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Comparison of Indices Proposed as Criteria for Assigning Skin Notation

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Objectives: Skin notations are used as a hazard identification tool to flag chemicals associated with a potential risk related to transdermal penetration. The transparency and rigorousness of the skin notation assignment process have recently been questioned. We compared different approaches proposed as criteria for these notations as a starting point for improving and systematizing current practice.

Methods: In this study, skin notations, dermal acute lethal dose 50 in mammals (LD_{50}s) and two dermal risk indices derived from previously published work were compared using the lists of Swiss maximum allowable concentrations (MACs) and threshold limit values (TLVs) from the American Conference of Governmental Industrial Hygienists (ACGIH). The indices were both based on quantitative structure–activity relationship (QSAR) estimation of transdermal fluxes. One index compared the cumulative dose received through skin given specific exposure surface and duration to that received through lungs following inhalation 8 h at the MAC or TLV. The other index estimated the blood level increase caused by adding skin exposure to the inhalation route at kinetic steady state. Dermal-to-other route ratios of LD_{50} were calculated as secondary indices of dermal penetrability.

Results: The working data set included 364 substances. Depending on the subdataset, agreement between the Swiss and ACGIH skin notations varied between 82 and 87%. Chemicals with a skin notation were more likely to have higher dermal risk indices and lower dermal LD_{50} than chemicals without a notation (probabilities between 60 and 70%). The risk indices, based on cumulative dose and kinetic steady state, respectively, appeared proportional up to a constant independent of chemical-specific properties. They agreed well with dermal LD_{50}s (Spearman correlation coefficients -0.42 to -0.43). Dermal-to-other routes LD_{50} ratios were moderately associated with QSAR-based transdermal fluxes (Spearman correlation coefficients -0.2 to -0.3).

Conclusions: The plausible but variable relationship between current skin notations and the different approaches tested confirm the need to improve current skin notations. QSAR-based risk indices and dermal toxicity data might be successfully integrated in a systematic alternative to current skin notations for detecting chemicals associated with potential dermal risk in the workplace.

Keywords: percutaneous absorption; QSAR; risk analysis; skin notation

INTRODUCTION

The assessment of occupational health risk has traditionally focused on inhalation of airborne contaminants. Only in the last two decades has the industrial hygiene community begun to work on the issue of health risk posed by dermal exposure. This late focus on the dermal exposure pathway is thought to be due to the gradual decrease in occupational exposure limits (OELs) since they first appeared, potentially increasing the relative contribution of the dermal pathway, and to the complexity of assessing dermal exposure and risk (Fenske, 2000).

Industrial hygiene practitioners therefore still have a limited set of tools at their disposal to recognize, assess and control the occupational risk related to dermal penetration. Among them, the skin notation has traditionally been used to identify substances potentially associated with such risk. Present in many lists of OELs proposed by governmental [e.g. the German maximum allowable concentrations (MACs), (Deutsche Forschungsgemeinschaft, 2006)] or nongovernmental

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[e.g. the threshold limit values (TLVs), American Conference of Governmental Industrial Hygienists (ACGIH) (ACGIH, 2006)] organizations, skin notations are meant to flag chemicals for which the assessment of inhalation-only exposure might not be sufficient to adequately evaluate health risk. Their presence should prompt the expert to perform detailed dermal exposure and risk assessment or use biological monitoring to evaluate the total absorbed dose.

The criteria used for assigning a notation generally include experimental data on dermal absorption in human or animals, studies reporting toxic effects following skin exposure, *in vitro* estimates of dermal penetration, acute dermal toxicity data in animals and quantitative structure–activity relationship (QSAR) models, suggesting an elevated skin absorption potential. While approaches chosen by different OEL-setting organizations generally include all these criteria (Nielsen and Grandjean, 2004), consensus on a specific way to prioritize and interpret them still seems to be lacking (Sartortelli *et al.*, 2007).

Recently, a comparative study of six lists of OELs from different countries and organizations showed important discrepancies in the assignment of skin notations across these institutions (Nielsen and Grandjean, 2004). Hence, while all lists contained approximately the same number of chemicals with a skin notation (~30% of all chemicals), pairwise comparisons revealed an average agreement of only 60–70% between the lists. Scansetti *et al.* reviewed the documentation of the 1986 ACGIH TLV list and recorded, for each chemical with a skin notation, the justification for its presence (Scansetti *et al.*, 1988). The most frequent criterion (40% of all cases) was a dermal lethal dose 50 in mammal (LD_{50}) <2000 mg kg^{-1}. It is noteworthy that for 8% of cases, evidence of local effects to the skin was the cause of the skin notation, while no rationale was provided for 20% of the cases. The need for an improvement of the current skin notation system was stressed in a recent international workshop on this topic (Sartorelli *et al.*, 2007).

Several quantitative criteria for assigning skin notations in a systematic way have been proposed over the last two decades. Fiserova-Bergerova *et al.* proposed a simple steady state kinetic model coupled with QSAR estimates of dermal penetration rates (Fiserova-Bergerova *et al.*, 1990; Fiserova-Bergerova, 1993). A skin notation would be assigned when skin exposure caused a significant increase in the blood level corresponding to inhalation at the OEL. Also using QSAR for penetration rates, Walker proposed to calculate a maximal exposure time (for a chosen exposed surface) corresponding to the dose received through skin being equivalent to that received through lungs during a workshift at the OEL (Walker *et al.*, 1996). A similar approach, comparing the dose received through skin after 1-h exposure of the hands and forearms to the workshift inhalation dose, has also been evocated (de Cock *et al.*, 1996; Sartorelli *et al.*, 2007). Kennedy discussed the use of dermal LD_{50} in animals as a criterion for skin notations (Kennedy *et al.*, 1993).

While the advantages and limits of these methods have been discussed by their respective authors and others interested in this issue, we found no study attempting to evaluate in a comprehensive manner to what extent they might agree or not with each other and with existing lists of skin notations.

Within the framework of the revision of the skin notation in Switzerland, we applied QSAR-based approaches to two lists of OELs (the Swiss MACs and the ACGIH TLVs). One approach is based on Fiserova-Bergerova *et al.*'s steady state kinetic model, while the other is based on the cumulative dose received through skin, similar to Walker's proposal. These two approaches were then compared with current skin notations in the Swiss and ACGIH OEL lists and acute dermal toxicity data in animals. The study ultimately aimed at obtaining insight on how to improve the current use of the concept of skin notation.

METHODS

List of equation terms and their units

- Kp (cm h^{-1}): coefficient of permeability
- MW (g mol^{-1}): molecular weight
- $\mathrm{Log}K_{ow}$: logarithm (base 10) of the octanol-water partition coefficient
- $J\mathrm{max}$ (mg cm^{-2} h^{-1}): maximal transdermal flux
- Sol_{water} (mg cm^{-3}): aqueous solubility
- V_{alv} (m^3 h^{-1}): alveolar flow rate
- %BL (%): percentage of blood level increase
- OEL (mg m^{-3}): occupational exposure limit
- $S_{exposed}$ (cm^2): surface of body exposed
- S_{body} (cm^2): total body surface (18 000 cm^2)
- J^* (mg cm^{-2} h^{-1}): critical flux
- $C_{equilibrium}$ (mg cm^{-3}): concentration of an aqueous solution in equilibrium with an atmospheric concentration at the OEL
- K_{Henri} (atm m^3 mol^{-1}): Henri's law constant
- V_m (l mol^{-1}): molar volume at standard temperature and pressure (STP) (24.4 l mol^{-1}).
- $V_{8\,h}$ (m^3): volume inhaled during an 8-h workshift
- $T_{exposed}$ (h): duration of skin exposure

QSAR model for skin penetration rates

Inherent in the application of the quantitative approaches mentioned above is the availability of dermal penetration rate estimates. Transdermal flux (J, the amount of chemical penetrating by unit of time and surface exposed) has been described using Fick's law of diffusion for membranes and can be expressed as the product of a coefficient of permeability and the concentration of the chemical in the vehicle (McDougal and Boeniger, 2002). Unfortunately,

such rates have been measured for only a limited set of chemicals and, until recently, with lacking standardization of the experimental settings (Walker *et al.*, 2003). In order to circumvent the scarcity of experimental data, QSARs have been established for skin penetration rates, mainly using the so-called 'Flynn data set', a compilation of experimental *K*p values measured in aqueous solution and presented by Flynn (Flynn, 1990). Several authors have reviewed the different QSAR models for skin absorption (Wilschut *et al.*, 1995; Moss *et al.*, 2002; Walker *et al.*, 2003; Cronin, 2006; Degim, 2006). While these models varied in the statistical methods, data sets, number of predictor variables and penetration indices modeled, satisfactory results were obtained by modeling the logarithm of the permeability coefficient as a function of molecular weight and the logarithm of the octanol/water partition coefficient using multiple linear regression (Potts and Guy, 1992). Only marginal improvement seems to have been achieved by adding additional parameters or using more complex statistical methods compared to the difficulty of acquiring relevant input information. We used the equation estimated by Vecchia and Bunge, who modeled log(*K*p) as a function of MW and logK_{ow} with a refined version of the Flynn data set (Vecchia and Bunge, 2003). Cronin underlined the quality of their effort to improve the original Flynn data, most notably by adjusting for the fraction of chemicals in ionized form in experimental data (Cronin, 2006). Vecchia and Bunge's QSAR equation (equation T1 in Table 1 pp. 88–89) is as follows:

$$\mathrm{Log}_{10}(Kp) = -2.44 + 0.514 \times \log K_{ow} - 0.0050 \times \mathrm{MW}. \quad (1)$$

Assuming exposure of the skin to a saturated aqueous solution of the chemical in question, it is possible to determine the maximal transdermal flux (in mg cm^{-2} h^{-1}) at steady state:

$$J\mathrm{max} = Kp \times \mathrm{Sol}_{water}. \quad (2)$$

Where Sol_{water} is the water solubility of the chemical.

Dermal risk indexes

Kinetic approach. This approach is based on the work by Fiserova-Bergerova *et al.* (Fiserova-Bergerova *et al.*, 1990; Fiserova-Bergerova, 1993). The potential for dermal penetration of a chemical, expressed as *J*max is compared to a 'critical flux' (*J**). The critical flux was defined by the authors as a hypothetical penetration rate through the stratum corneum, which, assuming simultaneous skin and inhalation exposure, causes the biological levels to increase above those reached during inhalation-only exposure at the OEL by a prespecified fraction.

Detailed derivation of *J** is presented in the appendix of Fiserova-Bergerova *et al.* (1990). Briefly, the authors used different equations for liquids, for which only a part of the body surface is exposed, and for gases/vapors, for which they assumed exposure of the entire body surface to an aqueous solution in equilibrium with the atmospheric concentration at the OEL. The liquid case is directly applicable to solids since we assume exposure to a saturated aqueous solution.

For the liquid/solid case, the critical flux can be expressed as:

$$J^* = \frac{V_{alv} \times \%\mathrm{BL} \times \mathrm{OEL}}{S_{exposed}}. \quad (3)$$

Where V_{alv} is the alveolar flow rate, $S_{exposed}$ is the skin surface exposed and %BL is the relative increase in blood levels at steady state caused by skin exposure.

From equation (3), we define the index R_{FB} as the ratio of *J*max (equation 2) to *J**:

$$R_{FB}^{liq} = \frac{J\ \mathrm{max}}{J^*} = \frac{J\ \mathrm{max} \times S_{exposed}}{V_{alv} \times \%\mathrm{BL} \times \mathrm{OEL}}. \quad (4)$$

$R_{FB} > 1$ implies that, assuming toxicokinetic steady state, exposure to a saturated aqueous solution of the chemical in question with a simultaneous inhalation exposure at the OEL causes an increase of at least %BL in blood levels compared to an inhalation-only exposure scenario.

For gases and vapors, the authors assumed the entire surface of skin was exposed to an aqueous solution of the chemical in equilibrium with an atmospheric concentration at the OEL. Since the equilibrium concentration is smaller than the saturated concentration, the transdermal flux to use in the kinetic model is not *J*max (equation 2), but a flux equal to $Kp \times C_{equilibrium}$. This correction results in the following expression for the critical flux:

$$J_{gas}^* = \frac{V_{alv} \times \%\mathrm{BL} \times \mathrm{OEL}}{S_{body}} \times \frac{\mathrm{Sol}_{water}}{C_{equilibrium}}, \quad (5)$$

where $C_{equilibrium}$ can be estimated by:

$$C_{equilibrium} = \frac{\mathrm{OEL} \times V_m}{10^9 \times K_{Henri}}, \quad (6)$$

with K_{Henri} the Henri's law constant for the chemical and V_m the molar volume at STP.

Equations (5) and (6) can be combined to obtain R_{FB} for gases.

$$R_{FB}^{gas} = \frac{J\mathrm{max}}{J^*} = \frac{J\ \mathrm{max} \times S_{body} \times V_m}{V_{alv} \times \%\mathrm{BL} \times \mathrm{Sol}_{water} \times K_{Henri} \times 10^9}. \quad (7)$$

Note: while the indices above are based on the approach published by Fiserova-Bergerova *et al.*, we did not use their equations for estimating fluxes which were subsequently shown to overestimate transdermal passage (Bunge, 1998).

Cumulative dose approach. The principle of this approach is to compare the dose received through skin following a given exposure scenario to that inhaled during a workshift at the OEL. It differs from the kinetic approach in that no simultaneous dermal and pulmonary exposure is assumed. Rather, this method measures the likelihood that, given a skin exposure scenario, the dose received through skin might reach the safety threshold dose set for respiratory exposure. Variations of this approach have been described by Walker *et al.* (1996) and de Cock *et al.* (1996) and in the review by McDougall and Boeniger (McDougal and Boeniger, 2002). We calculated the ratio of the dermal dose to inhalation dose as follows:

The dose received through inhalation is estimated assuming 100% pulmonary absorption:

$$D_{\text{inh}} = \text{OEL} \times V_{8\,\text{h}}, \tag{8}$$

with $V_{8\ \text{h}}$ the volume inhaled during an 8-h shift.

The cutaneous dose is expressed as:

$$D_{\text{cut}} = J \times S_{\text{exposed}} \times T_{\text{exposed}}, \tag{9}$$

with T_{exposed} exposure duration. S_{exposed} and J are the exposed surface and transdermal flux, both different for liquids/solids and gases/vapors:

$$D_{\text{cut}}^{\text{liq}} = J\ \text{max} \times S_{\text{exposed}} \times T_{\text{exposed}}, \tag{10}$$

$$D_{\text{cut}}^{\text{gas}} = J\ \text{max} \times \left(\frac{C_{\text{equilibrium}}}{\text{Sol}_{\text{water}}}\right) \times S_{\text{body}} \times 8\,\text{h}. \tag{11}$$

This yields the following expressions for the ratios cutaneous/inhalation:

$$R_{\text{cut/inh}}^{\text{liq}} = \frac{D_{\text{cut}}^{\text{liq}}}{D_{\text{inh}}} = \frac{J\ \text{max} \times S_{\text{exposed}} \times T_{\text{exposed}}}{\text{OEL} \times V_{8\,\text{h}}}, \tag{12}$$

$$R_{\text{cut/inh}}^{\text{gas}} = \frac{D_{\text{cut}}^{\text{gas}}}{D_{\text{inh}}} = \frac{J\ \text{max} \times S_{\text{body}} \times V_{\text{m}} \times 8\,\text{h}}{\text{Sol}_{\text{water}} \times V_{8\,\text{h}} \times 10^{9} \times K_{\text{Henri}}}. \tag{13}$$

$R_{\text{cut/inh}} > 1$ implies that exposure during 8 h to a saturated aqueous solution of the chemical in question causes absorption of a dose at least equivalent to that which would have been received after inhalation exposure at the OEL during 8 h.

Choice of exposure scenarios. Both the kinetic and cumulative dose approaches require selection of an exposed skin surface for exposure to liquids and solids, the latter also having exposure duration as an input. We selected arbitrarily an exposed surface of both hands (surface 840 cm^2) and an exposure duration of 8 h. Fiserova-Bergerova *et al.* selected an exposed surface of 2% of total body surface, corresponding to the palms of both hands (Fiserova-Bergerova *et al.*, 1990). In Walker's approach (Walker, 1996), one hand is considered, while both hands and forearms during 1 h is the scenario mentioned in de Cock *et al.* (1996).

Database construction

The starting database for this study was the list of OELs enforced in Switzerland by the Swiss Accident Insurance Fund (SUVA), which contains names, CAS numbers and regulatory OELs of ~700 chemicals. Information from the 2006 ACGIH TLVs and BEIs CDROM were then added. Physicochemical characteristics were retrieved using the PHYSPROP database (Syracuse Research Corporation, North Syracuse, NY, USA), which contains experimental, extrapolated, and estimated property values for over 40 000 chemicals.

Acute toxicity data was obtained through purchase of the Registry of Toxic Effects of Chemical Substances (RTECS), a compendium of data extracted from the open scientific literature which contains acute toxicity values for >130 000 chemicals. Due to the scarcity of acute toxicity data, we included in our study LD_{50}s for all mammals. For each chemical, the lowest of all available LD_{50} values was selected for each exposure route. LD_{50} data other than dermal were retrieved in order to calculate ratios of dermal to other routes ratios, used as proxies for the ability of a chemical to penetrate the skin. For each substance and for a specific comparison route (e.g. dermal to oral), the ratios were derived as follows: all available data were restricted to values available for both routes for at least one species. Then for each species, the lowest LD_{50} value was selected for each route and a ratio dermal/comparison route was calculated. The final ratio for the chemical in question was taken as the geometric average of the minimum and maximum ratios obtained with the different species.

The dermal LD_{50} data were also used to create a categorical variable simulating the 'risk phrases' used in the European Community to characterize risks associated with chemicals (see Annex III of European Union Directive 67/548/EEC, consolidated in Directive 2001/59/EC). Three such phrases refer specifically to health risks posed by penetration through skin: R21 Harmful in contact with skin, R24 Toxic in contact with skin and R27 Very toxic in contact with skin. These phrases are assigned to a chemical depending on the value of the dermal LD_{50} in rats or rabbits with the following limits: R21 $400 < LD_{50} < 2000$ mg kg^{-1}, R24 $50 < LD_{50} < 400$ mg kg^{-1} and R27 $LD_{50} < 50$ mg kg^{-1}.

RESULTS

Description of the databases

Abstracting the SUVA list of OELs yielded an initial database of 668 substances with a unique CAS

number. This database was refined by eliminating substances for which the skin penetration models are not relevant, i.e. dusts, fibers, metals and metallic oxides, and substances classified as corrosive according to the EC classification (risk phrases R34 and R35). Further elimination of chemicals with missing input parameters, without a numerical 8-h OEL in the SUVA list or having values of molecular weight or $\log K_{ow}$ outside of the modeling space recommended by Vecchia and Bunge (MW between 18 and 500 g mol^{-1} and $\log K_{ow}$ between –1.3 and 4.27) (Vecchia and Bunge, 2003) yielded a data set of 364 substances (data set BD1). The 509 dermal LD_{50}s retrieved in our study spanned the years 1915–2005, with 1974 as the median year.

Gases/vapors versus liquids/solids. As mentioned by McDougall and Boeniger (2002), penetration through skin of gases and vapors can in most cases be considered as minor compared to the inhalation route. This is reflected in the equations above by the fact that the transdermal flux is not calculated with the saturation concentration of a chemical, but with a concentration in equilibrium with the atmospheric contamination, resulting in most cases in a much smaller flux. Figure 1, which shows a boxplot of the $R_{cut/inh}$ index calculated with the SUVA OELs applied to the data set BD1 stratified by physical state at STP, clearly illustrates the bimodality of the distribution of the index values. To avoid potential confounding by the physical state, we therefore excluded gases and vapors from subsequent analyses. This yielded a data set BD2 of 320 chemicals. Table 1 presents descriptive statistics for the parameters of interest in this study in BD2.

OELs based on sensory irritation. A limitation associated with using inhalation OELs to estimate an internal threshold dose is that the toxic end point used to derive the OEL may not be relevant to systemic effects following absorption through skin (Fiserova-Bergerova *et al.*, 1990; Bos *et al.*, 1998; Nielsen and Grandjean, 2004). In particular, a number of OELs are based on irritation of the respiratory tract or eyes. Since the basis of an OEL is supposed to be the effect occurring at the lowest dose, calculating a risk index based on irritation will cause an overestimation of risk, the extent of which is unknown. For the ACGIH list, the OELs were distributed as follows: 66 based on irritation and 191 based on other effects. We obtained the data set BD.ACGIH by eliminating irritation-based OELs. The Swiss booklet does not indicate the critical effect of OELs and there is no publicly available documentation of these OELs. The Swiss OELs being very close to the German MAC values (Prof. Michel Guillemin, Swiss OEL committee), we imputed the rationale for the Swiss OELs using the German values. The OELs were distributed as follows: 57 based on irritation, 199 based on other effects and 64 unknown rationales. Keeping only OELs based on other effects yielded the data set BD.SUVA.

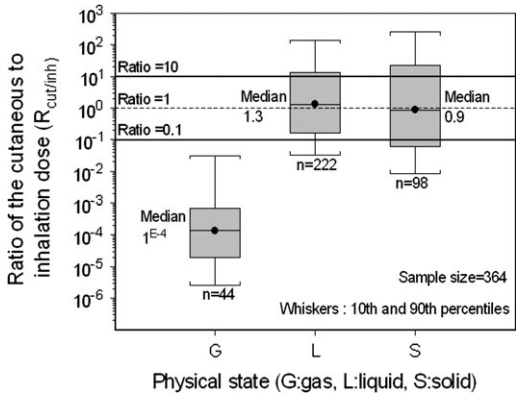

Fig. 1. Variation of the dermal to inhalation ratio ($R_{cut/inh}$) as a function of the physical state of chemicals.

Theoretical correspondence between R_{FB} and $R_{cut/inh}$

Equations (4), (7), (12) and (13) can be combined to obtain analytical formulas for the ratio $R_{cut/inh}/R_{FB}$:

$$\frac{R_{\text{cut/inh}}}{R_{\text{FB}}}(\text{liquid/solid}) = \frac{V_{\text{alv}} \times \%\text{BL} \times T_{\text{exposed}}}{V_{8\,\text{h}}}, \tag{14}$$

$$\frac{R_{\text{cut/inh}}}{R_{\text{FB}}}(\text{gas/vapor}) = \frac{V_{\text{alv}} \times \%\text{BL} \times 8\,\text{h}}{V_{8\,\text{h}}}.$$

The two approaches can therefore be taken as equivalent save for a proportionality factor that does not depend on the chemical studied. With $T_{exposed}$ = 8 h, $V_{8\ h}$ = 10 m^3 (Paustenbach, 2003) and V_{alv} = 0.9 $m^3\ h^{-1}$ (Fiserova-Bergerova *et al.*, 1990) and %BL = 30% (as in the paper by Fiserova *et al.*), the ratio is 0.22. In this case, the kinetic approach is more conservative than the cumulative dose approach. Considering this analytical correspondence, we limited the subsequent analyses to the $R_{cut/inh}$ index.

Relationship between SUVA and ACGIH lists

Using the initial SUVA list restricted to substances present in the 2006 TLV booklet (n = 501), Skin notations in both lists agreed for 87% of chemicals, with 45 substances with a SUVA skin notation but without an ACGIH skin notation and 21 substances without a SUVA notation but with an ACGIH notation. Restricting the comparison to the smallest data set in our analysis (BD.ACGIH, n = 191) yielded 82% of agreement, with 26 SUVA/non-ACGIH and 9 non-ACGIH/SUVA situations.

Relationship between $R_{cut/inh}$ and current skin notations

Figure 2 shows variations of the $R_{cut/inh}$ index for chemicals with and without a SUVA skin notation

Table 1. Descriptive statistics for parameters in the working database

Variable	Minimum	First quartile	Median	Third quartile	Maximum	*n*
MW[a] (g mol^{-1})	27	99	129	199	461	320
*P*vap[b] (mmHg)	1.3×10^{-13}	0.0013	1.29	21.07	760	320
Sol[c] (mg l^{-1})	0.2	222	4820	60 500	1 000 000	320
LogK_{ow}[d]	−1.28	0.58	1.60	2.70	4.21	320
SUVA-OEL[e] (mg m^{-3})	0.001	0.5	10	100	4 200	320
ACGIH-OEL[f] (mg m^{-3})	0.0047	1.27	10.15	203	7 664	257
*K*p[g] (cm h^{-1})	4.6×10^{-5}	0.0018	0.0044	0.0106	0.1360	320
*J*max[h] (mg cm^{-2} h^{-1})	3.5×10^{-7}	0.0026	0.0275	0.1340	3.71	320
$R_{cut/inh}$ SUVA[i]	7.8×10^{-5}	0.13	1.22	17.80	1.74×10^{5}	320
$R_{cut/inh}$ ACGIH[j]	1.3×10^{-4}	0.08	0.77	9.73	2.19×10^{4}	257
LD_{50}[k] (mg kg^{-1})	0.75	300	1580	5070	3.44×10^{4}	149

[a]Molecular weight.
[b]Vapor pressure.
[c]Water solubility.
[d]Logarithm (base 10) of the octanol/water partition coefficient.
[e]8 h occupational exposure limit in the SUVA list.
[f]8 h occupational exposure limit in the ACGIH list.
[g]Modeled skin permeability coefficient.
[h]Modeled transdermal maximal flux.
[i]$R_{cut/inh}$ calculated with the SUVA OEL.
[j]$R_{cut/inh}$ calculated with the ACGIH OEL.
[k]Lethal dose 50 in mammals.

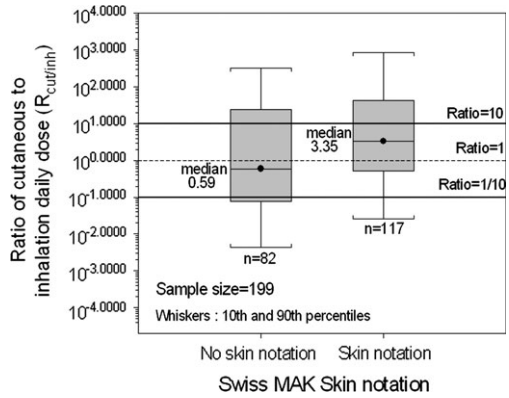

Fig. 2. Variations of the dermal to inhalation ratio ($R_{cut/inh}$) as a function of presence or absence of a Swiss skin notation.

(data set BD.SUVA). The results were similar for the ACGIH notation (data set BD.ACGIH), with a median $R_{cut/inh}$ of 3.6 for chemicals with a skin notation and 0.2 for those without. The discriminating power of $R_{cut/inh}$ can be expressed as the fact that a chemical randomly chosen within the 'skin notation' group of the SUVA list had a probability of 61% of having $R_{cut/inh}$ higher than a chemical without a skin notation (72% for the ACGIH list). Looking at variations of the two determinant parameters of $R_{cut/inh}$, *J*max and the OEL values, their median for chemicals with and without a notation were 0.033 versus 0.025 mg cm^{-2} h^{-1} and 3.2 versus 12.5 mg m^{-3}, respectively, for the Swiss list. The values were 0.026 versus 0.023 mg cm^{-2} h^{-1} and 4.6 versus 35.2 mg m^{-3} for the ACGIH list.

Relationship between acute dermal toxicity data and current skin notations

Figure 3 shows variations of the dermal LD_{50} in mammals with and without a SUVA skin notation. Since the OELs and their critical effect were not relevant in this comparison, we used the data set BD2 restricted to chemicals for which a LD_{50} was available ($n = 149$) in this analysis. Among the 57 chemicals without a skin notation, 19 and 5 were in the categories $400 < LD_{50} < 2000$ and $50 < LD_{50} < 400$ mg kg^{-1}, respectively; two substances (Fensulfothion CAS 115-90-2, Disulfoton CAS 298-04-4) had a dermal $LD_{50} < 50$ mg kg^{-1}. Comparing the dermal LD_{50} with the ACGIH classification yielded a similar pattern. There were 136 LD_{50} available, and the median values were 400 and 3228 mg kg^{-1} for chemicals with and without a skin notation, respectively. Among the 63 chemicals without a skin notation, 30 and 4 were in the categories $400 < LD_{50} < 2000$ and $50 < LD_{50} < 400$ mg kg^{-1}, respectively. Of the 30 substances with $400 < LD_{50} < 2000$, 23 had a $LD_{50} > 1000$ mg kg^{-1}, a criterion mentioned in the 2006 TLV booklet. A substance without a skin notation in the SUVA list had a 64% chance of having a higher LD_{50} than a substance with a notation (72% for the ACGIH list).

Relationship between $R_{cut/inh}$ and acute dermal toxicity data

Figure 4 shows the variations of $R_{cut/inh}$ calculated with the SUVA OELs (BD.SUVA) as a function of acute dermal toxicity categories. The Spearman

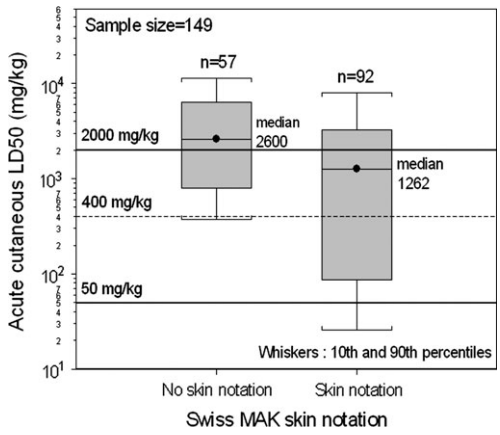

Fig. 3. Variations of the dermal LD_{50} in mammals as a function of presence or absence of a Swiss skin notation.

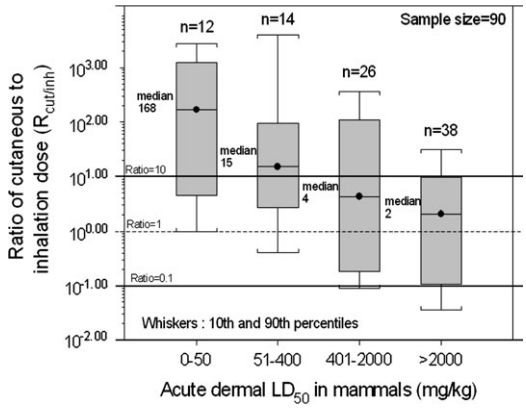

Fig. 4. Variations of the dermal to inhalation ratio ($R_{cut/inh}$) as a function of acute dermal toxicity categories.

correlation coefficient between $R_{cut/inh}$ and the LD_{50} values was −0.42 ($P = 0$, $n = 90$). Again, a similar pattern was observed with the ACGIH values (data set BD.ACGIH), with the following median $R_{cut/inh}$ values: 39 for $LD_{50} < 50$ mg kg^{-1}, 10 for $50 < LD_{50} < 400$ mg kg^{-1}, 4 for $400 < LD_{50} < 2000$ mg kg^{-1} and 1 for $LD_{50} > 2000$ mg kg^{-1}. The Spearman correlation coefficient between $R_{cut/inh}$ and the LD_{50} values was −0.43 ($P = 0$, $n = 102$). Looking at *J*max and the OEL values for the Swiss list, the correlation coefficients with the LD_{50} were 0.03 ($P = 0.73$) and 0.6 ($P = 0$), respectively. These values were 0.20 ($P = 0.05$) and 0.74 ($P = 0$) for the ACGIH list.

Relationship between transdermal penetration parameters and ratios of LD_{50}

Table 2 shows the Spearman correlation coefficients between the different parameters used to estimate skin penetration (*J*max, *K*p and Sol_{water}) and the ratios of dermal to other route LD_{50} estimated from RTECS. The results are presented for the whole PHYSPROP data for which *J*max and *K*p could be estimated within the modeling space defined by Vecchia and Bunger (2003) and for the main working data set (BD2).

DISCUSSION

Few tools are available to industrial hygienists to assess the systemic toxic risk posed by skin exposure to chemical at the workplace. Quite recently, conceptual models for skin exposure have been presented that mark the emergence of this particular field (Schneider *et al.*, 1999). RISKOFDERM (Oppl *et al.*, 2003), aimed at 'educated nonexperts', provides a risk banding approach similar to the COSHH

Table 2. Spearman correlation coefficients between dermal penetration parameters and ratios of dermal LD_{50} to LD_{50} from other exposure routes

Route	*n*	*J*max[a]	*K*p[b]	Sol_{water}[c]
Full database[d]				
Oral	451	−0.16 (<0.01)[e]	−0.15 (<0.01)	−0.07 (0.14)
Intraperitoneal	180	−0.08 (0.27)	−0.03 (0.66)	−0.04 (0.56)
Intravenous	79	−0.23 (0.04)	0.017 (0.88)	−0.23 (0.04)
Working database[f]				
Oral	93	−0.34 (<0.01)	0.02 (0.83)	−0.28 (<0.01)
Intraperitoneal	51	−0.18 (0.21)	0.01 (0.96)	−0.14 (0.31)
Intravenous	31	−0.33 (0.07)	−0.09 (0.62)	−0.21 (0.25)

[a]Maximal transdermal flux.
[b]Skin permeability constant.
[c]Water solubility.
[d]All chemicals in PHYSPROP for which *J*max could be estimated within the modeling space defined by Vechia and Bunge (2003).
[e]*P* value associated with the correlation coefficient estimate.
[f]Data set BD2.

toolbox (Jones and Nicas, 2006). The risk analysis is based on the European risk phrases and assumes 100% skin absorption in most cases. The DREAM model based on the work of Schneider *et al.* provides an interesting semiquantitative approach to dermal exposure assessment, but does not consider risk (Van-Wendel-De-Joode *et al.*, 2003). The skin notations therefore still appear as the main tool providing the industrial hygienist with a signal that they should consider the skin pathway in their assessment. It is therefore important that efforts be made to improve their rationale and justification.

Current skin notations

The two OEL lists examined in our study, the Swiss MAC values and the ACGIH TLVs, proved to be somewhat closer to each other than what could have been expected considering the results from Nielsen and Grandjean (2004). The higher agreement in our study comes from the fact that we looked at chemicals common to both classifications, whereas Nielsen *et al.* counted chemicals with a skin notation regardless if they were present in other lists. Despite these more favorable figures, hygienists looking for information will still get a contradictory message in close to 20% of cases.

Comparing the QSAR-based risk index for chemicals with and without a skin notation yielded a plausible but variable relationship, chemicals with a skin notation having generally a higher dermal risk according to $R_{cut/inh}$. The association appeared to be due to differences in OELs between chemicals with and without notations rather than differences in estimated transdermal flux.

A similar trend was observed with acute toxicity data, i.e. generally lower LD_{50} for chemicals with a skin notation. In this case, the contrast between chemicals with and without a skin notation was higher for the ACGIH list. This is probably explained by the explicit mention of a dermal LD_{50} criterion in the TLV booklet (1000 mg kg^{-1}). Kennedy *et al.*, before any numerical criterion was mentioned in the TLV booklet, observed that the relationship between the presence of a skin notation and dermal LD_{50} values was unclear and recommended a criterion of 1000 mg kg^{-1}. Fifteen years after this criterion was implemented (1991–1992), the relationship is clearer, but 11 substances without a skin notation still have LD_{50} values $<$1000 mg kg^{-1}, of which four are $<$400 mg kg^{-1}.

Comparison of the cumulative dose and kinetic approaches

The two QSAR-based approaches described in our study, although based on different assumptions, proved to be proportional, the proportionality being chemical independent. In fact, using a skin exposure duration equivalent to the inhalation exposure duration, and simplifying the alveolar flow rate as equal to the respiratory flow rate, the ratio between the two indices reduces to %BL. A doubling of the blood levels (%BL = 100%) corresponds to equivalence of the two approaches. This is explained by the fact that at steady state, the blood levels estimated using the simple kinetic model described by Fiserova-Bergerova *et al.* are proportional to the exposure dose rate. Hence, the two approaches differ only in that one compares dose rates while the other compares doses. They become numerically equivalent when inhalation and dermal exposure durations are equal.

Comparison of the QSAR-based approaches and acute dermal toxicity

We observed a moderate-to-good agreement between the QSAR-based indices and the available acute dermal toxicity (Spearman correlation $\sim$0.45). This agreement appeared due mainly to the strong inverse correlation between the LD_{50}s and the OELs and somewhat puts into question the relevance of our transdermal flux estimates. However, the possibility to calculate dermal to other route ratios of LD_{50} for a number of chemicals in our study offered a means of validating 'externally' these penetration rates. The observed correlation coefficients showed a weak-to-moderate but statistically significant inverse relationship with *J*max and the water solubility, while the relationship with *K*p was less clear (see Table 2). Given the variability linked with the derivation of the LD_{50} ratios (e.g. animals may have been exposed to the neat chemical), our results suggest that the estimated penetration rates actually influence the relation between dermal and other route acute toxicity and are relevant to the risk assessment.

Finally, the fact that the relationship with dermal to other route ratios seems stronger for the maximal flux and the water solubility than with the permeation constant is noteworthy. Indeed, *J*max is estimated by the product of *K*p and Sol_{water}, and Sol_{water} is available for many compounds in a reliable manner. Then, it could be inferred that although *K*p values are associated with much uncertainty because of QSARs based on a limited data set, this uncertainty is not critical in estimating the risk associated with dermal exposure. Mechanistically, the possible predominance of the solubility versus *K*p in determining the flux has been mentioned (Boeniger, 2003). Our results are, however, too limited to draw any firm conclusion on this issue and making the same comparison using available experimental data would be informative.

Exposure scenarios

Since our study was comparative, our particular choice of exposure scenario had no impact on the conclusions drawn. In assessing risk, however, absolute values of the indices will be needed and scenarios will have to be selected, each single one being

probably not universally realistic (de Cock *et al.*, 1996). Developing further the proposition of Walker's maximal skin exposure time (Walker *et al.*, 1996), an index based on the product of exposure duration and surface (e.g. a maximum time × surface, in h cm^2 corresponding to a dermal dose equal to the inhalation dose) might allow a wider space of scenarios to be included in the assessment. Such an approach is currently being developed at the Institute for Work and Health.

Limitations of each single method: a case for an integrated approach

The limits associated with each approach used in this study have generally been discussed by their authors or in reviews (see for example, McDougall and Boeniger, 2002). They can be separated in two categories: limitations due to assumptions and simplification of the real skin exposure and absorption process (e.g. exposure to a saturated aqueous solution and infinite dose/steady state scenarios or use of acute animal toxicity data as opposed to chronic human data) and limitations due to circumstances in which data are not available or not relevant for their implementation (e.g. an elevated LD_{50} is not useful because it indicates low acute toxicity but says nothing about potential chronic effects at low doses or the OEL is based on irritation). The first category involves in particular the uncertainty of current QSARs for dermal penetration, which according to some authors should be only used for hazard identification (Vande-Sandt *et al.*, 2007). In our view, such limitations are not much different than those existing in many risk assessment approaches and gradual improvement of experimental data and sensitivity analysis methods can help reduce their impact. Examples of advances in the field include the elaboration of a database of standardized *in vivo* and *in vitro* experimental permeation data within the EDETOX project and attempts to estimate finite dose permeation from infinite dose experiments (Kruse *et al.*, 2007;). The second category of limitations can be circumvented, at least partially, by using an integrated approach. Hence, while elevated acute LD_{50} are not informative, a low value certainly provides insight into potential dermal effects in human. On the other hand, a QSAR-based index using an OEL based on sensory irritation, although overestimating risk, will be useful if resulting in a low-risk prediction.

CONCLUSION

The approaches presented here cover only some aspects of the 'ideal' skin notation process, which is, for example, more thoroughly addressed in the position paper by Sartorelli *et al.* (2007). Thus, issues such as those of mixtures and penetration enhancers are not included. In particular, experimental penetration data and human dermal toxicity data are available for a number of chemicals and represent stronger evidence than the modeling approaches presented here. The purpose of our study was not to propose a new 'skin notation method', but to compare quantitative approaches that can be implemented for many chemicals. In this regard, we think these approaches can be successfully included as part of a global algorithm making use of all information available in a systematic and predefined way.

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REFERENCES

ACGIH. (2006) TLVs and BEIs threshold limit values for chemical substances and physical agents /biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

Boeniger MF. (2003) Occupational dermatotoxicology: significance of skin exposure in the workplace. In: Perkins JL, editor. Modern industrial hygiene. Vol. 2, Cincinnati, OH: American Conference of Governmental Industrial Hygienists; pp. 47–134.

Bos PM, Brouwer D, Stevenson H *et al*. (1998) 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.

Bunge AL. (1998) Re: dermal absorption potential of industrial chemicals: criteria for skin notation. Am J Ind Med; 34: 89–90.

Cronin MT. (2006) The prediction of skin permeability using quantitative structure-activity relationship methods. In: Riviere J, editor. Dermal absorption models in toxicology and pharmacology. Boca Raton, FL: Taylor & Francis; pp. 113–34.

de Cock J, Heederik D, Kromhout H *et al*. (1996) Strategy for assigning a 'skin notation': a comment. Ann Occup Hyg; 40: 611–14.

Degim IT. (2006) New tools and approaches for predicting skin permeability. Drug Discov Today; 11: 517–23.

Deutsche Forschungsgemeinschaft. (2006) List of MAK and BAT values 2006, commission for the investigation of health hazards of chemical compounds in the work area (report n.42). Weinheim, Germany: Wiley-VCH Verlag.

Fenske RA. (2000) Invited editorial: dermal exposure—a decade of real progress. Ann Occup Hyg; 44: 489–91.

Fiserova-Bergerova V. (1993) Relevance of occupational skin exposure. Ann Occup Hyg; 37: 673–85.

Fiserova-Bergerova V, Pierce JT, Droz PO. (1990) Dermal absorption potential of industrial chemicals: criteria for skin notation. Am J Ind Med; 17: 617–35.

Flynn GL. (1990) Physicochemical determinants of skin absorption. In: Gerrity TR and Henry DJ, editors. Principles of route-to-route extrapolation for risk assessment. New York, NY: Elsevier; pp. 93–127.

Jones RM, Nicas M. (2006) Margins of safety provided by COSHH Essentials and the ILO Chemical Control Toolkit. Ann Occup Hyg; 50: 149–56.

Kennedy GL, Brock WJ, Banerjee AK. (1993) Assignment of skin notation for threshold limit values for chemicals based on acute dermal toxicity. Applied Occup Environ Hyg; 8: 26–30.

Kruse J, Golden D, Wilkinson S *et al*. (2007) Analysis, interpretation, and extrapolation of dermal permeation data using diffusion-based mathematical models. J Pharm Sci; 96: 682–703.

McDougal JN, Boeniger MF. (2002) Methods for assessing risks of dermal exposures in the workplace. Crit Rev Toxicol; 32: 291–327.

Moss GP, Dearden JC, Patel H *et al*. (2002) Quantitative structure-permeability relationships (QSPRs) for percutaneous absorption. Toxicol In Vitro; 16: 299–317.

Nielsen JB, Grandjean P. (2004) Criteria for skin notation in different countries. Am J Ind Med; 45: 275–80.

Oppl R, Kalberlah F, Evans PG *et al*. (2003) A toolkit for dermal risk assessment and management: an overview. Ann Occup Hyg; 47: 629–40.

Paustenbach D. (2003) The history and biological basis of occupational exposure limits. In: Perkins JL, editor. Modern industrial hygiene. Vol. 2, Cincinnati, OH: American Conference of Governmental Industrial Hygienists; pp. 631–726.

Potts RO, Guy RH. (1992) Predicting skin permeability. Pharm Res; 9: 663–9.

Sartorelli P, Ahlers HW, Alanko K *et al*. (2007) How to improve skin notation. Position paper from a workshop. Regul Toxicol Pharmacol; 49: 301–7.

Scansetti G, Piolatto G, Rubino G. (1988) Skin notation in the context of workplace exposure standards. Am J Ind Med; 14: 725–32.

Schneider T, Vermeulen R, Brouwer D *et al*. (1999) Conceptual model for assessment of dermal exposure. Occup Environ Med; 56: 765–73.

Van-de-Sandt J, Dellarco M, Van Hemmen J. (2007) From dermal exposure to internal dose. J Expo Anal Environ Epidemiol; 17: S38–47.

Van-Wendel-De-Joode B, Brouwer D, Vermeulen R *et al*. (2003) DREAM: a method for semi-quantitative dermal exposure assessment. Ann Occup Hyg; 47: 71–87.

Vecchia B, Bunge AL. (2003) Skin absorption databases and predictives equations. In: Guy RH and Hadgraft J, editors. Transdermal drug delivery. New York, NY: Marcel Dekker; pp. 57–141.

Walker JD, Rodford R, Patlewicz G. (2003) Quantitative structure-activity relationships for predicting percutaneous absorption rates. Environ Toxicol Chem; 22: 1870–84.

Walker JD, Whittaker C, McDougal JN. (1996) Role of the TSCA interagency testing committee in meeting the U.S. government's data needs: designating chemicals for percutaneous absorption testing. In: Marzulli FN and Maibach HI, editors. Dermatotoxicology. Washington, DC: Hemisphere Publishing Corportation; pp. 371–81.

Williams FM. (2004) EDETOX. Evaluations and predictions of dermal absorption of toxic chemicals. Int Arch Occup Environ Health; 77: 150–1.

Wilschut A, ten Berge WF, Robinson PJ *et al*. (1995) Estimating skin permeation. The validation of five mathematical skin permeation models. Chemosphere; 30: 1275–96.