

December 14, 2015

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Dear Ms. Vela:

The American Congress of Obstetricians and Gynecologists (ACOG) California Chapter, distinguished atrazine researcher Dr. Tyrone Hayes, and the following 19 scientists and health professionals thank you for the opportunity to comment on the proposed Maximum Allowable Dose Level (MADL) of 100 micrograms per day for exposure to atrazine and other triazines. Atrazine is one of the most widely used herbicides in the U.S. Therefore, we strongly support the establishment of an appropriately protective MADL by the Office of Environmental Health Hazard Assessment (OEHHA). The establishment of a MADL should encourage businesses to reduce exposures to this chemical. As scientists, academics, health professionals, and others who work to improve public health, we strongly support this goal.

At the same time, we recommend that OEHHA reconsider recent research about the reproductive effects of exposure to low doses of atrazine. We have identified four important studies demonstrating that low-level exposure to atrazine causes endocrine effects in mammals. All four studies show Lowest Observable Adverse Effect Levels (LOAELs) below the No Observable Adverse Effect Level (NOAEL) currently being considered by the OEHHA. These studies are as follows:

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 NOAEL identified.
- * LOAEL = .09 mg/kg of body weight per day.
- * Endpoint - delayed mammary gland development.
- * Test material - atrazine plus metabolites.

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.

- * NOAEL = .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.

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 NOAEL identified.

* LOAEL = 1.4 mg/kg of body weight per day.

* Endpoint - decreased cognitive ability and altered neurotransmitter levels.

* Test material - atrazine.

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

* No NOAEL 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.

Based on these data, our suggested MADL is no higher than 8 micrograms per day. Further, given the LOAELs in the above studies and the low exposure levels in the supplemental studies outlined below, we recommend OEHHA consider an even lower MADL of less than 1 microgram per day.

The importance of a health protective MADL is reinforced by epidemiological studies in the U.S. that have correlated low-level atrazine exposure with adverse pregnancy outcomes and reproductive toxicities in women. These studies are as follows:

- 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.

- Rinsky, J.L., et al., Atrazine exposure in public drinking water and preterm birth. *Public Health Rep*, 2012. 127(1): p. 72-80.

- 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.

- 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.

Additional epidemiological studies also indicate that atrazine is a developmental toxin at environmentally relevant exposures:

- Agopian, A.J., et al., Case-control study of maternal residential atrazine exposure and male genital malformations. *Am J Med Genet A*, 2013. 161A(5): p. 977-82.

- Agopian, A.J., et al., Maternal residential atrazine exposure and risk for choanal atresia and stenosis in offspring. *J Pediatr*, 2013. 162(3): p. 581-6.

- 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.

- Agopian, A.J., et al., Maternal residential atrazine exposure and gastroschisis by maternal age. *Matern Child Health J*, 2013. 17(10): p. 1768-75.

In addition, we have included multiple studies in aquatic model systems that observed atrazine-induced reproductive toxicities, such as hermaphroditism, feminized behavior in males and the presence of eggs in the testes, and decreased fertility in both sexes. Many of these adverse effects were seen with atrazine concentrations as low as 0.1 µg/L, 30-fold lower than the legal limit in U.S. drinking water.

- 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.

- Hayes, T., et al., Herbicides: feminization of male frogs in the wild. *Nature*, 2002. 419(6910): p. 895-6.

- 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.

- 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.

- 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.

- 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.

- 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.

Finally, we note that the current Maximum Contaminant Level (MCL) for atrazine in drinking water established by the U.S. EPA based on reproductive effects is 3.0 micrograms per liter (*ppb*). With the primary mode of exposure to atrazine likely being through water consumption, and the average person consuming about 2 liters of water per day, a MADL_{oral} of 100 micrograms per day is an exposure 16x greater than that resulting from EPA's MCL. Therefore, a considerably lower MADL would more closely correlate with exposure criteria set forth by the federal government.

Thank you for consideration of our comments.

Sincerely,

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