

DISPOSITION AND EXCRETION OF  
TETRABROMOBISPHENOL A BIS[2,3-  
DIBROMOPROPYL ETHER] (TBBPA-DBPE) IN MALE  
FISCHER-344 RATS

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TBBPA-DBPE is a brominated flame retardant used in a wide range of polyolefins and polypropylenes. Although over 1 million lb TBBPA-DBPE is produced yearly, little information is available regarding its disposition and metabolism. For studies reported here, the disposition and excretion of  $^{14}\text{C}$ -TBBPA-DBPE (20 mg/kg, 50  $\mu\text{Ci/kg}$ ) was studied in normal, jugular-vein- and bile-cannulated male Fischer-344 (F-344) rats following a single oral bolus or *iv* dose. Doses were prepared in a mixture of cremophor/saline/DMSO. *In vitro* metabolism of  $^{14}\text{C}$ -TBBPA-DBPE was studied using F-344 and Sprague-Dawley rat hepatic microsomes and F-344 hepatocytes. Dosing solutions were prepared in DMSO and incubated at 10-100  $\mu\text{M}$  (0.45-1.9  $\mu\text{Ci/mL}$ ). Results of oral and *iv* administration indicate that the major route of elimination is fecal. Following oral dosing, 89% was excreted by 24 h; 95% by 96 h. Following *iv* dosing, 3% was excreted by 24 h; 71% by 96 h. Urinary excretion was <0.2% of the dose. Following *iv* dosing, 32% of the dose was in the liver at 36 h; 7.5% at 96 h.  $^{14}\text{C}$ -equivalents (as % dose) were also detected in adipose tissue (2.5%) muscle (2.2%) and skin (1.1%) at 96 h post dose. Approximately 5% of the dose was detected in bile collected from orally dosed, bile-cannulated, F-344 rats after 48 h. No metabolites of TBBPA-DBPE have been detected in *in vitro* assays that utilized hepatocytes or microsomes. The difference in the tissue disposition of  $^{14}\text{C}$ -TBBPA-DBPE following oral and *iv* administration results from poor absorption of TBBPA-DBPE across the gut lumen following oral exposure. The *iv* data indicate that most absorbed TBBPA-DBPE would be extracted and stored by the liver and ultimately exported into the bile (most likely as metabolites). Metabolism of TBBPA-DBPE is minimal and slow, as indicated by the lack of metabolism in *in vitro* systems and retention of it by the liver. (This work was funded by NIEHS, N01-ES-45529.)

593 DISPOSITION OF TETRABROMOBISPHENOL A  
(TBBPA) IN MALE FISCHER-344 RATS

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TBBPA is used as a reactive flame retardant in epoxy resin circuit boards, plastics, papers and textiles. It is of toxicological interest because of high production volume and potential for human exposures. This study assessed the pharmacokinetics and disposition of TBBPA in male F-344 rats following *iv* (20 mg/kg), single oral bolus (2, 20 or 200 mg/kg), and repeated daily oral (20 mg/kg for 5 and 10 days) administration. Doses were prepared in a mixture of ethanol/cremophor/saline, administered at 2 ml/kg (oral doses) or 1 ml/kg (*iv* dose) and provided 50  $\mu\text{Ci/kg}$  of  $^{14}\text{C}$ -TBBPA. Following *iv* administration,  $^{14}\text{C}$ -TBBPA disappeared from the blood at a terminal half life ( $t_{1/2}$ ) of 82 min and a clearance of 2.44 ml/min. The major route of elimination was via the biliary/fecal route; 82% of the administered dose eliminated in the feces in 36 h with less than 0.5% in the urine. Following administration of single oral bolus doses of  $^{14}\text{C}$ -TBBPA, 90% to 106% was eliminated in the feces by 72 h, with less than 2% in the urine. At the highest dose the rate of elimination of  $^{14}\text{C}$ -TBBPA appeared to be slower. In bile duct cannulated rats, 50% of an oral dose (20 mg/kg) appeared in the bile by 2 h as TBBPA-glucuronides. Following repeated oral doses for 5 and 10 d, the radioactivity eliminated in the feces was 85 and 98%, respectively. Repeated daily dosing did not alter the rate of excretion of TBBPA in the feces nor did it result in higher tissue concentrations of TBBPA. No significant accumulation of  $^{14}\text{C}$  was found in internal tissues (<0.2%) after single or repeated oral doses. The results indicate that TBBPA undergoes extensive absorption from the intestinal tract, but is extracted and metabolized by the liver to glucuronides that are exported into the bile. This highly significant "first pass effect" greatly reduces systemic exposure. Preliminary data indicate systemic bioavailability of TBBPA is <10% and enterohepatic circulation is minimal. (This work was funded by NIEHS, N01-ES-45529.)

594 PRELIMINARY TOXICOKINETIC STUDY AND  
ANALYTICAL METHOD DEVELOPMENT FOR BETA-  
MYRCENE IN RAT PLASMA

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Beta-myrcene is a monoterpene found in the essential oils isolated from the small tree *Xylopija aromatica*, lemon grass and other plants. Because of the recent interest in the use of these essential oils in food products, cosmetics and perfumes, beta-

myrcene has been selected for toxicological evaluation by the NIEHS, Environmental Toxicology Program (ETP). An un-optimized analytical method was developed to support a preliminary toxicokinetic study of beta-myrcene in F344 rats treated with a single IV dose. The method used gas chromatography with flame ionization detection (GC/FID). A nine-point spiked matrix (plasma) curve was prepared at a beta-myrcene concentration range of -0.06 to -100  $\mu\text{g/mL}$  in plasma. Each spiked standard was treated with acetonitrile to precipitate proteins and extracted with 400  $\mu\text{L}$  of a hexane solution of 1-undecene (internal standard). An aliquot of the hexane layer was transferred to a GC autosampler vial for analysis. The spiked matrix curve was found to be linear, with a correlation coefficient  $\geq 0.999$ . The mean percent recovery for the matrix curve was  $75.4 \pm 2.8$  (s)% relative to the corresponding solvent standards. For beta-myrcene in rat plasma, the experimental limit of quantitation (ELOQ) for the un-optimized method was 0.06  $\mu\text{g/mL}$ . Beta-myrcene was not detected in any of the blanks. Following method development, a pilot toxicokinetic study was conducted in five F344 female rats administered a single intravenous injection of beta-myrcene at 40 mg/ml, with plasma sampled at 5, 15, 30, 60, and 90 minutes post-dose. The plasma concentration was relatively consistent across all time-points, 0.14  $\mu\text{g/ml}$ , with individual samples ranging from 0.07 to 0.16  $\mu\text{g/ml}$ .

595 TOXICOKINETIC PROFILE OF BATRACYLIN IN  
BEAGLE DOGS

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This study aimed at determining toxicokinetics of batracylin (8-aminoisoin-dolo[1,2-b]quinazolin-12(10H)-one; NSC 320846) in dogs in order to establish the relation between systemic exposure and toxicity of batracylin. Batracylin was orally administered to beagle dogs as either a suspension (75% saline and 25% Tween 80) at 50 and 150 mg/kg or in gelatin capsules at 50, 150 and 300 mg/kg (0.1, 0.5 and 1 MELD10). A Waters HPLC system equipped with spectrofluorescence detector with excitation wavelength 413 nm and emission wavelength 470 nm was used to quantitatively determine batracylin. Batracylin was eluted from the HPLC column at flow rate of 2 mL/min with a mobile phase composed of acetonitrile and 5 mM ammonium acetate (25/ 75, v/v; pH 3.5). The resulting plasma concentration-time data were analyzed by using nonlinear regression analyses of the PCNONLIN program. Hematology, clinical chemistry, and toxic signs of batracylin were also determined. Lag time in absorption of batracylin ranged from ~11 min (50 mg/kg) to 50-57 min (150 and 300 mg/kg). Batracylin administered at 50, 150 and 300 mg/kg reached its mean  $C_{\text{max}}$  161, 365, and 3100 ng/mL at  $T_{\text{max}}$  65, 118 and 120 min, respectively. The absorption  $t_{1/2}$  of batracylin in suspension (37-60 min) seems longer than in gelatin capsules (28-35 min). The AUC of batracylin of 50, 150 and 300 mg/kg ranged from 20946, 64225 to 526501 ng/mLx min. The AUC following the 300 mg/kg was about 9-fold greater than that following the 150 mg/kg, probably due to higher plasma concentration and longer elimination  $t_{1/2}$  occurred at 300 mg/kg level. The chromatographic profile of dog plasma revealed two chemically-unidentified metabolites. The toxic signs observed included mild to moderate emesis occurred on the dosing day in all dogs. A few days after dosing, 300 mg/kg of batracylin caused diarrhea, pale mucous membranes, body weight loss and transient changes in clinical pathology in the dogs. The study indicated dose-plasma concentration-toxicity relationship of batracylin in dogs.

596 EFFECT OF AGE ON TISSUE DISTRIBUTION OF BDE  
47 IN MICE

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Despite its minor contribution to global polybrominated diphenyl ether production and usage, 2,2',4,4'-tetrabromodiphenyl ether (BDE 47) is the dominant congener found in most biotic samples in North America. The majority of public health concern has focused on potential hazardous effects resulting from exposure to infants and young children because of previous studies reporting adverse developmental effects in rodent studies. This study was designed to investigate the disposition of BDE 47 in young mice reported to be susceptible to the developmental neurotoxic effects of BDE 47. Infantile C57BL/6 mice pups were administered a single, oral 1.0 mg/kg dose of [ $^{14}\text{C}$ ]BDE 47 on postnatal day 10; tissue distribution was monitored 3, 8, 24 hours, 5, and 10 days following administration. Analyses of the carcass for total radioactivity were used as an indirect measure of excretion. The results show that the toxicokinetics of BDE 47 are different in developing mice than in adult mice. While patterns of tissue distribution were similar, concentrations of BDE 47 were consistently higher in pups. BDE 47 was found at the highest concentrations in lipophilic tissues (adipose, liver, and skin) 1-5 days following