A Quantitative Method for Estimating Dermal Benzene Absorption from Benzene-containing Hydrocarbon Liquids

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This study examines a method for estimating the dermal absorption of benzene contained in hydrocarbon liquids that contact the skin. This method applies to crude oil, gasoline, organic solvents, penetrants, and oils. The flux of benzene through occluded skin as a function of the percent vol/vol benzene in the liquid is derived by fitting a curve to experimental data; the function is supralinear at benzene concentrations ≤ 5% vol/vol. When a liquid other than pure benzene is on nonoccluded skin, benzene may preferentially evaporate from the liquid, which thereby decreases the benzene flux. We present a time-averaging method here for estimating the reduced dermal flux during evaporation. Example calculations are presented for benzene at 2% vol/vol in gasoline, and for benzene at 0.1% vol/vol in a less volatile liquid. We also discuss other factors affecting dermal absorption. *Key words*: benzene; dermal; exposure; modeling; quantification; flux; gasoline; mineral spirits; crude oil

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INTRODUCTION

Benzene, a human carcinogen, has long been recognized as a component of crude oil, gasoline, petroleum-derived solvents (e.g., hexane, heptane, toluene, xylene, naphtha, mineral spirits), and other chemical products (e.g., penetrants and degreasers). Benzene is dermally absorbed when pure benzene or a benzene-containing liquid is in contact with the skin. The benzene mass absorbed depends on 1) the benzene concentration in the hydrocarbon liquid; 2) the composition of the liquid; 3) the condition and body location/area of the skin; and 4) the duration of exposure.[1] Although inhalation of benzene vapor has traditionally received the most attention, more consideration is now being given to dermal exposures to benzene,[2,3] and to chemical contaminants, in general.[4,5]

For example, Sahmel, Boeniger, and Fehrenbacher[5] estimated benzene dermal absorption for automotive repair workers who used gasoline containing 2% benzene. They calculated that approximately 92% of the total daily benzene absorbed dose was due to dermal exposure. In making this estimate, they assumed that 1% of the benzene in the volume of gasoline contacting the skin was absorbed. The 1% value was based, in part, on the observations that 0.13% of pure benzene placed in a nonoccluded manner on human palmar skin is absorbed; damaged primate skin permits five-fold more benzene absorption *in vivo* than does non-damaged skin; and workers with frequent hand contact with solvents have damaged skin.

In the previous example, the mechanics' skin was nonoccluded, that is, open to the air. When benzene contacts nonoccluded skin, benzene evaporation limits the time over which the benzene can permeate into the skin. However, OSHA noted that where benzene is kept against the skin due to wetted clothing or gloves, benzene would not evaporate as quickly as it does on nonoccluded skin.[6] Due to the longer contact time in the occluded case, the percent of benzene absorbed could be substantially greater than the 1% it was for the nonoccluded case.

The benzene content in the portion of gasoline and other hydrocarbon fuels that permeate through nitrile and neoprene gloves was found to be enhanced above the content in the original bulk fuel.[7] Using seven glove types (latex, nitrile, vinyl, nitrile-Sol-Vex, neoprene, Viton, and SRM), the authors found that gasoline had breakthrough times of 2.1, 0.9, 208.1, 22.4 and 4.9 minutes for nitrile, vinyl, nitrile-Sol-Vex, neoprene, and SRM, respectively. Latex glove breakthrough data for gasoline was not determined, but it was rated the poor-

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est of the seven materials based on results for three other fuels. Thus, except for the nitrile-Sol-Vex material, the gloves provided less than five minutes' protection from gasoline. Perhaps more importantly, when the gasoline broke through, the amount of benzene in the gasoline was found to be enhanced by factors of ~2 and ~2.5 for neoprene and nitrile glove types, respectively.

The objective of this paper is to provide a scientifically sound method for estimating the dermal absorption of benzene due to skin contact with benzene-containing liquids. The focus is on the relationship between the benzene concentration in the liquid and the rate of benzene permeation, while accounting for benzene absorption as the benzene concentration in the liquid on the skin decreases due to preferential evaporation.

DERMAL EXPOSURE MODEL FOR BENZENE IN LIQUID

Dermal Dose from a Benzene-containing Liquid during Exposure without Benzene Loss

In some scenarios, a benzene-containing liquid continually contacts the skin during the exposure event, and benzene evaporation from the liquid (and absorption through the skin) negligibly changes the benzene concentration in the liquid on the skin. For example, a worker might submerge a hand in a container of the liquid or hold a rag wet with the liquid against the palmar surface. In this case, the dermally absorbed dose for the exposure event, DA_{noevap} (mg), can be estimated by the following equation[8]:

$$\text{Eq. 1: } DA_{noevap} = K_p \times C_B \times SA \times FA_{abs} \times ET$$

where K_p is the permeation coefficient (cm/hr) of benzene through skin referenced to a specific skin site and a specific liquid, C_B, is the benzene concentration (mg/ cm^3) in the liquid, SA (cm^2) is the surface area of the wetted skin, FA_{abs} is a skin site absorption factor (no units), and ET (hr) is the duration of the exposure event.

FA_{abs} = 1 is used for most skin areas, but this factor can be greater or lesser than 1 for specific skin areas of interest. For example, data suggest that benzene can be absorbed at a greater rate on the palm than on the forearm.[9] The total benzene mass absorbed over a series of such exposure events is the sum of the DA_{noevap} values for the respective individual events, although primate data indicate that successive episodic benzene exposures lead to increased absorption in the later exposures.[10] Note that the parameter "flux" is the mass absorbed per unit skin surface area per unit time (typically, mg/cm^2-hr), and equals the product of K_p and $C_{B:}$

$$\text{Eq. 2: } Flux = K_p \times C_B$$

Dermal Dose from a Benzene-containing Liquid during Exposure with Benzene Loss

In some scenarios, a benzene-containing liquid continually contacts the skin during the exposure event, but benzene evaporation from the liquid substantially changes the concentration of benzene in the liquid. For example, liquid may splash directly onto the worker's nonoccluded skin, or, following immersion of the hands in liquid containing a constant C_B value, the skin may remain wet before the worker dries off the skin or before the liquid evaporates completely. If the benzene evaporates at a faster rate than the major component(s) of the liquid, C_B decreases during the exposure event. Although benzene continues to be absorbed from the liquid, the flux decreases because C_B decreases, as shown by equation 2.

Where benzene evaporates from the liquid during an exposure event of duration ET (hr), the time-weighted-average (TWA) benzene concentration $C_{B,TWA}$ in the liquid is given by:

$$\text{Eq. 3: } C_{B,TWA} = \frac{1}{ET} \int_0^{ET} C_B(t)\,dt$$

where $C_B(t)$ is the benzene concentration in liquid as a function of time. In turn, the $C_{B,TWA}$ value permits approximating the benzene dose absorbed during the exposure event by the expression:

$$\text{Eq. 4: } DA_{evap} \cong K_p \times C_{B,TWA} \times SA \times FA_{abs} \times ET$$

The product $K_p \times C_{B,TWA}$ estimates the time-averaged flux, $Flux_{TWA}$. As will be explained, the more exact method of computing $Flux_{TWA}$ involves integrating a nonlinear function for benzene flux over the exposure interval ET. Finally, if an exposure period involving continuous contact with a liquid with a constant C_B value (for example, skin contact with fresh liquid) is immediately followed by an exposure period involving continuous contact with liquid containing a decreasing C_B value (for example, wetted clothing held against the skin), the total benzene dose absorbed is the sum of DA_{noevap} and DA_{evap}.

BENZENE IN GASOLINE

We discuss skin contact with gasoline because it was (and likely continues to be) a frequent event in some occupations, and because data are available to permit estimating the $C_B(t)$ function in gasoline. The time course of gasoline evaporation in a 13.9-cm petrie dish at 20 to 22 °C was experimentally measured by Fingas.[11] Hereafter, it was assumed that the temperature was 21 °C. The percent of the initial gasoline volume remaining with time is shown by the open circles in Figure 1.

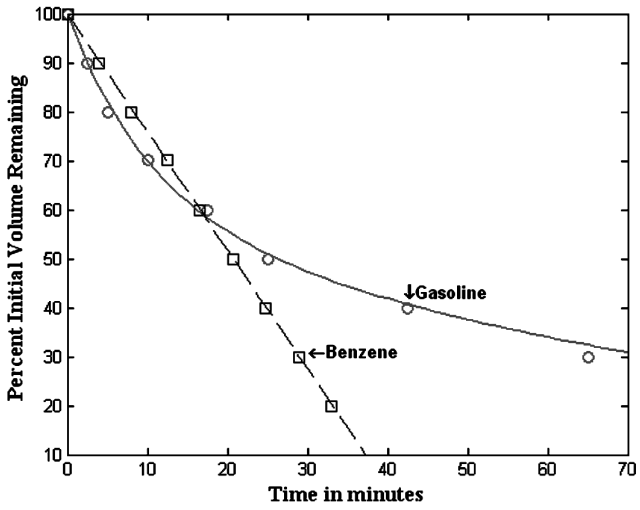

Figure 1—Evaporation data for gasoline at 20 to 22 °C and benzene at 24 °C; the solid-line curve corresponds to equation 5.

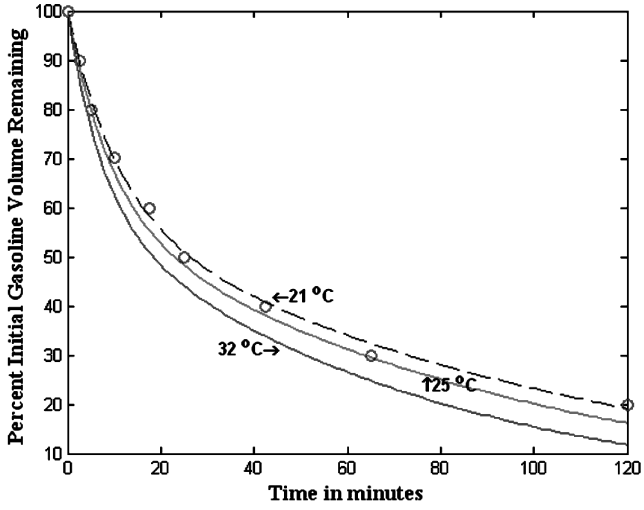

Figure 2—The evaporation of gasoline at 21 °C, at 25 °C and at 32 °C; the open circles are the values reported by Fingas, and the dashed-line curve corresponds to equation 5.

For comparison, evaporation data for pure benzene at 24 °C are also shown in Figure 1 by the open squares; the benzene data were generated by placing the liquid in a 6.5-cm pan with filter paper on the bottom surface.[12] Although there is a difference of several °C between the two evaporation time series and a difference in the experimental methods, the rate of loss of the initial 40% to 50% of the liquid volume is similar for gasoline and benzene. As will be described in more detail, Runion[13] reported that the percent vol/vol benzene content of gasoline remained fairly constant over the evaporation of the initial 40% to 50% of the gasoline volume, and thereafter decreased in an approximate linear fashion toward zero. The evaporation time series in Figure 1 are consistent with Runion's findings.

The Figure 1 gasoline data are well described as a double exponential (biphasic) process with an early first-order rate constant $\alpha_1 = 0.095\ min^{-1}$, and a subsequent first-order rate constant $\alpha_2 = 0.0095\ min^{-1}$. Figure 2 shows a more complete time series of the Fingas data for the percent of the initial gasoline volume remaining at time (t) at 21 °C, denoted $\%V_{G,21C}(t)$, and also shows the biphasic curve (the dashed-line curve), which is specified by the following equation:

$$\text{Eq. 5: } \%V_{G,21C}(t) = 40.1\% \times \exp(-0.095 \times t) + 59.9\% \times \exp(-0.0095 \times t)$$

Runion[13] measured the evaporation of benzene from gasoline at 25 °C, but reported the data as the percent vol/vol benzene ($\%C_B$) in gasoline as a function of the volume percent of the initial gasoline remaining. However, we seek to estimate the $\%C_B$ in gasoline as a function of *time* at 32 °C for two reasons. First, the average temperature of the skin on a person's hands is 32 °C.[14,15] Second, equation 3 shows that specifying $\%C_B(t)$ would permit computing the $\%C_{B,TWA}$ value.

The first step was adjusting the gasoline evaporation function at 21 °C for the higher temperatures of 25 °C and 32 °C. The Fingas and Runion papers did not specify the Reid vapor pressure (RVP) of the study gasolines, so regulatory limits on RVPs for gasoline were considered, which ranged from ~7 to ~9. For gasoline with RVPs from 7 psi to 9 psi, and at a temperature of 25 °C versus 21 °C, the respective vapor pressure ratio is a constant 1.15.[16] Using this vapor pressure ratio, both α_1 and α_2 were increased in equation 5 by 1.15-fold to account for the effect of increased temperature on the evaporation rate. In Figure 2, the solid-line curve labeled 25 °C shows the predicted evaporation time course specified by the following equation:

$$\text{Eq. 6: } \%V_{G,25C}(t) = 40.1\% \times \exp(-0.109 \times t) + 59.9\% \times \exp(-0.0109 \times t)$$

For gasoline with RVPs ranging from 7 psi to 9 psi and at an air temperature of 32 °C versus 21 °C, the respective vapor pressure ratios ranged from 1.43 to 1.45.[16] On average, the ratio of the higher to the lower vapor pressure was 1.44, so both α_1 and α_2 were increased in equation 5 by 1.44-fold to account for the effect of increased temperature on the evaporation rate. In Figure 2, the solid-line curve labeled 32 °C shows the predicted evaporation time course specified by the following equation:

$$\text{Eq. 7: } \%V_{G,25C}(t) = 40.1\% \times \exp(-0.137 \times t) + 59.9\% \times \exp(-0.0137 \times t)$$

The second step was converting the Runion data for $\%C_B$ versus percent gasoline remaining to the percent

TABLE 1 The Percent Benzene (vol/vol) in Liquid Gasoline Over Time Subsequent to the Start of Gasoline Evaporation*

Percent Gasoline Remaining	Percent Benzene (vol/vol) in Remaining Gasoline	Time (min) at 25 °C	Time (min) at 32 °C
100	5.18	0	0
90	5.18	2.2	1.8
80	5.18	4.9	4.8
70	5.18	8.7	6.9
60	5.1	14	11.2
55	5	17.8	14.2
50	4.5	22	18.2
45	3.8	29.5	23.5
40	3	38.4	30.6
35	1.8	49.7	39.6
30	1	63.5	50.7
25	0.3	80.2	63.8
20	0	100.6	80.1

*The gasoline and benzene percentages were taken from Figure 5 of Runion.[13] The times at 25 °C and at 32 °C were estimated based on equations 6, and 7, respectively.

of the initial benzene content (vol/vol), denoted $\%C_{B,0}$, versus time. Table 1 shows the pertinent data taken from Figure 5 in the Runion paper. For each $\%V_{G,25C}$ value, we found the corresponding time in minutes based on equation 6. Table 1 lists these times, and Figure 3 shows $\%C_{B,0}$ versus time at 25 °C (the open circles). $\%C_{B,0}$ = 100% until about nine minutes, at which point there is a decrease to $\%C_{B,0}$ = 0 by about 100 minutes. Finally, it was assumed that the form of Runion's $\%C_B$ versus percent gasoline remaining data at 25 °C would be approximately the same at 32 °C; in turn, equation 7 was used to find the corresponding times to reach the $\%V_{G,32C}$ values. Table 1 also lists these times, and Figure 3 shows $\%C_{B,0}$ versus time at 32 °C (the open diamonds). $\%C_{B,0}$ = 100% until about seven minutes, at which point there is a decrease to $\%C_{B,0}$ = 0 by about 80 minutes. The dashed-line curve is a fourth-order polynomial fit to the benzene concentration data at 32 °C. It is described by the following equation:

$$\text{Eq. 8: } \%C_B(t) = \%C_{B,0}\,[-1.63 \times 10^{-5} \times t^4 + 2.72 \times 10^{-3} \times t^3 - 0.13 \times t^2 - 0.0715 \times t + 110.8]$$

It would be informative to compare the benzene-in-gasoline $\%C_B(t)$ function to the $\%C_B(t)$ function for benzene in other hydrocarbon liquids. However, with two exceptions, published $\%C_B(t)$ data for other hydrocarbons could not be found. The exceptions involve benzene in a mineral spirits solvent used in commercial parts washers and direct/indirect data concerning benzene-in-air concentrations and benzene in crude oil on water. In the first case, manufacturer data indicated that over a 221-minute parts-washer use period at a room temperature of about 25 °C, an initial benzene concentration of 0.012% vol/vol decreased with first-order rate constant $\alpha = 0.0022\ \text{min}^{-1}$.[17]

In the second case, the benzene-in-air concentration above a contained pool of Louisiana crude oil on ocean water in the Gulf of Mexico was monitored at different times over a 387-minute period, during which the benzene concentration decreased from 90 ppm to 8 ppm; the concentration of the benzene in the same crude oil decreased from 996 ppm to less than 200 ppm over a 455-minute period.[18] The temperature of the air varied from 25.9 °C (78.6 °F) to 28.2 °C (82.8 °F) and the temperature of the crude oil varied from 27.3 °C (81.2 °F) to 51.2 °C (124.3 °F). The values of the benzene in the crude oil and benzene in the air above the crude oil, expressed as fractions of the respective initial concentrations, are shown in Figure 4; the ending value for the benzene in crude oil was set at 100 ppm, which was one-half the reported limit of detection. The benzene-in-air concentration time series was well described as a double exponential (biphasic) process with an early first-order rate constant $\alpha_1 = 0.022\ \text{min}^{-1}$, and a subsequent first-order rate constant $\alpha_2 = 0.002\ \text{min}^{-1}$, for which the fitted equation was as follows:

$$\text{Eq. 9: } C_{B,AIR}(t) = (90\ \text{ppm}) \times [0.65 \times \exp(-0.022 \times t) + 0.35 \times \exp(-0.002 \times t)]$$

The dashed line in Figure 4 shows the fit of equation 9 to the normalized benzene-in-air concentration data. Based on the assumption that the instantaneous benzene-in-air concentration above the outdoor spill was proportional to the corresponding benzene concentration in the crude oil, an approximation of $\%C_B(t)$ in evaporating crude oil is as follows:

$$\text{Eq. 10: } \%C_B(t) \cong \%C_{B,0} \times [0.65 \times \exp(-0.022 \times t) + 0.35 \times \exp(-0.002 \times t)]$$

where $\%C_{B,0}$ is the initial percent benzene content of the crude oil.

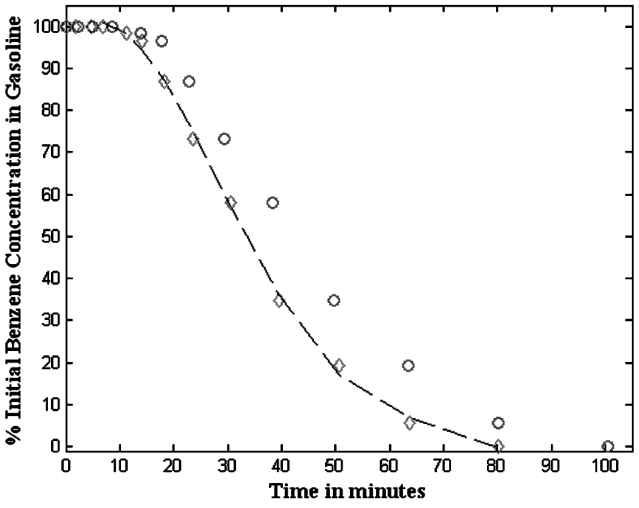

Figure 3—The percent of the initial benzene content (vol/vol) in gasoline over time as the gasoline evaporates at 25 °C (the open circles) versus 32 °C (the open diamonds); the dashed-line curve shows the fit of equation 8 to the data at 32 °C.

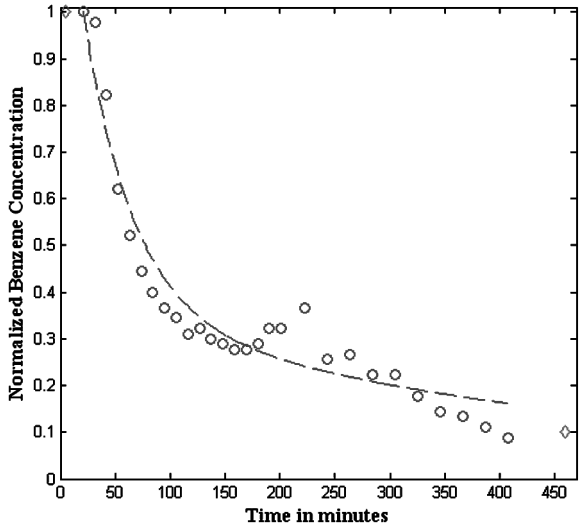

Figure 4—The concentration of benzene in air above a crude oil spill (open circles) and the concentration of benzene in the crude oil (open diamonds), normalized to the respective starting concentrations, over time in minutes from the start of the spill; the dashed-line curve shows the fit of equation 9 to the benzene-in-air data.

Whereas for the evaporation of benzene in gasoline there is an initial phase of no decrease followed by a curvilinear decrease to 0% in about 90 minutes (at 25 °C), for benzene in parts washer mineral spirits the decrease is a first-order rate at 0.22% per minute, and for benzene in crude oil the decrease is biphasic with an early first-order rate at 2.2% per minute and a later first-order rate at 0.2% per minute. While an explanation is not offered for these substantial differences, the following two observations are offered: The time course of benzene evaporation from a hydrocarbon mixture appears to depend on the specific mixture; if one were to naively use the benzene-in-gasoline or benzene-in-crude-oil $\%C_B(t)$ functions to describe the benzene loss from mineral spirits, one would substantially underestimate the benzene concentration in the mineral spirits over time.

DERMAL FLUX FOR OCCLUDED SKIN

Published Flux Data

To estimate the dermally absorbed dose through occluded skin for a given $\%C_B$ value, benzene flux (mg/cm^2-hr) must be quantified. Data available from the relatively small number of published *in vivo* and *in vitro* studies are summarized in Table 2. Other than for the three studies with pure benzene, the Table 2 flux values are not normalized to 100% benzene content. The basis for the listed flux values are provided in Appendix I. The data in these studies have been presented in various forms and units. For ease of interpretation, it would be best if future work were to use the same set of variables and units, preferably mg/cm^2-hr.

Of two *in vivo* studies, the most relevant was that of Hanke et al.[19] who measured the flux of pure benzene on the forearms of human volunteers. Of six *in vitro* studies, four involved human skin and used either the stratum corneum layer or a skin with the fatty layer removed (also termed partial or split-thickness skin) or full-thickness skin. The only human partial-thickness skin study was that of Blank and McAuliffe,[20] who measured K_p (or Flux = $K_p \times C_B$) by exposing the skin to neat benzene and to benzene at 5% vol/vol in isooctane, hexadecane, hexane, and gasoline. Partial-thickness skin *in vitro* (200 to 400 µm thick) is believed to best mimic dermal absorption *in vivo*,[21] because full-thickness skin *in vitro* contains a nonfunctional capillary bed, which acts as an additional diffusion barrier. Note that Hui et al.[22] used a relatively thick partial-thickness skin (500 µm). Both Franz[23] and Blank and McAuliffe[20] argued that human split-thickness skin *in vitro* is a good model of human *in vivo* dermal absorption of benzene.

Figure 5 is a log-log plot of the Table 2 flux values versus $\%C_B$, which follows from the method of Brenner.[3] Note that at similar $\%C_B$ values, the flux through full-thickness skin *in vitro* is substantially lower than through partial-thickness skin *in vitro* and through skin *in vivo*. Again, this result is expected due to the added diffusion barrier of the nonfunctional capillary bed of full-thickness skin *in vitro*.

TABLE 2 Published Benzene Dermal Flux Data for Occluded Skin

Reference	Liquid	Skin (thickness)	Benzene Conc. %	Flux mg/cm^2/hr
Hanke et al.[19]	Pure Benzene	Human/Forearm (*in vivo*)	100	0.4
Maibach et al.[10]	Pure Benzene	Monkey/Forearm (*in vivo*)	100	0.23
Blank and McAuliffe[20]	Pure Benzene	Human/Abdomen (partial–stratum corneum, *in vitro*)	100	1.85
Tsuruta[30,32]	Pure Benzene	Rat/Abdomen (partial, *in vitro*)	100	0.19
Franz[23,32]	Pure Benzene	Human/Abdomen (split, *in vitro*)	100	0.25
Loden[33]	Pure Benzene	Human/Breast (full, *in vitro*)	100	0.099
Blank and McAuliffe[20]	Pure Benzene	Human/Abdomen (partial–stratum corneum, *in vitro*)	100	0.66
Blank and McAuliffe[20]	Gasoline	Human/Abdomen (partial–stratum corneum, *in vitro*)	5	0.062
Blank and McAuliffe[20]	Hexadecane	Human/Abdomen (partial–stratum corneum, *in vitro*)	5	0.041
Blank and McAuliffe[20]	Hexane	Human/Abdomen (partial–stratum corneum, *in vitro*)	5	0.105
Blank and McAuliffe[20]	Iso-octane	Human/Abdomen (partial–stratum corneum, *in vitro*)	5	0.164
Susten et al.[31]	Naphtha Distillate	Mouse/Back (*in vivo*)	0.5	0.012
Adami et al.[29]	Gasoline	Human/Abdomen (full, *in vitro*)	1.06	0.00147
Adami et al.[29]	Gasoline	Human/Abdomen (full, *in vitro*)	0.74	0.00271
Adami et al.[29]	Gasoline	Human/Abdomen (full, *in vitro*)	0.39	0.0018
Maibach et al.[10]	Rubber Solvent	Monkey/Forearm (N/A/*in vitro*)	0.35	0.0062
Hui et al.[22]	Mineral Spirits	Human/Abdomen & Thigh (500 µm partial, *in vitro*)	10*	—**

*The study protocol indicates that 100 µL of radio-labeled benzene was added to 900 µL of a mineral spirits cleaning product.
**The skin permeation test cell configuration was such that benzene in the solvent placed on the skin was permitted to evaporate into the headspace of the test cell. Thus, the actual benzene concentration or radioactive benzene mass that remained on the skin is not known (see Discussion section).

Benzene Flux versus Concentration

Using only the *in vivo* and partial-thickness *in vitro* data from Table 2, we fit a least-squares line of the logarithm of benzene flux versus the logarithm of $\%C_B$. The linear fit is in Figure 5. Exponentiating the log-log line yields the following power function on the arithmetic scale:

$$\text{Eq. 11: Flux, mg/cm}^2\text{-hr} = 0.0204 \times (\%C_B)^{0.6616}$$

The power curve fits the data well and updates the work by Brenner et al.[3] Figure 6 uses arithmetic axes to show the equation 11 power curve and the data points on which it is based. The correlation coefficient $r^2 = 0.950$. Given the high r^2 value, it is reasonable (and unsurprising) to conclude that the benzene flux is strongly dependent on the $\%C_B$ value in the hydrocarbon liquid. In addition, the supralinear nature of the power function signifies that the benzene flux at $\%C_B \leq 5\%$ would be underestimated if flux was based on the strictly proportionate relationship: $(\%C_B \div 100\%) \times$ (flux of pure benzene).

At the same time, the proportionate relationship provides a conservative "lower-bound" point estimate of the benzene flux; the italics signify that the lower bound does not correspond to a statistical confidence limit. If one chooses to make a proportionate estimate and thereby forego relying on the entire data set, the pure benzene flux value should be the Hanke estimate of 0.4 mg/cm^2-hr, the only flux value based on human subject experiments for occluded skin. Thus, the "lower-bound" estimate is:

$$\text{Eq. 12: "Lower-bound" flux estimate} = \frac{\%C_B}{100\%} \times 0.4 \text{ mg/cm}^2\text{-hr}$$

As a technical note, Appendix II provides the derivation of a statistical two-sided 95% confidence interval for the Hanke[19] flux estimate. That interval is: 0.15 mg/cm^2-hr, 0.63 mg/cm^2-hr.

EQUIVALENT DERMAL FLUX FOR NONOCCLUDED SKIN

There are two published studies in which a known amount of radio-labeled benzene was applied to the nonoccluded skin of human subjects and the absorbed dose of radio-labeled benzene was measured. In the first study, 0.4 cm^3 benzene was applied to 80 cm^2 of forearm skin on each of four subjects; it was reported that the benzene completely evaporated within 30 seconds and that 0.05% of the benzene was absorbed, on average.[23] In the second study, 0.1 cm^3 benzene was applied to 4 square inches (25.8 cm^2) of palm skin on

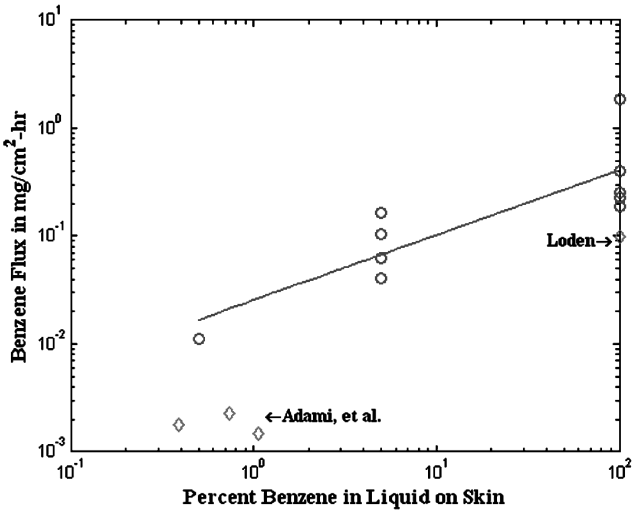

Figure 5—Benzene dermal flux on occluded skin versus % vol/vol benzene in the hydrocarbon liquid;circle symbols = in vivo and in vitro partial-thickness skin; diamond symbols = full-thickness skin.

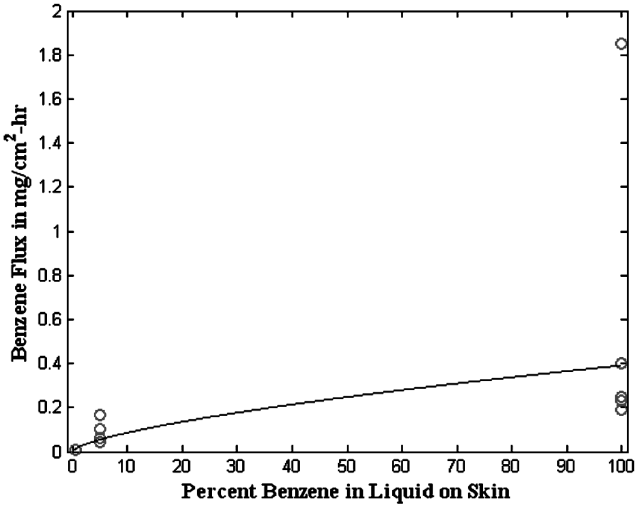

Figure 6—Benzene dermal flux on occluded skin versus % vol/vol benzene in the hydrocarbon liquid; in vivo and in vitro partial thickness skin data.

four subjects and to 4 square inches of forearm skin on four subjects; it was reported that, on average, 0.13% of the benzene on the palm and 0.07% of the benzene on the forearm, was absorbed.[9] The time to evaporation in the latter study was not stated. However, given that the nominal initial benzene film thickness in the second study (0.1 cm^3 ÷ 25.8 cm^2 = 0.004 cm) was less than in the first study (0.4 cm^3 ÷ 80 cm^2 = 0.005 cm), it is reasonable to conclude that benzene also completely evaporated within 30 seconds in the second study.

The benzene mass absorbed by the nonoccluded skin can be expressed as an equivalent benzene flux by dividing the absorbed mass by the product of the exposed skin surface area and exposure duration. The density of liquid benzene is 880 mg/cm^3. It was assumed in each study that skin contact with benzene liquid lasted 30 seconds (0.00833 hr). For the Franz study,[23] the equivalent flux for the forearm is: (0.0005 × 0.4 × 880 mg) ÷ (80 cm^2 × 0.00833 hr) = 0.26 mg/cm^2. For the Modjtahedi and Maibach study,[9] the equivalent flux for the forearm is: (0.0007 × 0.1 × 880 mg) ÷ (25.8 cm^2 × 0.00833 hr) = 0.29 mg/cm^2-hr; the equivalent flux for the palm is: (0.0013 × 0.1 × 880 mg) ÷ (25.8 cm^2 × 0.00833 hr) = 0.53 mg/cm^2-hr. These equivalent flux values bracket the equation 11 flux estimate of 0.43 mg/cm^2-hr, and the Hanke flux estimate of 0.4 mg/cm^2-hr, for pure benzene.

Maibach and Anjo[10] performed similar *in vivo* experiments on Rhesus monkeys, and Franz[23] performed similar experiments on Rhesus monkeys and mini-pigs. Maibach and Anjo[10] applied 0.05 cm^3 radio-labeled benzene to approximately 12.9 cm^2 of forearm skin on three monkeys; on average, 0.172% of the applied benzene mass was absorbed. The time to evaporation was not stated, but given the nominal initial benzene film thickness of 0.004 cm, it is reasonable to conclude that the benzene completely evaporated within 30 seconds. The equivalent flux is: (0.00172 × 0.05 × 880 mg) ÷ (12.9 cm^2 × 0.00833 hr) = 0.70 mg/cm^2-hr. Franz[23] applied 0.5 cm^3 radio-labeled benzene to approximately 65 cm^2 of back skin on each of six monkeys and two pigs; it was reported that the benzene completely evaporated within 30 seconds. The average benzene absorbed by the monkeys and by the pigs was, respectively, 0.14% and 0.09% of the applied mass. The equivalent flux for the monkey is: (0.0014 × 0.5 × 880 mg) ÷ (65 cm^2 × 0.00833 hr) = 1.14 mg/cm^2. The equivalent flux for the pig is: (0.0009 × 0.5 × 880 mg) ÷ (65 cm^2 × 0.00833 hr) = 0.73 mg/cm^2-hr.

ESTIMATING ABSORBED DOSE WITH A DECREASING BENZENE CONCENTRATION

When the benzene concentration in the liquid contacting the skin decreases during the exposure period, $Flux_{TWA}$ can be approximated by the product $K_p \times C_{B,TWA}$ and, in turn, used to estimate the absorbed dose. However, if one relies on equation 11 to describe benzene flux as a function of the benzene concentration in a hydrocarbon liquid, $Flux_{TWA}$ is more exactly computed as follows:

$$\text{Eq. 13: } Flux_{TWA}, \text{ mg/cm}^2\text{-hr} = \frac{1}{ET}\int_0^{ET} 0.0204 \times [\%C_B(t)]^{0.6616}\, dt$$

As seen in Figure 3, the $\%C_B(t)$ function for benzene in gasoline at 32 °C can reasonably be described in the fol-

TABLE 3 Skin Factors Used to Calculate a Dermally Absorbed Dose

Skin Area	Area, cm^2	F_{abs}	Reference/Notes
Fingertips (2 hands)	90.5	1	Fingers/4
Fingers (2 hands)	362	1	D=1.6M cm, L=7.2 cm
Palms	354	2	(Hands-Fingers)/2
2 Hands	1,070	1.5	2009 Handbook*
2 Wrists	365	1	Forearms/4
2 Arms (including hands)	3,176	1	2009 Handbook*
2 Arms (not including hands)	2,106	1	Arms with hands - hands
2 Forearms—without wrists	1,095	1	Forearms—wrists
2 Forearms—with wrists	1,460	1	2009 Handbook—including wrists*
Head	1,360	1	2009 Handbook*
Neck	408	1	3/5 Face (Brenner, 1998)**
Face	680	1	Head/2
Torso (including neck)	8,200	1	2009 Handbook*
Front of torso	4,100	1	Torso/2
Front of chest	2,050	1	Torso/4
2 Legs	6,860	1	2009 Handbook*
Front of 2 legs	3,430	1	Legs/2
2 Thighs	4,113	1	2009 Handbook*
Back of 2 thighs	2,056.5	1	Thighs/2
2 Lower legs	2,710	1	2009 Handbook*

*EPA Exposure Factors Handbook (2009), Table 7–11 – 50 percentile male; other tables available for an average female or children.
**Brenner et al.[3]; see also Keil[33] for data on skin areas.

lowing two phases: For times in the interval [0, 0.12 hr], $\%C_B(t) = \%C_{B,0}$, the initial benzene concentration in the gasoline, the $Flux_{TWA} = 0.0204 \times (\%C_{B,0})^{0.6616}$ mg/cm^2-hr; for times in the interval [t_1 = 0.12 hr, t_2 = 1.33 hr], $\%C_B(t)$ is given by equation 8, which is a curvilinear relationship. For the latter phase, the equation 13 integrand has to be numerically averaged over the appropriate time interval.

In contrast, if the loss of benzene from mineral spirits at 32 °C is described by the exponentially decreasing function $\%C_B(t) = \%C_{B,0} \times \exp(-\alpha \times t)$, equation 13 yields:

$$\text{Eq. 14: } Flux_{TWA}, \text{ mg/cm}^2\text{-hr} = \frac{1}{ET}\int_0^{ET} 0.0204 \times [\%C_{B,0} \times \text{esp}(-\alpha \times t)]^{0.6616}\, dt$$

$$= \frac{0.0204 \times (\%C_{B,0})^{0.6616}}{0.6616 \times \alpha \times ET} \times [1 - \exp(-0.6616 \times \alpha \times ET)]$$

SKIN AREA AND THE SKIN ABSORPTION FACTOR

The surface area, SA, and skin absorption factors, FA_{abs}, for different body areas of interest are provided in Table 3. The total area of the ten fingers (including the thumbs) can be estimated by multiplying the area of an average finger by 10. The average finger was represented as a right circular cylinder with a diameter of 1.6 cm (5/8 inch) and a length of 7.2 cm (2.8 inches). Therefore, the average finger area is approximately 36.2 cm^2 ($\pi \times 1.6$ cm $\times$ 7.2 cm), and the total finger area is 362 cm^2.

The skin absorption factor of 2 for the palms relevant to forearm skin was obtained from Maibach and Anjo[10] and Modjtahedi and Maibach.[9] For the skin on the hands overall, F_{abs} = 1.33 is the surface-area-weighted-average of F_{abs} for the palms and F_{abs} for the fingers and the back of the hands: [2 $\times$ (362/1070)] + [1 $\times$ (708/1070)] = 1.33. The skin on other body areas, for example, the scrotal skin, can have a higher F_{abs} value.

To simplify the dermal dose calculations, an effective surface area, SA_{eff}, can be used based on the fraction of time that different body areas are wet during a specific activity involving dermal exposure. This effective surface area is computed as follows:

$$\text{Eq. 15: } SA_{eff} = \sum_{i=1}^{n} SA_i \times FA_{abs,i}$$

where n is the number of body areas exposed, SA_i is the surface area of the ith body area and $FA_{abs,i}$ is the skin absorption factor for the ith body area. In turn, given SA_{eff}, $Flux_{TWA}$ and exposure duration, one can calculate the dermal dose in mg.

EQUIVALENT INHALATION DOSE DUE TO DERMAL ABSORPTION

To convert a dermally absorbed benzene dose in mg to an equivalent occupational inhalation exposure in ppm-years, the mass of benzene absorbed by inhaling one ppm benzene over one work year is estimated. One ppm benzene-in-air corresponds to 3.19 mg/m^3 at normal

pressure and temperature conditions. The standard breathing rate at work is assumed to be 1.2 m^3/hr, as pertains to an average adult male performing moderate activity.[24] We assume a pulmonary benzene absorption factor of 0.5.[25] We assume that the standard work year consists of eight hours a day, for five days a week, for 48 calendar weeks; the remaining four calendar weeks are attributed to holidays, vacation leave, and sick time. Thus, we assume 1,920 work hours in a work year. If the average benzene concentration in inhaled air is 3.19 mg/m^3, the exposed individual absorbs 3,675 mg in a work year, or: (3.19 mg/m^3) × (1.2 m^3/hr) × (1,920 hr) × 0.5. Thus, one ppm-year of occupational benzene inhalation exposure corresponds to absorbing 3,675 mg benzene. In turn, dividing the dermally absorbed benzene dose by 3,675 mg provides the equivalent occupational benzene inhalation exposure in ppm-years.

EXAMPLE DERMAL DOSE CALCULATIONS

To illustrate the dermal dose calculations, a scenario with two different versions is posed. In the scenario, a worker cleaned oily parts with a benzene-containing hydrocarbon solvent by immersing both hands in a container of fresh solvent six times a day for two minutes; the solvent temperature was 25 °C. After the hands were removed from the solvent, the worker did not dry the wet skin until two minutes later. This same daily regimen occurred for 240 work days per year for 30 calendar years, such that there were n = 43,200 dermal exposure events: (6 events/day) × (240 days/yr) × (30 yr). The wetted hand surface area was 1,070 cm^2. In the first version of the scenario, the solvent was gasoline containing benzene at 2% vol/vol. In the second version, the solvent was a less volatile hydrocarbon containing benzene at 0.1% vol/vol.

Gasoline

During the two minutes of immersing the hands in gasoline and the subsequent two minutes before the hands were dried, Figure 2 indicates that the benzene concentration in the gasoline would be the same as the initial concentration. According to the equation 11 power function:

$$\text{Benzene Flux} = 0.0204 \times (2\%)^{0.6616} = 0.0323 \text{ mg/cm}^2\text{-hr}$$

Thus, the dermally absorbed benzene mass per four-minute exposure event is:

$$DA_{noevap} = (0.0323 \text{ mg/cm}^2\text{-hr}) \times (1{,}070 \text{ cm}^2) \times 1.33 \times (0.0667 \text{ hr}) = 3.07 \text{ mg}$$

Given 43,200 dermal exposure events, the total dermally absorbed benzene mass is 132,624 mg, or (3.07 mg/event) × (43,200 events). The equivalent occupational benzene inhalation exposure due to dermal absorption is 36.1 ppm-years, or (132,624 mg) ÷ (3,675 mg/ppm-year). The 3.07 mg benzene absorbed in four minutes can also be expressed as an equivalent four-minute TWA inhalation exposure level of 24 ppm. That is, inhaling 24 ppm benzene (76.7 mg/m^3 at NTP conditions) for four minutes (0.0667 hr) at a breathing rate of 1.2 m^3/hr leads to absorbing 3.07 mg benzene, or: (76.7 mg/m^3) × (1.2 m^3/hr) × (0.0667 hr) × 0.5. In turn, six four-minute exposures to 24 ppm benzene in an eight-hour shift, with no other benzene exposure, leads to an equivalent eight-hour TWA benzene inhalation exposure of 1.2 ppm, or: (24 ppm) × (24 min ÷ 480 min).

In the gasoline scenario, the post-cleaning exposure time was limited to two minutes by assuming the worker did not dry his hands until two minutes after the cleaning task. It has been observed that gasoline should evaporate from skin in about five minutes.[26] However, post-activity dermal exposure to a volatile chemical can continue for a substantially longer time if the hands are not purposely dried or cleaned. For example, Franz[23] reported that when benzene was put on nonoccluded human skin *in vitro* at a volume density of 0.12 cm^3 per cm^2 (an initial film thickness of 0.12 cm), complete evaporation from the skin took approximately 45 minutes; during the experiment, the outer layer of the skin was exposed to room air at 21 °C, while the under layer of the skin was bathed in fluid at 37 °C. Franz also observed that greater initial volume densities of benzene on the skin led to longer evaporation times, and that the total benzene mass absorbed was proportional to the evaporation (exposure) time. In addition, for less-volatile benzene-containing hydrocarbon mixtures such as crude oil and penetrants, the evaporation half-time of the bulk liquid is on the order of hours, not minutes, which would likely result in longer dermal contact with benzene if the skin was not cleaned. Finally, repeated dermal contact with gasoline would overtly damage the skin, such that the benzene flux through the skin would be approximately fivefold greater than assumed in this example.

We note that Kalnas and Teitelbaum[2] discussed a similar exposure scenario for automotive mechanics who had frequent skin contact with gasoline containing benzene at 2% vol/vol while cleaning parts and their hands for episodes lasting one to two minutes. Those authors estimated that as a daily average, a mechanic had 32 minutes of gasoline contact with 500 cm^2 of damaged skin on the palms, and 16 minutes of gasoline contact with 500 cm^2 of nondamaged skin on the dorsal surface of the hands. It was estimated that 20 years of that regimen led to 104 ppm-years of equivalent benzene inhalation exposure; the exact number of work days per year was not specified. The estimate relied on a set of values offered by Susten, et al.[27]: The flux of pure benzene

through healthy skin is 3.36 mg/cm^2-hr; the volumetric breathing rate is 10 m^3/8-hrs or 1.25 m^3/hr; and 60% of inhaled benzene is absorbed into the bloodstream. It was assumed that the benzene flux was reduced in proportion to the benzene content of the gasoline (or 0.02 × 3.36 mg/cm^2-hr = 0.0672 mg/cm^2-hr), and that damaged skin permits a fivefold greater benzene flux.

We compare the Kalnas and Teitelbaum[2] estimate to that derived by our method and ppm-year metric. We assume a lower benzene flux of 0.0323 mg/cm^2-hr for benzene at 2% vol/vol in gasoline. We assume F_{abs} = 2 for the palmar skin (362 cm^2), which increases fivefold to F_{abs} = 10 due to skin damage. We assume F_{abs} = 1 for the rest of the skin on the hands (708 cm^2), which is undamaged. Given the same contact duration per day, we estimate the daily absorbed benzene dose at 68.5 mg:

$$\text{Daily dose} = (0.0323 \text{ mg/cm}^2\text{-hr}) \times [(362 \text{ cm}^2) \times 10 \times (32/60 \text{ hr}) + (708 \text{ cm}^2) \times 1 \times (16/60 \text{ hr})] = 68.5 \text{ mg}$$

For this example, we assume the number of work days per year is 240 days, or 4,800 days over 20 years. Thus, we estimate the cumulative benzene mass absorbed to be: 68.5 mg/day × 4,800 days = 328,800 mg. Dividing by 3,675 mg benzene per ppm-year yields 89.5 ppm-years of equivalent inhalation exposure, which is 14% lower than the 104 ppm-years estimated by Kalnas and Teitelbaum.[2] We do not consider a 14% difference to be substantial despite the differences in the flux values used, and the uncertainty regarding the number of exposure days assumed by Kalnas and Teitelbaum.[2]

A Less-volatile Solvent

In this scenario, we assume that the benzene concentration in the solvent in the container is relatively constant, but the benzene concentration in the solvent on the hands exponentially decreases with a first-order rate constant α = 2 hr^{-1} (a half time of about 20 minutes). Based on the equation 11 power function, the benzene flux is 0.00445 mg/cm^2-hr for benzene at 0.1% vol/vol. The dermally absorbed benzene mass in the first two minutes (0.0333 hr) is:

$$DA_{noevap} = (0.00445 \text{ mg/cm}^2\text{-hr}) \times (1{,}070 \text{ cm}^2) \times 1.33 \times (0.0333 \text{ hr}) = 0.211 \text{ mg}$$

During the two-minute post-cleaning, $\%C_B(t)$ in the solvent on the skin is exponentially decreasing with α = 2 hr^{-1}. Based on equation 14:

$$\text{Flux}_{TWA} = \frac{0.0204\ 3\ (0.1\%)^{0.6616}}{0.6616 \times 2 \times 0.0333} \times [1 - \exp(-0.6616 \times 2 \times 0.0333)] = 0.00435 \text{ mg/cm}^2\text{-hr}$$

The dermally absorbed benzene mass in the second two minutes is:

$$DA_{evap} = (0.00435 \text{ mg/cm2-hr}) \times (1{,}070 \text{ cm}^2) \times 1.33 \times (0.0333 \text{ hr}) = 0.206 \text{ mg}$$

There is little difference in the DA_{noevap} and DA_{evap} values because the loss constant α = 2 hr^{-1} results in very little benzene loss in a two-minute period. Adding DA_{noevap} and DA_{evap} yields 0.42 mg benzene absorbed per four-minute exposure event. Given 43,200 dermal exposure events, the total dermally absorbed benzene mass is 18,144 mg, which corresponds to 4.9 ppm-years of equivalent occupational benzene inhalation exposure. Again, repeated dermal contact with a hydrocarbon solvent would overtly damage the skin, such that the benzene flux through the skin would be approximately fivefold greater than assumed in this example.

DISCUSSION

Available information on dermal exposures to benzene and benzene-containing products has been reviewed and mathematical models have been proposed to estimate benzene dermal absorption at the time of application and post-application. A key aspect of the analysis is accounting for a decreasing benzene concentration in the liquid on the skin due to preferential benzene evaporation. As illustrated in the examples offered, the inhalation equivalent of the dermally absorbed benzene dose (both during application and post-application) can be substantial.

Because it is now considered unethical to use human subjects for *in vivo* dermal absorption experiments with benzene, it is likely that all future human work will use in vitro systems. In that regard, skin thickness is a critical parameter. Partial-thickness skin *in vitro* (200 to 400 µm thick) is believed to best mimic dermal absorption *in vivo*. Some researchers have used full-thickness *in vitro* skin, which as expected, results in reduced fluxes that do not appear to mimic *in vivo* data. Additional human *in vitro* data using benzene in different solvents (e.g., gasoline, toluene, xylene, naphtha) at levels below 5% would be helpful for the purpose of exposure reconstruction. Such data would also better define a supralinear concentration-dose relationship.

After the draft of this paper was completed, we became aware of a recent article that also concerned the dermal flux of benzene in occupational settings.[28] As part of their analysis, Williams et al. considered the set of benzene steady-state permeation rate (SSPR) estimates from the three *in vitro* human skin studies listed in Table 2[20,22,29] (Blank and McAuliffe; Adami et al.; Hui et al.), and concluded that the SSPR was not proportional to the benzene content of the liquid. It is true that the SSPRs reported across these three studies do not exhibit a proportionate relationship, and this

paper suggests that at benzene concentrations below 5%, the relationship is supralinear. However, the Williams et al.[28] conclusion, based on the reported SSPR values, is unwarranted, because it is not appropriate to make a simple comparison of the data from the three studies in the first place.

The Adami et al.[29] study used full-thickness skin. Williams et al.[28] argued that the greater thickness due to the presence of the dermis would only delay the time at which a SSPR was observed. However, they did not account for the circumstance that the presence of the nonfunctional capillary bed in the dermis layer would increase the length of the diffusion path and thereby decrease the SSPR.

The Hui et al.[22] study involved placing 10 µL, or alternatively 30 µL, of a mineral spirits solvent on a 500 µm thick piece of skin in a sealed diffusion cell with headspace volume 1,000 µL. Williams et al. described this skin as "split-thickness," but 500 µm is somewhat thicker than the 200 to 400 µm range used by Roberts and Walters[21] to describe split-thickness skin.[28] More importantly, the relatively large volume of headspace air above the skin in the diffusion cell (30- to 100-fold greater than the solvent volume applied) permitted benzene evaporation from the solvent into the headspace, which thereby decreased the nominal benzene concentration in the solvent on the skin. Because Hui et al. did not measure how much benzene evaporated into the headspace air, the actual benzene concentration in the solvent on the skin is unknown.[22]

Both the Adami et al.[29] and Hui et al.[22] studies were deficient in another important aspect; they lacked an internal control experiment in which the skin was challenged with neat benzene. Because the reported neat benzene SSPR differs between *in vitro* studies that used different permeation systems, the proper comparison standard for evaluating whether a given benzene SSPR value (for benzene in a hydrocarbon mixture) exhibits proportionality is the SSPR for pure benzene in the same system. The only human skin *in vitro* study that included this internal comparison standard was the Blank and McAuliffe study.[20] The latter investigators observed that the benzene SSPR from mixtures of benzene at 5% vol/vol in four hydrocarbons (hexadecane, gasoline, hexane, and iso-octane) was greater than proportionate compared to the SSPR of neat benzene.

Williams et al.[28] questioned the reliability of the Blank and McAuliffe[20] study. They appeared to argue that the well-hydrated skin in the study protocol and/or the solvents in which the benzene was present enhanced the permeation of benzene. With regard to hydration, the study itself suggested no effect of hydration on benzene permeation. Figure 2 of the Blank and McAuliffe[20] paper showed no significant difference in the permeation coefficient (K_p) of benzene when neat benzene was placed on skin that did or did not have three hours of prior contact with a 0.1% NaCl solution. With regard to the enhanced permeation of benzene from some hydrocarbons compared to permeation from neat benzene, Blank and McAuliffe[20] reported higher mean normalized permeation coefficients for benzene in hexadecane, gasoline, hexane, and iso-octane compared to permeation from neat benzene. The mean value for neat benzene was 6.4×10^{-4} cm/hr compared to 9.4×10^{-4}, 14×10^{-4}, 24×10^{-4}, and 37×10^{-4} cm/hr for the four hydrocarbons, respectively. However, there is nothing inherently suspicious about benzene showing a higher K_p value in various liquids compared to neat benzene. For example, for benzene in water, the reported K_p value was $1{,}110 \times 10^{-4}$ cm/hr.

CONCLUSIONS

The method presented in this paper for determining dermal uptake of benzene from benzene-containing hydrocarbon liquids is more comprehensive than methods currently used in industrial hygiene. The power curve for benzene flux through occluded skin as a function of the vol/vol percent benzene in the liquid is based on the complete set of pertinent published data. In addition, the method accounts for a possible dynamic decrease in flux during an exposure period due to an evaporative decrease in the benzene concentration in the liquid contacting the skin. The available data on dermal uptake of benzene on nonoccluded skin are consistent with this model for occluded skin.

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APPENDIX I

Basis for Conversion of Various Dermal Data to Flux Values

1. Tsuruta[30]—Neat BZ

Table 3, page 342: Penetration rate = 40.7 nmoles/min/cm^2
MW of benzene = 78.1 mg/mmole
C_1 = 60 min/hr.
C_2 = 1.00E+06 mmole/nmole
Flux = Penetration rate × C_1 × MW/C_2 = 0.19 mg/cm^2/hr

2. Franz[23]—Neat BZ

Figure 5, page 69
Total benzene absorbed/hour = 0.28 µL/cm^2/hr.
Slope of plot in Figure 5
Density of Benzene = 0.88 g/mℓ (mg/µℓ)
Flux = Total absorbed/hr × density = 0.25 mg/cm^2/hr

3. Maibach and Anjo[10]—Neat BZ and 0.35% BZ in rubber solvent

Only data for multiple (N_d = 10) exposures used in calculations (most like occluded case)

Table 1, page 258
%BZ = 0.35%, ABS = 0.431% rubber solvent
%BZ = 100%, ABS = 0.848 % neat benzene
%BZ in dosing solution = 0.35 % rubber solvent
%BZ in dosing solution = 100% neat benzene
Fraction of BZ in dose = FQ=%ABS/100 = 0.00350 rubber solvent
Fraction of BZ in dose = FQ=%ABS/100 = 1 neat benzene
Area dosed = S = 1.29 cm^2 rubber solvent
Area dosed = S = 12.9 cm^2 neat benzene
Benzene Loading on skin = Q = 68.1 mg/cm^2 rubber solvent
6.81 mg/cm^2 neat benzene; Total of 68.1 for 10 doses
Number of doses = N_d = 10 both solvent & neat

Dose Absorbed = DA = S × Q × FQ × (ABS/100) × N_d = 0.01325 mg rubber solvent
Dose Absorbed = DA = S × Q × FQ × (ABS/100) × N_d = 7.45 mg neat benzene

Dosing time = E_T = 1.67 hr rubber solvent; 10 × 10 min between doses – Page 257
Dosing time = E_T = 2.5 hr. neat benzene; 10 × 15 min between doses – Page 257

Flux = DA/(S × E_T) = 0.0062 mg/cm^2/hr rubber solvent
Flux = DA/(S × E_T) = 0.23 mg/cm^2/hr neat benzene

4. Blank et al.[20]—5% BZ in various materials

Table 2, page 525 provides K_p × 10^-3

K_p (5% BZ in Hexadecane) = 9.40E-04 cm/hr
K_p (5% BZ in Isooctane) = 3.73E-03 cm/hr
K_p (5% BZ in Hexane) = 2.40E-03 cm/hr
K_p (5% BZ in gasoline) = 1.40E-03 cm/hr
Concentration = C_d = 50 µL/mℓ = 50 µL/cm^3
Density of benzene = 0.88 mg/µℓ

Flux = K_p × C_d × Density

Flux (5% BZ in Hexadecane) = 0.041 mg/cm^2/hr
Flux (5% BZ in Isooctane) = 0.164 mg/cm^2/hr
Flux (5% BZ in Hexane) = 0.105mg/cm^2/hr
Flux (5% BZ in gasoline) = 0.062 mg/cm^2/hr

Pure benzene data—page 524, data from Figure 1, page 523, not used (see Kalnas and Teitelbaum[2] p. 118 for details)
Steady state flux: 2.11 µL/cm^2/hr (average flux of eight values, std. dev. 1.8)
Density of benzene = 0.88 mg/µℓ

Flux (100% benzene) = ~1.85 mg/cm^2/hr. (2.11 × 0.8786)

5. Susten et al.[31]—0.5% BZ in naphtha distillate

Table 3, page 331
Benzene mass absorbed/ unit area of skin = 0.0275 mg/cm^2
Absorption time = 2.3 hr. to 10% level in Figure 2, page 330
Flux = Amount absorbed/E_T = 0.012 mg/cm^2/hr

APPENDIX II

Construction of a Two-Sided 95% Confidence Interval on the Hanke[19] Flux Estimate

Hanke et al.[19] did not offer a statistical confidence interval on their 0.4 mg/cm^2-hr flux estimate, but we constructed a two-sided 95% confidence interval.

Study Data

In the study, 0.02 mL (17.6 mg) benzene was held against 8 cm^2 of forearm skin for 1.25 hour by using an inverted watch glass. The watch glass was enclosed by a suction device such that any benzene vapor escaping from the watch glass was drawn through a collection medium. At the end of the 1.25 hour, the watch glass seal was broken and the liquid benzene remaining on the skin was evaporated off by the suction device through the collection medium. The benzene mass collected was measured via a laboratory absorption assay. As a control, the same volume of benzene was held against glass (a nonabsorbing surface) for 1.25 hour. At the end of the period, the remaining benzene was collected and analyzed in the same manner.

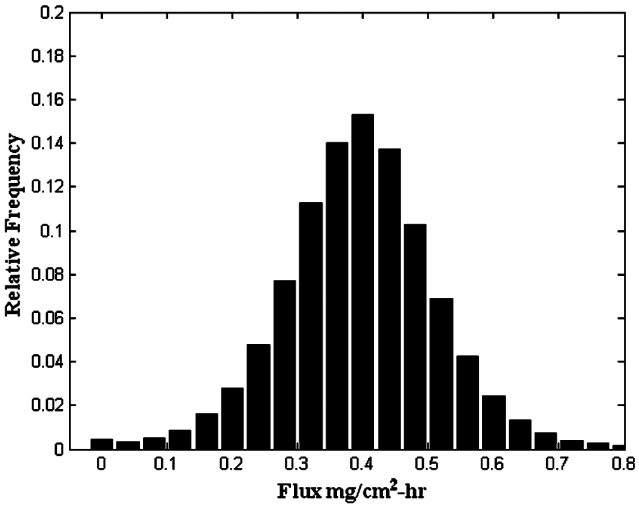

Figure 7—The uncertainty distribution for the Hanke pure benzene flux estimate of 0.4 mg/cm^2-hr as generated by a Monte Carlo sampling method.

There were $n_1 = 15$ glass control absorption measurements for which the mean and standard error were, respectively, $\bar{x}_1 = 0.49$ and $\bar{s}_{x_1} = 0.007$. There were $n_2 = 7$ human subject absorption measurements for which the mean and standard error were, respectively, $\bar{x}_2 = 0.38$ and $\bar{s}_{x_2} = 0.027$.[19] Hanke used the difference in the means to compute the mass of benzene absorbed via the expression: $[(0.49 - 0.38) \div 0.49] \times 17.6$ mg = 4 mg. This mass was divided by the product of the 8 cm^2 skin surface and the 1.25 hour exposure time (equal to 10 cm^2-hr) to arrive at the flux point estimate 0.4 mg/cm^2-hr.

Monte Carlo Method

The confidence interval was derived as follows. For each set of measurements, the reported mean and standard error were treated as the parameters of a t-distribution with $n - 1$ degrees of freedom. We performed 5×10^5 iterations of a sampling experiment via a computer code. For each iteration, one value was drawn from the t-distribution for $\bar{x}_1$, and one value was independently drawn from the t-distribution for $\bar{x}_2$. These two values were used in Equation (A1) below to generate a flux value. If the sampled $\bar{x}_2$ value was greater than the sampled $\bar{x}_1$ value, the flux was set equal to zero; approximately 0.35% of the flux values were zero.

$$\text{Eq. A1: Flux} = \left[1 - \frac{\bar{x}_2}{\bar{x}_1}\right] \times \frac{17.6 \text{ mg}}{10 \text{ cm}^2 - \text{hr}}$$

This sampling procedure generated a symmetrical distribution of flux estimates as shown in Figure 7. The mean is 0.4 mg/cm^2-hr and the central 95% of values lie between 0.15 and 0.63 mg/cm^2-hr. Thus, the two-sided 95% confidence interval is [0.15 mg/cm^2-hr, 0.63 mg/cm^2-hr].