

Love Song Blues: DEHP Alters Courtship Vocalizations in Mice

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<https://doi.org/10.1289/EHP2923>

Due to its prevalence and known endocrine-disrupting properties,^{1,2} DEHP [di(2-ethylhexyl) phthalate] has been subject to extensive research into potential human health effects, especially related to the reproductive system.^{3,4} An article in *Environmental Health Perspectives* reports evidence that even small doses of DEHP may alter the courtship behavior of otherwise healthy adult male mice by reducing the number of androgen receptors in the brain.⁵ These receptors perform vital functions related to reproduction and sexuality.⁶

Phthalates, including DEHP, are widespread in modern life.⁷ About a dozen variants are commonly used worldwide to make the plastics in consumer products, packaging, and medical devices more flexible or durable.⁸ DEHP, by far the most common of these, represents more than a third of the global plasticizer market⁹ and has been detected in more than 75% of analyzed individuals in industrial countries.^{10,11,12}

Over the years, experimental and epidemiological studies have implicated DEHP in a range of health effects,¹³ leading some countries, including the United States, to ban or limit its

use in certain applications.^{14,15,16} Less is known about the chemical's potential effects on the brain, but recent research has suggested associations between developmental exposure to DEHP and impaired neurodevelopment,^{17,18} behavioral problems,¹⁹ anxiety and depression,²⁰ and altered stress responses.²¹

In this new experimental study, researchers from France's National Center for Scientific Research fed healthy adult mice 0.5, 5, or 50 $\mu\text{g}/\text{kg}/\text{day}$ DEHP. The highest dose corresponds to the tolerable daily intake for humans established by the European Food Safety Authority,²² while the lower two are in the range of global exposure levels documented in previous studies.^{23,24,25,26}

After a period of 4 weeks, the researchers performed a series of tests to assess reproductive behavior in the DEHP-dosed mice and nonexposed controls. They found all three doses to be associated with altered courtship vocalizations—key to the reproductive behavior of not only mice, but also many fish, amphibian, bird, and mammal species. The two higher doses of 50 and 5 $\mu\text{g}/\text{kg}/\text{day}$ also were associated with delayed initiation of mating by the male mice.



For many species, distinctive vocalizations—from the ultrasonic chittering of a mouse to the subsonic song of a whale—are a critical part of attracting a mate. Images, clockwise from top left: © CreativeNature_nl/iStockphoto; © miblue5/iStockphoto; © stanley45/iStockphoto; © Zwilling330/iStockphoto.

The researchers then sacrificed the mice for further study and chemical analyses. This led to the study's second major finding, particularly in terms of potential implications for humans: Behavioral changes were associated with DEHP-induced changes in the neurons that control mating behavior. They also found that DEHP caused changes in the activity of androgen receptors in the region of the hypothalamus that controls male sexual behavior.

In a previous study, led by senior author Sakina Mhaouty-Kodja, a research director at the National Center of Scientific Research, the research team also saw mating delays after exposure to low doses of another nearly ubiquitous plastic additive, bisphenol A.²⁷ In that case, the change was not associated with a reduction in androgen receptor expression.

Carlos Dombret, who served as lead author of the new paper while a postdoc at France's Pierre and Marie Curie University under adviser Mhaouty-Kodja, cautions that the findings are both limited in scope and not directly translatable to humans. However, the study does contribute to an ongoing discussion on how researchers and governments view common endocrine-disrupting chemicals such as bisphenols and phthalates, Dombret says. "What was most surprising to me was seeing effects with very, very low doses," he says—levels below regulatory reference doses and on par with global exposure estimates.

Rutgers University associate professor Emily Barrett, lead author of a 2014 epidemiological paper showing an association between environmental exposure to DEHP and lower self-reported interest in sexual activity among pregnant women,²⁸ says the new animal experiments add an important dimension to the study of reproductive effects of DEHP and other endocrine-disrupting phthalates.

"The vast majority of interest has been in early-life exposures, and this paper is one of the relative few to look at adult exposures," says Barrett, who was not involved in the new study. "Sometimes we have the idea that it's only pregnant women who matter [in terms of phthalate exposures], and this paper makes the point that no, other adult exposures matter, too."

Jay Ko, an associate professor at the University of Illinois at Urbana-Champaign who has studied the effects of DEHP on fertility in male mice,²⁹ says he believes the researchers should have tested exposure periods of varying lengths as opposed to a single one-month window. As a result, he says, the findings should be interpreted with caution—especially when extrapolating to humans. Ko also was not involved in the study.

The study does, however, raise interesting questions about DEHP's potential effects on the brain, an area that demands greater attention, Ko says. "I think this will be the way research is heading," he says. "Initially [interest in DEHP] was all cancer or toxicity, but now it is heading toward the neurons. This type of a study . . . will be something that will really stimulate future research directions."

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