

## Bioavailability of Octamethylcyclotetrasiloxane (D<sub>4</sub>) After Exposure to Silicones by Inhalation and Implantation

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We developed a physiologically based pharmacokinetic (PBPK) model to predict the target organ doses of octamethylcyclotetrasiloxane (D<sub>4</sub>) after intravenous (IV), inhalation, or implantation exposures. The model used <sup>14</sup>C-D<sub>4</sub> IV disposition data in rats to estimate tissue distribution coefficients, metabolism, and excretion parameters. We validated the model by comparing the predicted blood and tissues concentrations of D<sub>4</sub> after inhalation to experimental results in both rats and humans. We then used the model to simulate D<sub>4</sub> kinetics after single and/or repeated D<sub>4</sub> exposures in rats and humans. The model predicted bioaccumulation of D<sub>4</sub> in fatty tissues (e.g., breast), especially in women. Because of its high lipid solubility (Log P<sub>oct/water</sub> = 5.1), D<sub>4</sub> persisted in fat with a half life of 11.1 days after inhalation and 18.2 days after breast implant exposure. Metabolism and excretion remained constant with repeated exposures, larger doses, and/or different routes of exposure. The accumulation of D<sub>4</sub> in fatty tissues should play an important role in the risk assessment of D<sub>4</sub> especially in women exposed daily to multiple personal care products and silicone breast implants. **Key words:** bioavailability, breast implant, D<sub>4</sub>, implantation, inhalation, octamethylcyclotetrasiloxane, PBPK, physiologically based pharmacokinetic model, risk assessment, silicone. *Environ Health Perspect* 109:1095–1101 (2001). [Online 11 October 2001] <http://ehpnet1.niehs.nih.gov/docs/2001/109p1095-1101luu/abstract.html>

Octamethylcyclotetrasiloxane or D<sub>4</sub> (CAS #556-67-2) is a low molecular weight siloxane (LMWS) fluid with a low surface tension, low aqueous solubility, high lipid solubility, and low vapor pressure (Figure 1, Table 1). It is present at 40–60% by weight in personal care products such as antiperspirants, cosmetics, and hair care products (2–4). Because of its widespread use in these products, a typical woman is exposed to an average daily intake (ADI) of 0.158 mg/kg/day (11.1 mg/day) of D<sub>4</sub> from daily use of such products (4).

D<sub>4</sub> is also used to manufacture polydimethylsiloxane (PDMS) polymer. PDMS is commonly used in orthopedic and breast implants (5). Although breast implants are composed mostly of stable high molecular weight siloxanes (HMWS), low molecular weight siloxanes (LMWS) still exist in the polymer as impurities (5–9). LMWS consist of both cyclic and linear molecules with repeating units of dimethylsiloxane, of which D<sub>4</sub> is a major component (47%) (7–9). Residual LMWS ranged from 0.2 to 2% by weight for the silicone gel and 0.01% to 0.1% for the silicone envelope (1.04–10.4 mg) (5–9). Numerous studies have documented the migration of significant amounts of LMWS out of breast implants into surrounding breast tissues and to the liver (8–11). This would add to the dermal or inhalation exposures from personal care products in a typical woman.

The disposition of [<sup>14</sup>C]D<sub>4</sub> in mice and rats revealed wide tissue distributions after

intravenous (IV), subcutaneous, and inhalation exposures, respectively (1,12–14). Female rats exposed to D<sub>4</sub> via inhalation induced more liver metabolizing enzymes such as cytochrome P<sub>450</sub> (CYP) and retained higher amounts of D<sub>4</sub> than did male rats (1,12,15). CYP is a family of enzymes that play a major role in the oxidative and reductive metabolism of many drugs, many xenobiotics, and steroids. Two major and three minor metabolites of D<sub>4</sub> have recently been identified in rat urine (16). At high doses, mice and rats had enlarged lungs and liver as well as developmental effects such as decreased live litter size, number of pups, and number of uterine implantation sites (1,4,12,13,15). There is little information concerning the effects of the highly lipid soluble D<sub>4</sub> in humans, but it is not expected to be inert if it accumulates in the body (9–12).

Previously, Andersen et al. (16) used physiologically based pharmacokinetic (PBPK) modeling to determine D<sub>4</sub> disposition in Fisher 344 rats after inhalation doses (16). Although the model provided a reasonable simulation of the disposition of D<sub>4</sub> during exposure, it underestimated the postexposure levels of D<sub>4</sub> experimentally found in blood and tissues. It failed to account for the gradual rate of decline of D<sub>4</sub> exhalation in rats after exposure, and the authors reported no extrapolation to human exposure (16).

A goal of this study was to develop a validated PBPK model to relate external exposure of D<sub>4</sub> to internal target dose

(bioavailability) in women with silicone breast implants. The model was first calibrated using previously reported data on tissue distribution in female rats after single and repeated IV administrations of <sup>14</sup>C-D<sub>4</sub> (1). We validated the predicted results in rats and in humans after inhalation exposure using published independent data (12,17,18). We then used the validated model to predict the pharmacokinetics of D<sub>4</sub> as leached from saline-filled breast implants in women.

### Methods

**PBPK model.** The PBPK model (Figure 2) uses the actual physicochemical properties of D<sub>4</sub> and physiologic measurements of animals or humans as a basis for calculating the disposition of D<sub>4</sub>. Material balances were written for D<sub>4</sub> for each of the model's compartments: lungs, blood, two fat compartments, richly perfused tissues, gastrointestinal tract, kidneys, and liver (see Appendix for details). This model was based on a previously published PBPK model for styrene (19) and 4,4'-methylenedianiline (MDA) (20).

In this model, D<sub>4</sub> was metabolized in the liver, and all the metabolites were excreted in the urine or feces (1,12). Generally lipids are transported in blood by various lipoproteins such as low-density lipoproteins (LDL), high-density lipoproteins (HDL), and chylomicrons (22). The highly lipid-soluble D<sub>4</sub> is likely to be transported in blood by one or more of these carriers. We found it necessary for D<sub>4</sub> to be bound to two lipoproteins of different binding affinities (weakly bound

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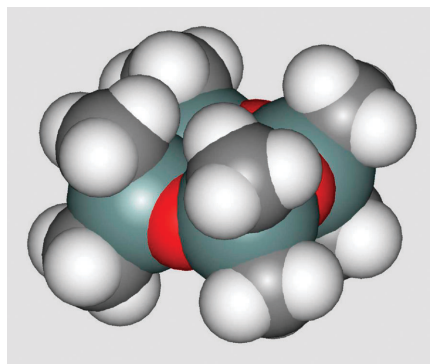
We thank R. Kammula, M. Myers, C.S. Kim, and L. Schroeder for helpful suggestions in this investigation. Without their help, this study would not have been possible.

This work was presented in part at the 219th Annual Meeting of the American Chemical Society, April 2000, Anaheim, CA.

The opinions or assertions about specific products identified by brand name herein are the private views of the authors and are not to be construed as conveying either an official endorsement or criticism by the U.S. Department of Health and Human Services or the Food and Drug Administration.

Received 23 March 2001; accepted 5 April 2001.

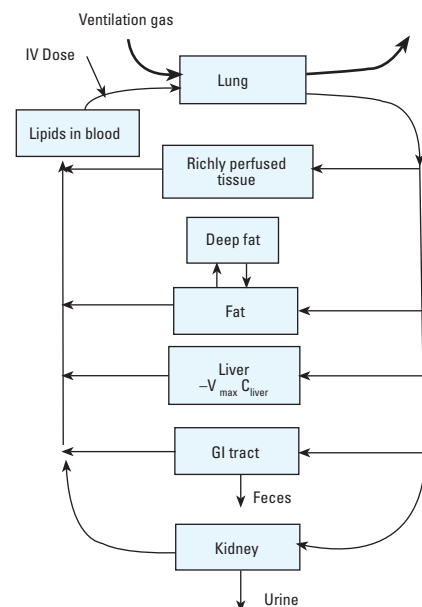
and strongly bound) to account for  $D_4$  kinetics in blood (1,12). Physiologic values (e.g., blood flows; tissue and organ volumes) in the model were taken from the literature (Table 2). We adjusted other parameters needed to calibrate the model—such as tissue distribution coefficients, metabolism and excretion parameters, and the blood:air distribution coefficient ( $H_{air}$ , reciprocal of Henry's Law constant)—to fit the experimentally determined tissue distribution



**Figure 1.** Three-dimensional structure of  $D_4$ . Unique chemical properties were caused by methyl groups (white), which shield the oxygen atom (red) and reduced the polarizability of the molecule.

**Table 1.** Physical properties of  $D_4$ .

| Property                | Measures        |
|-------------------------|-----------------|
| Molecular weight        | 296.62          |
| Vapor pressure          | 1 mm Hg at 25°C |
| Boiling point           | 175.4°C         |
| Surface tension         | 18.796 dynes/cm |
| Aqueous solubility      | 56 ppb          |
| Viscosity               | 2.3 cp at 25°C  |
| Melting point           | 17.5°C          |
| Log $P_{octanol:water}$ | 5.1             |



**Figure 2.** Flow diagram for the PBPK model.

plasma as reported by Kirkpatrick et al. (1). We solved the equations using an adaptive grid Runge-Kutta method (Mathcad 8.0; MathSoft, Inc., Cambridge, MA, USA). The solutions to these multiple stiff ordinary differential equations describe the time course of  $D_4$  in the rat. The model predicts the time course of  $D_4$  at target tissues, as well as excretion rates, and the variation of these responses as a function of the dose, duration, and route of exposure. Once we obtained the best fit for the rat IV experiments, the model parameters were scaled up to the known human physiology based on power law ( $Y = aM^{3/4}$ ) (23). The model was validated in both the rat and human by independent prediction and comparison to inhalation results in both rat and human (12,17).

**Model calibration.** We calibrated the PBPK model using blood/tissues distribution data by Kirkpatrick et al. (1). Briefly, three groups of 20 Sprague-Dawley (SD) rats (10 males and 10 females) were injected intravenously with single 7 mg/kg and 70 mg/kg and repeated 7 mg/kg daily doses of  $^{14}C$ - $D_4$  for 14 days. Blood samples were taken from tail vein at predose, 10, 20, 40 min and 1, 2, 4, 6, 12, 24, 36, and 48 hr postdose from two groups of rats comprising five animals of each sex. The animals were subsequently sacrificed and the liver, kidneys, lungs, and samples of fat were taken from each animal for radioactive determination of tissue distribution of  $D_4$ . In another group of 10 rats (5 males and 5 females),  $D_4$  was administered intravenously via tail vein at 7 mg/kg  $^{14}C$ - $D_4$  as described above. These animals were placed in metabolism cages and urine, feces, and expired air were collected from each animal 0- to 6-hr, 6- to 12-hr, and subsequent 24-hr intervals for up to 5 days. The animals were sacrificed at completion and the liver, kidneys, lungs, samples of fat, gastrointestinal (GI) tract, and remainder of carcass taken for measurements of radioactivity.

**Table 2.** Values of physiologic parameters used in the models.

| Parameters                            | Rat values  | Human values |
|---------------------------------------|-------------|--------------|
| Plasma volume ( $V_{blood}$ ) mL      | 8.5         | 2,800        |
| Blood flows mL/min                    |             |              |
| Richly perfused tissues ( $Q_r$ )     | 44          | 2,054        |
| Fat ( $Q_f$ )                         | 34.2        | 442          |
| Liver ( $Q_l$ )                       | 15.2        | 1,196        |
| GI tract ( $Q_{gi}$ )                 | 11.6        | 728          |
| Kidney ( $Q_k$ )                      | 11.7        | 780          |
| Total cardiac output mL/min ( $Q_t$ ) | 116.7       | 5,200        |
| Lung ventilation rate ( $Q_{air}$ )   | 93.6 mL/min | 10–30 L/min  |
| Tissue compartment volumes mL         |             |              |
| Lungs ( $V_{lung}$ )                  | 14          | 3,800        |
| Richly perfused tissues ( $V_r$ )     | 146         | 40,672       |
| Fat ( $V_f$ )                         | 14.2        | 14,562       |
| Liver ( $V_l$ )                       | 8.0         | 1,419        |
| GI tract ( $V_{gi}$ )                 | 6.0         | 948          |
| Kidney ( $V_k$ )                      | 1.9         | 243          |

See Appendix for nomenclature.

#### Model validation. Rat inhalation model.

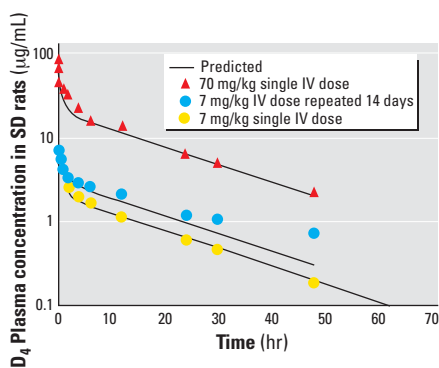
We extrapolated the rat IV model to simulate rat inhalation exposure as reported by Plotzke et al. (12). In this study, F344 rats were exposed to 7, 70, or 700 ppm  $^{14}C$ - $D_4$  by inhalation for 6 hr. Up to 168 hr after exposure, total body burden, excretion in urine, feces, exhalation, and accumulation in target tissues (liver, lungs, perirenal fat, ovaries, vagina, and testes) were measured (12).

**Human inhalation model.** We scaled the rat calibrated PBPK model to humans as described previously, and then compared the human model prediction for inhalation exposure with experimental data obtained from an independent inhalation study (17). In the human inhalation exposure study, Utell et al. (17) exposed 12 volunteers using a mouthpiece-exposure system for 1 hr to either air or 10 ppm (122  $\mu$ g/L)  $D_4$  vapor. Utell et al. (17) divided each exposure into three rest periods of 10, 20, and 10 min, respectively, and two exercise periods, each of 10-min duration. The order of  $D_4$  exposure was randomized. Exhaled air samples were collected before, immediately after exposure, and at 1 and 6 hr after exposure.  $D_4$  was extracted from plasma samples with tetrahydrofuran and the  $D_4$  analysis was performed using gas chromatography–mass spectrometry analysis as described elsewhere (21).

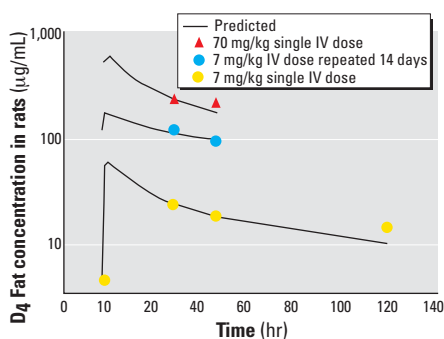
**Breast implant exposure.** In our simulation, the maximum dose of residual  $D_4$  that could migrate from silicone breast implants was estimated to be 0.1% wt of the silicone implant envelope (0.15 mg/kg or 10.4 mg) (5). The residual  $D_4$  was left by incomplete devolatilization of medical polymer (5,7–9).

Lykissa et al. (9) measured *in vitro* the diffusion rate of LMWS ( $D_4$ - $D_7$ ) from explanted silicone gel-filled breast implants into various surrounding media. The highest reported diffusion rate (40  $\mu$ g/g implant/day) was for a lipid-rich medium such as that

found in breast tissue, and the lowest reported rate was for an aqueous extraction media (< 1 µg/g implant/day). Given the *in vitro* results for D<sub>4</sub> into lipid rich medium, the estimated diffusivity of D<sub>4</sub> in the breast implant shell was  $5.4 \times 10^{-8}$  cm<sup>2</sup>/sec. Using published values of the diffusivity for different compounds in PDMS and free volume theory, we also estimated the diffusivity of D<sub>4</sub> to be  $2 \times 10^{-8}$  cm<sup>2</sup>/sec in the breast implant shell (24,25). Thus, the leaching rate of D<sub>4</sub> from the shell to the surrounding fatty tissues of the breasts was estimated to be 95% removal in 30 days. We obtained this rate by solving one-dimensional diffusion equation inside a breast implant shell (5–7 g) exposed to an infinite sink (the body) using estimated values of the diffusivity ( $5.4 \times 10^{-8}$  cm<sup>2</sup>/sec, 0.3 mm shell thickness) of D<sub>4</sub> (26). This conservative estimate for diffusion in a rubbery polymer allows for all of the D<sub>4</sub> to be removed from the breast implant shell rapidly within a month (9). In the actual human body, external mass transfer resistance will slow the rate down and allow the D<sub>4</sub> to persist in the body even longer (27). The dose of D<sub>4</sub> from silicone gel implant is expected to be higher (9), because the initial mass of D<sub>4</sub> in the silicone gel leaching out of the silicone polymer envelope (which is permeable to its own components) is higher, even years after implantation (9–11).



**Figure 3.** Predicted and experimental D<sub>4</sub> plasma concentrations in rats exposed by IV.



**Figure 4.** Predicted and experimental D<sub>4</sub> fat concentrations in rats exposed by IV.

## Results

The predicted and experimental plasma and fat results in the SD rats are shown in Figures 3 and 4, respectively. The model parameters in the rat are shown in Table 3. The experimental data showed higher accumulation of radioactivity in female rats than in male rats at all doses (1,12). We used only the data from female rats to develop our model because our goal was to assess the exposure of D<sub>4</sub> in women.

The plasma radioactivity profiles of <sup>14</sup>C-D<sub>4</sub> showed nonlinear kinetics for different dosage regimens (Figure 3). Single IV dose of 7 mg/kg <sup>14</sup>C-D<sub>4</sub> had two half-lives ( $t_{1/2} = 2.1$  hr and 12.7 hr) and 14-day repeated daily dose of 7 mg/kg <sup>14</sup>C-D<sub>4</sub> had three half-lives ( $t_{1/2} = 3.2$  hr, 15.9 hr, and 32.7 hr). Table 4 shows the tissue distribution results obtained

in the IV rat studies. The highest radioactivity accumulated in fat followed by richly perfused tissues (i.e., lungs, brain), blood, liver, and kidneys. Approximately 60–80% of the absorbed D<sub>4</sub> dose was exhaled and excreted in the urine and feces. Figure 4 shows the predicted and experimental time and dose response of <sup>14</sup>C-D<sub>4</sub> in fatty tissues of the treated rats.

Table 5 shows the pharmacokinetic results obtained in the IV rat studies. For the repeated doses, the exposure as defined by area under the curve (AUC = 43.4 vs. 663.3 µg hr/mL) substantially increased, but the clearance remained the same.

To validate the rat model, we compared the inhalation results obtained from the model with independent inhalation exposure data in F344 rats reported by Plotzke et al.

**Table 3.** Values of the parameters used in the models.

| Parameters                                                                              | Rat values                          | Human values                |
|-----------------------------------------------------------------------------------------|-------------------------------------|-----------------------------|
| Deep fat parameters <sup>a</sup>                                                        |                                     |                             |
| $Q_{f2}/Q_{f1}$                                                                         | 0.059                               | 0.059                       |
| $V_{f2}/V_{f1}$                                                                         | 0.73                                | 0.73                        |
| D <sub>4</sub> distribution coefficients <sup>b</sup>                                   |                                     |                             |
| Richly perfused tissue (D <sub>r</sub> )                                                | 10                                  | 10                          |
| Weakly bound fat compartment (D <sub>f1</sub> )                                         | 700                                 | 700                         |
| Strongly bound fat compartment (D <sub>f2</sub> )                                       | 2,000 <sup>b,c</sup>                | 2,000 <sup>b,c</sup>        |
| Liver (D <sub>l</sub> )                                                                 | 7.4 <sup>d</sup> , 160 <sup>e</sup> | 7.4                         |
| GI tract (D <sub>gi</sub> )                                                             | 0.41                                | 0.41                        |
| Kidney (D <sub>k</sub> )                                                                | 40                                  | 40                          |
| Blood air partition constant, (H <sub>air</sub> ) <sup>a</sup>                          |                                     |                             |
| $K_{el}$ h <sup>-1</sup> f <sup>b</sup>                                                 | 9 <sup>d</sup> , 4 <sup>e</sup>     | 728                         |
| Strongly bound plasma lipoproteins <sup>a</sup>                                         |                                     |                             |
| $V_{strong}$ mL <sup>g</sup>                                                            | 1.0                                 | 0.0                         |
| $K_{si}$ h <sup>-1</sup>                                                                | 0.4                                 | —                           |
| $K_{so}$ h <sup>-1</sup>                                                                | 0.07                                | —                           |
| Weakly bound plasma lipoproteins <sup>a</sup>                                           |                                     |                             |
| $V_{weak}$ mL <sup>g</sup>                                                              | 1.0                                 | 10.4                        |
| $K_{wi}$ h <sup>-1</sup>                                                                | 0.2                                 | 0.2                         |
| $K_{wo}$ h <sup>-1</sup>                                                                | 1.0                                 | 1.0                         |
| Capture efficiency, $\eta$                                                              | 0.04 <sup>e</sup>                   | 0.12 resting, 0.07 exercise |
| Initial inhalation fraction D <sub>4</sub> in weakly bound plasma lipoprotein, $\alpha$ | 0.07 <sup>e</sup>                   | 0.008                       |

Abbreviations:  $k_{el}$ , metabolism rate constant, per hour;  $k_{si}$ , forward rate constant for strong protein binding of D<sub>4</sub> in plasma, per hour;  $k_{so}$ , reverse rate constant for strong protein binding of D<sub>4</sub> in plasma, per hour;  $k_{wi}$ , forward rate constant for weak protein binding of D<sub>4</sub> in plasma, per hour;  $k_{wo}$ , reverse rate constant for weak protein binding of D<sub>4</sub> in plasma, per hour;  $Q_{f1}$ , blood flow rate to weakly bound fat compartment, mL/hr;  $Q_{f2}$ , blood flow rate to strongly bound fat compartment, mL/hr. See Appendix for nomenclature.

<sup>a</sup>Best fit parameters to experimental data. <sup>b</sup>Determined from distribution and excretion study in rats (1). <sup>c</sup>Estimated from Log P = 5.1. <sup>d</sup>Sprague-Dawley rat. <sup>e</sup>F344 rat. <sup>f</sup>Scale-up factor (70 kg/0.20 kg), 0.75. <sup>g</sup>Scale-up factor (70 kg/0.20 kg), 0.40.

**Table 4.** Comparison of D<sub>4</sub> tissue distribution results in rats as a percentage of doses. Experimental values in parentheses.

| Tissue compartment     | Rat IV <sup>a</sup><br>(7 mg/kg) | Rat IV <sup>a</sup><br>(70 mg/kg) | Rat IV 14-day<br>repeated dose<br>(7 mg/kg) |
|------------------------|----------------------------------|-----------------------------------|---------------------------------------------|
| Richly perfused tissue | 0.83                             | 0.84                              | 0.20                                        |
| Fat                    | 18.2 (16.3)                      | 18.2 (18.8)                       | 6.9                                         |
| Liver                  | 0.10 (0.15)                      | 0.10                              | 0.024                                       |
| GI tract               | 0.001                            | 0.001                             | 0.0003                                      |
| Kidneys                | 0.04 (0.07)                      | 0.04 (0.05)                       | 0.01                                        |
| Blood                  | 0.15                             | 0.15                              | 0.015                                       |
| Urine                  | 26.1 (22.3)                      | 26.1                              | 32.2                                        |
| Feces                  | 8.71 (5.93)                      | 8.71                              | 10.7                                        |
| Exhaled                | 42.2 (31.8)                      | 42.2                              | 50.2                                        |

<sup>a</sup>At the end of 48 hr.

(12). The F344 rat results were obtained using higher metabolism rate than in SD rats (12). Also, the higher ventilation rate in the rat produced lower capture efficiency than in the human ventilation model. As in the IV rat model, the experimental inhalation results in F344 rats also indicated a biphasic plasma profile as well as slow clearance in fat, in fairly good agreement with the predictions of the model (Figure 5). These results showed less accumulation in fat compared to rat IV exposure results. After 60 hr, the simulated plasma results were below the reported experimental data, which were reported as the limit of detection (0.01  $\mu\text{g/g}$ ). Hence, we cannot really compare, but the model does not conflict with the experimental results. Previous rat experiments indicated rapid clearance of  $\text{D}_4$  in plasma (1).

To validate the human model, we predicted the absorption, distribution, metabolism, and excretion of  $\text{D}_4$  after an inhalation dose and compared it to previously published experimental results by Utell et al. (17). Figure 6 displayed the predicted and experimental profiles of  $\text{D}_4$  after a single dose of 11.1 mg by inhalation for 1 hr in human plasma and fat, respectively. As shown, the model was an excellent predictor of the experimentally determined plasma concentrations.

Table 6 shows the simulated results for tissue distribution, exhalation, and excretion

in the urine and feces for human inhalation and implantation. Table 7 shows the pharmacokinetics of  $\text{D}_4$  in plasma. Like fat in rats, the human fat showed highest accumulation of  $\text{D}_4$  regardless of dose, regimen, or route of exposure.

A single low-dose  $\text{D}_4$  exposure by inhalation showed fast plasma absorption ( $C_{\text{max}} = 69.4 \text{ ng/mL}$  at  $t_{\text{max}} = 1 \text{ hr}$ ) and fast excretion [43.8% exhaled, 6.1% in urine, 2% in feces; Clearance = 407 mL/hr (Table 7)]. Repeated daily exposure to the same low dose of  $\text{D}_4$  for 14 days showed higher  $C_{\text{max}}$  value (76 ng/mL) at 145 hr after exposure, increased area under the curve (AUC = 3,628 ng hr/mL), increased volume of distribution ( $V_d = 1,022 \text{ L}$ ) and reduced systemic clearance (Clearance = 357 mL/hr). The implantation of silicone breast implants had a lower  $C_{\text{max}}$  of 2 ng/mL compared to a  $C_{\text{max}}$  of 69.4 ng/mL and 76 ng/mL after single or repeated inhalation of 11.1 mg/day for 7 days, respectively. Comparison of different routes of exposure in human showed largest volume of distribution ( $V_d = 4,100 \text{ L}$ ) after implantation, indicating longer retention in the body. We predicted that  $\text{D}_4$  systemic exposure would be longer after implantation ( $t_{1/2} = 18$  days for  $\text{D}_4$  in fat) compared to inhalation ( $t_{1/2} = 11$  days in fat). The maximum amount retained in fat for the breast implant case was 174 ng/mL at  $t_{\text{max}} = 11.7$  days after implantation compared to a corresponding  $C_{\text{max}} = 330 \text{ ng/mL}$  at  $t_{\text{max}} = 34 \text{ hr}$  after inhalation.

## Discussion

Women are prone to bioaccumulate  $\text{D}_4$  when exposed daily to such multiple personal care products as antiperspirants, skin care, or hair care products. A mean dose of 0.158 mg/kg  $\text{D}_4$  per day by inhalation was reported in a recent abstract by Shipp et al. (4). Added to this would be the estimated dose (10.4 mg/30 days/60 kg = 0.0057 mg/kg/day) of  $\text{D}_4$  leached from the saline-filled silicone breast implants (5–9). For the first time, the results of the PBPK model suggest that women accumulate  $\text{D}_4$  in their fatty tissues (e.g., breasts), richly perfused tissues, liver, and kidneys. The  $\text{D}_4$  accumulation increases with the dose, the regimen of dosing (single vs. repeated), and the routes of exposure (inhalation vs. implantation).

The resulting tissue distribution is attributed to the physical properties of  $\text{D}_4$ , which is highly lipid soluble and very insoluble in water (Figure 1, Table 1). Thus, once lipid-containing tissue (e.g., breast tissue) is exposed to  $\text{D}_4$ —as occurs when  $\text{D}_4$  leaches from breast implants— $\text{D}_4$  is rapidly absorbed and only slowly desorbed with a very long half-life (fat  $t_{1/2} = 18.2$  days).  $\text{D}_4$  is retained in the body if during exposure it contacts the lipophilic tissues. Thus neither inhalation exposure (about a 10% capture of the intake dose) nor dermal contact (0.5% absorption) is an efficient way to deliver  $\text{D}_4$  into internal target organs in the body (17,28). By contrast, leaching from an implant directly into breast tissue (mostly fat) would have great potential for allowing accumulation of  $\text{D}_4$  in the body. Repeated exposures increase accumulation in target tissues since the frequency of exposure is shorter than the elimination half-life, especially in certain target tissues.

Fat is the primary tissue depot following all routes of exposure, at low and high doses of  $\text{D}_4$ , with significant longer half-life than that of plasma (Table 4 and 5). In the rat, the highest  $\text{D}_4$  accumulation was in the fat, followed by richly perfused tissues (e.g., lungs, brain), blood, liver, and kidneys (Table 4). Single-dose inhalation results in rats were similar, with rapid clearance from plasma and a longer half-life in fat (Figure 5). The single inhalation route in rats also had poor absorption, which was consistent with both our inhalation model and published results (12). Predictions of the PBPK model regarding plasma, tissue distributions, and excretions were consistent with the above reported experimental results (1,12).

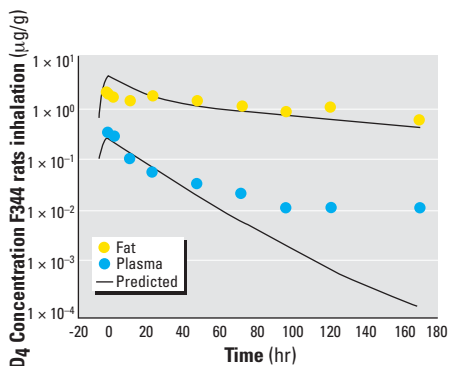
In the human inhalation case, the model predicted that the biphasic plasma half-life would be 1.7 and 7.4 hr, and the fat half-life would be 11.1 days. Similarly, the model predicted that after desorption of  $\text{D}_4$

**Table 5.** Pharmacokinetic results of  $\text{D}_4$  in rat plasma.

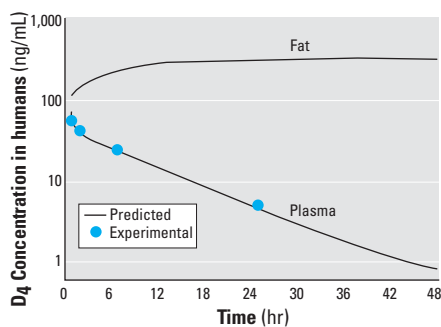
| Pharmacokinetic parameters            | Rat IV – single dose<br>7 mg/kg | Rat IV – 14 day repeated dose<br>7 mg/kg |
|---------------------------------------|---------------------------------|------------------------------------------|
| $C_{\text{max}}$ ( $\mu\text{g/mL}$ ) | 6.7                             | 7.6                                      |
| $t_{\text{max}}$ (hr)                 | 0                               | 312 <sup>a</sup>                         |
| AUC ( $\mu\text{g/hr/mL}$ )           | 43.4                            | 663.2                                    |
| Cl (mL/hr/kg)                         | 2.42                            | 2.46                                     |
| $V_d$ (L/kg)                          | 1.05                            | 0.92                                     |
| $t_{1/2}$ experimental (hr)           | 2.1, 12.7                       | 3.2, 15.9, 32.7                          |
| $t_{1/2}$ model (hr)                  | 2.7, 14.0                       | 3.4, 14.4                                |

Abbreviations: AUC, area under the curve of  $\text{D}_4$  concentration in plasma versus time; Cl, total body clearance;  $C_{\text{max}}$ , maximum concentration in plasma;  $t_{\text{max}}$ , maximum time;  $t_{1/2}$ , plasma elimination half-life of  $\text{D}_4$ ;  $V_d$ , volume of distribution. See Appendix for nomenclature.

<sup>a</sup>Maximum concentration occurs immediately after dosing at the beginning of day 14.



**Figure 5.** Predicted and experimental  $\text{D}_4$  plasma and fat concentrations in rats exposed by inhalation. Limit of detection = 0.01  $\mu\text{g/g}$ .



**Figure 6.** Predicted and experimental  $\text{D}_4$  plasma and fat concentrations in humans exposed by inhalation.

from the breast implant in the human, the plasma half-life would be 7.8 hr and the fat half-life would be 18.2 days (Table 7). If D<sub>4</sub> exposures were repeated in either case at a frequency shorter than the fat half-life, the net result would be accumulation in the fat tissues, because the input would exceed the elimination output.

These results were not evident from previous human exposure studies, because the target tissue disposition was not accurately determined (17,18). Utell et al. (17) exposed human volunteers to 129–137 mg D<sub>4</sub>; the lungs only captured 10% of D<sub>4</sub> exposure by inhalation (13 mg out of 129–137 mg of inhaled D<sub>4</sub>). Thus most of the inhaled dose (124 mg out of 137 mg) was not absorbed, which is expected from a combination of poor gas mixing in the lung, and alveolar tissue mass transfer resistance to hydrophobic materials such as D<sub>4</sub> because of the aqueous nature of the alveolar membrane. Utell et al. (17) reported that D<sub>4</sub> was rapidly cleared from plasma, but they did not identify D<sub>4</sub> tissues distribution or excretion as predicted by our model. Our PBPK model did confirm the plasma measurements reported by Utell et al. (17) as well as a nonlinear clearance with two half-lives of 30 min and 330 min and a mean peak value of 79 ng/g (Table 7 and Figure 6).

The pharmacokinetic results shown in Tables 5 and 7 for rats and humans, respectively, showed a disproportionate increase

in area under the curve and volume of distribution at high dose and repeated exposures of D<sub>4</sub>. The predicted D<sub>4</sub> plasma and fat behavior are similar to that observed with other volatile lipophilic chemicals such as styrene (12,20). Because the exposure was repeated daily, the D<sub>4</sub> concentrations in fat increased, as shown in Table 6. However, systemic clearance remained about the same regardless of the route of exposure (Table 7). The shape of the plasma and fat concentration–time curves shown in Figures 3–5 also suggested probable saturation of the elimination processes. On repeated dosing, saturation of the elimination processes may increase the delivered dose of D<sub>4</sub> to target organs such as fat, richly perfused tissues (e.g., lungs, brain), liver, and kidneys in both rats (Table 4) and humans (Table 6). In the liver and kidneys, such accumulation could produce liver enlargement confirming experimental results found in mice and rats (1,13,15). McKim et al. (15) reported some preliminary results suggesting that repeated inhalation exposure to high concentrations of D<sub>4</sub> produced liver enlargement with significant induction of cytochrome P<sub>450</sub> CYP2B1/2 in rats. Analysis of the rat excretion results (Table 4) showed no compelling evidence of D<sub>4</sub> CYP enzyme induction. Furthermore, there is a more reliable way (e.g., using yeast that contains human genes) to determine whether D<sub>4</sub> chemically induced P<sub>450</sub> in humans.

The model predicted 43% and 53% of the dose of D<sub>4</sub> in exhaled air after single and repeated inhalation exposures, respectively. Similarly, 59% of D<sub>4</sub> was exhaled in air after breast implantation (Table 6). The model results were comparable with the exhalation data reported by others (1,3,12,15,17). The PBPK model used the blood:air partition coefficient to estimate the exhalation data of D<sub>4</sub>. The blood:air partition coefficient that best fit the experimental data [shown in Table 3 as H<sub>air</sub> (20.0)], was not consistent with the water:air partition coefficient values for D<sub>4</sub>. The published Henry's law constants for D<sub>4</sub> (air:water) have been reported in the range of 3–32, which is equivalent to water:air partition coefficient of 0.33 to 0.031 (27,29–32). The discrepancy was attributed to both the low solubility of D<sub>4</sub> in water (56 ppb) and its binding to blood lipoproteins, which increased the value of the blood:air partition coefficient relative to its corresponding water:air partition coefficient (33). Beliveau and Krishnan (33) indicated that the blood:air partition coefficients of lipophilic volatile organic compounds (e.g., D<sub>4</sub>, styrene) could not be determined using water:air partition coefficients. They published a methodology to account for this solubility enhancement of protein binding for estimating the blood:air partition coefficients using oil:water and *n*-octanol:hemoglobin:water mixtures instead of a simple water:air measurements (33). The high lipid affinity of D<sub>4</sub> for blood proteins makes this effect even more significant for this case. We suspected that a smaller blood:air partition coefficient (< 20) was used in a reported model by Anderson et al. (16). This could have led the authors to underestimate the postexposure blood and tissues levels of D<sub>4</sub> in rat (16).

We developed a PBPK model to determine the time course of D<sub>4</sub> in the human body after exposure at different doses and routes in rats and humans. The simulation results suggest that D<sub>4</sub>'s unique physicochemical properties play an important role in the bioavailability of this chemical. It is absorbed rapidly and retained in the fatty tissues for a longer time when it contacts lipophilic tissues directly (e.g., breast implants). The repeated daily inhalation exposures to D<sub>4</sub> would accumulate this compound in fat, liver, and kidneys significantly to saturate its elimination processes. This accumulation is likely to occur in women because physiologically women have a large volume of adipose tissues and a slower metabolism than do men. Future studies are expected to extend our toxicokinetic evaluation of D<sub>4</sub> such that we could accurately assess the safety of D<sub>4</sub> based on its bioavailability and target doses, not by consideration of the dose level alone.

**Table 6.** Comparison of D<sub>4</sub> tissue distribution results in rats and humans as a percentage of doses. Rat experimental values in parentheses.

| Tissue compartment     | Rat IV <sup>a</sup><br>(7 mg/kg) | Human inhalation<br>single exposure <sup>b</sup><br>(11.1 mg) | Human inhalation<br>exposure, repeated <sup>c</sup><br>(77.7 mg) | Human breast<br>implant exposure<br>(10.4 mg) <sup>d</sup> |
|------------------------|----------------------------------|---------------------------------------------------------------|------------------------------------------------------------------|------------------------------------------------------------|
| Richly perfused tissue | 0.83                             | 7.9                                                           | 2.2                                                              | 1.7                                                        |
| Fat                    | 18.2 (16.3)                      | 39.7                                                          | 35.0                                                             | 27.6                                                       |
| Liver                  | 0.10 (0.15)                      | 0.14                                                          | 0.04                                                             | 0.04                                                       |
| GI tract               | 0.001                            | 0.005                                                         | 0.001                                                            | 0.002                                                      |
| Kidneys                | 0.04 (0.07)                      | 0.14                                                          | 0.04                                                             | 0.04                                                       |
| Blood                  | 0.15                             | 0.08                                                          | 0.01                                                             | 0.01                                                       |
| Urine                  | 26.1 (22.3)                      | 6.1                                                           | 7.3                                                              | 8.6                                                        |
| Feces                  | 8.71 (5.93)                      | 2.0                                                           | 2.4                                                              | 2.9                                                        |
| Exhaled                | 42.2 (31.8)                      | 43.8                                                          | 53.1                                                             | 59.1                                                       |

<sup>a</sup>At the end of 48 hr. <sup>b</sup>At the end of 24 hr. <sup>c</sup>At the end of 7 days. <sup>d</sup>At the end of 7 days.

**Table 7.** Pharmacokinetic results of D<sub>4</sub> in human plasma.

| Pharmacokinetic parameters | Human inhalation<br>exposure<br>(11.1 mg) | Human inhalation<br>exposure, 7-day<br>repeated dose<br>(77.7 mg) | Human breast<br>implant<br>exposure <sup>a</sup><br>(10.4 mg) |
|----------------------------|-------------------------------------------|-------------------------------------------------------------------|---------------------------------------------------------------|
| C <sub>max</sub> (ng/mL)   | 69.4                                      | 76.0                                                              | 2.0                                                           |
| t <sub>max</sub> (hr)      | 1                                         | 145                                                               | 35                                                            |
| AUC (ng/hr/mL)             | 453.4                                     | 3,628                                                             | 427.8                                                         |
| Cl (mL/hr)                 | 407                                       | 357                                                               | 329                                                           |
| V <sub>d</sub> (L)         | 159.8                                     | 1,022                                                             | 4,100                                                         |
| t <sub>1/2</sub> (hr)      | 1.7, 7.4 <sup>b</sup>                     | 1.1, 8.5 <sup>b</sup>                                             | 7.8                                                           |

Abbreviations: AUC, area under the curve of D<sub>4</sub> concentration in plasma versus time; Clearance (Cl), total body clearance; C<sub>max</sub>, maximum concentration in plasma; t<sub>max</sub>, maximum time; t<sub>1/2</sub>, the elimination half life of D<sub>4</sub> in plasma; V<sub>d</sub>, volume of distribution.

<sup>a</sup>81.4% of this dose of D<sub>4</sub> desorbed into the body at the end of 14 days. <sup>b</sup>Biphasic half-life.

## Appendix

The material balances for both  $D_4$  and its metabolites for the model shown in Figure 2 were solved using MathCad 8.0 (MathSoft, Inc., Cambridge, MA, USA). We used an adaptive grid Runge-Kutta method for the system of stiff ordinary differential equations. We calibrated the rat model using an IV dose; this was introduced as a forcing function partitioned to all of the compartments in the model. In that way, the  $D_4$  was distributed to all compartments in the body, allowing the numerical procedure to converge to a solution. In the human inhalation or breast implant case, the  $D_4$  was introduced directly to the lung or into the systemic circulation at the mix point, similar to previous models (12,13). A nomenclature list is included at the end of this appendix. The following equations are the material balances for  $D_4$ :

$$\text{For the lung, } V_{lung} \frac{dC_{lung}}{dt} = Q_t C_{ai} - Q_t C_{lung} H_{air} C_{lung}$$

$$\text{For the richly perfused tissues, } V_r \frac{dC_r}{dt} = Q_r C_{lung} H_{air} + \frac{Q_t \xi(t)}{Q_t} - \frac{Q_r C_r}{D_r}$$

$$\text{For the deep fat compartment, } V_{f2} \frac{dC_{f2}}{dt} = \frac{Q_{f2} C_{f2}}{D_{f2}} - \frac{Q_{f2} C_{f2}}{D_{f2}}$$

For the weakly bound fat compartment,

$$V_{f1} \frac{dC_{f1}}{dt} = Q_{f1} C_{lung} H_{air} + \frac{Q_{f1} \xi(t)}{Q_t} + \frac{Q_{f2} C_{f2}}{D_{f2}} - \frac{Q_{f1} C_{f1}}{D_{f1}} - \frac{Q_{f2} C_{f1}}{D_{f1}}$$

$$\text{For the liver, } V_l \frac{dC_l}{dt} = Q_l C_{lung} H_{air} + \frac{Q_l \xi(t)}{Q_t} - \frac{Q_l C_l}{D_r} - k_{el} C_l$$

$$\text{For the GI tract, } V_{gi} \frac{dC_{gi}}{dt} = Q_{gi} C_{lung} H_{air} + \frac{Q_{gi} \xi(t)}{Q_t} - \frac{Q_{gi} C_{gi}}{D_{gi}}$$

$$\text{For the kidneys, } V_k \frac{dC_k}{dt} = Q_k C_{lung} H_{air} + \frac{Q_k \xi(t)}{Q_t} - \frac{Q_k C_k}{D_k}$$

We determined the total metabolites generated by integrating the accumulation equation below,

$$\frac{dM_{metabolite}}{dt} = k_{el} C_l$$

In the blood,  $D_4$  exists dissolved in the plasma (aqueous), weakly bound to protein, and strongly bound to protein. The venous blood is well mixed before it is returned to the arterial circulation. At this mix point, the  $D_4$  protein binding is calculated. For  $D_4$  in the plasma,

$$V_{blood} \frac{dC_{ai}}{dt} = \frac{Q_r C_r}{D_r} + \frac{Q_{f1} C_{f1}}{D_{f1}} + \frac{Q_l C_l}{D_l} + \frac{Q_{gi} C_{gi}}{D_{gi}} + \frac{Q_k C_k}{D_k} + k_{wo} C_{wk} - k_{wi} C_{ai} - Q_t C_{ai}$$

$$\text{For the weakly bound } D_4 \text{ in the blood, } V_{strong} \frac{dC_{str}}{dt} = k_{si} C_{wk} - k_{so} C_{str}$$

For the strongly bound  $D_4$  in the blood,

## Appendix 1, Table 1. Nomenclature.

|                |                                                                                    |
|----------------|------------------------------------------------------------------------------------|
| $C_{ai}$       | Concentration of $D_4$ dissolved in plasma, mol/mL                                 |
| $C_{air}$      | Concentration of $D_4$ in inhalation air, mol/L                                    |
| $C_{f1}$       | Concentration of $D_4$ in weakly bound fat compartment, mol/mL                     |
| $C_{f2}$       | Concentration of $D_4$ in strongly bound fat compartment, mol/mL                   |
| $C_{gi}$       | Concentration of $D_4$ in GI tract, mol/mL                                         |
| $C_k$          | Concentration of $D_4$ in kidneys, mol/mL                                          |
| $C_{inj}$      | Concentration of $D_4$ in IV fluid, mol/mL                                         |
| $C_r$          | Concentration of $D_4$ in richly perfused tissue, mol/mL                           |
| $C_{wk}$       | Concentration of $D_4$ weakly protein bound in plasma, mol/mL                      |
| $C_{str}$      | Concentration of $D_4$ strongly protein bound in plasma, mol/mL                    |
| $D_0$          | Available dose of $D_4$ in breast implant shell, mol                               |
| $D_{f1}$       | Distribution coefficient of $D_4$ in weakly bound fat compartment, dimensionless   |
| $D_{f2}$       | Distribution coefficient of $D_4$ in strongly bound fat compartment, dimensionless |
| $D_{gi}$       | Distribution coefficient of $D_4$ in GI tract, dimensionless                       |
| $D_k$          | Distribution coefficient of $D_4$ in kidney, dimensionless                         |
| $D_l$          | Distribution coefficient of $D_4$ in liver, dimensionless                          |
| $D_r$          | Distribution coefficient of $D_4$ in richly perfused tissue, dimensionless         |
| $H_{air}$      | Blood:air partition constant of $D_4$ in plasma, dimensionless                     |
| $k_{ba}$       | Desorption constant of $D_4$ from breast implant shell, $h^{-1}$                   |
| $k_{si}$       | Forward rate constant for strong protein binding of $D_4$ in plasma, $h^{-1}$      |
| $k_{el}$       | Metabolism rate constant, $h^{-1}$                                                 |
| $k_{so}$       | Reverse rate constant for strong protein binding of $D_4$ in plasma, $h^{-1}$      |
| $k_{wi}$       | Forward rate constant for weak protein binding of $D_4$ in plasma, $h^{-1}$        |
| $k_{wo}$       | Reverse rate constant for weak protein binding of $D_4$ in plasma, $h^{-1}$        |
| $Q_{air}$      | Lung ventilation rate, L/hr                                                        |
| $Q_{exercise}$ | Lung ventilation rate during exercise, L/hr                                        |
| $Q_{rest}$     | Lung ventilation rate during rest, L/hr                                            |
| $Q_{f1}$       | Blood flow rate to weakly bound fat compartment, mL/hr                             |
| $Q_{f2}$       | Blood flow rate to strongly bound fat compartment, mL/hr                           |
| $Q_{gi}$       | Blood flow rate to GI tract, mL/hr                                                 |
| $Q_{inj}$      | Flow rate of IV, mL/hr                                                             |
| $Q_k$          | Blood flow rate to kidneys, mL/hr                                                  |
| $Q_l$          | Blood flow rate to liver, mL/hr                                                    |
| $Q_r$          | Blood flow rate to richly perfused tissues, mL/hr                                  |
| $Q_t$          | Total cardiac output, mL/hr                                                        |
| $t$            | Time, hr                                                                           |
| $t_{inj}$      | Duration of IV, hr                                                                 |
| $V_{blood}$    | Plasma volume, mL                                                                  |
| $V_{f1}$       | Volume of weakly bound fat compartment, mL                                         |
| $V_{f2}$       | Volume of strongly bound fat compartment, mL                                       |
| $V_{gi}$       | Volume of GI tract, mL                                                             |
| $V_k$          | Volume of kidneys, mL                                                              |
| $V_l$          | Volume of liver, mL                                                                |
| $V_{lung}$     | Volume of lungs, mL                                                                |
| $V_r$          | Volume of richly perfused tissue, mL                                               |
| $V_{strong}$   | Volume of strongly bound plasma, mL                                                |
| $V_{weak}$     | Volume of weakly bound plasma, mL                                                  |

$$V_{weak} \frac{dC_{wk}}{dt} = k_{wi} C_{ai} + k_{so} C_{str} - k_{wo} C_{wk} - k_{si} C_{str}$$

For the IV case in the rat, we solved the above equations with the initial conditions that all the compartments except the weakly bound  $D_4$  in the blood have zero concentration at  $t = 0$ . The weakly bound  $D_4$  in the blood was assigned an initial concentration of  $D_4$  equal to 5% of the IV dose at  $t = 0$ ; this was a better fit of the experimental data.

For the rat, the IV dose was input using the following forcing function.

$$\xi(t) = \text{if}(t < t_{inj}, Q_{inj} C_{inj}, 0)$$

For the human, the IV dose was replaced by either an inhalation dose or implant dose. Using the data of Utell et al. (11), we exposed subjects to 10 ppm  $D_4$  by inhalation for 1 hr. This exposure period consisted of 10 min rest, 10 min exercise, 20 min rest, 10 min exercise, and finally 10 min rest before the  $D_4$  inhalation was terminated.

To model this, we defined five forcing functions covering each period of exposure. The inhalation rate was set at 10 L/min during rest, and 30 L/min during exercise. Using Utell et al.'s (11) published capture efficiencies of the human lung of 0.12 during rest and 0.07 during exercise, we delivered a total dose of 11.1 mg of D<sub>4</sub> to the human body during the exposure. The following equations were used,

$$\begin{aligned}\chi_1(t) &= \text{if}(t < 10 \text{ min}, Q_{\text{rest}} C_{\text{in}}, 0) \\ \chi_2(t) &= \text{if}(10 \leq t < 20 \text{ min}, Q_{\text{exercise}} C_{\text{in}}, 0) \\ \chi_3(t) &= \text{if}(20 \leq t < 40 \text{ min}, Q_{\text{rest}} C_{\text{in}}, 0) \\ \chi_4(t) &= \text{if}(40 \leq t < 50 \text{ min}, Q_{\text{exercise}} C_{\text{in}}, 0) \\ \chi_5(t) &= \text{if}(50 \leq t < 60 \text{ min}, Q_{\text{rest}} C_{\text{in}}, 0)\end{aligned}$$

During the exposure, Q<sub>air</sub> in equation 1 is also stepped between Q<sub>rest</sub> and Q<sub>exercise</sub> during the 1-hr exposure. After exposure, the lung ventilation rate was set to the resting value. In the human case, unlike the rat, all of the compartments contained no D<sub>4</sub> at t = 0. Also, unlike the rat where 5% of the D<sub>4</sub> was initially bound to the blood plasma, in the human this value was set to 0.8% of the dose delivered by the functions

$$\chi 1(t) - \chi 5(t).$$

For the human breast implant exposure, the inhalation forcing functions were replaced by a first-order desorption.

$$k_{ba} D_0 \exp(-k_{ba} t)$$

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