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Assimilation, distribution and toxicity of tetrabromobisphenol A to female Wistar rats through subchronic dermal exposure

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ABSTRACT

Tetrabromobisphenol A (TBBPA) is one of the most widely used brominated flame retardants and is frequently detected in environmental and biological samples. While numerous studies have been conducted on the health effects and toxicokinetics upon oral exposure, few have explored other exposure routes. In the present study, TBBPA was administered to female Wistar rats for 90 days by repeated dermal exposure at 20, 60, 200 and 600 mg TBBPA/kg body weight, and subsequently the concentrations of TBBPA in serum, urine, and feces were determined. TBBPA concentration ranged between 38.26 and 115.9 μg/g lipid in serum, 0.62 and 1.02 ng/μM creatinine in urine, and 288.22 and 1815.66 μg/g in feces. Approximately 3.76–13.40% of the applied TBBPA were absorbed dermally and transported for distribution, but the amount of TBBPA detected in blood was relatively small. The majority of the TBBPA was excreted in feces after dermal exposure while small quantities of TBBPA were found in urine. No significant effects on animal growth or organ coefficients for the thymus, heart, lung, liver, kidneys, spleen, ovary, and brain were observed after subchronic dermal exposure to TBBPA. In addition, repeated dermal administration for 90 days did not induce visible skin pathologic lesions in the female Wistar rats. Our results show that the TBBPA via dermal exposure was mainly discharged through fecal route and residual concentration was low in blood, and the effects of TBBPA were not apparent in animals following subchronic dermal exposure.

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1. Introduction

Brominated flame retardants (BFRs) are widely used in plastics, electronic equipment, building materials, and textiles. Among the BFRs, tetrabromobisphenol A (TBBPA) is the most widely used compound and has the largest production volume worldwide (Bromine Science and Environmental Forum, 2010). TBBPA has been detected frequently in a wide range of environmental and biological samples (Shi et al., 2009; Feng et al., 2012; Yang et al., 2012; Chou et al., 2013; Zhang et al., 2013; Huang et al., 2014; Chang et al., 2016; Liu et al., 2016; Lv et al., 2016; Zhao et al., 2017). Because of potential consumer exposure, the toxicity of TBBPA has been extensively studied. Previous reports on TBBPA concluded there were no risks to human health (EU Risk Assessment Report, 2006). The low toxicity of TBBPA is consistent with their low bioavailability (Lai et al., 2015; Zhao et al., 2017). TBBPA is absorbed by the gastrointestinal tract and excreted rapidly via feces and urine mainly as the parent compound without chemical modification, and little is associated with tissue retention after oral administration (Hakk et al., 2000; Kuester et al., 2007; Knudsen et al., 2014; Colnot et al., 2014). However, some recent oral toxicity studies with TBBPA reported detectable changes in thyroid hormone levels in rodents and also the incidence of uterine tumors in rats (Colnot et al., 2014; NTP, 2014; Cope et al., 2015; Lai et al., 2015).

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More recently, scenarios for human exposure to TBBPA were developed and tested based on monitoring data. These results indicated that human exposure to TBBPA from environmental media is very low because TBBPA concentrations in most measured items were below the detection limit (FSAI, 2010; EFSA, 2011; Colnot et al., 2014). However, some researchers considered that previous investigations on TBBPA exposure levels were underestimated because TBBPA concentrations in dust were poor predictors of actual systematic intake via dermal exposure and hand-to-mouth contact route (Abdallah et al., 2015; Liu et al., 2016; Zhao et al., 2017). Several authors also discussed the absence of experimental data on dermal absorption and assimilation of various BFRs, and highlighted the potential inaccuracies of the current estimates of human exposure to these BFRs owing to a lack of general knowledge on the percutaneous route (Boyce et al., 2009; Trudel et al., 2011;US EPA, 1992). This paucity of information is evident in the EU risk assessment reports on TBBPA (EU Risk Assessment Report, 2006) in which the lack of sound experimental data has led to the assumption of dermal absorption efficiencies based on the consideration of compound-specific physicochemical properties and the extrapolation from data available for polychlorinated biphenyls for TBBPA (Abdallah et al., 2015). To date, a study based on parallelogram calculations (Knudsen et al., 2015) reported that TBBPA could be absorbed after dermal exposure, and that dermal contact with TBBPA represents an important route of exposure. However, *in vivo* studies on the bioavailability, distribution and toxic effects of TBBPA after subchronic dermal exposure are still very limited.

Our present work characterized the distribution, bioavailability and toxic effects of TBBPA following subchronic dermal exposure. The female Wistar rats were repeatedly exposed to TBBPA for 90 days by dermal administration. The concentration of TBBPA in the serum, urine, and feces of the experimental rats was determined to obtain data on dermal absorption, distribution and excretion. The body weight and organ coefficients of rats were also analyzed, and histopathological examination of skin from the exposed area of euthanized animals was conducted after 90 days of repeated dermal administration to observe any symptom. These data were used to evaluate the potential toxic effects of TBBPA after subchronic dermal exposure and to provide insights into the risk of long-term dermal exposure of TBBPA in humans.

2. Materials and methods

2.1. Animals

A total of 36 female Wistar rats (180 ± 20 g) were obtained from Academy of Military Medical Sciences of China at six weeks of age and housed in groups of six. Food and water were provided ad libitum and animals maintained on a 12 h light/dark cycle. Temperature and relative humidity were continually monitored with daily means in the range of 22 ± 1 °C and 40%–60%, respectively.

2.2. Preparation of testing animals

TBBPA (>98% in purity) was purchased from Tokyo Chemical Industry (Shanghai, China) and then grinded to median diameter of approximately 30 μm for better homogenization and absorption. Animals were acclimatized for 7 days prior to the first treatment. At the end of the acclimatization period the rats were randomly assigned to the respective control or exposure groups. During the exposure, rats were housed individually in rearing cages or in metabolism cages to collect their feces and urine samples. All toxicological procedures described were performed in compliance with Good Laboratory Practice (GLP) requirements (OECD, 2004) according to the animal welfare regulations.

2.3. Dosing experiments

The rats were exposed by 6 h/d dermal application to 20, 60, 200 and 600 mg TBBPA/kg body weight (bw) for a duration of 90 days. Dosage levels selected in the present study were based on the experimental animal strains, the half lethal dose (LD50) of TBBPA, duration of exposure and related literature (IPCS, 1995; EU Risk Assessment Report, 2006). A vehicle control group received normal saline only, while the control group was only shaved. Clinical observations of the rats were made every day.

The test material was slightly moistened with physiological saline and applied to an area of 6 × 6 cm^2 of the skin on the back region, which was been shaved 24 h prior to treatment. The hair in this area was shaved as required for the whole duration of the study. The application area was then covered with medical gauze and tape to prevent loss of compound by rubbing or physical falling off. The coverage allowed air circulation over the applied area to allow normal evaporation of surface water from the skin. The test preparation remained on the skin for 6 h, relating to potential human exposure. TBBPA was then removed by banister brush and adequate of warm water. Finally, paper towel was used to dry the skin and the hair.

2.4. Sample collection

During the first 24 h administration, the urine and feces were sampled at 0 and 24 h. Afterwards all excreta were sampled at intervals of 10 days during the 90 days of experiment. Urine and feces were collected overnight in metabolism cages (equipped with water bottles and powdered feed ad libitum). The urine collection equipment prevented contamination of the urine with water, chow or feces. At the end of the 90-day treatment period, all rats were anesthetized with pentobarbital. A total of 12 mL blood sample was collected by cardiac puncture in deeply anesthetized rats before sacrifice. Serum was isolated from blood by centrifugation (10 min, 3000×*g*).

2.5. Extraction of TBBPA

A sample of seminal plasmal (2 mL) was spiked with the ^{13}C-tetrachlorobisphenol A (^{13}C-TBBPA), HCl and dimethylcarbinol, and ultrasonic extracted with 20 mL of hexane/methyl tertiary butyl ether (MTBE) (1:1, v/v) for 3 times with MTBE (1:1) using Sonifier Cell Disrupter (SCIENTZ-JY92-II N, Ningbo Scientz Biotechnology Co., China). The mixtures were centrifuged and the supernatants were pooled and mixed with KCl to precipitate the protein. Distilled water was added to remove impurity. Water in extracting solution was removed passing through anhydrous sodium sulfate (baked for 6 h at 450 °C). Then the solvent was concentrated to 10 mL by rotary evaporation. One milliliter concentrate was used to determine the fat content of serum. The remaining concentrate (9 mL) was dried under nitrogen and eluted using methanol (1.5 mL). Then a Hybrid sep-pak cartridge (Supelclean, HybridSPE 30 mg/mL) was used to remove proteins and phospholipids in serum.

Urine samples were filtered to remove large particles and impurities, A sample of urine (2 mL) was spiked with ^{13}C-TBBPA, adjusted to pH 5.5 with HCl (6 M), buffered with 0.5 mL acetate buffer (pH 5.5) then enzymatically hydrolyzed by β-glucuronidase/arylsulfatase at 37 °C in darkness. A sep-pak C18 cartridge (Supelclean ENVI-18, 500 mg/3 mL) was used for the solid phase extraction of TBBPA. Then dichloromethane and HCl/water (1:100) were added into the solution to remove the impurities. The solution was mixed and centrifuged at 3000 r/min for 5min, and the lower layer

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