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Methods for Assessing Risks of Dermal Exposures in the Workplace

James N. McDougal
Pharmacology and Toxicology, Wright State University School of Medicine, Dayton, OH 45434–0001

Mark F. Boeniger
Niosh/CDC, 4676 Columbia Pkwy., Cincinnati, OH 45226

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ABSTRACT: The skin as a route of entry for toxic chemicals has caused increasing concern over the last decade. The assessment of systemic hazards from dermal exposures has evolved over time, often limited by the amount of experimental data available. The result is that there are many methods being used to assess safety of chemicals in the workplace. The process of assessing hazards of skin contact includes estimating the amount of substance that may end up on the skin and estimating the amount that might reach internal organs. Most times, toxicology studies by the dermal route are not available and extrapolations from other exposure routes are necessary. The hazards of particular chemicals can be expressed as "skin notations", actual exposure levels, or safe exposure times. Characterizing the risk of a specific procedure in the workplace involves determining the ratio of exposure standards to an expected exposure. The purpose of this review is to address each of the steps in the process and describe the assumptions that are part of the process. Methods are compared by describing their strengths and weaknesses. Recommendations for research in this area are also included.

GLOSSARY

Absorption — the general term for describing the process of chemical entering the skin. Differs from penetration because the focus is on what is in the skin.
Acute exposures — generally studies that last for hours or a up to a day.
Applied dose — the experimentally applied dose. Could be comparable to an external dose in a risk assessment.
Concentration — the term that describes the amount of chemical on the skin for chemicals in a vehicle or mixture. It has units of mass per volume.
Chronic exposures — generally studies that are long term, that is, greater than 90 days and up to 2 years.
Dermis — the deep layer of the skin. It contains structural components and blood vessels.
Diffusivity — a specific term that quantitatively describes movement of chemical over time. It has units of distance squared per hour.
Dose rate — rate at which a chemical passes through or into the skin, organ, or body. It has units of mass per time. Contrast with flux, which has units of mass per both area and time.
Epidermis — the thin living layer of skin exterior to the dermis. It receives its nutrients from capillaries, which bathe the bottom of the epidermis.

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External dose — the mass that is available on the skin for absorption. When expressed per surface area, it would be surface density. Experimentally would be called applied dose.

Extrapolation factor — a factor that is applied in route-to-route extrapolation to account for differences in the expression of systemic toxicity between exposure routes. It is a ratio that accounts for the differences in absorption between routes. Also used more generally to describe species extrapolation, high to low dose extrapolation, and extrapolation to lifetime exposures.

Fick's law — the postulate that relates flux to the concentration across the skin, membrane thickness and diffusivity. Comes in several related forms.

Finite dose — when the mass of chemical on the skin is small compared to the flux. The driving force (concentration or surface density) decreases with time.

Flux — a specific term that quantitatively describes movement of chemical over time. It has units of mass per both area and time. Flux could be movement into the skin (absorption) or movement through the skin (penetration). Contrast with dose rate that has units of mass per time.

Infinite dose — when the mass of chemical on the skin is large compared to the flux. The driving force (concentration or surface density) does not change with time.

Internal dose — the mass that is past the "barrier" and is available to cause toxicity.

Lag time — the time during an exposure before flux becomes constant.

Minimum risk level (MRL) — an estimate of the exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects. Standard determined by Agency for Toxic Substance and Disease Registry (ATSDR).

Monolayer — the amount of chemical that just covers the skin surface. Initially, the same as an infinite dose, but may become a finite dose as flux occurs.

No observable (adverse) effect level (NOEL) — an external measure of dose that, based on toxicity studies with several exposure concentrations, would cause no known effect. Adverse is sometimes added (NOAEL) to signify the level that caused effects that were considered adverse. When comparing chemicals, the chemical with the lowest NOAEL is the most toxic.

Occupational exposure level (OEL) — Level in the workplace that may cause toxicity if exceeded.

Partition coefficient — the term that describes the ratio of concentrations in two adjacent media when there is no net change in chemical concentration between them (equilibrium).

Penetration or permeation — the general term for describing the process of chemical going through the skin. Differs from absorption because the focus is on what goes through the skin. For industrial hygienists, permeation often means absorption through the skin and penetration often means passing a barrier such as a glove.

Permeability coefficient — a specific term that quantitatively describes the movement of chemical in a vehicle or mixture over time. The permeability coefficient has units of distance/time and usually describes movement through the skin (penetration). The permeability coefficient is concentration independent and therefore can be used to extrapolate between concentrations.

Reference concentration (RfC) — an external airborne concentration that would cause no harm during a lifetime, continuous exposure. An Environmental Protection Agency standard.

Registry of Toxic Effects of Chemical Substances (RTECS) — database of toxicological information, compiled and maintained by NIOSH.

Route of administration — the route chosen for a toxicity study where the chemical is administered to the animal.

Route of exposure — the route most likely to cause an internal dose in the occupational environment.

Steady-state diffusion — the condition when the flux is not changing. It usually occurs after the lag time and with an infinite dose.

Stratum corneum — the most superficial layer of the skin. It is composed of flattened epidermal cells held together in a lipid matrix and is in most cases the primary barrier to penetration of chemicals.

Subchronic exposures or toxicity — generally studies which are greater than acute (a day) and up to 90 days in duration.

Surface density — the term that describes the amount of a solid or liquid on the skin. It has units of mass per area.

Target tissue dose — the mass of chemical that enters the site of toxicity of a chemical. Usually, the mechanism of action of the chemical must be known to define the target tissue(s). The target tissue dose will be related to the external dose, but not necessarily in a linear way.

Thermodynamic activity — the actual activity of the chemical in the media. It is the concentration times an activity coefficient and is the driving force of diffusion.

Transfer factor — a measure of the mass transfer of chemicals from surfaces to the skin.

Threshold Limit Value (TLV) — airborne concentrations of substances and represent conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse health effects. They are developed by the American Congress of Governmental Industrial Hygienists (ACGIH).

I. INTRODUCTION

Assessing dermal exposures to chemicals in the workplace is a continuously evolving process that has the goal of assuring the safety of workers without a severe disruption of the efficiency and productivity of operations. The evaluation of risks involved in manufacturing, transportation, construction, and service industries (to name a few) incorporate many assumptions and uncertainties. Assumptions and uncertainties are unavoidable because of our inability to accurately know exposure conditions and systemic human responses. We are unable to know these conditions and responses both because they are hard to measure and extremely variable. One way to compensate for uncertainties is to use estimates that err on the side of safety. The risk assessment process involves the estimation of contact with a chemical (exposure), appraisal of protection provided by the skin, and evaluation of any resultant toxic effects. Toxicity depends on both the external dose and the exposure time. Different mechanisms of action of individual chemicals may cause the dermal dose or the exposure time to be more important, depending on metabolic rates and whether the toxic chemical is the parent or the metabolite. Haber's Law (Haber, 1924) suggests that the toxic effect of an inhaled chemical is related to the product of the air concentration and the exposure time. The effect of concentration and time on systemic toxicity is not so simple with dermal exposures. The ultimate goal of these assessments is to determine safe exposure levels that can be used as a maximum acceptable level in the workplace. There are two major areas of concern with skin exposures: the skin as a target for toxicity and the skin as a portal of entry for chemicals that cause systemic toxicity. Although the skin as a target organ is extremely important, it is not discussed here. The goal of this document is to discuss parts of the assessment process that are important for systemic toxicity from dermal exposures, not to be all-inclusive of the risk assessment process.

Estimating exposures in the workplace requires the determination of the amount of chemical in contact with the skin (the external dose) (Figure 1).

Chemicals can end up directly on the skin in any possible physical form — solid, liquid, vapor, or aerosol. Exposure to solids on the skin can occur as powders or larger particles, and they may persist on the skin until the hands are washed. Solids can also be mixtures of variable proportions. Particle size may affect the contact with the skin and therefore the rate of penetration. Penetration of chemicals through the skin from the solid form has not been studied extensively. Often, solid chemicals are applied experimentally in an acetone vehicle that has been shown to affect the rate of penetration (Scheuplein and Ross, 1970)

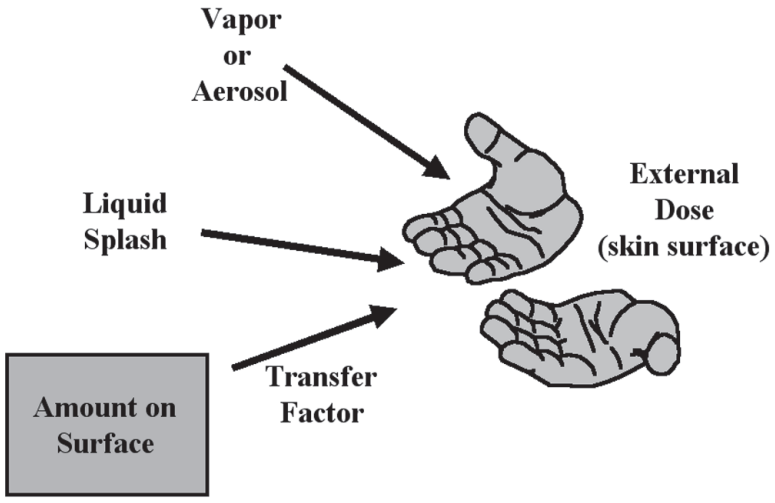

FIGURE 1. Possible contributions to external dose on the surface of the skin.

and therefore are not representative of an occupational situation.

Liquid exposures to the skin may be pure liquid, mixtures of nonaqueous liquids, or a primarily aqueous solution. Most of the skin penetration data are from aqueous vehicles, and this appears to be the primary concern with environmental regulations (USEPA, 1992). Liquid exposures can be a splash or immersion and evaporation from the skin surface may or may not occur, depending on the exposure scenario. Liquids have the potential to change their own rate of penetration by affecting hydration, defatting, or corroding the skin (Flynn et al., 1987). Liquid exposures are probably the most important type of exposure in the workplace.

Vapor or aerosol exposures to the skin are also possible. In general, the external concentration (and therefore the driving force) would be smaller with vapors than liquids or solids. Skin penetration of some volatile chemicals has been studied, and estimates of the amount of chemical that might come through the skin compared to inhalation when the whole body is exposed have been made (Tsuruta, 1989; McDougal et al., 1990). In some ways, vapor exposures are simpler than the other exposures because there is no vehicle other than air and minimal potential for defatting or changing hydration of the skin. Aerosols may act like a liquid on the skin surface if they condense. In most cases, vapor absorption through the skin would not be of concern unless a respirator is worn because the majority of the body burden would come from inhalation.

Chemicals can also be transferred to the skin by contact with clothing, tools, equipment, or other surfaces in the workplace. Transfer factors (or accumulation factors) are used to estimate the amount of chemical that ends up on the skin when chemical concentrations on surfaces are known. These factors are usually estimated empirically as the ratio between the amount of chemical that ends up on the skin after contact and the amount of chemical that was on the environmental surface. These factors can have a tremendous impact on the estimation of external dose. An accurate estimation of external dose is a key step in the risk assessment process.

Once the external dose has been estimated, the next step is to estimate penetration through the skin and therefore the internal dose for specific scenarios of interest (Figure 2). Exposure parameters (surface area exposed, exposure duration, and frequency of exposure) need to be estimated and have a big impact on the internal dose. The other big factor is the rate of chemical penetration through the skin, which is dependent on the vehicle or medium in which the chemical is presented to the skin. Penetration rates or flux are determined experimentally or estimated using a correlation approach.

The skin is a good barrier, particularly to hydrophilic chemicals and water. There are many methods that are used to measure penetration rates in the laboratory. Other chemicals or mixtures of chemicals that are on the skin may increase or decrease the penetration rate of the chemical of interest. Fick's Law of Diffusion (designed for

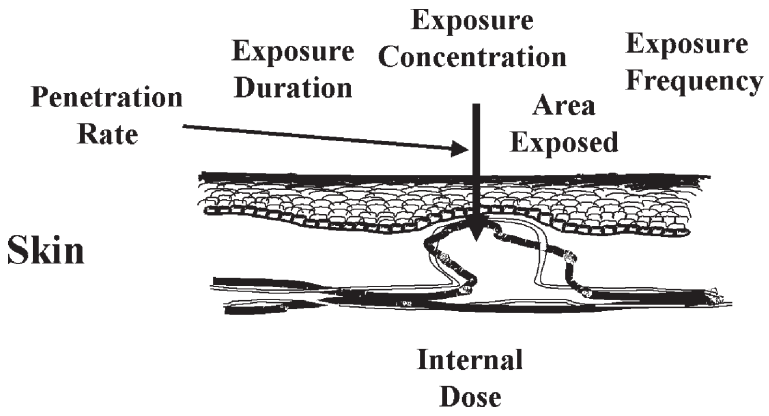

FIGURE 2. Factors that affect internal dose once the external dose is known.

membranes) is often used to predict the effects of concentration, surface area, and thickness of the skin on the flux across the skin.

Safe exposure levels can be estimated from external doses or internal doses, depending on the toxicology studies that are available (Figure 3).

Quality and type of toxicology studies available are extremely variable. The most useful toxicology study for dermal risk assessment would be a skin toxicity study in humans, which mimics the exposure scenario of concern. This type of study is almost never available. Sometimes studies in laboratory animals are available where the animals have been exposed by the dermal route and toxicology endpoints or lethality are quantified. Route-to-route extrapolation is frequently required to estimate toxicity from dermal contact. In order to use toxicology studies from oral or inhalation routes of exposure, it is often necessary to make estimates of internal dose from each route so that toxicological information can be extrapolated from the other routes of exposure to the dermal route.

Safe or recommended dermal exposure levels frequently can be estimated based on dermal toxicity studies, route-to-route extrapolations, and internal dose calculation. When used in conjunction with industrial hygiene measurements, these dermal exposure levels are used as "not to be exceeded" levels in the workplace and therefore affect processes and personal protection in the workplace. Another approach is to start with the industrial hygiene measurements and go through a process called "risk characterization", where the ratio of workplace levels to safe or recommended levels is determined and used as the basis for determining if changes in personal protection or processes need to be made in the workplace.

The purpose of this manuscript is to critically review some of the methods and assumptions that are currently used in calculating, predicting, or evaluating dermal exposures in the workplace. The focus here is on the calculations and models that are ultimately used in dermal risk assessment, that is, internal dose calculations, route-to-route extrapolations, safe level determinations, and risk characterizations. Recommendations for improvements in research methods or extrapolation procedures are made when possible.

II. INTERNAL DOSE ASSESSMENT

There are at least four different methods that are used for predicting an internal dose once an external dose has been estimated. They differ in the type and amount of information required for the calculations, in the simplifying assumptions that are made, and in the reliability of the answer. Internal dose can be predicted from external dose based on: (1) the empirical measurement of fraction of applied dose absorbed; (2) measured (or estimated by correlations) steady-state flux or permeability; (3) steady-state flux or permeability adjusted by the square root of time; and (4) biologically based mathematical models. Before reviewing these methods for internal dose assess-

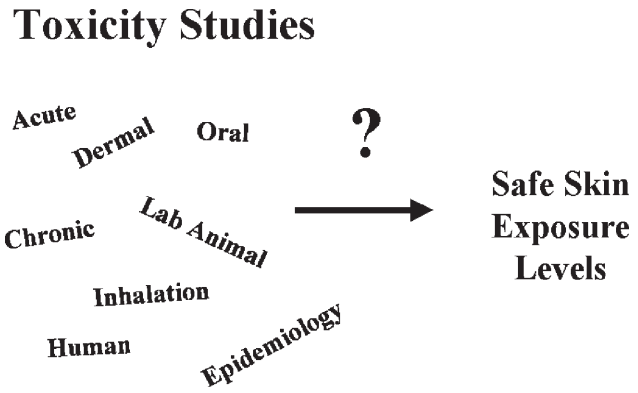

FIGURE 3. Safe skin exposure levels are determined from toxicity studies that usually do not directly address skin exposures in humans.

ment, it is useful to understand the theory and assumptions that are inherent in these assessments. See the Glossary for definitions.

A. Flux and Permeability Theory

Flux, or the amount of chemical that penetrates per unit of time, has been described mathematically by Fick's Law of Diffusion for membranes (Marzulli et al., 1969; Michaels et al., 1975):

$$J = D_m \frac{dC_m}{dx} \cong D_m \frac{\Delta C_m}{\delta_m} \qquad 1$$

where the flux ($\boldsymbol{J}$), in mg/cm^2 per h, of a chemical across a homogeneous membrane is proportional to the concentration difference between the membrane outer surface and the membrane inner surface ($\boldsymbol{\Delta C_m}$), in mg/cm^3, and inversely proportional to the thickness of the membrane ($\boldsymbol{\delta_m}$), in cm. $\boldsymbol{D_m}$ is chemical diffusivity in the membrane, in cm^2/h. Fick's Law with modifications is commonly applied to estimating the flux across the stratum corneum (McKone, 1993) or the skin as a whole (Michaels et al., 1975). In order to apply Fick's Law for membranes to skin penetration, many assumptions must be made. One assumption is that concentration is proportional to thermodynamic activity (which is the actual driving force in Fick's Law) with dilute concentrations and vapors. Another assumption is that the chemical concentration at the inside boundary of the membrane is at or near zero (Michaels et al., 1975), and therefore the concentration difference ($\boldsymbol{\Delta C_m}$) can be replaced by the concentration in the skin in contact with the chemical on the surface ($\boldsymbol{C_{skin}}$):

$$J \cong D_{skin} \frac{C_{skin}}{\delta_{skin}} \qquad 2$$

where the diffusivity ($\boldsymbol{D_{skin}}$) and the thickness ($\boldsymbol{\delta_{skin}}$) also refer to the skin. The concentration in the skin just below the surface ($\boldsymbol{C_{skin}}$) is hard to measure, but the concentration in the vehicle in contact with the skin ($\boldsymbol{C_{veh}}$) can be measured easily. The relationship between the concentration in the vehicle and concentration in the skin is predicted by a partition coefficient ($\boldsymbol{R_{Skin/veh}}$), assuming steady state (McKone and Howd, 1992):

$$R_{skin/veh} = \frac{C_{skin}}{C_{veh}} \qquad 3$$

The partition coefficient is determined experimentally by measuring the ratio of concentrations in two different media. Octanol/water partition coefficients are the most available partition coefficients (Hansch and Leo, 1979), and there are methods to predict them when they are not available (Gombar, 1999). This partition coefficient gives a measure of relative lipid/water solubility. Skin/vehicle partition coefficients have to be measured experimentally (Mattie et al., 1994), because there are very few available in the literature, and there is no accepted method for estimating them. Mattie and co-workers (1994) showed: (1) that the correlation between octanol/water partition coefficients and measured skin/air partition coefficients was poor ($r^2 = 0.20$), and (2) that skin/air partition coefficients correlated well with measured permeability coefficients ($r^2 = 0.93$). Combining Equations 2 and 3 gives:

$$J \cong D_{skin} \frac{R_{skin/veh} \times C_{veh}}{\delta_{skin}} \qquad 4$$

Experimentally, steady-state flux is divided by the concentration in the vehicle (when the concentration is constant) to estimate a permeability coefficient ($\boldsymbol{K_p}$) that is assumed concentration independent (Marzulli et al., 1969):

$$K_p = \frac{J}{C_{veh}} \qquad 5$$

If we solve for flux and compare with Equation 4, it is apparent that the permeability coefficient is a composite of diffusivity, thickness, and the partition coefficient:

$$J \cong K_p C_{veh} \cong \frac{D_{skin} \times R_{skin/veh}}{\delta_{skin}} C_{veh} \qquad 6$$

Therefore, the permeability coefficient ($\boldsymbol{K_p}$), which is also called $\boldsymbol{P}$, is specific for the species studied and the vehicle, if any, from which the penetration was measured. A modification of Equation 5

is the basis for many calculations of internal dose. Flux, as expressed in Equation 6, has units of mass per area-time. It is often useful in the internal dose calculations to express the internal dose as mass (***M***). We can get from:

$$J = K_p \times C_{veh} \quad 7$$

to:

$$M = K_p \times C_{veh} \times A \times t \quad 8$$

if we multiply both sides of Equation 7 by area and time. This is equivalent to:

$$M = P \times A \times C \times t \quad 9$$

where ***M*** is internal dose or mass, ***P*** is the permeability coefficient (same as K_p, area/time), ***A*** is skin area exposed, ***C*** is concentration on the surface (mass/volume), and ***t*** is exposure time. Equation 9 is commonly used in many risk assessment procedures (Paustenbach, 2000; Bos et al., 1998, Sartorelli et al., 1998). This equation is useful when the external chemical dose is in the form of a liquid or a mixture and the amount of chemical on the surface is expressed as a concentration. It is essential that the ***P*** was experimentally determined from the same liquid or mixture as the scenario of interest. The permeability coefficient is most useful for quantifying the penetration from chemical solutions that may vary in concentration, because the permeability coefficient is concentration independent for vehicles (Chandrasekaran et al., 1978) or vapors (McDougal et al., 1985).

The flux is most useful for quantifying the penetration of pure chemicals (solid or liquid), because the thermodynamic activity is always the same; therefore, the flux should theoretically be the same, assuming that all other conditions are equal (Barry et al., 1985). What does change with solids is the relationship between mass and surface area covered. When the external chemical dose is in solid or powder form, the external dose is often expressed as surface density (mass per area). As surface density increases, there becomes a point where a further increase in surface density does not increase flux. This is the point of maximum flux (J_{max}) that can be determined experimentally by placing excess solid chemical on the skin surface (monolayer or more). With a powder or dust, a slightly different modification of Fick's Law can be used:

$$M = J_{max} \times A \times t \quad 10$$

where ***M*** is internal dose or mass, J_{max} is maximum flux (mass/area-time), ***A*** is skin area exposed, and ***t*** is exposure time.

Assumptions — When Fick's Law is applied to skin penetration, the following assumptions are made regardless of the method of internal dose calculation:

- The skin is a homogeneous membrane.
- The flux of the chemical across the skin is solely due to passive diffusion.
- The concentration of chemical on the underside of the skin is not important.
- The measurement of flux is at steady-state.
- The values of permeability coefficient and the flux are assumed to be dependent on the thermodynamics of the exposure (i.e., solid or liquid and whether or not there is a vehicle).
- The permeability coefficient and the flux are assumed to be specific for the animal species in which they are measured.

B. Calculations Based on Empirical Measurements of Fraction Absorbed

Several calculations of internal dose use the "fraction of applied dose absorbed through the skin". The AIHA Exposure Assessment Strategies Committee recommends the following calculation of absorbed (internal) dose (Mulhausen and Damiano, 1998):

$$DA = S \times Q \times FQ \times ABS \times WF \quad 11$$

where ***DA*** is dermal absorbed dose rate per day (mass/time), ***S*** is skin surface area, ***Q*** is quantity deposited on the skin per event (mass/area-event), ***FQ*** is number of events per day (dimensionless), ***ABS*** is fraction of applied dose absorbed through the skin during the event (dimensionless), and ***WF*** is weight fraction of the substance in the mixture (dimensionless). This calculation uses surface area exposed (***S***) to make an adjustment

that is consistent with Fick's Law, which says the amount absorbed (***DA***) would be directly proportional to the area exposed (***S***). The mass on the surface per event (***Q***) is also directly proportional to the amount absorbed (***DA***), but the units of ***Q*** are mass per area (surface density) instead of mass per volume (concentration) as in Fick's Law. Surface density is a common way to express concentration on surfaces, but because the units are different from concentration, Fick's Law needs to be adapted to use surface density. ***ABS*** is the ratio of absorbed dose to applied dose.

U.S. EPA (1992) recommended a conceptually similar equation to calculate percutaneous absorption of chemicals from soil:

$$Uptake = C \times A \times r \times B \qquad 12$$

where ***C*** is concentration of chemical in soil (mg/g), ***A*** is surface area exposed, ***r*** is soil-to-skin adherence rate (g/cm^2), and ***B*** is the cutaneous bioavailability (unitless). In this case, uptake (mass) is directly proportional to concentration and area according to Fick's Law. A new parameter, ***r***, adjusts for the amount on skin surface. Because it is the fractional absorption parameter, ***B*** is equivalent to the ***ABS*** in Equation 11.

In the Superfund risk assessment guidance documents, EPA (1989) recommended a more complicated but similar approach to estimating internal dose from soil:

$$AD = \frac{CS \times CF \times SA \times AF \times ABS \times EF \times ED}{BW \times AT} \qquad 13$$

where ***AD*** is absorbed dose (mg/kg/day), ***CS*** is chemical concentration in the soil (mg/kg), ***CF*** is conversion factor (10^{-6} kg/mg), ***SA*** is skin surface area available for contact (cm^2/event), ***AF*** is soil-to-skin adherence factor (mg/cm^2), ***ABS*** is absorption factor (unitless), ***EF*** is exposure frequency (events/year), ***ED*** is exposure duration (years), ***BW*** is body weight (kg), and ***AT*** is averaging time (days).

Assumptions — When fractional absorption data are used to calculate internal dose, the following assumptions are made:

- The surface density (mg/cm^2) in the risk assessment scenario is identical to the experimental surface density. If there were "excess chemical" which was not available for absorption in the experimental determination, exactly the same amount of "excess chemical", would be present in the scenario for risk assessment.
- The time for absorption in the risk assessment scenario is identical to the time over which the experimental absorption was determined.
- The state of occlusion (occluded or nonoccluded) is assumed the same for the experimental study and the risk assessment scenario. Occlusion can drastically change the rate of penetration by increasing water content in the skin.
- If radioactive chemical was used to experimentally determine fractional absorption, the radioactivity accurately reflects parent chemical, not metabolite or degradation product.

Weaknesses — The primary weaknesses of this approach relate to the fact that it is a strictly empirical approach that is not based on first principles like flux measurements. The weaknesses fall into the general categories of dose and time extrapolations, as outlined below:

Equations 11 through 13 are somewhat logical and mathematically consistent, but a limitation lurks in the experimentally measured ratio of the absorbed to the applied dose. The fraction of applied dose absorbed (***ABS*** or ***B***) is a seemingly simple experimental parameter that is measured by determining disappearance of radioactive chemical from the surface (Feldman and Maibach, 1967; Anjo et al., 1980) or the appearance of radioactivity in the receptor solution of a diffusion cell (Franz, 1975; Anjo et al., 1980; Bronaugh et al., 1982). Expressing penetration as a fraction of applied dose may cause large errors, because this empirical measurement is not robust to variations in surface loading and exposure times.

The fraction of applied dose is not constant with different surface loading, even in the laboratory under controlled conditions. The fraction of ^{14}C testosterone absorbed (Table 1) illustrates this. (Although testosterone is not a workplace chemical, this article is used to illustrate several points, because the authors provided enough data for analysis.)

As the applied mass goes up 100-fold, the actual mass absorbed increases only 25-fold (0.51 to 12.6 μg), thus the percent absorbed *decreases*

TABLE 1
Time Course of percent of dose of ^{14}C-testosterone applied to the forearm (Anjo et al., 1980). Under each surface density, the percentage is listed for each collection interval with the mass in micrograms listed in parentheses. Data determined by urinary excretion after forearm application.

Hours	4 μg/cm^2 dose	40 μg/cm^2 dose	400 μg/cm^2 dose
0-12	1.78 (0.07)	0.41 (0.16)	0.47 (1.87)
12-24	4.40 (0.18)	2.28 (0.91)	0.60 (2.40)
24-48	3.77 (0.15)	3.02 (1.21)	0.94 (3.74)
48-72	1.61 (0.06)	2.14 (0.85)	0.53 (2.11)
72-96	0.86 (0.03)	1.06 (0.42)	0.34 (1.34)
96-120	0.43 (0.02)	0.53 (0.21)	0.29 (1.15)
Total	**12.9% (0.51 μg)**	**9.4% (3.77 μg)**	**3.2% (12.6 μg)**

by 75% ([12.9-3.2]÷12.9). The fact that percent absorbed and mass absorbed are inversely related when the surface density is increased illustrates the fundamental problem with using fractional absorption data to extrapolate to surface densities that were not included in the experimental determination.

If the empirical fraction absorbed determined from the 4 μg/cm^2 experiment were used to extrapolate to a risk assessment situation where 400 μg/cm^2 was applied over 1 cm^2, we would project an internal dose of 51 μg when the actual internal dose (according to the Anjo's experiment) would be 12.6 μg, a fourfold overestimation. Fractional absorption values should not be used to extrapolate to other skin loading conditions.

The error in the calculation is greatest when the surface density exceeds the surface density of a "monolayer". With a monolayer, the maximum amount of chemical possible is in contact with the skin and adding more chemical increases the external dose but will not affect the internal dose. Consider the experimental situation where a defined skin area is completely covered with chemical (monolayer) and more is added. The absorption rate cannot increase because the additional chemical is not in contact with the skin. Yet, the additional chemical would be included as applied chemical and would decrease the fraction absorbed. Figure 4 shows that somewhere between the middle and highest surface densities in the Anjo study, the surface loading was more than a monolayer; otherwise the relationship between applied and absorbed dose would be linear. Here the relationship is certainly not linear past 40 μg/cm^2.

The relationship described by Fick's Law (flux is proportional to mass on the surface) does not apply when there is excess chemical in the experimental situation or in the risk assessment situation. Fortunately, it is unlikely that a monolayer would be exceeded in a human exposure situation except with prolonged immersion in a liquid. However, unless the experimenter was careful not to exceed a monolayer, the fractional absorption number that was determined in the lab will not be representative of the risk assessment situation. Said another way: an experimental determination from an infinite dose (greater than monolayer) study will not give a good estimate of absorption from a finite dose (less than a monolayer) exposure situation.

Time is also an essential element that is embedded in any empirical fractional absorption number, because fractional absorption is greater at longer times. Fractional absorption increases with time with both infinite and finite doses. With an infinite dose, flux would be constant and the internal dose would be directly proportional to exposure time. With a finite dose (more realistic situation), the internal dose would still increase with exposure time but not as much, because flux would be decreasing as the amount on the surface was depleted. Figure 5 shows that measuring the fraction absorbed of a finite dose over a short period, such as 24 h, would underestimate the fraction of amount applied that was eventually absorbed if absorption was allowed to be essentially complete (120 h).

With a finite dose, the surface density of the chemical would decrease over time, and as the driving force becomes less, the percent of the initial dose absorbed per hour would decrease (Figure 5) with time. An accurate experimental assessment of total fraction absorbed requires data collection for a long enough period to assure absorption was complete.

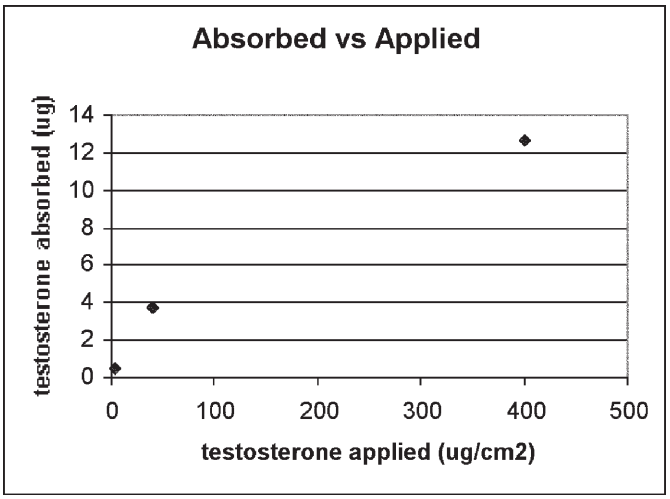

FIGURE 4. Nonlinear relationship between dose absorbed and dose applied. (From Anjo et al., 1980.)

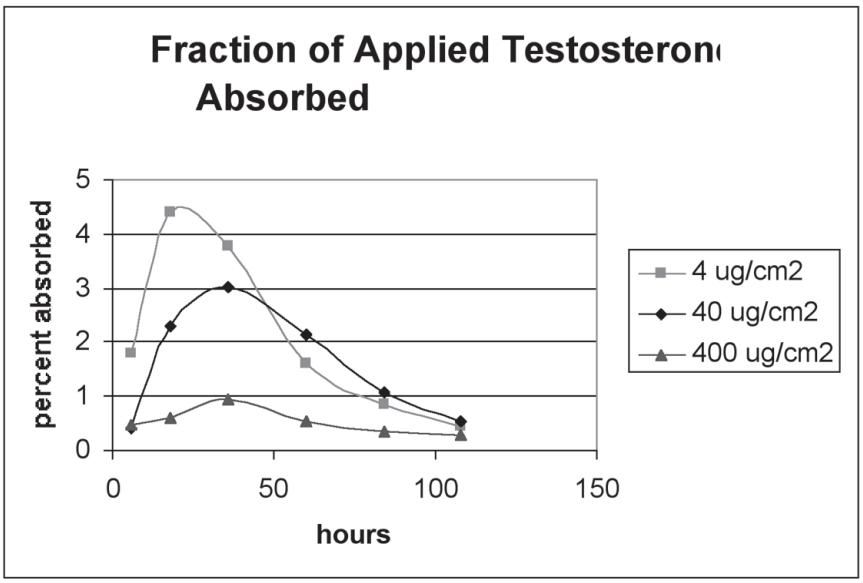

FIGURE 5. Time course of testosterone absorption for up to 5 days. (Data from Anjo et al. (1980) are plotted at the mid-points of the urine collection periods.)

An experimentally determined fraction absorbed should only be used to calculate an internal dose over the same duration, that is, 5 days in this example. If we used a fractional absorption number that represents a 5-day absorption period in the internal dose calculation (Equation 11), we could make a serious error and assume that the fraction absorbed could occur several times a day. Yearly or lifetime estimates of internal dose that are based on fractional absorption, such as Equation 13, could be even more inaccurate.

Strengths — The strength of the fractional absorption approach is that it can deal with a finite dose situation where the concentration of chemical on the skin decreases with time as long as the empirical determination of absorption is done under exactly the same exposure conditions as the risk assessment scenario. Once the external dose is known, the calculation using fractional absorption is simple and intuitive.

Summary/Conclusions — The fractional absorption approach is used by some regulatory agencies for several purposes, the most important of which is for absorption of pesticides from soil. Many laboratory studies report penetration results as percentage absorbed, because of the ease of these measurements using radioactive tracers. The result is a simple ratio that can be simply applied to any external dose. This type of study is useful for the pharmaceutical industry to compare penetration of chemicals, side by side, to determine penetration potential. Unfortunately, fractional absorption measurements do not extrapolate accurately to other surface loadings or exposure times and therefore are not as useful for risk assessments. Calculations of internal dose that use fractional absorption are problematic. Experimentally determined fractional absorption studies may be accomplished with finite or infinite doses. If infinite doses are used, they are inaccurate because some of the chemical is not available for absorption and penetration. If a finite dose is used, the study is only useful if the same dose is the hazard in the risk assessment study. Different exposure times compared to experimental times can cause inaccurate results. The fraction of applied dose should not be used for risk assessments, if possible.

C. Calculations Based on Steady-State Flux

Historically, the most common approach to calculating internal dose has been to use *in vitro* flux or permeability rates that have been determined experimentally under steady-state conditions (see section on *Dermatotoxicology* for experimental details). This method can be used for calculating internal dose from external dose. U.S. EPA (1992) recommended this approach for calculating absorbed dose for inorganic chemicals in water:

$$DA_{event} = K_p^W \; x \, C_W \; x \, t_{event} \qquad 14$$

where DA_{event} is dose absorbed per unit area per event (mg/cm^2-event), K^W_p is the permeability coefficient from water (cm/h), C_w is the concentration of chemical in water (mg/cm^3), and t_{event} is the duration of event (h/event). This equation is essentially the same form as Equation 9, except that the internal dose in Equation 14 is expressed as mass per surface area instead of just mass.

Recently, The Committee on Toxicology of the National Research Council (2000) used this approach for assessing the risks of dermal absorption of fire-retardant chemicals:

$$D = \frac{C_w \times K_p \times A_b \times f_c}{W_b} \qquad 15$$

where D is the dose rate (mass per unit body weight per unit time), C_w is the water solubility of the fire-retardant chemical, K_p is the permeability coefficient (length/time), A_b is the area of the body in contact with the fabric, f_c is the fraction of time spent in contact with the fabric (dimensionless), and W_b is body weight. This equation is conceptually similar to Equation 9.

In the context of these steady-state calculations (Equations 14 and 15), steady-state is defined as the condition when the amount of chemical penetrating through the skin is constant over time. The measurement of flux at steady-state in static diffusion cells (Marzulli et al, 1969; Durrheim et al., 1980) or flow through diffusion cells (Bronaugh and Stewart, 1985) is a well-recognized experimental procedure. The experi-

mental apparatus consists of two chambers, one containing the donor solution and the other holding the receptor solution. The skin membrane separates these two chambers. When done carefully, the determination of flux provides information that is useful for risk assessment purposes.

Flux is determined by placing chemical on the skin in the donor chamber in a way that the concentration on the surface is constant (infinite dose because of the large volume present). The mass of chemical that appears in the receptor solution is measured over time. Figure 6 illustrates how the increase in chemical mass in the receptor solution can become reasonably constant with time. It is during this time that "steady-state" is approached and this part of the plot is where flux is estimated by slope of the line.

In *in vitro* studies, there is nearly always a delay or "lag time" before the chemical shows up in the receptor solution because of the slow diffusion of chemicals through the skin. If we extrapolate the straight line in Figure 6 back to the time axis, we see that there is a lag time of about 2.5 h in this experiment. The lag time is important experimentally because it is necessary to be beyond it before the steady-state flux can be measured. However, lag time is not as important when it is applied to an internal dose calculation (Figure 7) for two reasons: first, lag times are not as apparent with *in vivo* studies as they are with *in vitro* studies; second, in an *in vivo* exposure, the lag time is only a delay of penetration on the front end of an exposure that may be made up on the back end of the exposure.

There is no lag time for *absorption* into the skin. Lag time refers to *penetration* through the skin that represents the time it takes for the chemical to diffuse across the skin and reach the receptor solution (*in vitro*) or the microcirculation in the viable epidermis (*in vivo*). For nonvolatile chemicals, the amount of chemical that is in the skin at the end of the exposure is likely to continue to be slowly absorbed unless it is eliminated by desquamation. For volatile chemicals, the chemical in the skin at the end of the exposure would undergo the competing processes of penetration and evaporation. The final amount penetrated would depend on the ratio of evaporation rate to flux rate. This ratio might be different for each chemical, so it is hard to generalize other than to say that the lag time would be more important to consider for volatile chemicals than nonvolatiles. For a nonvolatile chemical, the lack of penetration during the lag time may be com-

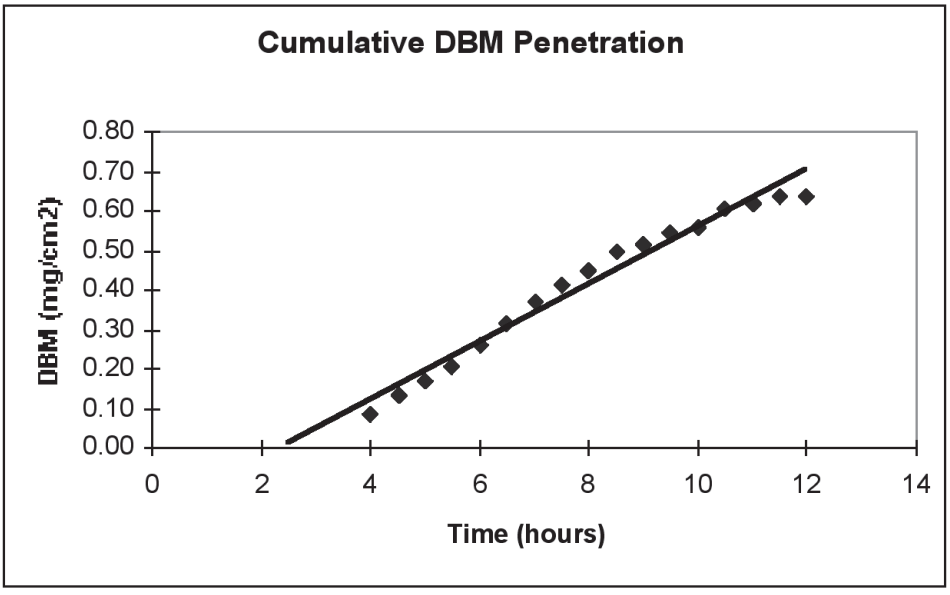

FIGURE 6. Cumulative penetration of dibromomethane (DBM) across a butyl membrane from an aqueous solution in a static diffusion cell. Lag time is where the linear regression is extrapolated back to zero mass in the receptor solution, or about 2.5 h.

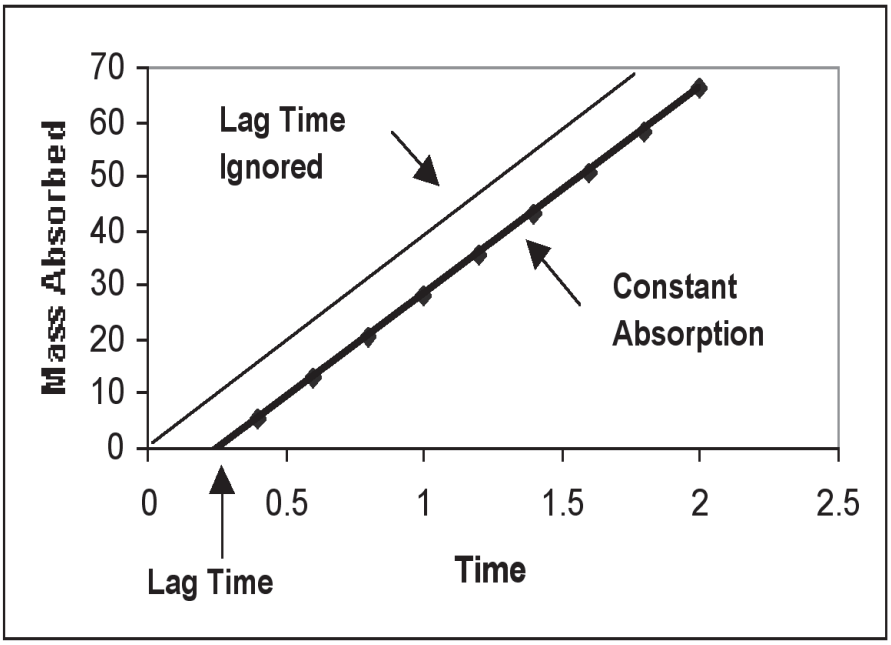

FIGURE 7. Effect of ignoring the lag time in a risk assessment. When the lag time is not taken into account, penetration of chemical would be predicted to start at time zero as shown above. The symbols show theoretical experimental points and the lag time.

pensated by penetration after the end of the exposure, because the chemical in the skin cannot evaporate. For volatile chemicals, the lack of penetration during the lag time may not be compensated by penetration after the end of the exposure because the chemical in the skin has the potential to evaporate rather than penetrate.

Assumptions — The assumptions that are made when the steady-state flux calculations are used to calculate internal dose are the following:

- Concentration on the surface during the exposure scenario does not change (infinite dose or constantly replenished).
- The lag time is relatively small compared with the exposure time.
- Flux measured at steady-state is representative of flux thoughout the exposure period.

Weaknesses — The weakness of the steady-state calculations in equations such as Equations 14 and 15 is disregarding the possibility of a lag time. The internal dose may be overpredicted for any exposure time, but the relative magnitude of the error would decrease as the exposure time increases. The lag time is seen in the receptor fluid, but there is no lag time in disappearance of chemical from the skin surface. If the chemical in the skin cannot evaporate or otherwise be lost, eventually it will penetrate after the end of the exposure and reduce the error. Permeability coefficients (K_p) in equations such as 14 and 15 are vehicle specific. Water is the most common vehicle, but the K_p used must be measured in the actual vehicle of interest. This steady-state calculation is not generalizable between vehicles.

Strengths — The strength of the steady state calculations is that steady-state flux data can be predictive of a wide variety of exposure situations that may differ in exposure time or exposure concentration. In the real world, every exposure situation is different and the ability to extrapolate to other than experimental conditions is essential. Equation 14 has been used widely and is generally accepted.

Summary/Conclusions — The steady-state approach, based on Fick's law, is used frequently by regulatory agencies to calculate internal dose. Not all laboratory studies report their data as flux or permeability coefficient, as required by this approach. Experimental studies that measure flux are more complicated than fractional absorption studies, because of the lag time and the require-

ment for determination of a penetration time course. This approach requires a constant surface concentration in the risk assessment scenario to be accurate. The steady-state approach to calculate internal dose is a very useful approach, especially for long exposure times. The approach is robust to changing exposure concentrations and exposure times. Flux or permeability (which may not always be available as experimental values) is a requirement for the calculation. However, there are several suggested methods to estimate permeability based on correlations of physical parameters (Bunge and McDougal, 1999).

D. Calculations Adjusted for Square Root of Time

A new method was suggested by a U.S. EPA working group in 1992 to improve the accuracy of steady state calculations over short time periods. This calculation was designed to account for the chemical that is in the skin during the lag time. This method was first detailed in the document called *Dermal Exposure Assessment: Principles and Applications* (U.S. EPA, 1992), but has undergone several evolutions (Cleek and Bunge, 1993; Bunge and Cleek, 1995; and Bunge et al., 1995). This equation describes the relationship between the mass and other parameters, such as permeability and time using the square root (Bunge and McDougal, 1999):

$$M = AC\sqrt{\frac{4(K_m\delta)K_p t}{\pi}} \qquad 16$$

where M is internal dose (mass), A is area exposed, C is exposure concentration (mass/volume), K_m is the stratum corneum partition coefficient (unitless), δ is the thickness of the stratum corneum (distance), K_p is the permeability coefficient of the stratum corneum (distance/time), t is time, and π is pi. This calculation was recommended when the exposure time is less than 2.4 times the lag time (if it is known) for that specific chemical. This calculation addresses the flux of chemical into and out of the skin as illustrated by Figure 8.

The flux into the skin from an aqueous solution is highest at the beginning of the exposure and decreases as the skin begins to fill up with chemical. The flux out of the skin into the blood or receptor solution is smallest (zero) at the beginning of the exposure and increases. During the time when the flux into the skin is much greater than the flux out of the skin, the amount of chemical in the skin is increasing. This chemical will eventually (1) be lost at the skin surface (evaporation or desquamation), (2) enter into the blood, or (3) remain in the skin, depending on the characteristics of the chemical and the exposure scenario. Both fluxes taper off as the chemical concentration decreases, either because of depletion

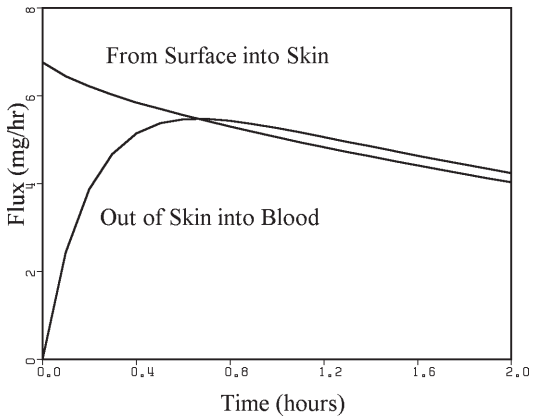

FIGURE 8. Illustration of fluxes into and out of the skin that occur with a finite dose during the time before steady state (when the in and out fluxes become parallel). (From Jepson and McDougal 1997.)

on the surface or chemical buildup in the blood. The square root of time equation compensates for the diminished flux out of the skin during short exposure times.

Assumptions — The assumptions that come with using the square root of time calculation are the following:

- The concentration on the surface during the exposure scenario does not change (infinite dose or constantly replenished).
- The stratum corneum is the primary barrier and sink for chemicals.
- The exposure time is two to three times less than the lag time.

Weaknesses — This calculation requires some parameters that are not always available, such as the stratum corneum partition coefficient. The calculation is nonintuitive and more complicated than the steady-state approach. There have been only a few short-term studies to validate this approach.

Strengths — The strength of this calculation is that laboratory data (permeability coefficients) can be used to predict internal dose over a wide variety of exposure concentrations and at short exposure times.

Summary/Conclusions — This modification of the steady-state approach to calculate internal dose is very useful for short exposure times. It uses permeability calculated from steady-state flux but requires some additional skin parameters (partition coefficients). Like the steady-state calculation, it also requires a constant surface concentration in the risk assessment scenario to be accurate. The approach is robust to different exposure concentrations and exposure times.

E. Calculations Based on Biologically Based Models

In the last decade, biologically based mathematical models have been applied to dermal penetration and estimation of internal dose from water or soil (Chinnery and Gleason, 1993; Rao and Brown, 1993; Corley et al., 2000; Poet et al., 2000). This approach uses skin compartments as a component of physiologically based pharmacokinetic (PBPK) models (McDougal, 1991, 1998; Robinson, 1998). Figure 9 shows a typical skin compartment for a biologically based model.

The schematic of a simple skin compartment (Figure 9) illustrates the processes that affect the amount of chemical in the skin. The upper compartment represents the chemical in contact with the skin surface. The chemical has a concentration (C_{sfc}) and a volume (V_{sfc}) that is spread over a defined surface area (A_{sk}). The skin compartment is represented by a certain volume (V_{sk}) related to the area and depth of the skin. The skin receives blood flow (Q_{sk}) that contains a known concentration of chemical (C_b). The venous blood leaving the skin is described by the skin concentration (C_{sk}) divided by the partition coefficient between skin and blood ($R_{sk/b}$). The concentrations in the skin and other body compartments are solved by simultaneous differential equations. This skin compartment is modeled as well stirred (instant mixing) and homogeneous (no concentration gradient). Other more complicated approaches, such as partial differential equations and multiple skin compartments, may be appropriate to model the skin. The equation for the skin compartment is:

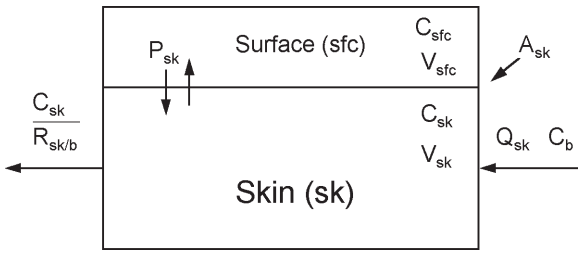

FIGURE 9. Schematic of a biologically based skin compartment.

$$\frac{dM_{sk}}{dt} = Q_{sk}\left(C_b - \frac{C_{sk}}{R_{sk/b}}\right) + P_{sk}A_{sk}\left(C_{sfc} - \frac{C_{sk}}{R_{sk/sfc}}\right) \quad 17$$

where the rate of change in mass in the skin is proportional to the amount of chemical, which is brought in by the blood and diffusion parameters related to Fick's Law. Other models that explicitly describe the concentration gradient in the skin have been developed (Fox et al., 1979; Hadgraft, 1979; Guy and Hadgraft, 1982; and Kubota and Twizell, 1992). These models add an extra degree of complexity that may or may not be necessary to accurately describe skin penetration — it depends on the chemical of interest.

Regulatory agencies have started to embrace the biologically based modeling approach to risk assessment. There are no standard or recommended approaches for modeling the skin to determine internal dose, but EPA has a project that will make recommendations based on the mode of action of the chemical (A. Jarabek, USEPA, ORD, personal communication). These models have the potential to be predictive of route-of-entry effects, that is, skin irritation by predicting not only the amount of chemical that penetrates the skin but also the time course of the amount of chemical in the skin.

Assumptions — The assumptions that are made when simple biologically based models of the skin are used to calculate internal dose are model specific, but in general they are the following:

- The skin can be treated as a homogeneous compartment.
- The concentrations of chemical in blood leaving the physiological compartments are adequately described by venous equilibration calculations.

Weaknesses — Internal dose calculations using biologically based models are complicated and require the ability to use computer engineering simulation software. They require knowing additional parameters, such as several tissue partition coefficients for the chemical of interest. Because of the assumptions inherent in these models, they are easy to abuse and persons without familiarity with them should not use them. This technique is not as available as steady-state calculations.

Strengths — These calculations can be used to extrapolate to a wide variety of exposure conditions. The models are capable of species extrapolation because they are based on biological and physicochemical parameters that can be measured for different species. They can be combined with models of absorption through other routes to address mixed route exposures. They can provide a great deal of information for hypothesis testing and understanding of mechanisms involved, such as metabolism in the skin, when additional parameters are included in the model for testing. Biologically based models can provide a rational method for extrapolating from experimental data on dermal absorption in animals to estimated human dermal uptake, even in the absence of human data.

Summary/Conclusions — Biologically based mathematical models are a recent phenomenon. Their use for calculating internal dose from external dose is becoming more frequent. They are the most accurate way to deal with internal dose because they have the ability to describe any process that can be described mathematically. This approach can estimate penetration from finite or infinite dose experiments because the change in concentration in the external dose can be modeled explicitly. They have the ability to keep track of chemicals absorbed in the skin as well as the amount of chemical that penetrated. The fate of the chemical in the skin after the end of the exposure can be included in the internal dose calculation. This approach is very flexible and can deal with different exposure concentrations and exposure times. The extra potential comes at the cost of extra complexity and requirements for data. The extra information needed is available only for limited number of chemicals. When the data are available, this approach would be the most reliable. The use of skin models would be facilitated by the availability of standard modeling software and validated sets of default physiological parameters.

F. Comparisons with Short-Term Skin Penetration Data

The dermal literature is full of scientists describing a recommended way of calculating internal dose for risk assessment purposes. Often there are claims that one method or another is better, but there are not many unbiased comparisons that

can be used to validate and compare methods. One study (McDougal and Jurgens-Whitehead, 2001) has collected short-term (20 min) skin penetratio1717n data in static diffusion cells for the purpose of comparing the steady state calculation, the square root of time calculation, and a biologically based model over the period of time that the square root of time approach was designed to handle.

Diffusion Cell Experiments — Static diffusion cells were used to determine rates of penetration of dibromomethane (DBM) from a saturated aqueous solution (McDougal and Jurgens-Whitehead, 2001). Rat skin was placed on the receptor chamber containing 6% Volpo/saline. Ten milliliters of DBM-saturated water (11.5 ± 0.6 mg/ml) was placed in the donor chamber. The donor solution, skin, and receptor solution were sampled at time zero and at 4-min intervals for 20 min. The chemical concentration was determined by headspace analysis using gas chromatography with electron capture detection. The experiment was repeated on 6 different days, and the results were pooled (Table 2).

DBM was present in the skin at 4 min, and the amount increased linearly for the duration of the experiment. DBM in the receptor solution was not detectable until 12 min. Nearly all of the chemical (95%) was accounted for either in the donor solution, the skin, or the receptor solution during the experiment. The concentrations in the skin and the receptor solution were considered to be absorbed, and they were combined to compare with the internal dose calculations.

Comparisons with Calculations — Figure 10 shows that the "steady-state" equation (Eq. 9) overestimates the total body burden by about 50% at each time point up to 20 min.

Equation 16, the square root of time calculation, gives a good estimate of the body burden as shown in Figure 11. The calculation overpredicts slightly at 4 min and underpredicts slightly at 20 min.

A biologically based model conceptually similar to Equation 17 provides a good prediction of the total mass of chemical absorbed and penetrated except for a slight under prediction at 20 min, as shown in Figure 12. It also accurately predicts the amount of chemical in the receptor solution during the lag time.

This comparison of the three different approaches to calculating internal dose from external dose illustrates the predictive utility of these equations over time frames less than the lag time for chemical absorption. It is really a hierarchy of approaches from the simple steady state equation to biologically based models. Steady-state calculations are simple and intuitive, square root of time calculations improve accuracy for very short exposures, but biologically based models provide the most accuracy and flexibility. As approaches become more accurate and more complex, the data requirements go up. There will always be a trade-off between the information that is available (or money that can be spent to develop it) and the need for accurate predictions of internal dose.

III. ROUTE TO ROUTE EXTRAPOLATIONS

A. Background and Theory

Route-to-route extrapolations are generally required when toxicity studies are not available for a potential exposure route. The purpose of route-to-route extrapolations is to use toxicity studies or exposure standards from one route to address safety with another route of exposure. Potential exposure routes in occupational scenarios are inhalation, dermal contact, and oral ingestion.

TABLE 2.
Mass (%) of DBM in each of the media during the experiment

Time (min)	0	4	8	12	16	20
Donor	100.0%	101.0%	95.3%	94.2%	96.0%	93.6%
Skin	0.2%	0.6%	0.9%	1.3%	1.6%	2.0%
Receptor	0.00%	0.00%	0.00%	0.04%	0.04%	0.21%
Total	100.2%	101.5%	96.2%	95.5%	97.6%	95.9%

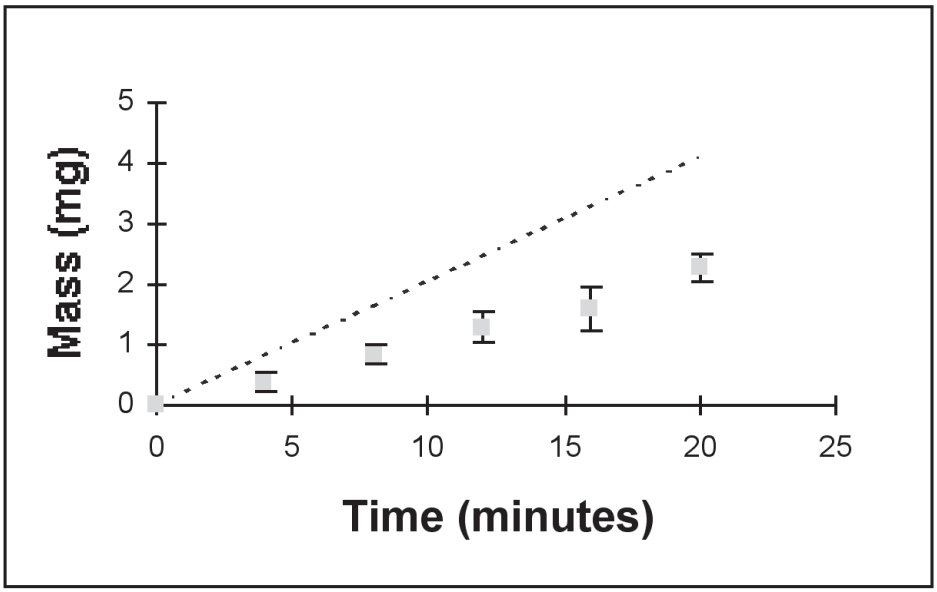

FIGURE 10. A comparison of prediction of total body burden from steady-state calculation (dashed line) with diffusion cell data (squares). Error bars are ± standard deviation.

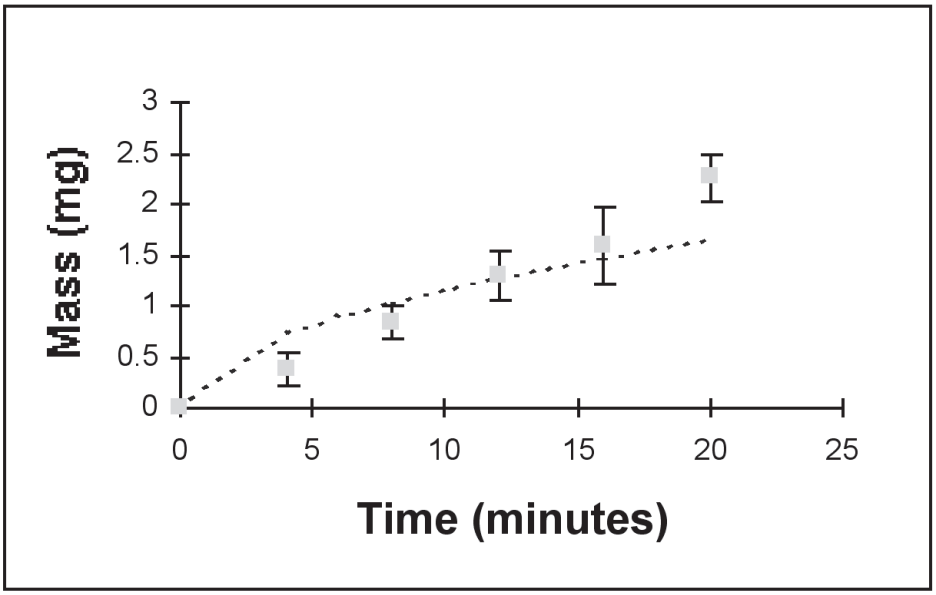

FIGURE 11. A comparison of prediction of body burden from "square root of time" calculation (dashed line) with experimental data (squares). Error bars are ± standard deviation.

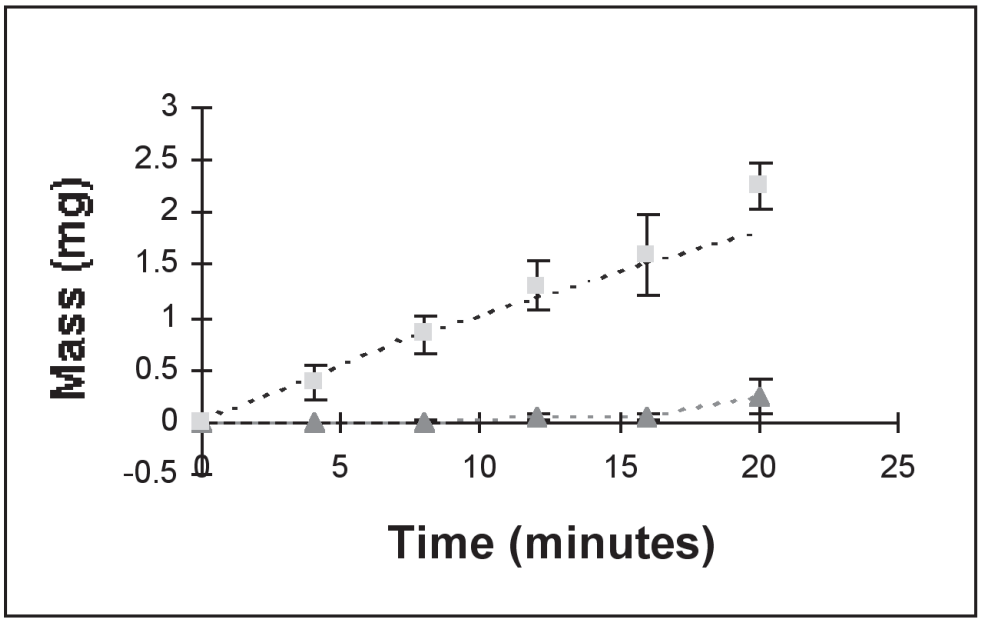

FIGURE 12. A comparison of predictions from biological simulation (dashed lines) with total body burden (squares) and mass in receptor solution (triangles). Error bars are ± standard deviation.

With toxicity tests, the administration of chemicals is often accomplished without the ultimate exposure scenario in mind. The route chosen for toxicity tests may be based on convenience more than potential exposure scenarios. If the chemical is a liquid or solid, the route of choice is often oral. If the chemical is a vapor or very volatile, inhalation is often the chosen route for toxicology testing. Dermal toxicology studies are occasionally accomplished if the route of expected exposure is dermal. Most toxicology tests in the literature are oral exposures, followed by inhalation and then dermal. An RTECS search for multiple dose toxicity studies (excluding skin irritation) revealed that there are more than four times as many inhalation studies (703) as dermal studies (160) and more than 16 times as many oral studies (2983) as dermal studies (RTECS online search, August 1999). Many toxicology tests are motivated by the desire to compare the toxicity of chemicals. In such a case, the route of administration is not particularly important as long as the chemicals to be compared are administered via the same route when that route is the primary exposure route. Otherwise first-pass and dose rate might alter the ranking so that different rankings would be seen across different routes of exposure (Paustenbach, 2000).

When studies from an appropriate route are not available, an extrapolation will be required for a risk assessment. Each route (oral, inhalation, and dermal) has unique characteristics, which makes extrapolation between them complicated. One of the first references available in the literature discussing methods for route-to-route extrapolation was Stokinger and Woodward (1958), who suggested a way to determine a drinking water standard based on an inhalation reference concentration.

With the oral route of exposure or administration, the chemical enters a complicated multicompartmented tube (gastrointestinal tract) that has extremely large surface areas (200 m^2) designed to absorb nutrients and water. This tube, which is open at both ends (mouth and anus), is basically outside the body. Nutrients and water are absorbed from this tube and digestive enzymes and waste products are excreted into it. Transit time for nutrients that enter at the mouth is controlled by physiological processes and may average around 24 to 48 h to allow for complete absorption. Once a dose is administered orally, it is in the gastrointestinal tract until it is absorbed or exits the other end. The simplest meaningful expression of an oral exposure (this is an external dose) is *mass*; that is all we need to know unless we want to compare with a person of another size or with another species. It

would not really matter much if the mass is dissolved in 6 ounces or a liter of water. With oral exposure there is plenty of time for absorption and, because of large fluid movements, concentration does not affect the mass absorbed very much.

With an inhalation exposure, the vapor or aerosol is taken into a "sack" (respiratory tract) that expands and contracts rhythmically. Once in the respiratory tract, the chemical may be absorbed in the very large surface area (80 m^2) of the conducting or gas exchange airways. From the air of the respiratory tract, the chemical can either be absorbed or exhaled. The simplest meaningful expression of an inhalation exposure (external dose) is *mass/volume*, because the volume of air inhaled is also a factor in absorption. In contrast to an oral exposure, the volume that contains the mass is important, because a 1-mg chemical per cubic millimeter air exposure concentration would result in a much higher internal dose than a 1-mg chemical per cubic meter air exposure concentration. Because of the short time available for absorption (due to the tidal nature of the breath), concentration has a big impact on the mass absorbed.

With dermal contact, the chemical is on the skin surface, which functions as a barrier. Once the chemical is on the skin, it must be absorbed into the stratum corneum and viable epidermis before being carried away in the blood. The amount of skin surface covered will affect the amount of chemical that penetrates. The simplest meaningful expression of a dermal dose (external) is *mass/area*. Area is important because it is directly proportional to the internal dose according to Fick's Law (see *Internal Dose Assessment* for details). There are two main approaches to route-to-route extrapolation: Extrapolation factor approaches and biologically based models.

B. Extrapolation Factor Approach

Chemical toxicity is a result of chemical interference with the normal processes of a cell, organ, or an organism. In order for this to occur, the chemical must be absorbed and distributed to tissues. Therefore, toxicity is more directly related to internal dose than external dose. Exposure guidance criteria (no observable effect levels, reference concentrations, threshold limit values, etc.) are external concentrations or levels, and as such are only potential doses, depending on the extent that they are absorbed. Internal doses are related to the external dose, but they are hard to measure because all of the chemical in the various tissues and fluids must be taken into account. When considering exposures by various routes, it is often assumed that toxicity would be the same at a particular internal dose regardless of the route of entry. This assumption forms the basis of the "extrapolation factor" approach to route-to-route extrapolations (Figure 13).

When an oral or inhalation standard has been established, the internal dose can be estimated based on the exposure scenario for which the

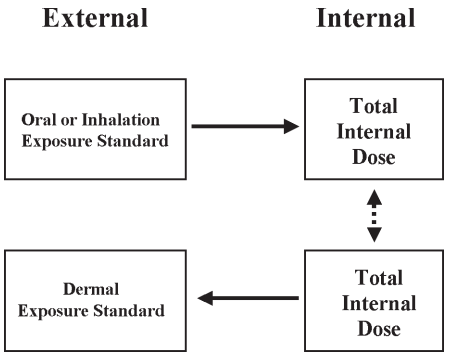

FIGURE 13. Block diagram of an approach to extrapolation of oral and inhalation standards to provide a dermal exposure standard.

standard was developed. Using the estimate of internal dose, the amount of chemical on the skin to get that internal dose can be estimated (sometimes called "backcalculation"). This technique is designed to give an equivalent dermal exposure standard. There are a several ways to convert inhalation and oral external doses to internal doses and then to dermal external doses. Most of them do not have an explicit internal dose calculation, but do it all in one step, using the extrapolation factor and other parameters.

The simplest approach is to use an extrapolation factor as recommended by Wilschut and coworkers (1998). They define extrapolation factor (EF) as "that factor that is applied in route-to-route extrapolation to account for differences in the expression of systemic toxicity between exposure routes."

$$NOAEL_{dermal} = EF \times NOAEL_{oral\ or\ inhalation} \qquad 18$$

This equation expresses the relationship between a no observed adverse effect level (***NOAEL***) based on toxicity studies from oral or inhalation studies and the dermal NOAEL. These authors suggest that the extrapolation factor for a specific chemical could be determined in these ways:

1. **A ratio of NOAELs** — When dermal dosing studies with comparable durations (preferably acute) are available to compare to oral or inhalation dosing studies, the extrapolation factor is the ratio between the NOAELs. This approach requires conversion of units so that the oral or inhalation and dermal NOAEL can be compared. As an illustration, assume an inhalation NOAEL in mg/m^3 and a dermal NOAEL in mg/cm^2 are available and both were performed using rats. In order to compare these standards, both must be converted to the same units — for example, mg/kg body weight:

$$EF = \frac{\left(NOAEL_{inh} \times VR\right) / BW}{\left(NOAEL_{dermal} \times A\right) / BW} \qquad 19$$

Conversion of the inhalation ***NOAEL*** (mg/m^3) requires multiplying by the volume of air breathed during the daily experiment (***VR***, m^3) and dividing by average body weight (***BW***, kg) of the species of interest. The conversion of the dermal NOAEL requires multiplying by the experimental surface area exposed (***A***, cm^2) and dividing by the average body weight (***BW***, kg) of the species of interest. Then, the ratio of both NOAELs, in mg/kg, is the unitless extrapolation factor. NOAELs from oral toxicology studies are often expressed as mg/kg and therefore would not require conversion.

Pepelco and Withey (1985) recommended a similar approach to determining internal doses from any exposure concentration rather than just the NOAEL. Their calculations were based on steady-state absorption and would be applicable for chronic studies. The amount taken up by inhalation was estimated by:

$$D_{inh} = \frac{MV \times C \times t \times F}{BW} \qquad 20$$

where:
D$_{inh}$ is the internal dose from inhalation (mg/kg)
MV is the minute volume (L/min)
C is the exposure concentration (mg/L)
t is the exposure time (min)
F is the fraction of the inhalation dose absorbed (unitless)
BW is the body weight (kg)

For the oral route, the steady state calculation would be:

$$D_{oral} = \frac{DI \times F}{BW} \qquad 21$$

where:
D$_{oral}$ is the internal dose from oral administration (mg/kg)
DI is daily intake (mg)
F is the fraction of the oral dose absorbed (unitless)
Bw is the body weight (kg)

For the dermal route, the steady state calculation would be:

$$D_{derm} = \frac{DD \times A \times F}{BW} \qquad 22$$

where:
D_{derm} is internal dose from dermal application (mg/kg)
DD is daily amount applied per surface area (mg/cm^2)
A is the area exposed (cm^2)
F is the fraction of the dermal dose absorbed (unitless)
BW is the body weight (kg)

Assumptions – The assumptions (which are often not valid) included with this calculation of the extrapolation factor are the following:

- The NOAEL is not based on a route of entry effect, such as respiratory irritation.
- The toxicity studies are based on the same systemic endpoint for determination of the NOAEL.
- The toxicity studies have the comparable exposure durations (ie., both acute or both 90 day).
- The rate of dose administration does not affect the toxic end point.
- The comparison of NOAELs on a dose per day basis doesn't invalidate the extrapolation factor. (In the case of single dose oral and dermal studies, it may take days for complete absorption, but that wouldn't be the case for inhalation.)
- The extrapolation factor calculated from the particular studies available will reflect the general differences in exposure scenarios by those routes for this chemical.
- No physiological change or damage occurs at the site of uptake that would affect uptake. (This could be, for instance, a change in respiratory rate or blood flow in the skin due to irritation.)

Weaknesses — The weakness of this approach is the requirement for appropriate and comparable toxicity studies by dermal and another route. Comparable laboratory studies frequently are not available. The dermal exposure is more likely to be a slow, prolonged delivery and the oral or inhalation exposures might have a more rapid absorption rate. The differences in dosing interval in the toxicity studies may have a big impact on the ratio of NOAELS, because each individual NOAEL is sensitive to the dosing interval. Because of metabolism, repair, or tolerance mechanisms, the rate of dose administration could have a big impact on toxicity. NOAELs have an inherent limitation because by definition they must be one of the tested doses. Ratios of benchmark doses, which are not restricted to the tested doses, would be an improvement, if available.

Strengths — The strength of this approach is the logical and straightforward calculation that requires only toxicity studies, not absorption or bioavailability factors. This approach could be expected to give better estimates of the extrapolation factor because the toxicity tests would reflect distribution, metabolism, and the dynamics of the toxic injury over the specific duration (i.e., acute, subchronic, or chronic).

Summary/Conclusions — Calculating the extrapolation factor using a ratio of effect levels may be useful when the required toxicology studies are available or the chemical is of enough interest to obtain the toxicology data. This would probably be the most accurate (or least uncertain) approach to calculating the extrapolation factor.

2. **A ratio of the estimates for absorption by each route** — When absorption or bioavailability data are available for each route, the extrapolation factor can be calculated as the ratio of the experimental absorption data (expressed as percentage absorbed) available for each route:

$$EF = \frac{oral\ or\ inhalation\ \%}{dermal\ \%} \qquad 23$$

The extrapolation factor can be simple as in Equation 23, or it may also incorporate safety factors or unit conversions (Equation 24).

The Netherlands Organisation for Applied Scientific Research (TNO) (Wilschut et al., 1995) has recommended the following approach to extrapolate from an animal oral NOAEL (mg/kg-day) to a dermal health-based recommended-exposure level (mg/day):

$$EF = \frac{dermal\ factor}{oral\ factor} \times \frac{1}{assessment\ factor} \times 70\ kg \qquad (24)$$

where:
EF is the extrapolation factor (1/kg);
dermal factor is the correction factor for dermal absorption (unitless);
oral factor is the correction factor for oral absorption (unitless);
assessment factor is a factor that accounts for the confidence in the available data (unitless). It is the same as a safety or uncertainty factor.

This equation adjusts the NOAEL for rats to humans by multiplying by the default human body weight, 70 kg. It also uses dermal and oral absorption factors that are unitless and would come from fractional absorption studies. One would expect that the ratio of the dermal to oral factors would be less than one to much less than one, because the skin is a barrier and the gastrointestinal tract is designed for absorption. When the ratio of the dermal to oral factors is small, the effect on the NOAEL would be to increase it or raise the safe level. The assessment factor is basically an uncertainty factor that can be used to lower the dermal NOAEL when confidence in the data is poor.
In vivo data characterizing fractional absorption can be very variable in quality because of experimental requirements. The oral route of administration is probably the most straightforward route to determine percentage absorbed, but oral bioavailability studies require collecting feces for several days to determine what is not absorbed. Some chemicals can be excreted in the bile and end up in the feces, so determining what percentage of the administered dose ends up in the feces may underestimate oral absorption. Accurately determining absorption from an inhalation study requires monitoring the difference between inhaled and exhaled breath, which is not something that is routinely done. The determination of fractional absorption from dermal studies is sensitive to surface loading and time over which the absorption is measured (see weaknesses under *Calculations based on Empirical Measurements of Fraction Absorbed*).
In vitro experiments characterizing fractional absorption, such as skin penetration studies in diffusion cells and oral absorption from isolated stomach or intestines, are much easier to carry out. However, these experiments may not be representative of the whole animal situation because hormonal, circulatory, metabolic and immune responses are usually not intact with *in vitro* experiments.

Assumptions – When extrapolation factors are calculated from an estimate of absorption by each route (not default), the assumptions are the following:

- The NOAEL is not based on a route of entry effect, such as respiratory irritation.
- Time over which the fractional absorption is measured is appropriate for both routes.
- If radioactive chemical was used to experimentally determine fractional absorption, the radioactivity accurately reflects parent chemical, not metabolite or degradation product.
- The experimentally determined absorption data reflect absorption in a realistic exposure scenario.
- One fractional absorption number can capture the dynamic process of absorption over time.
- The dynamics of injury (target tissue concentration, receptor activation, and repair processes) are not important.
- Toxicity is directly related to internal dose. This ignores the effect of dose rate on toxicity.

- If *in vitro* fractional absorption is used, it accurately reflects the *in vivo* exposure situation.

Weaknesses — When the difference in fractional absorption between the routes is very large (i.e., 0.01% vs. 80%), any variability or inaccuracy in the measured absorption number can have large effects on the extrapolation factor and the resulting route-to-route extrapolation. This approach would not take into account distribution, metabolism, or the dynamics of toxicity, and therefore would contain more uncertainty than the ratio of NOAEL approach.

Strengths — This is a good approach when carefully determined absorption estimates are available. It might be more cost-effective to determine the fractional absorption data required than to do the one or more dermal, oral, or inhalation exposure effect studies.

Summary/Conclusions — Determining an extrapolation factor using experimental fractional absorption data should give a fairly accurate route-to-route extrapolation. This approach would be good when resources are available to measure fractional absorption data for both the route where toxicity studies are available and for the dermal route. This would be the second best approach to calculating the extrapolation factor.

3. **A range of studies that define a default extrapolation factor between routes** — When neither toxicology data nor absorption data are available by dermal and another oral route, it still may be necessary to make some estimate of an extrapolation factor. In this case, TNO (Wilschut et al., 1998) recommends default values of extrapolation factors that range from 1 to 0.1. A default value of 1 would result when fraction of dose absorbed via the dermal route is equivalent to the fraction of dose absorbed via inhalation or oral administration. The fact that the skin is a barrier and the lungs and gastrointestinal tract are organs of absorption suggests that this would almost never be an accurate default. A default value of 1 for dermal penetration would err on the side of safety. Pepelco and Withey (1985) analyzed a set of 49 RTECs chemicals that had both oral LD_{50}s and inhalation LC_{50}s. They found, after conversion to equivalent doses, that toxicity was nearly always greater by the inhalation route than the oral route. They also suggested that if absorption efficiency, first-pass effects, and critical target organs were not considered, errors approaching three orders of magnitude could be made in the extrapolation. In contrast to this, Owen (1990) collected inhalation and oral absorption coefficients from the literature and reported that when the absorption values were not the same, they were evenly split between oral being higher and inhalation being higher. The reason Pepelco and Withey found differences is probably because they looked at the ratio of toxic doses in contrast to Owen who only looked at percentage absorbed. The differences suggest that it is important not to ignore dose rate and mechanisms of toxicity. Wilschut et al. (1998) concluded, based on limited data, that there was no correlation between observed dermal NOAELs and predicted dermal NOAELs using the default methodology. There is probably not much hope that a general default ratio could be found that would provide acceptable extrapolations for each chemical.

Assumptions — The assumptions included in this approach are the following:

- The relative absorption through all routes for all chemicals will be the same. (This approach ignores recognized differences in absorption across membranes due to ionization and lipid solubility that are important determinants of dermal absorption.)
- The dynamics of injury (target tissue concentration, receptor activation, and repair processes) are not important.

Weaknesses — Extrapolation factors calculated with default absorption ratios appear to provide a quantitative extrapolation, but they could be totally inaccurate. This

approach ignores the importance of pharmacokinetics and toxicity. Enough information to validate general choices for default extrapolation factors is not available.

Strengths — This simple default extrapolation factor approach between the routes would be very useful and easy to apply if it could be validated.

Summary/Conclusions — Determining default extrapolation factors for dermal absorption has not been shown to provide reliable information at this time. This approach should only be used when the other two methods for calculation of an extrapolation factor cannot be used.

C. Biologically Based Models

Route-to route extrapolation using biologically based pharmacokinetic models has the potential to more accurately deal with the relationship between external and internal concentrations. The strength of biologically based models is the ability to deal with non-linear processes such as metabolism, binding, repair, and nonlinear toxic responses. The general description of this approach to calculate internal dose from external dose was described in *Internal Dose Assessment*. Biologically based models can provide much more accurate extrapolations when they are designed to deal with target tissue dose.

An appropriate way to use a biologically based model for extrapolation to the dermal route would be to run an inhalation or oral model at the exposure standard or safe level and determine the target tissue dose. Once the target tissue dose is known, the dermal model can be run iteratively until the target tissue dose from the other route is matched. The external dose or concentration that gives the same target tissue dose as the other route will be the safe dose or standard extrapolated to the dermal route. Several examples of the usefulness of this approach are described below.

Corley and co-workers (1997) exposed one arm of each volunteer to 50 ppm 2-butoxyethanol for 2 h and measured parent chemical and (presumably) toxic metabolite in the blood for up to 24 h. They developed a biologically based model for 2-butoxyethanol pharmacokinetics and used it to compare total uptake from inhalation and dermal absorption at the American Conference of Governmental Industrial Hygienists (ACGIH) TLV of 25 ppm. Their purpose was to determine the proportion of internal dose that would result from inhalation and dermal routes in a whole body exposure. They used the validated model to predict total uptake and the maximum concentration of the metabolite in the blood for various skin exposure areas and respiratory rates. They could just as easily have determined the total absorbed or peak metabolite concentration at the TLV and then iteratively run the dermal model with different vapor concentrations to get the same parent or metabolite level as at the TLV.

Loizou and co-workers (1998) used a biologically based model to compare the dermal absorption and inhalation of *m*-xylene vapor. The model was calibrated and validated from a human study using 12-h exposures to *m*-xylene. The volunteers were exposed to xylene vapors via dermal absorption and inhalation, inhalation alone, and dermal absorption alone. Exhaled breath, blood samples, and urinary levels of the major metabolite, methyl hippuric acid, were used to validate the model. The authors used the model to "backcalculate" the dermal exposure concentration necessary to deliver the same body burden generated by inhalation of 50 ppm xylene for 12 h. They showed that the whole-body, dermal exposure concentration required to get the same body burden and urinary excretion profile was 3000 ppm.

Rao and Ginsberg (1997) used a biologically based model to recommend a safe water level for methyl *t*-butyl ether (MTBE) based on brain and blood levels after exposure to an inhalation standard. Central nervous system depression is a short-term effect of MTBE in animal studies and the basis for an acute Minimum Risk Level (MRL) developed by the Agency for Toxic Substances and Disease Registry (ATSDR). These authors used a validated MTBE model to compare blood and brain levels from the inhalation MRL (2 ppm) with showering and bathing scenarios that had inhalation and dermal components. Instead of "backcalculating" using the model, they chose a water level, 1 mg/L, and showed that the predicted brain and blood levels remained well below the blood and brain levels predicted from a 24-h exposure at the TLV.

Assumptions — The biologically based model approach has several assumptions:

- The NOAEL is not based on a route of entry effect, such as respiratory irritation.
- The assumptions inherent in the NOAEL (or other reference level), such as safety factors and mechanism of action will also be incorporated into the dermal reference level.
- Simplification of the complex biological system into tissue compartments connected by blood flow adequately expresses the pharmacokinetics important for assessing toxicity.
- Unless explicitly addressed in the model, the route of entry does not have a unique metabolism, binding, or sequestration of the chemical.

Weaknesses — Biologically based models require many chemical-specific parameters (tissue partition coefficients and metabolic rates) in addition to species-specific parameters (organ weights, blood flows, and respiratory parameters).

Strengths — The ability to address specific endpoints, such as neurotoxicity, hepatic damage, or cancer, provides a tremendous amount of power to toxicity evaluations. These models are only limited by our quantitative understanding of the biological and biochemical processes involved in pharmacokinetics and toxicity.

Summary/Conclusions — Properly validated biologically based models have a great deal of flexibility to address specific route-to-route extrapolations. This would be the preferred method for extrapolation if appropriate information were available for the models. This approach is very flexible and provides the greatest amount of confidence in an extrapolation.

IV. DERMAL EXPOSURE LEVELS

Recommended maximum or safe dermal exposure levels are often desired for workplace risk assessments. Exposure levels are based on toxicity and mechanism of action studies, and they can be completed without any reference to actual workplace exposure measurements (concentration) or use (duration and surface area) parameters. These dermal exposure levels frequently use internal dose calculations and route-to-route extrapolations as a foundation. In this category, a range of approaches to relay information about safety of dermal exposures is discussed. They range from a general warning ("skin" notation) to two more quantitative, dermal standards — one based on acceptable mass on skin and the other based on safe exposure time. Quantitative dermal standards are more complicated than inhalation standards because of the additional exposure parameter, surface area, which must be considered in addition to concentration and exposure time.

A. "Skin" Notation

ACGIH (2000) uses a "skin" notation to refer to chemicals that have "potential significant contribution to the overall exposure by the cutaneous route." Worldwide, only approximately 275 of the 30,000 chemicals in commercial use have a "skin" notation (Boeniger and Lushniak, 2000). The focus of the "skin" notation is systemic toxicity, not skin irritation or sensitization. ACGIH assigns the notation for any of three reasons:

1. Available data suggest that the potential for penetration via the hands/forearms during the workday could be significant, especially for chemicals with low TLVs;
2. The chemical has a relatively low dermal LD_{50} (1000 mg/kg of body weight or less);
3. Repeated dermal application studies have shown significant effects.

The "skin" notation is only a qualitative measure, that is, it merely separates chemicals into two categories: those for which there exists evidence for substantial absorption and/or toxicity and those for which there is a lack of such evidence. A lack of such evidence does not necessarily mean that toxicity will not occur if dermal exposure occurs. For many compounds there is simply very little information concerning percutaneous penetration or toxicity.

Assumptions — "Skin" notations based on the three criteria above have the following assumptions:

- Hands and forearms are the primary area of concern for penetration.

- Lethality is the only toxicity of concern. LD_{50} studies may not adequately represent all recognized forms of toxicity, such as reproductive, behavioral, and cancer.
- Knowing that a chemical might penetrate through the skin is sufficient information to provide a warning. It is not necessary to bring the rate of penetration into consideration.

There have been many attempts to improve on this approach, which has been suggested to be at least a little bit arbitrary (Scansetti et al., 1988). Fiserova-Bergerova (1990) suggested chemicals that would have the body burden increased 30% above intake at the TLV or chemicals that triple the biological exposures indexes when the skin route is present should be assigned a "skin" notation. She also suggested that a correlation approach could be used to estimate permeability data where none is available. Kennedy and co-workers (1993) suggested a quantitative method of assignment of the "skin" notation based on experimental data. Fiserova-Bergerova (1993) suggested that a criteria comparing dermal absorption rate and pulmonary uptake rate be used to replace the LD_{50} as a criteria for assigning a "skin" notation. This suggestion would improve the skin notation by addressing pharmacokinetics. de Cock et al. (1996) suggested that the criterion should be "when the amount absorbed by both arms and forearms in 1 h could amount to more than 10% of the amount absorbed via the lungs on exposure to the occupational exposure limit (OEL) for 8 h." de Cock's suggestion has the advantage of incorporating any toxic mechanisms that were considered in the determination of the OEL. These suggestions would all turn qualitative criteria into more rigorous criteria that would at least provide some uniformity between chemicals. They would all refine the criteria for giving a chemical a notation, but the result would still be a dichotomy: "skin" notation or no "skin" notation.

Weaknesses — The "skin" notation is qualitative — it only tells the industrial hygienist that he might consider skin absorption when there is a notation. A chemical without a "skin" notation is not necessarily safe; it is more likely that there is just no information available. The rationale behind the current "skin" notation assignments is not entirely clear or consistent.

Strengths — Provides some information about the skin as a potential absorption route.

Summary/Conclusions — The "skin" notation has recognized faults and it is likely that the assignment of the notation will become more consistent and scientifically based. Industrial hygienists should be cognizant of "skin" notations and try to minimize dermal exposures.

B. Banding Approach to Dermal Exposure Risks

Another approach to controlling risks from dermal exposures has been suggested by the Heath and Safety Executive of the United Kingdom (Brooke, 1998; Guest, 1998; Maidment, 1998; Russell et al., 1998; EU Dermal Exposure Network, 1999). This scheme uses readily available hazard information to categorize chemicals into bands of acceptable exposures. This is suggested as an alternative to OELs because according to Russell and co-authors (1998), OELs do not influence the control of exposures, particularly in small firms. Exposures from all routes are categorized under this scheme by the European Union (EU), but only the aspects that relate to dermal exposures will be discussed here. In the EU, suppliers of chemicals classify chemicals according to "risk phrases" on the Safety Data Sheets. There are approximately 27 risk phrases that relate to the type of toxicity, toxic potency, and routes of concern (Brooke, 1998). Table 3 shows the phrases that are related to the dermal route.

The idea is that these phases are available and can be used to assign chemicals to exposure "bands" that will allow control chemical exposures in the workplace. Brooke (1998) describes the exposure bands shown in Table 4.

For example, if a chemical safety data sheet contains the risk phrases R40 (possible risk of irreversible effects) and R21 (harmful in contact with the skin), the chemical would fall in Hazard band B and the acceptable concentrations would be less than 1 mg/m^3 dust or less than 50 ppm vapor. A potentially more hazardous chemical categorized as R39 (danger of very serious irreversible effects) and as R27 (very toxic in contact with the skin) would fall in Hazard band D, which has acceptable limits of less than 0.01 mg/m^3 dust

TABLE 3.

Hazard information (risk phrases) specifically related to dermal exposures that is required by the UK on Safety Data Sheets

R number	Risk phrase
R38	Irritating to the skin
R21	Harmful in contact with the skin
R24	Toxic in contact with the skin
R27	Very toxic in contact with the skin
R43	May cause sensitization by skin contact

TABLE 4.

Dermal risk phrases and the hazard band and target concentrations they are mapped to. See table 3 for description of the dermal risk phrases. From Brooke (1998).

Hazard band	Target airborne concentrations	Risk phrases
A	1-10 mg/m^3 dust 50-500 ppm vapour	1. R38
B	0.1-1 mg/m^3 dust 5-50 ppm vapour	2. R21; 3. R21 plus "possible risk of irreversible effects" (R40)
C	0.01-0.1 mg/m^3 dust 0.5-5 ppm vapour	4. R24; 5. R21 plus "danger of serious damage by prolonged exposure" (R48); 6. R24 plus "danger of very serious irreversible effects" (R39)
D	Less than 0.01 mg/m^3 dust less than 0.5 ppm vapour	7. R27; 8. R24 plus "danger of serious damage to health by prolonged exposure" (R48); 9. R27 plus "danger of very serious irreversible effects" (R39)
S: skin & eye contact	Prevention or reduction of skin (and eye) exposure	10. R38; 11. R43

and 0.5 ppm vapor. Notice that there are some combinations of risk phrases that are not covered, that is, R39 (danger of very serious irreversible effects) and R21 (harmful in contact with the skin), presumably because anything that would have an R39 phrase would have a greater dermal warning such as R24 (toxic in contact with skin).

In this scheme the cut-off values for the oral and dermal routes are the same as for the inhalation route. This effectively assumes that absorption through the skin (and the GI tract) is 100% (Brooke, 1998; EU Dermal Exposure Network, 1999) and tremendously reduces the usefulness and accuracy of this approach for dermal risk assessment.

Assumptions — When the banding approach to dermal risks is used, the following assumptions are made:

- The risk phrases on the safety data sheets are applied to chemicals, by the suppliers, consistently and appropriately. In the US and the EU, material safety data sheet information may be driven by fear of litigation and the desire to warn against every potential danger.
- Absorption through the skin is 100%. There is no distinction made between exposure routes.

Weaknesses — The banding approach is not appropriately adapted for dermal exposures because it does not take into account that the skin is a barrier to absorption.

Strengths — Banding provides more information about how to control dermal risks than a binary approach such as the "skin" notation. Categorical information (risk phrases) can be analyzed in detail and combined in meaningful ways without introducing a great deal of uncertainty. The control band could become part of the Safety Data Sheet and that would not require interpretation by individuals who are familiar with exposure risks.

Summary/Conclusions — This approach has potential, but needs to be refined to provide adequate dermal guidance.

C. Dermal Occupational Exposure Levels

Quantitative dermal occupational exposure levels have been proposed to replace the qualitative "skin" notation (Fenske, 1993; Fenske and van Hemmen, 1994; Bos et al., 1998; Brouwer et al., 1998). It has been suggested that dermal occupational exposure limits would encourage the development and implementation of corrective or preventive actions that could reduce exposures (Boeniger and Lushniak, 2000). Determining safe contact with the skin is not nearly as easy as determining the safe amount of inhaled chemical, because of the complications of surface area exposed and transfer rates from contaminated surfaces. Due to different exposure scenarios, there is no single point in the workplace that can be controlled to limit dermal exposures. There are a variety of surfaces that might become contaminated, and an almost infinite number of possible ways for workers to have dermal contact with them. Fenske (1993) suggests three places where control could be attempted:

1. Biological measures of exposure or internal dose,
2. Levels of deposition on clothing, or
3. Contaminated skin or surfaces in the workplace.

Biological measures of exposure or internal dose would be no different for dermal exposures or inhalation exposures and would give total dose by both routes. Where biological exposure indices (BEIs) are available (ACGIH, 2000), they could be used to determine whether workplace processes involving dermal absorption need to be modified or prevented. ACGIH recommends biological monitoring be considered for chemicals with a "skin" notation. If the BEI is exceeded and there is potential for dermal absorption, changing the process or adding personal protective equipment for the dermal route may reduce the BEI to acceptable levels. The purpose of dermal occupational exposure levels is to be able to monitor the workplace and decide if it is safe for workers to interact with it (Cherrie and Robertson, 1995; Mulhausen and Damiano, 1998); this is a different concept than the BEI, which is a measure of exposure that has already occurred.

Levels of deposition on clothing is a potential place where exposure standards can be set, and some processes such as pesticide use are especially amenable to these measurements. The as-

sumption is that the amount on the cloth would be the same as the amount deposited on the skin. There is uncertainty involved with fabric sampling because fabric is often more absorptive than the skin (Fenske, 1993; Cherrie and Robertson, 1995). Fenske (1993) suggests that patch sampling on clothing cannot provide an accurate measurement of dermal exposures, because of potentially large variability of surface concentrations at various parts of the body.

Recommendations for dermal occupational exposure limits (DOELs) have primarily focused on skin concentrations or workplace surface concentrations (Bos et al., 1998; Fenske and van Hemmen, 1994). Bos and co-authors (1998) suggest "a DOEL should represent the maximum amount of substance (mg) deposited on the skin surface within a given time (usually a workshift), without giving rise to adverse systemic health effects." They also point out that an (indirect) exposure level could be set based on the amount present in the occupational environment, that is, the surfaces of equipment or the outdoor equivalent, residues on foliage. It is recognized that an indirect exposure level such as a surface concentration would require transfer factors (Fenske, 1993), and these transfer factors would be dependent on the exposure scenario (frequency and duration of exposure). Although the preferred DOEL would be an external dose, its determination from existing toxicity studies may require calculations of internal dose and route-to-route extrapolations as described earlier in this document.

The European Dermal Exposure Network has endorsed a DOEL, proposed by Dutch scientists, that has been described (Bos et al., 1998) and partially validated (Brouwer et al., 1998). This DOEL refers to total dose deposited on the skin during a working shift, essentially a daily dose. The proposed DOEL either has units of area or mass, depending on the permeability measurements available and used in the calculation. When the units are area, the DOEL represents the maximum skin surface area that can be exposed without exceeding the internal occupational exposure level. When the units are mass, the DOEL should be interpreted as a product of acceptable dermal surface density (mg/cm^2), and exposed skin area (cm^2), and this gives the flexibility to apply the DOEL to various surface areas that might become exposed.

The DOEL is calculated by a two-step process:

1. derive an *internal* health-based occupational exposure limit (OEL_{int}, maximum dose absorbed without leading to adverse systemic effects) from an existing standard (see *Internal Dose Assessment*), and
2. use the OEL_{int} and derive an *external* DOEL based on flux rate or percent absorption.

For a DOEL based on flux, maximum flux (mass/area-time) is experimentally determined under the exposure conditions relevant to the occupational situation. As previously described in Equation 10, flux increases with increasing dermal dose, until the skin is completely covered and then flux remains constant. This maximum flux (J_{max}) represents worst-case penetration from a case where "excess chemical" is applied to the skin. The maximum dermal internal dose (M) from a specific chemical exposure can be calculated from the J_{max}, an exposed surface area (A) and time of exposure (t), often the workshift:

$$M = J_{max} \times A \times t \qquad 25$$

If we want the maximum internal dose to be equivalent to the OEL_{int}, we can set them equal:

$$OEL_{int} = J_{max} \times A \times t \qquad 26$$

Rearranging we get:

$$A\,(DOEL) = \frac{OEL_{int}}{J_{max} \times t} \qquad 27$$

In this case, the DOEL has units of area (cm^2). It can be interpreted as the maximum skin area that can be safely exposed to get the same internal dose as the existing standard over the chosen exposure time. Maximum flux will be applicable when the skin loading is large (an infinite dose situation), and it will apply primarily to pure chemicals, not solutions.

When maximum flux is not available, Bos and co-authors (1998) suggested that the DOEL

could be calculated using fractional absorption as the measure of penetration. In this case the relationship to the OEL_{int} is

$$DOEL\,(mg) = \frac{OEL_{\text{int}}}{F} \qquad 28$$

where ***F*** is the percent absorption by the dermal route.

This DOEL can be interpreted as the product of dermal surface density (mg/cm^2), and exposed area (cm^2), but there is no area or time used in the DOEL determination like there was in Equations 23 and 24. If one wanted to determine the maximum skin surface density over the hands and forearms that would not exceed the internal dose from the OEL, we could calculate it, because the mass penetrated (M) and the DOEL would be proportional to the surface density (SD) and the exposure area:

$$M \approx SD \times A \qquad 29$$

For example, if the DOEL equals M and were calculated to be 3 mg, an acceptable mass density over two hands and lower arms (≈2000 cm^2) would be 1.5 µg/cm^2.

Assumptions — When dermal occupational exposure levels are calculated based on OEL_{int} the following assumptions are made:

- Maximum flux will be the actual workplace flux, that is, surface mass will always be enough to form a monolayer.
- Percentage absorbed value used will be representative of penetration in the occupational scenario.
- This calculation assumes that the surface density over the whole exposure area will be great enough to cause maximum flux over the entire area.
- Adjusting the DOEL for skin surface density and skin area exposed will not cause the skin surface density to be greater than the amount in a monolayer.

Weaknesses — Because of the impact of exposure frequency, duration, and surface area, it is not possible to set a DOEL that would be generally applicable, like inhalation exposure standards. As a result, the DOEL has different units depending on the exposure scenario. For this reason, the proposed DOEL is neither intuitive to the industrial hygienist nor easy to calculate. This approach ignores one of the primary methods for representing dermal penetration for solutions and mixtures, the permeability coefficient. Having the option of using a permeability coefficient in the DOEL would make it possible to calculate a DOEL for different concentrations other than the one for which the J_{max} was measured.

Strengths — The DOEL provides a quantitative estimate of acceptable dermal exposure levels. All of the assumptions about the mechanisms of action that were used to determine the OEL become part of the DOEL. It can be modified to be applicable to occupational exposures with various surface areas.

Summary/Conclusions — The DOEL proposed by the Dermal Exposure Network is a good approach. It should continue to be explored and discussed.

D. Skin Absorption Time

Another approach to replacing the "skin" notation has been suggested by Walker and coauthors (1996). They described how to use fluxes (pure chemicals) and permeability coefficients (solutions and mixtures) to provide a quantitative way to assess the hazards of chemicals in the workplace called the skin absorption time. They calculated the skin absorption time (SAT) that would yield the same internal dose as the permissible exposure level (PEL) or TLV on a daily basis.

$$SAT = \frac{total\ absorption\ at\ PEL}{flux \times hand\ area} \qquad 30$$

or

$$SAT = \frac{total\ absorption\ at\ PEL}{K_p \times concentration \times hand\ area} \qquad 31$$

where:
SAT is exposure time in hours
Total absorption is in mg

Flux has units of mg/cm^2-h
Hand area has units of cm^2
K_p is the permeability coefficient with units of cm/hr
Concentration is surface concentration in mg/ml

Walker and co-authors proposed Equation 30 for use with pure chemicals and Equation 31 for use with solutions and mixtures. They assumed the surface area exposed was one hand, but suggested that the time could be easily adjusted by the industrial hygienist for anticipated surface areas based on the USEPA exposure factors handbook (1999). They calculated examples of a SAT of about 7 min for 2-methoxymethanol, about 6 h for butyl alcohol and about 67 h for an aqueous solution containing triphenyl phosphate. The SAT was not developed to be a precise measurement of safe exposure times, but rather a more general indication of the hazard involved with dermal absorption of the chemical. For example, an SAT of 7 min for 2-methoxymethanol suggests that you probably would not want to allow people to get 2-methoxymethanol on their hands. On the other hand, a SAT of 67 h for an aqueous solution of triphenyl phosphate suggests that as a typ17ical workshift is only 8 h, there is very little potential to get a systemically hazardous dose for this chemical through the skin of one hand. This type of quantitative information would help the industrial hygienist assess workplace procedures. The skin absorption time approach does not focus only on toxicity as the previous approaches, but takes a step toward risk characterization by incorporating exposure concentrations and default surface areas.

Assumptions — When dermal exposure times that would give the same body burden as 8-hour exposure to the exposure level are calculated some assumptions are made:

- Absorption of the exposure level concentration via inhalation is 100%. This is a nonconservative assumption.
- The rate of penetration through the hands would be equivalent to the area of the body that was used for determination of the permeability or flux.
- The rate of administration does not affect the toxic end point.
- All of assumptions about toxicity and safety factors used in determining the exposure level are still valid with a dermal exposure.

Weaknesses — This approach requires flux or permeability coefficients that may not be readily available.

Strengths — The skin absorption time approach has the advantage of being quantitative and providing times that could be used to limit daily exposures. All of the assumptions about the mechanisms of action that were used to determine the PEL became part of the skin exposure time. It is intuitive and easy to understand.

Summary/Conclusions — This new approach has not been mandated by a regulatory agency, but has the potential to provide information that is useful to the industrial hygienist. This method can provide genuinely practical information in a readily communicated form.

V. RISK CHARACTERIZATION

Methods discussed so far in this document have used toxicity information to address either recommended exposure levels or regulatory levels. Exposure parameters are the focus in risk characterization. In order to characterize the risks of a specific process, it is necessary to have a specific process in mind. This final step in the risk assessment process is to compare what is expected to be a safe level with the actual exposure levels in the workplace or environment (National Research Council, 1983) and ultimately make some judgment about safety. Human risk is a composite of toxicity and exposure. There is no risk without exposure and risk characterization is the process of factoring exposure into risk assessment.

An index approach is often used to compare the risk of a particular exposure with acceptable risks. These indexes are called by many names (exposure index, hazard index, toxicity index, margin of safety, etc.), but the general principle is to calculate the ratio of the expected exposure to an exposure standard (PEL, RfC, NOAEL, OEL, TLV, etc.):

$$index = \frac{\text{expected exposure}}{\text{exposure standard}} \quad 32$$

where the expected exposure and the exposure standard have the same units, such as mg/day. Equation 32 seems simple at first glance, but its appropriate use may require calculation of a dermal exposure standard, internal dose calculations, route-to-route extrapolations, and steady-state calculations based on Fick's law. When the index is one or less than one, the exposure would cause no more risk than acceptable. If the index is greater than one, industrial hygiene controls would be required.

Recently, The Committee on Toxicology of the National Academy of Sciences used the hazard index approach to characterize the risks of flame-retardant chemicals (2000). Worst-case dermal dose rates (mass/kg-day) from anticipated exposure scenarios, such as sitting on a couch, were calculated and divided by an oral reference dose (RfD, mg/kg-day) to determine the hazard index. Of 18 fire-retardant chemicals evaluated by the Committee on Toxicology, 8 had hazard indices less than 1 and were considered safe to use. The other 10 had hazard indices greater than 1 and the Committee decided that more research was required to refine the dermal dose rates for these chemicals.

Assumptions – The assumptions incorporated in risk characterization are the following:

- All of the assumptions or safety factors used in setting the airborne/inhalation exposure standard will apply to the dermal exposure standard.
- The NOAEL is not based on a route of entry effect, such as respiratory irritation.
- The toxicity studies are based on the same systemic endpoint for determination of the NOAEL.
- The toxicity studies have the comparable exposure durations, ie., both acute or both 90 day.
- The rate of dose administration does not affect the toxic end point.
- The comparison of NOAELs on a dose per day basis does not invalidate the risk characterization. (In the case of single dose oral and dermal studies, it may take days for complete absorption but that wouldn't be the case for inhalation.)
- No physiological change or damage occurs at the site of uptake that would affect uptake. (This could be for instance a change in respiratory rate or blood flow in the skin due to irritation.)

VI. CONCLUSIONS

Risk assessment methods for assessing dermal exposures in the workplace are in various states of development. A crucial part of nearly all the risk assessment methods is a quantitative understanding of the penetration of chemicals through the skin. This is the weakest part of the whole process whether we look at whole animal toxicity studies or *in vitro* diffusion cell studies using human or rodent skin. Risk assessment, and particularly dermal risk assessment, is a relatively new field. Appropriate ways to use data for risk assessment are being developed even as the studies that are used are evolving. It is essential that risk assessments and the experimental methods they are based on be evaluated and brought up to state of the art.

Generally, dermal toxicity studies have been done without an appreciation of the complexity and requirements of dermal risk assessments. The great majority of *in vivo* dermal toxicology studies have been lethality studies where the chemical is painted on the back, frequently in solvents or a vehicle, without regard to careful control of the surface area exposed or the actual surface density of the chemical on the skin. Many of these empirical tests were accomplished to compare the toxicity of various chemicals. The most important aspect of this comparison approach was to treat each chemical the same. It was not necessary to know the penetration rates, just whether a certain mass on the skin caused an "effect". Frequently, there was no attempt to test realistic exposure concentrations or conditions, and the result was toxicity tests that are very hard to extrapolate. Some dermal exposure guidelines still do not require that the results be expressed in useful terms such as mass/surface area.

The *in vitro* quantification of skin penetration originated in the drug industry, where the purpose for measuring skin penetration was to compare chemicals or formulations on a side-by-side basis. There has been a big push in the pharmaceutical industry in the last 15 to 20 years to develop transdermal drug preparations. Extensive dermal uptake studies have also been dose in the petrochemical industry. In contrast to all the animal toxicity studies mentioned above (where penetration is not explicitly determined), *in vitro* methods were developed to determine fraction absorbed and penetration rates, because these were required to estimate therapeutic efficacy. The *in vitro* test methods that where chosen for use by toxicologists produced percentage absorption results, primarily because of the ease with which they could be accomplished using radioactive chemicals. There are many issues with diffusion cell penetration tests and several international groups are working on standardization.

Internal dose assessment is a critical part of the risk assessment process, and the accuracy of this step affects the uncertainty in the whole process. Methods for the calculation of internal dose from external dose range from a simple fraction absorbed, through steady state flux estimations, to biologically based modeling. Frequently it is necessary to give the best answer possible with the information currently available, and as a result choices of methods would be limited. Increasing amounts of information and more laboratory studies are required as risk assessors attempt to reduce uncertainty. As might be expected, more information and more detailed computations and analyses provide more reliable information — it is a trade-off. It is important to understand the limitations of less than optimum methods when they have to be used.

Route-to-route extrapolations are required in many cases because of the lack of dermal toxicity information that is available. The route of exposure can have a tremendous impact on the systemic toxicity of chemicals, and that is not too surprising considering the physiology and anatomy of the various exposure routes. Extrapolation methods range from crude to sophisticated. Many of the assumptions inherent in these methods are not met (Wilschut et al., 1998). When comparable toxicity information (NOAEL) is available for dermal and another route, the ratio of those NOAELs can be taken as the extrapolation factor to apply to other NOAELs for different toxic endpoints for the same chemical. Another method of extrapolating to a dermal dose is to calculate the ratio of absorption factors ($\frac{oral\ or\ inhalation}{dermal}$) determined *in vivo* or *in vitro*. Biologically based models can also be used to determine the target tissue dose with the inhalation or oral study and then iteratively determining the external dermal dose that would cause the same target tissue dose. As with the internal dose calculations, the confidence in the extrapolation is indirectly proportional to the amount of information required.

Dermal exposure levels are needed to be able to do appropriate risk assessments for dermal hazards. This need is recognized and methods are being refined and developed. "Skin" notations provide qualitative information that may be useful, but the rationale for choosing to apply the notation to specific chemicals needs to be standardized, validated, and the rationale clearly stated and applied consistently. A banding approach to controlling dermal risks is a good idea, but an approach that does not make use of penetration measurements will not adequately address the differences between exposure routes. Approaches to calculate DOELs that are based on acceptable levels of chemicals on the skin have been recommended by the European Dermal Exposure Network. This approach is not fully evolved but can be expected to be used increasingly. Interpreting this mass as a product of surface density and exposure area allows flexibility to adjust the DOEL to different exposure scenarios. An approach called *Skin Absorption Time* has been developed that estimates safe exposure time for chemicals based on existing oral or inhalation standards. This SAT can be easily adjusted for different surface areas. The primary hindrance to developing dermal-specific exposure levels is the lack of appropriate dermal penetration data in the literature.

Risk characterization is an important aspect of dermal risk assessment that is under-utilized. This final step in the risk assessment process addresses specific exposures and processes in a way that the real workplace can be impacted. Unfortunately, an understanding of the methods and assumptions of internal dose assessments,

route-to-route extrapolations, and dermal exposure levels is required to complete this step. This may be beyond the reach of the busy industrial hygienist.

RECOMMENDATIONS FOR RESEARCH

1. In order to facilitate risk assessment methods, toxicology characterizations after dermal exposures should be improved. All dermal toxicity studies should have doses expressed as mass per surface area rather than mass per body weight.
2. Fractional absorption data should not be accepted as a means to express dermal penetration unless scientists characterize the surface density at which "excess chemical" occurs.
3. Short term skin penetration data (5 to 30 min exposures) should be collected for a wide range of occupational chemicals to increase the understanding of internal dose from realistic exposures.
4. Transfer factors from contaminated surfaces to skin need to be carefully investigated to provide the ability to assess risk from repeated contacts with workplace environments.
5. An attempt should be made to fill the data gaps that are required for use of biologically based models. Tissue and blood partition coefficients, metabolic parameters, and binding coefficients should be developed for the most important industrial chemicals.
6. Standard biologically based modeling software and approaches as well as validated sets of default physiological parameters should be developed.
7. Research on the role of vehicle effects, that is, vehicle alteration of the barrier properties of the skin should be accomplished.

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REFERENCES

ACGIH, Threshold Limit Values for Chemical Substances and Physical Agents, American Conference of Governmental Industrial Hygienists (2000).

Anjo, D.M., Feldmann, R.J. and Maibach, H.I., Methods for predicting percutaneous penetration in Man. In: *Percutaneous Absorption of Steroids* P. Mauvais-Jarvais, J. Wepierre and C.F.H. Vickers, Eds., Academic Press, San Diego, pp. 31–51, 1980.

Barry, B.W., S.M. Harrison, and P.H. Dugard. Vapor and liquid diffusion of model penetrants through human skin: correlation with thermodynamic activity. *J. Pharm. Pharmacol.* **37:**226–235 (1985).

Boeniger, M.F. and B.D. Lushniak. Exposure and absorption of hazardous materials through the skin. *Int. J. Occup. Environ. Health* **6:**148–150 (2000).

Bos, P.M.J., D.H. Brouwer, H. Stevenson, P.J. Boogaard, W.L.A.M. de Kort, and J.J. van Hemmen. Proposal for the assessment of quantitative dermal exposure limits in occupational environments: Part 1. Development of a concept to derive a quantitative dermal occupational exposure limit. *Occup. Environ. Med.* **55**:795–804 (1998).

Bronaugh, R.L. and Stewart, R.F. Methods for in vitro percutaneous absorption studies, IV. The flow through diffusion cell. *J. Pharm. Sci.* **74:**64–67 (1985).

Bronaugh, R.L., Stewart, R.F., Congdon, E.R., and Giles, A.L., Jr., Methods for in vitro percutaneous absorption studies, I. Comparison with in vivo results. *Toxicol. Appl. Pharmacol.*, **62:**474–480 (1982).

Brooke, I.M. A UK scheme to help small firms control health risks from chemicals: toxicological considerations. *Annal. Occup. Hyg.* **42:**377–390 (1998).

Brouwer, D.H., L. Hoogendoorn, P.M.J. Bos, P.J. Boogaard, and J.J. van Hemmen. Proposal for the assessment of quantitative dermal exposure limits in occupational environments. II. Feasibility study for application in an exposure scenario for MDA by two different dermal exposure sampling methods. *Occup. Environ. Med.* **55:**805–811 (1998).

Bunge, A.L. and J.N. McDougal. Dermal uptake. In: *Exposure to Contaminants in Drinking Water: Estimating Uptake through the Skin and by Inhalation,* S.S. Olin, Ed., CRC Press, Boca Raton, FL, 135–178,1999.

Bunge, A.L. and R.L. Cleek, A new method for estimating dermal absorption from chemical exposure. II. Effect of molecular weight and octanol-water partitioning. *Pharm. Res.* **12:**88–95 (1995).

Bunge, A.L., R.L. Cleek, and B.E. Vecchia. A new method for estimating dermal absorption from chemical exposure. III. Compared with steady-state methods for prediction and data analysis. *Pharm. Res.* **12:**972–982 (1995).

Chandrasekaran, S.K., W. Bayne, and J.E. Shaw. Pharmacokinetics of drug permeation through human skin. *J. Pharm. Sci.* **67(10):**1370–1374 (1978).

Cherrie, J.W. and Robertson, A. Biologically relevant assessment of dermal exposure. *Annal. Occup. Hyg.* **39(3):**387–392 (1995).

Chinery, R.L. and A.K. Gleason. A compartmental model for the prediction of breath concentration and absorbed dose of chloroform after exposure while showering. *Risk Anal.* **13(1):**51–62 (1993).

Cleek, R.L. and A.L. Bunge. A new method for estimating dermal absorption from chemical exposure. I. General Approach. *Pharm. Res.* **10:** 497–506 (1993).

Committee on Toxicology, *Toxicological Risks of Flame-Retardant Chemicals,* National Research Council, National Academy Press, Washington, DC, 2000.

Corley, R.A., D.A. Markham, C. Banks, P. Delorme, A. Masterman, and J.M. Houle. Physiologically based pharmacokinetics and the dermal absorption of 2–butoxyethanol vapor by humans. *Fundam. Appl. Tox.* **39:**120–130 (1997).

Corley, R.A., S. Gordon and L. Wallace. Physiologically based pharmacokinetic modeling of the temperature dependent dermal absorption of chloroform by humans following bath water exposures. *Toxicol. Sci.* **53:**13–23 (2000).

de Cock, J., D. Heederik, H. Kromhout, and J.S.M. Boleij, Strategy for assigning a skin notation: a comment. *Ann. Occup. Hyg.* **40(5):**611–614 (1996).

Durrheim, H., Flynn, G.L., Higuchi, W.I., and Behl, C.R., Permeation of hairless mouse skin. I. Experimental methods and comparison with human epidermal permeation by alkanols. *J. Pharm. Sci.* **69:**781–785 (1980).

EU Dermal Exposure Network, Issues relating to the risk assessment of dermal exposures, Jackson, J.R. Ed., Final Report, December 1999.

Feldman, R.J. and H.I. Maibach. Regional variation in percutaneous penetration of $^{[14]}$C cortisone in man. *J. Invest. Dermatol.* **48:**181–183 (1967).

Fenske, R.A. Dermal exposure assessment techniques. *Ann. Occup. Hyg.* **37(6):**687–706 (1993).

Fenske, R.A. and J.J. van Hemmen. Occupational skin exposure to chemical substances: Setting limits (editorial). *Ann. Occup. Hyg.* **36(4):**333–336 (1994).

Fiserova-Bergerova, V. J.T. Pierce, and P.O. Droz, Dermal absorption potential of industrial chemicals: criteria for skin notation. *Am. J. Indust. Med.* **17:**617–635 (1990).

Fiserova-Bergerova, V. Relevance of occupational skin exposure. *Ann. Occup. Hyg.* **37(6):**673–685 (1993).

Flynn, G. L., Linn, E. E., Kurihara-Bergstrom, T., Govil, S., and Hou, S. Y. E.. Parameters of skin condition and function. In: *Transdermal Delivery of Drugs*, A. F. Kydonieus, Ed., pp. 3–7. CRC Press, Boca Raton, FL, 1987.

Fox, J.L., Higuchi, W.I., and Ho, N.F.H., General physical model for simultaneous diffusion and metabolism in biological membranes. The computational approach for the steady-state case. *Int. J. Pharm.,* **2:**41–57 (1979).

Franz, T.J., Percutaneous absorption: on the relevance of in vitro data. *J. Invest. Dermatol.*, **64:**190–195 (1975).

Gombar, V.K., Reliable assessment of LogP of compounds of pharmaceutical relevance. *SAR QSAR Environ. Res.* **10:**371–380 (1999).

Guest, I. The chemical industries association guidance on allocating occupational exposure bands. *Annal. Occup. Hyg.* **42:**407–411 (1998).

Guy, R.H. and Hadgraft, J. Physicochemical interpretation of the pharmacokinetics of percutaneous absorption. *J. Pharmacokin. Biopharmacol.* **11:**189–203 (1982).

Haber, F. Zur geshichte des gaskrieges. In: *Fünf Vorträge aus den jahren 1920–1923*, Julius Springer, Berlin, 76–92, 1924.

Hadgraft, J. The epidermal reservoir: a theoretical approach. *Int. J. Pharmacol.* **2:**265–274 (1979).

Hansch, C. and A. Leo. *Substituent Constants for Correlation Analysis in Chemistry and Biochemistry*, John Wiley and Sons, New York, 1979.

Jepson, G.W. and J.N. McDougal. Physiologically based modeling of nonsteady state dermal absorption of halogenated methanes from an aqueous solution. *Toxicol. Appl. Pharmacol.* **144:**315–324 (1997).

Kennedy, G.L., W.J. Brock, and A.K. Banerjee. Assignments of skin notation for threshold limit values chemicals based on acute dermal toxicity. *Appl. Occup. Environ. Hyg.* **8(1):**26–30 (1993).

Kubota, K. and Twizell, E.H. A nonlinear numerical model of percutaneous drug absorption. *Math. Biosci.* **108:**157–178 (1992).

Loizou, G.D., K. Jones, P. Akrill, D. Dyne, and J. Cocker. Estimation of the dermal absorption of *m*-xylene vapor in humans using breath sampling and physiologically based pharmacokinetic analysis. *Toxicol. Sci.* **48:**170–179 (1999).

Maidment, S.C. Occupational hygiene considerations in the development of a structured approach to selecting chemical control strategies. *Annal. Occup. Hyg.* **42:**391–400 (1998).

Marzulli, F.N., D.W.C. Brown, and H.I. Maibach. Techniques for studying skin penetration. *Toxicol. Appl. Pharmacol.* **3:**76–83 (1969).

Mattie, D.R., G.D. Bates, Jr, G.W. Jepson, J.W. Fisher, and J.N. McDougal. Determination of skin: air partition coefficients for volatile chemicals: experimental method and applications. *Fundam.. Appl. Toxicol.*, **22:**51–57 (1994).

McDougal, J.N. and J.L. Jurgens-Whitehead. Short-term dermal absorption and penetration of chemicals from aqueous solutions: theory and experiment. *Risk Anal.* **21:**719–726 (2001).

McDougal, J.N., G.W. Jepson, H.J. Clewell, III, and M.E. Andersen. Dermal absorption of dihalomethane vapors. *Toxicol. Appl. Pharmacol.* **79:**150–158 (1985).

McDougal, J.N. G.W. Jepson, H.J. Clewell III, M.L. Gargas, and M.E. Andersen. Dermal absorption of organic chemical vapors in rats and humans. *Fundam. Appl. Toxicol.* **14:**299–308 (1990).

McDougal, J.N. Physiologically based pharmacokinetic modeling. In *Dermatotoxicology*, F.N. Marzulli and H.I. Maibach, Eds., 4th ed. Hemisphere Publishing Corporation, Washington, DC, 37–60, 1991.

McDougal, J.N. Prediction — physiological models. In: *Dermal Absorption and Toxicity Assessment*, M.S. Roberts and K.A. Walters, Eds., Marcel Dekker, New York, 189–202, 1998.

McKone, T.E. Linking a PBPK model for chloroform with measured breath concentrations in showers: implication for dermal exposure models. *J. Exposure Anal. Environ. Epidemiol.* **3(3):**339–365 (1993).

McKone, T.E. and R.A. Howd. Estimating dermal uptake of nonionic organic chemicals from water and soil. I. Unified fugacity-based models for risk assessments. *Risk Anal.* **12(4):**543–557 (1992).

Michaels, A.S., S.K. Chandrasekaran and J.E. Shaw. Drug permeation through human skin: theory and *in vitro* experimental measurement. *AlChE J.* **21(5):** 985–996 (1975).

Mulhausen, J.R. and J. Damiano. *A Strategy for Assessing and Managing Occupational Exposures*. 2nd ed., American Industrial Hygiene Association Exposure Assessment Strategies Committee, AIHA Press, Fairfax, VA (1998).

National Research Council, *Risk Assessment in the Federal Government: Managing the Process,* National Academy Press, Washington, DC, 1983.

Owen, B.A. Literature-derived absorption coefficients for 39 chemicals via oral and inhalation routes of exposure. *Regul. Toxicol. Pharmacol.* **11:**237–252 (1990).

Paustenbach, D.J. The practice of exposure assessment: a state-of-the-art review. *J. Toxicol. Environ. Health,* part B **3:**179–291 (2000).

Poet, T.S., R.A. Corley, K.D. Thrall, J.A. Edwards, H Tanojo, K.K. Weitz, Z. Hui, H. Maibach, and R.W. Wester. Assessment of the percutaneous absorption of trichloroethylene in rats and humans using MS/MS real-time breath analysis and physiologically based pharmacokinetic modeling. *Toxicol. Sci.* **56:**61–72 (2000).

Rao, H.V. and D.R. Brown. A physiologically based pharmacokinetic assessment of tetrachloroethylene in groundwater for a bathing and showering determination. *Risk Anal.* **13(1):**37–49 (1993).

Rao, H.V. and G.L. Ginsberg. A physiologically based pharmacokinetic model assessment of methyl *t*-butyl ether in groundwater for a bathing and showering determination. *Risk Anal.* **17(5):**583–598 (1997).

Robinson, P.J. Prediction — simple risk models and overview of dermal risk assessment. In: *Dermal Absorption and Toxicity Assessment*, M.S. Roberts and K.A. Walters, Eds., Marcel Dekker, New York, 203–229, 1998.

Pepelko, W.E. and J.R. Withey. Methods for route-to-route extrapolation of dose. *Toxicol. Indus. Health* **1(4):**153–170 (1985).

Russell, R.M., S.C. Maidment, I. Brooke, and M.D. Topping. An introduction to a UK scheme to help small firms control health risks from chemicals. *Annal. Occup. Hyg.* **42:**367–376 (1998).

Sartorelli, P., C. Aprea, A. Cenni, M.T. Novelli, D. Orsi, S. Palmi, and G. Matteucci. Prediction of percutaneous absorption from physicochemical data: a model based on data of *in vitro* experiments. *Ann. Occup. Hyg.* **42:**267–276 (1998).

Scansetti, G., G. Piolatto, and G.F. Rubino. Skin notation in the context of workplace exposure standards. *Am. J. Industr. Med.* **14(6):**725–732 (1988).

Scheuplein, R.J. and L. Ross. Effects of surfactants and solvents on the permeability of epidermis. *J. Soc. Cosmet. Chem.* **21:**853–873 (1970).

Stokinger, H.F. and R.L. Woodward. Toxicological methods for establishing drinking water standards. *J. Am. Water Works Assoc.* **50:**515–529 (1958).

Tsuruta, H. Skin absorption of organic solvent vapors in nude mice in vivo. *Ind. Health* **27(2):**37–47 (1989).

U.S. Environmental Protection Agency. Dermal Exposure Assessment: Principles and applications. Washington DC: U.S.E.P.A., Office of Health and Environmental Assessment, Office of Research and Development, EPA/600/8–91/011 (1992).

U.S. Environmental Protection Agency. Exposure Factors Handbook. Office of Research and Development, Washington, DC, EPA/600/C-99/001 (1999).

U.S. Environmental Protection Agency. Risk Assessment Guidance for Superfund, Volume 1, Human Health Evaluation Manual (Part A). U.S.E.P.A., Office of Emergency and Remedial Response, EPA/540/1–89/002 (1989).

Walker, J.D., C. Whittaker, and J.N. McDougal. Role of the TSCA Interagency Testing Committee in Meeting the U.S. Government's Data Needs: Designating Chemicals for Percutaneous Absorption Testing, in *Dermatotoxicology*, F.N. Marzulli and H.I. Maibach, Eds., 5th ed., Hemisphere Publishing Corporation, Washington, DC, 371–381 (1996).

Wilschut, A., G.F. Houben, and B.C. Hakkert. Evaluation of route-to-route extrapolation in health risk assessment for dermal and respiratory exposure to chemicals. TNO Report V97.520. TNO Nutrition and Food Research Institute (1998).