from V and M2 *in vitro* metabolism. This metabolite, in both cases had the same t_{ret} and using UV/Vis spectrum and negative ESI mass spectra ($[M]^-$ at *m/z* 294 and $[M-H]^-$ at *m/z* 293) was identified as 3', 5'-dichloro-2, 3, 4-trihydroxy-2-methylbutylanilide (M4). M3 was detected only from M2 but its formation was not NADPH-dependent. No metabolites from M1 were detected. Analysis of serum and liver extracts of treated rats showed the presence of M4, M1 and V. M4 levels were at least 5- and 9-fold higher in serum and liver, respectively, than M1 or V. These results indicate that metabolism of V is both enzymatic and non-enzymatic. M4 is an abundant metabolite of V, and may be used as an exposure biomarker for pharmacokinetic modeling of V. These results may clarify the relationship between toxicity and tissue dose of V and its metabolites. (Funded in part by NRC CR 828790. This abstract does not represent USEPA policy).

1451 *IN VITRO* METABOLISM OF CARBOFURAN BY HUMAN, MOUSE, AND RAT LIVER MICROSOMES, AND HUMAN CYTOCHROME P450 ISOFORMS.

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Carbofuran is a widely used carbamate pesticide in agricultural practice throughout the world. Its effect as a pesticide is due to its ability to inhibit acetylcholinesterase activity. The present study was designed to investigate the *in vitro* metabolism of carbofuran by pooled human liver microsomes (HLM), rat liver microsomes (RLM), mouse liver microsomes (MLM), and human cytochrome P450 (CYP) isoforms. Carbofuran is metabolized by CYPs leading to the production of a major ring oxidation metabolite, 3-hydroxycarbofuran, and two minor metabolites. Pooled HLM have a significantly higher Km value (1950 µM) than RLM Km (210 µM) and MLM Km (550 µM) for metabolism of carbofuran to its major metabolite, 3-hydroxycarbofuran. Intrinsic clearance rate calculations indicate that HLM metabolize carbofuran to 3-hydroxycarbofuran almost 14-fold lower than RLM and MLM. Among 16 human cDNA-expressed CYP enzymes examined, CYP3A4 and 2C19 were the major isoforms responsible for carbofuran metabolism to 3-hydroxycarbofuran. Use of phenotyped HLM demonstrated that individuals with high levels of CYP3A4 and 2C19 have the greatest potential to metabolize carbofuran to its major metabolite. The variation in carbofuran metabolism among 17 single-donor HLM samples is over 5-fold and the best correlation between CYP isoform activity and carbofuran metabolism was observed with CYP3A4. (Supported by NIOSH grant OH07551-ECU)

1452 COMPARISON OF DETOXIFICATION AND BIOACTIVATION PATHWAYS FOR BROMODICHLOROMETHANE IN THE RAT.

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Bromodichloromethane (BDCM) is metabolized *via* high-(CYP2E1) and low-(GSTT1) affinity pathways. The CYP2E1 pathway is thought to be a detoxification pathway at low concentrations. The GST pathway produces a labile genotoxic intermediate that is unlikely to escape from within cells where it is formed. Evidence for GSTT1-specific metabolism is supported by experiments which demonstrate that BDCM competitively inhibits GSTT1 activity toward the model substrate 1, 2-epoxy-3-(4-nitrophenoxy)propane (ENPP) (Ki = 4.2 mM). The flux of BDCM through the CYP2E1- and GSTT1-pathways has been investigated *in vitro* in non-target (liver) and cancer target tissues (kidney and large intestine) of the F344 rat. Compared to the liver, the intrinsic clearance (Vmax/Km) of BDCM *via* CYP-metabolism in target tissues was significantly reduced (8- and 16-fold for kidney and large intestine, respectively) while GST-metabolism in the same tissues was only slightly lower (~2-3-fold), suggesting less efficient detoxification particularly at high tissue concentrations of BDCM that saturate CYP2E1. The kinetic parameters of GSTT1 metabolism in liver and kidney have been incorporated into a previously published rat PBPK model for BDCM. Model simulations following constant inhaled exposures to BDCM indicate that CYP is the dominant pathway in liver and kidney following low inhaled concentrations; however, at high inhaled concentrations, the flux through CYP2E1 in kidney becomes saturated and the GSTT1 pathway becomes more pronounced than CYP in terms of total flux (at 3200 ppm, 235 mg BDCM metabolized by CYP2E1/liter per 6 h compared with 265 mg BDCM metabolized by GSTT1/liter per 6 h). Model simulations of oral doses in the dose range used in the cancer bioassay study do not result in saturation of hepatic or kidney CYP2E1 and thus flux through the GST pathway is limited. The model simulations suggest that greater genotoxic outcomes from BDCM exposure may occur from the inhalation route rather than the oral route. (Does not reflect USEPA policy. Supported by F32 ES11111-01).

1453 EFFECT OF DIMETHYL SULFOXIDE ON METABOLISM AND TOXICITY OF MODEL HEPATOTOXICANTS IN MICE.

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Effect of dimethyl sulfoxide (DMSO) pretreatment on the metabolism and hepatotoxicity of several model hepatotoxicants including acetaminophen, chloroform and carbon tetrachloride was examined in adult mice. Administration of DMSO (2.5 ml/kg, ip) decreased acetaminophen and chloroform-induced hepatotoxicity, but not the hepatotoxicity of carbon tetrachloride as measured by elevation of serum alanine aminotransferase and sorbitol dehydrogenase activities. Hepatic microsomal metabolizing enzyme activities were depressed by DMSO, but hepatic CYP2E1 activity measured with p-nitrophenol as a substrate was increased to 144% of control. *In vitro* study using hepatic microsomes showed that the metabolic degradation of acetaminophen, dichloromethane or chloroform was all inhibited by addition of DMSO, however, metabolism of carbon tetrachloride was not affected. Lineweaver-Burk plot analysis of acetaminophen metabolism *in vitro* indicated that the inhibition pattern produced by addition of DMSO was competitive in nature. To explain the observation that DMSO decreased the hepatotoxicity of acetaminophen and chloroform despite significant induction of CYP2E1 activity, a reconstituted enzyme study was conducted employing a hepatic microsomal fraction reconstituted with a hepatic cytosolic fraction each prepared from DMSO-treated or control animals. The metabolic degradation of acetaminophen, dichloromethane and chloroform was greater in a system containing cytosolic fraction from control mice (DMSO-free) plus microsomes from DMSO-treated mice than a system with control microsomes. However, addition of DMSO-present cytosol to microsomes from DMSO-treated animals failed to increase the metabolic degradation of these chemicals. This result suggests that the direct inhibitory activity of DMSO on metabolism of model hepatotoxicants be responsible for the reduction of hepatotoxicity. Competition of DMSO and model hepatotoxicants for CYP2E1 appears to play an important role here.

1454 METABOLISM OF ORALLY ADMINISTERED N, N-DIMETHYL-P-TOLUIDINE (DMPT) IN F344 RATS AND B6C3F1 MICE.

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DMPT is a high-production-volume chemical used in the manufacture of bone cements and dental materials, is found in industrial glues and artifical fingernail preparations, and is used as an intermediate in dye and pesticide synthesis. Human exposure to DMPT has resulted in methemoglobinemia and allergic responses; suspected from the formation of a toxic metabolite, p methylphenylhydroxylamine, an analog of the aniline metabolite phenylhydroxlyamine (thought to be responsible for methemoglobinemia from aniline exposure). We have previously reported results of disposition studies of DMPT in Fisher 344 (F344) rats and B6C3F1 mice after oral administration of [14C]DMPT. The majority of [14C]DMPT-derived radioactivity was excreted in urine by 24 hours. Here we report on the metabolism of orally administered DMPT. The profile of radiolabeled metabolites was determined by liquid chromatography (HPLC) using a C18 stationary phase and a mobile phase that transitioned from mostly water (polar) to mostly organic (neutral). The same four radiolabeled chromatographic peaks were observed in both rats and mice. Due to the limited volume of mouse urine, further work to elucidate the DMPT metabolite structures was performed with rat urine only. All four peaks have been isolated and preliminary structural elucidation by gas chromatography/mass spectrometry (GC/MS) and comparison to authentic standards confirmed excretion of the parent compound. We have tentatively identified a second peak by GC/MS as N-methyl-p-toluidine. A third peak had different HPLC and GC retention times than DMPT but an identical electron impact mass spectrum. Attempts at preliminary identification of the most polar metabolite have been unsuccessful. Further purification coupled with infrared and nuclear magenetic resonance spectroscopy will be employed along with incubation of isolated metabolites with glucuronidase and sulfatase enzymes (to assess conjugation) to complete structural elucidation/confirmation. Supported by NIEHS.

1455 SUBSTRATE SPECIFICITY OF THE INDIVIDUAL RAT UGT1A FAMILY OF ENZYMES.

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UDP-glucuronosyl transferases (UGT) are phase II enzymes that contribute to the elimination of xenobiotic substances and drugs. UGTs are expressed in a variety of tissues and play a major role in their metabolic activities. Due to the overlapping

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