Original Article

Endocrine Disruption Activity of 30-day Dietary Exposure to Decabromodiphenyl Ethane in Balb/C Mouse*

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Abstract

Objective This study aimed to evaluate the hepatotoxicity, metabolic disturbance activity and endocrine disrupting activity of mice treated by Decabromodiphenyl ethane (DBDPE).

Methods In this study, Balb/C mice were treated orally by gavage with various doses of DBDPE. After 30 days of treatment, mice were sacrificed; blood, livers and thyroid glands were obtained, and hepatic microsomes were isolated. Biochemical parameters including 8 clinical chemistry parameters, blood glucose and hormone levels including insulin and thyroid hormone were assayed. The effects of DBDPE on hepatic cytochrome P450 (CYP) levels and activities and uridinediphosphate-glucuronosyltransferase (UDPGT) activities were investigated. Liver and thyroid glands were observed.

Results There were no obvious signs of toxicity and no significant treatment effect on body weight, or liver-to-body weight ratios between treatment groups. The levels of ALT and AST of higher dose treatment groups were markedly increased. Blood glucose levels of treatment groups were higher than those of control group. There was also an induction in TSH, T3, and fT3. UDPGT, PROD, and EROD activities were found to have been increased significantly in the high dose group. Histopathologic liver changes were characterized by hepatocyte hypertrophy and cytoplasmic vacuolization. Our findings suggest that DBDPE can cause a certain degree of mouse liver damage and insufficiency.

Conclusion DBDPE has the activity of endocrine disruptors in Bal/C mice, which may induce drug-metabolizing enzymes including CYPs and UDPGT, and interfere with thyroid hormone levels mediated by AhR and CAR signaling pathways. Endocrine disrupting activity of DBDPE could also affect the glucose metabolism homeostasis.

Key words: Decabromodiphenyl ethane; Endocrine disruption activity; Cytochrome P450; Blood glucose; Thyroid hormone

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INTRODUCTION

Decabromodiphenyl ethane (DBDPE) is a brominated flame retardant (BFR) used as an additive of flammable material to decrease the risk of accidental fire. It is used in a broad range of polymers, in products ranging from consumer electronics to wire and cable coatings and insulating foams.

For several decades, BFRs have been a controversial

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group of chemicals. Flame-retardants protect lives by increasing fire safety, but at the same time, several BFRs are considered as environmental contaminants such as polybrominated diphenyl ethers (PBDEs), tetrabromobisphennol A (TBBPA), which have been extensively used. Due to their persistence, bioaccumulation and biomagnification at food webs, long-range transportation and toxicity, such as endocrine disruption activity, the production and use in European Union was banned, and subsequently was phased out from USA and other countries. Moreover, several BFRs were classified as persistent organic pollutants and listed for global elimination compounds under the Stockholm Convention[1,2].

Currently DBDPE is one commercially important alternative flame retardant which was predicted to be one of the most widely use flame retardants of the thermoplastics industry[3]. Due to large molecular size, low aqueous solubility and biological availability, DBDPE was believed to be rarely released into the environment and have low toxicity; DBDPE has a similar structure with PBDEs and has been produced and used for more than 20 years. First report on DBDPE was published in 2004[4]. Then it was found in sewage sludge, sediment, indoor air[4], birds[5] and in a benthic food web[6]. Research demonstrated that DBDPE is freely released to the surrounding environment, accumulated in animals and humans[7-10]. But only limited studies on the toxic effects of exposure of DBDPE have been conducted.

Although the *in vivo* or *in vitro* studies showed the toxicity of DBDPE was low, the potential endocrine disruptive action of BFRS, especially to PBDEs, has been of concerned recently. Many PBDEs are defined as endocrine-disrupting chemicals (EDCs) due to their structural similarity to endocrine hormones, such as thyroid hormones. A number of *in vivo* and *in vitro* studies on human, rodent and other models show that PBDEs have toxic effects on the hypothalamus-pituitary-thyroid axis, thyroid hormone metabolism and energy balance. These effects were typically observed in patients with obesity and metabolic syndromes. Short-term exposure to PBDEs also resulted in decline of thyroid hormones in rats[11,12].

The liver has been considered the primary target organ of PBDEs[13,14]. PBDEs could cause the induction in hepatic detoxification enzyme activities including Phase I cytochrome P450 monooxygenase (CYP) enzymes and Phase II conjugation enzymes [e.g., uridinediphosphate-glucuronosyltransferase (UDPGT), sulfotransferases] which lead to metabolism of these chemicals[15-17]. These results raised people's concern on the possibility of agonizing aryl hydrocarbon receptor (AhR)-mediated CYP1A induction; CYP1A1 induction was mediated primarily by AhR. The AhR was a transcription factor of cytosolic expression that is able to sense a wide range of both endogenous and exogenous ligands. The resulting structural composition of the AhR facilitates the translocation of ligand-AhR complexes into nuclei, where they were associated with the AhR nuclear translocater and bound to specific deoxyribonucleic acid (DNA) recognition sequences, notably dioxin-response elements or xenobiotic-response elements (XREs) in target genes. This increases the transcription of target genes such as gene encoding for CYP1A1. Subsequently, the affected xenobiotic substance is oxygenated to increase its solubility in water and to undergo further phase-II conjugation by enzymes such as UDPGT and sulfotransferase. This process either makes the substrate more polar or eliminates it altogether. However, the oxygenation also initiates the production of active intermediates or procarcinogens that form DNA and protein adducts, leading to toxicity. Besides the AhR-mediated CYP1A induction, the pregnant X receptor (PXR) is also a promiscuous nuclear receptor for both xenobiotic chemicals and endogenous metabolites, and has been reported to coordinate hepatic responses with the constitutive androstane receptor (CAR). It also regulates the expression of *CYP2* and *CYP3* genes which are related with liver injury[18,19].

Furthermore, while the mechanisms of PBDEs that induced the decline of circulating thyroid hormones concentrations are unclear, induction of metabolising enzymes *via* AhR, PXR, or CAR can interfere with the homeostasis of thyroid hormones. Their interaction initiates a cellular response, e.g. the transcription of specific genes, among them genes encoding proteins responsible for the metabolism of xenobiotics[20-23]. Research data demonstrated that environmental exposure to PBDEs was positively associated with human diabetes prevalence, which was strengthened by the animal experiment results showing that PBDEs could significantly increase high fasting glucose in rats. The result indicated that PBDEs might induce the disorder of glycometabolism and potentially result in the onset of diabetes[11,24-26].