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Distribution of tributyltin metabolites in the liver and brain of rats
- Evaluation in two-generation toxicity study of tributyltin chloride -

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We carried out two-generation reproductive toxicity study of tributyltin chloride (TBTCl) in rats and reported that TBTCl increased anogenital distance of female neonates (Ogata *et al. J Toxicol Environ Health* **63**, 127-144, 2001) and decreased circulating 17β-estradiol without decreases in serum concentrations of LH and testosterone in males (Omura *et al. Toxicol Sci* (in press)). These data indicate that TBTC1 may have endocrine disrupting effects *in vivo* in mammals. In this presentation, we showed the data concerning the tissue distributions of tributyltin (TBT) and its metabolites, dibutyltin (DBT) and monobutyltin (MBT), in our study.

Methods A two-generation reproductive toxicity study of TBTCl was conducted in rats using dietary concentrations of 5, 25 and 125 ppm TBTCl. When we killed rats of the F1 and F2 generations, the brain and liver were dissected and stored at -80℃. Each sample was spiked with surrogate mixture and then extracted in 0.1 % tropolone benzene by accelerated solvent extraction system (ASE, Dionex Co.). The extracts were derivatized by ethylation and products were analyzed by GC-MS. The detection limit for butyltins was 3 ng/g-tissue.

Results 1) MBT was the main metabolite in the liver of TBTCl-treated rats irrespective of sex and generation. Mean MBT concentration reached approximately 10 nmol/g in the liver of males fed 125 ppm TBTCl diets. DBT followed MBT and TBT showed the lowest concentration in the liver (the mean concentration was approximately 2 nmol/g in males fed 125 ppm TBTCl diets). In the brain, TBT is the main metabolite irrespective of sex and generation. Mean concentration of TBT was 15-20 nmol/g and those of DBT and MBT was 0.5-1.0 nmol/g in the brain of males fed 125 ppm TBTCl diets.

2) In the liver of TBTCl-treated rats of the F2 generation, TBT concentration in males was lower than that in females (approximately 70% of the female value). However, DBT and MBT concentrations of male liver were higher than those of the female liver and the sexual difference was largest in MBT concentration (approximately 300% of the female value). There was no remarkable sexual difference in TBT metabolite concentrations in the brain. Sexual difference was not evaluated in the F1 generation because in F1 females, we confirmed that TBT metabolites were transferred to F2 pups during gestation and lactation.

3)In female rats fed TBTCl, diets, there was no difference in TBT metabolite concentrations between the F1 and F2 generations. Generational difference was not evaluated in males because of the uncertainty in parent and child relationship.

Discussion In this study, we first reported the tissue distribution of TBT metabolites in multi-generation toxicity study. There was a difference in TBT metabolite distributions between the liver and brain irrespective of sex and generation. MBT is the main metabolite in the liver and TBT concentration exceeded those of DBT and MBT in the brain. These findings suggest that toxic effect of TBT to the brain should be carefully examined in rats. There was a sexual difference in TBT metabolite concentrations in the liver (male<female in TBT, and male>female in DBT and MBT). Probably, this indicates that male liver debutylates TBT faster than female liver. In females, there was no difference in tributyltin metabolite concentrations between the F1 and F2 generations. From this result, it seems that trans-generational accumulation of TBT metabolites does not occur in rats.