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Filser J.G.	~~et al~~		11
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1 2	61 62
	21
Pharmacokinetics of Halogenated Ethylenes	22
in Rats -- Metabolism, Uptake	23
	24

Source (Journal, Vol., Number, Pages, Date)

1 2	61 62
Arch. Toxicol. 42, pp. 123-136, 1979	31
	32

Brief Summary

1 2 10	61 62
SUMMARY:	61
	62
	63
	64

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Pharmacokinetics of Halogenated Ethylenes in Rats

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Abstract. Inhalation pharmacokinetics of the halogenated ethylenes vinyl fluoride (VF), vinylidene fluoride (VF_2), vinyl chloride (VCl), vinylidene chloride (VCl_2), cis- and trans-dichloroethylene (cis-DCE and trans-DCE), trichloroethylene (Tri), perchloroethylene (Per), and vinyl bromide (VBr) have been comparatively studied in the rat. Rats were exposed in a closed inhalation system to various initial atmospheric levels of halogenated ethylenes, and the decline of atmospheric concentration was followed using gas chromatographic analysis. From pharmacokinetic analysis of the experimental curves the following general patterns of the halogenated ethylenes were derived.

Distribution of the compounds in the organism and in the gas phase is determined by physical factors. For practical purposes, a relation of the equilibrium constants with the volatilities of the compounds, expressed by the boiling points, may be used: compounds with a low boiling point are enriched in tissues much less than those of a higher boiling point, and *vice versa*. Compounds with high accumulation in tissues (Tri, Per) need much more time for completion of the equilibration process than more volatile compounds.

Metabolic elimination of halogenated ethylenes is a saturable, dose-dependent process. If animals are exposed to atmospheric concentrations of a halogenated ethylene which exceed the "point of saturation (Sp)", elimination is determined by a zero-order law, i.e., its rate is independent of the concentration of the compound. In contrast, below saturation normal first-order kinetics apply.

If the rate of metabolic elimination is related to the concentrations of the compounds in the tissue compartment, very similar rates for first-order elimination of the different halogenated ethylenes are found. This suggests a common rate limiting factor applicable for the lower concentration range.

The maximal velocities (V_{max}) of metabolic elimination of halogenated ethylenes which are reached above the "saturation points" depend on the chemical structures of the individual compounds. In general, with the exception of Tri,

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R&S 107165

further halogen substitution inhibits metabolic conversion. Of the halogenated ethylenes, VF_2 and Per are extremely slowly metabolized.

The present report also provides the data necessary for calculation of the rates of metabolism of halogenated ethylenes in rats at a given concentration of atmospheric exposure.

Key words: Halogenated ethylenes — Vinyl fluoride — Vinylidene fluoride — Vinyl chloride — Vinylidene chloride — Cis-dichloroethylene — Trans-dichloroethylene — Trichloroethylene — Perchloroethylene — Vinyl bromide — Pharmacokinetics — Metabolism.

Introduction

Since the cancerogenic effects of vinyl chloride have been detected many experimental studies are concerned with the action of halogenated ethylenes on the living organism. It is now generally recognized that the cancerogenic and hepatotoxic effects of vinyl chloride, and also hepatotoxic effects of compounds related to vinyl chloride, are not directly elicited by these substances themselves, but by reactive metabolites (cf. Bonse and Henschler, 1976).

Gehring and coworkers (1977, 1978) very recently pointed out for vinyl chloride that toxicological dose-response considerations have to take into account the rates by which the compound is metabolically transformed. They also showed that metabolism of vinyl chloride is a saturable process, and that increase in atmospheric vinyl chloride concentrations does not similarly enhance the hepatic tumor rate. The general concept has been inferred that the toxicologically effective dose of a chemical which requires metabolic activation is not identical to the total dose acting upon the organism, but must be calculated from appropriate kinetic and metabolic data.

For the congeners of vinyl chloride such data are still lacking. The present report describes a pharmacokinetic approach which allows calculation of the rate of metabolism of vinyl fluoride (VF), vinylidene fluoride (VF_2), vinyl chloride (VCl), vinylidene chloride (VCl_2), cis- and trans-dichloroethylene (cis-DCE and trans-DCE), trichloroethylene (Tri), perchloroethylene (Per), and vinyl bromide (VBr), at a given atmospheric concentration. The considerations extend a previous assessment of the pharmacokinetics of vinyl chloride in the rat (Bolt et al., 1977).

Materials and Methods

Materials. VCl, VF and VF_2 were donated by Dynamit-Nobel AG, Troisdorf, Germany.

VBr, VCl_2, trans-DCE and Per were products of Aldrich Europe, Brussels, Belgium. Cis-DCE was manufactured by Ferak, Berlin, and Tri by Merck, Darmstadt. The purity of all the compounds was checked by GLC. If necessary, the compounds were redistilled to achieve a purity of at least 99%.

Animals. Male Wistar rats (250 g) of Ivanovas, Kisslegg, Germany, were used for the experiments. In some experiments metabolism of the halogenated ethylenes was inhibited by injecting (i.p.) 150 mg/kg 6-nitro-1,2,3-benzothiadiazole (Bolt et al., 1976, 1977) or 100 mg/kg dithiocarb (diethyldithiocarbamate, Merck, Darmstadt), 30 min prior to the exposure.

Exposure of Animals. Animals were exposed to the volatile halogenated hydrocarbons in a closed all-glass system as previously described (Bolt et al., 1976, 1977). The animals were placed into a desiccator which contained soda lime for CO_2 absorption and which was connected via a water trap to an oxygen supply. Air samples could be drawn via a teflon-coated rubber septum. After injection of the calculated amount of compound into the gas phase its concentration in the system's atmosphere was determined by GLC in short intervals.

Gas-Liquid-Chromatography (GLC). Air samples, drawn from the exposure system, were injected into a 5-ml loop, connected by a 6-port valve with a Varian 1440 gas chromatograph. The column (3 m, 1/8" stainless steel) was filled with Porapak Q (50–80 mesh). Column temperatures varied according to the individual compounds which were to be analyzed. Detector (FID) temperature was set 50° above column temperature. Gas flow rates were: nitrogen, 60 ml/min; hydrogen, 30 ml/min; air, 300 ml/min.

Calculations. In general, the computations followed the system previously employed for assessment of pharmacokinetics of vinyl chloride (Bolt et al., 1977) with the modifications described below in the results section. For the computations a programmed Texas Instruments TI 59 calculator, equipped with a PC 100 A printer, was used.

Results

Decline of Halogenated Hydrocarbon Concentration in the Gas Phase

Figures 1–3 show representative examples of declines in our exposure system of atmospheric concentrations of VBr, cis-DCE and trans-DCE. The air volume of the system was 10.3 l; it was occupied by three rats, each of 200–250 g. For analysis,

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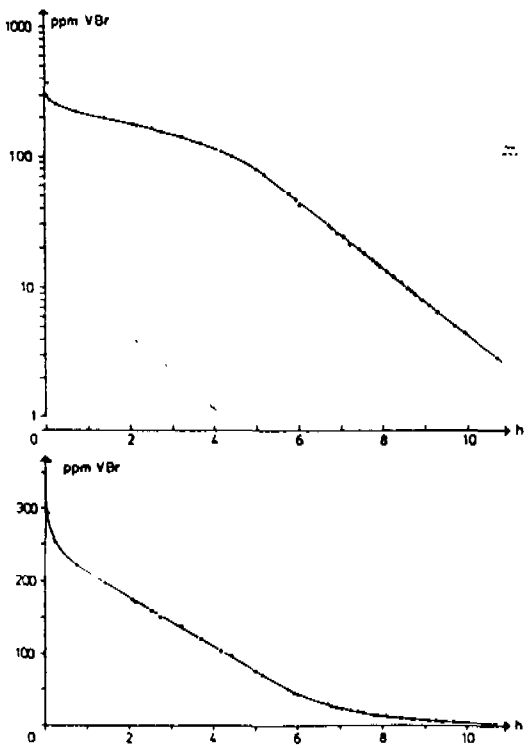

Fig. 1. Decline of concentration of vinyl bromide (VBr) in the gas phase of a closed exposure system (volume 10.3 l), occupied by three male Wistar rats, each of 200–250 g. Top: logarithmic plot (linear section = first order decline); bottom: linear plot (linear section = zero order decline)

R&S 107167

the curves obtained can be divided into three sections. The first phase in which the compound equilibrates between gas phase and the organism takes ½ h for VBr (Fig. 1), about 2 h for cis-DCE (Fig. 2) and about 1.5 h for trans-DCE (Fig. 3). After the initial equilibration period, a further decline in concentration of the compounds in the system represents the velocity by which metabolic conversions take place. At higher atmospheric concentrations of the compounds the equilibration phase is followed by a phase of apparent zero-order decline, as visualized in the linear graphs (Figs. 1 and 2). As time proceeds, a third phase is apparent (see Figs. 1 and 2) in which the kinetics now strictly follow a first-order law, as visualized in the logarithmic graphs.

Trans-DCE (Fig. 3) is an example for a compound with an only slow metabolism. However, Figure 3 shows that the pharmacokinetic behaviour also of this compound is dose-dependent; it shows different metabolic rates at high and at low concentrations. Also for this compound the experimental values can be described by assuming zero-order kinetics at the higher, and first-order kinetics at the lower concentration range.

The same type of analysis as shown for the three compounds in Figure 1–3 has also been performed with VF_2, VF, VCl, VCl_2, Tri and Per. Individual curves for these compounds are not shown in separate figures; they exhibited the same features as those in Figures 1–3. Experiments with the same compound were always re-

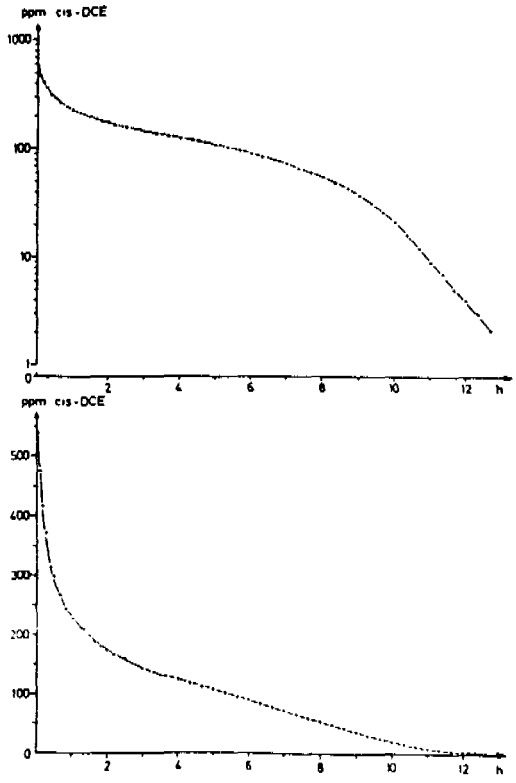

Fig. 2. Decline of concentration of cis-dichloroethylene (cis-DCE) in the gas phase of a closed exposure system (volume 10.3 l), occupied by three male Wistar rats, each of 200–250 g. Top: logarithmic plot; bottom: linear plot

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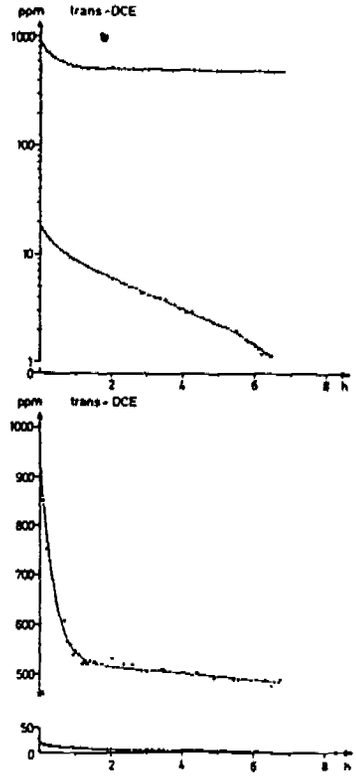

Fig. 3. Decline of concentration of trans-dichloroethylene (trans-DCE) in the gas phase of a closed exposure system (volume 10.3 l), occupied by three male Wistar rats, each of 200—250 g. Top: logarithmic plot; bottom: linear plot of the same experimental values. Two sets of experiments at a higher and a lower concentration range are shown, demonstrating dose-dependent pharmacokinetics

peated, and the pharmacokinetic parameters derived from different sets of analogous experiments showed always variations of less than 10%. For all compounds the "points of saturation" and the velocities of metabolism (zero and first order kinetics) were established (see below).

Equilibration of Halogenated Ethylenes with the Organism

The process of equilibration of the halogenated ethylenes between the gas phase and the animal organism was analyzed in rats in which the oxidative metabolic enzymes had been inhibited by previous administration of 6-nitro-1,2,3-benzothiadiazole, as described earlier (Bolt et al., 1976, 1977). During the course of the present investigation it was found that a nearly complete inhibition of metabolism, lasting a few hours, could also be achieved by a single i.p. dose of 100 mg/kg dithiocarb (in H_2O). Under these conditions the first model of Figure 4 was applied. In contrast to the previous pharmacokinetic approach (Bolt et al., 1977) the present calculations were done in a more generalizing manner, also taking into account different possible volumes of the gas phase and the tissue compartment. Concentrations of the halogenated compounds, in atmosphere as in organism, were considered both as concentrations by volume.

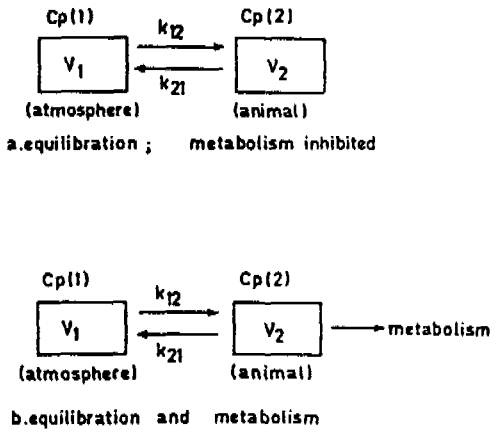

Fig. 4. Pharmacokinetic models for (a) equilibration of atmospheric halogenated ethylenes with the organism in a closed exposure system. Conditions of negligible metabolic turnover or inhibited metabolism; (b) distribution, as in (a), and metabolism. Metabolic elimination may follow zero-order or first-order kinetics

On influx of a volatile compound from the closed gas phase into the animal compartment [Cp(1) and Cp(2) of Fig. 4] the concentration in gas phase follows:

$$\frac{dy_1}{dt} = -k_{12} \cdot y_1 \tag{1}$$

For the opposite process of efflux from the body into the gas phase the concentration in tissues follows

$$\frac{dy_2}{dt} = -k_{21} \cdot y_2 \tag{2}$$

y_1 and y_2 are the concentrations of the volatile compound in question in the gas phase and in the tissues, respectively.

If we do not consider metabolic processes (conditions of low metabolic turnover or inhibited metabolic enzymes; Fig. 4a) the solution of (1) and (2) is

$$y_{2(t)} = y_{1(o)} \cdot \frac{k_{12} V_1}{k_{12} V_2 + k_{21} V_2} [1 - e^{-(k_{12} + k_{21})t}] \tag{3}$$

$y_{1(0)}$ = initial concentration in gas phase
V_1 = gas phase volume in the individual experiment
V_2 = volume of tissue compartment (animal volume) in the individual experiment.
For $V_1 \gg V_2$, and accordingly $k_{21} \gg k_{12}$, Eq. (3) approximates to

$$y_{2(t)} \approx y_{1(o)} \cdot \frac{k_{12} V_1}{k_{21} V_2} [1 - e^{-k_{21}t}]. \tag{4}$$

For conditions of equilibrium ($t \to \infty$), we obtain

$$y_{2(\infty)} \approx y_{1(o)} \cdot \frac{k_{12} V_1}{k_{21} V_2} = y_{1(o)} \cdot K_{eq} \tag{5}$$

K_{eq} = equilibrium constant.

R&S 107169

Table 1. Equilibration of atmospheric halogenated ethylenes with the rat organism, according to model fo Figure 4 a. K_{eq} = equilibrium constant; $k_{12}V_1$ and $k_{21}V_2$ = clearance values for the partial processes, see Eqs. (3–7)

Compound	K_{eq}	$k_{12}V_1$ (ml/h)	$k_{21}V_2$ (ml/h)
VF_2	0.23	5 000	21 200
VF	0.91	4 200	4 600
VCl	5.3	34 700	6 600
VBr	11.3	61 500	5 400
VCl_2	7.8	11 600	1 500
trans-DCE	11.5	11 300	985
cis-DCE	20	14 500	730
Tri	52	13 000	250
Per	105	7 200	68

In this calculation V_2 is the "animal volume" in the particular experiment. For any other "animal volume" (V_2^*) to be considered the concentration $y^*_{2(t)}$ in the animal compartment, according to (4) and (5), is:

$$y^*_{2(t)} \approx K_{eq} \cdot y_{1(o)} \left[1 - e^{-k_{21}\frac{V_2}{V_2^*}t}\right]. \tag{6}$$

Table 1 shows, for the different compounds examined, the "clearance values" for the partial processes, $k_{12}V_1$ and $k_{21}V_2$, and the "constant of equilibrium" between gas phase and animal compartment, i.e.,

$$K_{eq} = \frac{k_{12}V_1}{k_{21}V_2}. \tag{7}$$

The values of Table 1 are derived from experimental determinations of K_{eq} and from the observed first order rate constants k whereby k equals $k_{12} + k_{21}$ (see Eq. 3).

Metabolic Elimination of Halogenated Ethylenes

The linear (zero-order) and logarithmic (first-order) sections of all experimental curves obtained were subjected to regression analyses (*lin* or *log*, respectively). The constant velocity for each compound during the linear phase was called "V_{max}" and calculated as μmol/h per kg body weight (Table 2). For the logarithmic section, y_0 and k' of the process

$$y = y_o\, e^{-k't} \tag{8}$$

were calculated. In every individual regression analysis done r amounted to ≥ 0.99.

From k′ and the apparent volume of distribution the clearance values for first-order elimination of all compounds were calculated, expressed as l/h per kg body

R&S 107170

Table 2. First-order and zero-order metabolic elimination of halogenated ethylenes from a closed exposure system: saturation points (Sp) and metabolic rates, expressed as V_{max} and clearance, based on 1 kg body weight

Compound	Sp (ppm in air)	First order clearance liter / h · kg body wt	Zero order V_{max} µmol / h · kg body wt
VF_2	(100)	0.29	1.1
VF	(75)	2.5	7
VCl	250	11.0	110
VBr	55	18	40
VCl_2	150	17	100
trans-DCE	(15)	11	7
cis-DCE	20	30	25
Tri	65	77	210
Per	[a]	[a]	< 7

[a] Because of the very low metabolic elimination of Per, the appropriate values cannot be given
Sp-values given in brackets are not observed experimentally, but are obtained by extrapolation (intersection of observed zero-order and first-order declines)

weight (Table 2). For most of the compounds (VCl, VBr, VCl_2, cis-DCE, Tri) the atmospheric concentration point where elimination shifted from zero-order into first-order kinetics ("saturation point") could directly be taken from the experimental concentration curves (e.g., Fig. 1 or Fig. 2). However, for those compounds which were slowly eliminated a direct assessment was not possible because of the very prolonged experimental observation periods required. Therefore, with VF, VF_2 and trans-DCE different experiments were carried out at higher and at lower concentrations (e.g., see Fig. 3). From these figures the kinetic parameters for the zero-order and first-order sections were derived.

The theoretical "saturation point" (Sp) then was calculated as that point at which

$$\frac{dy}{dt} = - y_o k' e^{-k't} \tag{9}$$

equals V_{max}. It is obtained by

$$Sp = \frac{V_{max}}{k'} . \tag{10}$$

The appropriate values for Sp (expressed as ppm of compound in air at which "saturation" occurs) are included into Table 2.

However, Per is so extremely slowly metabolized in rats that we were not able to experimentally differentiate between zero and first order kinetics. Hence, the equivalent data cannot be given for Per (Table 2).

R&S 107171

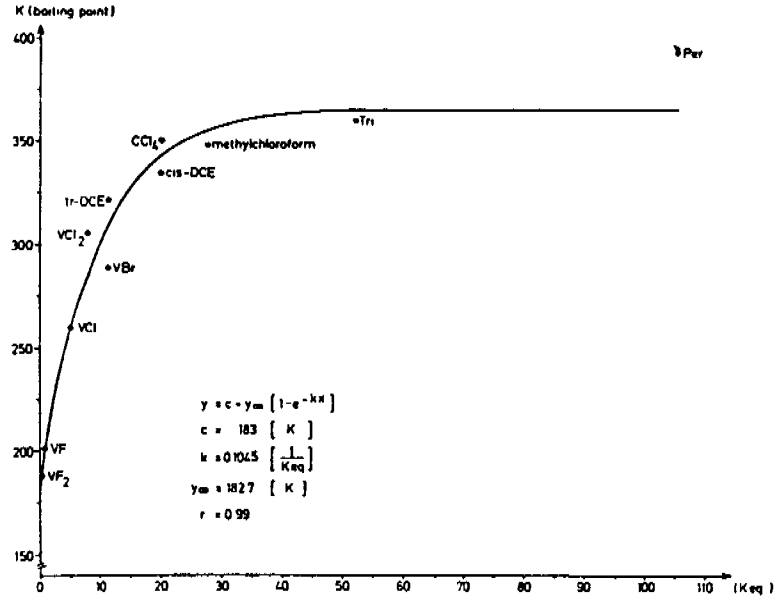

Fig. 5. Connection between distribution behaviour of halogenated hydrocarbons (equilibration constant K_{eq} on the abscissa) and volatilities (boiling points on the ordinate). Results of a *log* regression analysis are given. The calculated curve is drawn

Further Analysis Using the Kinetic Data

The behaviour of the volatile compounds during the initial phase of equilibration with the organism is largely determined by K_{eq} (Eq. 7); the latter depends on the physical properties of the compound in question. Figure 5 shows the connection between volatilities, expressed as the boiling points of the compounds, and K_{eq}. The curve also includes data for methyl chloroform (1,1,1-trichloroethane) and for CCl_4 which, in terms of distribution, behave in a manner similar to the halogenated ethylenes.

In order to give an idea how fast equilibrium is achieved, theoretical curves of concentration of the volatile xenobiotics in the tissues were drawn, assuming a constant concentration of xenobiotic in the atmospheric environment. Metabolic processes were not taken into account. Figures 6 and 7 show the calculated courses of concentrations of the halogenated ethylenes in tissues of rats exposed to a constant concentration of the individual compounds in the air of 100 ppm. VF, VF_2, VCl and VBr reach their equilibrium very rapidly, within 30 min after beginning of exposure. VCl_2, cis-DCE and trans-DCE take a middle position, and Tri and Per equilibrate so slowly that real steady-state conditions are not reached within an exposure period of 8 h.

The metabolic parameters (Table 2) can be used to plot the metabolic rates against the level of atmospheric exposure. This is shown in Figure 8. It must be stressed that this calculation presupposes adjustment of equilibrium between the compound in the gas phase and in the organism. All the compounds (Fig. 8) show different and apparently unrelated characteristics as far as first and zero order veloc-

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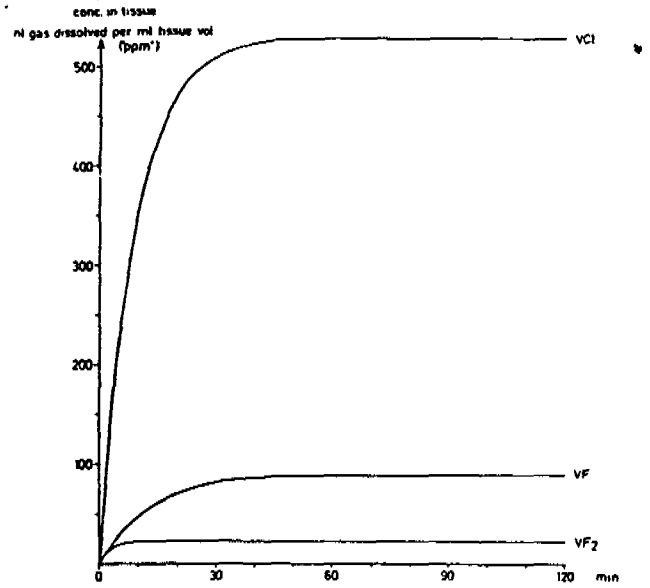

Fig. 6. Calculated concentrations of VCl, VF, and VF_2 in the tissue compartment on exposure to a constant atmospheric level of 100 ppm of the compounds, according to the data of Table 1

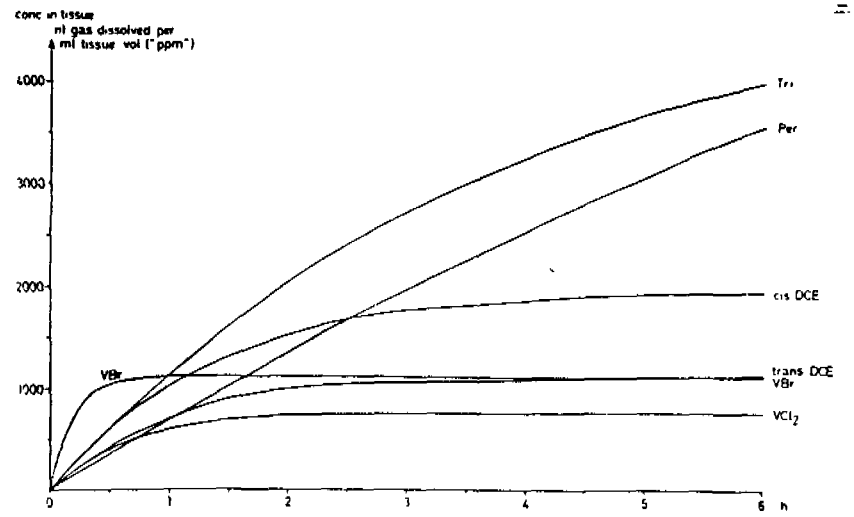

Fig. 7. Calculated concentrations of Tri, Per, cis-DCE, trans-DCE, VBr, and VCl_2 in the tissue compartment on exposure to a constant level of 100 ppm of the compounds, according to the data of Table 1

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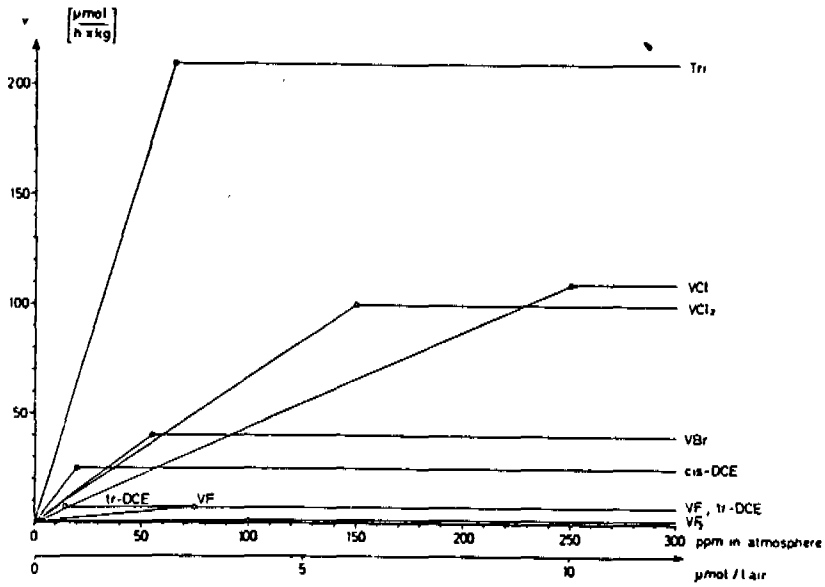

Fig. 8. Calculated velocities of metabolic elimination of halogenated ethylenes by rats at different levels of atmospheric exposure. (O) "Saturation points (Sp)"; transition from first-order to zero-order kinetics

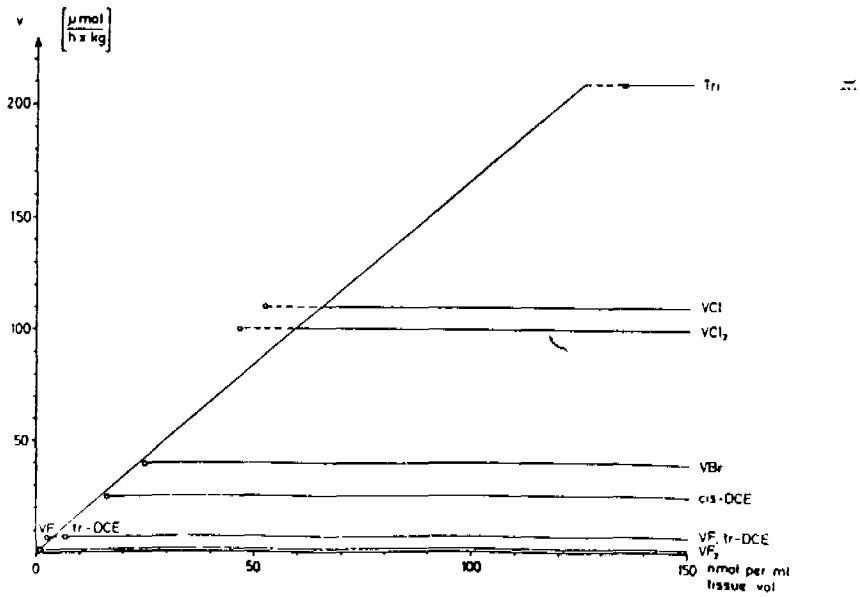

Fig. 9. Calculated velocities of metabolic elimination of halogenated ethylenes by rats at different concentrations of the compounds in the tissue compartment. (O) Transition points (Sp) from first-order to zero-order kinetics

ities of metabolic elimination and the transition points (Sp) between both kinetics are concerned. However, the picture completely changes when the (calculated) concentrations of the compounds in the tissue compartment are taken into account (Fig. 9). Based on similar concentrations in tissues, the velocities of first order elimination of all the compounds are similar. The coefficient of correlation for the line of Figure 9 connecting the points of tissue concentration where metabolic elimination shifts from zero to first order law is 0.987.

The rates of zero order elimination (V_{max}) very dissimilar among the individual compounds, even if the concentration of the compounds in tissues is considered.

Discussion

Pharmacokinetic Approach

Several recent publications have shown that the pharmacokinetic behaviour of halogenated ethylenes is dose-dependent; this phenomenon is due to saturability of the metabolic capacity of the organism (Gehring et al., 1977, 1978; Bolt, 1978; Reichert and Henschler, 1978; McKenna et al., 1978). Therefore we have here separately treated the distribution patterns of the compounds and the velocities of metabolic breakdown. The present system may be used to calculate the amount of an halogenated ethylene which is metabolized during exposure of rats in a toxicological experiment. From Figure 8a or from the data of Table 2 the metabolized amount of the compound can be taken, according to the underlying first-order or zero-order kinetics, below or above the point of exposure (Sp) where saturation occurs.

However, this calculation presumes an immediate adjustment of an equilibrium between the volatile compound in the air and in the animal compartment. Figures 6 and 7 show that the error introduced by this assumption is negligible for rapidly equilibrating compounds (VBr, VCl, VF, VF_2). It may be tolerable for VCl_2, cis-DCE and trans-DCE. However, as Tri and Per equilibrate with the organism only very slowly, this simple approach cannot be applied to these two particular compounds.

In their recent analysis of the pharmacokinetic behaviour of VCl in rats Gehring et al. (1978) used a Michaelis-Menten approach to account for the dose-dependent metabolism of VCl. Our calculation differs from theirs in that we assumed strict zero-order and first-order behaviour, respectively. We decided to do so from reasons of practicability, and because we could in fact describe our experimental curves (e.g., Fig. 1–3) with excellent accuracy by dividing them into linear and logarithmic sections. The r values for the individual *lin* or *log* regression analyses amounted always to > 0.99. Both approaches, that of Gehring et al. (1978) and ours, are describing essentially the same patterns, i.e., dose-dependence and "saturability" of metabolism in vivo of the compounds in question.

Biochemical Implications

Differences in pharmacokinetics and disposition of the halogenated ethylenes are seen in their distribution behaviour, in the atmospheric concentrations (Sp) of com-

R&S 107175

pounds necessary to achieve saturation of metabolism, and in the individual velocities by which metabolism occurs.

The first feature, distribution, is apparently dependent on the physical properties of the compounds (Fig. 5) whereas the metabolic parameters are determined by interaction of the compounds with the metabolizing enzymes. An important factor is the different enrichment of halogenated ethylenes in the organism; the same atmospheric exposure levels of different compounds lead to very dissimilar concentrations at the metabolic site, i.e., to dissimilar "substrate concentrations" in enzymological terms.

When comparison of metabolic elimination of the different compounds is based on their concentrations in tissues (Fig. 9) the rates of first order elimination of all the halogenated ethylenes are very similar. This suggests that, at lower concentrations of the compounds in tissues, a process must limit the rate of metabolic elimination which obeys the first order law and is apparently independent of the chemical reactivities (or the reactivities towards the monooxygenase enzyme system) of the compounds. Such a partial process may be transport to the enzymic site. On the other hand, under V_{max} conditions (Fig. 9) the enzymic turnover must be rate-limiting; hence, the different substrate qualities of the individual compounds towards the metabolizing enzyme system determine the comparative rates of metabolic elimination.

On the basis of studies using the isolated perfused rat liver preparation and of theoretical considerations Bonse et al. (1975) have established a tentative rule for the metabolic behaviour of chlorinated ethylenes. They showed that in general an inverse relation exists between the number of chlorine substituents and the rate of conversion. Our present experiments in vivo confirm this as the V_{max} values (Table 2, Fig. 8) decrease in the order VCl > VCl_2 > cis- and trans-DCE > Per. However, according to our data, this rule does not apply for Tri which has the highest V_{max} at all. An explanation for this unique behaviour of Tri is difficult to give, but studies in vitro using the rat liver microsomal system point to special properties of Tri as a substrate of the hepatic monooxygenase system. Under conditions of substrate saturation about 1 nmol of Tri metabolites was covalently bound within 60 min to 1 mg microsomal protein (Bolt et al., 1977a) whereas the corresponding value for VCl was only 0.44 nmol (Kappus et al., 1976) and that for VBr (Wistar rats) was about 0.2 nmol (Bolt et al., 1978).

The present pharmacokinetic data are valid only for Wistar rats. Other strains may show some differences as to the particular rates of metabolism of the halogenated ethylenes. Thus, it could be demonstrated that liver microsomes from Sprague-Dawley rats metabolize VBr about 50% faster that those obtained from Wistar rats (Bolt et al., 1978). Also, other species metabolize halogenated ethylenes at rates which differ from those calculated from rat experiments. For instance, mice and gerbils metabolize VCl faster than rats whereas in rabbits and in man metabolism of VCl is much slower than in the rat species (Buchter et al., 1978).

Because toxic actions of VCl and its congeners are attributed to activated metabolites, species variations in metabolism of these compounds must well be considered in evaluation of toxicological effects.

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R&S 107176

R&S 107177

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