

## 28-DAYS ORAL DOSE TOXICITY STUDY OF A PURIFIED TECHNICAL DE-71 MIXTURE IN WISTAR RATS: EVALUATION OF APOLAR LIVER RETINOID LEVELS

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### Introduction

Technical polybrominated diphenyl ethers (PBDEs) are frequently used in combustible materials to increase fire resistance. Several BDE congeners are bioaccumulating and have the potential of being transported far by air (de Wit 2002). Food is possibly the largest source of human exposure to PBDEs (Schechter 2005 and Harrad 2004). Inhalation and dermal routes may also contribute significantly, notably in occupational exposure (Harrad 2004 and Meironyté 1999). The most abundant BDE congeners in wildlife, as well as in humans are BDE47 and BDE99 (Watanabe & Sakai 2003, Meironyté et al 1999, She et al 2000 and Alaei et al 2003). Sufficient evidence demonstrates that these BDE congeners, which are the major constituents of DE-71, are toxic to the developing brain and/or interferes with hormonal pathways (Brachi 2002, Eriksson 2002, Eriksson 2001, Viberg 2002, Viberg 2004, Fernie 2005 and Hallgren & Darnerud 2002). In this study we investigated the effects of the technical PBDE mixture, DE-71, purified with respect to dioxinlike contaminants, on apolar liver retinoid levels.

### Materials and Methods

The study was a 28 day repeat dose toxicity study, performed according to the OECD407 guideline. However, in contrast to the published protocol, the animals were distributed among more dose groups each with fewer animals, i.e. five rats per sex per dose group, for improved assessment of dose-response relationships. The purified DE-71 mixture was given by gavage, dissolved in corn oil at doses ranging between 0 and 200 mg/kg bw per day. Livers were collected and stored at -70°C until analyses of apolar liver retinoid levels were carried out in duplicate by HPLC. Data was evaluated both by ANOVA analysis and by the Benchmark dose method (BMD). The lower 95% one-sided confidence bound (BMDL) was determined at the predefined critical effect size of 10%.

### Results and Discussion

At dose levels well below the dose level where liver weight changes were observed (data not shown), there were marked decreases in apolar liver retinoid levels both in female and male rats (Figure 1). The decreases in the high dose groups were 29% and 33%, respectively, when comparing with the corresponding controls. The NOAEL for decreases in apolar liver retinoid levels was 0.82 mg/kg bw for both female and male rats, while the corresponding BMDL was established at 1.1 mg/kg bw, in both sexes. Considering the absence of dioxinlike contaminants in the test substance, these results suggest that the retinoid system is highly sensitive to the mixture of BDE congeners present in the purified DE-71 mixture.

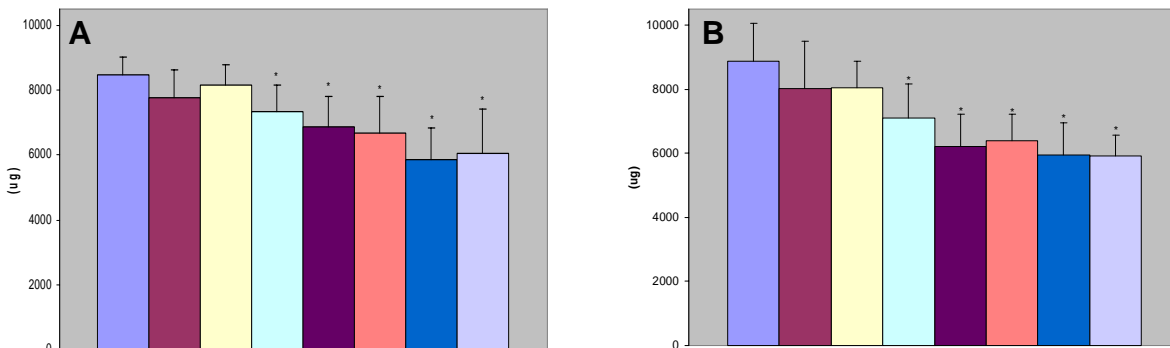


Figure 1 Apolar liver retinoids ( $\mu\text{g}$ ) in female (A) and male (B) Wistar rats treated with daily doses of 0, 0.27, 0.82, 2.47, 7.4, 22.2, 66.7 and 200 mg pentaBDE/kg bw for 28 days. Values represent the mean  $\pm$  SD of 4-5 animals. \* Indicates significant differences ( $p < 0.05$ ) between treatment groups and the corresponding control animals.

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