Regulatory Toxicology and Pharmacology 61 (2011) 53–62

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

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

The evolution of skin notations for occupational risk assessment: A new NIOSH strategy

G. Scott Dotson [a,*], Chen-Peng Chen [b], Bernard Gadagbui [c], Andrew Maier [c], Heinz W. Ahlers [d], Thomas J. Lentz [a]

[a] Centers for Disease Control and Prevention (CDC), National Institute for Occupational Safety and Health (NIOSH), Education and Information Division (EID), Cincinnati, OH, USA
[b] China Medical University, College of Public Health, Department of Occupational Safety and Health, Taichung, Taiwan
[c] Toxicology Excellence for Risk Assessment (TERA), Cincinnati, OH, USA
[d] CDC, NIOSH, National Personal Protection Technology Laboratory (NPPTL), Pittsburgh, PA, USA

ARTICLE INFO

Article history:
Received 12 April 2011
Available online 12 June 2011

Keywords:
Skin notations
Skin
Chemicals
Occupational
Hazard characterization
Risk assessment

ABSTRACT

This article presents an overview of a strategy for assignment of hazard-specific skin notations (SK), developed by the National Institute for Occupational Safety and Health (NIOSH). This health hazard characterization strategy relies on multiple SKs capable of delineating systemic (SYS), direct (DIR), and immune-mediated (SEN) adverse effects caused by dermal exposures to chemicals. One advantage of the NIOSH strategy is the ability to combine SKs when it is determined that a chemical may cause multiple adverse effects following dermal contact (e.g., SK: SYS-DIR-SEN). Assignment of the SKs is based on a weight-of-evidence (WOE) approach, which refers to the critical examination of all available data from diverse lines of evidence and the derivation of a scientific interpretation based on the collective body of data including its relevance, quality, and reported results. Numeric cutoff values, based on indices of toxic potency, serve as guidelines to aid in consistently determining a chemical's relative toxicity and hazard potential. The NIOSH strategy documents the scientific rationale for determination of the hazard potential of a chemical and the subsequent assignment of SKs. A case study of acrylamide is presented as an application of the NIOSH strategy.

Published by Elsevier Inc.

1. Introduction

Within some occupational settings, dermal contact with chemicals may represent a greater health risk for workers than inhalation exposure (Sartorelli, 2002). Exposures from skin contact cause a wide range of health effects, including dermatoses, systemic toxicity, and immune-mediated responses (Sithamparanadarajah, 2008). Despite the importance of the skin as a contributing route of exposure for many chemicals, current occupational exposure limits (OELs) characterize the acceptability of inhalation exposures and are not intended to denote a "safe" or "acceptable" level of exposure to chemicals via dermal contact. These OELs are supplemented with qualitative hazard indicators that serve as the primary means for communicating that a potential health hazard exists following skin exposure. One such notation category alerts to the potential for absorption (i.e., a skin notation). A second common notation refers to sensitization potential; different organizations may denote route specificity of the sensitization response. For direct skin effects, such as irritation, most OELs do not include a specific notation, but such issues are usually described in the toxicology sections of the full OEL documentation.

The purpose of a skin notation, traditionally represented by the symbol (skin) or (*S*), as applied by most existing OEL setting organizations, is to provide a warning that a chemical has the potential to be absorbed dermally in sufficient quantities to affect the interpretation of the risks from inhalation, if concomitant dermal contact may occur. Numerous governmental and non-governmental organizations (see Table 1) include skin notations as part of their occupational exposure guidelines for chemicals. The criteria and protocol for the assignment of skin notations vary among the different organizations, but the systems share the general interpretation that a skin notation represents the potential for dermal absorption.

Several publications have outlined the limitations of the skin notation assigned by the various organizations and expressed the need for an enhanced method for assignment of skin notations to enhance their use in identifying the health hazards that may occur when a chemical comes into contact with skin (Fiserova-Bergerova et al., 1990; ECETOC, 1998; Czerczak and Kupczewska, 2002; Sartorelli, 2002; Chen et al., 2003; Nielsen and Grandjean, 2004;

* Corresponding author. Address: Centers for Disease Control and Prevention (CDC), National Institute for Occupational Safety and Health (NIOSH), Education and Information Division (EID), 4676 Columbia Parkway, MS-C32, Cincinnati, OH 45227, USA. Fax: +1 513 533 8230.
E-mail address: fya8@cdc.gov (G.S. Dotson).

0273-2300/$ - see front matter Published by Elsevier Inc.
doi:10.1016/j.yrtph.2011.06.002

Table 1
Overview of the criteria used to assign skin notation within various countries and organizations.

Country (organization)	Criteria (definition) used to assign a skin notation
Denmark	When known that the substance can be absorbed via skin
Norway	Substances that can be taken up via skin
Finland	Absorbed amounts and health risks cannot be evaluated only from air concentrations
Sweden	Substances easily taken up by the body via skin
Germany (MAK)	When dermal exposure increases the body burden
EU (SCOEL)	Substantial contribution to total body burden via dermal exposure
USA (ACGIH)	Potential significant contribution to overall exposure by the cutaneous route, including mucous membranes and the eyes, either by contact with vapors or, of probable greater significance, by direct skin contact with the substance
USA (NIOSH)	Potential for dermal absorption; prevent skin contact
USA (OSHA)	Potential for dermal absorption
The Netherlands (DECOS)	More than 10% contribution to total exposure...
European industry (ECETOC)	More than 10% contribution to total exposure...

Abbreviations: American Conference of Governmental Industrial Hygienists (ACGIH); European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC); European Union Scientific Committee on Occupational Exposure Limits (SCOEL); German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK); National Institute for Occupational Safety and Health (NIOSH); Occupational Safety and Health Administration (OSHA); Occupational Standards of the Dutch Health Council (DECOS).
Source: adapted from WHO (2006).

Kupczewska-Dobewcka and Czercak, 2006; WHO, 2006; Sartorelli et al., 2007, 2010; Johanson and Rauma, 2008; Lavoue et al., 2008). Important limitations in the current notation approach include:

(1) A skin notation represents the potential for dermal absorption and does not take into account inherent toxicity (or toxicodynamics). For systemic toxicants, this may result in a chemical that is highly toxic following dermal absorption receiving the same notation as a chemical that exhibits limited toxicity following dermal uptake.
(2) The failure to provide a warning when a chemical may cause direct damage to the skin (e.g., irritation and corrosion) or potentially act as a sensitizing agent. These adverse health effects are not traditionally considered in assignment of a skin notation.
(3) Chemicals not assigned a skin notation are often perceived by workers and occupational health professionals as absent a serious health risk via the dermal route, and
(4) the rationale behind the designation of a chemical with a skin notation is often poorly documented, with limited description of a systemic decision approach. In many cases limited information is provided beyond "potential for dermal absorption".

NIOSH has developed a strategy intended to address many of the limitations in current skin notation approaches (NIOSH, 2009). This article describes the important elements of the strategy for the assignment of hazard-specific skin notations (SK), including the decision criteria embedded in the approach. An in-depth case study for assigning the hazard-specific SK to acrylamide has been included to illustrate application of the NIOSH strategy.

2. NIOSH Strategy for skin notation assignments

The NIOSH skin notation strategy has been developed to ensure that the logic and decision-making criteria behind the SK assignments are clearly defined and consistently applied (NIOSH, 2009). This strategy is a form of health hazard characterization in which the key step is to determine a chemical's hazard potential – i.e., potential for causing adverse health effects as a result of skin exposure. A weight-of-evidence (WOE) approach is used to integrate data from multiple sources into the hazard characterization. The WOE approach refers to the critical examination of all available data from diverse lines of evidence and the derivation of a scientific interpretation based on the collective body of data including its relevance, quality, and reported results. Ideally, this approach allows for the strengths and weaknesses of the different datasets to be critically evaluated and ensure that the most relevant data are used to determine a chemical's hazard potential. Assignment of a SK occurs when the WOE approach supports the conclusion that immediate, prolonged, or repeated contact of the skin with the chemical produces systemic, direct (localized), or immune-mediated effects.

The first step in determining the hazard potential involves critical evaluation of scientific data relating to the chemical. A comprehensive literature search and review of data relating to the following topics is required to accurately determine a chemical's hazard potential:

(1) Physicochemical properties.
(2) Toxicokinetics (in particular, dermal absorption kinetics).
(3) Epidemiology (including data from case reports and industrial hygiene studies and data on exposure and health effects).
(4) Toxicology and data from mechanistic studies (in vivo and in vitro), and
(5) The use of computer-based techniques, including predictive algorithms [e.g., quantitative structure–activity relationships (QSAR)] and mathematical models that describe a selected process (e.g., skin permeation) using analytical or numerical methods.

Within the WOE approach, reliable human data collected via epidemiological investigations, clinical reports, and industrial hygiene studies are preferred for assessing the health hazards of skin contact with chemicals. However, human health data are often limited for many chemicals, resulting in the need to assign the hazard-specific SK primarily on the basis of results of animal toxicology or mechanistic in vivo and in vitro studies. Standardized and widely accepted research protocols for in vivo and in vitro investigations have been developed by the Organization for Economic Cooperation and Development (OECD), European Centre for the Validation of Alternative Methods, the US Environmental Protection Agency, and the National Toxicology Program (NIOSH, 2009). The increased use of standardized protocols yields quantitative data that can be adopted for the assignment of skin notations. The results of experimental in vivo toxicity studies are commonly reported in terms of indices of toxic potency, such as the median lethal dose (LD_{50}) value, no observed adverse effect level (NOAEL),

lowest observed adverse effect level (LOAEL), and benchmark dose (BMD) to aid in the interpretation of the findings. The NIOSH strategy includes numeric cutoff values based on these indices to serve as guidelines for consistently determining each chemical's relative toxicity and hazard potential.

Computer-based techniques represent alternative information sources that may be applied during assignment of the SK. NIOSH has included, as one aspect of the computer-based approach, a predictive algorithm called the skin/inhalation (SI) ratio, intended for estimating and evaluating the health hazards of skin exposure to chemicals (ECETOC, 1998; NIOSH, 2009). The algorithm provides an estimate of a chemical's potential to be a skin hazard by comparing the uptake of a chemical through skin absorption to the uptake from inhalation associated with a reference OEL based on systemic toxicity. The SI ratio is intended to serve as a health hazard characterization tool by estimating whether skin exposure to a chemical under a reasonable occupational scenario results in a systemic dose that is at least 10% of the systemic dose expected from inhalation at the level of the OEL, and it is supportive of assigning the systemic (SYS) notation. Additional information on the SI ratio can be found within the appendix of this paper, in addition to NIOSH (2009) and Chen et al. (2011).

3. Hazard-specific skin notations (SK)

The NIOSH strategy presents the use of multiple hazard-specific SK designations that clearly distinguish between systemic (SYS), direct (DIR), and immune-mediated (SEN) effects caused by exposure of the skin to chemicals. In addition, specific health hazards are addressed through the inclusion of subnotations. Thus, with the strategy, chemicals labeled as SK: SYS are recognized as able to contribute to systemic toxicity through skin absorption. Chemicals assigned the SK: SYS (FATAL) notation have been identified as highly or extremely toxic and have the potential to be lethal or life-threatening at relatively low doses following acute contact with the skin. Chemicals identified as causing direct effects (i.e., reversible/irreversible tissue damage or disruption of skin barrier property) to the skin limited to or near the point of contact are labeled SK: DIR, and those resulting in skin irritation and corrosion at the point of contact are labeled as SK: DIR (IRR) and SK: DIR (COR), respectively. The SK: SEN notation is used for chemicals identified as causing or contributing to allergic contact dermatitis (ACD) or other immune-mediated responses, such as asthma, due to skin exposure. Candidate chemicals may be assigned more than one SK when they are identified to cause multiple effects resulting from skin exposure. For example, if a chemical is identified as corrosive and also contributes to systemic toxicity, it is labeled as SK: SYS-DIR (COR). The (SK) notation is assigned when scientific data indicate that skin exposure to a chemical does not produce systemic, direct, or sensitizing effects. The $ID^{(SK)}$ notation is assigned when, at the time of review, there are insufficient data to determine whether the chemical has the potential to act as a systemic, direct, or sensitizing agent. The ND notation indicates that a chemical has not been evaluated with the NIOSH strategy. Table 2 provides a summary of SK assignments. The following sections provide supplemental information on the criteria for the assignment of the SYS, DIR, and SEN notations, in addition to their subnotations. In Sections 3.1–3.3, because quantitative human data are often not available, the following discussion focuses upon the use of animal data.

3.1. SK: SYS and SK: SYS (FATAL)

The SK: SYS and SK: SYS (FATAL) are assigned to chemicals that are absorbed through the skin and contribute to systemic toxicity. Specific effects that would warrant the assignment of these notations include general indicators of systemic toxicity (e.g., lethality, clinical signs of toxicity, decreased body weight), specific target organ effects (e.g., nervous system, liver, or kidney toxicity), and endpoints of special concern or biologic system/function-specific effects (e.g., reproductive effects, developmental toxicity, or carcinogenicity) (NIOSH, 2009). Assignment of SK: SYS and SK: SYS (FATAL) are based on the evaluation of data relating to the toxicokinetics, acute toxicity, dermal repeat-dose toxicity, subchronic toxicity, chronic toxicity, carcinogenicity, or biologic system/function-specific effects associated with skin exposures to a specific chemical. Due to the unique mechanism of actions associated with systemic immune-mediated responses, such as asthma, and the fact that all immune-mediated responses have a systemic component to their onset, these effects are designated with the SEN notation to highlight the specific health risks associated with them.

Table 3 provides an overview of the decision process used for assignment of the SK: SYS notation. The basic approach recognizes the importance in evaluating the potential for a chemical to (1) induce systemic effects following skin contact, (2) penetrate the skin, and (3) induce toxicity once it reaches the target organ, following systemic distribution. The intent of this notation is to indicate whether the chemical is likely to be absorbed in toxicologically significant amounts and contribute to the overall body burden. For this reason, data on toxicity following skin exposure are given the greatest weight in the assessment. Absorption data (in the absence of toxicity data) are not sufficient to assign a SK: SYS notation, unless supplemented by data on other routes of exposure suggesting that the level of skin absorption for the chemical in question is toxicologically potent.

As part of the criteria for the assignment of SK: SYS and SK: SYS (FATAL), numeric cut point values have been included to aid in evaluation of the following characteristics of a chemical: acute toxicity; repeat-dose toxicity; subchronic toxicity; and chronic toxicity. Among all data that report the potential of systemic toxicity resulting from skin absorption, the most abundant type was generated by animal studies of acute toxicity, and the findings were commonly reported as LD_{50} values. With its superior availability compared to other dermal toxicity data, dermal LD_{50} values have been recommended for application in the assignment of skin designation (ACGIH, 2009) and adopted as a major criterion in the recognition of skin exposure hazards (UNECE, 2007). Numeric cutoff points based on LD_{50} values are provided to determine the relative acute toxic potential of a chemical following skin exposure. Chemicals identified as having LD_{50} values lower than the critical cutoff value of 2000 mg/kg animal body weight are considered systemically toxic following skin contact and are assigned SK: SYS. The critical cutoff point of 2000 mg/kg for LD_{50} values reflects the dose selected in standardized limit tests to identify chemicals with the potential for acute toxicity. This value corresponds with the numeric cutoff value used by the member countries of the Council of the European Communities for establishing a chemical as "harmful" (OECD, 1992) and by the *Globally Harmonized System* (GHS) *of Classification and Labeling of Chemicals* for signifying the chemical as "dangerous" (UNECE, 2007). When multiple dermal LD_{50} values are available for the same chemical, only those produced following standardized protocols are considered and, as a conservative approach, the lowest dermal LD_{50} value among the considered values is applied in the hazard characterization process. When the WOE suggests that the dermal LD_{50} values are lower than the critical cutoff value of 200 mg/kg, then the chemical is considered potentially lethal or life-threatening following acute exposure to relatively low doses and is assigned SK: SYS (FATAL). This value is consistent with the numeric cutoff value used by GHS to identify chemicals capable of causing death following skin contact (UNECE, 2007).

Table 2
Overview of the hazard-specific skin notations (SK) used in the NIOSH strategy and what they indicate with regard to exposure of the skin to the chemical.

SK	Definition
SYS	Potential to contribute substantially to systemic toxicity through absorption
FATAL	Subnotation of SK: SYS; highly or extremely toxic and potentially lethal or life-threatening
DIR	Potential for localized, non-immune-mediated adverse effects at or near the point of contact, including corrosion, primary irritation, changes in pigmentation, and reduction/disruption of skin barrier integrity
IRR	Subnotation of SK: DIR; potential to be an irritant
COR	Subnotation of SK: DIR; potential to be corrosive
SEN	May cause or contribute to the onset of allergic contact dermatitis or other immune-mediated responses, such as airway hyperreactivity (asthma)
SK	No associated health hazard; data does not support assignment of the SYS, DIR, or SEN notation
$ID^{(SK)}$	Insufficient data to determine the health hazards
ND	Not evaluated

Source: adapted from NIOSH (2009).

Table 3
Summary of the rationale for assigning the SK: SYS notation.

Skin absorption	Systemic toxicity		
	Yes	No	No data
Yes	SYS[a]	SYS	SYS
No	SYS	SYS	SYS
No data	SYS	SYS	No assignment[b]

Source: adapted from NIOSH (2009).
[a] Indicates categories where the SK: SYS notation would or would not be assigned.
[b] Indicates that insufficient data were identified to accurately assess the systemic hazards or potential for skin absorption associated with skin contact with a specified chemical.

Results from repeat-dose toxicity, subchronic toxicity, and chronic toxicity studies often include the NOAEL for the most sensitive relevant endpoint(s) selected from all evaluated health effects, as a reasonable estimate of the threshold dose for adverse systemic effects (i.e., the critical effect threshold). In some cases the LOAEL or statistical estimate of the effect threshold (such as BMD) might be selected as the critical effect threshold estimate. Judgment is used in weighing the NOAEL, LOAEL, and BMD values from the overall database to compare against the cutoff point value. If the critical effect threshold for a selected endpoint is lower than the critical cutoff value of 1000 mg/kg as a repeated daily dose (mg/kg/day), then the chemical is considered systemically toxic following skin exposure and is assigned SK: SYS. The critical value of 1000 mg/kg/day reflects the dose selected in the standardized limit tests to identify chemicals with the potential for repeat-dose toxicity following skin contact.

3.2. SK: DIR, SK: DIR (IRR), and SK: DIR (COR)

The SK: DIR notation denotes the potential for non-immune-mediated responses resulting in damage or destruction of the skin at or near the point of contact, including irritant contact dermatitis, corrosive effects, pigmentation changes, cancers of the skin resulting from direct dermal contact, and phototoxicity (NIOSH, 2009). Immune-mediated responses, such as ACD and allergic urticaria, associated with exposures of the skin to chemicals are not assigned SK: DIR; instead, chemicals capable of causing such responses are assigned SK: SEN.

Most available reports on the direct effects of chemicals on skin are qualitative descriptions summarized from the clinical observations of patients or the results of experimental investigations. For this reason, quantitative toxic endpoints, such as a NOAEL, are not commonly reported within such studies and for this reason numeric cutoff values are not included within the rationale for the assignment of the DIR notation or its subnotations. Assignment of the SK: DIR notation or its subnotations used to denote irritant (IRR) and corrosion (COR) are based on interpretation of the details provided within the individually reviewed studies. A thorough review of the study protocol, potential confounding factors, description of the observed reactions to the chemical, and supplemental information are crucial in the interpretation of the data provided within the individually reviewed studies. Because of the subjective nature of the data, generalized guidelines are applied to govern the assignment of the subnotations of the DIR notations. For example, descriptions of edema and erythema are strong indicators of irritations, while severe blistering and scarring of the skin following skin contact would point to corrosion. These guidelines are more subjective than the criteria used to assign the SK: SYS notation.

3.3. Sk: SEN

The SK: SEN notation is intended to be applied to chemicals determined to cause immune-mediated responses of the skin or systemically following dermal exposures. The most commonly recognized immune-mediated response in the workplace associated with skin contact is ACD, which has been linked to a wide range of chemicals including certain metals (e.g., nickel) and organic substances (e.g., amines, aldehydes, isocyantes, and epoxy resins). Other immune-mediated responses that may be considered include systemic responses, such as asthma, that occur following dermal exposures. Results of animal and human studies support a link between exposures of the skin to certain chemical allergens (e.g., isocyanates), systemic sensitization, and the development of lung allergic responses (Kimber, 1996; Beck and Leung, 2000; Day et al., 2006; Bello et al., 2007; Redlich and Herrick, 2008; Pauluhn, 2008). The unique mechanisms of action associated with immune-mediated responses necessitate the classification of these health effects into a distinct notation. For this reason, all immune-mediated responses regardless of their toxicological endpoint are assigned the SEN notation.

Data relevant for determining whether a chemical may cause immune-mediated responses include analytical or descriptive epidemiological studies, observational case reports, and clinical studies. Much like the assignment of the DIR notation, assignment of the SEN notation is based primarily on data that are qualitative in nature. For this reason, it is important that all relevant data be thoroughly vetted using the WOE approach. If it is determined following the review of human data that immune-mediated responses following skin exposures to a chemical are potentially isolated or rare events, supporting data from experimental animal studies, such as the murine local lymph node assay (LLNA) and the guinea pig maximization test (GPMT), should be obtained before the chemical is identified as a chemical allergen via the dermal route and assigned the SEN notation.

The refinement of standardized skin sensitization tests, such as the murine LLNA and the GPMT, has resulted in the reporting of quantitative toxicological endpoints, such as the stimulation index

(SI) or EC3 value (the estimated concentration needed to produce a response three times greater than a reference chemical without producing systemic toxicity and/or excessive local irritation) (ICCVAM, 2009). When available, quantitative toxicological endpoints, including the SI and EC3 value, are applied to ensure that a consistent and objective approach is included within the decision to assign the SEN notation.

4. Case study: SK assignment for acrylamide

The following section provides a summary of the assignment of the NIOSH SK to acrylamide (CAS #79-06-1). It is included as a case study to demonstrate the application of the scientific rationale and methodology presented in the NIOSH strategy. The full report is available via the NIOSH Web site (NIOSH, 2011). The case study highlights the characterization of the hazard potential for acrylamide and key studies that serve as the basis of the final NIOSH SK assignment [SK: SYS-DIR(IRR)-SEN].

4.1. Assignment of the SYS notation

Toxicokinetic studies involving humans and animals following skin exposure to acrylamide were identified. Fennell et al. (2006) reported the dermal absorption of 25–29% of the applied dose in a study using human volunteers. In rats, Sumner et al. (2003) reported 14–30% of the applied dose of acrylamide was dermally absorbed. Absorbed doses above 10% indicate a high percent of dermal uptake (NIOSH, 2009). The potential of acrylamide to pose a skin absorption hazard was also evaluated using the previously described SI ratio model. The SI ratio for acrylamide was estimated at 2955; an SI ratio of $\geqslant 0.1$ indicates that a chemical is capable of producing systemic toxicity from skin exposure (NIOSH, 2009). Additional information on the SI ratio and the variables used in its calculation are included in the appendix.

Dermal LD_{50} values of 252–1102 mg/kg were reported (American Cyanamid Company, 1973; Dow Chemical USA, 1975). Because the reported acute dermal LD_{50} values for the rabbit are lower than the critical dermal LD_{50} value of 2000 mg/kg body weight that identifies chemicals with the potential for acute dermal toxicity (NIOSH, 2009), acrylamide is considered acutely toxic following dermal exposure.

Occupational exposure studies and epidemiological investigations have revealed neurotoxic effects in workers partially contributed to dermal exposures to acrylamide (He et al., 1989; NIOSH, 1991; Bachmann et al., 1992). He et al. (1989) investigated the onset of neurotoxicity in 71 workers employed at a plant in China. The authors noted symptoms such as weakness and numbness in extremities, preceded by skin peeling, and reported that the total prevalence of acrylamide poisoning among the workers was 73.2%. Three of the cases involving acrylamide were classified as severe poisonings, six as moderate poisonings, and 43 as mild poisonings. The authors concluded that dermal contact contributed significantly to these cases and that dermal exposure to acrylamide should be prevented. NIOSH (1991) reported neurotoxic effects (peripheral neuropathies) following a latency period of days to weeks in workers who handled 27–30% aqueous solutions of acrylamide for 1–18 months. Dermatitis, characterized as peeling of skin at the site of contact (in this case, palms), was observed prior to the development of peripheral neuropathies, indicating that skin exposure had occurred. These workers were likely exposed repeatedly through both inhalation and dermal contact, but it is not clear whether the neuropathies were caused by skin absorption of acrylamide. Bachmann et al. (1992) investigated acrylamide exposures among 82 chemical industry workers. A significantly increased prevalence rate for several neurological symptoms, including numbness, limb pain, and sweating, in addition to skin peeling, was reported for acrylamide-exposed workers in comparison with unexposed controls. The results of this study indicate that dermal contact with acrylamide may have contributed to onset of the reported neurological effects.

Numerous animal dermal toxicity studies were identified that provide evidence of neurotoxic and reproductive effects following repeated exposures. A long-term study identified a NOAEL of 0.5 mg/kg/day when acrylamide was applied to rats' tails (equivalent to 5% body surface area) (Novikova, 1979). A LOAEL of 5 mg/kg/day was reported based on pronounced functional neurotoxic effects, characterized by a decrease in motor activity and impaired conditioned reflex response, in addition to a reduction in body weight. Drees et al. (1976) reported peripheral neuropathies at an LOAEL of 50 mg/kg/day when acrylamide was applied topically to the skin of newborn rabbits for 5–12 weeks. The NOAEL in this study was 5 mg/kg/day. Acrylamide induced a significant increase in the percentage of dead implants per female when male mice received five dermal applications of 25 mg/kg/day for 7–10 days prior to mating with female mice (Gutierrez-Espeleta et al., 1992). Adler et al. (2004) also reported heritable translocations when male mice were dermally exposed to acrylamide 1 day prior to mating with female mice. These findings suggest that acrylamide has the potential to cause reproductive effects via effects on sperm DNA. Because the reported NOAEL and LOAEL identified in these studies are lower than the critical numeric cutoff value of 1000 mg/kg/day for repeat-dose toxicity that identifies chemicals with the potential for subchronic dermal toxicity (NIOSH, 2009), acrylamide is considered to be capable of inducing neuro- and reproductive toxicity following repeated dermal exposure.

4.2. Assignment of the DIR (IRR) notation

Both occupational studies and experimental investigations using human volunteers reported adverse effects of the skin contributed to acrylamide were identified. Peeling and irritation of the skin were observed in workers repeatedly exposed to acrylamide via the dermal route, but the contribution from the inhalation of acrylamide could not be ruled out (He et al., 1989; NIOSH, 1991; Bachmann et al., 1992). A skin irritation test (American Cyanamid Company, 1952) treated human volunteers with 1–25% acrylamide solution demonstrated a dose-related increase in the number and degree of irritant responses, which led the author to conclude that acrylamide is a skin irritant. In animals, a 10% solution of acrylamide applied repeatedly to the ear and shaved intact abdomen of rabbits caused a slight reddening and edema of the skin (McCollister et al., 1964). Mukhtar et al. (1981) reported acrylamide-induced depletion of skin glutathione levels in mice topically exposed to the chemical. The authors concluded that such depletion may cause dermal membrane damage with increased loss of cellular enzymes and increased interactions of reactive metabolites with essential macromolecules, resulting in the dermatitis and irritation of skin observed in acrylamide-exposed workers.

Bull et al. (1984) conducted a skin initiation/promotion assay to investigate the potential for acrylamide to be carcinogenic in mouse skin. In that study, an acrylamide solution in ethanol was administered topically in six doses of 12.5, 25, and 50 mg/kg/day, which resulted in total doses of 75, 150, and 300 mg/kg, respectively, over a 2-week period. Following the topical applications of acrylamide, a known tumor promoter [12-*O*-tetradecanoylphorbol-13-acetate] in acetone was applied three times a week for 20 weeks to the shaved backs of test animals. Bull et al. (1984) reported that the incidences of skin tumors were significantly elevated in a dose–response manner. It should be noted that mice that did not receive the TPA applications did not develop tumors. On the basis of these results, the authors theorized that acrylamide may be capable of acting as a skin tumor initiator.

4.3. Assignment of the SEN notation

No reliable human data relating to the onset of allergic responses associated with dermal contract to acrylamide were identified. The European Chemicals Bureau (ECB, 2002) reviewed available occupational case reports and deemed the reported observations as inconsistent. In animals, acrylamide was observed to cause skin sensitization. In a GPMT, acrylamide elicited a positive skin response in excess of that seen in control animals in 40% of the test animals (Allan, 1995). Eastman Kodak Company (1978) also reported sensitization in three guinea pigs administered a 10% acrylamide solution.

4.4. Summary of evaluated data and SK assignment

Taken together, data from toxicokinetic studies involving humans (Fennell et al., 2006) and animals (Sumner et al., 2003), predictions of mathematical algorithms, acute toxicity studies in rabbits (American Cyanamid Company, 1973; Dow Chemical USA, 1975), and repeat-dose dermal toxicity studies in animals (Drees et al., 1976; Novikova, 1979; Gutierrez-Espeleta et al., 1992; Adler et al., 2004) were sufficient to demonstrate that acrylamide is absorbed through the skin and can cause systemic effects, including neuro- and reproductive toxicity, following dermal exposure. Occupational exposure studies and epidemiological investigations provided supplemental evidence of the onset of systemic toxic in workers partially contributed to dermal exposures to acrylamide (He et al., 1989; NIOSH, 1991; Bachmann et al., 1992). On the basis of a study using human volunteers (American Cyanamid Company, 1952) and two animal studies (McCollister et al., 1964; Mukhtar et al., 1981), acrylamide is identified as a skin irritant. Acrylamide is identified as a potential skin tumor initiator and may increase the risk of skin cancer (Bull et al., 1984). Although acrylamide yielded inconsistent results in exposed humans, positive sensitization results from two guinea pig maximization tests (Allan, 1995; Eastman Kodak Co., 1978) are sufficient to demonstrate that acrylamide is a skin sensitizer. Therefore, on the basis of these assessments, acrylamide is assigned a composite skin notation of SK: SYS-DIR (IRR)-SEN. For comparison purposes to the NIOSH SK, Table 4 provides dermal exposure recommendations previously assigned to acrylamide by governmental and nongovernmental organizations.

5. Discussion and conclusion

In this paper, we have demonstrated the application of a strategy (NIOSH, 2009) that offers multiple enhancements to prior systems for alerting workers of the potential hazards of skin contact with a chemical. Several elements of the system help to achieve the goal of clarity in worker hazard communication and risk management. The most significant improvement is the use of multiple-component SK that provides an integrated communication approach for various types of health effects that previously were addressed in the context of separate hazard classification or notation systems. The NIOSH strategy allows users to determine the status of concerns for all three common categories of skin-related hazard information in one notation, rather than referring to multiple notations or hazard statements, which are often found in different locations within a material safety data sheet. Moreover, the inclusion of a notation that provide indications that a chemical has been evaluated with no hazard found versus those for which data were inadequate to assign a notation provides a major clarifying point for users – who may assume under older systems that the absence of a notation suggests limited hazard potential.

As part of a comprehensive risk management plan, the use of multiple hazard-specific SK allows for more effective risk management, enabling occupational health professionals and workers information to support decisions on control strategies. The current system provides some information to gauge potency of systemic and direct effects, in that chemicals identified with SK: SYS (FATAL) or SK: DIR (COR) are a higher degree of concern than those chemicals with no such notation. In addition, the inclusion of a SK: SEN notation may also trigger additional considerations since information of doses that initiate sensitization are often hard to determine. Thus, the additional information provided by the tiered notations used in the new notations allows the user to judge if more stringent control methods are required to reduce dermal exposures, or whether there is a need for replacement with less hazardous chemical.

The underlying logic and decision-making criteria for assigning skin notations have not been well documented by most groups that assign such notations as part of their OEL documentation. The SK assignments rely heavily on the application of a WOE approach in interpretation of data from different experimental approaches. For this reason, the strategy describes the approach used to inform the WOE determinations. Providing methodology documentation is consistent with current international classification systems (UNECE, 2007), but is an improvement over the level of documentation associated with traditional OEL applications. NIOSH has attempted to provide well-defined criteria as a means to ensure consistency during the assignment of hazard-specific SK and through systematic documentation of the rationale and supporting data for the SK assignment for particular chemicals (NIOSH, 2009). Each chemical evaluated by the NIOSH strategy is accompanied by a support document, entitled *Skin Notation Profile*. The support

Table 4
Summary of the previously issued skin hazard designations for acrylamide.

Organization	Designation
ACGIH (2009)	(Skin): based on the limited data demonstrating toxicity following rapid absorption through intact skin of humans and animals
ECB (2011)	R21: harmful if in contact with skin; R24: toxic in contact with skin; R38: irritating to skin; R43: may cause sensitization by skin contact.
GHS (European Parliament, Council of the European Union, 2008)	Acute toxicity category 4 (hazard statement: harmful in contact with the skin); skin irritation category 2 (hazard statement: causes skin irritation); skin sensitization category 1 (hazard statement: may cause an allergic skin reaction); category 1B mutagen (hazard statement: May cause genetic defects)[a]; category 1B carcinogen (hazard statement: may cause cancer) [a]; category 2 reproductive toxicant (hazard statement: suspected of damaging fertility or the unborn child)[a]
NIOSH (2005)	[Skin]: potential for dermal absorption; prevent skin contact
OSHA (2007)	[Skin]: based on potential contribution to the overall exposure by the cutaneous route, including the mucous membranes and the eyes, either by airborne route or (more particularly) by direct contact

Abbreviations: American Conference of Governmental Industrial Hygienists (ACGIH); European Chemicals Bureau, Institute for Health and Consumer Protection, European Commission Joint Research Centre (ECB); Global Harmonization System (GHS) of Classification and Labeling of Chemicals (GHS); National Institute for Occupational Safety and Health (NIOSH); Occupational Safety and Health Administration (OSHA).

[a] Denote hazard designations that are not exclusive to dermal exposures.

document clearly summarizes the data and reasoning behind the SK assignment.

The primary goal of the NIOSH SK is to enhance communication of the hazards of dermal contact with chemicals. Thus, the SK approach was designed to align with the dermal hazard designations included within the GHS to encourage harmonization between the two systems (UNECE, 2007; NIOSH, 2009). GHS is an international classification and labeling system for chemicals adopted by the United Nations in 2003 to ensure their safe use, transport, and disposal (UNECE, 2007). The GHS classification system and the NIOSH strategy have been aligned for acute systemic toxicity (lethality), direct effects of the skin, and sensitization. It should be noted that differences associated with (1) interpretation of reviewed data, (2) deviations between the criteria outlined in the two strategies, (3) and availability of data at the time of review may result in differences between the NIOSH SK assignment and GHS hazard statements for a specific chemical. Nevertheless the underlying assignment criteria are very similar.

Limited tools are available to quickly estimate the impact of skin exposures to chemicals on workers. The SI ratio has the potential to serve as a hazard characterization tool beyond its intended application during the assignment of the SYS notation. As applied by NIOSH, it is based on a "reasonable occupational scenario," which includes default assumptions regarding the duration of exposure (8 h), the retention factor (RF) or the percentage of the airborne concentration of a chemical in the lungs retained during respiration (75%), and the surface area of unprotected skin exposed to a chemical (surface area of 360 cm^2, equivalent to the palms of both hands). Each assumption can be modified to more closely mimic the conditions found within a specific workplace. For example, in settings where dermal exposures include the arms and entire hands, the surface area estimates could be increased resulting in a SI ratio aligned more closely to the exposure conditions. This ability to be modified makes it an invaluable hazard characterization tool.

Despite the significant efforts to develop a system that employs robust criteria and decision-making approaches, there are potential limitations in the application of the NIOSH strategy. Knowledge of these limitations is useful to identify research needs that can improve methods for assessing dermal hazards. Three areas that require further research are (1) tools for reliance on limited available data for the route of interest, (2) assignment of SK to complex mixtures, isomers, and variable concentrations, and (3) the appropriate use of computer-based techniques and in silico methods.

One major limitation of the strategy and the SK assignments is their dependence upon the availability of reliable and relevant data related to chemical exposures to the skin. Because historical emphasis has been placed on characterizing the health hazards of oral and inhalation exposures to chemicals, information on the effects of skin contact is often limited. This shortcoming has been addressed in part by providing approaches for route-to-route extrapolation when dermal toxicity data are lacking (and there is an indication of absorption). In addition, specific notations that communicate the availability of data or the status of an updated review have been developed in the NIOSH SK system. The availability of the new notations is a significant enhancement that can be used to spur new chemical-specific research.

An additional issue involves performance of the computer-based techniques, such as the SI ratio or QSAR outputs. The reliability and accuracy of such techniques remain questionable. For example, Bouwman et al. (2008) investigated the applicability of four QSAR models suitable for use in regulatory risk assessment to predict the dermal absorption of 62 chemicals. When the predictions of the evaluated QSAR models were compared to experimentally derived skin absorption data for test chemicals, three of the models were considered poor predictors, while the remaining QSAR model demonstrated a relatively consistent correlation. Bouwman et al. (2008) concluded that none of the publicly available QSAR models are suitable for risk assessment purposes in their current state. For this reason, NIOSH has decided that predictions from in silico models should not be used as the primary bases for the assignment of SK. Their inclusion in the SK strategy serves only as supportive data. As the in silico techniques become better validated, their direct use for assignment of skin notations may be considered.

Another limitation of the strategy and SK assignments is their restricted utility for assessment of complex exposures. The SK assignments under the NIOSH strategy (like the former notations) are based on data for neat chemicals (or defined mixtures with test data). They may not accurately reflect kinetic or toxic interactions related to chemical mixtures, differing but related product formulations (including dilutions), the health effects of contaminants within neat chemicals, or isomeric variations of a chemical. For example, the systemic toxicity potential of a chemical normally considered insignificant may be enhanced by an increase in permeation rate when the skin barrier integrity is weakened by another component in the mixture. Because of the complexity of assessing the health hazards of chemical interactions associated with complex mixtures or because of the presence of multiple isomers of a chemical and contaminants, the SK assignments apply strictly to specified chemicals, isomers, or major components of a mixture for which test data are available. However, to the degree the data allow, pertinent information on related chemical formulations or dilutions is noted in the documentation for each SK assignment. For example, application of the approach includes documenting the change in irritancy potential (SK: DIR) with changes in chemical concentration. As mixture exposure and risk assessment approaches continue to develop (USEPA, 2003), the possibility for enhancement of the current system to address chemical interactions may also become available.

Chemical exposures, especially in the workplace, frequently occur simultaneously via multiple pathways (e.g., skin, inhalation). When such situations occur, the total systemic dose may exceed the dose associated with an established OEL, which is intended to denote a "safe" or "acceptable" level. Characterizing the cumulative exposure and risk associated with chemicals is an important component of risk management and protecting workers' safety and health. To address this issue, additional focus is needed to further the advancement and application of risk assessment approaches that accounts for the body burden arising from multiple routes of exposure to a chemical (USEPA, 2003). The current work describes a significant enhancement to the hazard notation systems for alerting workers to the impacts of dermal contact with chemicals. A natural extension of this work is to begin to develop methods that move from hazard characterization for the dermal exposure to integrated dose–response assessments that support an aggregate (i.e., multiple exposure route) risk assessment (USEPA, 2003; NIOSH, 2009). Further development of an aggregate risk assessment approach will require research efforts such as the following: (1) studies aimed at improving the characterization (or better predicting) of the dermal uptake of a chemical and its subsequent contribution to total body burden (van de Sandt et al., 2007; Kissel, 2010), (2) development of sampling techniques, including biomonitoring, capable of accurately measuring workplace exposures to chemicals via skin contact (Fenske, 2005; Boogrard, 2008; Van Nimmen et al., 2010), and (3) establishment of dermal OELs, intended to serve a role equivalent to that of traditional, inhalation-based OELs (Bos et al., 1998; Brouwer et al., 1998; Drexler et al., 2002).

Table A1
Calculation of the SI Ratio for Acrylamide.

Variables used in calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path(K_{psc})	cm/h	0.00058
Permeation coefficient of the protein fraction of the stratum corneum (K_{pol})	cm/h	1.80171×10^{-5}
Permeation coefficient of the watery epidermal layer (K_{aq})	cm/h	0.29653
Molecular weight (MW)[a]	amu	71.08
Base-10 logarithm of its octanol–water partition coefficient (Log K_{ow})[a]	None	−0.67
Calculated skin permeation coefficient (K_p)	cm/h	0.00059
Skin dose		
Water solubility (S_w)[a]	mg/cm^3	390
Calculated skin permeation coefficient (K_p)	cm/h	0.00059
Estimated skin surface area (palms of hand)	cm^2	360
Exposure time	h	8
Calculated skin dose	mg	664.86
Inhalation dose		
Occupational exposure limit (OEL)[b]	mg/m^3	0.03
Inhalation volume	m^3	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	0.2
Skin dose-to-inhalation dose (SI) ratio	None	2954.93

[a] Variables identified from SRC (2009).
[b] The OEL used in calculation of the SI ratio was the NIOSH recommended exposure limit (REL) (NIOSH, 2005).

Conflict of interest statement and funding sources

The authors declare that there are no conflicts of interest. This project was funded by the National Institute for Occupational Safety and Health (NIOSH).

Acknowledgments and Disclaimer

The development of the NIOSH strategy for the assignment of hazard-specific SK was a rigorous process that involved numerous individuals that provided technical expertise in the fields of industrial hygiene, toxicology, risk assessment, and occupational medicine. A complete listing of these individuals is included in the Acknowledgment section of the NIOSH publication (2009). In addition, we would like to thank Cathy Rotunda, Ph.D., James Couch, M.Sc., Larry Lowry, Ph.D., and H. Frederick Frasch, Ph.D. for their roles in the completion of this manuscript.

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

Appendix A. Calculation of the SI ratio for acrylamide

This appendix presents a brief overview of the calculation of the SI ratio for acrylamide. An in-depth discussion on the rationale and calculation of the SI ratio can be located within the NIOSH strategy (NIOSH, 2009).

The first step in the evaluation is to determine the transdermal penetration rate (K_p) of the chemical (NIOSH, 2009). The K_p, which represents the overall diffusion of the chemical through the stratum corneum and into the blood capillaries of the dermis, is estimated from the chemical's molecular weight (MW) and base-10 logarithm of its octanol–water partition coefficient ($\log K_{OW}$). K_p is determined for a chemical by using Eq. (1). A self-consistent set of units must be used, such as centimeters per hour (cm/h), outlined in Table A1.

Calculation of skin permeation coefficient (K_p):

$$K_p = \frac{1}{\left[\left(\frac{1}{K_{psc}+K_{pol}}\right) + \left(\frac{1}{K_{aq}}\right)\right]} \quad (1)$$

K_{psc} is the permeation coefficient in the lipid fraction of the stratum corneum, K_{pol} is the coefficient in the protein fraction of the stratum corneum, and K_{aq} is the coefficient in the watery epidermal layer. These components are individually estimated by the following equations (Eqs. (2)–(4)):

Calculation of K_{aq}:

$$\log K_{psc} = -1.326 + 0.6097 \times \log K_{ow} - 0.1786 \times MW^{0.5} \quad (2)$$

Calculation of K_{pol}:

$$K_{pol} = 0.0001519 \times MW^{-0.5} \quad (3)$$

Calculation of K_{aq}:

$$K_{aq} = 2.5 \times MW^{-0.5} \quad (4)$$

The second step is to calculate the biologic mass uptake of the chemical from skin absorption (skin dose) and inhalation (inhalation dose) during the same period of exposure. The skin dose (in mg) is calculated using Eq. (5) and is a mathematical product of the K_p, the water solubility (S_W) of the chemical, the exposed skin surface area, and the duration of exposure. Assume that the skin exposure continues for 8 h to unprotected skin on the palms of both hands (a surface area of 360 cm^2).

Determination of skin dose:

$$\begin{aligned}\text{Skin dose} &= K_p \times S_w \times \text{Exposed skin surface area} \\ &\quad \times \text{Exposure time} \\ &= K_p(\text{cm/h}) \times S_w(\text{mg/cm}^3) \times 360\text{cm}^2 \times 8\text{h}\end{aligned} \quad (5)$$

The inhalation dose (in mg) is calculated using Eq. (6) and is derived on the basis of the occupational exposure limit (OEL) of the chemical, if the OEL is developed to prevent the occurrence of systemic effects rather than sensory/irritant effects or direct effects on the respiratory tract. Assume a continuous exposure of 8 h, an inhalation volume of 10 m^3 inhaled air in 8 h, and a factor of 75% for retention of the airborne chemical in the lungs during respiration (retention factor, or RF).

Determination of inhalation dose:

$$\begin{aligned}\text{Inhalation dose} &= \text{OEL} \times \text{Inhalation volume} \times \text{RF} \\ &= \text{OEL}(\text{mg/m}^3) \times 10\text{m}^3 \times 0.75\end{aligned} \quad (6)$$

The final step is to compare the calculated skin and inhalation doses and to present the result as a ratio of skin dose to inhalation dose (the SI ratio). This ratio quantitatively indicates (1) the significance of dermal absorption as a route of occupational exposure to the chemical and (2) the contribution of dermal uptake to systemic toxicity. If a chemical has an SI ratio greater than or equal to 0.1, it is considered to be a skin absorption hazard.

Table A1 summaries the data applied in the previous equations to determine the SI ratio for acrylamide. The calculated SI ratio is 2955. On the basis of these results, acrylamide is predicted to represent a skin absorption hazard.

References

ACGIH, 2009. Introduction to the Chemical Substances—Definitions and notations. In: Documentation of the TLVs and BEIs with other worldwide occupational exposure values, CD-ROM version. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

Adler, I.D., Gonda, H., Hrabe de Angelis, M., Jentsch, I., Otten, I.S., Speicher, M.R., 2004. Heritable translocations induced by dermal exposure of male mice to acrylamide. Cytogenet. Genome Res. 104 (1–4), 271–276.

Allan, S., 1995. CT-566-94 Acrylamide skin sensitisation in the guinea pig. Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England. Report No. CTI 2/940899/55.

American Cyanamid Company, 1952. Preliminary patch tests with acrylamide in 25 persons. American Cyanamid Company, Toxicology and Product Safety Department, Pittsburgh, PA. TSCA Section 8(d) Health and Safety Study Admission. USEPA, OPPT, TSCATS. NTIS Report No. OTS-0206055. Doc#: 878211663. Available upon request via <oppt.ncic@epa.gov>.

American Cyanamid Company, 1973. Range finding studies: single oral, single dermal (FHSA), single inhalation. TSCA Section 8(d) Health and Safety Study Admission. USEPA, OPPT, TSCATS. Doc#: 878211677. Available upon request via <oppt.ncic@epa.gov>.

Bachmann, M., Myers, J.E., Bezuuidenhout, B.N., 1992. Acrylamide monomer and peripheral neuropathy in chemical workers. Am. J. Ind. Med. 21, 217–222.

Beck, L.A., Leung, D.Y.M., 2000. Allergen sensitization through the skin induces systemic allergic responses. J. Allergy Clin. Immunol. 106, S258–S263.

Bello, D., Herrick, C.A., Smith, T.J., Woskie, S.R., Streicher, R.P., Cullen, M.R., Liu, Y., Redlich, C.A., 2007. Skin exposures to isocyanates: reasons for concerns. Environ. Health Perspect. 115, 328–335.

Boogrard, P.J., 2008. Biomonitoring as a tool in the human health risk characterization of skin exposure. Hum. Exp. Toxicol. 27, 297–305.

Bos, P.M., Brouwer, D.H., Stevenson, H., Boogaard, P.J., de Kort, W.L., van Hemmen, J.J., 1998. Proposal for the assessment of quantitative skin exposure limits in occupational environments. Part I. Development of a concept for the derivation of a quantitative skin occupational exposure limit. Occup. Environ. Med. 55, 795–804.

Bouwman, T., Cronin, M.T., Bessems, J.G.M., van de Sandt, J.J., 2008. Improving the applicability of (Q)SARs for percutaneous penetration in regulatory risk assessment. Hum. Exp. Toxicol. 27, 269–276.

Brouwer, D.H., Hoogendoorn, L., Bos, P.M., Boogaard, P.J., van Hemmen, J.J., 1998. Proposal for the assessment of quantitative skin exposure limits in occupational environments. Part II. Feasibility study for application in an exposure scenario for MDA. Occup. Environ. Med. 55, 805–811.

Bull, R.J., Robinson, M., Laurie, R.D., Stoner, G.D., Greisiger, E., Meier, J.R., Stober, J., 1984. Carcinogenic effects of acrylamide in Sencar and A/J mice. Cancer Res. 44 (1), 107–111.

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

Chen, C.P., Ahlers, H.W., Dotson, G.S., Lin, Y.C., Chang, W.C., Maier, A., Gadagbui, B., 2011. Efficacy of predictive modeling as a scientific criterion in dermal hazard identification for assignment of skin notations. Reg Toxicol Pharmacol.

Czerczak, S., Kupczewska, M., 2002. Assignment of skin notation for Maximum Allowable Concentration (MAC) list in Poland. Appl. Occup. Environ. Hyg. 17, 187–199.

Day, G.A., Stefaniak, A.B., Weston, A., Tinkle, S., 2006. Beryllium exposure: dermal and immunological considerations. Int. Arch. Occup. Environ. Health. 79, 161–164.

Dow Chemical USA, 1975. Acute toxicological properties and industrial handling hazards of a 50% aqueous solution of acrylamide. Dow Chemical Company, Midland, MI. On file with the U.S. Environmental Protection Agency under TSCA Section 8D. OTS #0206684. Document #878214838.

Drees, D.T., Crago, F.L., Hopper, C.R., Smith, J.M., 1976. Subchronic percutaneous toxicity of acrylamide and methacrylamide in the newborn rabbit. Toxicol. Appl. Pharmacol. 37, 190.

Drexler, H., Goen, T., Schaller, K.H., 2002. Biological tolerance values: change in a paradigm concept from assessment of a single value to use of an average. Int. Arch. Occup. Environ. Health. 82, 139–142.

Eastman Kodak Company, 1978. Toxicity and health hazard summary. TSCA Section 8(d) Health and Safety Study Admission. USEPA, OPPT, TSCATS. NTIS Report No. OTS #0206536. Document #878214376. Available upon request via <oppt.ncic@epa.gov>.

ECB, 2002. European Chemicals Bureau, Institute for Health and Consumer Protection, European Commission Joint Research Centre. European Union risk assessment report: acrylamide. Vol. 24. Office for Official Publications of the European Communities, Luxembourg. <http://ecb.jrc.it/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/REPORT/acrylamidereport011.pdf>.

ECB, 2011. European Chemicals Bureau, Institute for Health and Consumer Protection, European Commission Joint Research Centre. European INventory of Existing Commercial chemical Substances (EINECS): Acrylamide. <http://ecb.jrc.ec.europa.eu/esis/>.

ECETOC, 1998. European Centre for Ecotoxicology and Toxicology of Chemicals. Special Report No. 15: Examination of a proposed skin notation strategy. Brussels, Belgium.

European Parliament, Council of the European Union, 2008. Regulation (EC) No. 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labeling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No. 1907/2006. OJEU, Off. J. Eur. Union L353:1–1355 <http://ur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:353:0001:1355:EN:PDF>.

Fennell, T.R., Sumner, S.C.J., Snyder, R.W., Burgess, J., Friedman, M.A., 2006. Kinetics of elimination of urinary metabolites of acrylamide in humans. Toxicol. Sci. 93, 256–267.

Fenske, R.A., 2005. State-of-the-art measurement of agricultural pesticide exposures. Scand. J. Work Environ. Health 31 (Suppl. 1), 67–73.

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

Gutierrez-Espeleta, G.A., Hughes, L.A., Piegorsch, W., Shelby, M.D., Generoso, W.M., 1992. Acrylamide: dermal exposure produces genetic damage in male mouse germ cells. Fund Appl. Toxicol. 18, 189–192.

He, F., Zhang, S., Wang, H., Li, G., Zhang, Z.M., Li, F.L., Dong, X.M., Hu, F.R., 1989. Neurological and electroneuromyographic assessment of the adverse effects of acrylamide on occupationally exposed workers. Scand J. Work Environ. Health 15, 125–129.

ICCVAM, 2009. Interagency Coordinating Committee on the Validation of Alternative Methods. Recommended performance standards: murine local lymph node assay. National Toxicology Program, Interagency Center for the Evaluation of Alternative Toxicology Methods. NIH Publication No. 09-7357. <http://iccvam.niehs.nih.gov/docs/immunotox_docs/llna-ps/LLNAPerfStds.pdf>.

Johanson, G., Rauma, M., 2008. Basis for skin notation. Part 1. Skin penetration data for substances on the Swedish OEL list. Aarbete Och Hälsa (Work and Health) series. Occupational and Environmental Medicine, Sahlgrenska Academy, Göteborg University, Sweden. <http://gupea.ub.gu.se/dspace/bitstream/2077/9876/1/ah2008_2.pdf>.

Kimber, I., 1996. The role of the skin in the development of chemical respiratory hypersensitivity. Toxicol. Lett. 889, 92.

Kissel, J.C., 2010. The mismeasure of dermal absorption. J. Expo. Sci. Environ. Epidemiol. 28, 1–8.

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

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

McCollister, D., Oyen, F., Rowe, V., 1964. Toxicology of acrylamide. Toxicol. Appl. Pharmacol. 6, 172–181.

Mukhtar, H., Dixit, R., Seth, P., 1981. Reduction in cutaneous and hepatic glutathione contents, glutathione-S-transferases and aryl hydrocarbon hydroxylase activities following topical application of acrylamide to mouse. Toxicol. Lett. 9, 153–156.

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

NIOSH, 1991. NIOH and NIOSH basis for an occupational health standard. Acrylamide: a review of the literature. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Cincinnati, Ohio. DHHS (NIOSH) Publication No. 91-115. <http://www.cdc.gov/niosh/91-115.html>.

NIOSH, 2005. NIOSH pocket guide to chemical hazards. DHHS, CDC, NIOSH, Cincinnati, Ohio. DHHS (NIOSH) Publication No. 2005-149. <http://www.cdc.gov/niosh/npg/default.html>.

NIOSH, 2009. Current intelligence bulletin 61: a strategy for assigning new NIOSH skin notations. DHHS, CDC, NIOSH, Cincinnati, Ohio. DHHS (NIOSH) Publication No. 2009-147. <http://www.cdc.gov/niosh/docs/2009-147/>.

NIOSH, 2011. Skin notation profile: Acrylamide. DHHS, CDC, NIOSH, Cincinnati, Ohio. DHHS (NIOSH) Publication No. 2011-139. <http://www.cdc.gov/niosh/docs/2011-139/pdfs/2011-139.pdf>.

Novikova, E.E., 1979. Toxic effect of acrylamide after entering through the skin. Gig Sanit 10, 73–74.

OECD (Council of the European Communities), 1992. Council Directive 92/32/EEC of 30 April 1992 amending for the seventh time Directive 67/548/EEC on the approximation of the laws, regulations, and administrative provisions relating to the classification, packaging, and labeling of dangerous substances. Off. J. Euro. Commun. L 154 (5.6.92).

OSHA, 2007. Occupational Safety and Health Administration hazard information bulletin: acrylamide exposure during chemical grouting operations. US Department of Labor, OSHA, Washington, DC. <http://www.osha.gov/dts/hib/hib_data/hib19900727.html>.

Pauluhn, J., 2008. Brown Norway rat asthma model of diphenylmethane-4,4′-diisocyanate (MDI): analysis of the elicitation dose-response relationship. Toxicol. Sci. 104 (2), 320–331.

Redlich, C.A., Herrick, C.A., 2008. Lung/skin connections in occupational lung disease. Curr. Opin. Allergy Clin. Immunol. 8, 115–119.

Sartorelli, P., 2002. Skin exposure assessment in occupational medicine. Occup. Med. (Oxf) 53, 151–156.

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

Sartorelli, P., Ahlers, H.W., Cherrie, J.W., Kezic, S., Johanson, G., Filon, F.L., Nielsen, J.B., Shepherd, A., Stull, J., Williams, F., 2010. The 2008 ICOH Workshop on skin notations. Med. Lav. 101, 3–8.

Sithamparanadarajah, R., 2008. Diseases Caused by Dermal Exposures to Chemicals. In: Evans, P.G. (Ed.), Controlling Skin Exposure to Chemicals and Wet-Work: A Practical Book. RMS Publishing, Stourbridge, U.K., pp. 15–24 (Chapter 3).

SRC, 2009. Syracuse Research Corporation, Interactive PhysProp database demo. <http://www.srcinc.com/what-we-do/databaseforms.aspx?id=386>.

Sumner, S., Williams, C., Snyder, R., Krol, W., Asgharian, B., Fennell, T., 2003. Acrylamide: a comparison of metabolism and hemoglobin adducts in rodents following dermal, intraperitoneal, oral, or inhalation exposure. Toxicol. Sci. 75, 260–270.

UNECE, 2007. Globally harmonized system of classification and labeling of chemicals (GHS). 2nd revised edition. United Nations Economic Commission for Europe, Geneva, Switzerland. <http://www.unece.org/trans/danger/publi/ghs/ghs_rev02/02files_e.html>.

USEPA, 2003. Framework for Cumulative Risk Assessment. Document# EPA/630/P-02/001F. Risk Assessment Forum, United States Environmental Protection Agency, Washington, D.C.

van de Sandt, J.J., Dellarco, M., Van Hemmen, J.J., 2007. From dermal exposure to internal dose. J. Expo. Sci. Environ. Epidemiol. 17 (Suppl. 1), S38–47.

Van Nimmen, N.F., Poels, K.L., Severi, M.J., Godderis, L., Veulemans, H.A., 2010. Selecting an appropriate biomonitoring strategy to evaluate dermal exposure to opioid narcotic analgesics in pharmaceutical production workers. Occup. Environ. Med. 67, 464–470.

WHO, 2006. Environmental Health Criteria 235: Dermal absorption. World Health Organization, Geneva, Switzerland. <http://www.inchem.org/documents/ehc/ehc/ehc235.pdf>.