

Dermal absorption from short-term exposure to contaminated water

KENNETH T. BOGEN & GARRETT A. KEATING

Health and Ecological Assessment Division, Lawrence Livermore National Laboratory,
PO Box 808, L-396, Livermore, California 94551, USA
e-mail: keating2@llnl.gov

Abstract Dermal exposure to drinking water containing chemical contaminants may result in chemical uptake from the water into skin. Models to estimate dermal absorption of water contaminants utilize Fick's laws of diffusion to describe the uptake process. Relatively few measurements of dermal uptake of organic chemicals from water *in vivo* are available to compare with the predictions of these models. An analysis of published *in vivo* dermal uptake studies, and data from an *in vitro* study measuring short-term (<1 h) dermal absorption of trichloroethylene, indicate that the models underpredict the dermal uptake of volatile organic chemicals from water.

INTRODUCTION

Dermal exposure to drinking water containing chemical contaminants may result in chemical uptake from the water into skin. Fick's (first) law of diffusion, $J_{ss} = K_p \Delta C_w$, relates the steady-state flux J_{ss} (in $\text{mg cm}^{-2} \text{h}^{-1}$) of chemical mass from water through the skin to the difference, ΔC_w (in g l^{-1}), in chemical concentration at the membrane's water-exposed surface and opposite (internal) surface. The constant of proportionality involved, K_p (in cm h^{-1}), is the chemical-specific permeability coefficient. If the steady-state conditions assumed in Fick's law actually pertained to a dermal surface area equal to $A \text{ cm}^2$ exposed for $t \text{ h}$ to a chemical in water at concentration C_w , then the total absorbed chemical mass per unit exposed surface area (or DA_{event} , in mg cm^{-2}) would be $K_p C_w t$, and the corresponding dermal exposure (in l_{eq}) could easily be calculated as:

$$E_d [\text{in } \text{l}_{eq}] = [10^{-3} \text{ l}_{eq} \text{ cm}^{-2}] K_p A t \quad (1)$$

where one "ingestive-equivalent" litre (l_{eq}) of dermal exposure (E_d) to a chemical in water is defined here as aqueous exposure resulting in uptake of all the chemical contained in one litre (l) of that water (i.e. an E_d value of 1 l_{eq} is equivalent to ingesting 1 l of the water, assuming 100% gastrointestinal absorption).

Most data on percutaneous absorption of organic chemicals from water have been obtained from experimental *in vitro* diffusion cell measurements (Flynn, 1990; EPA, 1992). In these experiments, dermal tissue is exposed to a neat or dissolved chemical, either by direct application or by passive diffusion from a donor solution. Measurements are then made, at specific time points, of the amount of chemical in a receptor fluid on the opposite side of the tested tissue. The receptor fluid volume is either static or flows past the tested tissue to facilitate mixing. The time points examined generally include a period during which a steady-state or equilibrium

concentration has been achieved within the tested tissue. This allows estimation of steady-state K_p as the slope of those among the measured receptor-fluid concentration points that increase linearly as a function of exposure time. Such measurements thus reflect the quantity of test chemical that diffuses through exposed dermal tissue at steady state.

Several statistical algorithms have been found to predict dermal K_p values reasonably well (Kasting *et al.*, 1987; Guy & Hadgraft, 1989; Flynn, 1990; Potts & Guy, 1992; McKone & Howd, 1992; EPA, 1992). Based on statistical analyses of data on organics in aqueous solution, Potts & Guy (1992) obtained the formula:

$$\log_{10}K_p = -6.3 - 0.0061MW + 0.71 \log_{10}K_{ow} \quad (2)$$

using molecular weight ($MW \times \text{mol g}^{-1}$, unitless) and octanol/water partition coefficient (K_{ow} , unitless) to predict *in vitro* steady-state K_p values. Unfortunately, for many common organic water pollutants, more than a few minutes are required after initial contact with skin for these steady-state conditions to hold, even approximately (EPA, 1992). During this non-steady-state period, mass transfer of chemical into skin reflects not only the mass absorbed through the skin, but also the mass required initially to "load" the skin, in order to reach that steady-state concentration. Therefore, equation (1) is expected to underestimate E_d for typically brief dermal exposures, such as from showering or bathing.

Recent efforts have sought to improve estimation of dermal exposure by addressing the non-steady-state phase of skin absorption. In particular, a model recently proposed by EPA (1992) and Cleek & Bunge (1993) is the first to specifically predict non-steady-state dermal uptake based on *in vitro* steady-state K_p values. Based on theoretical considerations concerning non-equilibrium mass transport through membranes, the EPA-Cleek-Bunge (EPACB) model states that if exposure time t (h) is less than kt , then total dermal uptake from water of an organic chemical at concentration C_w (mg l^{-1}) during exposure time t is approximately:

$$DA_{event} [\text{in mg cm}^{-2}] = 2K_p C_w [10^{-3} \text{ l cm}^{-3}] \sqrt{\frac{6\tau t}{\pi}} \quad (3)$$

where:

$$\tau \approx \frac{K_{ow}^{0.71} [\text{cm}]}{6000K_p} \quad (4)$$

and where K_p is defined in equation (3) and (4) as a value estimated using equation (2). Equations (3)–(4) imply a nonlinear relation between the time dependent, non-steady-state K_p , K_{p-us} , and K_p as a function of exposure time t :

$$K_{p-us} \approx K_p \left(10^{0.00305MW} \sqrt{\frac{2(\text{h})}{3t}} \right) \quad \text{if } t < kt \quad (5)$$

where (as in equation 2) MW is molecular weight ($\times \text{mol g}^{-1}$, unitless), and where, as in equations (3) and (4), K_p is estimated using equation (2). Dermal exposures predicted with equation (3) are expected to be greater than those predicted with equation (1) because it accounts for both chemical absorbed *into* the skin membrane as well as that which has diffused *through* the skin (Cleek & Bunge, 1993). There is virtually no dermal absorption

absorption data with which to validate the EPACB model so its applicability to drinking water risk assessment has yet to be determined.

Relatively few measurements of dermal uptake of organic chemicals from water *in vivo* are available to compare with the predictions of these two models. There are also insufficient short-term *in vitro* dermal uptake data with which to evaluate the two models. A recent analysis of published *in vivo* dermal uptake studies (Bogen, 1994) and data from an *in vitro* study measuring short-term (<1 h) dermal absorption of trichloroethylene (Bogen *et al.*, 1998) indicate that both models underpredict the dermal uptake of volatile organic chemicals from water.

METHODS

Analysis of *in vivo* K_p

Studies in which dermal absorption from water was measured *in vivo* were obtained from the literature. Table 1 lists the nine chemicals for which *in vivo* based K_p (K_{p-iv}) estimates were published or could be calculated from information provided in the study. The reader is referred to Bogen (1994) for the details of the studies and the calculation of K_{p-iv} . For the first comparison with K_{p-iv} values, crude *in-vitro*-based K_p estimates were taken to be the corresponding predicted, steady-state K_p values obtained using equation (2). For the second comparison, predicted K_{p-ns} values were obtained using the EPACB model given by equation (5), assuming $t = 0.2$ h. In addition, a third comparison was made between K_{p-iv} values and corresponding values predicted using a new multiple linear regression (MLR) model with the same independent variates (MW and K_{ow}) as the Potts-Guy MLR model, but fitted specifically to the nine K_{p-iv} values. For each of the three comparisons, predicted K_p or K_{p-ns} and the three data sets were fitted by linear regression. A complete discussion of the statistical comparison of the model predictions is provided in Bogen (1994).

Table 1 Summary of studies on *in vivo* dermal uptake of nine organic chemicals.

Chemical	MW	$\log_{10} K_{ow}$ (g mol^{-1})	K_{p-iv} (cm h^{-1})	E_d (l_{eq})	<i>In vivo</i> study
Aniline	93.1	0.90	0.061	0.22	Baranowska-Dutkiewicz (1982)
Butoxyethanol, 2-	118.0	0.83	0.012	0.11	Johanson & Fernstrom (1988)
Carbon disulphide	80.0	2.24	0.54	2.2	Baranowska-Dutkiewicz (1968,1982)
Chloroform	119.4	1.97	0.16	0.64	Jo <i>et al.</i> (1990a,b)
			0.13	0.47	Bogen <i>et al.</i> (1992)
Ethylbenzene	106.2	3.15	1.2	4.3	Dutkiewicz & Tyras (1967)
Styrene	104.1	2.95	0.67	2.2	Dutkiewicz & Tyras (1968)
Tetrachloroethylene	165.8	3.4	0.37	1.3	Bogen <i>et al.</i> (1992)
Toluene	92.1	2.73	1.0	3.6	Dutkiewicz & Tyras (1968)
Trichloroethylene	131.4	2.42	0.23	0.83	Bogen <i>et al.</i> (1992)

MW = molecular weight, K_{ow} = octanol water partition coefficient, K_{p-iv} = *in vivo* steady-state dermal permeability (for fixed A , C_w and E_d ; see Introduction), E_d = corresponding dermal exposure in units of l_{eq} , the equivalent ingested water volume (in litres) containing the specified compound.

MW and K_{ow} values were obtained from EPA (1992).

Reprinted with permission, *J. Exposure Assess. Environ. Epidemiol.*

Measurement of non-steady state K_p

Experimental design A detailed description of the *in vitro* dermal exposure experiments is presented in Bogen *et al.* (1998) with an abbreviated description provided here. Non-steady-state dermal absorption experiments were conducted with full-thickness human breast skin obtained from surgery. Tissue was exposed to an aqueous exposure solution (1,2- ^{14}C -trichloroethylene, $5.3 \mu\text{g l}^{-1} \pm 34\%$) at room temperature ($20.0 \pm 3.0^\circ\text{C}$) in a low-volume flow-through glass diffusion cell (LVDC) (RCR Inc., Novato, California) not operated under flow-through conditions. Tissue samples were each exposed for 1, 5, 15, 30 or 60 min, except the 5 min experiment was replicated three times for two of these samples.

Control experiments measuring ^{14}C in unexposed samples were done using tissue in a LVDC that contained only distilled water.

Sample analysis After each exposure was completed, exposed tissue was removed from the LFDC, blotted dry, and 3–5 tissue cores were taken by punch and placed into separate, glass sample tubes containing reactants used for analysis by accelerator mass spectrometry (AMS), described elsewhere (Vogel & Turteltaub, 1991; Vogel, 1992; Bogen *et al.*, 1996).

Tissue samples were oxidized and reduced to graphite for determination of ^{14}C concentration by AMS (Bogen *et al.*, 1998).

Dermal uptake models AMS results were expressed as normalized time-integrated clearance, $R(t)$ (cm), i.e. the equivalent vehicle volume (cm^3) cleared of chemical by time t (h) per cm^2 of exposed surface area. (Below, $R(t)$ is referred to simply as “integrated clearance”.) Measured uptake was compared to corresponding $R(t)$ predictions based on three different models.

Model 1 is the recommended approximate form of the EPACB model, equations (3) and (4), described above. Three different forms of Model 1 were analysed. Model 1A denotes Model 1 conditional on the best TCE-specific estimates for the model parameters specified by equation (2). Confidence bounds on Model 1A were obtained by Monte-Carlo simulation of equation (2) parameter errors. Model 1B, examined for comparative purposes, denotes Model 1 conditional on $t \leq t^*$ (i.e. assuming $R(t) \propto \sqrt{t}$). Model 1C denotes Model 1 optimized to the AMS data without reference to the parameter errors indicated in equation (2).

Model 2 is a compartmental model adapted from pharmacokinetic models that have considered dermal uptake (McDougal *et al.*, 1986; Shatkin & Brown, 1991; Chinery & Gleason, 1993) and is presented in greater detail in Bogen *et al.* (1998). In Model 2, the skin is treated as a single, well mixed compartment. Uptake and loss from this compartment *in vivo* are assumed to be first-order processes driven by concentration differences between water, skin-surface tissue (in equilibrium with exiting venous blood), and adjacent arterial blood.

Finally, the linear model $R(t) = R_0 + K_0 t$ (Model 3) was used to determine if measured uptakes were actually nonlinear and/or significantly correlated with time.

RESULTS

Analysis of *in vivo* K_p

Figure 1 compares K_{p-iv} values for the nine chemicals listed in Table 1 (indicated on the horizontal axis), with corresponding K_p , K_{p-ns} and K_{p-iv} estimates (indicated on the vertical axis), as described in Methods. For the third comparison shown (as solid points) in Fig. 1, estimated values were predicted using the new MLR model:

$$\log_{10}K_{p-iv} = -0.812 - 0.0104MW + 0.616\log_{10}K_{ow} \quad (6)$$

fitted directly to logs of K_{p-iv} estimates for the nine chemicals listed in Table 1 ($R^2 = 0.98$, $p = 3 \times 10^{-6}$). Notably, all nine of the K_{p-iv} estimates are underpredicted by the corresponding *in vitro*-based estimates. The former are underpredicted by an average factor of 20 (± 6) using K_p estimates from the steady-state model (equation 2), and by an average factor of 5 (± 2) using K_{p-ns} estimates based on the EPACB model (equations (3)–(4)). Analysis of the data sets associated with the two uppermost fits in Fig. 1(a) indicates that K_{p-ns} estimates are significantly lower than those based directly on *in vivo* data, as indicated by the highly significantly (4.1-fold) smaller intercept corresponding to K_{p-ns} estimates based on the EPACB model ($F_{1,14} = 50.7$, $p = 4 \times 10^{-6}$).

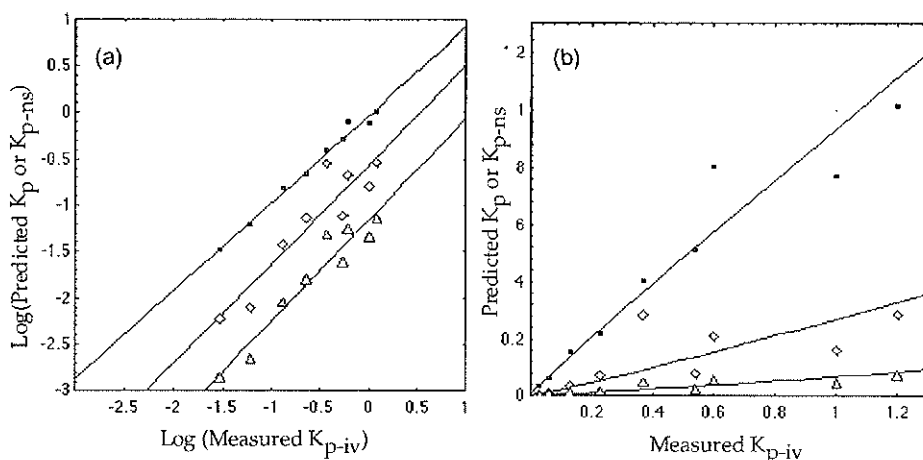


Fig. 1 Values of K_{p-iv} (horizontal axis), obtained for nine different chemicals based on *in vivo* uptake studies (Table 1) are compared to corresponding values (on the vertical axis) of: (1) *in vitro* measures of steady-state K_p (open triangles), (2) K_{p-ns} estimates implied by the model of non-steady-state permeability proposed by EPA (1992) and Cleek & Bunge (1993) (K_{p-ns} , open circles), and (3) K_{p-ns} estimates based on a model fit to the *in vivo* data (solid points). Plots are shown for (a) \log_{10} -transformed and (b) untransformed data. Estimated K_p values for data set 1 were obtained using the model of Potts & Guy (1992). Estimated K_{p-ns} values for data set 2 were obtained using the non-steady-state model for dermal uptake recently proposed by EPA (1992) and Cleek & Bunge (1993). $\log_{10} K_{p-ns}$ values for data set 3 were estimated as a linear function of MW and K_{ow} (the octanol/water partition coefficient) fit directly to logs of the 9 *in vivo* K_{p-iv} measures ($R^2 = 0.98$, $p = 3 \times 10^{-6}$). Curves shown through data sets 1–3 are least-squares linear fits to the log-transformed data. Reprinted with permission, *J. Exposure Assess. Environ. Epidemiol.*

Measurement of non-steady-state K_p

The ^{14}C measures obtained for tissue plugs obtained from the six exposure periods revealed significant ($p^* \leq 0.01$) heterogeneity among 5 min exposure data pertaining to three different individuals, which had corresponding mean $R(t)$ values equal to 92%, 60% and 140% of the 5 min grand mean ($0.022 \text{ cm} \pm 47\%$), and corresponding CVs all $< 30\%$. (The maximum 1 min and 5 min $R(t)$ measures obtained were 0.013 and 0.046 cm, respectively.) Inter-individual differences at all other time points were non-significant ($p^* > 0.05$), so models were fit to pooled data from all subjects.

Figure 2(a) compares the AMS data to predictions made by Model 1A (the EPACB model using its recommended parameter estimates), and by the upper and lower 99% and 99.99% confidence limits on Model 1A (which reflect the parameter uncertainties indicated in equation (2)). Figure 2(a) also compares the AMS data to the fit obtained for Model 1B (the uptake-proportional-to- \sqrt{t} model obtained by conditioning Model 1A on $t < t^*$). Note that the estimated 99.99% upper confidence limit on Model 1A nearly coincides with the simpler Model 1B fit to the AMS data (Fig. 2(a)). Model 1A is clearly statistically inconsistent with the AMS data ($c^2 > 275.8$, $df = 104$, $p \approx 0$), as is true for its plausible upper confidence limits ($c^2 > 267.0$, $df = 101$, $p \approx 0$; see Fig. 2(a)). The inconsistency here cannot plausibly be explained by statistical uncertainties arising from EPACB reliance on parameter relationships estimated (in equation 2) from physicochemical data on 93 organic chemicals. Unconditional on parametric assumptions reflected in equation (2), the

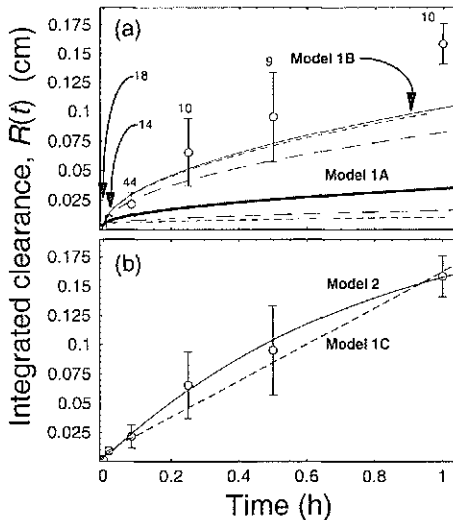


Fig. 2 Uptake of dilute (~5 ppb) aqueous ^{14}C -radiolabelled trichloroethylene into full-thickness human skin, plotted as measured integrated clearance $R(t)$ (cm) vs predictions based on Models 1–2 described in Methods. Data points shown are means ± 1 SD of n_j measures made at each exposure duration. (a) Fits obtained using Models 1A (bold curve) and 1B (light curve) are plotted, along with the values n_j and the 2-tailed 99% (long-dashed) and 99.99% (short-dashed) confidence bounds on Model 1A. (b) Model 1C (dashed curve) and Model 2 (solid curve) are shown fit to the same data as shown in (a). Reprinted with permission, *J. Exposure Assess. Environ. Epidemiol.*

structure of the EPACB model is certainly flexible enough to predict an uptake pattern consistent with AMS data we obtained for TCE, as shown by the good fit obtained for Model 1C (Fig. 2(b)). The AMS data are consistent with the one-compartment model (Model 2) examined ($c^2 = 115.8$, $df = 102$, $p = 0.17$). In particular, integrated clearance, $R(t)$, due to dermal TCE uptake was found to have an initial slope (± 1 CV) of $K_{p-ns} = 0.28 \text{ cm h}^{-1}$ ($\pm 7.0\%$).

DISCUSSION

Estimates of shower-related dermal exposure (E_d) reported in, or based upon, studies listed in Table 1 range from ~ 0.1 to 4 l_{eq} , for nine organic chemicals spanning roughly a 100-fold range in lipophilicity and a two-fold range in molecular weight. These exposure estimates are useful because they are largely based on human data, and most involve organic solvents found as chemical water pollutants. Reliability of the permeability measures obtained in these studies is supported by the consistency of measures obtained in the particular case of chloroform, which was studied by different investigators using very different methods involving both humans and experimental animals. There is also a general consistency across all these studies insofar as higher *in vivo* permeabilities were measured for the more lipophilic compounds, as might be expected from the strong, positive dependence on K_{ow} exhibited in the Potts-Guy model (equation 2), pertaining to steady-state *in vitro* permeabilities.

It is clear from the results obtained in this study that the EPACB model consistently underpredicts the K_{p-iv} estimates based on *in vivo* data for all nine chemicals listed in Table 1. As expected, for the reasons discussed in relation to equation (5) (see Introduction), this was quite evident for the steady-state K_p estimates obtained directly from the Potts-Guy model. However, short-term, non-steady-state uptakes predicted for these chemicals by the EPACB model also clearly and substantially fell short of the K_{p-iv} estimates based directly on *in vivo* data. The consistency of this discrepancy points out the likelihood that this model, although clearly better than simple application of steady-state *in vitro* K_p values assuming Fick's law, may systematically underestimate short-term human dermal uptake of organic chemicals from water. To address this problem for exposure assessments considering the dermal route during showering or bathing, K_{p-iv} estimates obtained for organic chemicals not listed in Table 1 using the EPACB model should be increased, e.g. 5-fold. Alternatively, equation (6) might be used directly for this purpose until new non-steady-state uptake data provide the basis for a superior model. Although the number of chemicals upon which this new model is based is relatively small, the fit of this model to the limited data set is rather good, and most of these chemicals are (or are similar to) ones commonly found as contaminants in US water supplies (EPA, 1992).

The AMS data obtained indicate short-term uptakes that correlate positively but nonlinearly with exposure time, but which are statistically inconsistent ($p \approx 0$) with the EPACB model represented here by Model 1A and its confidence bounds generated by considering uncertainty associated with equation (2). While a generalized EPACB-type model structure without *a priori* parameter constraints (i.e. Model 1C) allows a good fit to the data ($p = 0.37$), it does so only with parameter values for TCE that are not plausibly related to those recommended for EPACB model application to TCE (EPA,

1992; Cleek & Bunge, 1993; Bunge & Cleek, 1995). It is possible that Model 1C parameter estimates, although incompatible with equation (2), may nevertheless be physically meaningful for TCE. Alternatively, the AMS data are also consistent ($p = 0.17$) with the one-compartment pharmacokinetic model examined (Model 2). The Model 2 fit obtained indicates that TCE uptake (as integrated clearance) over the course of 1 h has an initial rate of $K_{p-n\text{s}} = 0.28 \text{ cm h}^{-1}$ ($\pm 7.0\%$). This $K_{p-n\text{s}}$ estimate is slightly greater than that of 0.20 cm h^{-1} ($\pm 11\%$) obtained in AMS experiments conducted using similarly exposed human cadaver skin (Bogen *et al.*, 1996). Note that in Bogen *et al.* (1996), dermal uptakes of aqueous TCE and chloroform were reported for exposures at concentrations of 5.0 (± 0.20) ppb, but the concentrations used were in fact 3.0 (± 0.04) ppb for TCE and 5.0 (± 0.20) ppb for chloroform, so TCE-related uptake data and parameter estimates derived from this study are 67% greater than those reported.

In vivo data from other studies support the parameter estimates we obtained for TCE using Model 2. An effective K_p estimate of 0.23 ($\pm 17\%$) cm h^{-1} was obtained in a study in which immersed, sedated hairless guinea pigs were exposed to dilute aqueous ^{14}C -TCE at 32°C for 70 min (Bogen *et al.*, 1992). The latter estimate does not differ significantly (by *t*-test, $p > 0.05$) from the estimate of $K_{p-n\text{s}}$ obtained in this study.

Notably, in those experiments, and in similar ones using ^{14}C -labelled tetrachloroethylene or chloroform, radiolabel declined in each exposure solution as an approximately linear function of exposure time (Bogen *et al.*, 1992), as predicted by Model 2. During controlled dermal exposures to neat chlorinated volatile solvents, such solvents were detected in human alveolar air and blood within 5–30 min after initial dermal contact, implying fairly rapid transfer through epidermis into blood (Stewart & Dodd, 1964; Sato & Nakajima, 1978). In experiments involving volunteers showering with and without full rubber wet suits in water containing $10\text{--}40 \mu\text{g l}^{-1}$ chloroform, increased alveolar-breath concentrations of chloroform in dermally vs non-dermally exposed subjects were detected 5 min after shower completion, again implying a quite rapid transit time through epidermis into blood (Jo *et al.*, 1990a,b; Chinery & Gleason, 1993; McKone, 1993). In similar experiments involving subjects bathing in water containing $40\text{--}100 \mu\text{g l}^{-1}$ chloroform while breathing pure air through a face mask, increased alveolar-breath concentrations of chloroform were detected within 5 min of immersing the subjects in water (Gordon *et al.*, 1998). Finally, the results of the present *in vitro* study of TCE uptake are consistent with *in vivo* data on TCE that were considered (along with *in vivo* data on eight other volatile organic compounds) by Bogen (1994) to indicate that the EPACB model mischaracterizes and underestimates human dermal exposures to organic water contaminants like TCE.

SUMMARY

Models proposed for estimating the short-term, non-steady-state uptake of water contaminants were found to underpredict measured uptake. The consistency of this discrepancy points out the likelihood that the models may systematically underestimate short-term human dermal uptake of organic chemicals from water. To address this problem for exposure assessments of drinking water contaminants considering the

dermal route, K_{p-ns} estimates obtained for organic chemicals using the EPACB model should be increased, e.g. 5-fold, or estimated directly with equation (6). Our experimental findings and that of others show that dermal absorption of certain water contaminants is considerable and that further investigation of this exposure route is warranted.

Acknowledgements This work was performed under the auspices of the US Department of Energy at Lawrence Livermore National Laboratory under Contract W-7405-ENG-48 and the US Environmental Protection Agency, Interagency Agreement #DW89937390-01-0.

REFERENCES

- Baranowska-Dutkiewicz, B. (1968) Investigations on the absorption of carbon disulphide through the human skin. II Absorption of liquid CS_2 and its aqueous solutions (in Polish). *Zes. Nauk. Bromat. Chem. Tsykol.* **1**, 59
- Baranowska-Dutkiewicz, B. (1982) Skin absorption of analine from aqueous solutions in man. *Toxicol. Lett.* **10**, 367–372.
- Bogen, K. T. (1994) Models based on steady-state *in vitro* permeability data underestimate short-term dermal exposures *in vivo*. *J. Exposure Assess. Environ. Epidemiol.* **4**, 457–476.
- Bogen, K. T., Colston, B. W. & Machicao, L. K. (1992) Dermal absorption of dilute aqueous chloroform, trichloroethylene, and tetrachloroethylene in hairless guinea pigs. *Fund. Appl. Toxicol.* **18**, 30–39.
- Bogen, K. T., Keating, G. A. & Vogel, J. S. (1996) Chloroform and trichloroethylene uptake from water into human skin *in vitro*: kinetics and risk assessment. In: *Prediction of Percutaneous Penetration* (ed. by K. R. Brain, V. J. James & K. A. Walters), vol. 4b, 195–198. STS Publishing Ltd., Cardiff, UK.
- Bogen, K. T., Keating, G. A., Meissner, S. & Vogel, J. S. (1998) Initial uptake kinetics in human skin exposed to dilute aqueous trichloroethylene *in vitro*. *J. Exposure Assess. Environ. Epidemiol.* **8**, 253–271.
- Bunge, A. L. & Cleck, R. L. (1995) A new method for estimating dermal absorption from chemical exposure. 2. Effect of molecular weight and octanol-water partitioning. *Pharmaceutical Res.* **12**, 88–95.
- Chinery, R. L. & Gleason, A. K. (1993) A compartmental model for the prediction of breath concentration and absorbed dose of chloroform after exposure while showering. *Risk Analysis* **13**, 51–62.
- Cleck, R. L. & Bunge, A. L. (1993) A new method for estimating dermal absorption from chemical exposure. 1. General approach. *Pharmaceutical Res.* **10**, 497–506.
- Dutkiewicz, T. & Tyras, H. (1967) A study of the skin absorption of ethylbenzene in man. *Br. J. Ind. Med.* **24**, 330–332.
- Dutkiewicz, T. & Tyras, H. (1968) Skin absorption of toluene, styrene, and xylene by man. *Br. J. Ind. Med.* **25**, 243.
- EPA (US Environmental Protection Agency) (1992) *Dermal Exposure Assessment: Principles and Applications*. EPA/600/8-91/011B. US EPA Office of Environmental Assessment, Washington, DC, USA.
- Flynn, G. L. (1990) Physicochemical determinants of skin absorption. In: *Principals of Route-to-Route Extrapolation for Risk Assessment* (ed. by T. R. Gerrity & C. J. Henry), 93–127. Elsevier, New York.
- Gordon, S. M., Wallace, L. A., Callahan, P. J., Kenny, D. V. & Brinkman, M. C. (1998) Effect of water temperature on dermal exposure to chloroform. *Environ. Health Perspect.* **106**, 337–345.
- Guy, R. H. & Hadgraft, J. (1989) Mathematical models of percutaneous absorption. In: *Percutaneous Absorption* (ed. by R. L. Bronaugh & H. Maibach), 13–26. Marcel Dekker, New York.
- Jo, W. K., Weisel, C. P. & Lioy, P. J. (1990a) Routes of chloroform exposure and body burden from showering with chlorinated tap water. *Risk Analysis* **10**, 575–580.
- Jo, W. K., Weisel, C. P. & Lioy, P. J. (1990b) Chloroform exposure and the health risk associated with multiple uses of chlorinated tap water. *Risk Analysis* **10**, 581–585.
- Johanson, G. & Fernstrom, P. (1988) Influence of water on the percutaneous absorption of 2-butoxyethanol in guinea pigs. *Scand. J. Work Environ. Health* **14**, 95–100.
- Kasting, G. B., Smith, R. L. & Cooper, E. R. (1987) Effect of lipid solubility and molecular size on percutaneous absorption. *Pharmacol. Skin* **1**, 138–153.
- McDougal, J. N., Jepson, G. W., Clewcll III, H. J., MacNaughton, M. G. & Andersen, M. E. (1986) A physiological pharmacokinetic model for dermal absorption of vapors in the rat. *Toxicol. Appl. Pharmacol.* **85**, 286–294.
- McKone, T. E. (1993) Linking a PBPK model for chloroform with measured breath concentrations in showers: implications for dermal exposure models. *J. Exposure Anal. Environ. Epidemiol.* **3**, 339–365.
- McKone, T. E. & Howd, R. A. (1992) Estimating dermal uptake of nonionic organic chemicals from water and soil. Part 1, Unified fugacity-based models for risk assessments. *Risk Analysis* **12**, 543–557.
- Potts, R. O. & Guy, R. H. (1992) Predicting skin permeability. *Pharmaceutical Res.* **9**, 663–669.

- Sato, A. & Nakajima, T. (1978) Differences following skin or inhalation exposure in the absorption and excretion kinetics of trichloroethylene and toluene. *Br. J. Ind. Med.* **35**, 43-49.
- Shatkin, J. & Brown, H. S. (1991) Pharmacokinetics of the dermal route of exposure to volatile organic chemicals in water: a computer simulation model. *Environ. Res.* **56**, 90-108.
- Stewart, R. D. & Dodd, H. C. (1964) Absorption of carbon tetrachloride, trichloroethylene, tetrachloroethylene, methylene chloride, and 1,1,1-trichloroethane through human skin. *Ind. Hyg. J.* **September-October 1964**, 439-446.
- Vogel, J. S. (1992) Rapid production of graphite without contamination for biomedical AMS. *Radiocarbon* **34**, 344-350.
- Vogel, J. S. & Turteltaub, K. W. (1991) Biomolecular tracing through accelerator mass spectrometry. *Trac-Trends Anal. Chem.* **11**, 142-149.