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Alternative Flame Retardants May Lead to Neurobehavioral Effects

Organophosphate flame retardant (OPFR) exposure early in life may be linked to behavioral impacts into adulthood, according to a new study in zebrafish. The results provide evidence that OPFRs, which have been introduced in commercial products in the past decade, may not be a safe alternative to brominated flame retardants, which were phased out because they were found to be harmful to normal development.

Duke University Superfund Research Program (Duke SRP) Center researchers led by Lilah Glazer, Ph.D., and Edward Levin, Ph.D., used zebrafish to characterize the life-long neurobehavioral effects of four widely used OPFRs. In the last ten years, indoor and outdoor levels of OPFRs have increased, and these compounds and their metabolites have been detected in house dust samples and human populations. The Duke SRP Center investigates how early-life exposure to priority and emerging chemicals of concern, including flame retardants, can lead to neurodevelopmental effects.

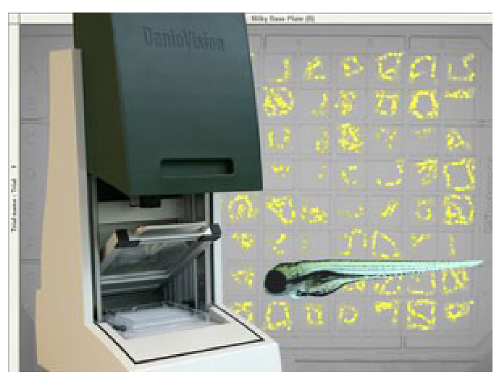
Identifying Behavioral Effects

The researchers investigated behavioral changes of zebrafish in response to early-life exposure to four OPFRs: isopropylated phenyl phosphate, butylphenyl diphenyl phosphate (BPDP), 2-ethylhexyl diphenyl phosphate (EHDP), and isodecyl diphenyl phosphate (IDDP). Zebrafish, which share many molecular, biochemical, cellular, and physiological characteristics with humans, have been widely used to study how exposure to toxic chemicals influences development and behavior.

Adult zebrafish underwent a variety of behavioral tests, including one examining their preference for social interaction with other zebrafish. (Photo courtesy of Edward Levin)

The researchers exposed zebrafish embryos to the OPFRs at different concentrations for five days. On day six, they measured the fish's ability to move around its tank under alternating light and dark conditions. The test can show how the fish responds to a change in stimuli, where limited or excess movement can indicate an overall change in behavior. At five to seven months, the adult zebrafish were given a variety of behavioral tests that assess anxiety-related responses, sensorimotor response, social interaction, and predator evasion.

The researchers observed short-term effects of altered movement in larvae in all of the tested compounds. They also observed long-term impairment of anxiety-related behaviors in adults following IPP, BPDP, or EHDP exposures. Of the four OPFRs, IPP was the most active in causing behavioral alterations in both larvae and adult fish, including increased movement of larvae and reduced response to anxiety-promoting situations in adults. In contrast to IPP, the main effect observed for BPDP and EHDP was increased anxiety-related response to a new environment.



Researchers tracked how larvae exposed to different concentrations of OPFRs moved around in 96-well plates in response to alternating light and dark conditions. (Photo courtesy of Edward Levin)

Making Predictions Moving Forward

Comparing the responses from each of the four chemicals, the researchers determined that the structure of the chemicals did not necessarily predict their neurobehavioral effects. For example, IPP and BPDP have structural similarities but caused very different behavioral effects in larvae and adults, indicating different pathways of toxicity. Additionally, BPDP and

EHDP, which are different in their chemical structure, caused similar behavioral alterations in zebrafish. As scientists are investigating ways to predict toxicity of poorly characterized chemicals based on structural similarities to known chemicals, the results of this screen suggest that predicting toxicity based on structural similarities may miss some impacts.

The researchers also observed behavior alterations in adults at lower concentrations of IPP and BPDP but did not see changes in larvae activity, suggesting a delayed effect for these chemicals at low exposure levels. Larval behavior testing is a popular endpoint when using zebrafish but according to the authors, this study indicates that using larval testing alone may underestimate the neurotoxicity of some chemicals that have delayed effects.

The earlier class of brominated flame retardants, which became popular in the 1970s, were phased out in the 2000s and replaced with OPFRs because the former were found to be developmental neurotoxicants. This study provides evidence that OPFRs may also have neurotoxic effects at low exposure levels. These effects, which may be similar or different in character from those caused by brominated flame retardants, could result in behavioral impacts that last into adulthood.

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To learn more about this research, please refer to the following source:

Glazer L, Hawkey AB, Wells CN, Drastal M, Odamah KA, Behl M, Levin ED. 2018. Developmental exposure to low concentrations of organophosphate flame retardants causes life-long behavioral alterations in zebrafish. Toxicol Sci 165(2):487-498. doi: 10.1093/toxsci/kfy173 PMID: 29982741