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Pharmacokinetics and Metabolism of o-Nitroanisole in Fisher-344 Rats. D. E. Carter, M. J. Miller*, D. F. Perry*, and I. G. Sipes, Tox. Prog., Univ. of Arizona, Tucson, AZ 85721.

The pharmacokinetics and metabolism of o-nitroanisole (ONA) were studied in male Fisher-344 rats. Following a single 25 mg/kg iv dose of ^{14}C-ONA, excreta, blood and tissues were collected at times ranging from 15 min to 7 days. Samples were oxidized to $^{14}CO_2$ and quantified by LSC. Urinary excretion accounted for 82% of the dose by 24 hrs and 86% by 7 days. Fecal excretion was minimal (7.5% by 24 hrs; 9.0% by 7 days). Fifteen min after ONA administration, most of the ^{14}C content was found in muscle (20%), skin (10%), fat (6.8%) and blood (6.5%). All other tissues contained <5% of the dose. Within 8 hr, <1% of the dose was present in any tissue. The initial elimination t1/2 for ^{14}C in all tissues was 1-2 hr and the terminal elimination t1/2 was ∿4 days. The elimination of parent ONA from blood followed 1st order biphasic elimination kinetics (initial t1/2 = 30 min: terminal t1/2 = 2.2 hr). Parent ONA was rapidly eliminated from all other tissues in a monophasic manner (t1/2 = 15 min-2 hr). Skin and fat demonstrated an uptake phase prior to the elimination of parent. Only 0.5% of the dose was excreted as parent in the urine. Urinary metabolites of ONA were predominately conjugated compounds (60% sulfates: 11% glucuronides). (Supported by NIEHS #NO1-ES-8-2130).

162 420

Inhalation Pharmacokinetics of Benzene in the Mouse Using Gas Uptake Studies. Christopher Kemper* and Donald Nerland* (SPON: C.H. Jarboe), Department of Pharmacology and Toxicology, University of Louisville, Louisville, KY 40292.

A description of the kinetics of benzene uptake, distribution and metabolism is important to explain the observed hemopoietic toxicity caused by this hydrocarbon. To examine the initial uptake and steady-state metabolism of benzene, male Swiss-Webster mice were placed in a sealed jar containing soda lime and connected to an external source of oxygen. The container was charged with a known quantity of benzene and the concentration of benzene in the atmosphere was monitored. At low initial concentrations, the benzene decay curve exhibited a rapid initial decline, followed by a slower first-order decrease. A computer fit of the data was found to conform to a classical two-compartment model. Pretreatment of the animals with the inhibitor 3-amino-1,2-4-triazole decreased the slow phase of benzene disappearance to approximately 10% of the rate observed in control animals. Exposure of the animals to a high initial concentration of benzene resulted in a rapid initial uptake of compound followed by a zero-order decline which became first order at concentrations below 80 PPM. These data suggest that benzene metabolism is readily saturated at low atmospheric concentrations. (Supported by USPHS Grant ES01901)

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Role of Dose Level, Food Intake and Diluent in Toxicokinetics of Orally Administered 1,1-Dichloroethylene (1,1-DCE). C.A. Counts*, J.V. Bruckner and S. Feldman*: Univ. Texas School of Public Health; Dept. Pharmacol., Div. Tox., Univ. Texas Med. School; Dept. Pharmaceutics, Univ. Houston, Houston, TX 77030.

Male Sprague-Dawley rats, acclimated for 4 weeks to reverse light/dark conditions, were implanted with a right jugular cannula and allowed to recover for 1 week prior to dosing. The cannula was connected by means of a spring and counterweight to a stopcock and heparin lock. This allowed the animals to move freely about their cages during serial blood sampling.

Fed and fasted animals were given 1,1-DCE by gavage 2 hr into their activity period at dose-levels of 50, 100, 300 and 400 mg/kg bw. The dose was diluted in either corn oil or a polyethoxylated vegetable oil (Emulphor EL620)/water emulsion.

There was a longer time to peak in fed rats and greater intersubject variability among fed than fasted animals in peak blood levels of 1,1-DCE. Animals receiving 1,1-DCE as an emulsion showed both more rapid absorption and a shorter apparent elimination half-life than those receiving 1,1-DCE in corn oil. Significantly increased elimination half-life was seen with increased dose.

These results point out the important roles of food intake, diluent and dose level in the toxicokinetics of orally administered 1,1-DCE. (Supported by EPA Grant R808282)

POSTER SESSION

HALOGENATED HYDROCARBONS II

TUESDAY, AUGUST 17 - 8:00 AM

EXHIBIT HALL

Posters will be manned twice by presenting authors:
8:00 am to 9:00 am and
4:00 pm to 5:00 pm.
Posters should be put up by 8:00 am and removed at 5:00 pm.

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Effect of phenobarbital and Aroclor 1254 pretreatment on the metabolism and biochemical effects of 1,2,4,5-tetrachlorobenzene in the rat. Ih Chu*, David C. Villeneuve and Algis Yagminas*. Environmental and Occupational Toxicology Division, Bureau of Chemical Hazards, Environmental Health Directorate, Ottawa, Canada.

Control and phenobarbital (PB) or Aroclor 1254 (polychlorinated biphenyls, AR) pretreated rats were given single oral doses of ^{14}C-1,2,4,5-tetrachlorobenzene (TCB) at 30 or 300 mg/kg. Urine and feces were collected daily for the analysis of ^{14}C-content. Half of the animals were killed 2 days after dosing and the remainder sacrificed 7 days later for the determination of hepatic microsomal enzyme activities and tissue ^{14}C-content. Pretreatment with PB and AR resulted in an increased rate of excretion of TCB together with increased levels of ^{14}C in the liver. Liver weight and glutathione were increased in the groups pretreated with PB and AR. A significant increase in hepatic ethoxyresorufin deethylase was observed in the AR-pretreated groups. These data suggest that pretreatment with PB and AR can cause an increased metabolic degradation of TCB which results in a change in its biochemical effects.

165 423

Evolution of Rat Liver Injury in Ketone-Induced Potentiation of CCl_4 Toxicity. M. Charbonneau*, M. Iijima*, M.G. Côté and G.L. Plaa, Département de pharmacologie, Université de Montréal, Montréal (Québec) Canada H3C 3J7.

This study characterized the evolution (induction/repair) of the hepatotoxic response of male Sprague-Dawley rats (200-250g) to CCl_4 following a single pretreatment (po) with ketones or ketogenic substances: isopropanol (I), acetone (A), 2.5 ml/kg; n-hexane (H), methyl n-butyl ketone (MBK), 2,5-hexanedione (2,5-HD), 15 mmol/kg, chlordecone (C) 2-50 mg/kg; vehicle (water, oil), 10 ml/kg. Animals had free access to food and water. 18 h later they received CCl_4 ip (0.1 or 1.0 ml/kg) and killed 24-120 h later. Liver damage was assessed biochemically (G-6-Pase, GPT, OCT) and histologically. Recovery from low-dose CCl_4 alone occurred by 48 h; with the high dose it occurred after 72 h. I, A, MBK, 2,5-HD or C (but not H) plus CCl_4 (0.1 ml/kg), produced damage comparable to that of 1.0 ml/kg CCl_4 given alone. Recovery time was related to the degree of damage observed. With C (50 mg/kg) plus CCl_4, deaths occurred after 48 h and no rats survived more than 96 h; with 2 mg/kg no rats died, but potentiation was observed. The results show that the evolution of hepatotoxicity correlates with the severity of the initial damage produced by CCl_4, regardless of the potentiation. (Supported by NSERC, Health and Welfare Canada, and IRSST Québec).

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