Bull. Environm. Contam. Toxicol. 29, 196–199 (1982)

In Vivo Suppression of 1,1,1-Trichloroethane Metabolism by Co-administered Tetrachloroethylene: An Inhalation Study

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The wide spread uses of methylchloroform (MC: 1,1,1-trichloroethane) and tetrachloroethylene (TETRA) as industrial solvents and degreasers have resulted in chronic exposure of many industrial workers to the vapor of these two chemicals. MC, thought to be a more preferable solvent, is less hepatotoxic (STEWART et al. 1969). The limited metabolism of MC (IKEDA & OHTSUJI 1972) is considered a likely reason for its low hepatotoxicity. The capacity of humans to metabolize TETRA is also small (IKEDA & OHTSUJI 1972), but TETRA is hepatotoxic (RAYNOLDS & MOSLEN 1977). Considering that both chemicals are metabolized by hepatic microsomal mixed function oxidase system (MFOS: VANDYKE 1977, LEIBMAN et al. 1977, COSTA et al. 1980) and that at present toxic effects of chlorinated ethylenes are thought to be related to the formation of highly reactive metabolite such as epoxide during their oxidation, the question whether or not the oxidation of TETRA by MFOS is suppressed by MC should be clarified for the estimation of joint toxicity under mixed exposures, as often observed in the practical workplaces.

MATERIALS AND METHODS

Chemicals: Inhibitor-free MC (purity ca. 99.95%) and TETRA (purity ca. 99.89%) were kindly supplied by Toa Gosei Co. Ltd., Nagoya, Japan. Chemicals without inhibitors were employed to exclude the possibility that the contaminating inhibitors used in commercial preparations might have some effects on the metabolism as stressed by Henschler et al. (1977).

Animals: Male Wistar littermate rats weighing 180-200 g were used. They were maintained on commercial laboratory chow, water ad libitum and were kept in a temperature-controlled room (25±2°C) with alterating 12 hours of light and darkness. During exposure, each rat was separately housed in a stainless steel metabolic cage with wired floor kept in the exposure chamber, and allowed free access to food and drinking water. Urine was collected separately from faeces. Rats were exposed during the

0007-4861/82/0029-0196 $01.00

light period of the day.

Urine collection and analysis: Urine samples (one sample per rat for a given period) were collected during two periods i.e., during 8 hours of exposure and the following 16 hours without exposure. Total trichloro-compound (TTC), trichloroacetic acid (TCA) and trichloroethanol (TRI-OH) were measured by the method after TANAKA & IKEDA (1968). Excretion rates per body weight per hour (μg/kg/hr) of TTC, TCA and TRI-OH were calculated from the amounts excreted during each time period.

Vapor exposure to MC and TETRA: Animals were exposed for 8 hours to the vapor of MC at 350 ppm (The MC group), or of TETRA at 100 ppm (The TETRA group) or a mixture of vapors of MC and TETRA at 350 ppm and 100 ppm (The MC+TETRA group). The concentrations were selected to meet the 8-hour occupational exposure limits (OELS: ACGIH 1981). Inhalation exposures were conducted in parallel in 350 liter pyramidal, stainless steel walled, dynamic flow type chambers equipped with a computerized regulating system as previously described (KOIZUMI & IKEDA 1981). Concentrations of the chemicals in the chamber atmospheres were monitored every 18.5 min using a FID-gas chromatograph (HITACHI MODEL 163) and were controlled automatically to produce desired concentrations. The coefficients of variation of the vapors generated were 1.4 to 6.7%.

RESULTS AND DISCUSSION

As shown in TABLE I, the main metabolites observed in the MC and TETRA groups were TRI-OH and TCA respectively, in agreement with other reports (IKEDA & OHTSUJI 1972, EBEN & KIMMERLE 1974, YLLNER 1961, DANIEL 1963). During the 8-hour-exposure and following 16 hours, the excretion rates of TTC by the MC+TETRA group were less than the total excretion rates of TTC by the MC and TETRA groups. Furthermore it should be emphasized that in the 8-hour-exposure the excretion rates of TTC and TRI-OH by the MC+TETRA group were significantly lower ($p<0.05$ and $p<0.01$, respectively) than those of the MC group. The approximate suppression rate of MC metabolism in terms of TTC excretion rate during the 8-hour-exposure is defined as;

$$\text{Suppression rate} = \frac{\text{TTC from MC+TETRA group} - \text{TTC from TETRA group}}{\text{TTC from MC group}}$$

The suppression rate was 0.42 for the 8-hour-exposure and 0.60 for the succeeding 16 hours. In both periods, the differences in TCA were insignificant ($p<0.10$) between the TETRA group and the MC+TETRA group, indicating that suppression of TETRA metabolism by MC is slight, if any. Thus, even under exposure at the OELs, MC metabolism was suppressed by TETRA dramatically, more intensively during exposure and

TABLE I. Suppression of MC metabolism by TETRA

Groups	No. of Rats	Exposure Concentrations (ppm; M±SD)[a]	During Exposure[b]			After Exposure[c]		
			TTC	TRI-OH	TCA	TTC	TRI-OH	TCA
MC	7	354.5±23.7	178.6±39.3	164.6±42.9	14.1±9.9	79.7±19.1	77.7±17.6	2.0±4.9
TETRA	7	99.0±1.4	48.4±16.7	—[d]	48.4±16.7	85.9±40.9	—[d]	85.9±40.9
MC + TETRA	7	361.0±21.8 99.3±2.3	122.6±37.1*	74.6±40.5**	48.0±16.0	134.0±47.5*	76.7±43.1	56.4±22.0

a/ The vapor concentrations were monitored every 18.5 min; 26 determinations for each chamber were carried out through the 8-hour-exposures.

b/ Urinary metabolites excreted during the 8-hour-exposure were calculated. Numbers shown are M±SD (in μg/kg/hr) of 7 determinations.

c/ Metabolites excreted during succeeding 16 hours after the termination of the exposure were calculated. Numbers are as in b/.

d/ Less than the detection limit of 1 mg/l.

The significance of the difference from the MC group (by t-test) is shown as follows; **, $p<0.01$; *, $p<0.05$.

In both periods, no significant difference of TCA excretion rate was observed between the TETRA and the MC+TETRA groups.

less intensively after termination of the exposure.

The apparent suppression of MC metabolism by TETRA suggests two possibilities: (1) suppression of oxidation of MC to TRI-OH:(2) suppression of excretion of TRI-OH. The rate-limiting stage in the MC metabolism is considered to be the oxidation step (EBEN & KIMMERLE 1974), and the mutual interactions among several organic solvents in most cases are at the steps of oxidation by MFOS (IKEDA 1979, IKEDA & HIRAYAMA 1978). Therefore the former probability is more plausible eventhough the latter could not be excluded in the present study. Thus, more predominant suppression of MC metabolism suggests that epoxide formation in TETRA metabolism may more preferentially occur than MC oxidation when MC and TETRA compete in MFOS.

The in vitro kinetic analysis in the interaction between MC and TETRA is currently under investigation to extend the present observation for establishment of the general principle of metabolic interaction among various chlorinated hydrocarbons.

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Accepted June 19, 1982