Environmental Management Science Program

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Improved Risk Estimates for Carbon Tetrachloride

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Research Objective

The overall purpose of these studies is to improve the scientific basis for assessing the cancer risk associated with human exposure to carbon tetrachloride. Specifically, the toxicokinetics of inhaled carbon tetrachloride is being determined in rats, mice and hamsters. Species differences in the metabolsim of carbon tetrachloride by rats, mice and hamsters is being determined in vivo and in vitro using tissues and microsomes from these rodent species and man. Dose-response relationships will be determined in all studies. The information will be used to improve the current physiologically based pharmacokinetic model for carbon tetrachloride. We will also determine whether carbon tetrachloride is a hepatocarcinogen only when exposure results in cell damage, cell killing, and regenerative cell proliferation. In combination, the results of these studies will provide the types of information needed to enable a refined risk estimate for carbon tetrachloride under EPA's new guidelines for cancer risk assessment.

Research Progress and Implications

As of April, 1998 (18 months into a 3-year project)

Species Differences in Responses of Liver Cytochrome P450 Isozymes to Inhaled Carbon Tetrachloride. The effects of repeated CCl4 inhalation on liver cytochrome P450 isozymes CYP2B and CYP2E1 levels and enzyme activity in rats, mice and hamsters have been determined. The effects vary with species and occurred after only 5 days of exposure.

Inhalation of carbon tetrachloride results in both increases and decreases in the levels of CYP2B in liver. The effect depends highly on exposure concentration within a given species. Hamsters appear to be most sensitive, with induction of protein levels occurring after only 1 week of exposure to 5 ppm. In mice, induction occurs after 1 week of exposure to 20, but not 5 ppm. In rats, induction occurs upon inhalation of 20 and 100 ppm. Inhalation of 100 ppm for 5 days drastically reduces the levels of CYP2B in mouse and hamster liver. Inhalation of 5 ppm CCl4 had no effect on CYP2B enzyme activity after 5 days of exposure. However, inhalation of 100 ppm decreased CYP2B enzyme activity in all species.

Inhalation of CCl4 for 12 weeks resulted in a concentration-dependent increase in CYP2B concentration in rats. CYP2B concentration in mice was decreased in animals inhaling 20 ppm and decreased in hamsters inhaling 20 and 100 ppm. CYP2B activity was decreased in a concentration-dependent manner in rats, mice and hamsters inhaling CCl4 for 12 weeks.

The responses of liver cytochrome P450 isozyme CYP2E1 to CCl4 inhalation also varied widely with species and did not parallel those of CYP2B. CYP2E 1 levels were significantly decreased in mice after 5 days of exposure to 20 and 100 ppm, and in hamsters after 5 days of exposure to 100 ppm.

Species Differences in Responses of Liver Cytochrome P450 Isozymes to Ingested Carbon Tetrachloride. The effects of repeated ingestion of 0.5 and 5 ppm carbon tetrachloride in drinking water on liver cytochrome P450 isozozymes are being evaluated. The 1-week studies have been completed. The 4-week study is underway.

Species Differences in Effects of Inhaled Carbon Tetrachloride on Cytolethality, Histopathological Changes and Regenerative Cell Proliferation In Liver. No lesions were observed at 5 ppm, the current TLV for CCl4.

Inhalation of high concentrations of CCl4 induces hepatic damage and regenerative cell proliferation. Hepatic cytotoxicity, necrosis and cell proliferation were greatest in hamsters, intermediate in mice, and least in rats inhaling 100 ppm CCl4.

Proliferation does not occur at concentrations that induce mild lesions.

Species Differences in Effects of Ingested Carbon Tetrachloride on Cytolethality, Histopathological Changes and Regenerative Cell Proliferation In Liver. No liver lesions were present in livers of rats, mice or hamsters drinking water containing 0.5 and 5.0 ppm CCl4 for 7 days.

Whole-Body Metabolism Studies of Inhaled Carbon Tetrachloride. Whole body metabolism studies have been conducted on rats (100, 250 and 1000 ppm) and mice (100 and 1000 ppm). PBPK modeling was performed using the data. Modeling of the rat data replicated results of a previous study, thus validating the model. Preliminary modeling results on the mouse data indicate that metabolism is under-predicted using body-weight-scaled constants from the rat.

Species Differences in the Toxicokinetics of Inhaled Carbon Tetrachloride. Rats and mice have been acutely exposed for 4 hours to 20 ppm 14C-labeled CCl4. Samples are being analyzed.

Results to date suggest that minimal toxic effects occur at the current threshold limit value for carbon tetrachloride (5 ppm) and that a no observed effect level can be determined for liver cell necrosis and proliferaton.

Planned Activities

Future Directions and Expected Progress

Studies on the effects of ingested CCl4 on liver cytochrome P45O isozymes, cytolethality and cell proliferation will be completed.

The in vitro metabolism of CCl4 by human, rat, mouse, and hamster liver microsomes will be compared.

Studies on species differences in the toxicokinetics of inhaled CCl4 will be completed.

Whole body metabolism studies on mice and hamsters will be conducted.

The current PBPK model for CCl4 will be revised based on the data obtained from the toxicokinetic and whole-body metabolism studies.