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HEPATIC TOXIC/CARCINOGENIC ACTIVITY OF PENTABROMODIPHENYL ETHERS

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Introduction

Pentabrominated diphenyl ether (PBDE) flame retardants have been phased out in Europe and in the United States, but these lipid soluble chemicals remain persistent in the environment and are found in the tissues of wild life (e.g. birds, whales, fish) and humans. In general, PBDEs or their metabolites have limited genotoxic activity. In a 2-year study, a mixture of PBDEs (DE-71) caused liver and other tumors in male and females rats and mice (National Toxicology Program, 2015). Both the PBDE mixture (DE-71) and the individual PBDE (BDE-47) can cause liver damage as early as PND22 after in utero and postnatal exposure.

Materials and Methods

In the 2-year cancer study, DE-71 (Great Lakes Chemical Corp., El Dorado, AR) was prepared for oral gavage administration in corn oil to deliver to rats 0, 3, 15, or 50 mg DE-71/kg bw/day and to mice 0, 3, 30, 100 mg DE-71/kg bw/day. Wistar Han rats [Crl:WI(Han)] rat dams (Charles River Laboratories (Raleigh, NC)) were dosed GD6-PND21, and pups dosed PND12 – PND21 daily. At PND22, 2 males and 2 females were randomly selected from up to 25 liters and assigned to the 2 year study, and thereafter, dosed 5 days per week for up to 2 years. B6C3F1 mice (Taconic Farms, Inc., Germantown, NY) were dosed starting at 5-6 weeks of age 5 days per week for up to 2 years.
The animals were housed by species and sex, two to three male rats per cage, five female rats per cage, one male mouse per cage, and five female mice per cage. Tap water and NTP-2000 diet (Zeigler Brothers, Inc. Gardners, PA) were made available ad libitum. The care of animals on this study were as described in the "The U.S. Public Health Service Policy on Humane Care and Use of Laboratory http://grants.nih.gov/grants/olaw/olaw.htm#pol". All tissue collections, tissue processing, and histopathological examinations were performed according to NTP specifications (http://ntp.niehs.nih.gov/ntp/test_info/finalntp_toxcarspecsjan2011.pdfz).
In another study, Wistar Han rat dams were dosed GD6-PND21, and pups dosed PND12 – PND21 daily by oral gavage in corn oil with either DE-71 at 0, 0.1, 15, or 50 mg/kg bw/day or BDE-47 (Cerilliant, Round Rock, TN; 99.6% pure) at 0, 0.1, 15, or 50 mg/kg bw/day. At PND4 all litters were culled to 3 males and 3 females per litter. At PND22 the liver of pups was examined for treatment-related liver lesions (~ 2-3 pups of each sex from 8-10 separate litters).

Results and discussion

PND22 Liver Lesions
Treatment-related DE-71 and BDE-47 liver lesions were seen in male and female Wistar Han rat pups at PND22 after in utero/postnatal exposure. This included increases in centrilobular hypertrophy and fatty change after both DE-71 and BDE-47 exposure. Increased liver mitoses were observed in the DE-71 treated animals.
2-Year Cancer Study Results
In the 2-year study, mean body weights of 0, 3, 15, and 50 mg/kg male rats and 3 and 15 mg/kg female rats were similar to controls at the end of the exposure period. Mean body weights of 50 mg/kg female rats were reduced. Mean body weights of 30 and 100 mg/kg male and female mice were reduced relative to controls. Early deaths and reduced body weights in rats and mice were attributed to the carcinogenic effects of DE-71. DE-71 caused treatment-related liver tumors in male and female rats and mice. In addition, there was evidence for a treatment-related carcinogenic effects at other organ sites including thyroid and pituitary gland tumors in male rats and stromal polyps/stromal sarcomas of the uterus in female rats.

The mechanism for these carcinogenic effects are thought to be related to oxidative damage and/or activation of several receptor pathways leading to a series of critical mutations and epigenetic changes on the path to cancer.

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