl Atrazine, and Des-isopropyl Atrazine

Dear Ms. Vela:

These comments are submitted on behalf of the Center for Biological Diversity (“Center”) and the Center for Environmental Health (“CEH”) (collectively “organizations”). Our organizations support the Office of Environmental Health Hazard Assessment (“OEHHHA”)’s proposal to adopt Maximum Allowable Dose Levels (“MADLs”) for oral exposure to atrazine, propazine, simazine, and their chlorometabolites 2, 3-diamino-6-chloro-s-triazine, des-ethyl atrazine, and des-isopropyl atrazine (collectively “triazines”) under the Safe Drinking Water and Toxic Enforcement Act of 1986 (“Prop 65”).

However, the proposed 100 micrograms per day MADLs for triazines is based on an outdated scientific study that does not adequately reflect the findings of newer studies of comparable or better quality. We therefore request that OEHHHA revise the triazine MADLs to no higher than 8 micrograms per day and recommend a level of 0.06 micrograms per day, the level indicated by the best available science.¹

¹ Cal. Health & Safety Code Sec. 25249.5 *et seq.*; see *People ex. rel. Lungren v. Super. Ct.* (American Standard, Inc.), 14 Cal. 4th 294, 307, 314 (1996) (Cal. Supreme Court upholds that the protective purposes of Prop 65 are to be broadly construed).

Our organizations are deeply committed to protecting environmental and community health. The Center for Biological Diversity is a non-profit environmental organization dedicated to the protection of native species and their habitats through science, policy, and law. The Center has over 900,000 members and e-activists throughout the United States, including over 120,000 supporters in California. The Center has worked for many years to reduce pesticide threats to humans, endangered species, and other wildlife.

The Center for Environmental Health protects people from toxic chemicals by working with communities, businesses, and the government to demand and support business practices that are safe for human health and the environment. CEH has been closely involved with Prop 65 enforcement and implementation for the last two decades. CEH has 20,000 supporters nationwide.

I. OVERVIEW

First registered in 1958, atrazine is the second most widely used pesticide in the United States.² Each year, 70-80 million pounds of atrazine is sprayed for weed control nationwide.³ Propazine, simazine, and other triazines are also highly potent and frequently applied herbicides.⁴

Atrazine is the most common herbicide found in surface water in the U.S. and is frequently found in groundwater supplies.⁵ Eighty percent of water samples taken from 153 drinking water systems across the U.S. Midwest and South were contaminated with atrazine, and 44 percent of these systems had levels exceeding EPA recommended concentrations of 3 parts per billion (“ppb”), or 0.003 milligrams per liter (“mg/L”), which is still above the baseline level noted to cause harm in organisms.⁶ Not surprisingly, atrazine and simazine are also listed as groundwater pollutants in California.⁷ Long term exposure to drinking water containing atrazine beyond the maximum contamination level of 3 ppb could damage cardiovascular and reproductive systems.⁸ In addition, long term exposure to drinking water containing simazine beyond 4

² EPA. *Pesticide Industry Sales and Usage: 2006 and 2007 Market Estimates*. U.S. Environmental Protection Agency, February 2011. . 2011; Available from: http://www.panna.org/sites/default/files/EPA%20market_estimates2007.pdf.

³ *Id.*

⁴ U.S. Env'tl. Prot. Agency. Propazine: Revised HED Risk Assessment for the Tolerance Reassessment Eligibility Decision Document (“TRED”) which includes a New Use on Grain Sorghum. Dec. 13, 2005. p.4.

⁵ Gilliom, R., et al., *The Quality of Our Nation's Waters: Pesticides in the Nation's Streams and Ground Water, 1992–2001*. US Geological Survey Circular 1291, 2007.

⁶ Wu, M., et al., *Still Poisoning the Well Atrazine Continues to Contaminate Surface Water and Drinking Water in the United States*. National Resources Defense Council, 2010.

⁷ Cal. Code Regs. Tit. 3, Div. 6, Ch.4, Subchapt. 1, Art. 1, Sec. 6800(a).

⁸ U.S. Env'tl. Prot. Agency. Table of Regulated Drinking Water Contaminants. Accessed 12/11/2015 Available at <http://www.epa.gov/your-drinking-water/table-regulated-drinking-water-contaminants>.

ppb or 0.004 mg/L could result in blood problems.⁹ The long term and widespread use of atrazine and other triazines is a significant threat to people as well as terrestrial and aquatic ecosystems and organisms.

Atrazine has been banned in the European Union for over a decade in order to reduce its contamination of groundwater sources.¹⁰ This ban has led to significant decreases of atrazine concentrations in parts of the Northern Aegean Sea.¹¹ In the United States, atrazine is regulated by the EPA and was last re-registered in 2006.¹² Due to a significant new body of scientific information documenting the pervasive presence and impacts of atrazine, the EPA began re-evaluating the registration in mid-2013.¹³ In 2013, the Center joined 250 groups in requesting that EPA ban atrazine.¹⁴ As a result of the Center's lawsuit challenging EPA's failure to consider the impacts of pesticides on endangered species, the agency will formally consult with the U.S. Fish and Wildlife Service on the impacts of atrazine, propazine, and simazine on over 1,500 endangered plants and animals nationwide.¹⁵

As a leader in environmental and public health protection, California has undergone a recent paradigm shift in the management of toxic chemicals. Now over 30 years old, Prop 65 has been applied to afford broad protections for the public from toxic chemical contamination.¹⁶ In 2007, the California EPA and other agencies established the California Green Chemistry Initiative to stimulate the design, use, and disposal of "green" or less hazardous chemical substances.¹⁷ In 2013, the Safer Consumer Products regulations were passed that require manufacturers or other responsible parties to seek

⁹ U.S. Env'tl. Prot. Agency. Table of Regulated Drinking Water Contaminants. Accessed 12/11/2015 Available at <http://www.epa.gov/your-drinking-water/table-regulated-drinking-water-contaminants>.

¹⁰ European Commission ("EC"). 2004/248/EC: Commission Decision of 10 March 2004 concerning the non-inclusion of atrazine in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing this active substance (Text with EEA relevance) (notified under document number C(2004) 731). Available at: <http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:32004D0248>.

¹¹ Nödler, K et al., *Twenty years later--atrazine concentrations in selected coastal waters of the Mediterranean and the Baltic Sea*. Mar Pollut Bull. 2013 May 15;70(1-2):112-8.

¹² U.S. Env'tl. Prot. Agency. Memorandum. Atrazine: Finalization of Interim Reregistration Eligibility Decision and Completion of Tolerance Reassessment and Reregistration Eligibility Process. 2006. Available at: http://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_PC-080803_1-Apr-06.pdf.

¹³ U.S. Env'tl. Prot. Agency. Atrazine Registration Review. Regulations.gov docket # EPA-HQ-OPP-2013-0266. Available at: <http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2013-0266>.

¹⁴ Letter Requesting U.S. Environmental Protection Agency to Ban Atrazine. Aug. 26, 2013. Available at: http://www.biologicaldiversity.org/campaigns/pesticides_reduction/pdfs/Atrazine_Sign_On_Letter_8_26_2013.pdf.

¹⁵ Settlement: EPA to Analyze Impacts of World's Two Most Widely Used Pesticides on 1,500 Endangered Species. Available at: http://www.biologicaldiversity.org/news/press_releases/2015/pesticides-06-23-2015.html.

¹⁶ People ex. rel. Lungren v. Super. Ct. (American Standard, Inc.) (1996) 14 Cal. 4th 294, 307, 314 (Cal. Supreme Court upholds that the protective purposes of Prop 65 are to be broadly construed.) .

¹⁷ State of California, California EPA. California Green Chemistry Initiative Final Report. Dec. 2008. Available at: http://www.sehn.org/pdf/GREEN_Chem.pdf.

safer alternatives to harmful chemical ingredients in widely used products.¹⁸ Once they are listed under Prop 65, the six triazines discussed in this letter will automatically become candidate chemicals and potentially be selected for the alternative assessment process.¹⁹ There is clear public and political momentum toward stricter regulatory standards for chemicals in general as well as for triazines, for which scientific evidence confirming their toxic effects has rapidly expanded over the past several years. We strongly urge OEHHA to uphold its statutory purpose to protect humans from the harmful impacts of triazines and lower the MADLs to no higher than 8 micrograms per day with a recommended level of 0.06 micrograms per day.

II. OEHHA'S PROPOSED MADLs RELY ON FLAWED STUDIES

The EPA used multiple lines of evidence to identify triazines as reproductive toxicants, which ultimately led OEHHA to list these chemicals under the “authoritative bodies” mechanism of Prop 65. OEHHA has identified the 1996 Morseth study²⁰ as the most sensitive study of sufficient quality to guide the suggested MADLs. We disagree with this assertion.

First, this study was funded by Ciba-Crop Protection, the original registrant of atrazine and the major manufacturer of atrazine at the time. This is an enormous conflict of interest. Scientists, and particularly regulatory bodies, must take conflicts of interest very seriously because they can lead to bias and, ultimately, misleading results. Just because a study adheres to good laboratory practice (GLP) guidelines does not necessarily make it of high scientific quality. GLP guidelines were designed to prevent fraud, not bias, and there is no way to prevent bias without removing potential conflicts of interest.

Second, this study was never published and did not undergo peer review. Peer review by experts in the field is an essential part of the scientific process and ensures that experiments were conducted properly and that data were interpreted correctly. The fact that U.S. government regulations are based, in part, on an industry-funded, unpublished study that is nearly 20 years old is of great cause for concern. This study is so outdated that an online version is not even available and the organizations had to pay \$250 to obtain it via a public records request from OEHHA. California can, and must, do better.

We have identified four studies in the primary literature that are of high scientific quality and demonstrate reproductive toxicities in female mammals at much lower doses

¹⁸ Safe Consumer Products regulations were enacted pursuant to Health and Safety Code Sections 25252 & 25253. *See* Final Statement of Reasons Safe Consumer Products. Sec. 2. Available at: <https://www.dtsc.ca.gov/LawsRegsPolicies/Regs/upload/Final-Statement-of-Reasons-corrected-Table-of-Contents.pdf>.

¹⁹ 22 C.F.R. Div. 4.5 Ch. 55 Sec. 69502.2(a)(1)(A); Cal. Dept. of Toxic Substances Control. Safer Consumer Products. Authoritative Lists. Available at: <http://www.dtsc.ca.gov/SCP/SourceLists.cfm>.

²⁰ Morseth, SL. 1996. EVALUATION OF THE LUTEINIZING HORMONE (LH) SURGE IN ATRAZINE-EXPOSED FEMALE SPRAGUE-DAWLEY RATS - 6-MONTH REPORT. Unpublished study submitted to the U.S. EPA by Ciba Crop Protection.

than the Morseth study. These studies are listed in section III below. Of note, the authors declared no competing interests in all four studies and each went through the peer review process. Therefore, these studies were held to a more rigorous scientific standard and, we believe, should supersede the Morseth study in guiding the MADLs for triazines.

III. OEHHA MUST CONSIDER ALL AVAILABLE SCIENCE THAT DEMONSTRATES LOWER MADLs ARE NECESSARY TO PROTECT HUMAN AND ENVIRONMENTAL HEALTH

OEHHA should have, but did not, consider all available science that provide “evidence and standards of comparable scientific validity” for determining the No Observable Effect Level (NOEL). Since Sec. 25803(a)(1) states that “[o]nly studies producing the reproductive effect which provides the basis for the determination that a chemical is known to the state to cause reproductive toxicity shall be utilized for the determination of the NOEL,” we limited our own search to studies that show reproductive, endocrine effects in female mammals.

We have identified four important studies demonstrating that low-level exposure to atrazine causes reproductive, endocrine effects in mammals. All four studies show Lowest Observable Adverse Effect Levels (LOAELs) below the NOEL currently being considered by the OEHHA. These studies are as follows:

1. Enoch, R.R., et al., Mammary gland development as a sensitive end point after acute prenatal exposure to an atrazine metabolite mixture in female Long-Evans rats. *Environ Health Perspect*, 2007. 115(4): p. 541-7.
 - * No NOEL identified.
 - * LOAEL = .09 mg/kg of body weight per day.
 - * Endpoint - delayed mammary gland development.
 - * Test material - atrazine plus metabolites.
2. Giusi, G., et al., The endocrine disruptor atrazine accounts for a dimorphic somatostatinergic neuronal expression pattern in mice. *Toxicol Sci*, 2006. 89(1): p. 257-64.
 - * NOEL = .001 mg/kg of body weight per day.
 - * LOAEL = 0.1 mg/kg of body weight per day.
 - * Endpoint - gender specific neuronal damage.
 - * Test material - atrazine.
3. Lin, Z., et al., Gestational and lactational exposure to atrazine via the drinking water causes specific behavioral deficits and selectively alters monoaminergic systems in C57BL/6 mouse dams, juvenile and adult offspring. *Toxicol Sci*, 2014. 141(1): p. 90-102.
 - * No NOEL identified.
 - * LOAEL = 1.4 mg/kg of body weight per day.
 - * Endpoint - decreased cognitive ability and altered neurotransmitter levels.

* Test material - atrazine.

4. Gojmerac, T., et al., Reproductive disturbance caused by an S-triazine herbicide in pigs. *Acta Vet Hung*, 1999. 47(1): p. 129-35.

* No NOEL identified.

* LOAEL = 1.0 mg/kg of body weight per day.

* Endpoint - decreased pre-estrus estradiol levels.

* Test material - atrazine.

All of these studies meet high standards of scientific quality and have been published in respected peer-reviewed journals. They meet the standards identified in Sec. 25803(a)(4). One of these studies, in particular, is superior to the Morseth study because "...the degree to which dosing resembles the expected manner of human exposure" (Sec. 25803(a)(4)) is much more relevant to actual exposure scenarios. Unlike the Morseth study, Enoch et al. measured exposure to a mixture of atrazine and its environmentally relevant metabolites hydroxyatrazine, diaminochlorotriazine, deisopropylatrazine, and deethyl-atrazine (three of which are grouped with atrazine for the proposed MADLs). In a real world scenario, exposure to a single chemical is highly unlikely without coming into contact with its degradates at the same time. The ratio of atrazine and its metabolites in the Enoch et al. study was proportional to levels that have been observed in surface water by multiple groups, indicating that this is a more accurate exposure scenario than atrazine alone.²¹

In addition, the NOELs and LOAELs in the above studies showing reproductive, endocrine effects in female mammals are consistent with epidemiological evidence finding reproductive health effects of atrazine at low environmental exposures.

- 1) Ochoa-Acuna, H., et al., Drinking-water herbicide exposure in Indiana and prevalence of small-for-gestational-age and preterm delivery. *Environ Health Perspect*, 2009. 117(10): p. 1619-24.
- 2) Rinsky, J.L., et al., Atrazine exposure in public drinking water and preterm birth. *Public Health Rep*, 2012. 127(1): p. 72-80.
- 3) Cragin, L.A. et al., Menstrual cycle characteristics and reproductive hormone levels in women exposed to atrazine in drinking water. *Environ Res*, 2011. 111: p. 1293–1301.
- 4) Winchester, P.D., J. Huskins, and J. Ying, Agrichemicals in surface water and birth defects in the United States. *Acta Paediatr*, 2009. 98(4): p. 664-9.

²¹ Balu et al. 1998; U.S. EPA 2001; U.S. Geological Survey 1999; Wade et al. 1997 studies cited in: Enoch, R.R., et al., Mammary gland development as a sensitive end point after acute prenatal exposure to an atrazine metabolite mixture in female Long-Evans rats. *Environ Health Perspect*, 2007. 115(4): p. 541-7.

The above studies are also consistent with a large body of research showing impacts on wildlife species at low exposure levels. The following studies are examples of high-quality wildlife research:

- 1) Hayes, T.B., et al., *Hermaphroditic, demasculinized frogs after exposure to the herbicide atrazine at low ecologically relevant doses*. Proc Natl Acad Sci U S A, 2002. **99**(8): p. 5476-80.
- 2) Hayes, T., et al., *Herbicides: feminization of male frogs in the wild*. Nature, 2002. **419**(6910): p. 895-6.
- 3) Flynn, K., et al., *Burrowing in the freshwater mussel *Elliptio complanata* is sexually dimorphic and feminized by low levels of atrazine*. J Toxicol Environ Health A, 2013. **76**(20): p. 1168-81.
- 4) Hayes, T., et al., *Atrazine-induced hermaphroditism at 0.1 ppb in American leopard frogs (*Rana pipiens*): laboratory and field evidence*. Environ Health Perspect, 2003. **111**(4): p. 568-75.
- 5) Hayes, T.B., et al., *Atrazine induces complete feminization and chemical castration in male African clawed frogs (*Xenopus laevis*)*. Proc Natl Acad Sci U S A, 2010. **107**(10): p. 4612-7.
- 6) Tavera-Mendoza, L., et al., *Response of the amphibian tadpole *Xenopus laevis* to atrazine during sexual differentiation of the ovary*. Environ Toxicol Chem, 2002. **21**(6): p. 1264-7.
- 7) Tavera-Mendoza, L., et al., *Response of the amphibian tadpole (*Xenopus laevis*) to atrazine during sexual differentiation of the testis*. Environ Toxicol Chem, 2002. **21**(3): p. 527-31.

IV. OEHHA IS PROPOSING MADLs THAT WOULD RESULT IN EXPOSURES THAT AN AUTHORITATIVE BODY DEEMS UNSAFE

Proposition 65 imposes labeling requirements that provide an added benefit above and beyond what federal government regulations afford. Current federal regulations cap the allowable levels of atrazine in drinking water at 3 micrograms per liter.²² Since water contamination has long been an issue with atrazine, and its use on food crops is limited to corn and a few other commodities, the most likely exposure route is through drinking water. Assuming the average adult drinks 2 Liters of water a day, that is a maximum exposure of 6 micrograms a day via drinking water based on US EPA regulations. California's proposed MADL of 100 micrograms per day is 16-fold higher than that amount. It is the EPA's official position that reproductive problems in humans may occur

²² U.S. Env'tl. Prot. Agency. Table of Regulated Drinking Water Contaminants. Accessed 12/11/2015 Available at <http://www.epa.gov/your-drinking-water/table-regulated-drinking-water-contaminants>.

from long-term exposure to water containing atrazine above 3 micrograms per liter.²³ Therefore, it is possible that the current MADLs would exempt some products from the labeling requirement even though their use would result in exposures the EPA (an authoritative body pursuant to Prop 65) deems unsafe.

CONCLUSION

The State of California has taken an important step in listing atrazine as a reproductive toxicant, but the listing is only as effective as the MADL will allow. Our knowledge of endocrine disruptors is still very poor, but so much better than it was in 1996 when the Morseth study was performed. That certainly does not preclude its use in risk assessment, but it's only been recently that researchers have begun to even analyze exposures to low doses of endocrine disruptors. Twenty years ago, low dose effects of endocrine disruptors were not appreciated or even widely accepted. The Morseth study did not identify a NOEL, so we are only left to guess what types of effects would be seen at lower doses. Now that we have studies that identify reproductive toxicities in females at much lower doses, we don't have to guess anymore. We also note that the restrictive nature of the listing forced us to consider only reproductive, endocrine effects in female mammals. During our literature searches, we identified numerous other high quality studies that showed reproductive toxicities to males, as well as toxicities that were not reproductive in nature, at doses lower than the NOEL used for the MADL calculation. It is our opinion that atrazine is not safe at any level of exposure, for humans or for wildlife.

Sincerely,

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²³ *Id.*

