TOXICITY OF A TECHNICAL MIXTURE OF POLYBROMINATED DIPHENYL ETHERS FOLLOWING 28 DAYS OF ORAL EXPOSURE IN MALE AND FEMALE RATS

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Introduction

Polybrominated diphenyl ethers (PBDEs) are widely used as flame retardants in textiles, computers, television sets and other household electrical appliances[1]. The world production of these compounds in the early 1990's was estimated to be 40,000 tonnes/year consisting of decaBDE (75%), octaBDE (15%) and pentaBDE (10%)[2]. The lower brominated diphenyl ethers (tetra- and penta-BDEs) are persistent and lipophilic compounds, which bioaccumulate in the food chain. It is not yet clarified whether the higher brominated diphenyl ethers (octa- and deca-BDEs) also bioaccumulate in the food chain. Today PBDEs are ubiquitous pollutants; they are found in sediments, wildlife and human tissues. The levels in human milk in Sweden increased exponentially from 1972 to 1997[3]. In samples from 1998 to 2000 the increasing trend has ceased[4]. Major congeners identified in human tissues are BDE-47 and BDE-99[4, 5].

The aim of this study was to investigate the toxicity of Bromkal 70-5 DE, a commercial mixture of PBDEs, following 28 days of oral exposure in the rat. Bromkal 70-5 DE, mainly contains the congeners 2,2',4,4'-tetraBDE (BDE-47) and 2,2'4,4',5-pentaBDE (BDE-99), as well as a small amount of the 2,2',4,4',6-pentaBDE (BDE-100)[6].

Methods and Materials

Groups of five male and five female Sprague-Dawley rats, 5-6 weeks old, were orally exposed to 0, 2.5, 25 and 250 mg/kg bw/day of Bromkal 70-5 DE for 28 days. The test substance was dissolved in peanut oil and administered by gavage once a day. The control groups were treated with an equivalent amount of vehicle or water. Clinical observations were performed daily. Food consumption and body weight was determined weekly. At the end of the exposure period, the animals were subjected to haematological examination and clinical chemistry analysis, according to the OECD guidelines. At the termination of the study animals were anaesthetised with pentobarbital and exsanguinated via the carotid artery. Liver, kidneys, lungs, thymus, spleen, heart, brain, ovaries, uterus, testis, pancreas and adrenal glands were removed and weighted. Full histopathology was carried out on the organs and tissues of all animals. In addition, liver was analysed for ethoxyresorufin-*O*-deethylase (EROD)[7] and pentoxyresorufin-*O*-deethyalse (PROD)[8]activities. The vitamin A content in liver, kidneys and lungs was determined, according to the method of Håkansson *et al.* [9].

Statistical analysis was carried out by one-way ANOVA and the Duncan Multiple range test to determine the groups that were significantly different ($p \leq 0.05$).

Results and Discussion

The behaviour and the health-state of the animals, as well as the growth rate and food consumption were not affected by the treatment. Blood chemical analysis showed an increase of total serum protein and serum cholesterol levels in both male and female rats at the highest dose-level. Dose-related increases in relative liver and kidney weights were observed (Fig. 1). The increases were significant at the highest dose-level. No significant differences were observed in the relative weight of other organs (thymus, spleen, lungs, heart, brain, ovaries, uterus, testis, pancreas, and adrenal glands) neither in male nor in female rats.

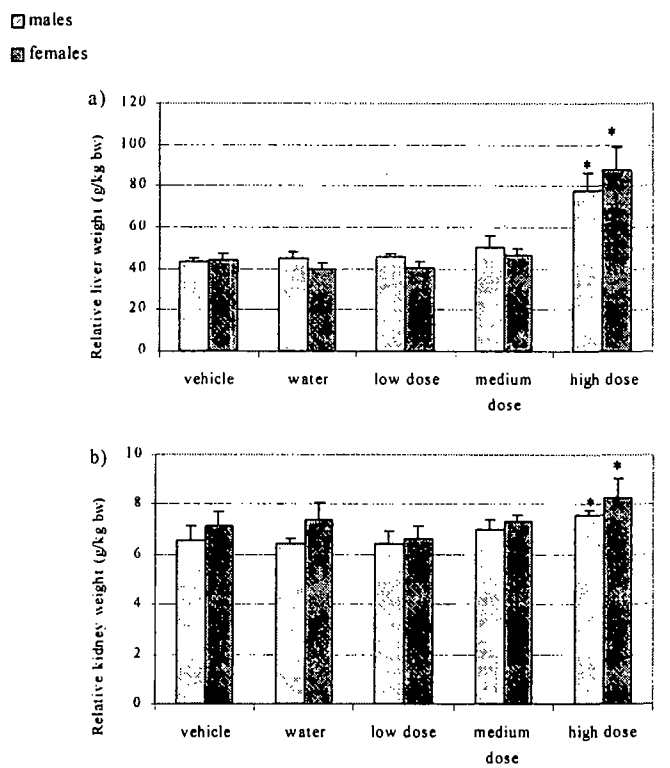

Fig. 1. Dose response relationship for a) relative liver weight and b) relative kidney weight in male and female rats treated orally with Bromkal 70-5 DE for 28 days. Low dose = 2.5 mg/kg bw/day; medium dose = 25 mg/kg bw/day; high dose = 250 mg/kg bw/day.
*Significantly different ($p \leq 0.05$) from the vehicle control.

Histopathological findings consisted of dose-dependent liver changes (i.e. an increase in the number of fat cells and enlargement of the hepatocytes). Dose-dependent increases in hepatic EROD and PROD activities, and reduction of the hepatic vitamin A content were observed in both male and female rats (Fig. 2). The increase in EROD activity and the decrease of hepatic vitamin A levels were significant for males and females at the medium and high dose-levels. The increase in PROD activity was significant for males and females at the high dose-level (Fig. 2).

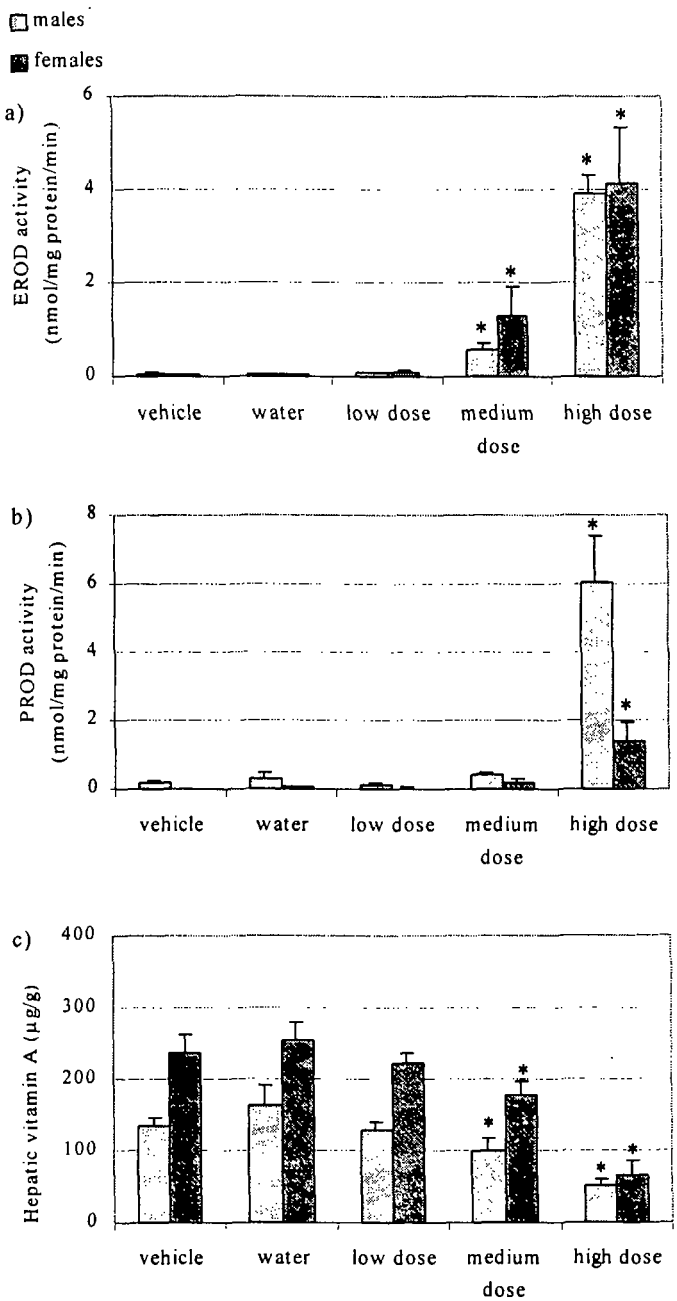

Fig 2. Effect of Bromkal 70-5 DE on hepatic microsomal a) EROD activity, b) PROD activity, and c) hepatic vitamin A concentrations. Low dose = 2.5 mg/kg bw/day; medium dose = 25 mg/kg bw/day; high dose = 250 mg/kg bw/day.
*Significantly different ($p \leq 0.05$) from the vehicle control.

The vitamin A content in kidneys and lungs was not affected by the treatment (data not shown).
The knowledge about the toxicity and the mechanism of action of PBDEs is limited. However there seem to be similarities between some PBDEs and other persistent organohalogen pollutants, such as polychlorinated biphenyls (PCBs) and dioxins. Available literature data suggest that some BDE congeners can be carcinogens[1], endocrine disruptors[10] and neurodevelopmental toxicants[11]. Some data show Ah-receptor agonist properties for BDE-99[12,13] and very low EROD induction potency for BDE-47 and Bromkal 70[13]. The present study shows that exposure of rats to the technical PBDE mixture Bromkal 70-5 DE induces low but significant hepatic EROD activity and reduces hepatic vitamin A levels. The results from this study indicate that Bromkal 70-5 DE, similar to dioxins and dioxinlike PCBs, has the ability to induce hepatic EROD activity and to reduce hepatic vitamin A levels. However, the levels of Bromkal 70-5 DE used in this study are orders of magnitude higher than the levels needed to induce these effects by dioxins and dioxinlike PCBs.

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