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RELEVANCE OF OCCUPATIONAL SKIN EXPOSURE

VERA FISEROVA-BERGEROVA

Department of Anesthesiology, University of Miami School of Medicine, Miami, FL 33101, U.S.A.

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Abstract—Dermal exposure gains in significance by the same token as permissible occupational inhalation exposures are lowered. The contribution of dermal absorption to the total dose absorbed during occupational exposure is apparent when dermal and pulmonary uptake rates are compared. Development of an experimental data base for evaluation and control of dermal exposure is hindered by: lack of suitable methods for measurement of dermal absorption in humans; interspecies differences in skin permeability; regional differences in absorption rates due to non-homogeneity of skin composition and perfusion rates over the body; possible skin damage induced by the chemical or dispersant; and exposure conditions in the workplace. In the absence of sufficient human data, theoretical models can provide satisfactory information on dermal absorption. It is advocated that the current practice of using acute dermal toxicity (LD_{50}) as a criterion for warning on the potential of significant dermal absorption be replaced by a criterion based on comparison of the dermal penetration rate with the pulmonary uptake rate at inhalation exposures permissible in the workplace.

NOMENCLATURE

ΔBI%	selected increase in arterial blood concentration
c_{alv}	alveolar concentration
c_{art}	arterial blood concentration
c_{derm}	concentration in skin
c_{ins}	inspired concentration
c_{mix}	mixed venous blood concentration
c_{sat}	concentration in saturated aqueous solution at 20°C
c_{ven}	concentration in regional (subcutaneous)venous blood
ΔC	concentration gradient across the stratum corneum
EA	surface area of exposed skin
F	perfusion rate
Fl	tlux, penetration rate through the stratum corneum
Fl^*_{liq}	critical flux of the chemical in the liquid state (i.e. dermal uptake becomes significantcompared to the inhaled amount)
Fl^*_{vap}	critical flux of the chemical in the gas state (i.e. dermal uptake becomes significant compared to the inhaled amount)
K	permeability coefficient
LD_{50}	median lethal dose
$\lambda_{bl/air}$	blood/gas partition coefficient
$\lambda_{bl/derm}$	blood/skin distribution coefficient
$\lambda_{w/d}$	water/dispersant distribution coefficient
MAK	maximum concentrations permissible at the Workplace approved by Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (Germany)
N	number of measurements
P	octanol–water distribution coefficient
Q	cardiac output
r	correlation coefficient
RV	reference value for acceptable workplace dermal exposure
T	exposure duration
TLV	threshold limit value for occupational inhalation exposure approved by the American Conference of Governmental Industrial Hygienists
TWA	time-weighted average concentration
V_{alv}	alveolar ventilation

INTRODUCTION

INDUSTRIAL chemicals in the workplace can lead to exposure by inhalation, through the skin and gastrointestinally. Although gastrointestinal exposure can be avoided by good hygiene it cannot be excluded when inhaled particles are removed by the ciliary process. Inhalation exposure has traditionally been considered as the main threat to workers' health. For half a century, the main concerns of industrial hygienists were the control of airborne concentrations and the setting of occupational exposure limits for airborne contaminants. The health hazard from dermal exposure was recognized for only a few compounds (pesticides, phenols, amines) known to induce acute systemic toxicity upon contact with the skin: these carry a skin notation in listings of exposure limits [e.g. American Threshold Limit Values, TLV (ACGIH, 1992), or German Maximale **Arbeitsplatzkonzentrationen,** MAK (COMMISSION FOR THE INVESTIGATION OF HEALTH HAZARDS OF CHEMICAL COMPOUNDS IN THE WORK AREA, 1991)]. Dermal exposure is becoming more important as permissible occupational inhalation exposures are lowered.

The significance of dermal absorption becomes evident when pulmonary and dermal absorption rates are compared. For example, it was estimated that, upon skin contact, liquid benzene penetrates the skin at a rate between 0.2 and 0.7 mg cm^{-2} h^{-1} (HANKE *et* al., **1961;** MAIBACH and ANJO, **1981**; FISEROVA-BERGEROVA *et al.*, **1990).** The first TLV-TWA published in **1946** for benzene was **100** ppm (ACGIH, **1984).** As the pulmonary uptake rate at this exposure (about 200 mg h^{-1}) is significantly higher than the dermal penetration rate, the expected dermal contribution to total absorbed amount is negligible. However, since **1946** the inhalation exposures permissible in the workplace have been reduced by a factor of **100** or more, thus making pulmonary and dermal uptake equally important.

Dermal absorption—and thus dermal toxicity—is affected by three factors:

(i) physicochemical properties of the chemical (mainly solubility and chemical structure);
(ii) differences in the nature of the skin (which varies from one part of the body to another, and differs between species); and
(iii) differences in occupational exposure (depending on the production and skill of the worker).

Factors (i) and (ii) involve the mechanism of dermal absorption.

MECHANISM OF DERMAL ABSORPTION

The skin is made up of various types of cells which form three distinct layers: (1) the ***epidermis*** (in which the stratum corneum functions as a diffusion barrier), which is formed by layers of dead and living cells of thicknesses of about **10** and **40** μm, respectively; **(2)** the ***dermis,*** which consists mainly of proteins and blood cells (about **1250** μm thick) and which is perfused by about 3.3% of cardiac output; and (3) the ***hypodermis,*** consisting mainly of connective tissues and fat (about 1000–6600 μm thick), is perfused by about 2.2% of cardiac output (ICRP, **1984).**

Percutaneous absorption involves diffusion of the chemical through these layers until it reaches capillaries in the epidermis and hypodermis, and enters the systemic

circulation. The diffusion is governed by Fick's law. The epidermis also has a limited enzyme system and thus can metabolize xenobiotics (KAO *et al.*, **1985).**

Dermal absorption involves two major diffusion processes, penetration through the stratum corneum and transfer into the capillary blood.

Penetration through the stratum corneum, by diffusion via polar and lipophilic pathways, is restricted to small molecules (molecular weight < 500). High solubility in water and in fat facilitates rapid penetration. The measure of penetration is either the permeability coefficient (which is the velocity constant in cm h^{-1}) or flux (which is the penetration rate in mg cm^{-2} h^{-1}). Flux (Fl) and permeability coefficient (K) are related by the equation:

$$Fl = K\,AC, \qquad (1)$$

where AC is the concentration gradient across the stratum corneum. Both K and Fl vary over the body, depending on the composition and thickness of the stratum corneum, the presence of skin appendages (hairs, glands) and the amount of perspiration. The differences among animal species are even larger (WESTER and MAIBACH, **1977).** Environmental temperature and humidity (DUTKIEWICZ and PIOTROWSKI, **1961)** and, most importantly, the dispersant (vehicle) in which the chemical is administered also affect penetration. Moreover, the nature of the skin—and thus flux—can be gradually altered by the applied chemical or by the dispersant.

K and Fl can be measured both ***in vivo*** and ***in vitro.*** The determination of the concentration on the receptor side of the skin is the most controversial step in the measurement. The methods were recently reviewed by EPA **(1992).** Because of differences in skin composition and in methodology the results reported vary widely. For example, the flux of xylene, measured in a diffusion chamber using excised rat skin, was 0.006 mg cm^{-2} h^{-1} (TSURUTA, 1982), whereas excretion of metabolites in humans indicates a flux of 0.13 mg cm^{-2} h^{-1} (ENGSTROM *et al.*, **1977)** and **7.0** mg cm^{-2} h^{-1} (DUTKIEWICZ and TYRAS, **1968).** Similar variability was reported for styrene: **0.03** (TSURUTA, 1982), 0.06 (BERODE **et al.,** 1985) and **12** mg cm^{-2} h^{-1} (DUTKIEWICZ and TYRAS, **1968);** and for ethylbenzene: **0.06** (TSURUTA, 1982), **0.16** and **28** mg cm^{-2} h^{-1} (DUTKIEWICZ and TYRAS, **1967).** The difference in values reported by DUTKIEWICZ and TYRAS **(1967)** for ethylbenzene is due to differences in the application (liquid ethylbenzene vs solutions).

Several theoretical approaches for the prediction of dermal penetration rate based on the physiological function of the skin and on the chemical structure and physical properties of the chemical were developed. Models based on similarity of chemical structure are reviewed in the EPA Interim Report on Dermal Exposure Assessment (EPA, **1992,** pp. **5.21–5.32).** Other models are based on the diffusion process and on the physicochemical properties of the chemical and skin composition. In these models penetration is defined either by permeability coefficients [reviewed in the same EPA Document (EPA, **1992,** pp. 5.33–5.64)] or by flux (models reviewed by OSBORNE, **1986).** Although the permeability constant is time-independent, the penetration rate changes during the exposure as does the concentration gradient across the skin [Equation (1)]. ***In vivo***, the change is apparent at the beginning of the exposure, but becomes negligible when the apparent steady state is approached.

A 'representative' flux is calculated for a skin with average characteristics (i.e. average thickness of stratum corneum and average diffusion coefficient), taking into

consideration the aqueous solubility, the octanol–water distribution coefficient, and the molecular weight of the chemical compound involved (BERNER and COOPER, **1987).** A simple equation for the prediction of flux of non-polar compounds from saturated aqueous solutions was derived by BERNER and COOPER **(1987):**

$$Fl = \frac{c_{sat}}{15}(0.038 + 0.153\ P)e^{-0.016MW}, \quad (2)$$

where Fl is flux in mg $cm^{-2}\ h^{-1}$, c_{sat} is saturated aqueous solution in mg ml^{-1}. P is the octanol–water distribution coefficient, MW is molecular weight, and e is the base of natural logarithm. Numerical constants are derived from 'representative' parameters which are pertinent to the diffusion process through polar and lipophilic channels of the stratum corneum.

Predictions based on physical properties and chemical structure usually provide values which are in the range of experimental data. Thus, fluxes calculated for xylene (0.50 mg $cm^{-2}\ h^{-1}$), styrene (0.52 mg $cm^{-2}\ h^{-1}$) and ethylbenzene **(0.53** mg $cm^{-2}\ h^{-1}$) (FISEROVA-BERGEROVA ***et al.*, 1990)** fall within the range of the measured values cited above. Other examples comparing calculated and measured data were reported by FISEROVA-BERGEROVA and PIERCE **(1989)** and by OSBORNE **(1986).**

The swelling of psoriatic skin immersed in a liquid chemical or its solution provides a rapid method for grading the penetration rate through the human skin (HANSEN, **1982).**

The transfer of the chemical from the dermis into the capillary blood depends on the perfusion rate of the dermis (and thus on physical activity of the worker and environmental temperature) and on the dermis–blood distribution coefficient of the chemical (and thus on body fat and on the hydration of the skin) (FISEROVA-BERGEROVA, **1990).** At the beginning of exposure, when the absorption rate is a function of time, the concentration builds up in the epidermis and dermis. During this period, the concentration gradient diminishes. The absorption rate becomes constant after the lag time period, when steady state is approached (that is, when the penetration and uptake rates are equal and the concentration gradients are constant). The rate-limiting step is usually the penetration rate through the stratum corneum, but for lipophilic chemicals in poorly perfused areas it may be the removal of the chemical from the skin by capillary blood. Pharmacokinetic models were developed to describe the distribution and elimination of percutaneously absorbed chemicals (FISEROVA-BERGEROVA, **1990;** GUY ***et al.*, 1985).** The passing of the chemical into the capillary blood at steady state can be described by a balance equation:

$$\text{INFLOW} = \text{OUTFLOW}$$

$$F c_{art} + Fl = F c_{ven}, \quad (3)$$

where F is the perfusion rate of skin under the exposed area and c_{art} and c_{ven} are concentrations of the chemical in arterial blood and venous blood under the exposed area, respectively. If the diffusion is rapid, as in the case of volatile organic solvents, the concentrations in blood, alveolar air and dermis are instantly equilibrated and Equation (3) can be rewritten in order to compare the penetration rate with uptake rate:

$$Fl = F(c_{derm}\lambda_{bl/derm} - c_{alv}\lambda_{bl/air}, \quad (4)$$

where c_{derm} and c_{alv} are concentrations of the chemical in skin under the exposed area and in alveolar air, respectively, and the λs are the appropriate partition coefficients.

Dermal absorption is affected by other routes of entry of the chemical into the body. The role of the lungs in the exposure to volatile chemicals deserves special attention. Dermal absorption increases the concentration in venous blood. Consequently, pulmonary uptake is reduced or is replaced by elimination, as evident in the following balance equation across the lung:

$$\text{INFLOW} = \text{OUTFLOW}$$

$$\underset{\text{inspired}}{V_{alv}\, c_{ins}} + \underset{\text{venous return}}{Q\, c_{mix}} = \underset{\text{exhaled}}{V_{alv}\, c_{alv}} + \underset{\text{systemic circulation}}{Q\, c_{art}}, \quad (5)$$

where V_{alv} denotes alveolar ventilation, Q is cardiac output, and c_{ins}, c_{art} and c_{mix} are concentrations in inspired air and arterial and mixed venous blood, respectively. To define the pulmonary uptake or wash-out, Equation (5) is rearranged:

$$V_{alv}(c_{ins} - c_{alv}) = Q(c_{art} - c_{mix}). \quad (6)$$

If $c_{mix} < c_{art}$, pulmonary uptake occurs. If $c_{mix} > c_{art}$, pulmonary wash-out occurs. Pulmonary wash-out of dermally absorbed solvents was documented experimentally for chlorine-containing solvents (STEWART and DODD, 1964; FUKABORI *et al.*, 1977), furfural (FLEK and SEDIVEC, 1978), methanol (SEDIVEC *et al.*, 1981; DUTKIEWICZ *et al.*, 1980), styrene (BERODE *et al.*, 1985) and xylene (ENGSTROM *et al.*, 1977). Extensive pulmonary clearance of volatile chemicals reduces their potential for dermal toxicity.

A physiologically based simulation model was used to demonstrate the effects of short-term exposure of the hands on the concentration of hydrophobic and hydrophilic organic solvents in exhaled air (FISEROVA-BERGEROVA, 1990). The simulation confirmed that short, intermittent contact of the hands with liquid solvent significantly increases alveolar concentrations of solvents, possibly above the concentration in the ambient air, and thus pulmonary uptake is replaced by pulmonary wash-out.

VARIABLES IN OCCUPATIONAL EXPOSURE

The variables which are critical in the evaluation of dermal absorption in the workplace are:

—form of the chemical;
duration of dermal exposure;
-exposed area (size as well as location on the body);
—presence of other chemicals (mixture constituent, dispersant); and
—workload and environmental factors (humidity and temperature).

Form of chemical

In an industrial setting dermal absorption can result from exposure to vapours or from skin contact with liquid chemicals or their solutions. Dermal absorption of gases and vapours of volatile chemicals (SVP > 5 torrs) is usually negligible compared to pulmonary absorption (RIIHIMAKI and PFAFFLI, 1978; FISEROVA-BERGEROVA et *al.*,

1990). However, the vapours of chemicals with low vapour pressure, such as furfural (FLEK and SEDIYEC, 1978), or chemicals with high aqueous solubility, such as methanol (SEDIVEC *et al.*, 1981), can condense on the body surface, and consequently their availability for dermal penetration can be increased. Dermal penetration of solids (dust, aerosols, etc.) can be facilitated by their dissolution in perspiration.

The duration of exposure

Unless special protective apparel is used, the duration of dermal exposure to gases and vapours can be assumed to be equal to the duration of the chemical's presence in the air of the workplace. The duration of dermal contact with liquids and solutions depends on work procedures and on the skill and fastidiousness of the worker. The evaporation of volatile chemicals makes the estimation of exposure duration difficult.

Another complication arising from the duration of dermal exposure is the change in the biochemical parameters of the skin induced either by the chemical itself or by the dispersant. The biochemical change, which can develop rapidly during the lag period or slowly on repeated contact, usually alters the skin permeability.

Exposed area of skin

While the surface area of skin exposed to vapours and gases is the same as the whole-body surface, the surface area of skin exposed to aerosols, dusts and liquids is difficult to estimate. Protective apparel can reduce the exposed area, but contaminated, dirty apparel can enhance the chemical availability for dermal absorption (TROJANOWSKA, 1959). The surface exposed to liquids is usually only a small fraction of the total body surface. For example, the surface of the hands accounts for about 5% of body surface, and the surface of an outstretched palm and fingers accounts for about 1% of body surface (ICRP, 1984). Spills can result in an unpredictable dermal exposure of a large body surface. Moreover, the thickness of the layers of skin cells on different parts of the body varies so that the penetration rate varies (SCHEUPLEIN and BRONAUGH, 1983).

Presence of other chemicals

Studies with drugs have proved that absorption and therapeutic effects depend on the vehicle by which the drug is administered (COOPER, 1985). The same applies to industrial chemicals. Dermal contact with a mixture of chemicals can alter the penetration rate by two mechanisms:

(1) if the chemical is readily soluble in the dispersant, then the large distribution coefficient between the dispersant and dermis slows the penetration. Thus, the dermal penetration rate of dissolved chemicals appears to be directly related to their concentrations and inversely related to their solubility in the dispersant; and

(2) prolonged contact with liquids usually results in biochemical changes in skin and skin permeability. If the dispersant damages the skin, then the penetration rate of mixture components is expected to increase.

The relation between duration of the exposure (T), exposed area (EA), solubility in the dispersant (defined by distribution coefficient of the chemical between water and dispersant $\lambda_{w/d}$) and the amount absorbed is given in Equation (7):

$$\text{Penetrated amount} = \text{Fl} \cdot T \cdot \text{EA} \cdot \lambda_{w/d}. \quad (7)$$

Workload and environmental factors

Since the dermal absorption depends on blood perfusion of the dermis and hypodermis under the exposed area the absorption rate increases with movement and ambient temperature; this means that increased workload and heat enhance dermal absorption (DUTKIEWICZ and PIOTROWSKI, 1961; FISEROVA-BERGEROVA, 1990).

In a recently published monograph, GRANDJEAN (1990)provides a comprehensive review on dermal absorption with respect to workplace exposure.

RISK ASSESSMENT OF OCCUPATIONAL DERMAL EXPOSURE

Development of the criteria for risk assessment of dermal exposure in the workplace has been hindered by three major problems:

—lack of quantitative methods for direct measurement of dermal exposure and dermal absorption;
—lack of data on chronic dermal toxicity;
—variables in dermal exposure in an industrial setting.

Methods for measurement of dermal exposure

Evaluation of dermal exposure can be based either on the amount percutaneously absorbed (which is related to the health effect) or on the contamination of the skin surface (which is related to the availability of the chemical). Biological monitoring of the chemical, which is a measure of the amount absorbed (internal dose), is recommended for assessment of occupational exposure to chemicals with potential dermal exposure, and appropriate reference values are being developed (ACGIH, 1992; COMMISSION FOR THE INVESTIGATION OF HEALTH HAZARDS OF CHEMICAL COMPOUNDS IN THE WORK AREA, 1991). Three basic techniques are used for the evaluation of skin surface contamination: wiping techniques are used to assess the presence of chemicals on the surface of workshop facilities and on the skin of workers (FENSKE *et al.*, 1987);fluorescent tracers are used to evaluate the efficacy of protective apparel (FENSKE et *al.*, 1987; FENSKE, 1988); and pad techniques using colorimetric indicators are being developed to warn instantly the worker that the skin protection against aromatic amines, isocyanates and organic solvents is inadequate (KLINGER, 1992).The contamination measurement may not reflect the health risk if the chemical does not readily penetrate the skin.

Database on dermal toxicity

The information on dermal toxicity is biased because of the diversity in interspecies skin composition, function and appendages (hairs, sweat), and because of the diversity in application of the tested material (immersion and open or covered topical application with or without the dispersant).

Dermal toxicity is usually tested in rabbits, but the existing data are sparse. For example, LD_{50} for acute dermal toxicity is given for only about 1% of the chemicals listed in the NIOSH REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES (1979). Data on chronic toxicity are even more sparse. The shortage of data on acute dermal toxicity may be circumvented by considering the similarity of oral and dermal LD_{50} (Fig. 1). The regression shows that the dermal LD_{50} is about double the oral LD_{50} and that the correlation between them ($r = 0.884$, $N = 50$) improves when data obtained in

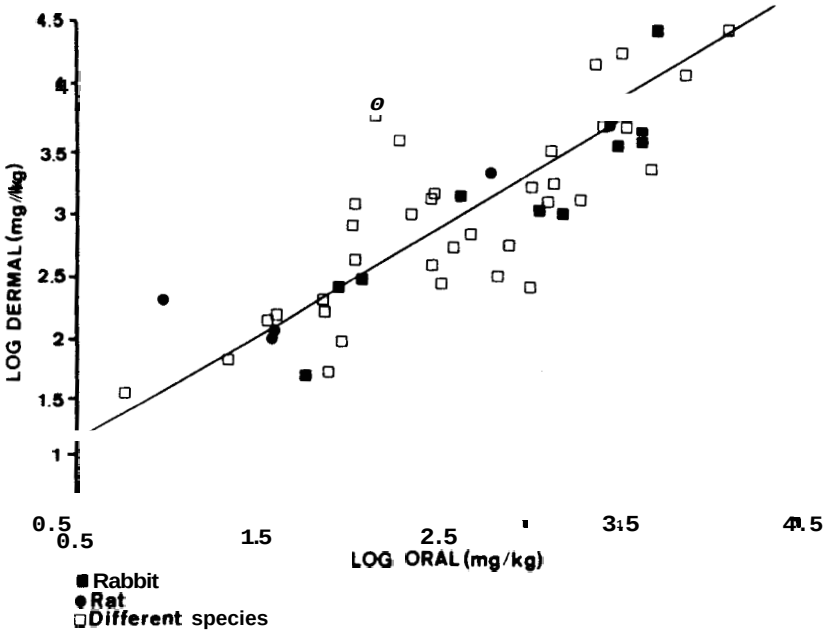

FIG. 1. Comparison of LD_{50} for acute oral and dermal toxicity. LD_{50} for dermal and oral administration (mg kg^{-1}) of 50 randomly selected chemicals from the NIOSH Registry of Toxic Effects of Chemical Substances are plotted in log–log scale. Each point represents the pair of data obtained in the same animal species (■ rabbit, ● rat) or in different species (○). The regression for all 50 chemicals, shown as a line, is: log dermal = 0.780 log oral + 0.873 (r = 0.844). The regression for 15 points obtained in the same species (not shown in the figure), closely follows the line for 50 points: log dermal = 0.763 log oral + 0.929 (r = 0.910). Both coefficients indicate a significant correlation ($P < 0.01$).

the same animal species are compared (r = 0.910, N = 15). Differences between animal species are greater than the effect of the route of administration.

CRITERIA FOR ASSESSMENT OF OCCUPATIONAL DERMAL EXPOSURE

Acute dermal toxicity

In the absence of data on chronic dermal toxicity, policy making organizations such as the American Conference of Governmental Industrial Hygienists (ACGIH) and Deutsche Forschungsgemeinschaft (DFG) base their criteria for skin notation mainly on acute dermal toxicity (usually dermal LD_{50} in rabbits or rats). Several articles criticise inconsistencies in skin notation (GRANDJEAN *et al.*, 1988; SCANSETTI *et al.*, 1988; FISEROVA-BERGEROVA *et* al., 1990; HANSEN, 1982). All critics concluded that the list of chemicals with skin notations is incomplete and should include additional chemicals which can be significantly absorbed through the skin.

According to the latest guidance from the TLV Committee of ACGIH, the chemical should carry a skin notation if its dermal LD_{50} is smaller than 1 g kg^{-1}, or if the likelihood of dermal absorption is otherwise indicated, for example, by solubility of the chemical or by its chemical structure (ACGIH, 1992). To test the LD_{50} criterion, 50 chemicals randomly selected from the NIOSH Registry of Toxic Effects of Chemical

Substances were plotted in Fig. 2. The figure shows that 21% of the chemicals with LD_{50} smaller than 1 g kg^{-1} (to the left of the vertical line) lack skin notation, and that 47% of the chemicals with LD_{50} larger than 1 g kg^{-1} (to the right of the vertical line) have skin notation. This means that the LD_{50} criterion does not stand in 34 instances (68%). The figure shows a correlation between the dose estimated to be inhaled by the worker during an 8-h exposure to the TLV-TWA and a dermal LD_{50} ($r=0.729$, $N=50$).

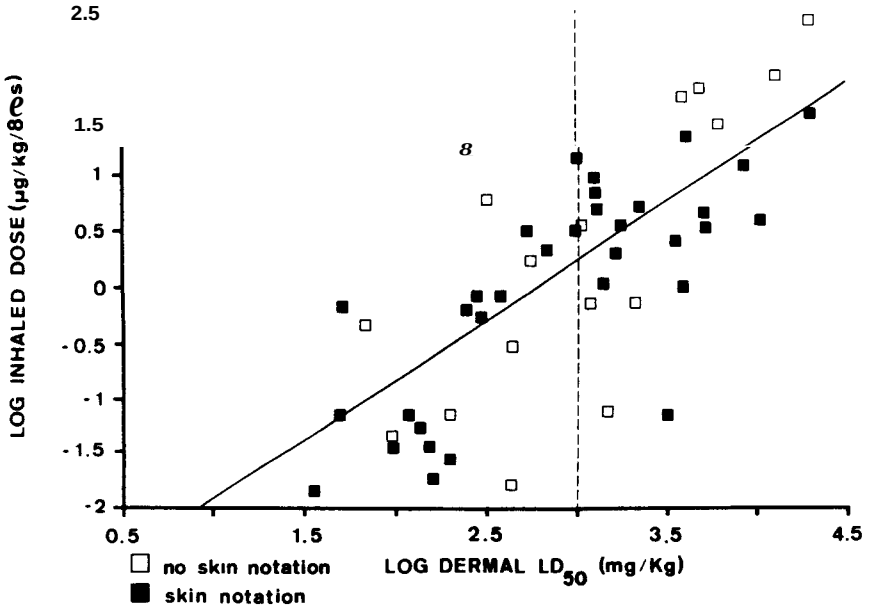

FIG. 2. Dermal LD_{50} as a criterion for skin notation. LD_{50} for acute dermal exposure is plotted against the dose inhaled by the worker during an 8-h shift. The inhaled dose was calculated by multiplying TLV-TWA (mg m^{-3}) by pulmonary ventilation during an 8-h shift (10 m^3) and divided by body weight (70 kg). The chemicals are the same chemicals as in Fig. 1. The vertical dashed line indicates the recommended criterion for skin notation (LD_{50} for acute dermal exposure = 1000 mg kg^{-1}). □ chemicals with no skin notation in TLV-BEI Booklet (1992–1993); ■ chemicals with skin notation. The regression equation, indicated by the line is: log inhaled = 1.057 log dermal − 2.978 ($r=0.729$; $P<0.01$).

Pulmonary and dermal uptakes

Basing the assessment of dermal exposure on acute toxicity data is inconsistent with the regulatory policy of basing permissible concentrations for inhalation exposure on the chronic effect. The main objection to using acute toxicity data is that the target organs for chronic and for acute toxicity can be different. For example, that for the acute toxicity of benzene is the central nervous system, whereas that for its chronic toxicity is the haemopoietic system.

To overcome the lack of data on chronic dermal toxicity, we compared the dermal penetration rate with the pulmonary uptake rate at exposure to permissible airborne concentrations (FISEROVA-BERGEROVA *et al.*, 1990; FISEROVA-BERGEROVA and PIERCE, 1989). The following equation, representing the steady state in the lung was used to

calculate a 'critical flux', that is, a flux which would increase the biological level by a chosen amount above that reached during the permissible inhalation exposure:

$$\text{INFLOW} = \text{OUTFLOW}$$

$$V_{alv} \cdot \text{TLV} + Q \cdot c_{mix} + \text{Fl} \cdot \text{EA} = V_{alv} \cdot c_{alv} + Q \cdot c_{art}, \quad (8)$$

where the symbols are the same as in Equation (5), with the exception of the concentration of the chemical in mixed venous blood (c_{mix}), which reflects the average concentration in venous blood from all tissues, excluding the amount absorbed from the skin under the exposed area, **EA.** Fl is flux.

If dermal exposure does not take place, $\text{Fl} \cdot \text{EA} = 0$ and Equation *(5)* applies; but if dermal absorption takes place, the concentration of the chemical in alveolar air, blood and tissues increases. **A** flux for the permissible increment of biological levels, Fl*, can be calculated when these two situations are compared and **EA** is defined. For example, contact with liquid will increase biological levels by **30%** if Fl_{liq} is defined by Equation (9):

$$\text{Fl}^*_{liq} = \frac{1.3Q(c_{art} - c_{mix} - V_{alv}(\text{TLV} - 1.3c_{alv})}{\text{EA}}. \quad (9)$$

After substituting from Equation **(6)** and defining **EA** ($\text{EA} = 360\ \text{cm}^2$, stretched palms and fingers) and V_{alv} ($V_{alv} = 90\ \text{l.h}^{-1}$) a simple formula for the calculation of critical flux (expressed in $\text{mg cm}^{-2}\ \text{h}^{-1}$) is obtained:

$$\text{Fl}^*_{liq} = 3/4\ \text{TLV}. \quad (10)$$

A similar calculation can be made for whole-body exposure to a vapour ($\text{EA} = 18\,000\ \text{cm}^2$)

$$\text{Fl}^*_{vap} = 15\frac{c_{sat}}{\lambda}, \quad (11)$$

where c_{sat} is saturated aqueous solution of the vapour and λ is its water–gas partition coefficient **(FISEROVA-BERGEROVA *et al.*, 1990).**

The Biological Exposure Indices Committee of **ACGIH** denotes chemicals with measured or predicted flux larger than the critical flux, in order to draw attention to the possibility that biological levels may not be a quantitative indicato'r of inhalation exposure.

A similar algorithm was suggested for the evaluation of the potential for dermal toxicity and the development of a criterion for skin notation. Tripling biological levels by exposure of hands to liquid is considered as critical, and recognition of the potential for dermal toxicity is suggested for all chemicals with a flux value (in $\text{mg cm}^{-2}\ \text{h}^{-1}$) greater than 5 x TLV value (in mg m^{-3}) **(FISEROVA-BERGEROVA *et al.*, 1990). From 122** chemicals for which flux was predicted **(FISEROVA-BERGEROVA et *al.*, 1990),** a significant dermal toxicity potential upon contact with liquid is indicated for **77** chemicals **(63%);** of those, only 40 (52%) carried a skin notation in the **1987–1988** TLV-BEI Booklet, and only 41 **(53%)** carry a skin notation in the **1992–1993** booklet (skin notation was added to methyl n-butyl ketone and methyl chloride and removed from p-phenylene diamine) **(ACGIH, 1987, 1992).**

In the workplace, the threshold for flux can vary depending on the exposed area, the

duration of dermal exposure, and the selected threshold for the biological level. To estimate a reference value (RV) for dermal exposure existing in the workplace conditions, the following formula can be derived from Equation (8):

$$RV = \frac{\Delta BI\%}{100} \cdot V_{alv} \cdot TLV \cdot \frac{100}{EA\% \cdot SA} \cdot \frac{8}{h}. \quad (12)$$

The formula can be simplified to:

$$RV = 0.4 \frac{\Delta BI\% \cdot TLV}{EA\% \cdot h}, \quad (13)$$

where $\Delta BI\%$ denotes the chosen increased biological level expressed as a percentage of the level reached during exposure to TLV-TWA only, EA% denotes the percentage of body surface dermally exposed, h denotes the duration of dermal exposure in hours, and TLV is the TLV-TWA in mg l^{-1}. If flux exceeds the reference value ($FI > RV$), then a dermal overexposure at the selected BI-level is predicted (FISEROVA-BERGEROVA et *al.*, 1990).

CONCLUSION

The amount of chemicals percutaneously absorbed in the workplace can be as significant as the amount inhaled during the current permissible exposures in the workplace. The database for quantitative evaluation of dermal exposure is scattered and suffers from a lack of data on chronic dermal toxicity, from a lack of methods suitable for routine evaluation of dermal penetration, from variability of dermal exposure in the workplace, and from variability of skin composition. At present, theoretical models fill the gap resulting from lack of experimental data on dermal absorption. Criteria based on comparison of pulmonary and dermal uptake rates (which relate to chronic toxicity) should be preferred to criteria based on acute dermal LD_{50} (which are burdened by interspecies differences in skin composition, differences in acute and chronic toxic endpoint, and effect of mode of application and dispersant).

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