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Letter to the editors

Different pharmacokinetics of dichlorofluoromethane (CFC 21) and chlorodifluoromethane (CFC 22)

H. Peter[1], J. G. Filser[2], L. v. Szentpály[3], and H. J. Wiegand[1]

[1] Institut für Arbeitsphysiologie an der Universität Dortmund, Abteilung Toxikologie und Arbeitsmedizin, Ardeystr. 67, D-4600 Dortmund 1
[2] Gesellschaft für Strahlen- und Umweltforschung, Abteilung Toxikologie, Ingolstädter Landstr. 1, D-8042 Neuherberg
[3] Institut für Theoretische Chemie der Universität Stuttgart, Pfaffenwaldring 55, D-7000 Stuttgart 80, Federal Republic of Germany

Abstract. Inhalation pharmacokinetics of dichlorofluoromethane (CFC 21) and chlorodifluoromethane (CFC 22) were studied in male Wistar rats by use of a closed inhalation chamber system. CFC 21 was readily eliminated via metabolism.

However, CFC 22 underwent no detectable metabolism; pretreatment of the rats with DDT or phenobarbital did not stimulate metabolic transformation of the compound. Hence, formation of biologically relevant amounts of reactive intermediates from CFC 22 as a mechanism of toxicity seems unlikely.

Key words: Pharmacokinetics – Dichlorofluoromethane – Chlorodifluoromethane

The replacement of chlorine in the chloroform molecule by fluorine leads to changes in metabolism and toxicology. Two chloroform analogs, dichlorofluoromethane (CFC 21) and chlorodifluoromethane (CFC 22), are of technical importance. Trochimowicz et al. (1977) have shown that CFC 21 is partially metabolized in rats and dogs, probably by a cytochrome P-450-dependent pathway; they identified fluoride as a metabolite. After long-term exposure to CFC 21 severe lesions of the liver parenchyma, similar to those induced by chloroform, were observed in laboratory animals (Weigand et al. 1971). By contrast, the metabolic transformation of CFC 22 seems to be low, although some carcinogenic activity of CFC 22 at a high concentration (50 000 ppm) in male rats was recently suspected with a "no-effect-level" of 10000 ppm (Litchfield and Longstaff 1984). This led us to compare the inhalation pharmacokinetics of CFC 21 and CFC 22 in rats.

Male Wistar rats (280–330 g) were obtained from the Zentralinstitut für Versuchstierzucht, Hannover, FRG. Dichlorofluoromethane (CFC 21) and chlorodifluoromethane (CFC 22), purity 99.95%, were supplied by Hoechst AG, Frankfurt, FRG.

The experiments were conducted in a closed desiccator system as described previously (Filser and Bolt 1979, 1981). Experiments were performed on groups of two rats each. The animals were placed into the desiccator (volume 6.38 l), which contained soda lime (50 g) for CO_2 absorption. The system was connected to a pressureless oxygen supply via a water trap. Different initial concentrations of CFC 21 and CFC 22 were introduced into the system by a gas-tight syringe.

CFC 21 and CFC 22 were monitored in the gas phase by gas chromatography. A Carlo Erba gas chromatograph with 5 ml gas sample loop and FID was used. The chromatographic conditions were: 5 m steel column (1/8 inch) with Tenax GC^R, 80–100 mesh; carrier gas N_2 (30 ml/min); oven temperature 135 °C. Retention times of 1.3 min (CFC 21) or 0.85 min (CFC 22) were observed under these experimental conditions. No peaks of impurities could be detected in the chromatograms.

IP administration of CFC 21 or CFC 22 was done with a gas-tigth syringe. Injected animals were then transferred to the closed chamber (see above). Analysis of exhalation curves was performed as previously described (Bolt and Filser 1984). The kinetic parameters of metabolic transformation after inhalation were calculated based on the two compartment open pharmacokinetic model developed by Filser and Bolt (1979, 1981). For CFC 21 and CFC 22 this model adequately fitted the experimental data.

Figure 1 shows the concentration-time course of CFC 21 (Fig. 1a) and CFC 22 (Fig 1b) in the atmosphere of the closed system when the compounds were administered IP to rats. In parallel experiments, the same amounts of compounds (see legend) were introduced into unoccupied systems (desiccators of the same size, also containing soda lime, but no animals (open circles in Fig. 1).

A slow decline of both compounds occurred in the unoccupied system which was due to absorption and/or reaction with the soda lime (as demonstrated by control experiments without soda lime, data not shown).

Both injected compounds showed different behaviour. Injected CFC 22 was almost completely exhaled, and its further decline in the system could not be distinguished from that of CFC 22 introduced into the atmosphere of the unoccupied system. Injected CFC 21, however, was only partly exhaled and showed then a consistent decline (Fig. 1a). From these figures, total clearance values from the system (occupied by rats) were calculated to be 120 ml $\times h^{-1} \times kg^{-1}$ (CFC 22) and 4400 ml $\times h^{-1} \times kg^{-1}$ (CFC 21), respectively. The static equilibrium constant (K_{eq}; Filser and Bolt 1979) was 0.1 for CFC 22 and 6.0 for CFC 21. The clearance (Cl_{tot}) of CFC 22 from an unoccupied system (only soda lime) was 109 ± 80 ml $\times h^{-1}$ (ten experiments), that of CFC 21 was 250 ± 120 ml $\times h^{-1}$ (ten experiments).

Offprint requests to: H. Peter

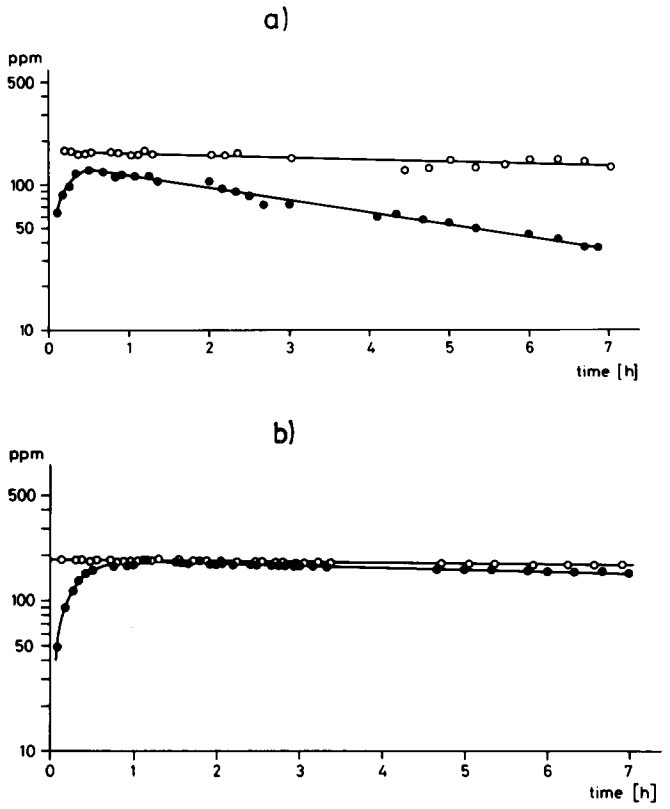

Fig. 1. a Concentration decline of CFC 21 in a closed chamber (6.38 l desiccator, with 50 g soda lime), after adjustment of an initial concentration of 160 ppm CFC 21 *(open circles*; system not occupied by rats), or *(closed circles)* after injection of the same amount of CFC 21 IP into rats (equivalent to a theoretical initial concentration of 3250 nl gas/g body wt.; body wt. =308 g); **b** concentration decline of CFC 22 in the same chamber, after adjustment of an initial concentration of 160 ppm CFC 22 *(open circles;* system not occupied by rats), or *(closed circles)* after injection of the same amount of CFC 22 IP into rats (equivalent to a theoretical initial concentration of 3080 nl gas/g body wt.; body wt. 325 g)

Experiments where CFC 22 was added directly to the gas phase of the system (occupied by rats) resulted in clearance values which did not differ from those of controls (without animals). In addition, pretreatment with phenobarbital (80 mg/kg IP, followed by 3 days of 0.1% phenobarbital in the drinking water) or DDT (200 mg/kg, 1 week prior to the experiments) did not result in elimination rates of CFC 22 which differed from those in control experiments (without animals). Based on these results, metabolic elimination of CFC 22 by rats is not detectable. Further experiments also confirmed this for $B_6C_3F_1$ mice.

By contrast, the clearance values for CFC 21 are in the range observed for compounds like 1,3-butadiene (Bolt et al. 1984) or methyl chloride (Peter et al. 1985).

One factor which partially explains this difference is the high accumulation of CFC 21 in the body; its K_{eq} (6.0) is 60-fold higher than that of CFC 22 ($K_{eq}=0.1$). Because significant metabolism of CFC 22 is not detected, it seems unlikely that the tumorigenesis observed in a long-term bioassay with rats at high concentrations (Litchfield and Longstaff 1984) is due to action of active CFC 22 metabolites.

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