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Simulating long-term occupational exposure to decabrominated diphenyl ether using C57BL/6 mice: Biodistribution and pathology

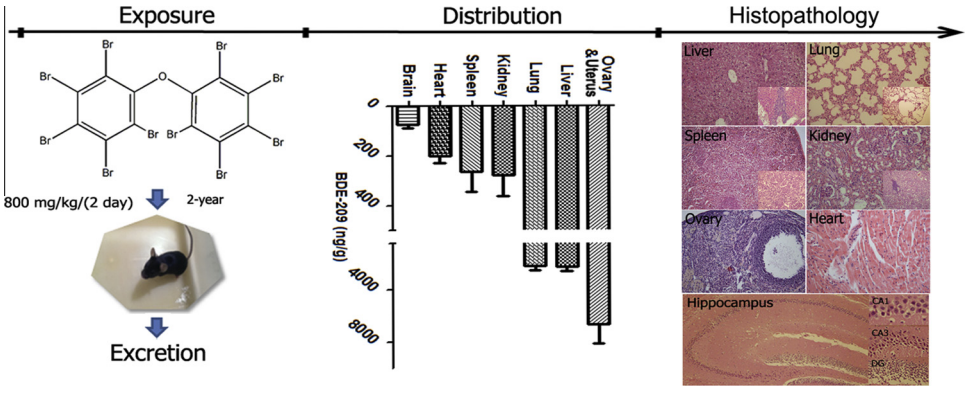
Yan Feng [a,1], Qingliang Hu [a,1], Ge Meng [a], Xiaomeng Wu [a], Weihong Zeng [a], Xing Zhang [a], Yingxin Yu [b,*], Yan Wang [a,*]

[a] Faculty of Public Health, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, PR China
[b] Institute of Environmental Pollution and Health, School of Environmental and Chemical Engineering, Shanghai University, Shanghai 200444, PR China

HIGHLIGHTS

- A 2-year BDE-209-exposed mouse model was set up to simulate occupational exposure.
- BDE-209 preferentially accumulated in the ovary and uterus, liver and lung.
- Obvious pathological changes were observed in some organs of the exposed mice.
- No neoplastic lesions were observed in the exposed mice.

GRAPHICAL ABSTRACT



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ABSTRACT

Decabrominated biphenyl ether (BDE-209) is a fully brominated diphenyl ether compound used widely as an additive brominated flame retardant in a variety of consumer products. In recent years, BDE-209 has been reported to be abundant and persistent in the environment, and comparatively high burdens have been found in occupational environmental compartments and exposed individuals. In the present study, an animal model for simulating long-term occupational exposure to BDE-209 was set up. Female C57BL/6 mice ($n = 10$) were intragastrically administered BDE-209 at a dose of 800 mg kg^{-1} bw at 2-d intervals for 2 years with an internal blood level of approximately 200 ng mL^{-1}, which was comparable to the high level of BDE-209 detected in the occupational population, and the biodistribution and biological effects were evaluated systematically. The results showed that large amounts of the chemical accumulated in most tissues, and the preferential organs were the ovary and uterus, liver and lung. Decreased survival was observed in the exposed mice. The subsequent pathological analysis revealed hepatomegaly in the exposed mice, accompanied by obvious histopathological changes in the liver, lung, brain, spleen, kidney and ovary. No neoplastic lesions were observed in this lifetime exposure study. Although the number of experimental mice was limited, our observations offer a comprehensive understanding of the chronic toxicology of BDE-209 after continuous high-dose exposure.

* Corresponding authors at: Room 605, Building of Science and Teaching, 227 South Chongqing Road, Shanghai 200025, PR China. Tel.: +86 21 63841056; fax: +86 21 63842157 (Y. Wang). Box 150, 99 Shang Da Road, Shanghai 200444, PR China. Tel.: +86 21 66137736; fax: +86 21 66136928 (Y. Yu).
E-mail addresses: yuyingxin@staff.shu.edu.cn (Y. Yu), wangyan@shsmu.edu.cn (Y. Wang).
[1] These authors contributed equally to this manuscript.

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1. Introduction

Polybrominated diphenyl ethers (PBDEs) are a class of brominated flame retardants (BFR) that have been widely used in a variety of consumer products, including textiles, plastics, polyurethane foam, and electronic equipment. PBDEs are additive flame retardants, and they can leach from the products and release into the environment. Three primary formulations (pentaBDE, octaBDE, and decaBDE) of PBDEs have been produced and marketed. The pentaBDE and octaBDE formulations are composed mainly of tetra- to octaBDE, and both have been restricted from production and use due to concerns of environmental persistence, bioaccumulation, and adverse health effects (U.S. EPA, 2009). The decaBDE formulation is composed of essentially all decabrominated biphenyl ether (BDE-209), which was assumed to have lower bioavailability and less toxicity in earlier studies due to its large molecular size and poor solubility and remains in production and is widely used in many countries. In recent years, however, an increasing number of studies have revealed its persistence in the environment and biomagnification through food chains (Bartrons et al., 2012; Salvado et al., 2012). Its ecotoxicological effects have also been reported (Zhang et al., 2012). In addition, BDE-209 is also detected in human tissues, including hair, peripheral blood, milk, cord blood, and so on (Illinois EPA, 2006). Laboratory and population studies have provided evidence of its accumulation organisms as well as its potential toxicities, including developmental neurotoxicity (Costa and Giordano, 2011), immunotoxicity (Liu et al., 2012), and thyroid and reproductive endocrine disturbances (Lee et al., 2010; He et al., 2011). Currently, BDE-209 is undergoing further review with an emphasis on its toxicokinetics, degradation to more harmful chemicals, adverse health effects, and potential alternatives.

BDE-209 is used in ABS-plastics, high impact polystyrene, epoxy resins, and rubber, and thus, may appear in electronic appliances and e-waste products, such as obsolete or end-of-life printed circuit boards, cables, and television sets. Accordingly, higher concentrations of BDE-209 have been detected in the environmental compartments around relevant factories and e-waste districts (Mandalakis et al., 2008), which created a high potential for the continuous exposure of the nearby population, especially the occupational workers, via inhalation, ingestion of dust or soil and dermal absorption. As a consequence, higher body burdens of BDE-209 were detected in these persons compared to the general population. In Guangdong, China, the median concentration of blood BDE-209 was 83.5 ng g^{-1} lipid in electronic waste dismantling workers, 18.5 ng g^{-1} lipid in residents living 50 km away from the dismantling region, and 5.7 ng g^{-1} lipid in a reference group (Qu et al., 2007). The highest concentration even exceeded 3000 ng g^{-1} lipid in dismantling workers. Higher levels of BDE-209 have also been reported in rubber workers and electrical appliance factory workers (Thuresson et al., 2005; Wang et al., 2012). Additionally, a significant linear correlation was observed between serum BDE-209 and length of employment but not the age of the workers in an electrical appliance factory, which indicated that occupational exposure may be one of the main sources for BDE-209 (Wang et al., 2012). It is believed that the body burden of BDE-209 in the occupational population would continue to elevate along with exposure time. Until now, little research has been carried out to investigate the biological effects of BDE-209 and the associated health risks under conditions of long-term, high-level exposure.

In 1986, a 2-year dietary exposure study was conducted by the National Toxicology Program (NTP) to investigate the chronic toxicity and carcinogenicity of BDE-209 in rats and mice (NTP, 1986). For $B6C3F_1$ female mice, the average consumption of BDE-209 in the feed per day was estimated to be 3760 or 7780 mg kg^{-1} for the low-dose or high-dose group, respectively, and low levels of toxicity were observed after short-term and long-term exposure. In a supplemental experiment for this study, greater than 99% of the radioactivity dose was excreted in the feces within 72 h, and gastrointestinal absorption was estimated to be only 0.33% ± 0.19% of the dose. Taking the rapid turnover rate (short half-life) of BDE-209 into account (Thuresson et al., 2006), it was not surprising that trace levels of the chemical were detected in most major organs, indicated the low levels of internal exposure. It was also suggested that the low or high dose in the NTP study might not represent a significant difference and may explain the lack of dose–response in some instances. To investigate the chronic toxicity with a relative high level of exposure, C57BL/6 mice were gavaged with BDE-209 at a dose of 800 mg kg^{-1} bw (body weight) at 2-d intervals for 2 years in the present study. In our previous report, 2 months after dosing under these exposure conditions, the BDE-209 concentration in the plasma of exposed mice reached a steady-state level of approximately 200 ng mL^{-1} (Zeng et al., 2014), which was comparable to the high level of BDE-209 detected in the occupational population, while taking the interspecies uncertainty factor into account. It was suggested that these mice were continuously exposed to a relatively high dose of the chemical, thus modeling long-term occupational exposure. Excretion and accumulation analyses and morphological and histopathological examinations of various organs were then used to systematically investigate the biodistribution and biological effects of BDE-209 *in vivo*. To our knowledge, this is the first animal study to evaluate the deleterious effects of BDE-209 systematically along with the actual internal tissue burden after continuous exposure.

2. Material and methods

2.1. Animals and treatment

Six to eight week-old female C57BL/6 mice were obtained from Shanghai Laboratory Animal Center, Chinese Academy of Science and were housed under specific pathogen-free conditions. The mice were free access to water and a formula feeds. The nutrients met the requirement of China Standard for Laboratory animals (GB 14924.3–2010) and the detailed information was listed in Table S1 in the Supplementary material. All of the animal experiments were approved by the Animal Ethics Committee of Shanghai Jiao Tong University School of Medicine (Project Number 2014094) and conducted in compliance with the guidelines of the Care and Use of Laboratory Animals (certificated by Shanghai Committee of Science and Technology).

BDE-209 (98% purity) was obtained from Wako Pure Chemical Industries, Ltd., Japan. The mice were randomly separated into experimental and control groups (n = 10 for each group) and there were five mice per cage with the same treatment. The experimental mice were intragastrically administered BDE-209 (dissolved in 400 μL of corn oil) for 2 years at a dose of 800 mg kg^{-1} bw at 2-d intervals, while the control mice were administered 400 μL of corn oil.

2.2. Sampling and sample preparation

The feces and urine of 7-month-exposed mice were collected using metabolic cages 24 h after dosing and were then stored at −20 °C for further BDE-209 analysis. At the end of the present study, all mice were sacrificed 24 h after the last administration, and the brain, lung, liver, heart, spleen, kidney, ovary and uterus were dissected and accurately weighed. The organ index was calculated as the ratio of the organ's wet weight to the body weight.