

Evidence for Existence in Human Tissues of Monomers for Plastics and Rubber Manufacture

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Although exposure to many industrially important monomers is controlled by law, few of these reactive chemicals have been determined in human tissues. Analogy with other fat-soluble organic substances strongly implies that these monomers may be retained in tissue, subject to the usual physiological constraints of metabolism, solubility and volatility. The storage of DDT and PCBs is discussed, as well as tetrachloroethylene (PCE) and trichloroethylene (TCE), which are chemically similar to many industrially used monomers. Styrene in blood and breath and its metabolites in urine have been studied in humans. Styrene and vinyl chloride have been measured in fat tissue of polymerization workers.

Evidence for the presence of monomers and other unmetabolized organic materials in humans is surprisingly scarce, in spite of exposures to a large number of substances in the environment that are very fat soluble, and therefore prime candidates for prolonged body residence.

Recent epidemiological and clinical field studies have been conducted by this laboratory among workers exposed to organic materials, including polymerization workers, anesthesiologists and workers making capacitors and transformers (PCB workers), and our interest has been directed toward the study of the storage and turnover in blood and adipose tissue of fat-soluble organic compounds.

The distributional dynamics of many such compounds in the body can be derived using the compartmental model, with which anesthesiologists have studied uptake and elimination of anesthetics. Thus, during acute exposures (in anesthesia amounting to 1-2% of a halogenated anesthetic in breathing air) the blood-vessel rich organs and tissues are rapidly saturated due to high blood flow and medium solubility, while fat tissues are slowly saturated,

having a high capacity and low blood flow. Fat tissues comprise about 20% of the normal body weight (1). The converse pathway is followed during elimination from tissues of a halogenated anesthetic, or any nonpolar organic material, but this is affected by three factors: fat solubility (more soluble, more slowly eliminated); volatility (more volatile, more easily expired); and metabolism (more readily metabolized, more quickly excreted). The variability of the latter route is affected by many factors, including enzymatic activity (determined in part by heredity and by dietary, drinking and smoking habits) and the chemical nature of the substance (nitrous oxide and cyclopropane are 97% and 99% expired unchanged (2), while styrene is 95% metabolized (3).

Anesthesiologists have further contributed to our knowledge of body retention of halogenated hydrocarbons by extensive studies of blood and breath levels of anesthetic agents in operating room personnel. Fat-soluble anesthetics are typically detectable in breath for a day or so following exposures (usually less than 100 ppm exposure and 1-10 ppm in expired air) indicating tissue retention, which has been presumed, but not demonstrated, to occur in the fat depot (4, 5).

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Demonstrated precedents for fat storage in humans are limited to pesticides and PCBs. DDT is perhaps the most extensively studied material in humans and animals and is a substance which defies all normal excretory attempts: it is nonvolatile, very lipid soluble and very difficult to metabolize. In the occupational setting, a relationship between exposure level and fat level of DDT has been observed, with 300–600 ppm found in adipose tissue of workers (6, 7). The health implications of DDT retention are not established, although Poland et al. demonstrated, among workers with high fat and blood DDT, an elevated, but not linearly correlated, enzymatic capacity for phenylbutazone (6). In animals a threshold of DDT in fat (11 $\mu\text{g/g}$) is necessary to affect phenobarbital metabolism rate (8). An ingested dose of DDT is retained in human fat tissue for as long as 3 yr, while in corresponding animal tissues, elimination of similar levels was accomplished in 0.5–1.5 yr (9). Clearly, extrapolation from the animal to human situation is not straightforward.

PCBs are a similarly chemically inert organic family (contributing to their industrial utility), which have been detected in water, birds, fish, and human tissues. Severe cases of symptomatic PCB exposures occurred in Japanese persons who consumed contaminated rice oil (Yusho disease, Table 1). Levels of about 40 ppm PCB in fat tissue were observed initially in these persons, declining over a period of 2–5 yr to that of the general population in Japan (0.2–4 ppm) (10). PCBs have been found at trace–2ppm levels (11) in the United States general population (Table 2). Blood levels of Japanese PCB workers were determined to be ca. 0.4 ppm (10). Trace amounts (parts per billion) of polybrominated biphenyls were observed in livestock and produce in Michigan following a recent incident in which a polybrominated biphenyl compound was mistakenly mixed into livestock feed. The resulting contamination forced the extermination of thousands of livestock and hundreds of thousands of chickens and eggs (12).

Tetrachloroethylene and trichloroethylene (PCE and TCE) are important industrial solvents. Their tissue turnover patterns are useful as model studies for similar monomers such as vinyl chloride and vinylidene chloride, for which no human data exist. TCE, which has been used as an inhalation anesthetic, recently

Table 1. Adipose tissue levels of PCBs in Japanese Yusho patients.^a

Time since exposure, yr	PCB level, ppm
0	40
1	3
2	0.7
4	3
7	0.2
National survey ^b	0.2–4

^a Data of Kuratsune et al. (10).

^b Males/females, 25–49 yr old.

Table 2. PCBs in adipose tissues of U.S. general population.^a

PCB level, ppm	% of total cases (N = 688)
0	34
Trace–1	33
1–2	27
> 2	5

^a Data of Yobs (11).

has been found to be carcinogenic in mice at high levels of oral administration (13).

PCE is readily absorbed during inhalation by humans and very slowly excreted. After exposure at 100 ppm (the present TLV), for 7 hr on each of 5 successive days, PCE was detected in the breath at levels of about 1 ppm 14 days later. The expirational half-life was 3 days. Exposure for only 1 day produced a similar half-life, with 1 ppm in breath reached at 5 days (14).

TCE in breath of humans is detectable (ca 1 ppm) for at least 4 days after exposure to 100–200 ppm (TLV 100 ppm), 7 hr/day for 5 days, with a half-life of 1 day (15). As with PCE, persistence in breath is accentuated among persons exposed for the longest times. Breath levels of persons exposed once to 100–200 ppm for 1–4 hr were reduced to 1 ppm within 2 days (15). The metabolic half-life of PCE and TCE are about twice as long as that in breath, 144 and 41 hr, respectively, for urinary metabolites (16). These half-lives are many times longer than similar determinations

for the nonhalogenated hydrocarbons toluene, xylene, styrene, and phenol (16, 17).

Vinyl chloride (VC) exposure has been associated with excess cancer incidence among vinyl chloride-exposed workers, and in animals (18). In laboratory animals most of the VC absorbed during inhalation was metabolized. Of a radiolabeled dose, only 0.02% was detected as expired monomer, with 98% of the dose recovered. A small amount of radioactivity was retained after 75 hr, mainly in the liver (19).

VC has been detected in the subcutaneous fat of polymerization workers (Table 3). In spite of its volatility and its facile metabolism by rats, the lipophilicity of VC appears to allow fat retention in humans (20).

Table 3. Presence of vinyl chloride in fat of polymerization workers.^a

Exposure estimate ^b		VCM in subcutaneous fat, (No. samples/ no. samples analyzed)
Intensity	Most recent	
L-M	Present	5/7
H	Present	2/4
L-M	3 months	1/2
H, long	3 months	6/8
H, < 1 yr	3 months	0/2
H, long	1-12 yrs.	5/5
None		0/1
Total		19/29

^a Data of Knittle et al. (20).

^b Exposure intensity estimated as heavy (H) or light to medium (L-M).

Human uptake and metabolism of styrene has been fairly well studied. Styrene can be absorbed by inhalation or skin contact. During exposure to 20-100 ppm, about 60% of the styrene inhaled is absorbed by the body (3, 21). Of this amount, metabolism to mandelic acid (85%) and phenylglycolic acid (10%) accounts for most of the absorbed styrene (3). Metabolism to hippuric acid and conjugates of phenylglycol also occurs (17). Exhalation accounts for about 1% of the styrene absorbed (22, 23).

Styrene is very soluble in blood and fat, more so than many halogenated hydrocarbons. Following exposure at 100 ppm, blood levels of 0.2-15 ppm styrene have been determined

(22, 23). As with PCE and TCE, blood and breath levels are proportional to the intensity and not duration, of exposure. Persistence in breath is related to duration of exposure. Thus, after 2 and 7 hr exposure to 100 ppm styrene, breath levels decrease from 2-3 ppm to 0.05 and 0.5 ppm, respectively over a period of 6 hr (23). Exertion during exposure to styrene changes blood, but not breath, concentrations. During exposure to 150 ppm styrene, blood levels varied with exercise from 2 ppm (at rest), to 6 ppm (50-watt exercise), to 16 ppm (150-watt exercise) (22).

The urinary half-life of styrene metabolites is about 8 hr, with detectable levels continuing for 30 hr (17). (The breath half-life of styrene is 1-3 hr, with detectable levels persisting as long as 20 hr (ca. 0.1 ppm) (23).

Table 4. Styrene and ethylbenzene in subcutaneous fat of styrene polymerization workers.^a

Estimated exposure ^b	Time since last exposure	Styrene concentration, ppm ^c	Ethylbenzene in fat, ppm ^c
H	0	0.2	0.1
M	0	0.2	0.1
H	4 hr	0.3	0.4
M	8	1.0	0.7
M	2 days	—	0.1
H	2	0.4	0.7
H	2.5	0.2	0.2
H	2.5	0.1	0.1
H	3	0.2	0.2
L	3	—	0.2
M	4	—	0.1
M	14	—	—
H	90	—	0.2
C ₆ H ₆	—	—	—
CF ₃ CHBrCl	—	—	—

^a Data of Wolff et al. (unpublished, work in progress).

^b Exposures estimated as H (heavy), M (medium), L (light).

^c Limit of detection in 10 mg fat sample, 0.2 ppm styrene, 0.1 ppm ethylbenzene by gas chromatography.

We have measured styrene and ethyl benzene in the subcutaneous fat of workers and found levels of 0.2-1 ppm, roughly related to the degree of exposure and time since last exposure (Table 4). The blood levels of these workers have been measured separately and are in the 0-10 ppb range (J. Eisinger and W. Blumberg, work in progress.).

Fat levels of styrene were detected more than 48 hr following the last exposure, longer than detectability in breath of experimental subjects after sustained exposure at 100 ppm (23). This finding is of interest, since styrene is a monomer more readily metabolized than the halogenated hydrocarbons.

Several recent studies suggest important areas for future investigations. Exposure to dichloromethane has recently been correlated to high carboxyhemoglobinemia (24). The persistence of bromine in rat tissue for 24 hr following exposure to brominated fire retardants has been reported at this conference. The demonstration by Montesano of marked mutagenic assay activity by chloroprene (25) (greater than for vinyl chloride) should stimulate study of this monomer in human and animal tissue. Its nonchlorinated analog, butadiene, has a very rapid turnover in animal tissues following very high exposures, similar to that of styrene under the same conditions (26).

Another important industrial monomer which has not been adequately studied is acrylamide, a potent neurotoxin (TLV 0.3 mg/m³). It has been measured in urine of

polymerization workers, although no published data exist (27). Exposure of acrylamide, a solid (mp 85°C) vinyl amide, can occur via dust inhalation or dermal contact. Up to 2% monomer can be retained in the polymer. Its cumulative neurotoxicity has a demonstrated threshold in animals, and the biological half-life in animals is 24 hr. Most of a radioactive dose in animals appears to be bound to blood and tissue protein, persisting in significant amounts for more than 14 days (27).

Table 5 summarizes some of the reported findings of industrial chemicals in blood and fat. Table 6 summarizes some available turnover data for fat-soluble industrial chemicals.

Table 5. Levels of industrial chemicals in blood and fat of workers.

Chemical	Concentration, ppm		Reference
	Blood	Fat	
DDT	1.4	310	(6) ^a
PCBs	0.4	40 (Yusho)	(10)
Styrene	0.2-3	ca. 1	(23)
Vinyl chloride		ca. 1	(20)

^a Control: 0.05 ppm (blood), 2 ppm (fat).

Table 6. Respiratory and urinary excretion of some industrial compounds.

Compound	TLV, ppm (mg/m ³)	Half-life, hr		Breath detectability	Reference
		Respiratory	Urinary		
Acrylamide CH ₂ =CHCO ₂ NH ₂	(0.3)		~ 24 (¹⁴ C) ^a		(27)
Butadiene CH ₂ =CH-CH=CH ₂	1000 (2200)	Rapid			(26)
Styrene C ₆ H ₅ -CH=CH ₂	100 (420)	0.5-3	8	20 hr	(16,17,23)
Ethylbenzene C ₆ H ₅ -CH ₂ CH ₃	100 (435)	~ Styrene	8		(3,26)
Phenylacetylene C ₆ H ₅ -C≡CH		24 ^a	24 ^a		(23)
Toluene C ₆ H ₅ -CH ₃	100 (375)		7		(16)
Xylene CH ₃ -C ₆ H ₄ -CH ₃	100 (435)		7		(16)
Trichloroethylene ClCH=CCl ₂	100 (535)	25	41	40-100 hr	(15,16)
Tetrachloroethylene Cl ₂ C=CCl ₂	100 (760)	65	144	14 days	(14,16)

^a In animals.

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