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Predicted Infant Exposure to Tetrachloroethene in Human Breastmilk

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Based on a variety of maternal occupational and residential inhalation exposure scenarios, estimates of infant exposure to the dry-cleaning solvent tetrachlorothylene (perchloroethylene, PCE) in breastmilk were made. Physiologically based pharmacokinetic (PBPK) modeling indicates that infants may be exposed to elevated levels of PCE in breastmilk due to their mothers' inhalation of PCE. The PBPK-predicted breastmilk PCE concentrations agree very well with measured concentrations, where available. Based on this analysis, infants may be exposed to this workplace chemical via breastmilk at doses corresponding to rather high levels of risk. Predicted breastmilk doses provide the infant with little margin of exposure to doses associated with adverse health effects. In addition, the estimated increased cancer risks associated with these infant exposures are large under certain exposure scenarios. The actual concentrations of PCE in breastmilk of exposed mothers can only be known with certainty if monitoring is conducted. Due to the widespread exposure potential, monitoring studies should be undertaken so that the appropriate risk management alternatives can be better evaluated.

KEY WORDS: Tetrachloroethene; breastmilk; pharmacokinetic modeling; indoor air contamination; dry cleaners.

INTRODUCTION

Physiologically based pharmacokinetic (PBPK) modeling can be used to predict human tissue concentrations of tetrachloroethene (perchloroethylene, PCE) under various inhalation exposure scenarios. The concentrations of PCE in breastmilk can be predicted from maternal exposure to airborne PCE concentrations or from measured or estimated maternal blood PCE concentrations. The results indicate that infants may be exposed to levels of PCE in breastmilk corresponding to rather high levels of risk. The PBPK-estimated breastmilk PCE concentrations agree very well with measured concentrations, where available.

The contamination of human breastmilk by environmentally stable halogenated organic compounds such as polychlorinated biphenyls (PCBs), 1,1-bis(p-chlorophenyl)-2,2,2-trichloroethane (DDT) and metabolites, and other persistent compounds has been recognized for decades.[1–4] The mothers' exposure to these substances usually occurs via the ingestion of low levels of these contaminants in the diet followed by their storage in adipose tissue. The contaminants are subsequently mobilized from adipose tissue to breastmilk upon lactation.[5]

Due to its volatility, inhalation is the pathway by which most people are exposed to PCE.[6,10] Absorption via the lungs to the systemic circulation takes place rapidly. Because of accumulation in lipid-rich tissues, removal of PCE from blood and breath is slow, with a proportional relationship between exposure and concentrations in blood and breath. The half-lives of PCE in vessel-rich, muscle, and adipose tissue groups were calculated to be 12–16 hr, 30–40 hr, and 55 hr, respectively.[6] PCE is eliminated rather slowly via the lungs

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with only a small amount (less than 5%) metabolized to trichloroethanol and trichloroacetic acid.[6] In national surveys, PCE has been identified as a frequent contaminant of adipose tissue,[11] but seldom has its presence in breastmilk been investigated.[4,12,13]

PCE is known to cause adverse acute and chronic health effects in people exposed to high concentrations[6] and is also categorized as a possible human carcinogen by the U.S. Environmental Protection Agency.[18,19] Due to its lipophilic nature, rapid absorption after inhalation exposure and slow metabolism, PCE has the potential to be present in lipid-containing tissue such as blood, adipose tissue, and breastmilk of women exposed to it. This paper evaluates a variety of occupational and residential maternal inhalation exposure scenarios, predicts breastmilk PCE concentrations based on pharmacokinetic modeling and tissue partitioning, and estimates potential increases in cancer risk and other adverse health endpoints in infants exposed to contaminated breastmilk.

2. OCCUPATIONAL EXPOSURE

Dry-cleaning workers, especially those involved in transfer of dry-cleaned garments during the cleaning process, can be exposed to PCE in concentrations approaching the Occupational Safety and Health Administration (OSHA) time-weighted average Permissible Exposure Level (PEL) of 170 mg/m^3.[15,20,21] The American Conference of Governmental Industrial Hygienists (ACGIH) 8-hr Threshold Limit Value (TLV) for PCE is 340 mg/m^3.[22] Geometric mean time-weighted average (TWA) exposures of dry-cleaning workers range from about 20–150 mg/m^3, depending on job category and differences in individual dry-cleaning establishments. The approximate arithmetic and geometric mean concentrations of PCE for pressers, tailors, and counterworkers are 40 and 20 mg/m^3, respectively.[15,21,53]

3. RESIDENTIAL EXPOSURE NEAR DRY CLEANERS

People living near dry-cleaning establishments can also be exposed to considerably elevated PCE concentrations. An investigation by Verberk and Scheffers[24] found that the breath of residents living above dry-cleaning shops in the Netherlands contained a mean concentration of 5000 μg/m^3, while the breath of residents living adjacent to the shops contained 1000 μg/m^3. Reports from Germany and the Netherlands found widely variable, elevated levels of PCE in the indoor air of apartments located near dry cleaners, ranging from 300–28,000 μg/m^3.[25,26]

The New York State Department of Health[17] conducted an investigation to determine if PCE levels in the indoor air of residences located in the same building as a dry-cleaning facility were higher than levels in residences not near a dry cleaner. Elevated levels of PCE were found in the indoor air of the apartments located above each of six dry cleaners in the AM samples (7 AM to 7 PM) (range 300–55,000 μg/m^3) compared to the control residences (range >6.7 to 103 μg/m^3). Similar results were found in the PM samples (7 PM to 7 AM) and a strong statistical correlation was found between AM and PM PCE levels in the apartments. Although air concentrations in the apartments were usually less at night than during the day, the study residences always had higher concentrations of PCE than the control residences. The PCE concentrations in outdoor air near the dry cleaners were also significantly elevated compared to control locations away from the dry cleaners, and these levels were less than the indoor levels. The type of dry-cleaning machine was strongly correlated with the concentration of PCE found in the apartment above, even though only six residences were evaluated (see Table I).

4. GENERAL POPULATION EXPOSURE

The general population is also exposed to PCE. People living in rural locations are exposed to low levels of PCE in ambient air ranging from 0.008–0.5 μg/m^3, whereas people living in U.S. urban areas are exposed to levels ranging from 0.2–52 μg/m^3.[10] The arithmetic mean and median ambient (outdoor) PCE concentrations are 5.9 and 2.4 μg/m^3, respectively.[50] The arithmetic mean and median indoor PCE concentrations are 21.1 and 5.1 μg/m^3, respectively.[50] The mean concentrations reported may be skewed high due to the inclusion of a few high values. The NYSDOH study[17] found 24-hr mean indoor and outdoor PCE concentrations of 28 and 6 μg/m^3, respectively, at six control homes (Table I). The PCE concentrations are greater indoors than outdoors, which is consistent with the existence of strong indoor sources of PCE, thought to be associated with volatilization of PCE from freshly dry-cleaned clothes.[16] PCE residues have been measured in clothing that has been dry cleaned.[27,51,52]

5. BREASTMILK

PCE is excreted in the milk of exposed animals and in human breastmilk[4,12,13,28,29] and may be a significant

Table I. Summary of PCE Concentrations for Study and Control Residences (μg/m³)*

Sample type residence type (no.)	PCE Range	PCE Mean
Indoor air, AM		
Study homes (6)	300–55,000	13,000
Above "transfer" cleaners (3)	1730–17,000	7500
Above "dry-to-dry" cleaners (2)	300–440	370
Above old dry-to-dry unit (1)	55,000	55,000
Control homes (6)	<6.7–103	28
Indoor air, PM		
Study homes (6)	100–36,500	10,000
Above "transfer" cleaners (3)	1350–14,000	7900
Above "dry-to-dry" cleaners (2)	100–160	130
Above old dry-to-dry unit (1)	36,500	36,500
Control homes (6)	<6.7–77.0	28
Outdoor air, AM		
Study homes (6)	195–2600	1000
Outside "transfer" cleaners (3)	530–1400	1000
Outside "dry-to-dry" cleaners (2)	195–300	250
Outside old dry-to-dry unit (1)	2600	2600
Control homes (6)	<6.7–21	8.4
Outdoor air, PM		
Study homes (6)	66–1400	580
Outside "transfer" cleaners (3)	441–1400	880
Outside "dry-to-dry" cleaners (2)	66–400	230
Outside old dry to dry unit (1)	360	360
Control homes (6)	<6.7–6.9	3.9

* PCE, perchloroethene; μg/m³, micrograms per cubic meter; AM, sample collected from 7AM to 7 PM; PM, sample collected from 7 PM to 7 AM.

route of PCE exposure for nursing infants. In cows, PCE was absorbed following administration in the feed and identified as present in blood and milk, although quantitative estimates were not provided.[28] Only limited sampling of human breastmilk for the presence of PCE has been conducted.

Bagnell and Ellenberger[12] reported a case of obstructive jaundice and hepatomegaly in a 6-week-old breastfed infant exposed to PCE. The father was employed at a dry-cleaning factory where he worked as a leather and suede cleaner. He had experienced repeated episodes of personality change, dizziness, and confusion following recurrent exposures to PCE solvent vapors at work. Although the airborne levels in the workplace were not reported, the reported dizziness and personality changes observed in the exposed father suggest that the workplace PCE concentrations in air were highly elevated. The mother regularly visited her husband during lunch hour at the plant. She occasionally experienced mild dizziness after the 30–60 min exposures. (The concentrations of PCE in the air were not reported.) The child was never directly exposed to the father's work environment or to freshly dry-cleaned clothes. Analysis of specimens of the parents' blood and mother's breastmilk indicated that the father and mother's blood samples taken 2 hr after the lunch visit contained 30,000 μg/L and 3000 μg/L PCE, respectively. The breastmilk sample, expressed 1-hr after the lunch visit, contained 10,000 μg/L PCE. Avoidance of exposure to solvent vapors for the next 24 hr allowed the breastmilk concentration to decrease to 3000 μg/L PCE. The cessation of breastmilk exposure resulted in rapid improvement of the child's condition. The child grew normally and had normal liver function during 10 years of intermittent follow-up.[14]

Pellizzari *et al.*[13] qualitatively identified a large number of volatile organic compounds (VOCs) in breastmilk samples from 42 women in the general population from four U.S. urban areas. The feasibility of measuring trace organics in milk was demonstrated, although concentrations of VOCs were not quantified. PCE was identified in about 60% of the samples analyzed.

The Nursing Mothers Study[4] was conducted as part of the Total Exposure Assessment Methodology (TEAM) Studies to determine the concentrations of selected toxic substances in environmental samples, and in blood, breath, urine, and mother's milk. The study participants were 17 lactating women identified from a larger group of participants from approximately 300 randomly selected residences in the main TEAM study. The Nursing Mothers Study provides the only human data for PCE in personal air, exhaled breath, blood, and milk of nonoccupationally exposed nursing mothers. Of the 17 nursing mothers, detectable levels of PCE were consistently found in the media sampled. All overnight and daytime personal air samples had detectable levels of PCE. The PCE concentrations in the milk samples ranged from nondetectable to 43 μg/L with a mean of 6.2 μg/L. The mean PCE concentration in daytime and overnight personal air samples was 27 μg/m³ (range of 1.1–210 μg/m³). The milkfat content was not provided. Spearman correlations between milk PCE and breath PCE concentrations were significant ($R^2 = 0.73$) as were milk PCE and daytime personal air PCE concentrations ($R^2 = 0.75$). The relationship between milk PCE and venous blood PCE concentrations were not significant ($R^2 = 0.45$), probably due to the lack of sensitivity of blood PCE analysis at low concentrations. However, blood and breath PCE concentrations were highly correlated ($R^2 = 0.81$). Individual values for PCE in overnight and daytime personal air samples were not provided in the published report.

No breastmilk sampling has been reported of women

who currently or previously were employed in the dry-cleaning industry, or of women residing in proximity to dry-cleaning establishments. The elevated airborne levels of PCE typically found in dry-cleaning establishments and nearby residences, coupled with the relatively long adipose tissue storage of absorbed PCE, point to the likelihood of finding significant concentrations of PCE in the milk of exposed women.

6. METHODS OF PREDICTING CONCENTRATIONS OF PCE IN MILK

Pharmacokinetics is the study of absorption, distribution, metabolism, and elimination of chemicals in humans and animals.[32] Several investigators have developed physiologically based pharmacokinetic (PBPK) models which predict the concentrations of chemicals in biological tissues.[30,32-35] The models use actual physiological parameters for humans or experimental animals such as breathing rates, blood flow rates, tissue volumes and chemical specific parameters. An advantage of the PBPK model is that by using the appropriate physiological, biochemical, and metabolic parameters, the model can describe the dynamics of chemical transport and distribution without actual sampling and analysis.[32]

PBPK modeling and physicochemical relationships can be used to predict maternal tissue PCE concentrations for different exposure conditions. In this assessment, a commercially available 4-compartment PBPK model by Sielken[35] was used to predict adipose tissue and breastmilk PCE concentrations (see Fig. 1). The physiologic and chemical-specific parameters used for this assessment are shown in Appendix A. The assumptions are that the fat content of blood and milk are 0.65%[31] and 4%,[5] respectively, and that equilibrium has been reached between the air PCE concentration to which the woman is exposed and the resultant tissue PCE concentrations. The predicted adipose tissue concentration can be used to predict the breastmilk concentration, assuming the milk fat is in equilibrium with adipose tissue, and that milk contains 4% fat.

In addition to PBPK modeling, measured or predicted blood-PCE concentrations can be used to predict milk-PCE concentrations using the physicochemical properties of PCE. The partition coefficient relates the relative solubility of a substance in different tissues. The fat-blood partition coefficient for PCE relates the concentrations of PCE in fat and blood based on solubility. A fat-blood partition coefficient of 159 for PCE was found experimentally,[34] which indicates that at equilibrium the concentration of PCE in fat is 159 times the concentration of PCE in blood. The predicted adipose tissue (fat) concentration can then be used to predict the breastmilk concentration, assuming the milk fat is in equilibrium with adipose tissue, and that milk contains 4% fat.

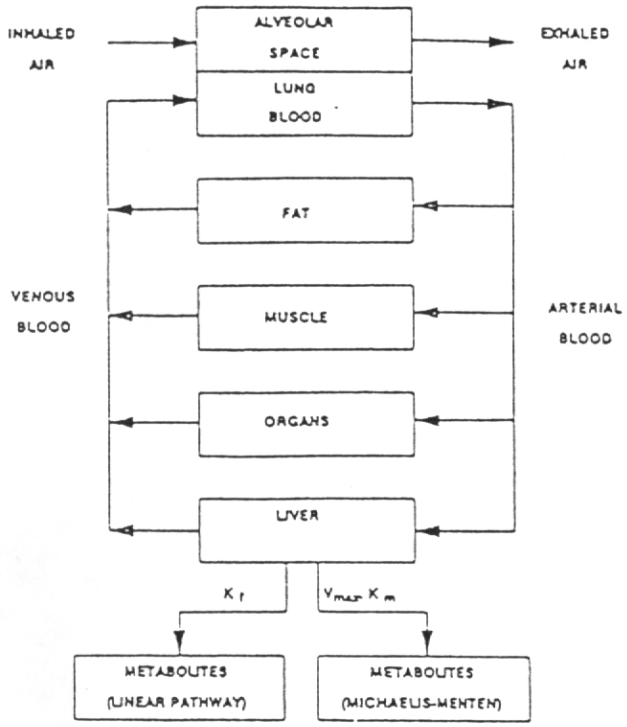

Fig. 1. Physiologically based pharmacokinetic model.

7. SPECIFIC EXPOSURE SCENARIOS EVALUATED BY PBPK MODELING

The following chronic maternal exposure scenarios were assessed:

a. Occupationally exposed mother inhaling air containing PCE at the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 340 mg/m^3, 8 hr per day, followed by exposure to an indoor residential background concentration of 28 μg/m^3.[17]

b. Occupationally exposed mother inhaling air containing PCE at the OSHA Permissible Exposure Limit (PEL) of 170 mg/m^3, 8 hr per day, followed by exposure to an indoor residential background concentration of 28 μg/m^3.[17]

c. Occupationally exposed mother inhaling air containing PCE of 40 mg/m^3 (approximate arithmetic mean concentration for counter-workers, pressers, and seamstresses) 8 hr per day,[21] followed by exposure to an indoor residential background concentration of 28 μg/m^3.[17]
d. Nonoccupationally exposed mother inhaling air containing PCE of 45.8 mg/m^3 (24-hr average concentration of PCE reported by NYSDOH[17] in one apartment above a dry cleaner using an old dry-to-dry machine).
e. Nonoccupationally exposed mother inhaling air containing PCE of 7.7 mg/m^3 (24-hr average concentration reported by NYSDOH,[17] in three apartments above dry cleaners using transfer machines).
f. Nonoccupationally exposed mother inhaling air containing PCE of 250 μg/m^3 (24-hr average reported by NYSDOH,[17] in two apartments above dry cleaners using dry-to-dry machines).
g. Nonoccupationally exposed mother inhaling air containing PCE at an indoor residential background concentration of 28 μg/m^3.[17]

8. RESULTS

Using the PBPK model, the predicted breastmilk PCE concentrations for women exposed under occupational conditions range from 857–8440 μg/L. The predicted breastmilk concentrations for women exposed to PCE in residences near dry cleaners range from 16–3000 μg/L. Typical residential exposure results in a predicted breastmilk PCE concentration of 1.5 μg/L, similar to the mean of 6.2 μg/L reported by Sheldon *et al.*[4] for nonoccupationally exposed women. The milk concentrations and doses expressed as mg PCE per kg infant body weight are displayed in Table II.

Table III shows the predicted milk PCE concentrations based on the measured or estimated blood PCE concentrations using the fat-blood partition coefficient. The predicted milk PCE concentrations are all within an order of magnitude of the measured concentrations, where available.[4,12] The PBPK and partition coefficient methods of estimation both clearly indicate that elevated levels are expected to result in the blood and milk of women exposed to PCE at current occupational standards. The agreement between the milk concentrations predicted by the partition coefficient methodology and by PBPK modeling implies that for PCE the simple relationship of chemical partitioning and tissue fat content is adequate to describe the resultant milk concentration.

Others have estimated the relationship between environmental and biological PCE concentrations. The ACGIH[22] and Koizumi[37] used pharmacokinetic modeling to predict a blood-PCE concentration from an air PCE concentration. Chronic exposure to PCE at the TLV of 340 mg/m^3 for 8 hr is estimated by ACGIH[22] and Koizumi[37] to result in blood PCE concentrations of 1000 μg/L (which was adopted as a biological exposure index) and 2300 μg/L, respectively. Using these modeled blood concentrations and applying the partition coefficient methodology, milk PCE concentrations of greater than 6000–14,000 μg/L are predicted. Using the Sielken PBPK model, exposure to PCE at the TLV of 340 mg/m^3 is estimated to result in a blood PCE concentration of 1300 μg/L and milk PCE concentration of 8400 μg/L. The PBPK-modeled results for blood PCE are comparable to those of ACGIH and Koizumi. Using a PBPK model with a milk compartment, Fisher *et al.*[46] estimated a milk PCE concentration of 4800 μg/L (about half the milk PCE concentration estimated using the Sielken PBPK model) after maternal occupational exposure to an 8-hr time-weighted average concentration of 50 ppm.

Also of note are the highly elevated blood PCE measurements made by Ohde and Bierod,[38] in samples obtained from 26 nonoccupationally exposed neighbors of dry-cleaning establishments. They measured blood PCE concentrations up to 2500 μg/L, similar to the blood concentrations expected from occupationally exposed workers, and almost as high as the blood concentration of 3000 μg/L measured in the mother whose infant suffered liver damage after nursing exposure.[12] Similar findings of elevated blood PCE concentrations (up to 1800 μg/L) were reported by Popp *et al.*[23] in neighbors living close to dry-cleaning facilities in Germany.

9. EXPOSURE ASSESSMENT

Exposure to PCE is of concern due to its toxicological properties demonstrated in humans and animals. Detailed toxicology and health assessments can be found in several reviews on PCE.[6,10,39,40] The dose of PCE to which an infant is exposed via breastmilk can be estimated based on the predicted and/or measured PCE breastmilk concentrations. In this assessment, a 7.2 kg infant is assumed to ingest 700 ml breastmilk per day[5] for the first year of life. The infant doses range from 0.0001–0.82 mg/kg/day for the seven exposure scenarios evaluated (Table II). These doses can be compared to

Table II. PBPK-Simulated Concentrations of PCE in Biological Media[a]

Mother's chronic exposure scenario		Maximum simulated concentration (μg/L)			Infant dose from milk[c] (mg/kg/day)	Excess cancer risk[d] from milk ingestion
		Blood	Fat	Milk[b]		
A.	8 hr at 340 mg/m³, then 16 hr at 28 μg/m³	1320	211,000	8440	0.82	6×10^{-4} (600 per million population)
B.	8 hr at 170 mg/m³, then 16 hr at 28 μg/m³	557	88,350	3530	0.34	2.5×10^{-4} (250 per million population)
C.	8 hr at 40 mg/m³, then 16 hr at 28 μg/m³	132	21,400	857	0.08	5.8×10^{-5} (58 per million population)
D.	24 hr at 45.8 mg/m³	470	74,900	3000	0.3	2.2×10^{-4} (220 per million population)
E.	24 hr at 7.7 mg/m³	79.	12,600	500	0.05	3.6×10^{-5} (36 per million population)
F.	24 hr at 250 μg/m³	2.6	400	16.2	0.0015	1.4×10^{-6} (1.4 per million population)
G.	24 hr at 28 μg/m³	0.23	38	1.5	0.0001	1×10^{-7} (0.1 per million population)

[a] Sielken PBPK model results.
[b] 4% of fat concentration.
[c] Assumes 7.2 kg infant ingests 700 ml breastmilk per day.
[d] q_1^* of 5.1×10^{-2} $(mg/kg/day)^{-1}$ multiplied by the mg/kg/day exposure, multiplied by 0.0143 (1 year of exposure over a 70-year lifetime).

Table III. PCE Concentrations in Blood and Milk Based on Fat/Blood Partition Coefficient (all values in μg/L)

Measured PCE in blood	PCE predicted in fat[a]	PCE in Milk[b]		Reference
		Predicted	Measured	
8.7	1380	55.3	43.0	(4)
4.2	668	26.7	2.7	(4)
2.9	461	18.4	1.4	(4)
3.9	620	24.8	26	(4)
3000	447,000	19,100	10,000	(12)
1000[c]	159,000	6360	NA	(22)
2300[c]	366,000	14,600	NA	(37)
2500[d]	398,000	15,900	NA	(38)

[a] Based on fat/blood partition coefficient (λ_f) of 159.
[b] Fat concentration times 4%.
[c] Blood concentration predicted after exposure to PCE at TLV of 50 ppm (344.5 mg/m³) for 8 hr.
[d] Maximum blood concentration measured in neighbors of dry-cleaning establishments.

levels of PCE associated with acute or chronic adverse health effects and to doses associated with increases in cancer risk.

Table IV shows the margins of exposure between the estimated exposure and the no-observed effect level (NOEL), low-observed effect level (LOEL), or frank effect level (FEL). The margin of exposure is the ratio of the effect level to the actual exposure dose; the smaller the margin of exposure, the more likely the adverse effect will occur. The lowest margin of exposure (1.7) occurs between the FEL of Bagnell and Ellenberger[12] and the highest maternal exposure Category A, indicating little difference between the estimated exposure and the exposure associated with possible adverse effects. Hepatomegaly and jaundice were observed in the infant reported by Bagnell and Ellenberger[12] at a breastmilk dose about twice that predicted for the highest maternal exposures evaluated. Comparing the milk doses to the oral reference dose (RfD of 0.01 mg/kg/day) calculated by the USEPA,[45] reveals that most of the modeled exposures result in infant milk doses which exceed the RfD, in some cases by several orders of magnitude. Only category F and background residential exposure result in predicted milk PCE exposures which do not exceed the oral RfD.

PCE is classified as a possible human carcinogen (EPA group C) based on the results of an animal bioassay conducted by the National Cancer Institute[43] and weight-of-evidence considerations.[10,19,44] A cancer potency factor, q^*, has been calculated by the USEPA for oral and inhalation exposures to PCE. The q^* for inhalation and oral exposures were calculated to be 3.3×10^{-3} and 5.1×10^{-2} $(mg/kg/day)^{-1}$, respectively.[18] The q^* can be used in conjunction with the dose to

Table IV. Margins of Exposure Between Infant Exposure to PCE via Breastmilk[a] and Adverse Health Endpoints

Health endpoint	Exposure duration	NOAEL (N)[c] LOAEL (L) or FEL (F) (mg/kg/day)	Breastmilk exposure category, MOE[b]						
			A	B	C	D	E	F	G
Intoxication	Acute	60 (N) human	73	176	750	200	1,200	30,000	600,000
Reduced survival	6 weeks	714 (N) rat	870	2100	9000	2400	14,000	357,000	7,000,000
Hepatic changes	6 weeks	20 (N) mice	24	60	250	67	400	10,000	200,000
Inc. relative liver and kidney weights	90 days	14 (N) rat	17	41	175	47	280	7,000	140,000
Obstructive jaundice and hepatomegaly	6 weeks	1.4 (F) human	1.7	4.1	17.5	4.7	28	700	14,000
Oral reference dose		0.01	0.01	0.03	0.13	0.03	0.2	5	100

[a] Breastmilk exposures of (A) 0.82, (B) 0.34, (C) 0.08, (D) 0.3, (E) 0.05, (F) 0.0015, (G) 0.0001 mg/kg/day from Tabale V.
[b] Margin of exposure is the ratio of the NOAEL, LOAEL, or FEL in mg/kg/day divided by the PCE ingested via breastmilk in mg/kg/day.
[c] NOAEL, No observed adverse effect level; LOAEL, low observed adverse effect level; FEL, frank effect level.

estimate increased lifetime cancer risk. To apply the oral q^* to assess exposure to PCE via breastmilk, the duration of exposure must be adjusted from a 70-year lifespan to an exposure of 1 year which represents breastfeeding exposure duration. The estimated cancer risks which are normally associated with a lifetime of continuous exposure are therefore adjusted by 1/70 or 0.0143 to account for the shorter exposure period. A similar approach was used by the USEPA in estimating increased cancer risks due to the ingestion of daminozide (Alar) in applesauce over an 18-month period.[8] The cancer risk estimates for infants exposed to PCE via breastmilk for 1 year are shown on Table II. The increased cancer risks range from 58–600 per million for infants in occupationally exposed maternal categories A, B, and C. The increased cancer risks for infants in nonoccupational categories D, E, and F range from 1.4–220 per million exposed infants. The background residential exposure scenario results in increased infant cancer risk of less than one in a million (1×10^{-7}).

10. DISCUSSION

The physicochemical properties of PCE, and its distribution to lipid-containing tissues, suggest that elevated levels of PCE are likely in the breastmilk of exposed lactating mothers. Monitoring of potentially exposed women, however, has not been conducted. PBPK modeling predicts significant PCE levels in the milk of heavily exposed women, at levels which provide the infant with little margin of exposure to doses associated with adverse health effects. In addition, the estimated increased cancer risks associated with these infant exposures are large under certain exposure scenarios.

A potential limitation of this model is the absence of a "milk compartment," resulting in predicted milk concentrations which do not include a mathematical treatment to account for removal of milk from the mother's body. Therefore, the predicted milk PCE concentrations may be overestimated. However, the ongoing maternal inhalation of PCE will result in continuing recontamination of maternal fat despite removal of milk (and contaminated milk fat) by the nursing infant. Given the mother's continued exposure (a pseudo steady-state condition), the contaminant concentrations in blood, adipose tissue, and breastmilk should be equivalent when expressed on a fat basis. This can be shown mathematically by applying the equations derived by Fisher *et al.*[36] to express the change in milk concentrations over time.

The Nursing Mothers Study[4] identified PCE in blood, exhaled breath, personal air, and breastmilk of 17 study participants. Wallace[9] compared the results for the nursing mothers to the results for nonnursing females between ages 16 and 40 (without breastmilk samples) in the main TEAM study. For all the prevalent volatile organic chemicals, including PCE, median personal air exposures were comparable or greater for the nursing mothers, but median exhaled breath levels were lower, usually by a factor of 2. This observation is consistent with the lipophilic nature of volatile organic chemicals, and suggests that the milkfat of nursing mothers may provide a reservoir for PCE and other lipophilic chemicals delivered by the blood, thereby reducing the level in exhaled breath.

If one assumes that milk contains 4% fat and the

infants ingests an average of 700 ml breastmilk per day,[5] a total of 28 ml of fat is removed from the mother's body each day due to lactation. Assuming that maternal blood contains 0.65% fat and women have an average of 3900 ml blood,[31] 25 ml blood fats are circulating in the mother's bloodstream at any given time. The circulating blood fats arise from maternal adipose tissue stores as well as from recently ingested dietary fats. The circulating blood fats, independent of their origin, are taken up by the mammary gland to be incorporated as breastmilk fat. The contaminated fats that leave the mother's body via breastmilk are replenished by dietary fats and adipose tissue fats which are continually recontaminated via the blood by the mother's ongoing inhalation exposure. Therefore, the loss of contaminated breastmilk fat via nursing allows a greater amount of inhaled PCE to be retained in the mothers fat reservoirs. The removal via breastmilk of the mother's PCE contaminated fats may account for the reduced exhaled breath concentrations of PCE observed by Wallace.[9]

In contrast to PCBs, which are present in maternal adipose tissue as a result of years of accumulation, PCE is present in maternal adipose tissue (and breastmilk) due to more recent maternal exposures. Whereas PCB milk concentrations are observed to decrease during the period of lactation,[1] continual reexposure to high levels of inhaled PCE during lactation would be expected to keep the maternal blood, adipose tissue, and milk PCE concentrations elevated. For PCBs, virtually the only route of maternal excretion is via breastmilk. For PCE, excretion occurs via breastmilk and exhaled breath, with an additional small amount (about 5%) metabolized and excreted via the urine.

Of particular concern are residential exposures where both the mother and the infant are exposed to contaminated indoor air and the infant is also exposed to PCE via breastmilk. The PCE dose the infant receives via inhalation is larger than the dose ingested via breastmilk. Unlike occupational exposure, residential exposure may continue for up to 24 hr per day and directly impacts both the mother and her infant. The public health implications of the inhalation exposure on residential neighbors of dry-cleaning establishments will be the topic of a future publication.

Monitoring studies should be conducted to validate the PBPK predicted milk concentrations since no information is available for women exposed to PCE under these conditions. These studies should quantify the relationship between exposure to particular air PCE concentrations and the resultant biological tissue levels, especially breastmilk, to verify the levels predicted by PBPK modeling.

11. BENEFITS OF BREAST FEEDING

The potential adverse effects of infant exposure to contaminants in breastmilk should not be evaluated without an assessment of the benefits of breastfeeding. The benefits of breastmilk for the health and welfare of infants are well known,[5,47] and breastmilk should not be casually dismissed as the best food for infants. Quantitative assessments of the benefits associated with breastmilk indicate that breastfed infants demonstrate improved neonatal mortality rates of about 3000–4000 per million compared to infants nourished by formula.[48] These estimates are similar to those of Rogan *et al.*,[49] who estimated by mathematical modeling an improved mortality rate of 2560 per million infants nourished by breastmilk rather than infant formula.

It is difficult to weigh the potential adverse effects of exposure to a contaminant via breastmilk against the recognized benefits afforded by breastmilk. On the one hand, the levels of PCE predicted in breastmilk of heavily exposed women are predicted to result in breastmilk PCE doses close to the levels at which adverse health effects have been demonstrated, and are also predicted to contribute significant excess cancer risk. On the other hand, the risks predicted are estimates which have a large degree of uncertainty associated with them, while the benefits are well known and can be measured by evaluating infant health. In addition, the infant is exposed via breastmilk for a relatively short period of time, usually 1 year or less. Ideally, providing uncontaminated breastmilk to an infant is the best choice. If the modeled PCE milk concentrations are verified by monitoring data, then public health interventions may be advisable.

From a public health perspective, the avoidance of risk by minimizing exposure is sound public health policy. The risks associated with infant exposure to PCE are unnecessary risks since they can be reduced by avoiding exposure. If a mother were aware of her potential exposure and the contribution to breastmilk, she could minimize her exposure by changing her occupation (or particular job function) and/or residence to reduce her exposure to PCE. Installing emission control equipment, improving ventilation and vent location in the workplace, sealing routes of contaminant dispersal, and improving general maintenance and housekeeping in the workplace will help minimize worker and residential exposure.[17]

The levels of PCE in breastmilk can be reduced. Due to the exhalation of PCE after cessation of exposure, breastmilk concentrations are estimated by PBPK modeling (data not shown) to return to preexposure concentrations about 4–8 weeks after cessation of maternal

exposure. In contrast, the presence of PCBs in milk are unlikely to be reduced substantially due to longer-term storage in adipose tissue, the mothers' continual reexposure via the diet, and no significant route of excretion other than breastmilk. The concentration of PCE in milk can be reduced since the mother's body burden of PCE can be lowered by exhalation and excretion, and continual reexposure can be avoided or reduced by changes in the mother's behavior and/or conditions in the workplace.

12. CONCLUSIONS

PBPK modeling predicts highly elevated milk PCE concentrations as a result of maternal occupational exposure and from elevated residential exposure to PCE. The predicted levels of PCE in breastmilk under several of the exposure scenarios evaluated suggest that the infant may be exposed to doses of PCE within an order of magnitude of doses associated with adverse health effects. This exposure also contributes to increased estimates of excess cancer risk. The actual concentrations of PCE in milk of exposed women can only be known with certainty if monitoring of exposed women is conducted. Due to the widespread exposure potential, monitoring studies should be undertaken so that appropriate risk management alternatives can be better evaluated.

APPENDIX A. Physiological and Biochemical Parameters Used in Describing the Pharmacokinetics of Tetrachloroethene in Women*

	Parameter	*Woman*
Body weight (kg)	W	60
Alveolar ventilation (ml/min)	V_A	5.25E3
Total blood flow rate (ml/min)	Q_T	5.52E3
Blood flow to tissue (% Q_T)		
Muscle	Q_m	19
Liver	Q_l	25
Fat	Q_f	5
Kidney (vessel rich)	Q_k	51
Tissue volume (% W)		
Muscle	V_m	62
Liver	V_l	4
Fat	V_f	20
Kidney (vessel rich)	V_k	5
Lung	V_a	1.1
Partitioning coefficients		
Blood:air	λ_b	10.3
Muscle:blood	λ_m	7.77
Liver:blood	λ_l	6.82
Fat:blood	λ_f	159
Kidney:blood	λ_k	6.82
V_{max} (ng/ml/min)	V_{max}/V_l	24.3
K_m (ng/ml)	$K_m\lambda_l$	2046

*Adapted from Ward et al., (1988), except V_A and Q_T scaled by $(W)^{0.75}$

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