1537 SAFETY/RISK ASSESSMENT OF THE CONSUMPTION OF DOMESTIC AND IMPORTED PEAR BRANDIES CONTAINING METHANOL.

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Some pear brandies can contain methanol (MeOH), a compound associated with pronounced visual and central nervous system toxicity. This assessment addresses the potential health hazards due to MeOH exposure of acute and chronic consumption of domestic and imported pear brandy. Various pear brandy products were analyzed for MeOH content by gas chromatography with a flame ionization detector. The mean MeOH content of the domestic (n=51) and imported (n=83) products were 4827 and 2585 ppm, respectively. The estimate of exposure to MeOH from brandy consumption was based on brandy MeOH content and point estimates of brandy intake (USDA, CFSII, 1989-1992). Mean and 90-99th percentiles of the average MeOH exposures were estimated for one-day and chronic consumption of brandy. The tolerable daily intake (TDI, mg/kg/day) for MeOH for one-day exposure is 7.1 (human NOAEL, FDA, 1984) and for chronic exposure is 0.5 (RfD, IRIS, EPA, 1993). The average one-day exposure to MeOH from ingestion of domestic pear brandy exceeded the TDI at the 90-99th percentile brandy intake levels; whereas, one-day exposure to methanol from ingestion of imported pear brandy only exceeded the TDI at the 99th percentile intake level. One-day MeOH exposure for the individual pear brandies exceeds the one-day TDI at the mean, 90th, 95th and 99th percentile intake levels 19.6, 88.2, 88.2, 98.0 % of the time for the domestic and 0, 21.7, 28.9, 78.3% of the time for the imported products, respectively. The average chronic exposure to MeOH associated with drinking domestic or imported pear brandies exceeds the chronic TDI at several intake percentiles (mean, 90-99th). Thus, based on the estimates derived in this assessment, exposure to MeOH associated with both acute and chronic consumption of pear brandy can exceed levels of toxicological concern. Also differences in the level of MeOH exposure, and thus, in the margin of safety, exist between drinking domestic and imported pear brandies.

1538 13-WEEK DIETARY TOXICITY STUDY OF EPIGALLOCATECHIN GALLATE (EGCG) IN RATS.

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Epigallocatechin gallate (EGCG), the most abundant polyphenol in green tea, demonstrates antioxidant, anti-inflammatory, chemopreventive, and other biological activities in several in vivo experimental model systems. A 13-week dietary toxicity study was conducted to evaluate the toxicity of EGCG, to establish a no observed effect level (NOEL), and to determine the reversibility of any observed toxic effects. Sprague-Dawley rats (10/sex/group) were fed EGCG at nominal dose levels of 0 (control; basal diet), 50, 150 and 500 mg/kg/day for 13 weeks. An additional 10 rats/sex in the high dose and control groups were held for a 4-week recovery period in which they were fed basal diet without supplemental EGCG. Blood levels of EGCG were determined after one day of feeding and again during week 13. Toxicologic endpoints included survival, body weight, food consumption, clinical signs, clinical pathology, ophthalmology, organ weights, gross pathology, and microscopic pathology. No treatment-related deaths occurred during the study, and no signs of systemic toxicity were seen in any animal during the 13-week feeding period. No treatment-related effects were seen on body weights or food consumption. Mean total body weight gain at the end of the 13-week feeding period was comparable across all groups for both sexes. Administration of EGCG did not induce ocular toxicity, and had no effect on either clinical pathology parameters or organ weights. No treatment-related histopathological lesions were seen in the high dose males or females sacrificed at the end of the 13-week treatment period. In conclusion, dietary administration of EGCG to Sprague-Dawley rats for 13 weeks did not induce any treatment-related toxicological or histopathological effects in either males or females at dose levels up to 500 mg/kg/day. Based on these results, the NOEL in this study was 500 mg/kg/day.

1539 L-TARTARIC ACID-INDUCED NEPHROTOXICITY.

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We have evaluated the safety of a potential drug formulation containing L-tartaric acid. The dose regimen for the formulation was a 1-hour IV infusion protocol. The formulation was administered daily to cynomolgus monkeys (low dose = 1.8, mid-dose = 18 or, high dose = 188 mg tartaric acid/kg/day) with the start of infusion staggered over 5 days. Clinical signs consistent with acute renal failure developed in several high dose monkeys starting on Day 2 following the start of dosing. As additional high dose monkeys developed renal failure, high dose infusions were stopped on Study Day 7 (Dosing Days 3-7), and the monkeys were euthanized. Acute renal failure characterized by clinical signs and by marked elevations in BUN and serum creatinine was confirmed histopathologically by the presence of acute tubular necrosis. Daily infusions in low- and mid-dose groups continued for 27 days as there were no clinical signs or clinical pathology abnormalities noted in these groups. At necropsy there was no gross or histopathologic evidence of acute renal failure in these groups. In summary, L-tartaric acid can be highly nephrotoxic to cynomolgus monkeys, and caused severe acute renal tubular necrosis when delivered IV over a 1-hour period at high concentration (188 mg/kg). L-tartaric acid, at the high dose, was deemed inappropriate for use in this drug formulation for this dosing regimen. Caution is warranted when new or rarely used excipients are being introduced into drug formulations, as excipients may be toxic under certain dosing regimens.

1540 TOXIC RESPONSE FOLLOWING LATEX DRAIN IMPLANTATION.

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These studies were initiated to investigate the potential role of implanting latex surgical drains on the development of latex allergy. Protein and allergen levels of 5 different brands of Penrose drains were quantified by the Lowry method and an immunoassay. Protein values ranged from 44 to 2566 ng/mg drain material, and latex allergen ranged from 70 to 4528 pg/mg. Drain material (200 mg) was implanted subcutaneously in anesthetized female BALB/c or B6C3F1 mice 6-8 weeks old (N = 5/group). Serum was collected by tail-bleed prior to implantation and weekly, thereafter. Exposure to drain brand (A) induced significant elevation in total IgE (5748 ng/ml *vs.* 347 ng/ml for the sham control) by day 21. No elevation in IgE or systemic toxicity was observed with brand (B). IgE was not measured for mice implanted with brand (C) due to systemic toxicity within 14 hours. In a dose response study, implants of 10, 100 and 200 mg of brand (C) drain material produced dose-dependent clinical signs (severe vasodilatation, hypothermia, and ataxia) and elevations in serum alanine amino-transferase, blood urea nitrogen, and creatinine. Kidney and liver weights were decreased in the 200 mg group. The principal histopathologic alteration in the 200 mg group was acute, fibrinosuppurative dermatitis with suppurative vasculitis of dermal venules. No bacteria were seen in tissue sections. Hepatic changes were consistent with glycogen depletion. Endotoxin levels in the drain material were <1 EU/mg. Leaching drain material for 24 hours in methanol or acidic water reduced the toxic effects of brand (C), but leaching in sterile phosphate buffered saline, water and alkaline water had no effect on the toxicity of the material. In summary, responses other than latex sensitization that ranged from no effect to acute toxicity occurred after implantation of various Penrose drains. These studies were supported in part by NIEHS interagency agreement #Y1-ES-0049-03.

1541 SAFETY OF A RIBOZYME TARGETING HER2 RECEPTOR mRNA (HERZYME™) IN CYNOMOLGUS MONKEYS FOLLOWING A SINGLE SUBCUTANEOUS OR AN INTRAVENOUS BOLUS INJECTION.

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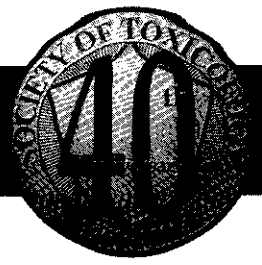
A stabilized ribozyme (HERZYME™) targeting the mRNA of the human epidermal growth factor receptor-2 (HER2) has been developed. HER2 is a member of the epidermal growth factor receptor (EGFR) family. In normal adult tissues, HER2 expression is low. However, HER2 is overexpressed in at least 25-30% of breast and ovarian cancers. Overexpression of HER2 in malignant breast tumors has been correlated with increased metastasis, chemoresistance and poor survival rates. Thus, HERZYME™ is indicated for use in treating breast (and other cancers) in which HER2 overexpression may play a role in disease progression. In this study, cynomolgus monkeys received a single subcutaneous (SC), bolus injection of HERZYME™ at 100, 300 or 1200 mg/m^2. One group of animals received HERZYME™ at 300 mg/m^2 as a single intravenous (IV) bolus injection. Control animals received an equivalent volume of saline as a SC and an IV bolus. Blood samples for toxicokinetic analyses were collected at various timepoints following administration of HERZYME™. Animals were followed for 14 days following HERZYME™ administration. There were no effects of HERZYME™ on body weight, food consumption, urinalysis, heart rate, blood pressure, clinical hematol-



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Preface

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An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 451.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 479.

The abstracts are reproduced as accepted by the Program Committee of the Society of Toxicology and appear in numerical sequence.

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