Fluorocarbon Aerosol Propellants VI: Interspecies Differences in Solubilities in Blood and Plasma and Their Possible Implications in Toxicity Studies

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Abstract □ Solubilities of the three most commonly used fluorocarbon aerosol propellants were determined in the blood and plasma of humans, monkeys, dogs, rats, and mice. Differences as large as ~fourfold in blood and more than 33-fold in plasma were found in different species. The partitioning of fluorocarbons between blood cells and plasma showed even greater differences between species. An indirect method was suggested for the calculation of plasma concentrations from total blood concentrations. A comparative evaluation was reported for the nonprotein bound fractions of fluorocarbons in the blood samples of various species. A correlation was drawn for the pharmacokinetic properties of the fluorocarbons within and between species, and a rationale was provided for the extrapolation of toxicity data from animals to humans.

Keyphrases □ Fluorocarbon aerosol propellants—interspecies differences in blood and plasma solubilities, toxicity implications □ Aerosol fluorocarbon propellants—interspecies differences in blood and plasma solubilities, toxicity implications □ Trichloromonofluoromethane—interspecies differences in blood and plasma solubilities, toxicity implications □ Dichlorodifluoromethane—interspecies differences in blood and plasma solubilities, toxicity implications □ Dichlorotetrafluoroethane—interspecies differences in blood and plasma solubilities, toxicity implications

Due to 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 extensively studied in recent years. These studies have concerned the effects on the cardiovascular system (1–10), enzyme activities (7, 11–13), mutation (14), and ozone concentrations in the stratosphere (15, 16).

The prediction of acute toxicity of the propellants in humans has often been made by extrapolating the toxicity data from various animal species to humans (2, 10, 17, 18). However, the possibility of interspecies differences may render such extrapolations less important. One means of evaluating such differences is the study of absorption, distribution, metabolism, and elimination of these compounds in various species and of possible differences in the acute and chronic accumulation following accidental or normal exposures to these compounds.

The three most commonly used fluorocarbon aerosol propellants, trichloromonofluoromethane, dichlorodifluoromethane, and dichlorotetrafluoroethane, exist in gaseous form at 37°. Therefore, the absorption, distribution, elimination, and accumulation of these compounds are likely to be subjected to parameters that have been shown to be important for gaseous anesthetics (19, 20). Two such parameters are the solubilities of the gaseous compound in the blood and plasma of various species.

For gaseous or volatile compounds, the term "solubility" is commonly defined as the ratio of concentration of the compound between the liquid phase and the gaseous phase at the equilibrium state (19, 20). Such a ratio is, in fact, identical to the partition coefficient, P, between the two phases, as used conventionally for nonvolatile compounds between organic and aqueous phases. The purpose of this paper is to report the results of a study on the solubilities of the three most commonly used fluorocarbon propellants in the blood and plasma of various species. The possible correlation between the solubilities and the pharmacokinetic properties and a rationale for extrapolation of animal toxicity data to humans also will be discussed.

EXPERIMENTAL

Propellants and GC Analyses—The three pure propellants were supplied by the manufacturer[1]. These compounds were analyzed using a dual-column gas chromatograph equipped with a tritium electron-capture detector. The exact procedure followed was reported previously (21).

Blood and Plasma—Blood samples were freshly drawn and were used within 2 hr. Plasma samples were prepared by centrifuging either pooled or individual blood samples for 20 min in a clinical centrifuge and were also used within 2 hr after the withdrawal of blood samples. Blood samples were collected in 7.0-ml vacuum tubes[2], each containing 60 mg of ethylenediaminetetraacetate (humans, monkeys, dogs, and rats) or heparin (mice) as the anticoagulant.

Humans—About 15 ml of blood was collected from each of four healthy male volunteers, 24–35 years of age and weighing 50–70 kg.

Dogs—About 15 ml of blood was collected from four male German pointer dogs, weighing 12–16 kg.

Monkeys—About 20 ml of blood was collected from each of four rhesus monkeys, weighing 6–8 kg.

Rats—Four Sprague–Dawley-strain male rats, weighing ~300 g, were anesthetized with 65 mg/kg ip of pentobarbital sodium. The chest was opened with a quick incision, and blood samples were drawn directly from the ventricles of the heart.

Mice—Twenty BDF_1-strain male mice, weighing ~25 g, were given a deep incision in the throat, and the oozing blood was collected in a tube containing heparin. Only initial samples were collected, however, to avoid contamination with clotting factors. From 0.5 to 1 ml of blood was obtained from each mouse, and all blood samples were pooled together. There was no visible precipitation or coagulation in the pooled blood sample.

All plasma prepared from each individual was pooled, although the blood samples were studied individually except in the case of mice.

Partition Coefficient Determination—The partition coefficient or solubility, S, was determined based on the head-space method (21, 22) and can be expressed as:

$$S = \frac{A_t - C_h(V_t - V_l)}{V_l C_h} \qquad \text{(Eq. 1)}$$

where A_t = total amount of fluorocarbon added to a sealed serum bottle, V_h = volume of the head space, C_h = concentration of fluo-

[1] E. I. duPont de Nemours & Co., Wilmington, Del.
[2] Vacutainer, Scientific Products, McGraw, Ill.

Table I—Solubilities of Fluorocarbon Aerosol Propellants in the Blood and Plasma of Various Species[a]

Liquid Phase	Dichlorodifluoromethane	Dichlorotetrafluoroethane	Trichloromonofluoromethane
Human:			
Blood[b]	0.282 ± 0.009 (1)	0.264 ± 0.011 (1)	0.940 ± 0.021 (1)
Plasma[c]	0.349 ± 0.007 (1)	0.474 ± 0.018 (1)	0.924 ± 0.006 (1)
Dog:			
Blood[b]	0.449 ± 0.011 (1.59)	0.285 ± 0.017 (1.08)[d]	2.330 ± 0.107 (2.48)
Plasma[c]	0.126 ± 0.013 (0.36)	0.172 ± 0.007 (0.36)	0.877 ± 0.049 (0.95)[d]
Monkey:			
Blood[b]	0.339 ± 0.015 (1.20)	0.140 ± 0.015 (0.53)	0.993 ± 0.032 (1.06)[d]
Plasma[c]	0.162 ± 0.018 (0.46)	0.150 ± 0.014 (0.31)	0.770 ± 0.007 (0.83)
Mouse[e]:			
Blood	0.660 ± 0.017 (2.34)	0.303 ± 0.014 (1.15)	3.501 ± 0.016 (3.72)
Plasma	0.170 ± 0.004 (0.48)	0.121 ± 0.019 (0.25)	0.602 ± 0.023 (0.65)
Rat:			
Blood[b]	0.288 ± 0.014 (1.02)[d]	0.123 ± 0.008 (0.47)	1.024 ± 0.028 (1.09)[d]
Plasma[c]	0.035 ± 0.001 (0.10)	0.017 ± 0.003 (0.03)	0.399 ± 0.004 (0.43)

[a] Values in parentheses are for comparison purposes; the solubility value in human blood or plasma was considered unity. [b] Mean ± *SE* (n = 8). [c] Mean ± *SE* (n = 4). [d] Values not statistically significant compared to humans at p = 0.05. [e] Mean ± range (n = 2).

Table II—Partition Coefficients of Fluorocarbon Propellants between Blood Cells and Plasma of Various Species[a]

Species[b]	Dichlorodifluoromethane	Dichlorotetrafluoroethane	Trichloromonofluoromethane
Human	0.591 (1.00)	0.057 (1.00)	1.036 (1.00)
Dog	6.634 (11.22)	2.444 (42.87)	4.641 (4.47)
Monkey	3.601 (6.09)	0.841 (14.75)	1.689 (1.63)
Mouse	7.946 (13.44)	4.625 (81.14)	12.604 (12.16)
Rat	16.714 (28.28)	14.555 (255.35)	4.405 (4.25)

[a] Values in parentheses are for comparison purposes; the partition coefficient in humans was considered unity. [b] Hematocrit values used in calculations were: human, 47%; dog, 45.5%; monkey, 42%; mouse, 41.5%; and rat, 46%.

rocarbon in the head space, V_t = internal volume of the sealed bottle, and V_l = volume of liquid phase in the sealed bottle.

The partition coefficients were determined at two concentrations, and the equilibrium concentration in the liquid phase, C_l, was determined using the following mass balance equation:

$$C_l = \frac{A_t}{V_l + V_h/S} \qquad \text{(Eq. 2)}$$

The effect of ethylenediaminetetraacetate and heparin on the partition coefficient was studied by comparing the solubility of the three fluorocarbon propellants in normal saline with or without heparin (1%) or ethylenediaminetetraacetate (1%).

RESULTS

The solubility values of the three fluorocarbon propellants in blood and plasma of five species are summarized in Table I. The solubility in human blood and plasma is also compared to that in other species.

The partition coefficient between blood cells and plasma ($P_{bc/plasma}$) was calculated using the information in Table I through the following mass balance equations:

$$P_{blood/air} = (\text{hematocrit})(P_{bc/air}) + (1 - \text{hematocrit})(P_{plasma/air}) \qquad \text{(Eq. 3)}$$

Rearranging Eq. 3 gives:

$$P_{bc/air} = \frac{[P_{blood/air} - (1 - \text{hematocrit})(P_{plasma/air})]}{\text{hematocrit}} \qquad \text{(Eq. 4)}$$

The partition coefficient between blood cells and plasma can be expressed as:

$$P_{bc/plasma} = \frac{P_{bc/air}}{P_{plasma/air}} \qquad \text{(Eq. 5)}$$

Substituting Eq. 4 into Eq. 5 gives:

$$P_{bc/plasma} = \frac{P_{blood/air}}{(\text{hematocrit})(P_{plasma/air})} - \frac{(1 - \text{hematocrit})}{\text{hematocrit}} \qquad \text{(Eq. 6)}$$

Table II shows the partition coefficient values of the three fluorocarbon propellants between blood cells and plasma along with the comparison of the values in humans to other species. The hematocrit values for various species were obtained from the literature (23).

The concentration of fluorocarbons in the plasma could be calculated using the following relationship:

$$\frac{C_{plasma}}{C_{blood}} = \frac{C_{plasma}/C_{air}}{C_{blood}/C_{air}} = \frac{P_{plasma/air}}{P_{blood/air}} = \text{constant} \qquad \text{(Eq. 7)}$$

and, hence:

$$C_{plasma} = (C_{blood})(\text{constant}) \qquad \text{(Eq. 8)}$$

Table III shows the comparative concentrations in the plasma for an arbitrary concentration of 10 μg/ml in the blood of the five species. Table IV shows the head-space concentration if the plasma obtained from a 10-μg/ml blood sample is equilibrated to obtain estimates of nonprotein bound fractions as discussed later.

The solubility values determined at two concentration levels (50 and 100 ng/ml for dichlorodifluoromethane and 30 and 60 ng/ml for trichloromonofluoromethane and dichlorotetrafluoroethane) did not show any dependence on the equilibrium concentration. Similarly, no effect was observed due to the presence of heparin and ethylenediaminetetraacetate.

DISCUSSION

Table I shows the solubilities of the three fluorocarbons in the blood and plasma of five species. These values are higher than the solubilities of these fluorocarbons in water (22), but the order of the solubility is the same as that found in water, *i.e.*, trichloromonofluoromethane > dichlorodifluoromethane > dichlorotetrafluoroethane. Marked differences were seen, however, in the solubilities in the blood and plasma of the five species studied. For example, an almost fourfold difference was seen in the solubility of trichloromonofluoromethane in the blood of five species (Table I). Similarly, an almost 30-fold difference was noted for the solubility of dichlorotetrafluoroethane in the plasma of the five species. Such large differences can only be attributed to differences in the interaction of these fluorocarbons with the components of the blood. In general, the higher solubility of fluorocarbons in the plasma compared to water can be attributed to binding to plasma proteins.

Table III—Concentrations (Micrograms per Milliliter) of Fluorocarbon Propellants in Plasma for an Arbitrary Propellant Concentration of 10 μg/ml in Whole Blood[a]

Species	Dichlorodifluoromethane	Dichlorotetrafluoroethane	Trichloromonofluoromethane
Human	12.37 (1.00)	17.95 (1.00)	9.82 (1.00)
Dog	2.80 (0.23)	6.03 (0.33)	3.76 (0.38)
Monkey	4.77 (0.38)	10.71 (0.60)	7.75 (0.79)
Mouse	2.57 (0.21)	3.99 (0.22)	1.71 (0.17)
Rat	1.21 (0.10)	1.38 (0.08)	3.89 (0.40)

[a] Values in parentheses are for comparison purposes; the concentration in human plasma was considered unity.

Table IV—Gas Phase Concentrations[a] (Micrograms per Milliliter) of Equilibrated Plasma Obtained from Blood Samples with an Arbitrary Concentration of 10 μg/ml[b]

Species	Dichlorodifluoromethane	Dichlorotetrafluoroethane	Trichloromonofluoromethane
Human	35.44 (1.00)	37.87 (1.00)	10.63 (1.00)
Dog	22.22 (0.63)	35.06 (0.92)	4.29 (0.40)
Monkey	29.44 (0.83)	71.40 (1.88)	10.06 (0.95)
Mouse	15.12 (0.43)	32.97 (0.87)	2.84 (0.27)
Rat	34.57 (0.97)	81.18 (2.14)	9.75 (0.92)

[a] These values are proportional to nonprotein bound fractions in the blood. [b] Values in parentheses are for comparison purposes; the concentration for humans was considered unity.

This observation recently was confirmed in several reports (24–27) where the binding of these fluorocarbons with human and bovine albumins was demonstrated. Not all proteins show specific interactions resulting in an increase in the solubility, and it was recently demonstrated in this laboratory that bovine globulin in fact caused a decrease in the solubility of fluorocarbons compared to water. The net solubility in the plasma, therefore, reflects the effect of the presence of several proteins showing varying degrees of interactions with the fluorocarbons.

The solubility of fluorocarbons in the blood is contributed to not only by specific interactions with plasma proteins but also to blood cells as shown in Table II, where the partition coefficients between blood cells and plasma were calculated based on Eq. 6. Differences much larger than those reported for the solubility in blood and plasma (Table I) were found for partitioning between blood cells and plasma. A 255-fold difference was seen for dichlorotetrafluoroethane between human and rat blood, the latter showing a greater degree of partitioning.

In general, dichlorotetrafluoroethane showed greater partitioning into blood cells compared to the other two fluorocarbons in all species studied. In all cases, however, the blood cells possessed a higher concentration than in the plasma, indicating the possibility of specific interactions of fluorocarbons with various structures of the blood cells. It is obvious, however, that the blood cells show a higher magnitude of interaction than the net interaction of fluorocarbons in the plasma. The postulation of the interaction of fluorocarbons with cellular components, as already mentioned, was demonstrated recently (12); trichloromonofluoromethane was shown to bind with the phospholipid of a microsomal preparation and also to another site that appeared to be similar to the carbon monoxide binding site.

The solubility values reported here form an important basis for a comparative evaluation of the absorption, distribution, elimination, and toxicity of the fluorocarbon in various species.

The effect of solubility of volatile compounds in blood on their uptake and distribution has been emphasized (20, 28, 29). The elimination of fluorocarbon propellants takes place mainly through the lungs. In a recent study (30), almost 97% of a single dose of trichloromonofluoromethane was expired unchanged from Wistar rats. The possibility of the metabolism of trichloromonofluoromethane was also studied. No possible metabolites were, however, detected following incubation with microsomal preparations from chickens, rats, mice, guinea pigs, and hamsters pretreated with phenobarbital. The resistance of fluorocarbon propellants against metabolism is mainly due to the higher stability of C—F bonds as compared to C—Cl bonds (31). Since the elimination of fluorocarbon takes place mainly through the lungs, it is believed that the observations that have been made regarding the uptake and elimination of many volatile anesthetics also eliminated through the lungs could be applied to the fluorocarbon propellants.

Stoelting and Eger (32) studied the effect of solubility on recovery from anesthesia from various gaseous anesthetics. They showed that the solubility in blood of the three anesthetics, methoxyflurane, halothane, and nitrous oxide, was directly proportional to their recovery time. Recovery time was defined as the time required for the alveolar concentration to drop to a certain fraction following various degrees of equilibration of these anesthetics with body tissues. They also showed that compounds with high solubility such as methoxyflurane (solubility = 13) and halothane (solubility = 2.3) showed a significant distribution to the tissues, which was reflected in the longer recovery times following equilibration for longer periods as compared to nitrous oxide (solubility = 0.47). Consequently, higher solubility compounds also will have larger uptakes and longer biological half-lives if they are absorbed and eliminated primarily from the lungs.

For example, it was shown (33) that upon inhalation in humans of a mixture of four fluorocarbons, including the three in this report, the most soluble, trichloromonofluoromethane, was absorbed in the blood to a greater extent than dichloromonofluoromethane and dichlorotetrafluoroethane, which have lower solubility in the blood (Table I). Trichloromonofluoromethane also showed a comparatively slower elimination from the body.

Detailed pharmacokinetics of these fluorocarbons recently were studied (34, 35) in dogs following intravenous dosing, and it was found that the biological half-lives of dichlorotetrafluoroethane and dichlorodifluoromethane ranged from 40 to 60 min but the half-life of trichloromonofluoromethane was significantly longer (90–100 min). This difference corresponds very well to the differences in solubility values (Table I) in the dog blood. The differences in the solubility of the three fluorocarbons in the dog blood were very well represented in their elimination behavior. For example, the pulmonary clearance of the high solubility fluorocarbon trichloromonofluoromethane was 0.9 liter/min compared to 2.05 and 2.53 liters/min for dichloromonofluoromethane and dichlorotetrafluoroethane, respectively (34).

The distribution of these fluorocarbons from the central (blood) compartment to the tissue compartments followed the general principle that compounds having low solubility in the blood are distributed faster to the tissue. For example, it took 5 min to obtain peak concentration in one tissue compartment and 10 min for the other tissue compartment for both dichloromonofluoromethane and dichlorotetrafluoroethane, but the corresponding time periods were 10 and 30 min for the two compartments for trichloromonofluoromethane in dogs (34).

These observations suggest that solubility values indeed offer an important index for the evaluation of absorption, distribution, and elimination and can be used to study toxicity correlations and differences between species. Since these fluorocarbons are primarily eliminated from the lungs, interspecies variations of several properties can be anticipated. For example, an almost fourfold difference in the blood solubility of trichloromonofluoromethane be-

tween humans and mice is most likely to result in a significant difference in the uptake and disposition characteristics between the two species; any extrapolation of possible toxicity based on these properties is probably less justified than between monkeys and humans where the solubility of this fluorocarbon is in good agreement. On the other hand, placing great confidence in solubility values to anticipate uptake and disposition patterns is also not justified in view of the differences in the pulmonary ventilation and cardiac output both within and between species (23) since these factors can seriously affect the uptake and disposition patterns.

It is generally agreed that the plasma concentrations of the drugs correlate better with various pharmacological and toxicological properties than the dose administered. In some instances, the nonprotein bound fraction of the drug in a blood sample correlates even better. However, it is not very practical to measure directly the plasma concentrations of fluorocarbon propellants by first centrifuging the blood samples, since the high volatility of these compounds can result in a significant loss to the atmosphere, especially at room temperature during handling. An indirect method can be easily employed if the partition coefficients between blood cells and plasma are available, as described earlier (Eq. 6). The plasma concentration can then simply be calculated using Eq. 8.

Table III shows the plasma concentrations of the three fluorocarbons in the five species for an arbitrary whole blood concentration equal to 10 μg/ml. Differences as large as 13-fold existed in the plasma concentrations between various species; in all instances, the human plasma showed the highest concentration at equal blood concentrations. These differences are attributable to the differences in the partitioning between blood cells and plasma. This observation can have an important bearing on comparative evaluations of toxic blood concentrations in various species if the plasma concentrations correlate better with the possible toxic manifestations. Nevertheless, this conclusion can be misleading if due consideration is not given to the nonprotein bound fraction in the plasma. Although no such measurements were made directly, an indirect comparison can be made easily by dividing the plasma concentration by the partition coefficient between plasma and air to obtain the concentration in the gaseous phase equilibrating with the plasma. In such a hypothetical equilibration, the concentration in the gaseous phase will be directly proportional to the unbound fraction in the plasma. These values are shown in Table IV.

Although the relative nonprotein bound concentration was generally higher for humans, except for dichlorotetrafluoroethane, the maximum difference decreased to about 3.5-fold compared to a 13-fold difference in the plasma (Table III).

In conclusion, the large differences in the solubilities of fluorocarbon aerosol propellants can result in significant differences in the pharmacokinetics of these fluorocarbons. Thus, any interspecies extrapolation of toxicity data based on parameters such as dose, toxic blood concentration, accumulation, and uptake should take into account the various solubility parameters described here.

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