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The Role of Skin Absorption as a Route of Exposure for Volatile Organic Compounds (VOCs) in Drinking Water

HALINA SZEJNWALD BROWN, PHD, DONNA R. BISHOP, MPH, AND CAROL A. ROWAN, MSPH

Abstract: Assessments of drinking water safety rely on the assumption that ingestion represents the principal route of exposure. A review of the experimental literature revealed that skin penetration rates for solvents are remarkably high, and that the stratum corneum is a less effective barrier to penetration than traditionally assumed.

Based on published skin absorption rates, we used Fick's law ($J_s^o = K_p^o \Delta C_s^o$) to determine permeability constants for selected compounds. We then calculated dose per kilogram for nine different exposure situations and compared this to the oral dose per kilogram. We found that skin absorption contributed from 29-91 per cent of the total dose, averaging 64 per cent. Dose per kilogram body weight ranged from .0002 mg/kg–.18 mg/kg, with an average of .03 mg/kg. In weak aqueous solutions, flux of the solute is directly proportional to concentration. Laboratory approaches differ markedly from environmental exposures and can underestimate absorption.

We conclude that skin absorption of contaminants in drinking water has been underestimated and that ingestion may not constitute the sole or even primary route of exposure. (*Am J Public Health* 1984; 74:479–484.)

Introduction

Regulators today face complex problems in assessing the health hazards associated with contamination of drinking water supplies. Due to the general absence of federal drinking water standards for the volatile solvents commonly found in contaminated water, state and local regulatory agencies must decide whether to discontinue or restrict use of water supplies on a case by case basis. Such decisions are heavily, if not exclusively, based on the recommendation of a toxicologist.

Materials and Methods

The methodology to calculate an acceptable level of a chemical in drinking water has been developed by the National Academy of Sciences[1] and is incorporated in the Environmental Protection Agency (EPA) SNARLs (Suggested No Adverse Response Level). These figures represent the highest level or dose of a chemical which produced no observed adverse effect in chronic or subchronic tests with animals or humans, divided by a safety factor to obtain an Acceptable Daily Intake (ADI). ADI is in turn divided by the volume of water consumed by an average adult (two liters) or child (one liter) in order to calculate the acceptable concentration of the chemical in water (mg/liter or ppm). One of the underlying assumptions here is that ingestion constitutes the chief route of exposure to the contaminant. Such an assumption disregards other routes of exposure such as skin absorption during bathing or swimming, and inhalation of vapors while showering.

We reviewed the existing literature on absorption rates of volatile solvents in aqueous solutions having direct contact with skin, and estimated the likely dermal and oral doses resulting from normal daily use of contaminated water.

Recent EPA surveys indicate that both finished and ground water supplies throughout the United States have been contaminated with volatile organic compounds.[2] Concentrations vary considerably by location, but are generally highest in the industrialized areas east of the Mississippi River. Data from studies reported by the EPA and the Council on Environmental Quality (CEQ) in 1981[3] emphasize the magnitude of the problem. Levels of contamination in surface and ground waters are given in Table 1. While contamination of surface waters is more frequent, ground water degradation is of particular concern because of the high levels detected, and because pollution of ground water is not reversible. There are no known natural cleansing processes associated with ground water movement in the earth. Since about 50 per cent of the population relies on ground water for its drinking supplies,[2] this is a matter of concern for regulators. Acute and chronic effects have been demonstrated for most of these compounds, and several are suspected or known carcinogens.[4-7] Others have shown mutagenic and/or teratogenic capacity.[8-10] The volatile compounds found most commonly in EPA surveys of drinking water supplies are listed below.*

There are many sources of contamination. Synthetic organic solvents have wide commercial use, and are detectable in air, water, soil and food.[11] Virtually all members of the general population may be routinely exposed to these compounds due to the ordinary use of paints, thinners, lacquers, degreasers, fuels, dry-cleaning agents, dyeing materials, glues, cements, pesticides, pharmaceuticals, cleaning supplies, foods, and beverages.

Outside of occupational settings, little attention has been paid to skin absorption as a route of entry for volatile organic compounds, and regulators have been primarily concerned with exposures via inhalation and ingestion. During the past 20 years, numerous investigators have explored the mechanisms of epidermal barrier function in relation to solvents and solvent mixtures. Although a complex process, dermal uptake of compounds occurs mainly through passive diffusion, involving selective mechanisms in the various lipid and protein structures of the stratum corneum. Many investigators have reported on the toxicity and unexpectedly high penetration rates of volatile organics.[12-19] Nevertheless, most studies have focused on occupational and laboratory exposures to pure liquids, and much less has been written about absorption from aqueous solutions. Reports on exposure to solvents or other volatile organics via contaminated water supplies are difficult to

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*trichloroethylene, tetrachloroethylene, carbon tetrachloride, benzene, 1,1,1-trichloroethane, 1,2-dichloroethane, vinyl chloride, methylene chloride, 1,1-dichloroethylene, cis-1,2-dichloroethylene, trans-1,2-dichloroethylene, chlorobenzene, dichlorobenzene, trichlorobenzene

TABLE 1—Drinking Water Contamination Levels

Compound	Ranges Detected in Ground Water (ug/liter)		Ranges Detected in Surface Water (ug/liter)	
Trichloroethylene[2]	trace—	35,000	trace—	3.2
Tetrachloroethylene[2]	trace—	3,000	trace—	21
Carbon Tetrachloride[2]	trace—	379	trace—	30
1,1,1-Trichloroethane[2]	trace—	401,300	trace—	3.3
1,2-Dichloroethane[2]	trace—	400	trace—	4.8
Vinly Chloride[2]	trace—	380	trace—	9.8
Methylene Chloride[2]	trace—	3,600	trace—	13
1,1-Dichloroethylene[2]				
Cis-1,2-Dichloroethylene	trace—	860	trace—	2.2
Trans-1,2-Dichloroethylene				
Ethylbenzene[3]	trace—	2,000		
Xylene[3]	trace—	300		
Toluene[3]	trace—	6,400		

SOURCES: EPA, 1981; pp 6, 10, 13, 20, 24, 27, 30 (State Data).[2] Council on Environmental Quality, 1981, p 36.[3]

obtain. Even without detailed analyses of absorption from specific compounds, however, it is possible to estimate potential absorption using Fick's Law.[20] Dose may then be calculated using published skin absorption rates for various chemicals (Table 2).[21,22]

Fick's Law

Fick's law may be used to determine the permeation rate of solvents in an aqueous solution, and is expressed by the formula ($J_s^o = K_p^o \Delta C_s^o$) where J_s^o is the permeation rate (flux) of the solute expressed as mg/cm² × hour; K_p^o is the permeability constant (liters/cm² × hr); and ΔC_s^o represents the concentration difference of the solute across specified tissue in mg/liter.[20] The (o) superscript refers to the aqueous system. Fick's law describes the behavior of dilute aqueous solutions, such that absorption of the solute will be directly proportional to concentration. This rule applies to weak aqueous solutions and will not necessarily hold for pure or highly concentrated liquids.[20,23] Figure 1 demonstrates the rate of absorption of toluene as a function of concentration in water.[22] That such a relationship exists at low concentrations and across broad classes of compounds has been amply demonstrated by Tregear and others.[17,20,23-27]

Regulators have relied upon data obtained using pure liquids to estimate the significance of skin absorption, which

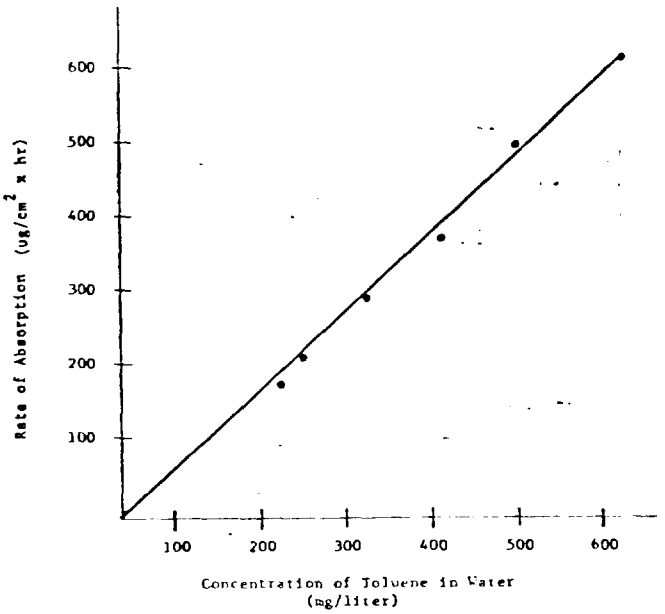

FIGURE 1—Rate of Absorption of Toluene as a Function of the Concentration in Water

SOURCE: Dutkiewicz and Tyras, 1968

may not be accurate for practical purposes. Scheuplein, Blank, and others have shown that permeation rates are actually increased with dilute aqueous solutions as compared to pure liquids.[23,24,27] Scheuplein cites the following example:

> "Liquid hexanol (8.2M) is approximately 150 times more concentrated than saturated aqueous hexanol (0.055M); yet the permeation rate of aqueous hexanol, far from being 150 times less than the pure liquid, is almost twice as great."[20]

Investigators attribute this effect to the compaction and dehydration of the stratum corneum when in contact with pure liquids, as well as to the distribution factors of changing gradients and partition coefficients understood in Fick's law.[25,26] In addition, the necrotizing effects of concentrated liquids in contact with skin act to limit absorption.[20,28-30] Such data indicate that skin absorption rates may be seriously underestimated.

TABLE 2—Average Skin Absorption Rates for Pure Liquids and Aqueous Solutions

	Experimental Skin Absorption Rates (mg/cm² × hr)—Direct Method				
		Aqueous Solution			
Compound	Pure Liquid	Absorption Rate (flux) J_s^o (mg/cm² × hr)	Concentration C_s^o (mg/l)	Reference	Calculated Permeability Constant (K_p^o) (1/cm² × hr)
Ethylbenzene	22–33	.11	112	Dutkiewicz & Tyras[21]	.001
		.21	156		.001
Styrene	9–15	.04	66.5	Dutkiewicz & Tyras[22]	.0006
		.18	269		.0007
Toluene	14–23	.16	180	Dutkiewicz & Tyras[22]	.0009
		.60	600		.001
Xylene	4.5–9.6	*		Dutkiewicz & Tyras[22]	

*Proportional to concentration. Values for J_s^o and C_s^o not given.
NOTE: Using Fick's law ($J_s^o = K_p^o \Delta C_s^o$) and assuming that the concentration gradient C_s^o equals the concentration in solution C.

Measurement of Absorption Rates for Selected Solvents

Dutkiewicz and Tyras quantified skin absorption rates for ethylbenzene, toluene, styrene, and xylene.[21,22] Their results are presented in Table 2. Absorption was calculated as the difference in solute concentration before and after a one-hour immersion of one hand in aqueous solutions of known concentration ("direct method"). Loss of the compound was prevented by a polythene bag. This method proved effective in control experiments where a solution protected in this manner did not change concentration in two hours. They conducted 14 experiments with seven male subjects, six on one subject. The results were checked against a second set of experiments using excretion of major metabolites to measure absorption ("indirect method"). In this case, five experiments were carried out with five male subjects in which both hands were exposed for a period of two hours. Urine samples were collected every two hours for the 14 hours beginning with exposure, and again 10 hours later. Determinations of the compound were also obtained from expired air. The same procedure was followed for each compound.[22] The data obtained were confirmed by Guillemin, *et al*, in 1974.

Both methods showed rapid absorption from aqueous solutions, and the authors concluded that, "Compared with its absorption through the respiratory system, skin absorption could be the major route of penetration into the body."[21] Other writers agree that skin absorption represents a principal route of entry for several classes of compounds.[16,17,31,36] Despite such evidence, however, there have been few attempts to quantify absorption during normal use of contaminated water, or to assess the potential hazards associated with such use.

Using Fick's law, the permeability constants (K_p^o) calculated from these findings varied from .0006 to .001 (average .001) for the series of compounds in the range of concentrations from 66.5 to 600 mg/l (Table 2). This finding further supports the assumption of linearity for the relationship between absorption rate and solute concentrations within a wide range of low concentrations in aqueous solutions.

Variables Involved in Rate and Amount of Skin Absorption

The conditions under which exposure occurs, and the specific characteristics of both the compounds and subjects involved will each affect the rate and amount of absorption through the skin. Variables such as duration of exposure, type of skin exposed (thickness, vascularity, age, and chemical composition), and amount of surface area exposed will influence absorption.[37,40] In addition, each of the following is associated with uptake in the skin:

Hydration—The more hydrated the skin, the greater the absorption. In contrast, a pure liquid solvent will dehydrate skin and elicit compaction of the stratum corneum, which will act to slow absorption of the chemical. If the skin is hydrated (perspiration, immersion in water) or the compound is in solution, diffusion and penetration will be enhanced.[17,20,24,27,33,41]

Temperature—Increased skin or solute (water) temperature will enhance skin absorption capacity proportionately. By contrast, measurements of skin absorption are typically carried out in temperature-controlled settings using normally hydrated skin. During swimming or bathing, however, it may be expected that greater hydration of skin surfaces will take place. In addition, water, ambient, and skin temperatures may well be greater in certain situations, and thus diffusion will be greater.[17,40,42,43]

Skin Condition—Any insult (i.e., sunburn) or injury (cuts, wounds, abrasions) to the stratum corneum will compromise its ability to act as a barrier against foreign substances. A history of skin disease such as psoriasis or eczema will similarly compromise the stratum corneum, as will rashes, dermatitis, or any chronic skin condition which acts to remove stratum corneum or limit barrier function.[33,40,44–46]

Regional Variability—Skin absorption rates are derived from experimental situations in which the thumb or hands are immersed in the test solution. Rates obtained in this manner, however, will underestimate actual absorption in cases of whole-body immersion during swimming or bathing. The epidermis of the hand represents a relatively greater barrier to penetration than many other parts of the body, including the scalp, forehead, abdomen, postauricular area, underarm, fossa cubitalis, and scrotum.[47] Penetration through the scrotum, in fact, is estimated to be 100 per cent, as compared to 8.6 per cent for the forearm.

Other Routes of Entry—Other significant routes of absorption include oral, buccal, and sublingual, orbital, nasal, and aural, and are known to be particularly permeable to lipophilic substances in aqueous solutions.[48] Experimental procedures do not account for uptake via other routes, and will thus underestimate dose and absorption during immersion in water.

Inhalation serves as yet another route. Calculations of rate and dose necessarily rely on the assumption that concentration will remain constant throughout the exposure period. The solvents under consideration are likely to volatilize in small amounts near the surface of a body of water. In the case of swimming or bathing, however, this effect will be offset by the fact that amounts volatilized will be readily inhalable, along with ambient air levels of the compounds.[48,49] In addition, water may be swallowed in these situations.

Individual Variability—Absorption rates vary among individuals, and even for the same individual over time.[39,40,43,50,51] Variables such as age, sex, ratio of body fat, previous exposure, nutrition, type and amount of skin exposed as well as the specific conditions of exposure will all affect actual absorption. Rates obtained from healthy adults will again tend to underestimate absorption for younger or more sensitive populations.

Physical and Chemical Properties of the Compound—Factors affecting absorption include lipophilicity, polarity, volatility, molecular weight, carbon number, and solubility in the stratum corneum.[38]

The pH of a solution will also bear on its absorption. Matoltsy, *et al*,[50] have shown that water diffusion rates are increased with solutions in pH ranges of 1.5–4.0 and 11–12, and solvent solutions within these ranges are absorbed more readily. Matoltsy, *et al*, also demonstrated the differential effects of various buffer solutions on lipid and protein structures of stratum corneum. As the pH of our water supplies becomes increasingly acidic, this factor will gain more relevance outside the laboratory setting.

Appropriate methodology is crucial to determine epidermal absorption efficiency. For example, the common practice of calculating absorbed dose from expired air samples has been shown to be misleading in many instances, since these compounds tend to be distributed slowly and may be sequestered in the body for relatively long periods.[33,35,43,52–58]

TABLE 3—Estimated Dose and Contribution per Exposure for Skin Absorption versus Ingestion

A. Dose (mg/kg)		Case 1[a]		Case 2[b]		Case 3[c]	
Compound	Concentration (mg/l)	Dermal	Oral	Dermal	Oral	Dermal	Oral
Toluene	.005	.0002	.0001	.0004	.0005	.002	.0002
	.10	.005	.003	.008	.0095	.033	.0045
	.5	.02	.014	.04	.048	.17	.023
Ethylbenzene	.005	.0003	.0001	.0004	.0005	.002	.0002
	.10	.005	.003	.008	.0095	.036	.0045
	.5	.03	.014	.04	.048	.18	.023
Styrene	.005	.0002	.0001	.0002	.0005	.001	.0002
	.10	.003	.003	.005	.0095	.023	.0045
	.5	.02	.014	.02	.048	.11	.023
B. Relative Contribution		Dermal	Oral	Dermal	Oral	Dermal	Oral
		%	%	%	%	%	%
Toluene	.005	67	33	44	56	91	9
	.10	63	37	46	54	89	11
	.5	59	41	45	55	89	11
Ethylbenzene	.005	75	25	44	56	91	9
	.10	63	37	46	54	89	11
	.5	68	32	45	55	89	11
Styrene	.005	67	33	29	71	83	17
	.10	50	50	35	65	84	16
	.5	59	41	29	71	83	17

(a) 70 kg adult bathing 15 minutes, 80% immersed (skin absorption)
2 liters water consumed per day (ingestion)
(b) 10.5 kg infant bathed 15 minutes, 75% immersed (skin absorption)
1 liter water consumed per day (ingestion)
(c) 21.9 kg child swimming 1 hour, 90% immersed (skin absorption)
1 liter water consumed per day (ingestion)

Thorough biological monitoring of the compounds and their metabolites is necessary to assess absorption and potential systemic effects.[59]

Vehicles and Accelerants—Substantial data exist demonstrating the permeability-enhancing effects of various compounds, including alcohols, solvents, and chloroform.[20,30,50,60] Moreover, Blank and Shappirio[61] and Fredriksson[62] have investigated the effects of soap solutions on barrier function, and have found that soaps and surfactants will likewise increase skin permeability significantly. While the data presented do not permit precise quantification of effects, such information is clearly relevant to environmental exposures.

Synergistic Effects—Measurements of skin absorption rely on data obtained from single-compound solutions, which will underestimate absorption in the more common situation of multiple exposures or exposure to solvent mixtures in contaminated water. Studies show that combinations of compounds have greater effect on the stratum corneum, and are absorbed more readily.[26,63]

Calculations of Dose from Contaminated Water

In environmental settings, water may be contaminated with one or more organic solvents in the low parts per billion (ppb) range or higher. Using available data, Table 3 compares the estimated dose per exposure from ingestion versus skin absorption under various conditions. Ingestion data assume two liters of water consumed per day by an adult, and one liter for children.[1] Gastrointestinal absorption efficiency is assumed to be 100 per cent.[64] Skin absorption data assume body weights of 70kg, 10.5kg, and 21.9kg for an adult, infant and child, respectively. Corresponding body surface areas are 18,000cm², 4000cm², and 8800cm², respectively.[65,66]

Three different concentrations were used. Doses have been calculated using the permeability constants (K_p^o) from Table 2 in the following formulae:

Oral Dose = concentration (mg/l) × amount consumed (liters/day) ÷ body weight (kg)

Dermal Dose = permeability constant (l/cm² × hr) × duration of exposure (hr) × total body surface area (cm²) × amount of body surface area exposed (%) × concentration (mg/l) ÷ body weight (kg)

Calculations of dose are based on the following assumptions:

1. *Linearity*—Fick's law is assumed to hold at low concentrations, such that a linear relationship between dose and concentration will exist throughout a range of weak aqueous solutions. In fact, such a relationship does exist, and numerous investigators have demonstrated linearity throughout a range of concentrations.[27,67] Consistency of K_p^o values for similar solutes ranging 10-fold in concentration (Table 2) further support this assumption.

2. *Independence*—each chemical will penetrate at its own rate, independently of other chemicals present in solution.

3. *Uniformity*—rates of absorption and flux through the skin remain constant throughout the period of exposure.

4. *Additivity*—the doses and effects of compounds occurring together in aqueous solutions are only additive.

5. *Elimination*—within the time periods presented, elimination will not significantly change sustained dose. Given the fact that distribution and elimination of these compounds occur very slowly in the case of skin absorption, it is likely that elimination will not be relevant in the scenarios presented.

6. *Limited Exposure*—the doses calculated are limited to absorption through the stratum corneum, and do not include

penetration through the more permeable membranes of the body. In addition, absorption rates for the entire body are assumed to be equal to that of the hand.

7. *Temperature and Hydration*—rates were obtained experimentally at temperatures between 23°–25°C. We will therefore assume water and ambient temperatures which do not exceed those used in the laboratory. Likewise, hydration of skin surfaces is assumed to be equal to that of experimental subjects.

Table 3 shows that skin absorption represents a significant route of exposure. Depending on exposure conditions, it can contribute from 29–91 per cent of the total daily dose, for an average contribution of 64 per cent. Since uptake via each route is proportional to concentration, and the diffusion constant is therefore independent of concentration, the small differences in contribution percentage for each case are due to rounding off. Three cases were given to illustrate this point. These figures are based on the conservative assumptions described above, and should be regarded as estimates of lower bound absorption through the stratum corneum.

Discussion

When factors such as hydration, skin condition, additional routes of entry, individual and anatomical site variations are taken into account, skin absorption can become a significant portal of entry for contaminants. Moreover, the estimated skin absorption rates have been derived in occupational or laboratory settings which may differ markedly from environmental conditions. Such rates, particularly those obtained using pure liquids or single agents, should not be directly extrapolated to environmental exposures. Nevertheless, the information suggests that when doses from skin absorption are considered, margins of safety may be significantly narrowed, and currently established guidelines compromised.

It will be necessary to generate comprehensive data on the relative contributions of various types of exposures on selected populations if we are to ensure adequate protection of public health. Studies indicate that contamination of water supplies is greater than previously believed, and is likely to increase without stringent controls. On this basis, we recommend that regulatory guidelines and policies be reconsidered.

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