Regulatory Toxicology and Pharmacology 61 (2011) 63–72

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

# Efficacy of predictive modeling as a scientific criterion in dermal hazard identification for assignment of skin notations

Chen-Peng Chen [a,*], Heinz W. Ahlers [b], G. Scott Dotson [c], Yi-Chun Lin [a], Wei-Chen Chang [a], Andrew Maier [d], Bernard Gadagbui [d]

[a] China Medical University, Department of Occupational Safety and Health, No. 91 Hsueh-Shih Road, Taichung 40402, Taiwan
[b] Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, National Personal Protective Technology Laboratory, P.O. Box 18070, 626 Cochrans Mill Road, Pittsburgh, PA 15236, USA
[c] Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Education and Information Division, MS C-32, 4676 Columbia Parkway, Cincinnati, OH 45226, USA
[d] Toxicology Excellence for Risk Assessment, 2300 Montana Avenue, Suite 409, Cincinnati, OH 45211, USA

ARTICLE INFO

*Article history:*
Available online 25 June 2011

*Keywords:*
Occupational skin exposure
Skin notation
Hazard characterization
Predictive modeling
Dermal lethal dose 50%
Octanol–water partition coefficient
Globally Harmonized System of Classification and Labeling of Chemicals
Hazard ranking

ABSTRACT

Skin notations (SNs) represent a hazard characterization tool for alerting workers of health hazards associated with dermal contact with chemicals. This study evaluated the efficacy of a predictive model utilized by the National Institute for Occupational Safety and Health to identify dermal hazards based on potential of systemic absorption compared to hazard assignments based on dermal lethal dose 50% or logarithm of octanol–water partition coefficient. A total of 480 chemicals assigned an SN from at least one of seven institutes were selected and partitioned into seven hazard categories by frequency of SN assignment to provide a basis of evaluation for the predictivity of the examined criteria. We find that all three properties serve as a qualitative indicator in support of a dichotomous decision on dermal hazard; the predictive modeling was identified from a multiple regression analysis as the most significant indicator. The model generated estimates that corresponded to anticipated hazard potentials, suggesting a role of the model to further serve as a hazard-ranking tool. The hazard-ranking capability of the model was consistent with the scheme of acute toxicity classification in the Globally Harmonized System of Classification and Labeling of Chemicals.



## 1. Introduction

The occupational exposure of the skin to toxic chemicals has become an important issue in industrial health and regulatory toxicology. An estimated 13 million workers in the United States alone were potentially exposed to chemicals that could be absorbed through the skin (BLS, 1999). In current practice, the skin notation (SN) is typically assigned to industrial chemicals as part of the hazard characterization and dose–response assessment and documented in the rationale for the occupational exposure limit (OEL). These notations represent a key tool used for alerting workers to the presence of skin absorption hazards in the workplace (Chen and Sartorelli, 2005; Sartorelli et al., 2007). In the absence of quantitative dermal exposure limits for workplace settings, the SN serves as a qualitative indicator that a chemical substance is capable of causing systemic health effects via dermal uptake.

Most agencies and organizations of occupational health management worldwide have SN as a part of their OELs, but the number of SNs assigned differs among organizations and the level of documentation of the underlying assignment criteria varies. Despite the common use of the SN approach in occupational risk assessments, the SN has not been used effectively in identifying chemicals having significant hazard potential following dermal contact (Boeniger and Ahlers, 2003). The ineffective use of SN as a hazard characterization tool could be attributed to, primarily, the inconsistent application of rationales in the assignment process and, to a greater extent, the lack of clinical and laboratory data of a robust quality in support of hazard characterization (Chen et al., 2002, 2003, 2004). Since the late 1990s, the development and application of scientific criteria in the SN assignment process has been a focal area of efforts directed at improving the reliability of the SN approach (Chen et al., 2003; de Cock et al., 1996; ECETOC, 1998; Fasano and McDougal, 2008; Federal Register, 2004; Fiserova-Bergerova et al., 1990; Johanson et al., 2009; Kennedy et al., 1993; Kupczewska-Dobecka and Czerczak, 2006; Lavoué et al., 2008; Nielsen and Grandjean, 2004; Sartorelli, 2002; Walker et al., 1996). Nielsen and Grandjean (2004) compared the SNs

* Corresponding author. Fax: +886 4 22071326.
*E-mail address:* chencp@mail.cmu.edu.tw (C.-P. Chen).

0273-2300/$ - see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.yrtph.2011.05.013

assigned by Denmark, Germany, The Netherlands, Poland, Slovakia, and the American Conference of Governmental Industrial Hygienists (ACGIH) for agreement among notations and observed substantial differences existing between countries, both in the number of notations and in how the notations overlapped. The authors pointed out that the lack of agreement was likely a result of inconsistency in the criteria used for assigning SN. Sartorelli et al. (2007) in a position paper representing the ICOH Scientific Committee on Occupational and Environmental Dermatoses also indicated that a general agreement on criteria adequate for use in SN assignment did not exist.

The scientific data typically used in identifying potential systemic toxicity as a result of skin absorption may include the physicochemical and toxicological properties of a chemical. The ACGIH, in *Documentation of the TLVs and BEIs with Other Worldwide Occupational Exposure Values* (ACGIH, 2008), recommended that integration of data from acute dermal studies and repeated-dose dermal studies in animals and humans, along with the ability of the chemical to be absorbed, be used in deciding on the appropriateness of SN. A weight-of-evidence approach relying on similar data streams is also used in the SN methodology published by the National Institute for Occupational Safety and Health (NIOSH) (NIOSH, 2009). The examples of data that may be used in SN assignment, as provided in the TLV documentation, include (1) acute animal toxicity data (e.g., the dermal lethal dose 50%—dermal $LD_{50}$), (2) physicochemical properties of a chemical compound that may be indicative of a chemical's ability to penetrate the skin (e.g., the octanol–water partition coefficient—log $K_{OW}$), and (3) extrapolations of systemic effects from other routes of exposure, suggesting a significant role of dermal absorption in the expressed toxicity.

The dermal $LD_{50}$ and log $K_{OW}$ are frequently applied as criteria in the SN assignment due to their relative availability compared to other data describing the toxicological and physicochemical properties of chemicals. In recent years the $LD_{50}$ has also been applied as a tool for assigning chemicals to various hazard categories (based on ranges of $LD_{50}$ values) in the evaluation of acute toxicity arising from skin exposure. Such an approach is used in the *Globally Harmonized System (GHS) of Classification and Labeling of Chemicals* (UNECE, 2009) and in the improved strategy of SN assignment developed by NIOSH (NIOSH, 2009). The ACGIH describes that a chemical of a relatively low dermal $LD_{50}$ (i.e., 1000 mg/kg or less) would be given a TLV skin designation. In the GHS classification system, a chemical agent may be assigned to one of five hazard categories, depending on the magnitude of dermal $LD_{50}$, with the first three categories indicating a "danger" upon skin contact and the last two serving as a warning (Table 1). In the NIOSH strategy, a chemical could be assigned an SK: SYS notation or SK: SYS (FATAL) subnotation, depending on its dermal $LD_{50}$, with the former corresponding to GHS Categories 3 and 4 and the latter Categories 1 and 2. As a quantity describing the lipophilicity of a chemical, log $K_{OW}$ is frequently applied as a criterion to indicate a "potential significant contribution to the overall exposure by the cutaneous route" (ACGIH, 2008). The application of log $K_{OW}$ as a stand-alone criterion in the SN assignment is less universal than that of dermal $LD_{50}$. The potential significance of dermal absorption as suggested by the $K_{OW}$ may not be sufficient for establishing an SN, if the SN is defined to alert the systemic toxicity arising from skin exposure to toxic chemicals (Chen et al., 2003). In some regulatory context, a causal indication of skin absorption and consequent systemic toxicity is required to meet the SN definition (Federal Register, 1989).

For most chemicals, data of adequate reliability that report toxic effects of skin exposure other than dermal acute toxicity are relatively scarce. Thus, the evaluation of potential systemic effects from repeated doses by the dermal route often must be inferred from extrapolations of systemic effects from other routes of exposure. Predictive modeling taking into account the relative importance of dermal absorption compared to inhalation exposure at the OEL is commonly applied as a means of route-to-route extrapolation for determining the dermal exposure hazard of a chemical (Fiserova-Bergerova et al., 1990; McDougal and Boeniger, 2002; Schneider et al., 1999; Vecchia and Bunge, 2003; Walker et al., 1996). In fact, using a modeling approach as an alternative to in vivo and in vitro testing was recommended for regulatory acceptance by the Organisation for Economic Co-operation and Development (OECD) to supplement the existing process of dermal toxicity evaluation (OECD, 2004). The Toxic Substances Control Act (TSCA) Interagency Testing Committee (ITC) in their recommendation for the improvement of Occupational Safety and Health Administration SN suggested a mathematical algorithm for use in the SN assignment when data of clinical reports or laboratory studies on dermal toxicity were insufficient to support an assignment (Walker et al., 1996). Conceptually, the algorithm estimated the

**Table 1**
Assignment of acute toxicity hazard level in GHS and of skin notation indicating systemic toxicity by NIOSH based on dermal $LD_{50}$ of chemical[a,b].

| Health hazard | GHS assignment (mg/kg animal body weight) | NIOSH assignment (mg/kg animal body weight) |
|---|---|---|
| Acute toxicity (lethality) | Dermal Category 1:<br>• Symbol: skull and crossbones<br>• Signal word: danger<br>• Statement: fatal in contact with skin (*Criterion: dermal $LD_{50} \leqslant 50$*) | SK: SYS (FATAL) (*Criterion: dermal $LD_{50} < 200$*) |
| | Dermal Category 2:<br>• Symbol: skull and crossbones<br>• Signal word: danger<br>• Statement: fatal in contact with skin (*Criterion: $50 <$ dermal $LD_{50} \leqslant 200$*) | |
| | Dermal Category 3:<br>• Symbol: skull and crossbones<br>• Signal word: danger<br>• Statement: toxic in contact with skin (*Criterion: $200 <$ dermal $LD_{50} \leqslant 1000$*) | SK: SYS (*Criterion: $200 <$ dermal $LD_{50} < 2000$*) |
| | Dermal Category 4:<br>• Symbol: exclamation mark<br>• Signal word: warning<br>• Statement: harmful in contact with skin (*Criterion: $1000 <$ dermal $LD_{50} \leqslant 2000$*) | |
| | Dermal Category 5:<br>• Symbol: no symbol<br>• Signal word: warning<br>• Statement: may be harmful in contact with skin (*Criteria: $2000 <$ dermal $LD_{50} \leqslant 5000$*) | No equivalent assignment |

[a] GHS, Globally Harmonized System of Classification and Labeling of Chemicals; NIOSH, National Institute for Occupational Safety and Health; Dermal $LD_{50}$, dermal lethal dose 50%.

[b] Table modified from Table G.2, "Coordination of the GHS classification system and the new NIOSH skin notations", presented in *NIOSH Current Intelligence Bulletin 61: a strategy for improvement of skin notations* (NIOSH, 2009).

significance of transcutaneous penetration as a route of uptake for a chemical by comparing the dose of the chemical absorbed via the skin (skin dose—SD) to the dose absorbed via the lungs (inhalation dose—ID) during the same period of exposure. The ID represented a critical presence of the chemical in the body following inhalation exposure at the OEL, and the SD and ID provided quantifiable measures for the levels of absorption by different routes of uptake. This conceptual model was modified (Chen et al., 2002) and incorporated into the improved NIOSH strategy for SN assignment to overcome the limitations inherent in the availability of empirical data and was recommended for use with other criteria following a weight-of-evidence logic (NIOSH, 2009). Walker et al. (1996) and Fasano and McDougal (2008) suggested that the TSCA ITC-originated model could be applied in dermal risk assessment, estimating the period that the exposure of a fixed area of skin to a target chemical would need to build up a critical internal dose.

The study described here evaluated the utility of predictive modeling employing the route-to-route extrapolation technique in dermal hazard characterization compared to and in combination with applying SN assignment criteria based on the dermal $LD_{50}$ and log $K_{OW}$. The mathematical algorithm described in the strategy for assignment of NIOSH SN (the NIOSH model) was adopted as the predictive tool in this study. The performance of predictive modeling in differentiating the potential of skin exposure hazard of SN chemicals was compared to that of the dermal $LD_{50}$ and log $K_{OW}$. The dermal hazard potentials of SN compounds projected by the NIOSH model were compared to their acute toxicity-based GHS ranks to examine the consistency of the NIOSH model with the GHS classification scheme as well as the possible role of predictive modeling serving as a hazard-ranking tool.

## 2. Material and methods

### 2.1. Selection and classification of candidate chemicals

Chemicals selected as candidate compounds were those for which published OELs were available from major OEL-setting organizations. To be included in this study, a chemical had to have an assigned SN from at least one of following published OELs: NIOSH Recommended Exposure Limit (REL), ACGIH TLV, United Kingdom Work-place Exposure Limit (WEL), Germany Maximum Arbeitsplatz-Konzentration (MAK), Netherlands Maximale Aanvaarde Concentratie (MAC), Finland Maximal Allowed Concentration (MAC), or Sweden Occupational Exposure Limit (OEL). These OELs represent worldwide efforts in developing policies and strategies for controlling occupational skin exposures. A chemical selected for study might carry one to seven SNs, depending on how consistent these organizations were in considering the chemical as a skin exposure hazard. By the definition of SN commonly shared among the studied organizations, the dermal hazard potential described here refers to the potential of a chemical to provoke systemic toxicity as a result of skin absorption or being substantially absorbed following skin contact (ACGIH, 2008). Based on the number of SNs assigned, chemicals were categorized into seven SN number groups. The SN and its source information were extracted from ACGIH TLV Documentation.

### 2.2. Dermal $LD_{50}$, log $K_{OW}$, and physicochemical properties required in modeling

Dermal $LD_{50}$ values for candidate compounds were collected from the NIOSH Registry of Toxic Effects of Chemical Substances (RTECS) Database (NIOSH, 2007). The array of potential $LD_{50}$ values for a given chemical was refined to increase comparability by ensuring that current protocols were used for testing acute toxicity and to reduce the uncertainty in dermal $LD_{50}$ values that might be attributed to discrepancy in exposure duration or flawed experimental design. For example, $LD_{50}$ values were limited to those experimentally generated using traditional toxicity test rodent species (i.e., rat, mouse, guinea pig, and rabbit) to reduce the interspecies uncertainty in the reported toxicity. When multiple entries of dermal $LD_{50}$ values were found for a chemical, the lowest value (i.e., the greatest toxicity) was used in the analysis. Dermal $LD_{50}$ values were excluded if they were generated using protocols that deviated substantially from the OECD guidelines for testing of acute dermal toxicity (OECD, 1987). In addition, only dermal $LD_{50}$ values reported as a fixed number were included; those expressed as "greater than" or "smaller than" a threshold were excluded to decrease the impact from potential deficiency in the dose–response relationships by which these $LD_{50}$ values were derived.

The log $K_{OW}$ values of candidate compounds were collected from the Syracuse Research Corporation PhysProp Database (SRC, 2008). Only experimental values of log $K_{OW}$ were collected, as the focus in the study was to compare the utility of the predictive algorithm with those of empirical data generated from laboratory testing. To operate the NIOSH model, the following physicochemical properties of each chemical were required: log $K_{OW}$, molecular weight (MW), water solubility ($S_W$), and OEL time-weighted average (OEL-TWA). The former three values were collected from the PhysProp Database and the latter from the TLV Documentation.

### 2.3. Modeling of dermal exposure hazard

The NIOSH model evaluates the potential of skin exposure hazard by comparing the internal dose of a chemical absorbed via the skin (SD) to that of inhalation uptake (ID) during the same period of exposure at an air concentration equivalent to the OEL. The final output of modeling presents a ratio of SD to ID (SI ratio) to indicate the significance of skin exposure compared to inhalation exposure, with the ID in the formulation representing the critical presence of the target chemical in the body without raising concern of adverse health impact (i.e., consistent with the assumption that an exposure at the OEL is not expected to generate adverse effects). The NIOSH model may be conceptually expressed as:

$$\text{SI ratio} = \text{SD}/\text{ID} \tag{1}$$

where:

$$\begin{aligned}\text{SD (mg)} = {} & \text{transdermal permeation coefficient (Kp) of a chemical} \\ & \text{(cm/hr)} \times S_W\,\text{(mg/cm}^3\text{)} \times \text{exposed skin surface area (cm}^2\text{)} \\ & \times \text{exposure time (hr)}\end{aligned} \tag{2}$$

$$\begin{aligned}\text{ID (mg)} = {} & \text{OEL (mg/m}^3\text{)} \times \text{inhalation volume (m}^3\text{)} \\ & \times \text{retention factor (RF)}\end{aligned} \tag{3}$$

In Eq. (2), Kp represents the overall diffusion of the agent through the stratum corneum into blood capillaries of the dermis and is determined using a validated quantitative structure–permeability relationship (QSPR) that predicts the transport behaviors of a chemical in the stratum corneum based on their MW and log $K_{OW}$. The MW is used to represent the molecular size of a chemical and the log $K_{OW}$ to describe the lipophilicity. This QSPR, also known as the revised Robinson model (Wilschut et al., 1995), is mathematically expressed as:

$$\text{Kp} = \frac{1}{\frac{1}{\text{Kpsc}+\text{Kpol}} + \frac{1}{\text{Kaq}}} \tag{4}$$

where Kpsc is the permeation coefficient in the lipid fraction of the stratum corneum, Kpol the coefficient in the protein fraction, and

Kaq the coefficient in the watery epidermal layer. These components are individually estimated by:

$$\log \mathrm{Kpsc} = -1.326 + 0.6097 \times \log K_{\mathrm{OW}} - 0.1786 \times \mathrm{MW}^{0.5} \quad (5)$$

$$\mathrm{Kpol} = 0.0001519 \times \mathrm{MW}^{-0.5} \quad (6)$$

$$\mathrm{Kaq} = 2.5 \times \mathrm{MW}^{-0.5} \quad (7)$$

In Eq. (3), the ID is derived based on the OEL of the substance, if and when the OEL is developed to prevent the occurrence of systemic effects rather than of sensory/irritant effects on the respiratory tract. In this study, a continuous exposure of 8 h and an exposed skin surface of 360 $cm^2$ (palmer skin) were assumed. For the calculation of ID, an inhalation volume of 10 cubic meters in 8 h and an RF of 0.75 for the absorption of an airborne chemical via the lungs were used. The RF represented the percentage of xenobiotics present in the alveoli that might be successfully exchanged into systemic circulation. Typically, a retention rate of 75–100% was assumed for the pulmonary absorption of a gaseous chemical (ECB, 2003), and a default value of 0.75 was selected to avoid underestimating the significance of skin absorption, because a complete pulmonary absorption was unlikely to occur for most chemicals. The OEL used in Eq. (3) was the 8-h TWA of ACGIH's TLV. When TLV-TWA was not available, the TWA of an alternative OEL would be used instead, in the order of NIOSH's REL, UK's WEL, German MAK, Dutch MAC, Finnish MAC, and Swedish OEL. The SN chemicals regulated as chemical groupings, fumes, and particulates were excluded from modeling. In the NIOSH improved strategy of SN assignment, a chemical of an SI ratio equal to or greater than 0.1 would be considered a potential skin exposure hazard and assigned an SK: SYS notation.

### 2.4. Availability and applicability of scientific data

The availability of dermal $LD_{50}$, $\log K_{\mathrm{OW}}$, and inputs to calculate the SI ratio for chemicals in each of the seven SN groups was evaluated. The availability was compared between these data as well as among the SN groups to explore any change in the availability in association with the change in dermal hazard potential as suggested by the number of SNs. To explore the relationship between the change in hazard indicator and the estimated dermal hazard potential, the dermal $LD_{50}$, $\log K_{\mathrm{OW}}$, and SI ratio of candidate compounds carrying four or more SNs were distributed by number of SNs and evaluated using box-plots. The Spearman rank-transformed correlation test was performed to evaluate the relationship between the distributed hazard indicator and the hazard potential suggested by the number of SNs. Of the 480 chemicals included in the overall evaluation, 145 chemicals had four or more SNs. The difference in distribution of each type of data by the number of SNs was analyzed for statistical significance using the Kruskal–Wallis analysis (Rosner, 2006). To realize the interrelationships between the investigated criteria, the values of dermal $LD_{50}$, $K_{\mathrm{OW}}$, and SI ratio of all SN compounds were logarithmically transformed and distributed against each other, and for each distribution the Spearman rank-correlation coefficient was determined.

### 2.5. Relative significance of scientific criteria to skin notation

Multiple linear regression of the number of SNs against the studied scientific criteria was performed to quantitatively evaluate the overall and relative significance of these criteria contributing to the formulation of an SN. In this analysis, a polynomial multiple linear regression model was first developed with the number of SNs being the dependent variable and the logarithmic values of dermal $LD_{50}$, $K_{\mathrm{OW}}$, and SI ratio being the independent variables. The coefficient of multiple correlation, coefficient of multiple determination, and adjusted coefficient of multiple determination were determined to evaluate the power of the regression analysis (Rosner, 2006). In the regression, the quantity of the partial-regression coefficient for each independent variable as generated from model-fitting was influenced by the numerical scale adopted in the unit of the independent variable. To remove the bias in the regression due to this scale difference, the variables in the regression model were standardized against their means and standard deviations so that the partial-regression coefficients for all independent variables became comparable. In the final approach, a stepwise regression was performed on the standardized equation to remove the criteria that did not correlate well with the current SN so as to identify the criteria of critical importance to the assignment of SN. The regression analysis was conducted using the statistical software SPSS (SPSS Inc., Chicago, IL, USA).

### 2.6. Consistency of modeling results with GHS classification scheme

To evaluate the possibility of the NIOSH model serving as a semiquantitative hazard-ranking tool, the modeling results were evaluated for consistency with the results of the GHS scheme supporting the dermal $LD_{50}$-based classification of acute toxicity. In the analysis, the SN compounds were classified by their dermal $LD_{50}$ values into the five distinct GHS hazard categories as described in Table 1. The SI ratios corresponding to the compounds in different hazard groups were then distributed by the hazard category. The overall distribution of the SI ratio was evaluated for its correlation to the GHS rank by the Spearman rank-correlation, and the distributions between hazard categories were examined for statistically significant difference using the Kruskal–Wallis analysis. The quartile distribution of the SI ratio in each category was also determined. The analysis was repeated for the $\log K_{\mathrm{OW}}$ for comparison.

## 3. Results

### 3.1. Availability of scientific data for assignment of skin notation

As Table 2 shows, a total of 480 chemicals were found to carry at least one SN and were included in the study. Approximately 3% ($n = 16$) of the included chemicals were considered by all of the evaluated organizations as a skin exposure hazard, whereas 47% ($n = 225$) were assigned with only one SN. In general, the number of chemicals in an SN group decreased as the number of SNs increased, indicating that the studied organizations varied significantly in the assignment of SNs. The availability of $\log K_{\mathrm{OW}}$ was over 90% in different SN groups except for the group of only one

**Table 2**
The distribution of chemicals by the number of skin notations assigned (SNs) and the availability of dermal $LD_{50}$, $\log K_{\mathrm{OW}}$, and SI ratio for chemicals in each SN group[a].

| Number of SNs | Number of chemicals | Availability (%) | | |
|---|---|---|---|---|
| | | Dermal $LD_{50}$ | $\log K_{\mathrm{OW}}$ | SI ratio |
| 7 | 16 | 81 | 94 | 75 |
| 6 | 30 | 53 | 100 | 73 |
| 5 | 48 | 75 | 100 | 83 |
| 4 | 51 | 67 | 98 | 73 |
| 3 | 40 | 58 | 93 | 75 |
| 2 | 70 | 46 | 91 | 63 |
| 1 | 225 | 26 | 80 | 46 |
| Total | 480 | | | |
| Mean ± std. dev. | | 58 ± 19 | 94 ± 7 | 70 ± 12 |

[a] Dermal $LD_{50}$, dermal lethal dose 50% in unit of mg/kg; $\log K_{\mathrm{OW}}$, logarithmic value of octanol–water partition coefficient; SI ratio, ratio of skin dose to inhalation dose estimated by the predictive model as described in Eqs. (1)–(3) and used by the National Institute for Occupational Safety and Health (NIOSH) to facilitate assignment of NIOSH skin notation.

SN. Despite being a frequently tested endpoint for dermal toxicity, a dermal $LD_{50}$ estimate was available for less than 60% of the examined compounds. The availability of dermal $LD_{50}$ values decreased as the number of SNs decreased; for compounds of one SN, the dermal $LD_{50}$ was only available for about one-fourth (26%) of the chemicals. The modeling-based estimation of the SI ratio was performed for approximately 70% of the examined compounds; as for the other 30%, their OELs were developed to prevent respiratory or skin irritation/sensitization rather than to prevent system toxicity. While the overall amount of dermal $LD_{50}$ values and SI ratios was less than that of log $K_{OW}$s, the increase in the availability of dermal $LD_{50}$ and SI ratios with increasing number of SNs suggested that the studied organizations shared a more consistent view on the potential dermal exposure hazard for a given chemical when the dermal $LD_{50}$ and/or predictive modeling result were available. This observation suggests that the three types of scientific data recommended by the ACGIH for application in the deliberation of SN were also the predominant criteria adopted by the other organizations compared in this study in SN assignment. A change in availability tracking the change in the number of SNs was not clearly observed for the log $K_{OW}$, possibly because of the overall abundance of log $K_{OW}$ values (over 90%).

### 3.2. Distribution of dermal $LD_{50}$, log $K_{OW}$, and SI ratio by number of notation

Fig. 1 shows the distribution of dermal $LD_{50}$, log $K_{OW}$, and SI ratio of chemicals assigned four or more SNs. The distributions as shown compared each SN group against the number of SNs ($n$ = 4 to 7 SNs). The results of the correlation test indicated a correlation coefficient of 0.13 ($p$ = 0.21), −0.20 ($p$ = 0.02), and 0.23 ($p$ = 0.02), respectively, for the distribution of dermal $LD_{50}$, log $K_{OW}$, and SI ratio against the number of SNs. The dermal $LD_{50}$ and SI ratio tended to increase with increasing SN number, and the increasing trend for the SI ratio was statistically significant. A statistically significant decrease with increasing number of SNs was observed for the log $K_{OW}$. To minimize the impact of uneven sample size to the analysis, chemicals of six and seven SNs were combined into a single group so that the sample size in the new group ($n$ = 46) was comparable to those in the groups of four and five SNs. The quartile distribution of dermal $LD_{50}$, log $K_{OW}$, and SI ratio was determined and summarized in Table 3. For all three dermal hazard indicators, the difference in the distribution of indicator among SN number groups was statistically significant. The change in the median of each indicator by the number of SNs reflected the overall trend as observed in the correlation analysis. The increase in the SI ratio with increasing number of SNs corresponded to the anticipated trend, i.e., the greater the skin exposure hazard, the higher the SI ratio. In contrast, the increase of dermal $LD_{50}$ and decrease of log $K_{OW}$ along with an increase in the number of SNs did not correspond to the anticipated trends. If the dermal $LD_{50}$ reported for the examined compounds were applied as a major criterion in the assignment of the evaluated SNs and reflective of the anticipated hazard level, its numerical value would decrease as the number of SNs increased. Similarly, a rise in the log $K_{OW}$ would be expected when the dermal hazard potential increased, as the likelihood of a chemical being substantially absorbed into the stratum corneum was greater at higher log $K_{OW}$. It should be noted that the median of dermal $LD_{50}$ for the combined 6/7 SN number group was identical to the hazard-recognizing threshold of 1000 mg/kg suggested by the ACGIH.

### 3.3. Correlation between scientific criteria

The inter-criteria correlation analysis was performed between the SI ratio and dermal $LD_{50}$, the $K_{OW}$ and dermal $LD_{50}$, and the

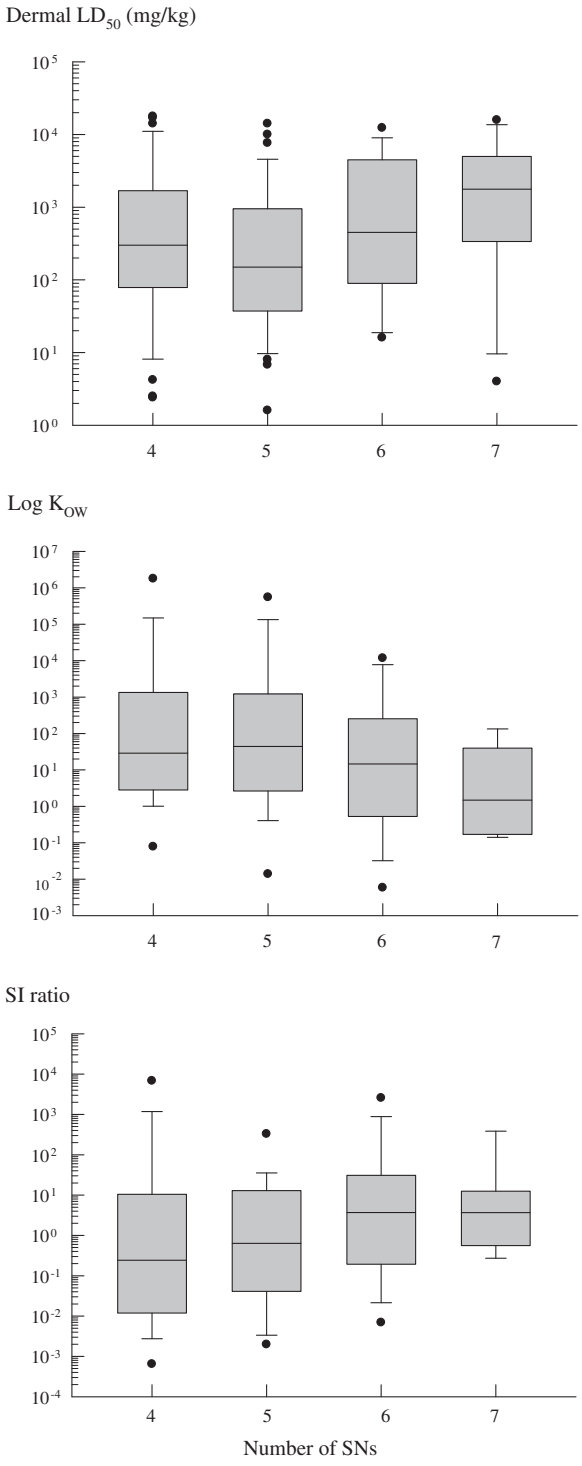



**Fig. 1.** Distribution of dermal lethal dose 50% (dermal $LD_{50}$), logarithmic value of octanol–water partition coefficient (log $K_{OW}$), and ratio of skin dose to inhalation dose (SI ratio) against number of skin notation (SN) assigned to chemicals of four or more SNs.

$K_{OW}$ and SI ratio for a total of 153, 207, and 287 compounds, respectively. Fig. 2 shows the distribution of log SI ratio and log $K_{OW}$ against log dermal $LD_{50}$ of the chemical and the distribution of log $K_{OW}$ against log SI ratio. The results of the correlation test indicated a potential linear relationship in the distribution of log $K_{OW}$ by log SI ratio (Spearman's $r$ = −0.66; $p$ < 0.01), therefore a linear regression was performed for this distribution and yielded a model:

**Table 3**
The quartile distribution of dermal $LD_{50}$, log $K_{OW}$, and SI ratio for chemicals of four or more skin notations (SNs)[a,b].

| SN number | Dermal $LD_{50}$ | | | log $K_{OW}$ | | | SI ratio | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1st quartile | 2nd quartile | 3rd quartile | 1st quartile | 2nd quartile | 3rd quartile | 1st quartile | 2nd quartile | 3rd quartile |
| 6/7 SNs | 170 | 1000 | 4720 | −0.30 | 0.83 | 1.85 | 0.36 | 3.70 | 17.49 |
| 5 SNs | 44 | 150 | 850 | 0.45 | 1.65 | 2.85 | 0.04 | 0.64 | 11.73 |
| 4 SNs | 90 | 300 | 1600 | 0.48 | 1.46 | 3.06 | 0.01 | 0.24 | 9.75 |
| *p* value[c] | 0.05 | | | 0.02 | | | 0.04 | | |

[a] Dermal $LD_{50}$, dermal lethal dose 50% in unit of mg/kg; log $K_{OW}$, logarithmic value of octanol–water partition coefficient; SI ratio, ratio of skin dose to inhalation dose estimated by the predictive model as described in Eqs. (1)–(3) and used by the National Institute for Occupational Safety and Health (NIOSH) to facilitate assignment of NIOSH skin notation.
[b] Dermal $LD_{50}$ value rounded up to the nearest integer; values for log $K_{OW}$ and SI ratio rounded to two places after decimal.
[c] *p* value indicating the level of statistically significant difference in the distribution of investigated property (dermal $LD_{50}$, log $K_{OW}$, or SI ratio) among different SN number groups as determined by the Kruskal–Wallis analysis.

$$\log K_{OW} = -0.91\ (\log \text{SI ratio}) + 1.83, \quad r^2 = 0.55 \tag{8}$$

The log SI ratio and log $K_{OW}$ correlated negatively with log dermal $LD_{50}$; both correlations were consistent with the trends anticipated given the characteristics of these indicators as discussed in Section 3.2. This finding suggested that, while the dermal $LD_{50}$ and log $K_{OW}$ might not serve well as quantitative indicators of SN, they were sufficient to facilitate qualitative recommendations that would be useful in preliminary screening of dermal hazard, e.g., for prioritization of a chemical in dermal toxicity testing.

### 3.4. Relative significance of criteria to skin notation

Table 4 shows the models of multiple regression, standardized multiple regression, and stepwise regression as generated from the multiple linear regression of number of SNs against the included scientific criteria. The low level of adjusted $r^2$ for the established models suggested a potential presence of scientific indicators other than dermal $LD_{50}$, $K_{OW}$, and SI ratio that might be significantly associated with the formulation of current SN. The three criteria in the models were not found to be collinear in the regression model. When the partial-regression coefficients of the criteria were compared, the SI ratio was found to be the most influential criterion in the formulation of current SN, with the coefficient for its logarithmic quantity being 2.4 and 32.6 folds greater than the coefficient for the log $K_{OW}$ and log dermal $LD_{50}$, respectively. When the standardized model was evaluated using stepwise regression in which all predictive variables were tested for statistical significance, the dermal $LD_{50}$ and log $K_{OW}$ were removed and the SI ratio was the only criterion in sufficient association with the number of SNs; the linearity of the stepwise model (also a simple linear regression model) was statistically significant.

### 3.5. Consistency of modeling results with GHS hazard classification scheme

Fig. 3 shows the distribution of the log SI ratio of SN chemicals with a dermal $LD_{50} \leqslant 5000$ mg/kg ($n = 124$) in the five GHS categories of acute toxicity hazard, as sorted by the dermal $LD_{50}$ of the compound. The distribution was statistically different among GHS hazard categories (the Kruskal–Wallis analysis, $p = 0.04$), and the log SI ratio was negatively correlated to the GHS rank at a significant level, suggesting a general trend of SI ratio decreasing when the dermal hazard lessened as characterized by the increase in the GHS rank. Consistent with the trend observed for SI ratio when distributed by the number of SNs, the median SI ratio for more potent chemicals was higher for GHS Category 1 chemicals than those for the less potent GHS categories. However, a wider quartile distribution of SI ratios were observed in GHS Categories 1 to 3 (dermal $LD_{50} \leqslant 1000$ mg/kg) than in Categories 4 or 5, indicating that the SI ratio and dermal $LD_{50}$ were less in agreement when used as criteria in dermal hazard identification for chemicals of higher hazard potential. When the log $K_{OW}$ was paired with the GHS rank based on dermal $LD_{50}$ ($n = 173$) and distributed by the GHS hazard category (Fig. 4), the distribution was not statistically different between categories ($p = 0.58$). Although the log $K_{OW}$ was negatively correlated to the GHS rank, conforming to the anticipated reduction of log $K_{OW}$ with decrease in dermal hazard, the trend was not statistically significant. This result suggests a lesser consistency of the log $K_{OW}$ with the GHS system compared to that of the SI ratio.

## 4. Discussion

The consistency in the underlying rationales and criteria applied in SN assignment has long been a focal point of discussions in the occupational health management community. This led us to examine the relationship between alternative criteria that are often used as the basis for assigning SN.

As this study shows, the number of SN assigned to chemicals varied significantly among different countries. This variation could be partly explained by a difference in the priority of OEL/SN development between countries or by the availability of empirical data when the hazard characterization was conducted. However, an important issue also may be the lack of harmonization in the types of criteria used in the assignment process.

In the current study, the grading of dermal hazard by the number of organizations that have assigned an SN provided an opportunity to observe the utility of different indictors in dermal hazard evaluation. Our findings suggest that the dermal $LD_{50}$ alone may not serve well as a quantitative indicator of the number of agencies that have established an SN in this study. Several factors might have contributed to this observation.

First, the dermal $LD_{50}$ values reported for a chemical substance could be generated from multiple studies that employed different animal species. As a result, these values might vary substantially, and the cause of animal death as observed might not distinguish if the fatalities were a result of systemic toxicity from dermal absorption or from corrosive effects at the site of administration (Chen et al., 2004). Fig. 5 shows the variation of dermal $LD_{50}$ values reported for 14 chemicals in the RTECS Database employing rabbit, rat, or mouse (NIOSH, 2007). For these compounds, the difference in the dermal $LD_{50}$ values of a chemical varied from 1.3 (xylidine) to 12636.4 folds (paraquat), with a median of 5.44 folds.

Secondly, in addition to interspecies difference, the variation in the dermal $LD_{50}$ values reported for a chemical might be a result of inconsistency in the experimental protocols used to generate the dose–response relationships required in establishing the dermal $LD_{50}$ values. For example, in compliance with the standardized protocols developed in the OECD *Guideline for Testing of Chemicals 402* (OECD, 1987) and the USEPA *Health Effects Test Guidelines OPPTS 870.1200* (USEPA, 1998), when conducting a test of dermal acute

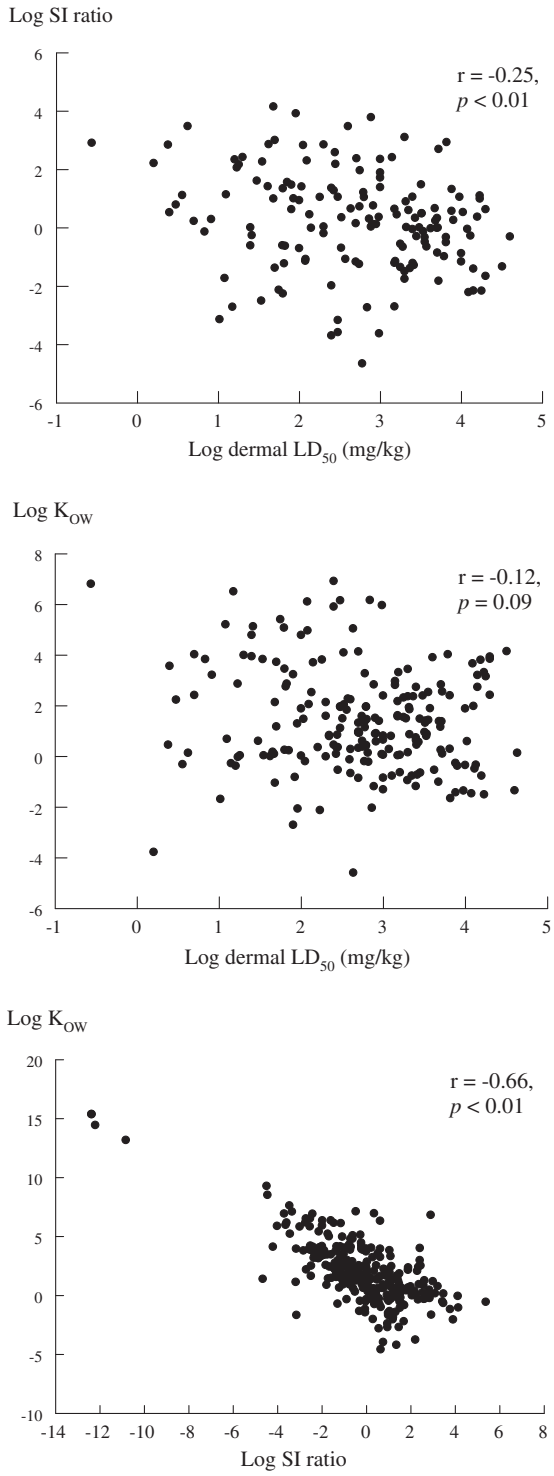



**Fig. 2.** Distribution of logarithmic value of ratio of skin dose to inhalation dose (log SI ratio) against logarithmic value of dermal lethal dose 50% (log dermal $LD_{50}$), of logarithmic value of octanol–water partition coefficient (log $K_{OW}$) against log dermal $LD_{50}$, and of log $K_{OW}$ against log SI ratio for chemical of skin notation. The $r$ values are Spearman rank-correlation coefficients. The $p$ values indicate statistical significance of Spearman rank correlation.

toxicity using rodents, the exposure duration should be 24 h unless signs of skin irritation/ulceration appeared and called for a premature termination. However, the dermal $LD_{50}$ data generated prior to the development of standardized protocols often employed a different exposure scenario. In addition, the absorption of a chemical via the skin and thus the systemic toxicity incurred following absorption may be influenced by the conditions of chemical loading on the skin. Kissel (2011) discussed dermal absorption-related phenomena using the ratio of mass delivery to plausible absorptive flux ($N_{DERM}$) as an index and suggested that dermal toxicity testing at high $N_{DERM}$ was unlikely to show dose dependence due to the saturation of the absorptive flux when the skin was high loaded.

Third, the dermal $LD_{50}$ represented the acute toxicity of a chemical that arose following dermal absorption, but might not indicate toxicological consequence of a chemical when cumulative exposure at a lower exposure level occurred, and thus would not be an appropriate indicator when an SN was assigned to caution the chronic toxicity from long-term skin exposure. In fact, it was unclear the levels to which the dermal $LD_{50}$ was applied in the assignment of SN by the organizations included in this study, which might partly explain the poor correlation between the dermal $LD_{50}$ level and the dermal hazard potential as suggested by the number of SNs. Some of the issues leading to limited correlation between dermal $LD_{50}$ value and number of SN assignments can be addressed through careful application of study quality criteria (e.g., Klimisch scoring). Nevertheless, the limitations in this metric (due to historic experimental variability and lack of accounting for longer-term, low-dose effects) suggest that the $LD_{50}$ value should be supplemented by other criteria using a weight-of-evidence approach to increase confidence in SN assignments.

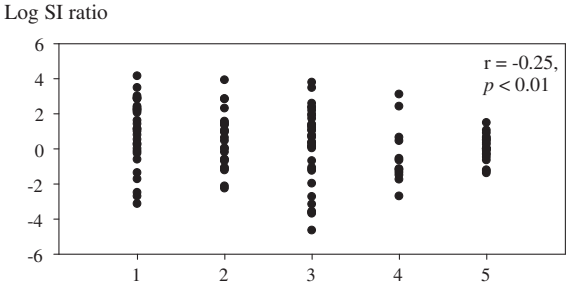
Lavoué et al. (2008) compared the SNs on the lists of Swiss maximum allowable concentrations (MACs) and ACGIH TLVs to the dermal $LD_{50}$ values and modeling-based dermal risk indices of these SNs. One of the risk indices investigated was based on route-to-route extrapolation of toxicity, an approach similar to that employed in the NIOSH model using the SI ratio. Compounds with a MAC or TLV notation were associated with higher dermal risk index and lower dermal $LD_{50}$ than those without a notation, and the dermal risk index agreed with dermal $LD_{50}$ for selected chemicals on the MAC ($r = -0.42$) and TLV lists ($r = -0.43$). In Lavoué et al. (2008), both the dermal $LD_{50}$ and model-based index were evaluated primarily for their capability providing a qualitative answer to the need of SN, and the findings indicated that both were effective in facilitating a dichotomous decision. In our study, the negative correlation between the NIOSH model output and dermal $LD_{50}$ also indicated that both criteria would agree when used as a qualitative tool in dermal hazard identification. However, as our findings show, the utility of dermal $LD_{50}$ as a ranking tool for classification of dermal hazard appears to be less than that of the SI ratio. Lavoué et al. (2008) also cautioned that, as a majority of the compounds employed in their study were those of TLV, the SNs compared could have been assigned following the explicit criterion of 1000 mg/kg for dermal $LD_{50}$. As a result, a significant association between the dermal $LD_{50}$ and SN could be expected.

In dermal hazard characterization, the log $K_{OW}$ was frequently used to indicate the ease of skin penetration of a chemical. As the most commonly used parameter of chemical solubility in water versus fat, this property was expected to appropriately correlate with the skin absorption of a chemical (Kezic and Nielsen, 2009). In our study, the availability of log $K_{OW}$ was the highest among the examined criteria. However, the log $K_{OW}$ did not correspond well to the anticipated level of skin exposure hazard based on the number of organizations that had assigned an SN notation. The adequacy of low $K_{OW}$ as a criterion in the hazard characterization also suffers when the systemic toxicity as a result of skin absorption rather than the skin absorption is the primary concern used in assigning an SN. The strong linear relationship between experimental log $K_{OW}$ and log SI ratio observed in this study suggested that the predictive model, while initially constructed to evaluate the potential of systemic effects as caused by skin absorption, was also indicative of the skin-penetrating capacity of a chemical.

**Table 4**
Models of multiple regression, standardized multiple regression, and stepwise regression of the number of skin notations assigned (SN number) against the logarithmic value of octanol–water partition coefficient (log $K_{OW}$), of dermal lethal dose 50% (log dermal $LD_{50}$), and of the ratio of skin dose to inhalation dose (log SI ratio) and the results of statistical analyses for these models[a].

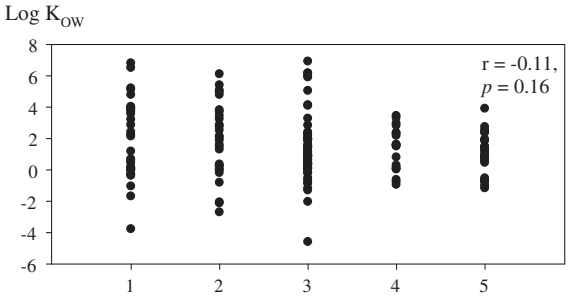
| | $r$ | $r^2$ | Adj. $r^2$ | $p$ |
|---|---|---|---|---|
| *Multiple regression equation* | | | | |
| SN number = 0.222 log $K_{OW}$ + 0.031 log dermal $LD_{50}$ + 0.785 log SI ratio + 4.165 | 0.48 | 0.23 | 0.14 | 0.08 |
| *Standardized multiple regression equation* | | | | |
| SN number = 0.433 log $K_{OW}$ + 0.032 log dermal $LD_{50}$ + 1.042 log SI ratio + 4.586 | 0.48 | 0.23 | 0.14 | 0.08 |
| *Stepwise regression* | | | | |
| SN number = 0.598 log SI ratio + 4.579 | 0.44 | 0.19 | 0.16 | 0.02 |

[a] Statistical power of regressional analysis determined for each model and presented as multiple correlation coefficient ($r$), coefficient of multiple determination ($r^2$), adjusted coefficient of multiple determination (Adj. $r^2$), and significance of linearity present in the regression model ($p$).




| GHS rank | Sample number | SI ratio percentile | | |
|---|---|---|---|---|
| | | 25% | 50% | 75% |
| 1 | 30 | 0.80 | 13.28 | 207.43 |
| 2 | 24 | 0.23 | 3.52 | 26.43 |
| 3 | 36 | 0.08 | 3.39 | 30.98 |
| 4 | 12 | 0.04 | 0.14 | 3.19 |
| 5 | 22 | 0.47 | 0.99 | 3.08 |

**Fig. 3.** Logarithmic value of ratio of skin dose to inhalation dose (log SI ratio) corresponding to different categories of acute toxicity in Globally Harmonized System (GHS) of Classification and Labeling of Chemicals for chemical of skin notation and their quartile distribution. The $r$ value is Spearman rank-correlation coefficient. The $p$ value indicates statistical significance of Spearman rank correlation.




| GHS rank | Sample number | Log $K_{OW}$ percentile | | |
|---|---|---|---|---|
| | | 25% | 50% | 75% |
| 1 | 34 | 0.03 | 1.65 | 3.83 |
| 2 | 28 | 0.18 | 1.97 | 3.51 |
| 3 | 64 | 0.32 | 0.91 | 1.95 |
| 4 | 19 | 0.10 | 1.54 | 2.34 |
| 5 | 28 | 0.53 | 1.06 | 1.86 |

**Fig. 4.** Logarithmic value of octanol–water partition coefficient (log $K_{OW}$) corresponding to different categories of acute toxicity in Globally Harmonized System (GHS) of Classification and Labeling of Chemicals for chemical of skin notation and their quartile distribution. Statistical measures are the same as for Fig. 3.

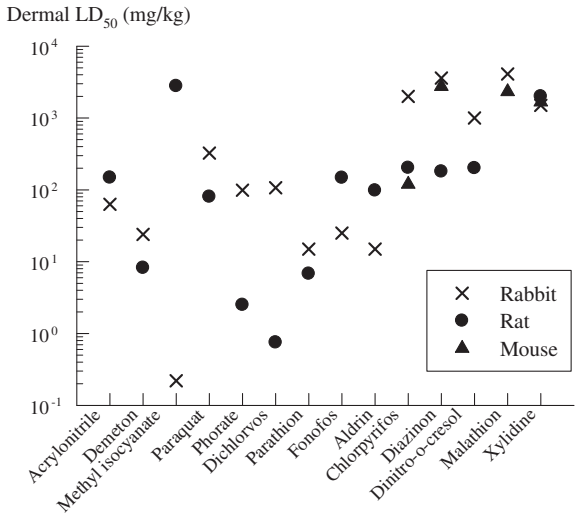



**Fig. 5.** Distribution of dermal lethal dose 50% (dermal $LD_{50}$) values for selected toxic industrial chemicals as reported from in vivo studies using rodents as experimental species.

The SI ratio approach depends on the potential for dermal absorption and the likelihood for generating systemic doses that might lead to longer-term adverse health effects. Thus, it possesses the capability of identifying a chemical as a skin exposure hazard and has the potential of serving as a GHS-consistent hazard-ranking tool. These characteristics explain the results that show SI ratio as a better predictor of SN assignment than either $K_{OW}$ or dermal $LD_{50}$ values. In the last decades, the research that applied mathematical modeling in health hazard evaluation had gained momentum, largely due to the needs of scientific data in the development of regulatory policy, particularly as the use of in vivo animal tests in support of regulatory decisions were discouraged. For instance, the GHS discouraged animal-based acute toxicity testing for chemicals classified as a Category 5 hazard (i.e., chemical of relatively low acute toxicity potential with circumstantial presence to vulnerable populations), unless there was a strong likelihood that the results of in vivo testing would have a direct relevance for protecting human health (UNECE, 2009). The use of alternative assessment approaches, including the approach of predictive modeling as investigated in the current study, is also encouraged by the new European Community regulations *Registration, Evaluation, Authorization and Restriction of Chemical Substances* (The European Parliament and the Council of the European Union, 2006).

In the NIOSH model, a chemical substance with an SI ratio equal to or greater than a threshold of 0.1 would be recognized as a skin absorption hazard (i.e., dermal uptake of a chemical exceeded 10% of its uptake by inhalation at the systemic dose associated with current OEL for protecting against systemic effects). This criterion is consistent with the approach proposed by the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) for recommendation of SNs (ECETOC, 1998). The ECETOC algorithm also determined the skin exposure hazard posed by a chemical agent through comparing its dermal uptake to its systemic absorption from inhalation, and an SN would be recommended when the

amount of chemical absorbed by both hands and forearms in 1 h exceeded 10% of the amount absorbed by inhalation for 8 h at a concentration at the OEL (de Cock et al., 1996). The defaults of the exposed skin surface area, the air volume inhaled in 8 h, and the respiratory RF in the ECETOC algorithm were 2000 $cm^2$, 10 $m^3$, and 50%, respectively. The SI ratio calculated in the NIOSH model (SI $Ratio_{NIOSH}$) can be modified to derive an SI ratio following the assumptions proposed in the ECETOC algorithm (SI $Ratio_{ECETOC}$), and a comparison between the SI $Ratio_{NIOSH}$ and SI $Ratio_{ECETOC}$ reveals:

$$\begin{aligned}\text{SI Ratio}_{ECETOC} &= \text{SI Ratio}_{NIOSH} \times [2000\ \text{cm}^2\ (\text{hands/arms}) \\ &\quad \div 360\ \text{cm}^2(\text{palms})] \times [1\ \text{h} \div 8\ \text{h}] \\ &\quad \times [75\%\ (\text{default RF in NIOSH algorithm}) \\ &\quad \div 50\%\ (\text{default RF in ECETOC algorithm})] \\ &= \text{SI Ratio}_{NIOSH} \times 1.04 \end{aligned} \quad (9)$$

As this comparison shows, the SI ratio determined using the NIOSH model is approximately the same as the SI ratio generated following the assumptions made in the ECETOC algorithm. That is, in both models the thresholds for dermal hazard recognition are based on essentially the same level of skin absorption. A similar concept was suggested by the ACGIH for SN assignment. Without detailing a quantitative threshold dosage, the ACGIH recommended that an SN was justified when data were available to suggest a significant potential for absorption via the hands and forearms during the workday, especially for chemicals with lower TLV values.

The NIOSH model in its current form is limited, in that it cannot be used to evaluate chemical substances with an OEL set to prevent occurrence of localized health effects. Caution should also be exercised in applying the current model to evaluate sensory irritants that might also permeate the skin and increase potential of systemic toxicity, as the Kp adopted in the SD derivation was limited to values representative of healthy, intact skin. An approach that may broaden the model's applicability is to replace the OEL used in calculating the systemic dose absorbed via inhalation with a toxicologically based property. The use of a toxicological property could also reduce the uncertainty in the SI ratio originating from inconsistent use of safety factors when the OEL was developed that circumvented the quantitative application of SI ratio. A second improvement lies in the estimation of SD. Currently, this dose is determined by multiplying the Kp of a chemical with its $S_W$, the exposure time, and the exposed skin surface area. The use of $S_W$ as the source concentration in estimating transdermal flux may deviate significantly from the patterns of dermal uptake that take place in the workplace. Schneider et al. (1999) discussed the modeling in dermal exposure assessment and suggested a division of the contaminated skin layer into an outer and an inner layer that were in intimate contact in the model. As it is the concentration gradient of a chemical between the contaminated skin and the perfused tissue that drives dermal uptake, developing a sub-algorithm in the model that describes the transdermal profile of a chemical in the epidermal skin to a better precision may effectively improve the utility of the NIOSH model.

In our study, all candidate compounds selected had an airborne OEL value assigned by the investigated organizations. For SN compounds of a common interest to the majority of the studied organizations (i.e., an SN was assigned by four or more organizations), the potential of the chemical being a skin exposure hazard was assumed to increase with the number of SNs increasing. Chemicals of three or fewer SNs were not included to support this assumption, as it was uncertain if the minority vote in the SN assignment of these compounds was an indication of the chemical possessing little hazard potential or a reflection on the lack of common regulatory interest among these organizations. When introduced in the analysis, this uncertainty might interfere with the number of SNs serving as a semiquantitative indicator for the level of skin exposure hazard, given the significant number of compounds with 3 or less SNs ($n = 335$). It should be noted that, in our analysis, the number of SNs was used to establish a general trend of change in dermal hazard potential among the selected chemicals. It should not be interpreted as a surrogate for the absolute exposure risk of individual compounds.

## 5. Conclusions

This study evaluated the utility of predictive modeling in the assignment of skin notations compared to those of dermal $LD_{50}$ and log $K_{OW}$. The correlations between scientific criteria indicated that these toxicological and physicochemical properties served as a qualitative indicator in support of a dichotomous recognition of skin exposure hazard. The predictive modeling was the most influential criterion in association with the current notations, and the output of model prediction was consistent with the GHS classification of acute toxicity. These results suggest that the predictive model examined in this study may be considered for application as a semiquantitative criterion in dermal hazard ranking.

## Conflict of interest

The authors declare that there are no conflicts of interest.

## Disclaimer

The findings and conclusions in this presentation have not been formally disseminated by the National Institute for Occupational Safety and Health and should not be construed to represent any agency determination or policy.

## Acknowledgments

The authors are grateful to the assistance of the following individuals: Mr. Chieh-Ming Wu of the China Medical University for assistance in statistical analysis; Drs. Frederick Frasch and Matthew Wheeler of the NIOSH; Dr. Youcheng Liu of the University of North Texas Health Science Center; and Ms. Jennifer Sahmel of the ChemRisk, LLC, for providing technical comments; and Dr. Cathy Rotunda of the NIOSH for editorial review. The funding for this study was supported by the National Science Council, Taiwan, ROC, under project number NSC 96-2221-E-039-003-MY2 and by the China Medical University under number CMU95-183. The funding sources were not involved in the study design, the collection, analysis and interpretation of data, the writing of report, or the decision to submit the paper for publication.

## References

ACGIH, 2008. Introduction to the chemical substances TLVs. In: Documentation of the TLVs and BEIs with Other Worldwide Occupational Exposure Values, CD-ROM version. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

BLS, 1999. Occupational Injuries and Illnesses in the United States. BLS bulletin No. 2518. US Department of Labor, Bureau of Labor Statistics, Washington, DC.

Boeniger, M.F., Ahlers, H.W., 2003. Federal government regulation of occupational skin exposure in the USA. Int. Arch. Occup. Environ. Health 76, 387–399.

Chen, C., Ahlers, H., Boeniger, M., 2004. Application of data from animal toxicity testing and alternative methods in assignment of skin notations. In: American Industrial Hygiene Conference and Expo 2004, May 8–13, Atlanta, GA.

Chen, C.-P., Boeniger, M.F., Ahlers, H.W., 2002. A mathematical approach for evaluating dermal exposures and facilitating assignment of skin notations. In: International Conference on Occupational and Environmental Exposures of Skin to Chemicals: Science and Policy, September 8–11, Washington, DC.

Chen, C.-P., Boeniger, M.F., Ahlers, H.W., 2003. Use of dermal $LD_{50}$ as a criterion for skin notation. Appl. Occup. Environ. Hyg. 18, 154–155.

Chen, C.-P., Sartorelli, P., 2005. Proceedings of the international conference on occupational and environmental exposures of skin to chemicals: science and policy—session II: health effects and hazard identification. Regul. Toxicol. Pharmacol. 41, 150–158.

de Cock, J., Heederik, D., Kromhout, H., Boleij, J.S., 1996. Strategy for assigning a 'skin notation': a comment. Ann. Occup. Hyg. 40, 611–614.

ECB, 2003. Technical Guidance Document on Risk Assessment in Support of Commission Directive 93/67/EEC on Risk Assessment for New Notified Substances and Commission Regulation (EC) No 1488/94 on Risk Assessment for Existing Substances and Directive 98/8/EC of the European Parliament and of the Council Concerning the Placing of Biocidal Products on the Market, second ed. European Commission, Joint Research Centre, Institute for Health and Consumer Protection, European Chemicals Bureau, Ispra, Italy.

ECETOC, 1998. Examination of a Proposed Skin Notation Strategy. ECETOC Special Report No. 15. European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels, Belgium.

Fasano, W.J., McDougal, J.N., 2008. In vitro dermal absorption rate testing of certain chemicals of interest to the Occupational Safety and Health Administration: summary and evaluation of USEPA's mandated testing. Regul. Toxicol. Pharmacol. 51, 181–194.

Federal Register, 1989. Occupational Safety and Health Administration: air contaminants, VI. Health effects discussion and determination of final PEL, 18. Substances for which OSHA is adding skin designations. Final rule. 29 CFR Part 1910. Fed. Reg. 54, 2718–2724.

Federal Register, 2004. In vitro dermal absorption rate testing of certain chemicals of interest to the Occupational Safety and Health Administration. Final rule. Fed. Reg. 69, 22402–22441.

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

Johanson, G., Mohlin, P., Rauma, M., 2009. Dermal uptake of industrial chemicals—should evaporation from skin be included in the basis for skin notation? In: Society of Toxicology 48th Annual Meeting, March 15–19, Baltimore, MD.

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

Kezic, S., Nielsen, J.B., 2009. Absorption of chemicals through compromised skin. Int. Arch. Occup. Environ. Health 82, 677–688.

Kissel, J.C., 2011. The mismeasure of dermal absorption. J. Expo. Sci. Environ. Epidemiol. 21, 302–309.

Kupczewska-Dobecka, M., Czerczak, S., 2006. The skin notation in the MAC list and classification of dangerous chemicals. Int. J. Occup. Med. Environ. Health 19, 84–91.

Lavoué, J., Milon, A., Droz, P.O., 2008. Comparison of indices proposed as criteria for assigning skin notation. Ann. Occup. Hyg. 52, 747–756.

McDougal, J.N., Boeniger, M.F., 2002. Methods for assessing risks of dermal exposures in the workplace. Crit. Rev. Toxicol. 32, 291–327.

Nielsen, J.B., Grandjean, P., 2004. Criteria for skin notation in different countries. Am. J. Ind. Med. 45, 275–280.

NIOSH, 2007. Registry of Toxic Effects of Chemical Substances (RTECS) Database, CD-ROM. DHHS (NIOSH) Publication No. 2005-151. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Cincinnati, OH.

NIOSH, 2009. NIOSH Current Intelligence Bulletin 61: A Strategy for Improvement of Skin Notations. DHHS (NIOSH) publication no. 2009-147. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Cincinnati, OH.

OECD, 1987. Guideline for Testing of Chemicals 402: Acute Dermal Toxicity. Organisation for Economic Co-operation and Development, Paris, France.

OECD, 2004. OECD Guideline for Testing of Chemicals 428: Skin Absorption—In Vitro Method. Organisation for Economic Co-operation and Development, Paris, France.

Rosner, B., 2006. Fundamentals of Biostatistics, sixth ed. Thomson Higher Education, Belmont, CA.

Sartorelli, P., 2002. Dermal exposure assessment in occupational medicine. Occup. Med. 52, 151–156.

Sartorelli, P., Ahlers, H.W., Alanko, K., Chen, C., Cherrie, J.W., Drexler, H., Kezic, S., Johanson, G., Filon, F.L., Maina, G., Montomoli, L., Nielsen, J.B., 2007. How to improve skin notation. Position paper from a workshop. Regul. Toxicol. Pharmacol. 49, 301–307.

Schneider, T., Vermeulen, R., Brouwer, D.H., Cherrie, J.W., Kromhout, H., Fogh, C.L., 1999. Conceptual model for assessment of dermal exposure. Occup. Environ. Med. 56, 765–773.

SRC, 2008. PhysProp Database. Syracuse Research Corporation, Arlington, VA. Available from: <http://www.syrres.com/esc/physprop.htm>. [Accessed 20 August 2008].

The European Parliament and the Council of the European Union, 2006. Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), Regulation (EC) No. 1907/2006. Offic. J. Euro. Union L396, 1–849.

UNECE, 2009. Globally Harmonized System of Classification and Labeling of Chemicals (GHS). ST/SG/AC.10/30/Rev.3. United Nations Economic Commission for Europe, New York.

USEPA, 1998. Health Effects Test Guidelines OPPTS 870.1200: Acute Dermal Toxicity. EPA 712–C–98–192. US Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances, Washington, DC.

Vecchia, B.E., Bunge, A.L., 2003. Evaluating the transdermal permeability of chemicals. In: Guy, R.H., Hadgraft, J. (Eds.), Trandermal Drug Delivery, second ed. Marcel Dekker Inc., New York, pp. 25–55.

Walker, J.D., Whittaker, C., McDougal, J.N., 1996. Role of the TSCA Interagency Testing Committee in meeting the US government data needs: designating chemicals for percutaneous absorption rate testing. In: Marzulli, F.N., Maibach, H.I. (Eds.), Dermatotoxicology, fifth ed. Taylor and Francis, Washington, DC, pp. 371–381.

Wilschut, A., ten Berge, W.F., Robinson, P.J., McKone, T.E., 1995. Estimating skin permeation: the validation of five mathematical skin permeation models. Chemosphere 30, 1275–1296.