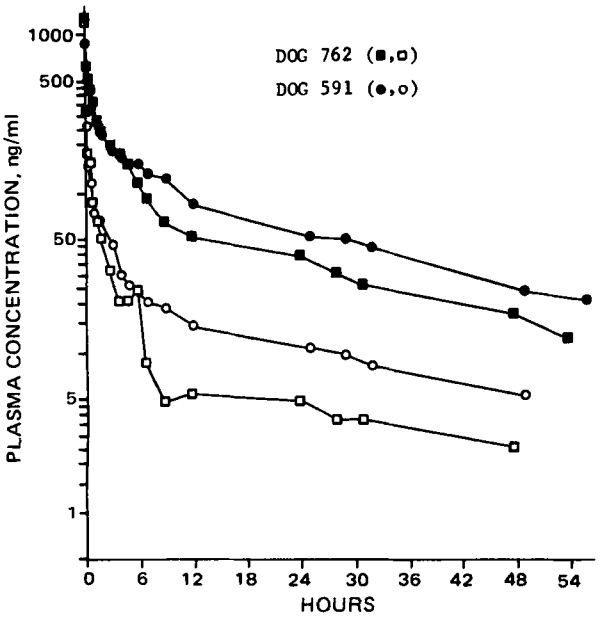

Figure 8—*Concentration-time plots of phenformin (○,□) and total radioactivity (●,■) in plasma resulting from 1.5-mg/kg iv doses of ^{14}C-phenformin hydrochloride administered to two beagle dogs.*

scanning comparisons, and the identity of III was determined by enzymatic hydrolysis experiments similar to those described for rats. Metabolite IV remains to be identified.

The amounts of renally excreted I–IV, as percentages of total administered radioactivity, are presented in Table V. The relatively high urinary radioactivity levels and the lengthy time of collection permitted the preparation of "sigma minus" plots for phenformin, for each metabolite, and for total radioactivity (as apparent drug). These plots allowed the estimation of apparent disposition half-lives for I–IV and total radioactivity. The values averaged 35–37 hr. Figure 6 illustrates the results obtained from one dog after oral drug administration. Similar data were obtained from the second dog after intravenous drug administration. The theoretical considerations and an appraisal of this method were discussed by Martin (8).

Plasma metabolic profiles were obtained after oral and intravenous drug administrations. Quantitative TLC results (Table VI) indicate the presence in plasma of significant amounts of unchanged drug and of each of the three metabolites. Plasma concentration–time curves resulting from single oral and intravenous doses were obtained for both animals (Figs. 7 and 8). The terminal log-linear parts of the curves indicate comparable elimination half-lives for phenformin and for total radioactivity. They averaged about 26 hr.

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Fluorocarbon Aerosol Propellants XII: Correlation of Blood Levels of Trichloromonofluoromethane to Cardiovascular and Respiratory Responses in Anesthetized Dogs

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Abstract □ Anesthetized mongrel dogs were exposed to various concentrations of trichloromonofluoromethane. Before, during, and after the inhalation, arterial and venous blood samples were obtained for fluorocarbon analysis. After the cessation of fluorocarbon inhalation, a multiexponential decline from the blood was observed. This finding was similar to that of a previous study in which the fluorocarbon was administered intravenously to unanesthetized dogs. The half-life calculated from the terminal phase was about 280 min, and the pseudodistribution equilibrium was reached about 100 min after dosing. Study of the relationship between blood fluorocarbon levels and effects on the respiration rate and arterial blood pressure indicates that the sites of these pharmacological activities are located in the blood or central compartment rather than in the peripheral compartment. The effect on the heart rate appears to be quite instantaneous after inhalation. These results might shed some light on the fast effect of the fluorocarbon propellants, which caused sudden deaths after inhalation of a large quantity.

Keyphrases □ Trichloromonofluoromethane—blood levels correlated to cardiovascular and respiratory responses in dogs □ Cardiovascular responses—trichloromonofluoromethane, correlated to blood levels in dogs □ Respiratory responses—trichloromonofluoromethane, correlated to blood levels in dogs □ Aerosol propellants—trichloromonofluoromethane, blood levels correlated to cardiovascular and respiratory responses in dogs □ Fluorocarbon aerosol propellants—trichloromonofluoromethane, blood levels correlated to cardiovascular and respiratory responses in dogs

Because of the wide use of fluorocarbon aerosol propellants in various household, cosmetic, and pharmaceutical pressurized packages, the possible adverse effects or toxicities of these compounds have been studied extensively. These studies concerned the effects on the cardiovascular system (1–8), enzyme activities (5, 9–11), muta-

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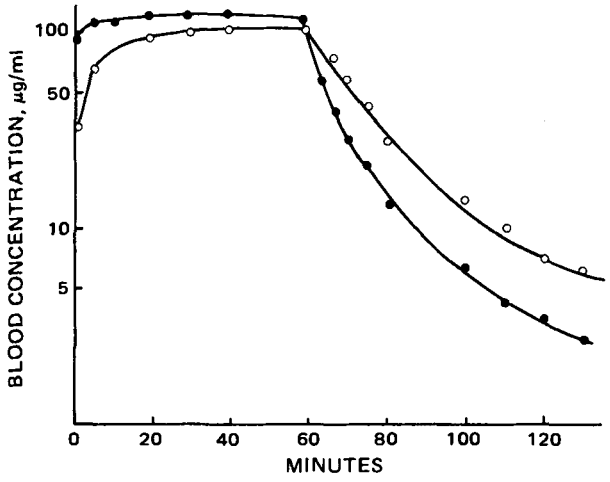

Figure 1—*Arterial (●) and venous (○) blood concentrations of fluorocarbon in a dog inhaling 2% (v/v) of the compound in pure oxygen for 60 min.*

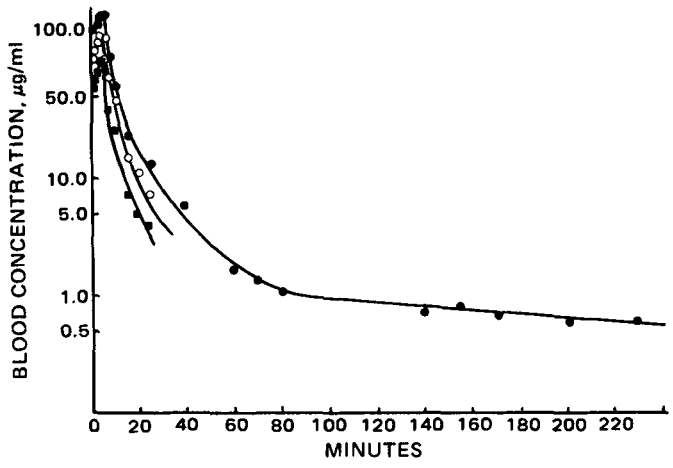

Figure 2—*Arterial blood concentrations of the fluorocarbon in Dog III inhaling 2% (■), 5% (○), and 7.5% (●) of the fluorocarbon in air for 5 min.*

tion (12), and ozone concentrations in the stratosphere (13).

Most investigations of cardiovascular effects predicated the observed cardiotoxicity on the basis of concentrations inhaled rather than blood concentrations of the fluorocarbons. The disposition kinetics of trichloromonofluoromethane, a widely used fluorocarbon, after intravenous administration to unanesthetized dogs are best described by a three-compartment open model (14). The accumulation of the fluorocarbon in the tissue or peripheral compartment following multiple or chronic exposures may have an important bearing on its potential toxicity (14).

The major objective of the present study was to correlate pharmacokinetically blood levels of trichloromonofluoromethane with some cardiovascular and respiratory responses in dogs following brief inhalations of the fluorocarbon.

EXPERIMENTAL

Materials—Trichloromonofluoromethane[1] (bp 23.7°), heparin sodium[2], pentobarbital sodium[3], and normal saline[3] were used.

Method—Mongrel dogs, fasted overnight and weighing 20–25 kg, were anesthetized with 25 mg of pentobarbital sodium/kg iv. The trachea, carotid and femoral arteries, and femoral vein were cannulated. The carotid artery and femoral vein were used for obtaining arterial and venous blood samples, respectively; the femoral artery was used for measuring arterial pressure with a pressure transducer[4] placed two-thirds of the transthoracic distance from the back. The heart rate derived from the ECG (lead II), arterial blood pressure, and respiration were recorded continuously at a paper speed of 25 mm/sec on a polygraph[5]. Some of the data obtained from these measurements were expressed as change or percent change from control values.

The dogs breathed the room air except during exposure to the fluorocarbon when they exhaled into a well-ventilated room but inhaled only the gaseous mixture of the fluorocarbon in air or oxygen contained in a 30-liter plastic bag. The outlet of the bag was connected to the tracheal cannula by a nonrebreathing valve[6]. The fluorocarbon concentration of the content of the bag proximal to its orifice, sampled with a 100-μl syringe[7], was confirmed by GLC (15).

Preliminary studies, in which the dogs were exposed to a 2% (v/v) concentration of fluorocarbon in oxygen, showed that the blood concentration increased rapidly from the time of exposure and approached steady state in less than 5 min. Consequently, following 30–45 min of equilibration after the preparation of the dog, various fluorocarbon concentrations were administered by inhalation through the inlet of the plastic bag for 5 min. An interval of 45 min elapsed before the subsequent concentration of the fluorocarbon was administered.

Dog I was exposed to 2, 5, and 10% (v/v) concentrations of the fluorocarbon in air; Dog II was exposed to 2, 5, 7.5, and 10% (v/v) concentrations in air; and Dog III was exposed to 2, 5, and 7.5% (v/v) concentrations in air. The lower concentration of the fluorocarbon was always studied first. Arterial and venous blood samples (0.5–1.0 ml) were withdrawn at appropriate intervals immediately before, during, and after the end of fluorocarbon inhalation. Blood fluorocarbon concentrations were analyzed by a headspace GLC method (15).

In the early phase of study involving several dogs, mixtures of different concentrations of the fluorocarbon with pure oxygen were used. This approach was considered more unrealistic, and the study was repeated using the fluorocarbon–air mixture. The reported results are based primarily on the fluorocarbon–air mixture study.

RESULTS AND DISCUSSION

Blood Level Profiles following Trichloromonofluoromethane Inhalation—In preliminary studies in which several dogs were exposed to a low concentration mixture of the fluorocarbon in oxygen for 60 min, the fluorocarbon concentrations in the arterial blood increased rapidly after the inhalation and approached steady-state levels in about 3–4 min. The arterial blood level then remained essentially constant throughout the inhalation period. After the cessation of fluorocarbon inhalation, both the arterial and venous blood levels decreased in an apparent triexponential decay pattern. Typical results are shown in Figs. 1 and 2.

In a previous study on four anesthetized dogs, the average terminal half-life of trichloromonofluoromethane after inhalation was 18.34 min (16). This value is in marked contrast with the much longer terminal half-life (average of 92.7 min from four dogs) reported earlier for unanesthetized dogs (7, 14, 15). The difference was attributed to the intravenous administration (7, 14, 15) as compared to the inhalation administration (16). Such reasoning appears to be pharmacokinetically unsound.

The long terminal half-life was again found in the present inhalation study in which blood sampling was continued for about 4 hr following the cessation of inhalation (Fig. 2). The terminal half-life for the anesthetized dog shown in Fig. 2 was approximately 280 min, about 14 times longer than the average half-life reported previously for anesthetized dogs (16).

The fluorocarbon levels in the venous blood always rose more slowly and were also always lower than the corresponding arterial blood levels during inhalation. A similar finding was reported earlier (17). Similar to the earlier intravenous study (14), approximately 100 min was required before a pseudodistribution equilibrium was reached for the fluorocarbon in dogs (Fig. 2). Such a slow equilibrium may be explained by the slow uptake of the fluorocarbon by fatty tissues. Its high solubility in fatty tissues of dogs was reported previously (18). The blood level data shown

[1] E. I. du Pont de Nemours & Co., Wilmington, Del.
[2] Fisher Scientific Co., Fair Lawn, N.J.
[3] Abbott Laboratories, North Chicago, Ill.
[4] Statham Laboratories, Hatorey, Puerto Rico.
[5] Model 7B, Grass Instrument Co., Quincy, Mass.
[6] Rudolph valve, Warren E-Collins, Inc., Braintree, Mass.
[7] Hamilton Co., Reno, Nev.

Table I—Effects of Inhalation of Various Concentrations of the Fluorocarbon on Cardiovascular and Respiratory Parameters at the End of 5 min of Inhalation [a]

Dog	Percent of Fluorocarbon (v/v)	Heart Rate, beats/min		Respiratory Rate, breaths/min		Systolic Pressure, mm Hg		Diastolic Pressure, mm Hg	
		C	R	C	R	C	R	C	R
I	2	144	162	10	14	134	108	77	63
	5	150	150	11	25	129	67	75	38
	10	150	ND	11	ND	129	ND	77	ND
II	2	210	200	14	16	168	132	100	84
	5	212	192	16	21	187	124	115	79
	7.5	216	192	15	20	180	91	109	65
	10	208	198	17	26	153	68	90	43
III	2	174	180	10	16	136	119	105	94
	5	162	156	9	17	117	89	92	69
	7.5	165	162	11	21	122	79	96	60

[a] ND = not determined, C = control, and R = response.

in Fig. 2 are typical of all dog studies using multiple inhalation of various concentrations of the fluorocarbon in air or oxygen.

Cardiovascular and Respiratory Effects following Fluorocarbon Inhalation—In this study, the time-course effects after the fluorocarbon inhalation on the increase of the respiratory rate and the decrease of the systolic and diastolic pressure were evaluated using various concentrations of the fluorocarbon in air or pure oxygen. In more than a dozen dogs, the same general response profiles were observed with either the fluorocarbon-air or the fluorocarbon-oxygen mixture. Since the data from the fluorocarbon-air study were thought to be more relevant, only the results from the more extensive study on three dogs with the air mixture will be presented. Typical results using 5% (v/v) fluorocarbon-95% air are plotted in Fig. 3. The magnitudes of the pharmacological effects were calculated after the correction of their respective control values.

The intensities of all three pharmacological effects evaluated increased with time during inhalation, reached their peaks at the end of inhalation, and dropped quickly afterwards. Such a time course effect is similar to the blood level profile in Fig. 3. Furthermore, the same general pattern was observed during the lower and higher fluorocarbon level studies carried out prior to and after the 5% concentration study on the same day. These results are consistent with the notion that the sites of actions for these pharmacological effects are located in the plasma or central compartment in a multicompartmental open model system (14, 19). However, if the sites of these actions are located in the "peripheral" compartment, the maximum responses should occur some time after the end of inhalation since the concentration in that compartment would continue to rise for a while after inhalation (14). This behavior was postulated for the therapeutic effect of digoxin (20) and theophylline (21).

The composite data showing the relation between the depression of the systolic pressure and the logarithm of the blood fluorocarbon concentrations for Dogs I–III are shown in Fig. 4. Although the data were obtained from three dogs using various fluorocarbon concentrations for each dog study, the same general pattern of correlation prevails. This finding further substantiates the contention that the site of action is located in the blood or central compartment.

A similar plot showing the relation between the depression of the diastolic pressure and the logarithm of the blood fluorocarbon concentrations is shown in Fig. 5. In both Figs. 4 and 5, the plateau effect seen in the conventional logarithm dose or concentration *versus* response plot is absent. Higher blood concentrations in these and other dogs after inhalation of much greater strengths of the fluorocarbon all quickly resulted in their deaths.

The numerical data for the effect on the respiration rate and blood pressure at the end of the 5-min inhalation of various strengths of the fluorocarbon in three dogs are summarized in Table I. These data represent the maximum effect for each inhalation study. A larger dose–response variation usually was seen in the respiratory effect than in the blood pressure effect. For example, after the 5% fluorocarbon inhalation, the percent changes in respiratory rates were +127, +31, and +89% for the three dogs while their corresponding changes were −48, −34, and −24% for systolic pressure, respectively, and −49, −31, and −25% for diastolic pressure, respectively.

During the time course study, the area under the curve for each respiratory cycle was also calculated and compared with the control value. Following inhalation of the fluorocarbon, these values decreased from the control whereas after cessation of the fluorocarbon inhalation, these values returned to the preexposure levels. The observed decrease in the area under the curve, representative of the approximate tidal volume, may have been due to an increase in respiratory rate. The decrease in the systemic arterial blood pressure could have been due to the depression of the myocardial contractile force and/or the relaxant action of the fluorocarbon on the systemic vasculature (22).

The increase in the respiratory rate during inhalation could have been due to the hypoxic drive caused by the lack of oxygen or to the stimulating effect of the fluorocarbon on the chemoreceptors. The possibility of an increase in the respiratory rate due to the lack of oxygen is untenable based on the fact that the studies performed on dogs inhaling various concentrations of the fluorocarbon mixture prepared in pure oxygen also showed a similar increase in the respiratory rate as the concentration of the fluorocarbon in the blood increased.

The effect on the heart rate in all dogs was less consistent and pro-

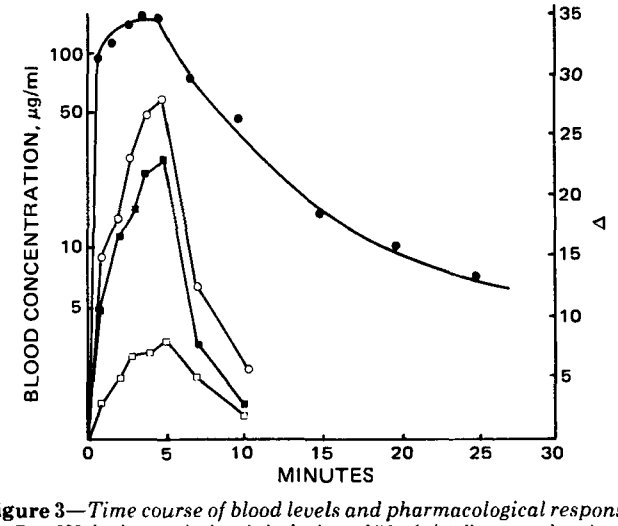

Figure 3—*Time course of blood levels and pharmacological responses for Dog III during and after inhalation of 5% (v/v) fluorocarbon in air. Key: ●, arterial blood concentration; ○, hypotensive effect (systolic pressure, mm Hg); ■, hypotensive effect (diastolic pressure, mm Hg); □, respiratory rate (breaths per minute); and Δ, change in response from control.*

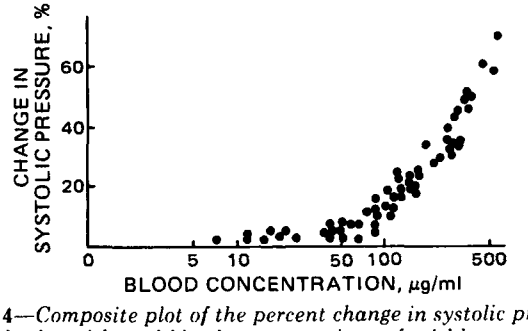

Figure 4—*Composite plot of the percent change in systolic pressure* versus *the logarithm of blood concentrations of trichloromonofluoromethane in three dogs following inhalation of various strengths of the fluorocarbon in air.*

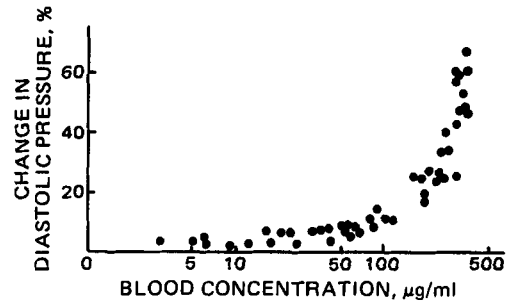

Figure 5—*Composite plot of the percent change in diastolic pressure versus the logarithm of blood concentrations of trichloromonofluoromethane in three dogs following inhalation of various strengths of the fluorocarbon in air.*

nounced. Most dogs showed biphasic responses, with an increase in the heart rate at lower doses and a decrease at higher doses (Table I). The effect on the heart rate in some dogs appeared to be instantaneous and reached a maximum within the 1st min during the inhalation in spite of the fact that the blood level continued to rise in the next few minutes.

The mechanism for such an effect is probably very complex and could not be rationalized by the multicompartmental model proposed for this fluorocarbon in dogs (14). The apparent "instantaneous" effect on the heart rate and the direct correlation between the blood level and the effect on the blood pressure and respiration rate could shed some light on the fast action of the fluorocarbon aerosol propellants, which have caused sudden death of individuals shortly after or during inhalation of large quantities of these propellants (2).

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Solution Rate of Crystals at Fluid–Fluid Interface

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Received December 27, 1977, from the *Department of Pharmaceutics, Subfaculty of Pharmacy, University of Groningen, Anthonius Deusinglaan 2, Groningen, The Netherlands.* Accepted for publication June 30, 1978.

Abstract □ A model system was developed in which the dissolution behavior of a single crystal of potassium ferricyanide was studied at a liquid paraffin–water interface. Since the equilibrium position of a crystal at the interface is independent of its size, the lifetime of a crystal dissolving at the interface is determined entirely by its initial size and its dissolution rate in the water phase. The dimensions of every crystal were measured microscopically before dissolution. A continuous-flow recording dissolution apparatus was used to measure spectrophotometrically the mass flow of dissolved potassium ferricyanide. The dissolution cell in this system was mounted in an optical bench, making it possible to follow dissolving crystals visually by projecting them on a screen. The results show that the lifetime of a crystal is proportional to the shortest length of the crystal face in contact with the liquid paraffin and is rather independent of its form. Furthermore, crystal shape changes during dissolution, which is explained partly by the nonisometric dissolution of potassium ferricyanide crystal faces and partly by the nonconstancy of film thickness.

Keyphrases □ Dissolution—potassium ferricyanide crystals at fluid-fluid interface □ Potassium ferricyanide—dissolution of crystals at fluid-fluid interface □ Crystal dissolution—potassium ferricyanide at fluid-fluid interface

The lifetime of a solid particle dissolving in a liquid is governed by its rate of change in surface area. Assuming a constant hydrodynamic boundary layer, Hixson and Crowell (1) derived the cube root law for the dissolution of sodium chloride crystals:

$$w_0^{1/3} - w_t^{1/3} = Kt \qquad \text{(Eq. 1)}$$

where w_0 is the weight of the particle at $t = 0$, w_t is the weight of the particle at time t, and K is a dissolution rate constant also composed of density and a shape factor. Many deviations from the cube root law were found, but it was difficult to explain the results because of the experimental design (in which often a number of particles were employed in a stirred system). In the experiments of Niebergall *et al.* (2) and Hixson and Crowell (3), the rate constant increased as dissolution proceeded. A linear re-

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