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Washington, D.C. 20460-0001

Re: TSCA Section 8(e) Reporting For PFOA



Dear Mr. Hefter:

As a further supplement to our July 3, July 31, and August 5, 2003, letters on the referenced topic, we have enclosed a copy of a C-8 blood model developed by E.I. duPont de Nemours and Company ("DuPont"), which relates to DuPont's knowledge of estimated levels of perfluorooctanoate concentrations in the blood of the communities exposed to DuPont's C-8 emissions in air and water, as of October 10, 2001.

Very truly yours,

Robert A. Bilott
Robert A. Bilott

RAB:mdm
Enclosure

- cc: Dr. Charles M. Auer (USEPA OPPT) (w/o encl.)
- Mary Dominiak (USEPA OPPT) (for inclusion in AR-226) (w/ encl.)
- Jennifer Seed (USEPA) (w/ encl.)
- R. Edison Hill, Esq. (w/ encl.)
- Larry A. Winter, Esq. (w/ encl.)
- Gerald J. Rapien, Esq. (w/o encl.)

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**A Simple, Conservative Compartmental Model to Relate
Ammonium Perfluorooctanoate (APFO) Exposure to
Estimates of Perfluorooctanoate (PFO) Blood Levels in
Humans**

Paul M. Hinderliter, Ph.D.

Gary W. Jepson, Ph.D.

**Biochemical Toxicology
DuPont Haskell Laboratory for Health and Environmental Sciences**

10 October, 2001

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Abstract

A simple and conservative compartmental model was developed to relate ammonium perfluorooctanoate (APFO) exposures to estimates of perfluorooctanoate (PFO) concentrations in human blood. The model was based on kinetic principles, but it did not include mechanistic or physiological descriptions. Further, the model was not intended to replace the need for more robust models that include mechanistic and appropriate physiological descriptions. The model included zero-order mathematical descriptions of oral and inhalation input and a first order elimination description. Standard estimates of the volumes of daily water consumption and air breathed were used to relate daily intake of APFO to concentrations of APFO in air and drinking water. The model was exercised under a variety of exposure conditions and used to create a table relating APFO intake via drinking water and/or air to PFO blood concentrations. The simplicity and utility of this model provide decision-makers with an easily applied tool to relate APFO exposures to estimates of resulting PFO concentrations in human blood.

Introduction

A simple compartmental model was developed and used to estimate the concentration of perfluorooctanoate (PFO) in blood following inhalation or ingestion of ammonium perfluorooctanoate (APFO). The model presented is intended to complement various consequence analysis and planning activities and is not intended to be a substitute for a robust, mechanism based physiological model. In order to realize both the strengths and limitations of the model, it is important to carefully consider the assumptions and caveats relevant to the model development and application.

Approach

Model Development:

The model developed for this application was a two-compartment open model with one compartment defined as the blood compartment and the other as the body compartment. While the model is constructed as a two-compartment model, transfer of PFO is confined to only one compartment (blood compartment) in order to provide a conservative estimate of PFO concentrations in blood following APFO exposure. Functionally, this reduces to a one-compartment open model with two zero-order-input processes and one first-order elimination process. In other words, PFO is confined to the blood compartment and the PFO concentration in blood cannot be reduced by the distribution of PFO into other body tissues. In order to contribute to the conservative estimates produced by this model, any APFO that is ingested or inhaled is not subject to diffusional resistance and is assumed to be completely and instantly absorbed into the blood compartment. Since PFO is not metabolized, elimination from the blood is via renal excretion. In this model the elimination is described as a pseudo first-order process. A schematic of the model is shown in Figure 1.

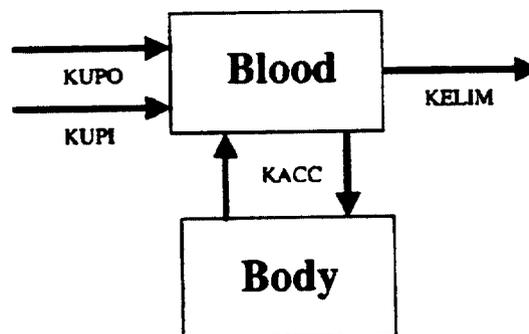


Figure 1. Schematic of PFO Compartmental Model.

In Figure 1, KACC is the distribution coefficient for transfer of PFO between the blood and body compartments. It has the units of day^{-1} , but as discussed earlier, it is set to zero

in order to create a conservative one-compartment model. KUPO is a zero-order term to describe PFO input into the blood compartment (ug/day) via the oral route. KUPI is a zero-order term to describe PFO input into the blood compartment (ug/day) via the inhalation route. KELIM is a pseudo first-order elimination coefficient (day⁻¹) that describes removal of PFO from the blood compartment via renal excretion. Differential rate equations were developed from the schematic in Figure 1 and the equations were solved using Advanced Continuous Simulation Language (ACSL, Aegis Corp.). The mathematical equations used to describe the concentration of PFO in the blood compartment (CBLOOD) are shown in the series of equations below.

$$\frac{dAB}{dt} = KUPO + KUPI - KELIM * CBLOOD * VOL - RAF \quad (1)$$

$$dAB = (KUPO + KUPI - KELIM * CBLOOD * VOL - RAF)dt \quad (2)$$

$$\int_{AB=0}^{AB} dAB = \int_{t=0}^t (KUPO + KUPI - KELIM * CBLOOD * VOL - RAF)dt \quad (3)$$

$$AB = \int_{t=0}^t (KUPO + KUPI - KELIM * CBLOOD * VOL - RAF)dt \quad (4)$$

$$CBLOOD = AB / VOL \quad (5)$$

In the equations above, AB is the amount (ug) of PFO in blood, t is time (days), VOL is the volume (ml) of the blood compartment and RAF (ug/day) is the rate of PFO movement between the blood and body compartments (RAF=0 in this model). The ACSL coding of the above equations is given immediately below and in Appendix 1. The corresponding ACSL command file is provided in Appendix 2.

$$RA=KUPO + KUPI - KELIM*CBLOOD*VOL - RAF \quad (6)$$

$$CBLOOD=INTEG(RA,0)/VOL \quad (7)$$

Model Input Assumptions/Descriptions:

Blood Compartment Volume: The blood volume of 3.5 L used in the model was that of a 50-Kg human (average human female weight). The female weight was selected to maintain the conservative approach desired for this model. Obviously, blood volume is a function of body weight so larger body weights will equate to larger blood volumes. PFO concentrations in blood will therefore decrease for a given APFO exposure as body weights increase.

Elimination Rate Constant: The elimination rate constant, KELIM, was assigned a value of 0.0019/day. This was derived assuming a PFO half-life (t_{1/2}) in humans of 365 days and that first order kinetics apply. While current human half-life estimates are placed in the 200-300 day range, the 365-day half-life is a conservative value for initial model conditions. The actual value for KELIM was derived using the relationship between the half-life and the elimination rate constant where first order kinetics are obeyed.

$$KELIM = \frac{\ln 2}{t_{1/2}} \quad (8)$$

Input of APFO via Drinking Water: Drinking water concentrations of APFO were converted to micrograms (ug) of APFO ingested per day using the assumption that approximately 2L of the water are consumed per day. An example follows where drinking water containing 1 part per billion (ppb) APFO was consumed:

$$1 \text{ ppb} = \frac{1 \text{ ug}}{L} \quad \text{so} \quad \frac{1 \text{ ug}}{L} \times \frac{2L}{\text{day}} = \frac{2 \text{ ug}}{\text{day}} \quad (9)$$

Input of APFO via Inhalation: Inhaled concentrations of APFO were converted to micrograms of APFO absorbed into the blood using the assumption that approximately 20 m³ of air are breathed per day. An example follows where air containing 1 ug/m³ APFO was inhaled.

$$\frac{1 \text{ ug}}{\text{m}^3} \times \frac{20 \text{ m}^3}{\text{day}} = \frac{20 \text{ ug}}{\text{day}} \quad (10)$$

General Assumptions:

The simple model described here is designed to be conservative and is not intended to be a substitute for a more robust, mechanism based physiological model. Consistent with the design of this model, several general assumptions have been made.

- ~~No~~ (1) The PFO is distributed only in the human blood compartment. *Conservative*
- ~~No~~ (2) There is no metabolism of PFO.
- ~~No~~ (3) No binding or mechanistic descriptions are included in the model. *Conservative*
- ~~No~~ (4) Elimination occurs by a single first-order pathway. It is likely that elimination actually displays biphasic elimination with an initial rapid elimination phase followed by a slower or terminal phase elimination. In order to be consistent with the conservative nature of the model, only the slow (terminal) phase *terminal* elimination is included in the model. *Conservative*
- probably* ? (5) All APFO inhaled or ingested in drinking water is instantly and completely absorbed into the blood compartment. *Conservative*
- real situation* ? (6) APFO exposures occur every day throughout the exposure period modeled.

Results

The simulated PFO levels in human blood resulting from repeated ingestion of 6 ug/day APFO are shown in Figure 2. As would be expected based on the estimated half-life of PFO in the human body, the simulation illustrates that steady-state PFO blood levels are reached only after repeated exposure for over 6 years. Figure 3 is a simulation of the elimination of PFO from the blood once PFO levels are at steady state and PFO exposure is terminated.

Figure 2. Simulated PFO Concentration in Human Blood Following Continuous Intake of 6 ug/day

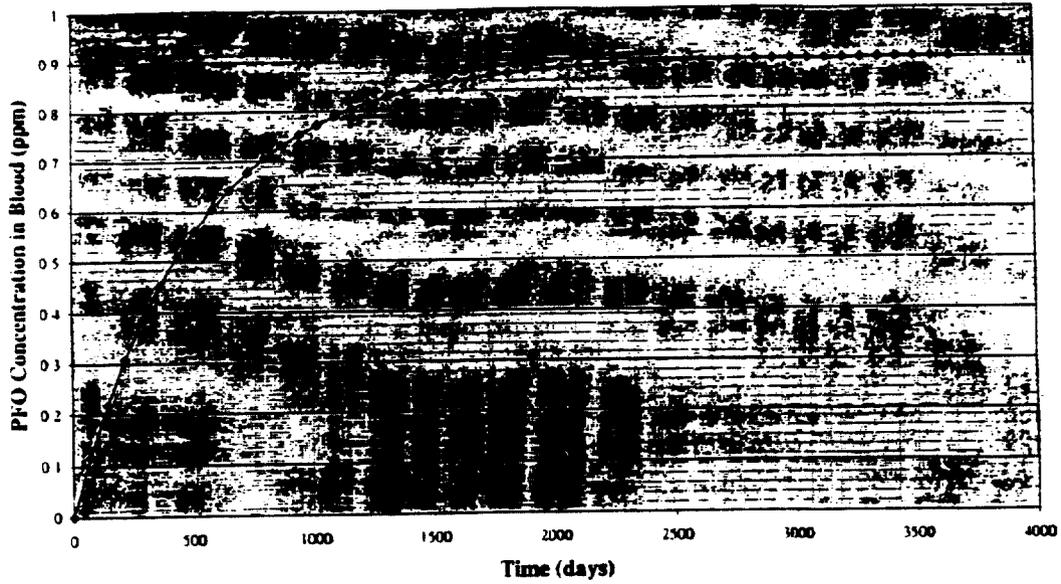
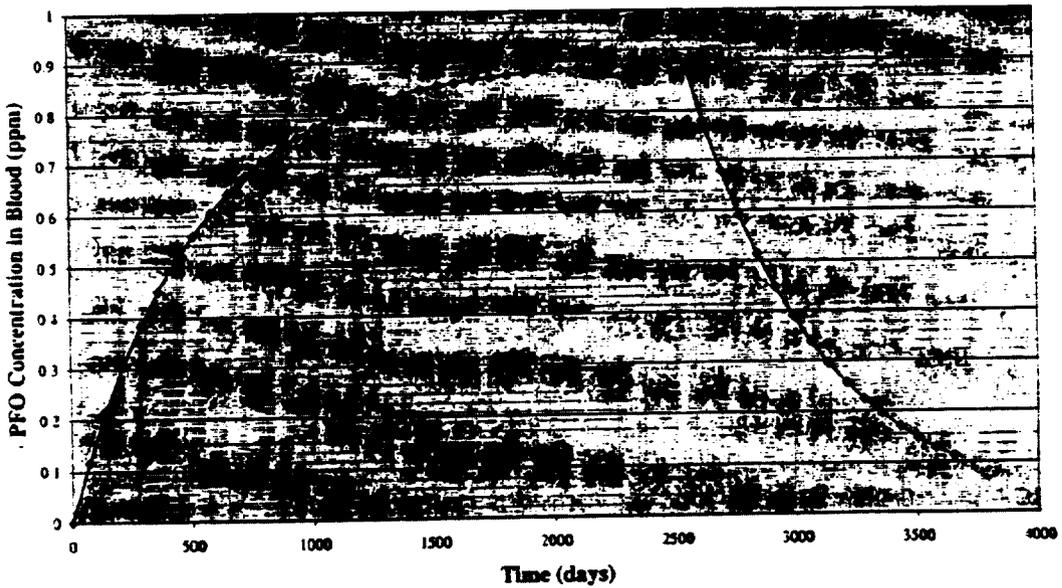


Figure 3. Simulated PFO Concentration in Human Blood During and After 2600 Days of Exposure to 6 ug/day APFO



A series of model simulations were run to estimate the steady-state human PFO blood levels resulting from drinking water containing APFO, breathing air containing APFO or combinations of the two. The resulting estimates of PFO concentrations in human blood are shown in Table 1. Table 1 can be used under the conditions described in the text, to assign a PFO blood concentration to a particular exposure. Example 1: If drinking water containing 1 ppb APFO was consumed and no APFO was present in the inhaled air, the resulting steady-state PFO concentration estimate in human blood would be 0.30 ppm. Example 2: If no APFO was present in the drinking water and 0.05 $\mu\text{g}/\text{m}^3$ APFO was in the inhaled air, the resulting steady-state PFO concentration estimate in human blood would be 0.15 ppm. Example 3: If APFO was present in the drinking water at 1ppb and in the air at 0.3 $\mu\text{g}/\text{m}^3$, the resulting steady-state PFO concentration estimate in human blood would be 1.20 ppm.

Table 1. Estimated human steady-state PFO blood levels (ppm) following exposure to APFO via air and/or drinking water.

		Parts per billion APFO in drinking water													
		0	1	2	3	4	5	6	7	8	9	10	15	30	40
$\mu\text{g}/\text{m}^3$ APFO in air	0.00	0.00	0.30	0.60	0.90	1.20	1.50	1.80	2.10	2.40	2.70	3.00	4.50		12.02
	0.05	0.15	0.45	0.75	1.05	1.35	1.65	1.95	2.25	2.55	2.85	3.16	4.66		12.17
	0.10	0.30	0.60	0.90	1.20	1.50	1.80	2.10	2.40	2.70	3.00	3.31	4.81		12.32
	0.15	0.45	0.75	1.05	1.35	1.65	1.95	2.25	2.55	2.85	3.16	3.46	4.96		12.47
	0.20	0.60	0.90	1.20	1.50	1.80	2.10	2.40	2.70	3.00	3.31	3.61			12.62
	0.30	0.90	1.20	1.50	1.80	2.10	2.40	2.70	3.00	3.31	3.61	3.91			12.92
	0.40	1.20	1.50	1.80	2.10	2.40	2.70	3.00	3.31	3.61	3.91	4.21		10.22	13.22
	0.50	1.50	1.80	2.10	2.40	2.70	3.00	3.31	3.61	3.91	4.21	4.51		10.52	13.52
	1.00	3.00	3.61	4.21	4.81	5.41	6.01	6.61	7.21	7.81	8.41	9.01		12.02	15.02
	2.00													10.52	15.02
3.00					10.22	10.52	10.82	11.12	11.42	11.72	12.02	13.52	18.03	21.03	
4.00	12.02	12.32	12.62	12.92	13.22	13.52	13.82	14.12	14.42	14.72	15.02	16.53	21.03	24.04	

PFO Blood levels less than or equal to 5 ppm
 PFO Blood levels greater than 5 ppm but less than or equal to 10 ppm

* Use of this table requires careful consideration of assumptions and limitations described in the text.

Discussion

A relatively simple and conservative compartmental model was developed and exercised to create an estimate of the PFO concentration in human blood following exposure to APFO in drinking water and/or inhaled air. The model was then used to create a table relating APFO exposures to estimates of steady-state PFO blood concentrations. Within the constraints of the assumptions and descriptions provided in this report, a variety of

exposure combinations could be evaluated using the model. Given a specific PFO concentration in blood, the model could also be used to create a plausible exposure scenario that could produce the observed PFO blood level. For example, if one had a hypothetical steady-state PFO concentration of 5 ppb in blood, the corresponding APFO exposure estimate using the model would be approximately 16 parts per trillion (ppt).

The model and approach presented in this report may be valuable for consequence analysis or planning activities, however, it should not serve as a substitute for more robust mechanistic, physiologically based models as they become available. The model presented here is based on sound compartmental analysis principles and is exclusive of mechanistic or physiological descriptions. As discussed earlier, this model is based on conservative assumptions and therefore is likely to provide high estimates of PFO concentrations in blood following ingestion or inhalation of PFO. Nevertheless, the simplicity and utility of this model provide decision-makers an easily applied tool to relate APFO exposures to estimates of resulting PFO concentrations in human blood.

Appendix 1: ACSL Model Code

```
PROGRAM
!MODEL TO SIMULATE PFO BLOOD LEVELS FOLLOWING ORAL AND
!INHALATION OF APFO
VARIABLE TIME

INITIAL

!CONSTANTS CAN BE GIVEN VALUES TO SIMULATE EXPOSURE AND
!SYSTEM OF INTEREST

CONSTANT KUPI      = 0.    !ZERO ORDER INHALATION UPTAKE (ug/day)
CONSTANT KUPO      = 0.    !ZERO ORDER ORAL UPTAKE (ug/day)
CONSTANT KELIM     = 0.    !FIRST-ORDER ELIMINATION (/day)
CONSTANT KACC      = 0.    !FIRST-ORDER DISTRIBUTION TO BODY (/day)
CONSTANT VOL       = 1.    !BLOOD VOLUME (ml)
CONSTANT VF        = 1.    !BODY VOLUME (ml)

!TIMING COMMANDS

CONSTANT TSTOP     =3650.   !LENGTH OF EXPOSURE (days)
CONSTANT POINTS    =3650.   !NO. OF POINTS IN PLOT
CONSTANT TOFF      =3650.   !END OF EXPOSURE TIME (DAYS)

CINT=TSTOP/POINTS   !COMMUNICATION INTERVAL
END                 !END INITIAL

DYNAMIC

ALGORITHM LALG=2

DERIVATIVE
IF (TIME.GT. TOFF) THEN
KUPI = 0.
KUPO=0.

END

IF TERMT(TIME.GE.TSTOP)

!CONCENTRATION OF PFO IN THE BLOOD COMPARTMENT (ug/day)
RA=KUPO + KUPI - KELIM*CBLOOD*VOL - RAF
CBLOOD=INTEG(RA,0.)/VOL

!CONCENTRATION OF PFO IN THE BODY
RAF = KACC*(CBLOOD*VOL-CF*VF)
CF = INTEG(RAF,0.0)/VF

END !END DERIVATIVE
END !END DYNAMIC
END
```

Appendix 2: ACSL Command File for Assigning Appropriate Parameter Values

```
TSTOP=10*365;  
POINTS=50;  
TOFF=TSTOP+1;  
VOL=3500;
```

```
KACC=0.;  
KELIM=0.0019;  
KUPO=2;  
KUPI=6;
```

```
keyboard  
figure;  
!!START  
line(_time, _cblood, @linestyle="+");  
_cblood(POINTS)
```

```
xlabel('Time (Days)');  
ylabel('Conc. in blood (ug/mL)');  
title('BLOOD CONCENTRATION');
```