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Exposure to Organic Solvents and Breast Cancer in Women: A Hypothesis

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Incidence rates for breast cancer have increased steadily over the last 25 years, particularly among postmenopausal women. Secular changes in accepted and suspected risk factors can explain only a part of this increase. Given the increasing number of women in the workforce, it is possible that increases in breast cancer incidence may be caused by occupational exposure to hazardous agents. In particular, we hypothesize that organic solvents act directly as genotoxic agents or indirectly through their metabolites. Most organic solvents are highly lipophilic and are readily absorbed and distributed throughout the body via the bloodstream. Organic solvents are biotransformed mostly in the liver and the kidneys through a series of oxidative and reductive reactions, some of them resulting in bioactivation. There are indications of P-450 enzymatic oxidative activity in the breast parenchyma, but there appears to be limited detoxification of highly reactive metabolites. The physiology of the breast may also accentuate the accumulation of chemicals: breast parenchyma is embedded in a fat depot capable of storing lipophilic xenobiotics; it is conceivable that organic solvents and their metabolites, once stored in fat tissues, migrate to the breast parenchyma and are then transferred to the mammary lobules through continuous apocrine secretions. These secretions may reside in the ductular system long enough for the solvents and their bioactivated metabolites to locally exert detrimental effects. The evidence supporting this hypothesis is that many organic solvents have been detected in breast milk, the majority of carcinomas occur in the ductular system, and some organic solvents have been shown to produce mammary gland cancer in experiments on rodents. Further toxicological and epidemiologic studies are required to test this hypothesis, to elucidate the mechanisms, and to identify specific carcinogenic organic solvents. Am. J. Ind. Med. 32:1–14, 1997. *© 1997 Wiley-Liss, Inc.*

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INTRODUCTION

Breast cancer is the most frequently occurring cancer among women. In Canada, for example, it accounts for 30.7% of all new cancer cases, and it is the second leading cause of cancer death in Canadian women [National Cancer Institute of Canada, 1996]. Although advances have been made in limiting the progression of female breast cancer through surgical and chemical adjuvant treatments, we are left with the grim picture that breast cancer incidence continues to increase unabated. In Canada, breast cancer incidence rates have increased by 27.9% over the last 25 years, with steeper increases observed in women 50 years and over [National Cancer Institute of Canada, 1993]; the age-standardized (to the standard World population) incidence rate now is 107 per 100,000 [National Cancer Institute of Canada, 1996]. Secular increases in incidence rates have also been observed in other jurisdictions (e.g., Connecticut, Denmark, Japan, the United Kingdom) [Coleman et al., 1993; Holford et al., 1991; Stevens et al., 1982]. It is

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estimated that about one in nine [National Cancer Institute of Canada, 1996] to one in 10 women [Campbell et al., 1994] will develop breast cancer during their lifetime.

The reasons for these increases in incidence are largely unknown. They do not appear to be due to changes in the pathologic definition of breast cancer or to an artifact of detecting ''histologically malignant but biologically benign'' tumors [Doll and Peto, 1987; Holford et al., 1991]. Part of the increase may be due, however, to early detection in mass screening programs operating in many western countries [Feuer and Wun, 1992; Swanson et al., 1993; Wun et al., 1995]. In addition, heightened awareness of the risks of breast cancer in the last few decades may have led to increased opportunities for early detection outside of dedicated screening programs. Secular changes in accepted and suspected risk factors (e.g., having fewer children and at later ages) may explain some of the long-term increases. It is likely that these risk factors can explain only a fraction of the incident cases [Kelsey, 1993; Rockhill et al., 1996], and probably cannot explain all of the increase in incidence rates.

While important contributions have been made in identifying potential risk factors, new directions for research are required. In recent years, a few studies have investigated risks associated with exposure to organochlorine pesticides and polychlorinated biphenyls (PCBs), both at the animal [Mason and Schulte, 1981; Ahlborg et al., 1995], and at the human [Wolff et al., 1993; Dewailly et al., 1994; Krieger et al., 1994] level, with no conclusive results yet [Ahlborg et al., 1995].

It has been recently hypothesized that exposures to exogenous carcinogens and breast tissue susceptibility to these exposures affect breast cancer incidence [Krieger, 1989]. As women have been entering the workforce in greater numbers since the 1960s [Statistics Canada, 1990], it is important to inquire whether occupational exposures may be linked to breast cancer incidence. Of particular concern are the organic solvents. These are widely used in the workplace and are also present in lower concentrations in ambient air and in potable water [Andrews and Snyder, 1991; Morris and Seifter, 1992]. In this paper we present the hypothesis that these lipophilic substances, and their metabolites, can migrate to adipose tissue in the breast where they can be stored, probably biotransformed in situ, and then excreted into the ductular systems where they may remain in contact with the parenchyma for significant amounts of time, thereby initiating or promoting carcinogenesis through genotoxic or related mechanisms. This hypothesis is different from that presented by Davis et al. [1993], where it was postulated that the estrogenic properties of halogenated hydrocarbons may be implicated in the etiology of breast cancer.

Breast Parenchyma

Breast parenchyma is made up of a series of apocrine glands, their primary function being to produce milk in lactating women. These epithelial cells are arranged into lobules (or acini) that are connected to a ductular system ending at the nipple. This glandular structure is embedded in fat and connective tissue serviced by an ample supply of blood and lymphatic vessels. There are a number of unique features of breast physiology that may render it more sensitive to the effect of organic solvents and their metabolites. First, the apocrine glands proliferate continuously from menarche, increasing their cell population over each ovulatory cycle, thus resulting in a continued development of the budding structure until about age 35 [Vorherr, 1974]. Breast tissue could thus be at high risk for mutations arising from DNA transcription and other errors during replication [Ames and Gold, 1990].

Physiologic changes during the menstrual cycle could enhance the accumulation of xenobiotics in the breast tissue. These are: 1) increased blood flow resulting in an increased accumulation of solvents or their lipophilic metabolites in the fat tissues surrounding the breast parenchyma; 2) secretion into the ductular system of colostrum-like fluid containing harmful xenobiotics (see below); and 3) epithelial cell death resulting in the release of substances that had accumulated in breast cells into extracellular spaces [Vorherr, 1974].

Petrakis demonstrated that fluids are secreted by the apocrine glands not only in the lactating but also in the non-lactating breast [Petrakis, 1986]. Secretions in the non-lactating breast have been inferred from the identification of lactoferrin, in concentrations similar to those found in colostrum and breast milk [Yap et al., 1981], and of lactose, alpha-lactalbumin, immunoglobulins, cholesterol, fatty acids, colostral cells, and breast epithelial cells. The secreted fluid is thought to be recycled through a continuous absorptive mechanism that makes the breast fluids seep through the ductal cells to the lymphatic vessels and the blood capillaries. Animal experiments in the 1950s demonstrated that fluids in the breast ducts of rabbits could make their way to the lymphatics surrounding the mammary gland [Petrakis, 1986]. There is evidence that this recycling process leads to bioaccumulation of endogenous and exogenous compounds, probably even more so for large molecules. For example, cholesterol and nicotine levels, along with their metabolites cholesterol epoxide and cotinine, have been found to be higher in breast fluid than in plasma, thereby indicating selective accumulation in ductular structures during the reabsorptive process [Petrakis et al., 1978, 1981]. In addition, a small study of apparently normal and neoplastic breast tissues showed higher levels of metabolites of organochlorine insecticides and PCBs in the breast tissue than in adjacent adipose tissue, for both normal and neoplastic

TABLE I. Organic Solvents Detected in Human Milk

Refs.	Organic solvent	Refs.	Organic solvent
a	Acetaldehyde	a	Ethyl methyl ketone
a	Benzaldehyde	a	β-Hexachlorocyclohexane
a	Benzene	a	Methyl alcohol (Methanol)
a–c	Carbon disulfide	a	Methyl amyl ketone (2-Heptanone)
c	Carbon tetrachloride	a	Methyl ethyl ketone
a	Chlorobenzene	a	Methyl isobutyl ketone
a	Chloroethane	a	Methyl propyl ketone
	(Ethyl chloride)	a	Methylene chloride
a	Chloromethane	a,c	Styrene
a	Chloropentane	a,b	Tetrachloroethylene
a	Crotonaldehyde	a	Toluene
a	Cyclohexane	a	1,1,1-Trichloroethane (Methyl chloroform)
a	Cyclopentane	a	Trichloroethylene
a	Dichlorobenzene	a	Trichloromethane (Chloroform)
a	1,2-Dichloroethane	a	Xylenes
c	Dichloroethylene		
a	Ethyl alcohol		
b	Ethylbenzene		

[a]Pellizzari et al., 1982.
[b]Wolff, 1983.
[c]Jensen, 1991.

tissues [Wassermann et al., 1976]. Many solvents also have reportedly been detected in human milk [Coté et al., 1976; Pellizzari et al., 1982] (see Table I), often in higher concentrations than in the blood [Wolff, 1983]. Because of the reduced metabolic and clearance activity of breast tissue, by-products of metabolic oxidative and reductive processes could conceivably remain in contact with the parenchyma long enough to be able to act as early stage initiators, through alterations in DNA bases and other hydroxyl radical-induced adverse reactions [Malins et al., 1993], or as promoters to already initiated cells. This theory is consistent with the observation that about 70% of breast tumors originate in the ductular system [Berg and Hutter, 1995].

Although not specific to organic solvents, the hypothesis that exogenous carcinogens are secreted into breast fluids, is supported in part by anecdotal observations from a retrospective study among boat women of Aberdeen in Hong Kong. Traditionally, these women used to nurse their infants only from their right breast; the risk of developing cancer in the left breast, where milk would stagnate, was twice that of developing cancer in the right breast, and the ratio rose to 3:1 for women over 55 years of age [Petrakis, 1977a]. The effect of lactation on breast cancer is still not completely delineated, some studies showing no protective effect [Kvåle and Heuch, 1987; MacMahon et al., 1970; Thomas and Noonan, 1993], but some recent studies tend to show a slightly protective effect among premenopausal women after cumulative lactation of more than three months [Newcomb et al., 1994; Yuan et al., 1988]. Petrakis et al. [1980, 1982] showed that nipple aspirates (breast secretions and colostrum) can be mutagenic on the Ames test. They observed a higher proportion of positive Ames tests among pregnant farm workers than among pregnant women living in urban areas [Petrakis et al., 1982], a finding that is consistent with the assumption that farm workers have been more highly exposed to a variety of hazardous chemicals.

Organic Solvents

Absorption and distribution

Common to most organic substances are their volatility, their ability to dissolve a large array of materials, and their lipophilicity, although there is wide variability across organic solvents. Most of them are used as solvents *per se*, whereas some of them are used in chemical syntheses (e.g., monomers).

Organic solvents can enter the human body by ingestion, inhalation, and cutaneous absorption. Exposure can occur through food and water, from pollution of water sources and soil, or inadvertent contamination during processing or packaging [Agency for Toxic Substances and Disease Registry, 1992c, 1992h, 1993j]. Dermal absorption can be a significant route of entry when the skin is immersed in solvents [Sato and Nakajima, 1987] and, although this situation is usually avoidable, cutaneous contact may nevertheless be important in certain occupations. We assume here that inhalation is the primary route of exposure.

The toxicity of organic solvents is governed by the extent to which they are absorbed, distributed, and metabolized in the body. Whatever the route of entry, solvents will enter the bloodstream and will then migrate to different organs [Klaassen and Rozman, 1991]. The lung is the only organ in which all blood passes through; thereafter, about 75% of blood flow is directed to the vessel-rich tissues, with the liver receiving 25% of the total. Fat tissues and white bone marrow receive approximately 5% of the total flow [Sato and Nakajima, 1987].

The affinity of solvents for tissues and body fluids is described by partition coefficients. For any two media in equilibrium, the partition coefficient is defined as the ratio of the concentrations of the substance in the two tissues. Table II shows blood/air and fat/blood partition coefficients for some common organic solvents. Alcohols and ketones tend to have blood/air coefficients above 100 and fat/blood coefficients close to unity. This indicates that they are fairly hydrophilic: they will pass rapidly from inhaled air to the bloodstream, but their concentration in fat tissues will remain much lower than in blood. On the other hand, aromatic solvents (e.g., benzene, styrene, toluene, xylene) and halogenated solvents (e.g., methylene chloride, trichloroethylene, and tetrachloroethylene) are much more lipo-

TABLE II. Partition Coefficients for Some Widely-Used Organic Solvents

Reference	Solvent	Blood/air coefficient	Fat/blood coefficient
Sato and Nakajima, 1987	Acetone	245	0.35
Sato and Nakajima, 1987	Benzene	7.7	63.1
Sato and Nakajima, 1987	2-Butanone (Methyl ethyl ketone)	202	1.3
Sato and Nakajima, 1987	Carbon tetrachloride	2.4	150.4
Sato and Nakajima, 1987	Chloroform	10.3	38.9
Sato and Nakajima, 1987	Cyclopropane	0.4	22.2
Sato and Nakajima, 1987	Dichlorobenzene (*o*-/*m*-)	201–423	94.3–134.8
Sato and Nakajima, 1987	1,1-Dichloroethane	4.7	39.8
Sato and Nakajima, 1987	1,2-Dichloroethane	19.5	22.9
Sato and Nakajima, 1987	Dichloromethane (Methylene chloride)	9.7	15.7
Sato and Nakajima, 1987	Diethyl ether	14	4.6
Taneko et al., 1994	Ethanol	1440	0.08
Sato and Nakajima, 1987	2-Hexanone (Methyl *n*-butyl ketone)	127	12.9
Åstrand, 1975	Halothane	2.3	≈60
Perbellini et al., 1986	n-Hexane	0.8	130
Sato and Nakajima, 1987	Methanol	2100	0.03
Sato and Nakajima, 1987	Methyl isobutyl ketone	90	10.3
Sato and Nakajima, 1987	Monochlorobenzene	30.8	122.1
Sato and Nakajima, 1987	Styrene	51.9	105.4
Koizumi, 1989	Tetrachloroethylene	11.0	118.6
Reitz et al., 1988	1,1,1-Trichloroethane (Methylchloroform)	2.5	103.9
Sato and Nakajima, 1987	1,1,2-Trichloroethane	38.6	58.8
Fernández et al., 1977	Trichloroethylene	9	66.7
Sato and Nakajima, 1987	Toluene	15.6	94.2
Sato and Nakajima, 1987	Xylenes	26–37	98.1–140

philic, with fat/blood coefficients several orders of magnitude greater than their blood/air coefficients. They will thus pass more slowly from alveolar air to blood, but once in the blood, it will be transferred readily to the fat tissues.

The distribution of solvents in the body is described by pharmacokinetic models. These models attempt to separate lungs, vessel-rich tissues, muscles, and fat tissues [Csanády et al., 1994; Perbellini et al., 1986; Sato and Nakajima, 1987]. Perbellini et al. [1986] provided an excellent model (validated among shoe manufacturers) of the accumulation of metabolites to be expected from occupational exposure to n-hexane, when there is insufficient time for concentrations to relax to their baseline levels. The accumulation in fat tissue follows a sawtooth pattern, by which concentrations start off the workweek at a certain baseline level, increase until the end of the workshift (when they reach their maximum values), and slowly decrease during the evening and the night but never reach the previous day's minimum. Thus, concentrations in fat tissue increase until saturation, or until exposure ceases for at least 10 days [Perbellini et al., 1986]. To our knowledge, pharmacokinetic models of solvent metabolism incorporating the breast as a separate compartment have not been developed.

With blood flow being mostly to the blood rich organs, a large fraction of organic solvents will be taken up by the liver and the kidneys, and the remainder will be distributed to and absorbed by fatty tissues and other tissues. The liver and kidneys are active sites for the biotransformation of these xenobiotics. Depending on the detoxification mechanisms and the resulting types of by-products, some of these compounds will be excreted, but others will enter the bloodstream. Given its good vascular supply and its relatively large number of lipid cells, the breast can be an important depot for lipophilic untransformed xenobiotics and lipophilic by-products.

Once stored in surrounding fat tissues, organic solvents can migrate into the lobules and then be transported to the ductular system as a secretory product of the epithelial cells, and by simple, passive or active diffusion through cell membranes, by direct transport via inter-cellular spaces and via water-filled pores in the cell membranes [Sim and McNeil, 1992].

The accumulation of organic solvents in fat tissues has been documented by Engström and Bjurström [1977] who exposed 12 volunteers (six ''slim'' and six ''obese'') to methylene chloride for 1 hour while they worked at four different levels of intensity of exercise on a bicycle ergometer. Obese subjects had a higher total solvent intake, but the slim subjects had a higher rate of uptake per unit weight (mg/kg); however, the solvent was eliminated at a slower pace in obese subjects compared to leaner ones. The authors calculated that between 10% to 33% of the total solvent uptake was stored in the fat tissues (from samples taken from the buttocks) [Engström and Bjurström, 1977]. In animal experiments, the increased toxicity observed for females exposed to benzene could be related to longer retention times because of the larger volume of body fat in females [Sato et al., 1975; Sato and Nakajima, 1987]. Engström and Bjurström [1977] also reported that solvent concentrations in fat tissues probably vary according to blood perfusion, so that well perfused tissues would accumulate a higher concentration of solvents. This suggests that the cyclic increase in blood flow to the breast tissue could thus result in higher levels of solvents and their metabolites in the surrounding fat tissues.

Metabolism

Most xenobiotics undergo two types of detoxification processes occurring mostly in the liver and the kidneys: phase I processes, consisting of oxidation and reduction reactions, and phase II processes, consisting of conjugation reactions rendering them water-soluble and more easily excretable [Klaassen and Eaton, 1991]. However, the metabolism of organic solvents through the phase I processes may produce more toxic compounds (bioactivation) [Andrews and Snyder, 1991]. The oxidation reactions, mediated mostly through the cytochrome P-450 enzymatic system, produce alcohols, aldehydes or ketones, and epoxides, and the reduction reactions produce reactive free radicals. The extent and rates of biotransformation of each substance are affected by numerous factors, including age, sex, dose [Toftgård and Gustafsson, 1980], and the presence of other endogenous or exogenous chemicals that act as inducers of P-450 cytochromes [Arınç et al., 1991; Toftgård and Gustafsson, 1980] and of glutathione transferases [Bounous et al., 1991]. It has been shown that several chlorinated hydrocarbons induce microsomal enzymes [Alvares et al., 1977; Poland et al., 1970]. Because the liver and the kidneys are the main organs responsible for the P-450 system-mediated metabolic reactions, they are also the primary target organs for in situ toxicity related to highly reactive metabolites (e.g., epoxides, free radicals, alkylating agents).

Table III shows toxicologic features of P-450 biotransformation reactions for some of the most widely used aromatic and halogenated solvents, as well as a summary of the evidence of carcinogenic effects from human and animal studies. As an example, styrene undergoes oxidation through microsomal enzymes, mainly the P-450 cytochromes in the liver, and is subjected to epoxidation and hydroxylation reactions, and the resulting glycol is conjugated with β-glucuronic acid, or is oxidized. Styrene-7,8-oxide is thus formed but is detoxified very rapidly by microsomal epoxide hydrolase, another enzyme found near the P-450 complex, so that the epoxide is metabolized more rapidly than it diffuses across the cell [Csanády et al., 1994; Löf et al., 1986]. There is some evidence, however, that styrene-7,8-oxide is not completely detoxified, as it has been measured in the blood of styrene exposed workers [Korn et al., 1994; Löf et al., 1986].

Halogenated solvents also undergo metabolic activation by the cytochrome P-450 system. For example, carbon tetrachloride is thought to be cleaved to form a trichloromethyl radical that reacts with unsaturated fatty acids to produce an epoxide, which is particularly reactive when there is asymmetrical chlorine substitution [Toftgård and Gustafsson, 1980].

For some xenobiotics, it has been shown that a significant fraction can be metabolized outside the liver, e.g., up to 25% for trichloroethylene in dogs [Hobara et al., 1986]. Mammary glands are not a major site of metabolic activity, but they display cytochrome P-450 mediated [Eldridge et al., 1992; Gould, 1980; Maack et al., 1986] and glutathione-S-transferase mediated [Batist et al., 1991; Schecter et al., 1992] metabolic activity originating from different cell types [Gould, 1982]. Breast tissue, however, lacks certain enzymes (e.g., hydroxylases) capable of detoxifying hydrocarbons, so that they may accumulate unchanged [Dao, 1969; Dao and Varela, 1966]. There are no estimates of the extent to which organic solvents are bioactivated within the breast or whether metabolites produced by the liver and other organs find their way to breast tissue. We are also not aware of any studies investigating the presence of epoxides in human breast fluids, except for cholesterol epoxides [Petrakis et al., 1981].

Epoxides and free radicals are electrophilic and bind covalently to different proteins, thereby providing a potential mechanism for organ-specific toxicity, mutagenicity, and carcinogenicity. Some examples include covalent binding of: benzene metabolites to proteins in the bone marrow of exposed animals (benzene is a bone marrow depressant); carbon tetrachloride, a potent hepatotoxic agent, to macromolecules in the liver cells of exposed animals; and oxidized metabolites of vinyl chloride, a recognized hepatic carcinogen, to nucleic acids in the liver of exposed animals [Andrews and Snyder, 1991].

Another possible pathway for producing detrimental effects could be through estrogenic properties of some organic solvents or their interaction with estrogenic substances, thereby increasing cellular proliferation and geno-

TABLE III. Toxicological Profile of Some Organic Solvents Following Inhalation[a]

Organic solvent (reference)	Human studies: Cancer site	Human studies: Job/industry	Animal studies: Cancer site	Animal studies: Species	IARC class*	Short-term assays	Absorption and distribution	Metabolism and excretion
Acetone ATSDR,** 1992g	N/A	N/A	N/A	N/A	NC	Mostly negative results	Highly water soluble Lung absorption ≈75–80%. No significant differences between sexes	Even distribution with longest half-life in fat tissues Gluconeogenic pathways to acetol, then methylglyoxal, then propanediol, and ultimately to glucose and CO_2
Automotive gasoline ATSDR, 1993d	Stomach Kidney, possibly other sites	Male workers exposed to gasoline Male workers exposed to hydrocarbons	Kidney Liver	Rat Female mice	Group 2B	↑ micronuclei in lymphocytes (H) Mostly negative studies (A)	Patterns of absorption and distribution vary with proportion of individual components Accumulation of some hydrocarbons in fat tissues	Vary with individual components
Benzene ATSDR, 1989; NTP,*** 1986b	Hematopoietic system	Rubber workers, chemical workers	Mammary gland Skin, oral cavity, etc. Mammary gland (ingestion)	Rat Mouse and rat Mouse	Group 1	Chromosomal aberrations (H and A) ↑ SCEs and micronuclei DNA binding	Lung absorption ≈50% Complete equilibrium within a few days Amount of body fat influences toxicokinetics	Epoxide intermediate Hydroxylation, mostly to phenols, hydroquinones and catechol ≈64% metabolised
Bromoform ATSDR, 1990a	N/A	N/A	Large intestine (ingestion)	Rat	Group 3	↑ SCE in mouse bone marrow cells Inconsistent findings	No inhalation studies; observed toxicity implies absorption and distribution to liver, kidney and central nervous system	Oxidation through mixed function oxidases ⟶ formation of highly reactive dihalocarbonyl molecule 45–84% exhaled as CO_2 in mice
2-Butanone (methyl ethyl ketone) ATSDR, 1992a	No excess cancer deaths	Exposed workers in dewaxing plant	N/A	N/A	NC	Mostly negative results	Lung uptake ≈41–56% No accumulation in any tissue (blood/tissue partition coefficients all ≈1)	Metabolism to 2-butanol and other hydroxy derivatives ≈20–40% exhaled unchanged
Carbon disulfide ATSDR, 1993h	Possibly leukemia	Rubber workers	N/A	N/A	NC	Equivocal results	Lung retention ≈40–80% Fat accumulation	≈90% metabolized Oxidation and conjugation reactions ⟶ dithiocarbamates and organic sulfates among others CS_2 exhaled unchanged
Carbon tetrachloride ATSDR, 1992c	Possibly liver	Exposed workers	Liver (ingestion) No inhalation studies	Rat, hamster, mouse	Group 2B	DNA binding	Lung absorption ≈60% Accumulation in lipid-rich tissues	Dehalogenation by P-450 enzymes and formation of free radicals Saturable metabolism (63–85%) ⟶ CO_2 and $ClCH_3$ (chloroform)
Chlorobenzene ATSDR, 1990b	N/A	N/A	Liver and kidney (ingestion)	Rat and mouse	NC	Equivocal results	Absorption ≈38–45% Distribution proportional to concentration Fat accumulation	Oxidation to 4-chlorocatechol and conjugation to *p*-chlorophenol-mercapturic acid (with epoxide formation)
Chloromethane ATSDR, 1990c	No excess deaths	Butyl rubber plant (males)	Kidney (1000 ppm/24 months)	Mouse	Group 3	Mutagenic for S.t. Mutagenic and effects on SCEs in mammalian cells in vivo	Rapid absorption and distribution Concept of fast and slow metabolizers	Conjugated as S-methylcysteine Consistent with 2-compartment model
1,2-Dibromoethane ATSDR, 1992b; NTP, 1992a	No excess deaths	Chemical workers (studies with limitations)	Mammary gland Hemangiosarcomas of circulatory system, etc.	Rat and mouse	Group 2A	Mutagenic for S.t. and D.m.; DNA binding Chromosomal aber. + SCEs	Absorption and distribution poorly documented in humans and animals	Oxidation ⟶ acetaldehyde (evidence of covalent binding) and reduction ⟶ glutathione conjugate (highly reactive alkylating agent)
1,1-Dichloroethane ATSDR, 1990d	N/A	N/A	Mammary gland (ingestion)	Rat	NC	N/A	Previously used as anesthetic agent: Rapid absorption and distribution Fat accumulation	≈59% metabolised according to pharmacokinetic models, mainly through P-450 enzymes Acetaldehyde and possibly free radicals intermediates
1,2-Dichloroethane (ethylene dichloride) ATSDR, 1992h	Not clear	Petrochemical workers	Mammary gland, etc. (ingestion)	Rat	Group 2B	DNA binding and positive effects on SCE	Rapid absorption and fat accumulation Rapid distribution (few hours)	Saturable metabolism, mainly through glutathione-mediated conjugation Chlorohydrin and acetaldehyde intermediates Probably >80% metabolised
Dimethyl-formamide NTP, 1992b	Testicular and buccal cavity	Aircraft maintenance workers and leather tanners	N/A	N/A	Group 2B	Mostly negative results	Skin absorption can be important	Rapid metabolism, with about 5% hydroxylated into N-hydroxymethyl-N-methylformamide Hydroxy radicals involved

TABLE III. Toxicological Profile of Some Organic Solvents Following Inhalation[a] (continued)

Organic solvent (reference)	Human studies: Cancer site	Human studies: Job/ industry	Animal studies: Cancer site	Animal studies: Species	IARC class*	Short-term assays	Absorption and distribution	Metabolism and excretion
Ethylbenzene ATSDR, 1990e	No cancer cases	''Chronically exposed'' workers	? Total malignant tumors (ingestion)	Rat	NC	Mostly negative results	Lung retention 49–64% Adipose tissue retention after 2-hour exposure ≈5%	Hydroxylation and glucuronide conjugation. Major metabolites: mandelic and phenylglyoxylic acids
Ethylene glycol ATSDR, 1993e	No excess renal cancer deaths	Chemical workers (small sample size)	Lack of effect (ingestion studies)	Mouse and rat	NC	Mostly negative results	No available information on inhalation uptake Rapid absorption and distribution after ingestion	Nephro- and neuro-toxicity Metabolism to aldehyde → glyoxylic and oxalic acids
Fuel oils (kerosene) ATSDR, 1993f	No excess cancer	''Chronically exposed'' male and female workers	Skin and liver	Mouse	NC	Inconclusive studies	Patterns of absorption and distribution vary with proportion of individual components	Vary with individual components
2-Hexanone (methyl butyl ketone) ATSDR, 1992d	N/A	N/A	N/A	N/A	NC	N/A	Lung absorption ≈75–92% No available studies on distribution	Reduction to 2-hexanol and oxidation to 2,5-hexanedione (responsible for well-known neurotoxic effects)
Jet fuels JP-4 and JP-7 ATSDR, 1993g	N/A	N/A	Inconclusive evidence	Mouse and rat	NC	Inconclusive studies	Evidence of absorption, but no hard data	No data
Methylene chloride (dichloromethane) ATSDR, 1991a; NTP, 1986a	No excess deaths	Workers in photo development plant	Mammary gland (benign) Liver and lung	Mouse and rat	Group 2B	Mutagenic for S.t. Chromosomal aberrations (A)	Lung absorption ≈70–75% Amount of body fat influences toxicokinetics	Mixed function oxidase pathway → CO and glutathione transferase pathway → CO_2 Possible free radicals intermediates
Styrene ATSDR, 1992e	Leukemia, lymphoma (?)	Workers in styrene-based products (Problem of multiple exposures)	Possibly mammary gland Stomach (ingestion of styrene oxide)	Rat Mouse and rat	Group 2B	Chromosomal aberrations (H); increase in micronuclei (H?) Genotoxic metabolites (A)	Lung retention ≈60–70% Rapid accumulation in fat tissues (H)	Saturable metabolism >200 ppm >90% metabolised Oxidation to epoxide (detected in workers' blood), hydrolysation to glycol Major metabolites: mandelic and phenylglyoxylic acids
Tetrachloroethylene ATSDR, 1993b; NTP, 1986c	Doubtful: liver, kidney, bladder, cervix?	Dry cleaning workers Exposed craftsmen	Liver, leukemia and kidney	Mouse and rat	Group 2A	Negative findings for the solvent Glutathione conjugated metabolites mutagenic	Pulmonary uptake ∝ ventilation rate, duration of exposure and concentration in the inspired air Fat accumulation (A)	Saturable metabolism (≈10% metabolised) → trichloroacetic acid; some thioethers? Epoxide intermediate
Toluene Andrews and Snyder, 1991; Toftgrd and Gustafsson, 1980	N/A	N/A	N/A	N/A	Group 3	Equivocal results	Lung absorption ≈53% Fat accumulation	≈80% metabolised (20% exhaled unchanged) Hydroxylation and oxidation → benzoic acid and conjugation → hippuric acid
1,1,1-Trichloroethane ATSDR, 1993i	N/A	N/A	Negative study	Mouse and rat	Group 3	Equivocal results	Lung retention ≈25–30%, increasing with workload Rapid distribution from blood, primarily to fat and liver	<10% metabolised, mainly to trichloroacetic acid and trichloroethanol Free radical intermediate
Trichloroethylene ATSDR, 1993c; NTP, 1988	Bladder, lymphomas	Exposed men	Testicles, kidney, lung, etc. Liver, kidney (ingestion)	Mouse and rat Rat	Group 2A	Clastogenic effects (H) Mutagenic to mouse lymphoma cells	Lung retention ≈37–64%, varies with concentration, duration of exposure and alveolar ventilation rate Accumulation in fat and blood	40–75% of inhaled dose is metabolised Metabolites: trichloroacetic acid, trichloroethanol and its glucuronide; epoxide intermediate Higher levels of urinary TCE in women
Trichloromethane (chloroform) ATSDR, 1993a	Colon and bladder	Population exposed to chlorinated drinking water (ingestion)	Liver, kidney	Mouse and rat	Group 2B	Equivocal results	Lung retention documented by anesthetic effects Accumulation in fat and brain	≈50% excreted as CO_2 Bioactivation to phosgene, then bound to glutathione ≈17% exhaled unchanged
1,2,3-Trichloropropane ATSDR, 1992f	N/A	N/A	Mammary gland Forestomach and others sites (gavage)	Rat Mouse and rat	Group 2A	Mutagenic to S.t.	No studies available on absorption via inhalation Oral exposure: 80% absorption Rapid distribution to vessel-rich tissues and fat	Rapid elimination Cytochrome P-450 mediated oxidation with free radical intermediates and possibly alkylating agents (glutathione-mediated reduction reactions) Unchanged solvent and CO_2 exhaled

TABLE III. Toxicological Profile of Some Organic Solvents Following Inhalation[a] (continued)

Organic solvent (reference)	Human studies		Animal studies		IARC class*	Short-term assays	Absorption and distribution	Metabolism and excretion
	Cancer site	Job/ industry	Cancer site	Species				
Vinyl chloride ATSDR, 1991b	Angiosarcoma of the liver Other sites (less evidence)	Exposed workers	Mammary gland Liver and other sites	Mouse and rat	Group 1	Clastogenic effects (H) Mutagenic in S.t. DNA alkylation (A)	Lung retention ≈42%. Rapid and widespread distribution. Not detected in fat tissues, probably because of rapid and complete metabolism	Human data: formation of electrophiles Animal data: oxidation to epoxides, aldehydes and alcohols; conjugation to glutathione
Xylenes (*m*-, *o*-, *p*-) ATSDR, 1993j; Low et al., 1989; NTP, 1986d	Possibly leukemia	Workers exposed to coal-based xylenes (multiple exposures, limited studies)	No evidence (ingestion)	Mouse and rat	Group 3	Mostly negative studies (A and H)	Lung retention ≈62–64%. Rapid distribution with fat accumulation (≈5% of absorbed xylenes) In rat fat tissue, 75% as xylenes and 25% as metabolites	≈90% metabolised according to a 3-compartment model ≈5% excreted unchanged in expired air Animal data: oxidation through epoxides to acids and alcohols; glycine and glucuronide conjugation

[a]Note: Unless otherwise stated, increase in cancers in animals are reported for inhalation studies.
NC, Not classified; N/A, No studies available; (H), Human studies/(A): Animal studies; SCE, Sister chromatid exchange; DNA, Desoxyribonucleic acid; S.t., *Salmonella typhimurium*; D.m., *Drosophila melanogaster*.
*IARC. Overall evaluations of carcinogenicity: an updating of IARC monographs Volumes 1 to 42. Lyon, France: IARC, 1987; *Suppl. 7, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*: 120, 143, 194, 204.
**ATSDR: Agency for Toxic Substances and Disease Registry.
***NTP: National Toxicology Program.

toxic effects simultaneously [Davis et al., 1993]. There are a few anecdotal reports of the estrogenic properties of phenols, organic solvents used to synthesize plastics, leached from laboratory ware [Krishnan et al., 1993; Soto et al., 1991]. Although one cannot infer estrogenic activity solely from chemical structure, it is reasonable to believe that other organic solvents display some estrogenic activity [Soto et al., 1991].

Carcinogenicity of Organic Solvents

Short-term studies

Short-term assays can be useful in detecting potential carcinogens through the investigation of genotoxic effects of pure substances in microbial, mammalian, or human cells. Genotoxic effects are not necessarily precursors of carcinogenic activity, but they can be regarded as indicators of possible carcinogenic effects. Few assays have been carried out using metabolites, which are often the biologically active molecules. Short-term assays carried out in vivo in mammals may be a promising approach [Bridges, 1986].

Several solvents have exhibited certain cytotoxic effects in short-term studies (see Table III). Chromosomal aberrations in peripheral blood lymphocytes of exposed workers have been found for exposure to benzene, methylene chloride, and styrene [Pelkonen and Raunio, 1995; Agency for Toxic Substances and Disease Registry, 1991a, 1992e]; increased incidence of sister chromatid exchanges in mammalian cells were observed for chloromethane and 1,2-dichloroethane [Agency for Toxic Substances and Disease Registry, 1990c, 1992h]; mutagenicity in Ames tests was indicated for chloromethane, 1,2-dibromoethane, methylene chloride, 1,2,3-trichloropropane, and vinyl chloride [Agency for Toxic Substances and Disease Registry, 1990c, 1991a,b, 1992b,f]; and DNA binding to microsomal lipids, proteins, and other cellular macromolecules has been reported for carbon tetrachloride, 1,2-dichloroethane and vinyl chloride [Agency for Toxic Substances and Disease Registry, 1991b, 1992c,h].

Long-term animal studies

Carcinogenicity experiments in laboratory animals have led to the identification of a number of organic solvents as potential human breast carcinogens, including benzene, 1,2-dibromoethane, 1,1-dichloroethane, 1,2-dichloroethane, methylene chloride, styrene, 1,2,3-trichloropropane, vinyl chloride [Agency for Toxic Substances and Disease Registry, 1989, 1990d, 1991a,b, 1992b,e,f,h; National Toxicology Program, 1986a,b, 1992a]. Results from these studies may not necessarily be generalizable to humans because, for a given route of absorption, major differences exist between

species in uptake, distribution, and metabolism [Klaassen and Eaton, 1991]. For example, after exposure to styrene, much higher quantities of styrene oxide are produced by mice than by rats or humans. As well, humans have the highest capacity of the three species to metabolize styrene oxide [Agency for Toxic Substances and Disease Registry, 1992e]. In addition, most animal studies are based on single exposures rather than on mixtures. Human exposure is invariably to complex mixtures and interactions between different solvents may inhibit or potentiate known effects of individual solvents [Andrews and Snyder, 1991].

Epidemiology

The effects of exposure to organic solvents and the risk of female breast cancer have been reported in only a handful of occupational studies [Goldberg and Labrèche, 1996]. We will summarize here a few cohort and case-control studies that focused on solvent-exposed workers (Table IV).

Laundry and dry cleaning workers (exposed at varying degrees and at different time periods to stoddard solvent, carbon tetrachloride, perchloroethylene, trichloroethylene, and fluorocarbons [Blair et al., 1990; Brown and Kaplan, 1987; Ruder et al., 1994] were investigated in two mortality cohort studies and no excess risks were observed. Mortality rates among aircraft maintenance workers exposed to trichloroethylene were not greater than expected, although excess risks were observed, for exposure to isopropyl alcohol and methylene chloride [Spirtas et al., 1991]. Axelson and coworkers [1978, 1994] also investigated cancer incidence and mortality in trichloroethylene exposed workers, but no risk estimates were provided for cancer of the breast, and one must assume that very few cases were observed. An excess risk for breast cancer incidence was observed among women employed for 5 years and more in coiling and wire drawing [Shannon et al., 1988] in the manufacturing of lamps, in which methylene chloride and trichloroethylene may have been used. A cohort study of female shoe manufacturers [Paci et al., 1989], who were exposed to a number of substances including organic solvents (benzene, toluene, hexane, methyl ethyl ketone, acetone, and solvent-based adhesives) observed no association for breast cancer mortality, but statistical power was very low. A cohort study of garment workers exposed to formaldehyde was also negative [Stayner et al., 1985, 1988]. Mikoczy and coworkers [1994] conducted a cohort study of leather tannery workers exposed to a number of compounds, including benzene and other chlorinated solvents, and found incidence rates to be between 30% and 50% above expected. A case-control analysis of a small cohort of polyvinylchloride workers showed a nonsignificantly elevated risk of death from breast cancer [Chiazze et al., 1977, 1980]. No associations were observed for mortality among styrene-exposed workers [Kogevinas et al., 1994; Wong, 1990; Wong et al., 1994], or for incidence among workers exposed to halogenated solvents [Anttila et al., 1995]; the latter study constituted its cohort from a database of workers monitored for halogenated solvent exposure between 1965 and 1982, and followed-up for cancer incidence between 1967 and 1992. Finally, a case-control study on the effect of hormone replacement therapy and breast cancer found an increased risk for the group of painters, sculptors, and printmakers [Habel et al., 1995]. Studies of organic solvents may, however, be beset with health-related, differential selection into and out of work arising from early-onset toxic effects (e.g., dermatitis, hepatic and renal toxicity, central nervous system depression, peripheral neuropathy) [Andrews and Snyder, 1991]. Thus, a selection bias may occur in cohort studies if susceptible or sensitive workers are at higher risk for developing breast cancer and are more likely to leave exposed jobs early (less highly exposed than insensitive persons).

Important limitations of these cohort and case-control studies restrict their usefulness: 1) only one was designed specifically to study breast cancer, information on major confounders was missing, and separate analyses were not provided according to menopausal status; 2) most of these studies investigated cancer mortality, whereas incidence figures are more appropriate given the relatively long survival rates for breast cancer; 3) statistical power was low as women constituted a small proportion of the work force in many studies; 4) most studies relied on broad occupational groupings as a proxy for exposure assessment. In summary, the available epidemiologic data are inconclusive regarding the relation between organic solvents and female breast cancer risk.

SUMMARY AND CONCLUSIONS

Our theory is based on three elements: 1) the toxicokinetic distribution of lipophilic solvents in the body favoring accumulation in and around breast tissue; 2) a theory of chemical deposition and retention in the breast, previously suggested by Petrakis and coworkers [Petrakis, 1977b, 1986; Petrakis et al., 1982]; and 3) carcinogenic properties of certain organic solvents and their metabolites.

While there are scant epidemiologic data related to organic solvent exposures and breast cancer, other lines of evidence support the hypothesis. First, it is well known that some organic solvents will accumulate in fat tissue after typical occupational exposures. Second, a number of organic solvents have been detected in human milk, often in higher concentrations than in the blood. Third, the observation that a high proportion of breast cancers are ductular is consistent with the stagnation model of Petrakis. Fourth, nipple aspirates have been shown to be mutagenic in some women. And fifth, a few organic solvents (benzene, styrene, vinyl chlo-

TABLE IV. Relative Risks of Breast Cancer in Occupations or Industries With Organic Solvent Exposure

Reference	Type of study	Occupation or industry	Organic solvents	Total number of women	Number of breast cancers	Risk	95% Confidence interval or *P* value
Chiazze et al., 1977, 1980	Cohort (mortality)	Polyvinylchloride fabricators	Vinyl chloride	NR*	44	PMR = 1.8	$P > 0.05$
Axelson et al., 1978, 1994	Cohort (mortality)	Trichloroethylene exposed workers	Trichloroethylene	249	NR (<11)	NR	—
Stayner et al., 1985, 1988	Cohort (mortality)	Garment industry	Formaldehyde	9,022	33	SMR = 0.7	0.5–1.0
Brown & Kaplan, 1987; Ruder et al., 1994	Cohort (mortality)	Dry cleaning	-Entire cohort	1,109	19	SMR = 1.1	0.7–1.7
			-Tetrachloroethylene + other solvents	695	13	SMR = 1.1	0.6–1.9
			-Tetrachloroethylene	414	6	SMR = 1.0	0.4–2.2
Shannon et al., 1988	Cohort (incidence)	Lamp manufacturing	Methylene chloride, trichloroethylene	1,044	21	NR	NR
		-Total cohort in coiling/wire drawing		203	8	SMbR = 2.0	0.9–4.0
		-≥5 years work, ≥15 years latency		NR	5	SMbR = 3.2	1.1–7.5
Paci et al., 1989	Cohort (mortality)	Shoe manufacturing	Benzene and other solvents	1,005	4	SMR = 0.9	0.2–2.3
Blair et al., 1990	Cohort (mortality)	Dry cleaners	Tetrachloroethylene and other solvents	4,046	36	SMR = 1.0	0.7–1.4
Wong et al., 1990, 1994	Cohort (mortality)	Reinforced plastics and composites industry	Styrene	3,868	14	SMR = 0.6	0.3–1.1
Spirtas et al., 1991	Cohort (mortality)	Aircraft maintenance	-Mixed solvents	3,138	30	SMR = 0.7	0.5–1.0
			-Trichloroethylene		9	SMR = 0.8	0.4–1.5
			-Isopropyl alcohol		NR	SMR = 3.1	1.3–6.4
			-Methylene chloride		3	NR	$\chi^2 = 6.2$, $P = 0.01$
Kogevinas et al., 1994	Cohort (mortality)	Styrene exposed workers	Styrene	6,128	13	SMR = 0.5	0.3–0.9
Mikoczy et al., 1994	Cohort (incidence)	Leather tanning: No latency period	Benzene and other chlorinated solvents	482	20	SIR = 1.3	0.8–2.0
		Latency ≥20 years		NR	19	SIR = 1.5	0.9–2.3
Anttila et al., 1995	Cohort (incidence)	Workers exposed to halogenated solvents	Trichloroethylene, tetrachloroethylene, 1,1,1-trichloroethane	1,924	34	SIR = 0.9	0.6–1.2
Habel et al., 1995	Case control (incidence)	Painters, sculpters, printmakers	Various solvents	537 cases and 487 controls	5 cases and 3 controls	RR = 1.7	0.4–7.4

*NR: Not reported, SMR: Standardized mortality ratio, SMbR: Standardized morbidity ratio, SIR: Standardized incidence ratio, RR: relative risk.

ride, 1,2-dibromoethane, 1,1-dichloroethane, 1,2,3-trichloropropane), previously shown to be biotransformed to electrophilic metabolites (epoxides, free radicals, alkylating agents), have been found to cause mammary gland cancers in experiments on rodents.

Organic solvents could then act directly in carcinogenesis according to the following patterns: 1) intact solvent molecules reach the breast epithelium where they are bioactivated into electrophilic metabolites that cannot be detoxified effectively because of the reduced activity of the necessary enzymes in breast cells. Because of the unique physiology of mammary glands, the solvents and/or their metabolites accumulate in the milk ducts, long enough to exert detrimental effects locally. 2) A proportion of electrophilic metabolites produced in the liver, kidneys, and other detoxifying organs escape detoxification and migrate to the breast cells, and accumulate in the milk ducts where they exert toxic effects in situ. 3) Some unknown interaction between these two patterns and estrogenic effects of endogenous and, possibly, exogenous substances.

In view of the fact that breast cancer incidence is increasing with time, and that the known risk factors can explain only part of the increase, new areas of breast cancer research are warranted. Occupational exposure to organic solvents is one possible and interesting research area. Toxicological and biochemical studies could elucidate the distribution and metabolism of organic solvents in the breast parenchyma, and identify the solvents that display estrogenic properties. Cohort and case-control studies would be invaluable in testing these hypotheses. One difficulty is the large number of organic solvents in use today. We do not expect effects to be uniform across substances, so a judicious choice is warranted by focusing on, for example, organic solvents shown to be mammary carcinogens in animal experiments (e.g., benzene, styrene, vinyl chloride, 1,2-dibromoethane, 1,1-dichloroethane and 1,2,3-trichloropropane). Another approach is to carry out a population-based case-control study that can be used to investigate many exposures simultaneously. Such a study requires detailed occupational histories of subjects and a method for translating these histories into exposures to specific substances. State-of-the-art methods, such as those developed by Siemiatycki et al. [1981], Gerin et al. [1985], and others [Stewart and Stewart, 1994a,b] can be used for this purpose. Of critical importance to the statistical power of the study is the prevalence of occupational exposure, which we have estimated to be between 4 and 17% among all women. Such a study is indeed feasible and we are currently carrying out a case-control study of postmenopausal breast cancer in Montreal.

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