Low doses of penta-brominated diphenyl ether flame retardants alter gene expression

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Polybrominated diphenyl ethers (PBDEs) are chemicals that have been widely used as flame retardants and are now classified as persistent organic pollutants. Health concerns in humans have arisen based primarily on studies with laboratory animals exposed to high levels of PBDEs.

Three commercial mixtures of PBDEs have been manufactured in or imported into the United States which include penta-, octa-, and deca-brominated diphenyl ethers (BDEs). Of particular concern has been the penta-BDEs used primarily in foams in computers, televisions, mattresses, pillows, carpets, and furniture. The components of penta-BDEs mixtures are present in water, soil, animal products and air, and people are exposed primarily through ingestion of food or inhalation. Penta-BDEs have been measured in human blood, fat, breast milk, and umbilical cord blood. Since 2004, the penta- and octa-BDEs are no longer being manufactured in the USA and deca-BDE manufacture in the USA will be phased out by the end of 2013. Even so, due to their chemical nature, PBDEs will persist in the environment long after their use in manufacturing has ended. It is unclear what impact PBDEs have on human health as people are typically not exposed to the high concentrations of PBDE compounds that have detrimental neurological and endocrine effects in laboratory animals. There is a need to determine the impact of low doses of PBDEs in laboratory animals which approach the levels that humans are exposed to in daily life, and in addition to determine the effects of these compounds in offspring exposed during critical developmental periods.

In the work published in the April issue of Experimental Biology and Medicine, Blake, LaVoie, and co-investigators set out to determine the effects of a relatively low dose of the commercial penta-BDE mixture, DE-71, on reproductive and endocrine function in a laboratory rat model. Female rats were orally administered 60 micrograms/kilogram body weight/day during pregnancy and lactation to expose them and their developing offspring to DE-71. The offspring were followed to adulthood and mated to evaluate their reproductive outcomes, thyroid hormone concentrations, body and organ weights, and gene expression in selected organs. The work was carried out jointly by the laboratories of Charles A. Blake and Holly A. LaVoie at the University of South Carolina School of Medicine in Columbia, South Carolina.

Dr. LaVoie, who led the research team, stated "we were happy to see that low doses of DE-71 did not overtly affect reproductive outcome of pregnancy in terms of resorbed embryos and number of viable offspring of either the mothers receiving DE-71 or their first generation offspring. However, gene profiling of reproductive organs of offspring identified a single gene spp1 that encodes osteopontin, which exhibited 3-fold or higher expression in both the immature testes of male offspring and adult ovaries of female offspring that were exposed to low dose DE-71 in utero and via their mother's milk. This shows that molecular changes are occurring in reproductive organs and that some of these molecular changes appear even after the penta-BDE delivery was ceased."

Additional cell culture studies further confirmed that the osteopontin gene promoter is a novel target of PBDEs. Osteopontin is a multi-functional extracellular matrix protein. The long-term implications of elevated osteopontin gene expression in gonads is unclear at this time, however, osteopontin protein is known to be elevated in ovarian and other cancers. PBDEs are formed by adding 1-10 bromine groups to a double ring structure to form different congeners. Different PBDE congeners can mimic or inhibit thyroid hormone, estrogen, and androgen

function. The mechanism of how PBDEs regulate the osteopontin gene will require further study. Also in need of further study are the long-term implications of altered osteopontin in ovaries and testes.

In contrast to prior studies with much higher concentrations of penta-BDEs that demonstrated reduced serum thyroid hormone concentrations, the study showed that first generation females during their own pregnancies had elevated serum thyroid hormones. Furthermore, the DE-71 exposed female offspring sacrificed two months after their own pregnancies, had enlarged thyroids without altered serum thyroid hormones.

Dr. Blake, who led the endocrine studies remarked, "Our thyroid findings, taken together with previous work with high doses of penta-BDEs, indicate that these compounds may have biphasic effects depending on exposure levels where low dose exposures may increase thyroid hormone concentrations and higher PBDE doses may decrease them. In addition, the physiological status of the animal (i.e., pregnant versus non-pregnant) may determine if the thyroid hormone levels are affected. These studies could potentially be critical to understanding the effects of PBDE accumulation in the tissues of pregnant women. They also emphasize the potential importance of reducing exposure to PBDEs in homes and the environment and regulating the import of manufactured items that contain PBDEs."

The first generation offspring in the study received DE-71 via maternal exposure to a low dose, showing that in utero and lactational exposure of offspring can have effects lasting into adulthood. Moreover, most differences were observed in female rat offspring, suggesting sex differences in the physiological responses to PBDEs. This study sets the stage for future investigations of long-term effects of low level PBDE ingestion.

Dr. Steven R. Goodman, Editor-in-Chief of *Experimental Biology and Medicine*, said "This important environmental health study by Holly Lavoie, Charles Blake and colleagues has looked at the effect of low doses of polybrominated diphenyl ethers (PBDEs) on laboratory animals. Their findings indicate these organic pollutants, found in flame retardents, caused pregnant and lactating rats to have increased levels of thyroid hormone in female offspring and increased gonadal osteopontin gene expression. It is clear that this sets the stage for future studies aimed at understanding the long term consequences of PBDE exposure."

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