1324 VEHICLE, VOLUME AND TIME DEPENDENT EFFECTS OF CHLOROFORM ($CHCl_3$) INDUCED HEPATOTOXICITY.

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Digestible oils have been used frequently as vehicles for oral administration of volatile lipophilic chemicals. Previous results from our laboratory have shown that both the hepatotoxicity and nephrotoxicity of $CHCl_3$ were modulated by gavage vehicle with delivery in corn oil resulting in substantially greater toxicity than aqueous vehicle delivery. As a large gavage volume (10 ml/kg) was used in these studies, and gavage volume is also known to modulate toxicity, our objective in the present study was to examine the influence of vehicle at a lower gavage volume on the hepatotoxicity of Male F-344 rats (~70 days) received by oral gavage 0, 0.25, and 0.50 ml $CHCl_3$ /kg (N=6) in both corn oil and aqueous (10 % Alkamuls) based vehicles at a gavage volume of 5 ml/kg. Hepatotoxicity was assessed at 24, 48 and 72 hr post gavage. Little or no apparent change was evident in body and relative liver weight at any $CHCl_3$ dosage administered in either vehicle over 72 hr. Serum enzymes sorbitol dehydrogenase (SDH), and alanine (ALT) and aspartate (AST) aminotransferase showed that a dose–dependent increase in $CHCl_3$ hepatotoxicity occured following delivery in either vehicle. At the lower dosage, serum levels of AST, ALT and SDH were highest at 24 hr with recovery evident by 48 hr. In contrast, at the higher dosage, serum SDH, ALT and AST were similar at 24 and 48 hr with apparent recovery delayed until 72 hr. Statistically significant differences between oil and aqueous–based delivery of $CHCl_3$ were not detected at either $CHCl_3$ dose level at any time. This stands in contrast to the large differences seen in $CHCl_3$ toxicity between oil and aqueous vehicles at a large gavage volume. In conclusion, $CHCl_3$ toxicity observed in oil and aqueous vehicles appears to be modulated by gavage volume. (This abstract does not necessarily reflect EPA policy.)

1325 FURTHER REFINEMENT OF A PHYSIOLOGICALLY BASED PHARMACOKINETIC/PHARMACODYNAMIC MODEL FOR THE TOXICOLOGIC INTERACTION BETWEEN KEPONE AND CARBON TETRACHLORIDE.

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The earlier PBPK/PD model for Kepone/CCl_4 interaction from our laboratory (El-Masri et al, 1996) was refined further by incorporating: (1) the liver zonal concept advanced by Andersen et al (1997); (2) the liver zonal distribution of P450 2E1 and P450 2B1/2, enzymes likely responsible for generating free radicals from CCl_4; (3) the concept of energy metabolism as related to hepatocellular regeneration (Soni et al, 1993); (4) the new categorization of liver histopathological changes resulting from studies in our own laboratory. The reason for these refinements is for a better capacity of predicting lethality as well as hepatocellular changes over a range of doses. In PBPK modeling, we simulated liver zonal bioactivation of CCl_4 mediated by cytochrome P-450 2E1 and P-450 2B1/2 with the incorporation of zonal expression and inductions of these P-450 isoenzymes. In PBPD modeling, the simulated liver dynamic process was composed of two stages: hepatocellular injury and hepatocellular regeneration. The construction of PBPD modeling was based on the liver histopathological study and PCNA study conducted in our lab. In histopathological study, hepatocytes were categorized as normal, injured, balloon changed and necrotic cells. In PCNA study, mitotic cell and G2 cell were counted as proliferative cells. This integrated PBPK/PD model can be used to predict liver histopathological change in rats treated with Kepone/CCl_4 at different doses of CCl_4. When coupled with Monte Carlo simulation, this model can be used to predict lethality. In Kepone/CCl_4 treated rats, at CCl_4 dose levels of 0.26, 0.52, 1.04 mmol/kg, mortality by 48 hours was 19.7%, 69.5%, 96.1% respectively in simulation involving 1,000 rats. In comparison, we observed 6.6%, 74.1%, 100% lethality from experiments in 9 to 27 rats. (Supported by NIEHS Superfund Basic Research Program Project P42 ES05949.)

1326 OLDER RATS ARE RESILIENT TO THE HEPATOTOXICITY OF CCl_4 AND CHLORDECONE + CCl_4.

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While a considerable age-dependent variation in the incidence of chemical-induced hepatotoxicity is known, the reasons for this variation remain to be fully explored. The objective of the current studies was to investigate the effects of CCl_4 alone and chlordecone + CCl_4 in 24 month old rats. Male S-D adult (60 day) and aged (24 months) rats were challenged with 2.5 ml CCl_4/kg alone or were maintained on chlordecone (CD, 10 ppm) diet for 15 days and challenged with CCl_4 (100 µ l/kg, ip). In aged rats no mortality was observed at high dose of CCl_4 as against 30 % lethality in adult rats. Exposure to CD + CCl_4 resulted in 100 % mortality in adult rats, whereas, no mortality was observed in aged rats. Liver injury was assessed by plasma enzymes (ALT and SDH) and by histopathology at 0, 6, 24 and 48 h. In high dose treated rats comparable increase in plasma enzymes at 6 and 24 h was observed in both age groups. At 48 h a decline in plasma enzymes was noted in aged rats, whereas in adult rats these enzymes remained elevated. Both plasma enzymes showed a significant progressive elevation in adult rats exposed to CD + CCl_4. Interestingly, aged rats exposed to CD + CCl_4 showed marginal and transient increase in plasma enzymes. Histological studies supported the plasma enzyme observations. Hepatocellular regeneration as measured by [^{3}H]-thymidine incorporation into DNA was suppressed in adult rats. Interestingly, in aged rats undergoing either high dose CCl_4 toxicity or interactive toxicity, S-phase stimulation occurred early at 24 h. Further studies are needed to establish the role of tissue repair in aged rats in the protection against hepatotoxicity. These initial studies suggest that the liver of aged rats has greater plasticity for repair after toxic injury, compared to adult rats. (Supported by Louisiana Board of Regents Support Fund.)

1327 ARSENIC STIMULATES BLADDER EPITHELIAL CELL PROLIFERATION.

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Epidemiological studies have demonstrated a strong correlation between increased arsenic concentrations in drinking water and the incidence of bladder cancer in human. Additionally, it has been reported that dimethylarsinic, one of the metabolites of inorganic arsenicals, promotes nitrosamine - induced rat urinary bladder carcinogenesis. We have used in vivo and in vitro models to analyze the effect of inorganic arsenic (As3+) on bladder epithelial cells. Rats treated with arsenic in the drinking water (0.02%) had high levels in the urine of total arsenic represented by DMA, MMA and As3+, and demonstrated an increase in bladder epithelial cell proliferation in 4 weeks. The proliferative changes were documented by HE staining, PCNA immunostaining and electron microscopy. Consistent with the in vivo data, arsenic induced an increase in [3-H] thymidine incorporation in several bladder epithelial cell lines, a marker for DNA synthesis and cell proliferative response. Furthermore, arsenic stimulated the activation of transcription factors associated with modulation of the growth factor expression and control of the cell cycle of bladder epithelial cells, including AP-1. Taken together, these studies suggest that arsenic-induced bladder cancer may be associated with the ability of arsenic to directly stimulate bladder epithelial cell growth. Cell proliferation alone can provide an explanation of carcinogenesis. Arsenic can promote cell proliferation of previously initiated cells or the rapid cell proliferation can be prerequisite for increased mutational rate.

1328 PERTURBATION OF MOUSE LEYDIG CELL PROLIFERATION BY ESTROGENS.

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Estrogen is a testicular carcinogen in animal models. Leydig cell tumors in human are estrogen secreting and/or estrogen sensitive. Recently, estrogenic chemicals have been implicated in the etiology of testicular cancer. The roles estrogenic chemicals play in the etiology of testicular cancer are not clear, as estrogens typically induce testicular atrophy in man when administered at pharmacological doses. In this study, we have conducted a cell proliferation

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