Current Intelligence Bulletin (CIB): A Strategy for Assigning the New NIOSH Skin Notations for Chemicals

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Foreword

Workplace skin diseases are one of the leading causes of occupational diseases and affect workers in every industrial sector within the United States. The most common form of workplace skin diseases is contact dermatitis, an inflammation of the skin associated with exposure to an irritant, allergen or other hazardous agent. Despite the relatively high incidence of dermatitis and other workplace skin diseases, the impact and risk of dermal contact with chemicals and other hazardous agents are not well understood hampering the recognition and prevention of these disorders.

The National Institute for Occupational Safety and Health (NIOSH) has estimated that workplace skin diseases account for 15% to 20% of all reported occupational diseases in the United States, with estimated total annual costs (including lost workdays and lost productivity) up to $1 billion. Dermal exposures to chemicals can cause a wide array of injuries and illness including contact dermatitis, immunological responses, and irreversible damage to the skin. Additionally, skin contact represents a significant route of exposure for chemicals that have the potential to be dermally absorbed and subsequently cause systemic effects including, but not limited to, acute toxicity, cancers, neurotoxicity and reproductive effects.

NIOSH has long recognized the hazards of dermal contact with chemicals in the workplace as well as the importance of quality research and policies to prevent

such exposures. In 1999, NIOSH launched an Interdisciplinary Cross-Sectional Research Program as part of the National Occupational Research Agenda (NORA). This Dermal Exposure Research Program (DERP) was to promote the identification and control of dermal exposures to hazardous agents and conditions in the workplace. The focus of DERP was to expand the current knowledge base through laboratory and field research and to apply scientific decision-making processes for policy development. NIOSH has entered the second decade of NORA and continues to investigate methods for protecting workers from hazardous dermal exposures and for reducing the prevalence of occupational skin diseases through the NIOSH Immunological and Dermal Cross-Sector Program.

NIOSH skin notations are hazard warnings used worldwide to alert workers and employers to the health risks of dermal exposures to chemicals in the workplace. This Current Intelligence Bulletin (CIB) provides the rationale for assigning new NIOSH skin notations. The new system reflects the current state of scientific knowledge and involves critical evaluation of scientific data so that scientists can assign multiple skin notations that distinguish between the systemic, direct, and sensitizing effects of dermal exposures to chemicals. This new strategy is a form of hazard identification that advances our understanding of the risks posed by dermal exposures to chemicals. Such improved understanding will enable us to implement better risk management practices and controls for the prevention of workplace skin diseases.

Draft Document (D26) - Current Intelligence Bulletin (CIB): A Strategy for Assigning the New NIOSH Skin Notations for Chemicals

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Executive Summary

For 20 years, the occupational safety and health community has relied on skin notations from the National Institute for Occupational Safety and Health (NIOSH) to warn workers about the health risks of dermal exposures to chemicals. These notations have proved to be useful risk management tools for occupational health professionals concerned about protecting workers from injuries and illnesses caused by skin contact with chemicals. However, according to the current definition, a NIOSH skin notation may be assigned to a chemical only if that substance has been scientifically determined to be dermally absorbed. The currently widespread practice of using a skin notation to indicate that a substance poses other health effects from dermal exposure is inaccurate and misleading.

• Difficulties with Assigning Current NIOSH Skin Notations

NIOSH adopted the skin notation for 142 chemicals as part of its 1988 testimony to the Occupational Safety and Health Administration's (OSHA) proposed rule on Air Contaminants [Permissible Exposure Limit (PEL) update]. The skin notations for these chemicals are listed in the NIOSH *Pocket Guide to Chemical Hazards* by the symbol [skin]. Despite the usefulness of the skin notations as a risk management tool, NIOSH has identified several conceptual difficulties with the ways in which skin notations have been assigned:

1. The current NIOSH system relies on a single skin notation that is intended to warn against the potential for a chemical to be dermally absorbed and contribute substantially to systemic toxicity. This skin notation is not intended to be applied to chemicals that would cause direct effects to the skin or to chemicals that have the potential to act as a sensitizer.
2. The NIOSH skin notation has not been assigned on the basis of a standardized methodology. As a result, chemicals have been improperly assigned a skin notation as a warning for nonsystemic effects, such as corrosion, and thereby causing confusion about what types of risk management practices should be undertaken to prevent dermal exposure.
3. The NIOSH skin notation does not reflect the contemporary state of scientific knowledge or recommendations made in NIOSH criteria documents.

• New Strategy for Assigning NIOSH Skin Notations

This document, *Current Intelligence Bulletin (CIB): A Strategy for Assigning the New NIOSH Skin Notations for Chemicals*, provides a new strategy for assigning skin notations. The strategic framework outlined within this document is a form of hazard identification that has been designed to 1) to ensure that the assigned skin notations reflect the contemporary state of scientific knowledge, 2) to provide transparency behind the assignment process, 3) to communicate the hazards of dermal chemical exposures, and 4) to meet the needs of health professionals, employers and other interested parties in protecting workers from chemical contact with the skin. This strategy involves the assignment of multiple

skin notations for distinguishing systemic (SYS), direct (DIR), and sensitizing (SEN) effects caused by exposure of skin (SK) to chemicals. Chemicals which are identified to be potentially lethal following acute dermal exposures are designated with the systemic subnotation (FATAL). Potential irritants and corrosive chemicals are indicated by the direct effects subnotations (IRR) and (COR), respectively. Thus with the new strategy, chemicals labeled as SK: SYS are recognized to contribute to systemic toxicity through dermal absorption. Chemicals assigned the notation SK: SYS (FATAL) have been identified as highly or extremely toxic and have the potential to be lethal following acute contact of the skin. Substances identified to cause direct effects to the skin are labeled SK: DIR and those resulting in dermal irritation and corrosion at the site of contact are labeled as SK: DIR (IRR) and SK: DIR (COR), respectively. The SK: SEN notation is used for substances identified as causing allergic contact dermatitis (ACD) or other allergic effects. Candidate chemicals may be assigned more than one skin notation when they are identified to cause multiple effects resulting from dermal exposure. For example, if a chemical is identified as corrosive and also contributes to systemic toxicity, it will be labeled as SK: SYS-DIR (COR). When review of the scientific data for a chemical indicate that dermal exposure does not produce systemic, direct, or sensitizing effects, the compound will be assigned the notation (~~SK~~).

The new skin notation strategy is a form of health hazard identification that standardizes the method for deriving skin notations. Assignment of the new

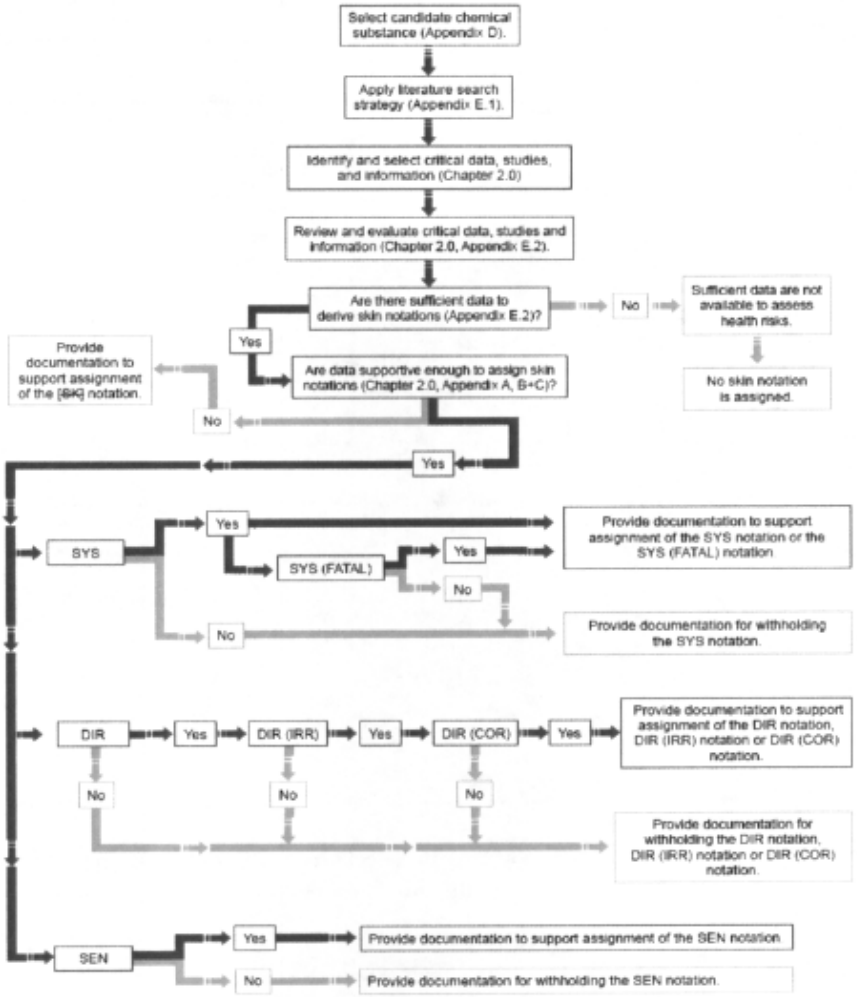
NIOSH skin notations relies on a critical assessment of data on the physiochemical properties of chemicals as well as reports of human exposures and health effects, empirical data from *in vivo* and *in vitro* laboratory testing, and considerations provided by predictive algorithms and mathematical models. A weight-of-evidence approach is applied in evaluating the quality and constituency of the scientific data when conflicting findings are reported. Figure 1 illustrates an overview of the process used to assign skin notations.

The new strategy for assigning the NIOSH skin notations was designed to preserve the conventional wisdom about them and also to address the issues associated with their historic misuse— including their assignment to nonsystemic effects. This system provides a framework for assigning multiple skin notations which incorporates the current scientific database on workplace chemicals and dermal toxicity to warn users about the direct, systemic, and sensitizing effects of exposures of the skin to chemicals. The labeling of a chemical with a hazard-specific skin notation (and in some cases multiple notations) will greatly enhance the quality of dermal hazard communication and the associated risk management process. The new strategy will be periodically updated as more information about the mechanisms of toxicity becomes available.

A support document called a Skin Notation Profile will be developed for each chemical evaluated via the strategic framework and scientific rationale presented within this CIB. The Skin Notation Profile will summarize all relevant data used to

aid in determining the hazards associated with dermal exposures to the evaluated chemical.

Figure 1: Decision tree for assigning the new NIOSH skin notations



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Abbreviations

ACD	Allergic Contact Dermatitis
BgVV	German Federal Institute for Health Protection of Consumers and Veterinary Medicine
CFR	Code of Federal Regulations
CIB	Current Intelligence Bulletin
cm	centimeter(s)
cm^2	square centimeters
cm/hr	centimeter(s) per hour
(COR)	Subcategory of SK: DIR indicating the potential for a chemical to be corrosive following dermal exposure
DEREK™	Deductive Estimation of Risk from Existing Knowledge
DERP	Dermal Exposure Research Program
DNA	deoxyribonucleic acid
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECVAM	European Centre for the Validation of Alternative Methods
EU	European Union
(FATAL)	Subcategory of SK: SYS indicating chemicals are highly or extremely toxic and may be potentially lethal or life threatening following acute dermal exposures
g	gram(s)
g/kg	grams per kilograms of animal body weight
GHS	Globally Harmonized System of Classification and Labeling of Chemicals
GPMT	guinea pig maximization test
hr	hour(s)

ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
ICSC	International Chemical Safety Cards
(IRR)	Subcategory of SK: DIR indicating the potential for a chemical to be a dermal irritant
K_{aq}	Coefficient in the watery epidermal layer
kg	kilogram(s)
K_{OW}	Octanol-water partition coefficient
K_p	Skin permeation coefficient
K_{pol}	Coefficient in the protein fraction of stratum corneum
K_{psc}	Permeation coefficient in the lipid fraction of stratum corneum
LD_{50}	Lethal dose 50% by dermal, oral, and intradermal routes
LLNA	Local Lymph Node Assay
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
m	meter(s)
m^3	cubic meter(s)
MEST	Mouse Ear Swelling Test
mg/kg-day	milligrams/kilograms animal body weight as a daily dose
mg/m^3	milligrams per cubic meter of air
min	minute(s)
MW	molecular weight
NICEATM	NTP Interagency Center for the Evaluation of Alternative Toxicological Methods

NIOSH	National Institute for Occupational Safety and Health
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
NTP	National Toxicology Program
OECD	Organization for Economic Cooperation and Development
OEL	Occupational Exposure Limit
OSHA	Occupational Safety and Health Administration
PEL	Permissible Exposure Limit
QSARs	Quantitative structure-activity relationships
QSPRs	Quantitative structure-permeability relationships
REACH	Registration, Evaluation, Authorization and Restriction of Chemicals
REL	Recommended Exposure Limit
RF	Retention factor
RTECS	Registry of Toxic Effects of Chemical Substances
R-Phrases	Risk phrases
SAR	Structure-activity relationships
SI Ratio	Ratio of the skin dose to the inhalation dose
SK	Skin notation
~~SK~~	Skin notation indicating that the reviewed data did not identify a health risk associated with dermal exposure
SK: DIR	Skin notation indicating the potential for direct effects to the skin
SK: SEN	Skin notation indicating the potential for sensitization of skin
SK: SYS	Skin notation indicating the potential for systemic toxicity
S_W	water solubility

TER	Transcutaneous Electrical Resistance assay
TEWL	Trans-epidermal water loss from the stratum corneum
US EPA	United States Environmental Protection Agency

Glossary

Contaminant: A chemical 1) that is unintentionally present within a neat substance or mixture in concentrations less than 1.0% (<1.0%), or 2) a chemical that is recognized as a potential carcinogen present within a neat substance or mixture in concentrations less than 0.1% (<0.1%).

Dermal absorption: The transport of a chemical from the outer surface of the skin both into the skin and into systemic circulation (including penetration, permeation and resorption).

Direct effects: Localized adverse health effects of the skin, including corrosion, primary irritation, changes in skin pigmentation including bleaching (blanching) and staining, and reduction/disruption of the dermal barrier integrity, following dermal exposure to chemicals.

Isomers: Molecules that exhibit unique physical structures, but consist of the same elemental composition and weight that may result in significant difference in toxic potency.

Photocarcinogenesis: The elicitation or increase of a carcinogenic response after dermal exposure to a photo reactive chemical and subsequent exposure to sunlight.

Photosensitization: The elicitation or increase of an immunological response after dermal exposure to a photo reactive chemical and subsequent exposure to sunlight.

Phototoxicity: The elicitation or increase of a toxic response after dermal exposure to a photo reactive chemical and subsequent exposure to sunlight.

Sensitizing effects: Sensitization of the skin, mucous membranes, or airways, including allergic contact dermatitis (ACD), following dermal exposure to chemicals.

Systemic effects: Systemic toxicity associated with dermal absorption of chemicals after exposure of the skin.

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1.0 Introduction

The National Institute for Occupational Safety and Health (NIOSH) currently uses [skin] as the skin notation on 142 chemicals listed in the NIOSH *Pocket Guide to Chemical Hazards* [NIOSH 2005]. These skin notations were adopted by NIOSH in their testimony on the Occupational Safety and Health Administration (OSHA) Proposed Rule on Air Contaminants on August 1, 1988 [NIOSH 1988]. The use of that skin notation for these chemicals was to indicate the potential for dermal absorption. However, the notation [skin] provides little guidance about a chemical other than a warning about its possible absorption through the skin.

Several inconsistencies and limitations have been identified in how skin notations have been assigned. These inconsistencies include the following:

1. *The skin notation is based in theory on the potential contribution a chemical makes to systemic toxicity when it is absorbed by the skin [54 Fed. Reg. 2718 (1989)].* However, the notation has not been consistently assigned according to this principle. Many skin notations are based only on the potential or reported transdermal penetration of chemicals—with no consideration of the causality between dermal absorption and overall toxicity.
2. *Use of a single skin notation to warn of systemic toxicity often resulted in the use of that warning for other serious dermal effects such as irritation, corrosion and sensitization.* According to its current definition, a skin

notation is assigned to a chemical only when the substance has been scientifically established to be dermally absorbed and potentially contribute to systemic toxicity. Use of the notation [skin] as an indicator for other health effects from dermal exposure is inappropriate and misleading.

3. *Skin notations assigned after the 1988 PEL update project do not include the skin exposure precautions made in NIOSH criteria documents.* For example, the criteria document for ethylene glycol monomethyl ether, ethylene glycol monoethyl ether and their acetates, recommends that dermal exposures with these chemicals should be avoided due to their ability to be readily absorbed by the skin [NIOSH 1991]. However, none of these chemicals has been assigned a skin notation.

2.0 Assigning Skin Notations

The *Current Intelligence Bulletin (CIB): A Strategy for Assigning the New NIOSH Skin Notations for Chemicals* provides an updated and formalized strategy for the assignment of skin notations capable of distinguishing between systemic, direct and sensitizing effects caused by dermal chemical exposures. The strategic framework outlined within this document is a form of hazard identification that has been designed to 1) to ensure that the assigned skin notations reflect the contemporary state of scientific knowledge, 2) to provide transparency behind the assignment process, 3) to communicate the hazards of dermal chemical exposures, and 4) to meet the needs of health professionals, employers and other interested parties in protecting workers from chemical contact with the skin. The system preserves the conventional wisdom for assigning skin notations to chemicals that pose a risk from dermal contact. In addition, this system attempts to prevent possible misclassifications by assigning a notation that specifies potential adverse effects. The skin notation classification scheme presented within this CIB is as follows:

- **SYS** Indicates the potential for a chemical to contribute substantially to systemic toxicity through dermal absorption.
    - **(FATAL)** A subcategory of SYS assigned when a chemical is identified as highly or extremely toxic and may be potentially lethal or life threatening following acute dermal exposures

- **DIR** Indicates direct effect(s) of a chemical on the skin, including corrosion, primary irritation, bleaching (blanching), staining, and reduction/disruption of the dermal barrier integrity.
    - **(IRR)** A subcategory of SK: DIR assigned when a chemical is identified as a dermal irritant.
    - **(COR)** A subcategory of DIR assigned when a chemical is identified as a corrosive.
- **SEN** Indicates that dermal exposure to a chemical may cause allergic contact dermatitis (ACD) or sensitization of skin, mucous membranes, or airways.
- ~~**SK**~~ Indicates that sufficient data were identified and evaluated for a chemical that did not identify a health risk associated with dermal exposure and did not support assignment of the SYS, DIR, or SEN notation.

The new system also permits the assignment of several skin notations for a chemical when multiple skin hazards exist. For example, if the health data indicate that the chemical causes systemic toxicity when dermally absorbed and is also corrosive to the skin, the notation assigned to the chemical would be SK: SYS-DIR (COR). Additional skin notations may be added as the scientific data, test methods, and understanding about the toxicological mechanisms of skin injuries improve. Also, current criteria for assigning skin notations may be revised to enhance the usefulness of the notations for selecting exposure prevention strategies. Hazard categories that are added later may follow the current

scheme, which makes skin corrosives a subcategory under the DIR notation and acute lethality a subcategory under the SYS notation.

It should be noted that the strategy and skin notations outlined in this CIB are not intended to provide a risk-based exposure value for dermal exposures to chemicals, and should not be used to infer toxic potency for evaluated chemicals. Other issues associated with the skin notations include their application to chemical mixtures, the health effects of contaminants within neat substances and isomeric variations of a chemical. Due to the complexity of assessing the hazards of chemical interactions associated with complex mixtures or due to the presence of contaminants, the skin notations are intended to apply to neat compounds and may not be health protective against additional effects associated with complex mixtures (See Appendix G.1). Also, assigned skin notations are applicable only to the specified forms of an evaluated compound and may not provide adequate warnings about unique hazards of the non-specified isomeric forms of the chemical (See Appendix G.1).

• 2.1 Criteria for Assigning Skin Notations

The critical step in assigning skin notations to a chemical is determining its "hazard potential"—that is, it's potential for causing adverse health effects as a result of skin exposure. This determination involves a health hazard identification process that assesses the following: (1) scientific data on the physiochemical properties of a chemical, (2) human exposures and health

effects, (3) empirical data from *in vivo* and *in vitro* laboratory testing, and (4) the use of predictive algorithms such as quantitative structure-activity relationships (QSARs) and mathematical models that describe a selected process (e.g., skin permeation) using analytical or numerical methods. A weight-of-evidence approach is applied when available data are inconsistent. Figure 2 illustrates the hierarchy of scientific data used for assigning skin notations.

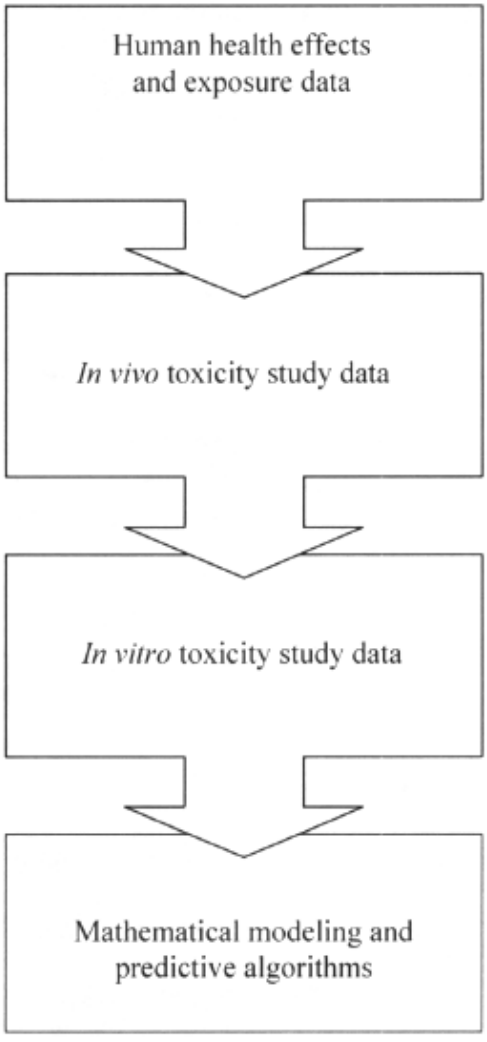

Figure 2: Hierarchy of evaluated scientific data

The following sections discuss the skin notation assignments in each category. Exceptions to this approach are also described. This strategy for assigning skin notations has been developed to correspond with the classification strategy adopted in the *Globally Harmonized System of Classification and Labeling of Chemicals* (GHS) developed by the United Nations [UNECE 2005].

• 2.2 SYS

The SYS notation is assigned to chemicals that are absorbed through the skin and contribute to systemic toxicity. Chemicals that are identified as highly or extremely toxic and may be potentially lethal or life threatening following acute dermal exposures would also receive the subnotation (FATAL) [i.e., SK: SYS (FATAL)]. The following are examples of adverse systemic effects that have been associated with dermal exposures to chemicals through the use of human and animal data that require the assignment of the SYS notation or its subnotation (FATAL):

- Cardiotoxicity
- Carcinogenesis and photocarcinogenesis (excluding cancers of the skin)
- Hematotoxicity
- Hepatotoxicity
- Histopathological changes
- Immunotoxicity
- Lethality
- Neurotoxicity

- Nephrotoxicity
- Reproductive and developmental effects

Standardized and widely accepted research protocols exist for using animals to test the systemic toxicity of skin exposures to chemicals. The following are examples of such standardized protocols:

- Protocols for testing chemicals developed by the Organization for Economic Cooperation and Development (OECD) and Registration, Evaluation, Authorization and Restriction of Chemical (REACH)
- Health effects testing guidelines developed by the U.S. Environmental Protection Agency (US EPA) Office of Prevention, Pesticides and Toxic Substances
- Protocols established by the National Toxicology Program (NTP) for determining the pre-chronic toxicity and chronic toxicity/carcinogenesis of toxic substances

Results from dermal studies using these protocols frequently report quantitative data that can be used in assigning skin notations.

The SYS notation is assigned to a chemical when one or more of the following criteria are met:

A Credible evidence indicates that systemic effects in workers result from dermal exposure to a chemical in the absence of significant inhalation or oral exposures.

B Data from experimental animal studies indicate the following:

- Systemic effects occurred from dermal exposures.
- Fatalities or health effects in exposed animals were not associated with skin damage by the chemical or the vehicle containing the chemical.
- Dermal exposure results for animals included data on acute toxicity, repeated-dose toxicity, subchronic toxicity, chronic toxicity, carcinogenicity, or biological system/function-specific effects.

Appendix A describes the study protocols used and the criteria selected for assigning the SYS notation and its subcategory.

C Studies of scientific merit followed protocols other than those in Criteria A and B and demonstrated systemic effects from dermal exposure to a chemical. The protocols other than those in Criteria A and B may be modifications of the standardized protocols (e.g., the research protocols introduced in Appendix A) with variations in the evaluation procedures; or may be designs that examine health endpoints other than those evaluated by the standardized protocols. Examples of the latter studies include the following:

- Investigation of the relevant toxicokinetics and potential toxic effects of metabolic transformation(s) of chemicals following skin absorption

- Examination of the adverse effects of chemical mixtures whose skin absorption or potential systemic toxicity is different from the level anticipated for individual components of the mixture because of synergistic effects
- Investigation of altered skin permeability characteristics of toxic components resulting from the presence of a solvent or vehicle in a chemical preparation.

D If no acceptable-quality empirical data exist for systemic effects from dermal exposure to a chemical, systemic toxicity data may be extrapolated from toxicity data associated with other routes of exposure (such as oral and inhalation) when

—quality dermal kinetics data demonstrate the ability of a chemical to be absorbed by the skin, and

—a direct link can be determined between the health effects caused by the alternative routes of exposure and dermal exposures.

Both conditions must be satisfied to assign a SYS notation.

E When no acceptable-quality empirical data exist on the systemic effects of dermal exposure, the potential for dermal absorption and consequent systemic toxicity of the chemical may be mathematically estimated. To mathematically determine the risk for systemic toxicity (e.g., predictive algorithm), the following information is needed: (1) the skin permeation rate, (2) the chemical dose calculated to be absorbed through skin (skin dose), (3) a reference dose representing the threshold of acceptable body

accumulation (a chemical dose to be absorbed via inhalation during the same period of exposure), and (4) a comparison of the skin dose to the reference dose (which indicates the significance of skin absorption and its potential contribution to systemic toxicity).

Appendix B presents an algorithm that can be used for determining the potential for systemic toxicity. When the predictive algorithm is used as the basis for identification, a positive result indicates that a chemical is capable of producing systemic toxicity from dermal exposure and should be assigned the SYS notation. If the predictive algorithm indicates no potential for systemic toxicity from dermal absorption, the chemical should be further evaluated with accepted tests.

Table 2.2 provides a paradigm for the assignment of the SYS notation based on the criteria outlined within this section, in addition to Appendixes A and B. Variables considered for the assignment of the SYS notation within this model include 1) systemic toxicity associated with dermal exposures of the skin and 2) dermal absorption. Table 2.2 illustrates when the assignment of the SYS notation is appropriate based on the results of the critical review of all relevant scientific data.

Table 2.2 Paradigm for the assignment of the SYS notation

		Systemic Toxicity		
		Yes	**No**	**No Data**
Dermal Absorption	**Yes**	SYS[†]	~~SYS~~[‡]	SYS[¥]
	No	SYS	~~SYS~~	~~SYS~~
	No Data	SYS	~~SYS~~	No assignment[±]

[†] SYS indicates categories where the SYS notation would be assigned; [‡] SYS indicates categories where the SYS notation would not be assigned; [¥] Assignment of the SYS notation for this category is based on the criteria outlined in Section A.1.8; [±] No assignment indicates that insufficient data were identified to accurately assess the systemic hazards or potential for dermal absorption associated with contact of the skin with a specified chemical (See Appendix E.2 Evaluation of Data).

• 2.3 DIR

Most currently available reports on the direct effects of chemicals on skin (not immune-mediated) are related to irritation and corrosion and are qualitative descriptions summarized from the clinical observations of patients or the results of experimental animal studies. Manifestations of erythema and edema observed in humans and in experimental animal studies are frequently used as indicators of skin irritation. In addition to these reports, *in vitro* studies have shown that the integrity of skin as a barrier to the penetration of chemicals may be reduced as a result of chemical contact with the skin. Semi-quantitative information can also be obtained from irritation/corrosion testing such as the Draize patch test or its modifications [NAS 1977]. Chemicals producing a direct effect on the skin that is not a result of an immunological response are labeled SK: DIR. Chemicals that are identified as irritants would be identified with the subnotation (IRR) [i.e., SK: DIR (IRR)]. Additionally, chemicals that cause

necrosis of skin tissues or destruction of stratum corneum following skin exposure would also receive the subnotation (COR) [i.e., SK: DIR (COR)]. The following are examples of direct health effects on the skin that would result in the assignment of the DIR notation or one of its subcategories:

- Carcinogenesis and photocarcinogenesis at the site of chemical contact
- Changes in pigmentation including bleaching (blanching) and staining of the skin
- Chloracne
- Compromise of the skin barrier integrity
- Corrosion
- Defatting or drying of skin
- Irritant contact dermatitis
- Phototoxicity

An SK: DIR notation is assigned when one or more of the following criteria are met:

A Credible evidence indicates that immediate, prolonged, or repeated contact of skin with the chemical produces direct effects on the skin of exposed workers. The direct effects reported were based on incidents of worker exposures and consist of primary irritation, including irritant contact dermatitis (macroscopically manifested as erythema and edema), corrosion (manifested as ulceration, visible necrosis of epidermis/dermis, bleeding, eschar formation, and discoloration), changed pigmentation

including bleaching (blanching) and staining of the skin, chloracne caused by chemicals such as halogenated aromatic hydrocarbons, defatting/drying of skin, and skin cancer at the site of contact. Information about acute or cumulative irritation of human skin may also be available from the results of predictive patch tests conducted on human volunteers (e.g., the acute dermal irritation study in human volunteers [OECD 1997]). Such information will be considered when assigning skin notations.

B Data from laboratory tests indicate direct effects on skin as a result of chemical exposures. These data include *in vivo* animal studies reporting the acute irritancy, corrosivity, and carcinogenicity of chemicals, *in vitro* assays identifying corrosivity potentials, and *in vitro* evaluations examining alteration in the barrier properties of skin as a result of dermal exposure to chemicals. Appendix A describes protocols and the criteria that can be used for deriving SK: DIR notations.

C Other relevant scientific data not generated using study protocols described in A and B can be used if they provide adequate qualitative data on the direct effects on skin as a result of skin exposure to a chemical. Protocols may be modifications of standardized protocols (e.g., the research protocols introduced in Appendix A) with variations in the evaluation procedures or study design that examine health endpoints other than those evaluated by the standardized protocols. Examples of the latter include reports of histopathological examinations indicating impairment of skin tissues, disintegration of skin components (e.g.,

defatting and discoloration), or the presence of neoplastic lesions or tumors in the epidermis and dermis in association with changes in the transdermal penetration of chemicals.

D When no acceptable-quality empirical data exist on the direct effects of skin exposure to a chemical, information from the structure-activity-relationship (SAR)-based analysis and the physicochemical properties and reactivity of the chemical may be used as an alternative method for identifying hazards [OECD 2001]. Examples of SAR analysis are the clinical and/or experimental observations of the adverse effects occurring at the site of exposure to a structurally related or similar chemical in question. Physicochemical properties such as extreme pH and buffering capacity can be used to estimate the dermal corrosivity potential of acidic or alkaline chemicals. See Appendix C for further discussion about using pH and acid/alkali reserves for assigning SK: DIR notations. When the algorithm is used as the basis of identification, a positive result is sufficient to classify a chemical as capable of provoking direct effects on the skin and assigning an SK: DIR notation.

• 2.4 SEN

Immune-mediated reactions associated with exposures of the skin to chemicals encompass a wide spectrum of dermal disorders and systemic allergic responses, including respiratory sensitization, airway hyperactivity and mucosal inflammation. Occupationally, the most common and significant reaction is

allergic contact dermatitis (ACD). For ACD, the skin-sensitizing potential of the chemical is typically evaluated by two endpoints—the immunological induction of sensitization and the elicitation of ACD.

Findings reported within multiple published studies support a link between exposures of the skin to certain chemical allergens and the induction and/or elicitation of systemic allergic responses, including respiratory sensitization, airway hyperactivity and mucosal inflammation (Kimber et al., 1996; Beck et al., 2000; Tinkle, et al., 2003; Day et al. 2006; Bello et al., 2007; Kreiss et al., 2007; Redlich et al., 2008). For example, despite decreased inhalation exposures to isocyanates and beryllium within various occupational settings, immune-mediated respiratory diseases associated with these compounds continue to persist (Bello et al., 2007; Kreiss et al., 2007; Redlich et al., 2008). The results of these investigations point to skin contact with certain chemical allergens as having a potentially significant role within the onset of immune-mediated respiratory diseases (Bello et al., 2007; Kreiss et al., 2007; Redlich et al., 2008). The exact mechanisms responsible for immune-mediated systemic responses following dermal exposures are not fully understood. It has been theorized that one possible pathway involves the absorption of a chemical allergen across the stratum corneum, its subsequent penetration of the epidermis and the initiation and/or elicitation of an immune-mediated response associated with dendrite cells (Kimber 1996). Regardless of the mechanism, dermal exposures to chemical

allergens appear to be capable of inducing and/or elicitating systemic allergic responses beyond ACD.

The allergic reactions of skin, mucous membranes, or respiratory tract resulting from dermal exposure to allergenic chemicals are commonly associated with two immune mechanisms: the immediate hypersensitivity response (Type I) (which normally occurs within minutes of exposure in a previously sensitized person) and the delayed hypersensitivity response (Type IV) (which occurs 24 to 72 hr following exposure). The Type I reaction (e.g., contact urticaria) is primarily mediated by immunoglobulin E (IgE) antibodies when the chemical-specific antibodies in systemic circulation contact antigens such as exogenous proteinaceous molecules. In the Type I reaction, the respiratory tract may respond in addition to the skin after dermal exposure to the causative agent. The Type IV reaction is a T-cell-mediated immune response that requires a procession of cellular events within the body (the induction phase) leading up to the inflammatory response (the elicitation phase). This procession includes (1) association of antigens (haptens) with proteins, (2) presentation of the protein-hapten conjugates to the regional lymph nodes, (3) recognition of the conjugates by specific T cells, and (4) proliferation of the specific T cells in draining lymph nodes. The following types of immune-mediated reactions of the skin, mucous membranes, or respiratory tract resulting from dermal exposure will receive the SEN notation:

- Allergic Contact Dermatitis (ACD)

- Delayed hypersensitivity response (Type IV)
- Immediate hypersensitivity response (Type I)
- Photosensitization

In laboratory testing, contact allergens are largely identified *in vivo* using the conventional guinea pig sensitization test or the more innovative murine local lymph node assay (LLNA). Data relevant for determining whether the chemical may cause an allergic response include the following [ECETOC 2002]:

- Analytical or descriptive epidemiological studies
- Observational case reports from health surveillance programs and/or poison control centers
- Clinical studies with human volunteers

Note: clinical tests with human volunteers are mostly conducted to confirm the safety of test materials or preparations rather than to identify skin sensitization hazards.

An SEN notation is assigned when one or more of the following criteria are met:

A Credible evidence indicates the occurrence of ACD or sensitization as a result of chemical exposure to the skin. Skin sensitization among workers is often characterized clinically by immunologically mediated cutaneous reactions such as pruritus, erythema, edema, papules, vesicles, bullae, or a combination of these injuries. Information about human allergic reactions from skin exposure may also be used from the results of

predictive patch tests conducted on human volunteers (e.g., the human repeat insult patch test [ECETOC 2000]). Such information will be considered when assigning skin notations. When human data are used as the basis of identification, one of the following types of evidence is sufficient to classify a substance as a sensitizer [Kimber et al. 2003] :

- Studies in which sensitization is clearly evident from scientifically valid clinical investigations (e.g. patch testing)
- Confirmed case reports describing several subjects in more than one independent study
- Clear epidemiological evidence establishing a causal relationship between exposure and skin sensitization

When only isolated episodes of ACD are observed, supporting evidence should be obtained (including data available from animal tests and an appropriate SARs) before the chemical is recognized as a contact allergen [European Commission 1996].

B Animal data indicate the potential for ACD and sensitization from dermal exposure. Such animal data include the guinea pig sensitization tests identifying skin sensitization or ACD as well as the LLNA and the mouse ear-swelling test reporting skin sensitization potentials. Appendix A describes protocols and criteria that can be used in assigning the SEN notation.

C Scientific data may be used other than those described in A and B that demonstrate sensitization as a result of skin exposure to a chemical.

Protocols other than those indicated in A and B may be modifications of the standardized protocols (e.g., the research protocols introduced in Appendix A) with variations in the evaluation procedures or study designs that examine health endpoints other than those evaluated by the standardized protocols. An example is studies that evaluate the induction of IgE (antibody)-mediated respiratory hypersensitivity by allergens as a result of skin exposure.

D When no acceptable-quality empirical data exist, the occurrence of sensitization or ACD as a result of skin exposure to a chemical, information from the SAR-based analysis, and other computational chemistry methods can be used as an alternative method for identifying hazards. An example of a SAR analysis is the use of the knowledge-based expert system Deductive Estimation of Risk from Existing Knowledge (DEREK™) to evaluate the relationship between the molecular structure of the chemical to its allergenic properties. Appendix C describes the DEREK™ expert system for identifying sensitizers. When the algorithm is used as the basis of identification, a positive result is sufficient to classify a chemical as an agent capable of provoking ACD or sensitization from dermal exposure and assigning the SEN notation.

- **2.5 ~~SK~~**

The ~~SK~~ notation is assigned to indicate that a chemical underwent a critical assessment of the scientific data and was not identified as a systemic, direct, or sensitizing health risk from dermal exposure based on the criteria described

above for the assignment of the SYS, DIR, and SEN notations. It should be noted that for a chemical to receive the ~~SK~~ notation the scientific data must be classified as *sufficient* based on the criteria outlined in Appendix E.2).

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APPENDIX A: Protocols Used in Studies of Health Effects from Dermal Exposure and the Determination of Criteria Derived for Assigning Skin Notations

This appendix presents the experimental protocols used in laboratory studies of the systemic effects, direct effects on skin, and sensitization potentials of chemicals resulting from dermal exposure using animal models or alternative methods (e.g., *in vitro* bioassays). The protocols included have generally been standardized and validated by various regulatory agencies and research institutes in the United States (US) and Europe. For each protocol, the introduction contains (1) concise discussions of the underlying principles and methods and (2) criteria for assigning skin notations based on results of studies that followed the protocol. As the investigative methods are developed or improved, other protocols with scientific merit may become available. Depending on their status, additional protocols may be selected to develop criteria for assigning skin notations.

• A.1 Experimental protocols for investigating systemic effects of dermal exposure and derived criteria for assigning the SYS notations

A.1.1 Dermal absorption

Dermal absorption is the transport of chemicals from the outer surface of the skin both into the skin and into systemic circulation. This process is often described using terms including penetration, permeation and resorption. Assignment of the

In addition to predictive models, *in vitro* and *in vivo* test methods have been developed to estimate the rate of absorption (of one or more of its phases) of chemicals through the skin [OECD 2004 a, b, c; WHO 2006]. *In vitro* dermal absorption tests generally rely on the application of a radiolabeled test substance to a sample of nonviable or metabolically active excised skin suspended between two chambers of a diffusion cell, and are used to measure the rates of penetration and permeation [Bronaugh and Stewart 1985; US EPA 2004; OECD 2004b]. *In vivo* studies use a physiologically and metabolically active system in the form of human volunteers or test animals, such as rats, to assess the dermal penetration, permeation and resorption of test chemicals [OECD 2004a; OECD 2004c; WHO 2006]. Predictive algorithms and mathematical models, such as quantitative structure-permeability relationships (QSPR), have been developed to offer a relatively inexpensive method for determining dermal penetration of chemicals [Moss et al. 2002; Riviere and Brooks 2005; WHO 2006]. The predictive algorithms utilize the physiochemical properties (i.e. molecular weight, solubility, pH) of a test substance to estimate the potential biological effects or transport properties within a biological system [Moss et al. 2002; Riviere and Brooks 2005; OECD 2004a; WHO 2006]. The results of dermal absorption tests are frequently presented as the estimated or predicted percentage (%) of the test substance dermally absorbed. To differentiate between low and high dermal absorption, a 10% absorption rate has been selected as the cutoff value. This value corresponds to OECD guidelines [OECD 2004a], and is based on

recommendations proposed by the Netherlands Organization for Applied Scientific Research (TNO) [De Heer et al. 1999]. If the dermal absorption rate values reported within reviewed data are consistently higher than 10%, the chemical is considered to have a high potential for dermal absorption and contributes to systemic dose.

A.1.2 Acute dermal toxicity

Acute dermal toxicity testing examines the mortality of test animals after single, short-term exposures to a toxic chemical [OECD 1987; US EPA 1998a]. Typically, the test chemical is applied to the skin and remains in place for 24 hr. The animals are then observed for 14 days. The results of acute toxicity tests are presented as the dermal dose that is lethal for 50% of the exposed animals (LD_{50}), with observations of behavioral/clinical abnormalities and pathological findings from gross necropsy. If the LD_{50} values are consistently lower than the numeric cutoff value of 2000 mg/kg of animal body weight, the chemical is considered systemically toxic by the dermal route and is assigned the SYS notation. The critical value of 2000 mg/kg for the dermal LD_{50} reflects the dose selected in standardized limit tests to identify chemicals with the potential for acute dermal toxicity. This value corresponds with the upper dermal LD_{50} limit for establishing a chemical as a "harmful" substance in the general classification and labeling requirements for chemicals in member countries of the OECD [Council of the European Communities 1992] and by GHS [UNECE 2005].

If the LD_{50} values are consistently lower than the numeric cutoff value of 200 mg/kg of animal body weight, the chemical is potentially lethal following acute dermal exposures and is assigned the (FATAL) notation. This value is consistent with the numeric cutoff value used by GHS to identify chemicals capable of causing death following contact with the skin.

A.1.3 Repeated-dose dermal toxicity

Repeated-dose dermal toxicity testing examines the toxic effect(s) of repeated exposure to a chemical for 21 or 28 days [OECD 1981a; US EPA 1998b]. The animals are observed for behavioral and clinical abnormalities during the study. At the end of the study, they are examined for gross organ lesions, hematology, clinical chemistry, ophthalmology, and histopathology. Test results often include the reporting of a no-observed-adverse-effect level (NOAEL) as the most sensitive endpoint(s) selected from all evaluated health effects. If the NOAEL for a selected endpoint is lower than the numeric cutoff value of 1000 mg/kg as a daily dose (mg/kg-day), the chemical is considered systemically toxic by the dermal route and is assigned the SYS notation. The critical dermal NOAEL value of 1000 mg/kg-day reflects the dose selected in the standardized limit tests to identify chemicals with the potential for repeated-dose dermal toxicity. If a creditable NOAEL is not identified within the reviewed toxicological data, other toxicity threshold measurements, such as the lowest-observed-adverse-effect level (LOAEL), lowest-observed-effect level (LOEL) or no-observed-effect level

(NOEL) may be substituted in its place when available for comparison to the numeric cutoff value of 1000 mg/kg-day.

A.1.4 Subchronic dermal toxicity

Subchronic toxicity testing examines the cumulative toxic effect(s) from continuous or repeated exposure to a toxic chemical for at least 90 days [OECD 1981b; US EPA 1998c]. The animals are observed for behavioral/clinical abnormalities during the study. At the end of the study, they are examined for gross organ lesions, hematology, clinical chemistry, ophthalmology, and histopathology. Test results often include the NOAEL for the most sensitive endpoint(s) selected from all evaluated health effects. If the NOAEL for a selected endpoint is lower than the numeric cutoff value of 1000 mg/kg-day, the chemical is considered systemically toxic by the dermal route and is assigned the SYS notation. The critical dermal NOAEL value of 1000 mg/kg-day reflects the dose selected in the standardized limit tests to identify chemicals with the potential for subchronic dermal toxicity. If a creditable NOAEL is not identified within the reviewed toxicological data, a LOAEL, LOEL or NOEL may be substituted when available for comparison to the selected cutoff value of 1000 mg/kg-day.

A.1.5 Chronic dermal toxicity

Chronic dermal toxicity testing examines the cumulative toxic effect(s) of continuous or repeated exposure to a chemical for at least 12 months [OECD

1981c; US EPA 1998d]. The animals are observed for behavioral/clinical abnormalities during the study. They are evaluated using hematology, clinical chemistry, urinalysis, and ophthalmology during and at the end of the study. At necropsy, they are examined for gross organ lesions and tissue histopathology. Test results often include the NOAEL for the most sensitive endpoint(s) selected from all evaluated health effects. If the NOAEL for a selected endpoint is lower than the numeric cutoff value of 1000 mg/kg-day, the chemical is considered systemically toxic by the dermal route and is assigned the SYS notation. The critical dermal NOAEL value of 1000 mg/kg-day reflects the dose selected in the standardized limit tests to identify chemicals with the potential for chronic dermal toxicity. If a creditable NOAEL is not identified within the reviewed toxicological data, a LOAEL, LOEL or NOEL may be substituted when available for comparison to the selected cutoff value of 1000 mg/kg-day.

A.1.6 Carcinogenicity

Carcinogenicity testing examines the development of neoplastic lesions or tumors in organs and tissues, excluding the skin (See Section A.2.3), as a result of long-term dermal exposure to a chemical for 18 to 24 months [OECD 1981d; US EPA 1998e]. The test period constitutes a major portion of the life span of test animals. The animals are observed for behavioral/clinical abnormalities during the study. They are investigated for clinical pathology during and at the end of the study, in addition to gross organ lesions and tissue histopathology at necropsy. Carcinogenicity from dermal exposure to a chemical may be studied

and reported jointly with chronic dermal toxicity [OECD 1981e; US EPA 1998f; NTP 2001a]. Other systemic toxicants in this category are chemicals reported to cause photocarcinogenesis (the elicitation or increase of a toxic and/or carcinogenic response after dermally absorbed and subsequent exposure to sunlight) [NTP 2002a; OECD 2004d]. If a candidate chemical is identified by NIOSH as a potential carcinogen following dermal exposure or is determined to produce a statistically significant increase in the incidence of neoplastic lesions or tumors in test animals, it is considered to be carcinogenic and assigned the SYS notation.

A.1.7 Toxic effects of dermal exposures on organ systems or biological functions

Several types of tests examine the destruction or disruption of target organ systems and/or biological functions from dermal exposure to chemicals. Examples include (1) prenatal development toxicity (maternal and fetal toxicity) testing [US EPA 1998g; NTP 2001b; OECD 2001a] and (2) two-generation reproduction and fertility effects testing [US EPA 1998h; OECD 2001b], and (3) immunotoxicity (suppression of the immune system) testing [US EPA 1998i]. Ideally, a no-observed-adverse-effect level (NOAEL) is identified and reported for the studied effect(s). If the NOAEL for a selected endpoint is lower than 1000 mg/kg-day, the chemical is considered systemically toxic by the dermal route and assigned the SYS notation. The critical dermal cutoff value of 1000 mg/kg-day reflects the dose selected in the standardized limit tests used to identify chemicals that are potentially toxic to organs or biological functions. In the event

that a NOAEL can not be identified within reviewed toxicological data, a lowest-observed-adverse-effect level (LOAEL) may be substituted when available for comparison to the selected cutoff value of 1000 mg/kg-day.

A.1.8 Assignment of the SYS notation based on nondermal routes of exposures

Toxicity data associated with nondermal routes of exposures (i.e. oral and inhalation) may be considered during the assignment of the SYS notation. The primary criteria applied for determining the appropriateness of the use of toxicity data associated from nondermal routes of exposures are:

1. No quality dermal toxicity were identified,
2. Toxicokinetics data clearly demonstrates that the chemical has a high potential to be dermally absorbed and contributes significantly to systemic dose (See Section A.1.1),
3. The critical health endpoint(s) being investigated must be systemic in nature, and
4. The critical systemic endpoint(s) is independent of the route of exposure.

• A.2 Experimental protocols for investigating direct effects of dermal exposure and derived criteria for assigning the DIR notations

A.2.1 *In vivo* animal tests for acute irritancy and corrosivity

Most research protocols available for *in vivo* testing for skin irritation and corrosion follow the Draize procedure, with modifications in exposure duration, test animal species and number, and intervals between observations. In the standardized protocols [US EPA 1998j; OECD 2002a], a single dose of the test chemical is applied to the skin of albino rabbits, normally for 4 hr unless corrosion is observed. The animals are examined for signs of erythema and edema, and the responses are scored at intervals over 72 hr. These procedures are also used to examine and grade any persistent or delayed effects that may occur within 14 days after exposure and to fully evaluate the reversibility of observed effects. A chemical that induces reversible inflammation, dryness, or redness without pain of the skin is considered an irritant and is assigned the (IRR) notation. A chemical that causes tissue lesions, blisters, in addition to pain and burns of varying degrees at the site of contact is considered corrosive and is assigned the (COR) notation.

A.2.2 *In vitro* tests for corrosivity using human or animal skin models

In vitro methods using human or animal skin models are used as alternatives to conventional *in vivo* tests for assessing the dermal corrosivity of chemicals. The following methods have been (1) standardized by the OECD as guidelines for

testing of chemicals and (2) peer-reviewed and recommended for regulatory acceptance by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM):

- Corrositex® [NTP 1999a]
- The human skin models [OECD 2004e], including EPISKIN™ and EpiDerm™ [NTP 2002b]
- The rat skin transcutaneous electrical resistance (TER) assay [NTP 2002b; OECD 2004f]

The Corrositex® assay evaluates the pH-sensitive destruction of a reconstituted, collagen-based biobarrier and determines the corrosivity potential by measuring the time required for the test material to pass through the biobarrier membrane (i.e., the breakthrough time) and produce a visually detectable change in the Chemical Detection System. Chemicals of high acid/alkaline reserves (Category I materials) and those of low acid/alkaline reserves (Category II materials) are considered corrosive when their breakthrough times are less than 4 hr and 1 hr, respectively [Fentem et al. 1998; US EPA 1996]. The EPISKIN™ and EpiDerm™ models evaluate the corrosivity potential of a test substance by measuring the decreased viability of human skin cells in reconstructed epidermis/dermis after exposure. In EPISKIN™, a test substance is identified as potentially corrosive when it induces ≥35% decrease in cell viability. In EpiDerm™, the substance is classified as corrosive if it induces ≥50% decrease in relative cell viability after 3 min of exposure or ≥85% decrease after 60 min. The TER assay measures the

reduction of inherent TER on the skin of young rats due to the loss of normal stratum corneum integrity and barrier function. A test substance is considered potentially corrosive and assigned the (COR) notation if it reduces the TER to a threshold below 5 kilohms.

A.2.3 Carcinogenicity

Carcinogenicity testing examines the development of neoplastic lesions on skin as a result of long-term dermal exposure to a chemical for 18 to 24 months [OECD 1981d; US EPA 1998e]. The test period constitutes a major portion of the life span of test animals. The animals are observed for behavioral/clinical abnormalities during the study. They are investigated for clinical pathology during and at the end of the study. They are also examined for gross organ lesions and tissue histopathology at necropsy. Carcinogenicity from dermal exposure to a chemical may be studied and reported jointly with chronic dermal toxicity [OECD 1981e; US EPA 1998f; NTP 2001a]. If dermal exposure to a chemical induces a statistically significant increase in the incidence of neoplastic lesions or tumors in test animals, it is considered to be a potential skin carcinogen and is assigned the DIR notation. Additionally, toxicants identified as being capable of causing photocarcinogenesis when topically applied in conjugation with exposure to sunlight will also be included within this category [NTP 2002a; OECD 2004d].

A.2.4 *In vitro* tests of skin integrity using human donor skin

Examples of *in vitro* methods for evaluating skin integrity include those for measuring the movement of a standard compound such as tritiated water through the stratum corneum, the transepidermal water loss (TEWL) from the stratum corneum, and the electrical resistance of skin to an alternating current at up to 2 volts [OECD 2004a,b].

• A.3 Experimental protocols for investigating sensitization from dermal exposure and derived criteria for assigning the SEN Notation

A.3.1 Identifying skin sensitization or ACD with guinea pig test methods

Standardized guinea pig test methods include the guinea pig maximization test (GPMT) and the Buehler test [OECD 1992; US EPA 2003]. In these tests, the animals are initially exposed to the test substance by intradermal injection and/or epidermal application to induce an immune response. After 10 to 14 days, the animals receive a challenge exposure to the test substance to establish whether a hypersensitive state has been induced. The disease-analogous skin reactions (e.g., local irritation in the forms of erythema/edema) following the challenge exposure are measured and graded (usually 24 and 48 hr post-challenge) to determine the degree of skin sensitization or ACD. A chemical that induces allergic skin reactions is considered a sensitizer and is assigned the SEN notation.

A.3.2 Identifying skin sensitization potential with the murine LLNA

The LLNA has been peer-reviewed by the ICCVAM and the NICEATM panel and recommended for regulatory acceptance [NTP 1999b]. OECD [2002b] and US EPA [2003] have adopted this assay as a standard test method for evaluating the skin sensitization potential of chemicals. The LLNA determines the induction of skin sensitization by identifying cell proliferation in the lymph node that drains the site of chemical application. The LLNA also provides quantitative data for assessing the dose-response relationship. In the test, cellular proliferation is measured as a function of *in vivo* radioisotope incorporation into the DNA of dividing lymphocytes. The ratio of lymphocyte proliferation in treated groups to that in vehicular controls (stimulation index) is determined to serve as a quantitative criterion. A substance is considered a sensitizer and assigned the SEN notation if it has a statistically significant stimulation index ≥3 and is supported by a fitting dose-response relationship.

A.3.3 Identifying skin sensitization potential with the mouse ear swelling test (MEST)

The MEST [Gad et al. 1986; Thorne et al. 1991a,b] is accepted by OECD [1992] and US EPA [2003] as a screening test for detecting chemicals with sensitization potential. In the noninvasive MEST, the animals are initially exposed to the test substance by topical application on the abdomen to induce an immune response. After the induction period, the test substance is applied topically to the ears of animals (challenge exposure). Ear thickness as a function of swelling is

measured at 24-hr intervals for 2 to 3 days post-challenge to determine whether a delayed hypersensitivity has occurred. A chemical is considered a sensitizer if it yields a positive result in the MEST. If this test indicates no sensitization potential, the chemical should be further examined with an accepted test such as the guinea pig sensitization test or the LLNA [US EPA 2003] before the substance is considered a nonsensitizer.

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APPENDIX B: Algorithm for estimating dermal absorption and systemic toxicity and suggested application for assigning SYS notations

• B.1 Algorithm for estimating and evaluating dermal exposure hazards

Appendix B presents a predictive algorithm for estimating and evaluating the health hazards of dermal exposure to chemicals. The algorithm is designed to evaluate the potential for a chemical agent to penetrate the skin and induce systemic toxicity. The goals for incorporating this algorithm into the proposed strategy for assigning SYS notation are as follows:

- Provide an alternative method to evaluate chemicals for which no clinical reports or animal toxicity studies exist or for which empirical data are insufficient to determine systemic effects.
- Use the algorithm evaluation results to determine whether a chemical poses a skin absorption hazard and should be labeled with the SYS notation.

The algorithm evaluation includes three steps: (1) determining a skin permeation coefficient for the chemical; (2) estimating chemical uptake by the dermal and respiratory absorption routes; and (3) evaluating whether the chemical poses a

skin exposure hazard. This algorithm has an advantage for evaluating the systemic toxicity of a chemical from skin absorption: the algorithm is flexible in the data requirement and can operate entirely on the basis of the physicochemical properties of a chemical and the relevant exposure parameters. Thus the algorithm is independent of the need for biological data. Or it can function using both the physicochemical properties and the experimentally determined permeation coefficients when the latter data are available and appropriate to use.

B.1.1 Step 1: Determining the skin permeation coefficient

The first step in the evaluation is to determine the skin permeation coefficient (K_p) for the chemical to describe the transdermal penetration rate of the substance. The K_p determined for a chemical is expressed in cm/hr and represents the overall diffusion of the substance through the stratum corneum and into the blood capillaries of the dermis. This value may be determined from laboratory tests or by QSPRs or QSARs.

Experimentally, the permeation of chemicals through human skin can be determined *in vitro* using diffusion cell techniques such as those described in the protocols standardized by OECD [2004a,b] and US EPA [69 Fed. Reg. 22402(2004)]. These methods typically measure the diffusion of a test substance into and across the excised skin (which consists of epidermal membranes or split-thickness skin) to a fluid reservoir; they report the K_p as a

quantitative measurement of the rate of skin diffusion at the steady state when an infinite dose is employed. Measured K_p values from the actual workplace vehicle should be used when available. The experimentally determined K_p values are not always available or generated following standardized protocols. An alternative approach is to use the QSPRs that predict the K_p of chemicals based on the physicochemical properties relevant to their transport behavior in the stratum corneum, such as the molecular size and solubility in the lipids of the stratum corneum. Vigorous research in the modeling of skin permeation has led to the development of various validated QSPRs—for example, the refined Potts and Guy equation [US EPA 2004], the revised Robinson model [Wilschut et al. 1995], and the Random Walk model [Frasch 2002].

As an example to demonstrate the determination of K_p by predictive QSPRs, the revised Robinson model is presented here for its mathematical descriptors and operation. The revised Robinson model has been shown to be among the QSPRs that provide reasonable K_p estimates when compared with the experimentally derived values [Wilschut et al. 1995; Vecchia and Bunge 2003]. The revised Robinson model estimates K_p based on the molecular weight of a chemical (MW, representing the molecular size) and the logarithm of its octanol-water partition coefficient (log K_{OW}, representing the hydrophobicity). This model is mathematically expressed:

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

where 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

$$\log K_{psc} = -1.326 + 0.6097 \times \log K_{OW} - 0.1786 \times MW^{0.5}$$

$$K_{pol} = 0.0001519 \times MW^{-0.5}$$

$$K_{aq} = 2.5 \times MW^{-0.5}$$

Exercise caution when a QSPR is used in the derivation of K_p: constrained by the experimental data used in the development and validation, many of the empirical QSPRs are subject to limitations in the types of chemicals that the models may be applied to. These QSPRs may not provide reliable K_p estimates for inorganic compounds, ionized substances, very high-MW chemicals, small hydrophilic molecules, or highly volatile compounds. Chemicals in the first three categories are not readily absorbed through the skin, and their experimental K_p values are often not readily available for model validation. Hydrophilic compounds of small MW tend to penetrate hair follicles and sweat glands and therefore are not sufficiently covered in the assumed pathway of penetration by many models. In addition, with a few exceptions, the QSPRs typically do not account for the

evaporation of chemicals from the skin; as a result, the predicted K_p for volatile compounds could be overstated.

B.1.2 Step 2: Estimating chemical uptake from skin and inhalation exposures

Step 2 in the evaluation (as initially proposed by the Toxic Substances Control Act Interagency Testing Committee [Walker et al. 1996]) is to calculate the biological uptake of the chemical from skin absorption (skin dose) and inhalation (inhalation dose) during the same period of exposure. The inhalation dose represents a critical presence of the examined substance in the body. Beyond this dose, bioaccumulation of the substance is a cause for concern for health effects. The skin and inhalation doses provide quantifiable measures for absorption of the chemical by different routes. These doses serve as the basis for determining whether the substance constitutes a skin absorption hazard.

The skin dose is calculated as a mathematical product of the Kp acquired in Step 1, the water solubility (S_W) of the chemical, the exposed skin surface area, and the duration of exposure. In the calculation, the transdermal flux of the substance is assumed to originate from a saturated aqueous solution. Assuming that the skin exposure continues for 8 hr and occurs to the unprotected skin on both palms (a surface area of 360 cm^2),

Skin dose = $K_p \times S_W \times$ Exposed skin surface area $\times$ Exposure time

= K_p (cm/hr) $\times$ SW (mg/cm^3) $\times$ 360 (cm^2) $\times$ 8 (hr)

The inhalation dose is derived on the basis of the occupational exposure limit (OEL) of the substance—if the OEL is developed to prevent the occurrence of systemic effects rather than sensory/irritant effects or direct effects on the respiratory tract. Assuming a continuous exposure of 8 hr, an inhalation volume of 10 m^3 in 8 hr, and a factor of 75% for the retention of the airborne substance in the lungs during respiration (retention factor, RF),

$$\text{Inhalation dose} = \text{OEL} \times \text{Inhalation volume} \times \text{RF}$$

$$= \text{OEL } (mg/m^3) \times 10\ (m^3) \times 0.75$$

In the above equation, a default value of 0.75 is used for the RF to represent the respiratory retention of chemicals. The percentage value for the absorption of xenobiotics via the lungs is commonly assumed to be 75% to 100% [European Chemicals Bureau 2003], and the default RF of 0.75 in the above equation represents the lower limit of the assumed range. This value is selected to avoid underestimating skin absorption as a significant route of biological uptake, since complete absorption is unlikely to occur for most chemicals inhaled into the lungs. When scientifically justified, chemical-specific RFs may be used in place of the default value, especially for chemicals whose systemic bioavailability is lower than the default value (e.g., because of the extensive metabolism of compounds in the lungs or accumulation in the blood leading to an absorption that is no longer "perfusion limited").

B.1.3 Step 3: Evaluating the skin exposure hazard

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 percutaneous absorption as a route of occupational exposure to the substance and (2) the contribution of dermal uptake to systemic toxicity. If a chemical has an SI ratio ≥0.1, it is considered a skin absorption hazard.

• B.2 Criterion for assigning the SYS notations

The SYS notation will be assigned to a chemical when the mathematical evaluation indicates an SI ratio ≥0.1 and when no data of scientific merit suggest that the potential health effects exclude systemic effect(s). An SI ratio of 0.1 is selected as the reference level based on a recent examination of chemicals recognized as skin absorption hazards by NIOSH. In this examination, 108 chemicals were calculated for their SI ratios; all had assigned NIOSH skin notations and were suggested by the literature to be agents of systemic toxicity following dermal exposure. Approximately 76% of the examined compounds had SI ratios >0.1. This result suggests that a chemical be treated as a skin absorption hazard when its dermal uptake exceeds 10% of its uptake by inhalation. The result also supports an SI ratio of 0.1 as the threshold value for assigning SYS notation. For the 24% of examined compounds predicted to have an SI ratio <0.1, the preliminary analysis indicates that two factors may have contributed significantly to the low ratio:

- The OELs used to calculate inhalation dose were initially developed with a small safety margin compared with the OELs for compounds having an SI >0.1.
- The health effects basis for skin notations may not be adequate.

These factors are being further investigated as a part of the ongoing NIOSH effort to re-evaluate the health effects of skin exposure to these chemicals using scientifically up-to-date data. Results of these analyses will be used to improve the NIOSH skin notations.

This criterion agrees with the findings from similar research conducted by other international occupational safety and health organizations. One example is the proposal of the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) to recommend skin notations based on a semi-quantitative approach [ECETOC 1998]. The algorithm proposed by ECETOC is similar to the one intended for assigning NIOSH SK:SYS notations. The ECETOC algorithm determines the skin exposure hazard posed by a chemical agent by comparing its dermal uptake to its systemic absorption from inhalation. ECETOC concluded that a skin notation should be assigned to a chemical when the amount of chemical absorbed by both hands and forearms in 1 hr could exceed 10% of the amount absorbed by inhalation when airborne concentrations are at the OEL for 8 hr. The defaults of the exposed skin surface area, the air volume inhaled in 8 hr, and the respiratory RF in the ECETOC algorithm are 2,000 cm^2, 10 m^3, and 50%, respectively. The SI ratio calculated in the algorithm proposed for

recommending the NIOSH SK: SYS notations (SI $Ratio_{NIOSH}$) can be modified to derive an SI ratio following the method proposed by the ECETOC (SI $Ratio_{ECETOC}$). A comparison between the SI $Ratio_{NIOSH}$ and the SI $Ratio_{ECETOC}$ reveals that

SI $Ratio_{ECETOC}$ = SI $Ratio_{NIOSH}$ × [2,000 cm2 (hands/arms) ÷ 360 cm^2 (palms)]
× [1 hr ÷ 8 hrs] × [75% (default RF in NIOSH algorithm) ÷
÷ 50% (default RF in ECETOC algorithm)]
= SI $Ratio_{NIOSH}$ × 1.04

This comparison shows that for any chemical where the modeling approach may applied, the SI ratio determined using the algorithm for assigning the SYS notation is approximately the same as the SI ratio generated by following the assumptions made in the algorithm proposed by ECETOC. Similarly, in both methods, the criteria for determining the health hazard of a dermal exposure are based on essentially the same level of skin absorption.

In view of these findings, percutaneous absorption of a chemical is considered a systemic toxicity hazard if the substance is evaluated by the algorithm as demonstrated in this appendix and is shown to have an SI ratio >0.1. The SYS notation will be assigned accordingly. For these substances, additional toxicological evaluations are recommended to clinically or experimentally verify the adverse systemic effect(s).

Note that in the context of Appendix B, the predictive algorithm is intended as a tool of hazard identification for determining whether dermal exposure to a chemical agent is inherently capable of provoking systemic toxicity and thus calls for assigning the SYS notation. The SI ratio of 0.1 was determined as the threshold level by modeling chemicals that currently carry NIOSH skin notations. To provide a consistent basis for comparing modeling results, the following exposure parameters were treated as constants during the investigation (with assumptions made for reasonably representing the conditions of skin exposures): (1) concentration of the chemical on the skin surface, (2) surface area of exposed skin, and (3) exposure duration. If exposure conditions are not known, these parameters will remain as constants when the algorithm is used to estimate the SI ratio for assigning the SYS notation. Note that in actual workplace situations, these exposure parameters are likely to vary from the values assumed here, depending on the chemicals and the industrial processes or tasks involved. Before using the predictive algorithm to assess the risk of a given chemical exposure during a specific task, an exposure assessment should be conducted to sufficiently characterize all relevant information. The mathematical model described here may be improved and updated as more dermal absorption data become available and other facets of dermal penetration are incorporated into the model.

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APPENDIX C: Identifying skin corrosives and sensitizers using physicochemical properties and structure activity relationship (SAR)-based analysis

• C.1 Using pH and acid/alkali reserve to identify skin corrosives

In the Supplement to the *OECD Guideline for Testing of Chemicals 404* [OECD 2002a] (*A Sequential Testing Strategy for Dermal Irritation and Corrosion*), the OECD recommends using a weight-of-evidence analysis on existing relevant data before undertaking *in vivo* testing to evaluate skin corrosion. Relevant data encompass data generated from alternative methods to biological testing—including "evidence of corrosivity/irritation of one or more structurally related substances or mixtures of such substance" and "data demonstrating strong acidity or alkalinity of the substance." The OECD *Guideline* also specifies that the acid/alkali reserve (or buffering capacity) be considered if a chemical is recognized as a skin corrosive on the basis of its extreme pH. Using pH and acid/alkali reserve to identify potential skin corrosives is in accordance with the approach adopted in the GHS [UNECE 2005]. In this system, the appropriate evaluation of extreme pH values (≤2.0 or ≥11.5) (including acid/alkaline reserve capacity) is accepted as a decision logic for recognizing corrosive agents.

When a chemical is evaluated for potential skin corrosivity based on pH and buffering capacity, the substance is to be recognized as corrosive following two predictive models [Worth et al. 1998]:

- The pH of a chemical is ≤ 2.0 or ≥ 11.5.
- pH – acid reserve/6 ≤ 1 or
- pH + alkali reserve/12 ≥ 14.5

where the acid reserve of a substance is the amount (grams) of sodium hydroxide required to bring 100 g of a test substance (in a 10% solution or suspension) to a pH of 4, and the alkali reserve is the amount of sulfuric acid required to bring 100 g of a test substance to a pH of 10. (See Young et al. [1988] for details about the generation and use of acid/alkali reserve measurements.)

• C.2 Using structural alerts implemented in the DEREK™ expert system to identify sensitizers

The knowledge-based DEREK™ expert system contains algorithms to predict the toxicity of chemical substances based on a series of structure-activity rules (also known as structural rules or structural alerts). These rules or alerts describe the sub-structures of chemical molecules potentially responsible for adverse health effects [Ridings et al. 1996]. As part of the DEREK™ expert system architecture, a rule base for identifying potential contact allergens was derived using results of the GPMT conducted for 294 chemical substances classified as strong or moderate sensitizers [Barratt et al. 1994]. The rule base initially

consisted of 40 structural rules and has been continuously updated since its inception. Workshop 19 of the European Centre for the Validation of Alternative Methods (ECVAM) discussed the DEREK™ skin sensitization rule base as an alternative to skin sensitization testing. The Workshop recommended that QSAR and expert systems serve as screens for identifying positive compounds [de Silva et al. 1996].

Zinke et al. [2002] assessed the effectiveness of these structural alerts for identifying the skin-sensitizing properties of chemicals. The researchers evaluated the 40 originally published structural alerts against a database developed in the German Federal Institute for Health Protection of Consumers and Veterinary Medicine (BgVV). The BgVV database contained data submitted under its procedure for notification about new chemicals within the European Union and data on the skin-sensitization potentials of 1,039 substances [Zinke et al. 2002]. Zinke et al. [2002] reported that among the structural alerts examined, eight could be used to identify contact allergens without further refinement. These alerts are for acid halides, acid anhydrides, isocyanates, isothiocyanates, β-lactams, aldehydes, epoxides, and quaternary ammonium cation.

These structural alerts will be used to evaluate chemical substances for their potential as skin sensitizers when no human or biological testing data are available. As the DEREK™ structural rules continue to be refined, it is

anticipated that additional alerts will be validated and available to identify hazards and facilitate the assignment of SK: SEN notations.

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APPENDIX D: Selecting and Prioritizing Candidate Chemicals

• D.1 Selecting Chemicals for Evaluation

Chemicals can be identified and selected for evaluation based on the strategic framework outlined in this CIB via three primary pathways: 1) chemicals recognized as potential emerging issues or existing occupational hazards, 2) nominations from interested parties including NIOSH stakeholders, other governmental agencies, and the public, and 3) chemicals listed in the *NIOSH Pocket Guide for Chemicals Hazards.* Chemicals identified as emerging issues, existing occupational hazards or nominated for evaluation will be assessed by NIOSH based on the availability of quality data that clearly outlines the risk posed by the candidate chemical. For chemicals listed within the *NIOSH Pocket Guide to Chemical Hazards,* a hierarchal ranking scheme has been developed to prioritize candidate chemicals (See Appendix D.1).

• D.2 Selecting and Prioritizing Candidate Chemicals found within the NIOSH Pocket Guide to Chemical Hazards

One hundred forty-two chemicals listed in the *NIOSH Pocket Guide to Chemical Hazards* have been previously assigned the skin notation [skin] which indicates the potential for dermal absorption. These compounds have been selected to be the first group of compounds to be evaluated via the strategic framework outlined in this CIB. As part of this process, a hierarchal ranking scheme which applied a

binominal hazard ranking approach has been developed to aid in the ranking of the large number of the candidate chemicals. Parameters addressed within the hierarchal scheme of prioritizing the candidate chemicals include 1) potential health hazards, 2) potential for occupational exposure, 3) the annual production volume and 4) OELs recommended by both governmental and non-governmental organizations. A diverse array of information resources containing data related to the outlined parameters were assessed to aid in choosing ranking the chemicals to be classified according to the new strategy. The following information resources were applied within this scheme:

ATSDR Toxicological Profiles (ToxProfiles)
(http://www.atsdr.cdc.gov/toxpro2.html)

European Inventory of Existing Commercial chemical Substances (EINICS) (http://ecb.jrc.it/esis/index.php?PGM=ein)

National Occupational Exposure Survey (NOES)
(http://www.cdc.gov/noes/)

NIOSHTIC-2
(http://www2a.cdc.gov/nioshtic-2/advsearch2.asp

NIOSH Immediately Dangerous to Life and Health (IDLH) Values
(http://www.cdc.gov/niosh/idlh/idlh-1.html)

NIOSH International Chemical Safety Card (ICSC)
(http://www.cdc.gov/niosh/ipcs/nicstart.html)

NIOSH Pocket Guide to Chemical Hazards
(http://www.cdc.gov/niosh/npg/)

NIOSH Registry of Toxic Effects of Chemical Substances (RTECS)
(http://www.cdc.gov/niosh/rtecs/rteccas1.html)

NIOSH Recommendations for Occupational Safety and Health, Compendium of Policy Documents and Statements
(http://www.cdc.gov/niosh/pubs/all_date_desc_nopubnumbers.html)

NIOSH Skin Exposures and Effects Topic Page
(http://www.cdc.gov/niosh/topics/skin/)

OSHA Permissible Exposure Limits
(http://www.osha.gov/SLTC/pel/)

US EPA High Production Volume Information System (HPV)
(http://www.epa.gov/hpvis/)

The 142 chemicals previously assigned the [skin] notation by NIOSH were systematically assigned a score ranging from 0 to 7 to determine which substances posed the greatest potential occupational health hazard based on the parameters outlined in Table D.1. The scores for 30 chemicals are illustrated within Table D.2.

Table D.1 Definition scoring of parameters applied with hierarchal ranking scheme

Parameter	Definition and scoring
OEL Potency	If OEL is < 1 mg/m3, assign score of 1; if not, assign score of 0.
Carcinogen	If identified as a carcinogen, assign score of 0.5; if not, assign score of 0.
Reproductive/ Development Toxicant	If identified as a reproductive or development toxicant, assign score of 0.5; if not, assign score of 0.
Irritant/Corrosive	If identified as a corrosive, assign score of 1; if identified as an irritant only, assign score of 0.5; if identified as neither, assign score of 0.
Sensitizer	If identified as a sensitizer, assign score of 1; if not, assign score of 0.
HPV Chemical	If identified as a HPV chemical, assign score of 1; if not, assign score of 0.
Exposure Potential	If identified within NOES data as having > 75,000 potential workers exposures, assign score of 1; if not, assign score of 0.

RTECS or RiSK:Phrases (R-Phrases) Skin Hazard	If identified within RTECS as either extremely or highly hazardous or within the R-Phrases as either highly toxic or toxic, assign score of 1; if not assign 0.

Table D.2 Example of the application of the hierarchal ranking scheme ranking of 30 candidate chemicals

Chemical	CAS No.	OEL[1] Potency	CAN[2]	R/DT[3]	IRR/ COR[4]	SEN[5]	HPV[6]	Exposure Potential	Skin Hazard[7]	Overall Score
Epichlorohydrin	106-89-8	0	0.5	0.5	1	1	1	1	1	6
Acrylonitrile	107-13-1	0	0.5	0.5	0.5	1	1	1	1	5.5
Dichlorvos	62-73-7	1	0.5	0.5	0.5	1	1	0	1	5.5
Hydrazine	302-01-2	1	0.5	0.5	1	1	0	0	1	5
p-Phenylene diamine	106-50-3	1	0.5	0	0.5	1	1	0	1	5
Acrylamide	79-06-1	1	0.5	0.5	0.5	1	1	0	0	4.5
Dimethyl sulfate	77-78-1	1	0.5	0	1	1	1	0	0	4.5
Phenol	108-95-2	0	0	0.5	1	0	1	1	1	4.5
Acrylic Acid	79-10-7	0	0	0	1	1	1	1	0	4
Diethylenetriamine	111-40-0	0	0	0	1	1	1	1	0	4
Heptachlor	76-44-8	1	0.5	0.5	0	0	1	0	1	4
Methyl isocyanate	624-83-9	1	0	0.5	0.5	0	1	0	1	4
o-Cresol	95-48-7	1	0	0	1	0	1	0	1	4
Phenylhydrazine	100-63-0	1	0.5	0	0.5	1	0	0	1	4
1,3-Dichloropropene	542-75-6	0	0.5	0.5	0.5	1	1	0	0	3.5
2-Ethoxyethanol	110-80-5	0	0	0.5	0	0	1	1	1	3.5
Aniline	62-53-3	0	0.5	0	0	1	1	0	1	3.5
Captafol	2425-06-1	1	0.5	0.5	0.5	1	0	0	0	3.5
Dinitro-o-cresol	534-52-1	1	0	0	0.5	1	0	0	1	3.5
Disulfoton	298-04-4	1	0	0.5	1	0	0	0	1	3.5
Ethyl acrylate	140-88-5	0	0.5	0.5	0.5	1	1	0	0	3.5
Ethylene glycol dinitrate	628-96-6	1	0	0	0.5	0	1	0	1	3.5
Isophorone diisocyanate	4098-71-9	1	0	0	0.5	1	1	0	0	3.5
Methyl Cellosolve	109-86-4	1	0	0.5	0	0	1	1	0	3.5
Nitrobenzene	98-95-3	0	0.5	0.5	0.5	0	1	0	1	3.5
Nitroglycerine	55-63-0	1	0	0	0.5	0	1	0	1	3.5
o-Anisidine	90-04-0	1	0.5	0	0	0	1	0	1	3.5
o-Dinitrobenzene	528-29-0	1	0	0.5	0	0	1	0	1	3.5
Pentachlorophenol	87-86-5	1	0.5	0.5	0.5	0	0	0	1	3.5
Tetraethyl lead	78-00-2	1	0	0.5	0	0	1	0	1	3.5

[1] OEL = Occupational Exposure Limits; [2] CAN = Carcinogen; [3] R/DT = Reproductive and Development Toxicant; [4] IRR/COR = Irritant/Corrosive; [5] SEN = sensitizer; [6] HPV = High Production Volume Chemical; [7] Skin Hazard = Based on information provided by RTECS and EU Risk Phrases

The hierarchal ranking scheme presented in this section of the CIB may be modified in the future to aid NIOSH in prioritizing 1) chemicals listed within the

Pocket Guide to Chemical Hazards that do not have the skin notation [skin] and

2) chemicals nominated for evaluation from stakeholders, governmental agencies and public interest groups.

APPENDIX E: Guidelines and Criteria for the Search Strategy, Evaluation, and Selection of Supporting Data Used for the Assignment of Skin Notations

• E.1 Literature Search

The literature search strategy has been developed to identify critical scientific data on 1) the physical and chemical properties of candidate chemical substances, 2) human health effects associated with exposures to chemical compounds, 3) the reported results of *in vivo* and *in vitro* toxicity testing, and 4) estimates of chemical toxicokinetics and toxicity based on mathematical modeling (i.e. predictive algorithms). The primary sources of information reviewed during the literature search are: 1) peer-reviewed journals, 2) domestic and international governmental agencies reports, 3) reference books, 4) private industry reports and 5) scientific evaluations from public interest organizations. The literature search strategy includes search terms within electronic databases to ensure the identification of relevant scientific data.

E.1.1 Primary sources

E.1.1.1 Electronic databases

The following databases are searched:

Chemical Identification (ChemID)

(http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?CHEM)

European Inventory of Existing Commercial chemical Substances (EINICS) (http://ecb.jrc.it/esis/index.php?PGM=ein)

EMBASE
(http://www.embase.com/)

Extension Toxicology Network (EXTOXNET)
http://extoxnet.orst.edu/pips/ghindex.html

Haz-Map: Occupational Exposure to Hazardous Agents (Haz-Map)
(http://www.nlm.nih.gov/pubs/factsheets/hazmap.html)

Hazardous Substances Data Bank (HSDB)
(http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB)

Integrated Risk Information System (IRIS)
(http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?IRIS)

International Toxicity Estimates for Risk (ITER)
(http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?iter)

MICROMEDEX
(http://intra-apps.cdc.gov/scripts/elib.pl?url=http://csi.micromedex.com)

NIOSH Registry of Toxic Effects of Chemical Substances (RTECS)
(http://www.cdc.gov/niosh/rtecs/)

NIOSHTIC-2
(http://www2a.cdc.gov/nioshtic-2/advsearch2.asp)

National Toxicology Program Report on Carcinogens (NTPA)
(http://ehis.niehs.nih.gov/roc/)

OSH References Collection
(http://ccinfoweb.ccohs.ca/bibliographic/search.html)

Public Medline (PubMed)
(http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed)

Toxicology Information Online (TOXLINE) database from the U.S. National Library of Medicine's TOXNET (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE)

U.S. Environmental Protection Agency (US EPA) Substance Registry System
(http://www.epa.gov/srs/)

Web of Science
(http://publishorperish.nih.gov/)

E.1.1.2 Published books, technical documents, and Web sites

The list of published books, technical documents and websites represent common information sources used during the derivation of the new NIOSH skin notations:

Agency for Toxic Substance and Disease Registry (ATSDR) Public Health Statements (PHSs)
(http://www.atsdr.cdc.gov/phshome.html)

ATSDR Toxicological Frequently Asked Questions (TOXFAQS)
(http://www.atsdr.cdc.gov/toxfaq.html)

ATSDR ToxProfiles
(http://www.atsdr.cdc.gov/toxpro2.html)

American Conference of Government and Industrial Hygienists (ACGIH) Documentation of the Threshold Limit Values (TLV) for Chemical Substances and Physical Agents

American Industrial Hygiene Association (AIHA) Workplace Environmental Exposure Limits (WEELs)
(http://www.aiha.org/webapps/taxonomy/documentrepository/erpgweels/7d11ed78-37da-4ce1-99f2-763603376151.pdf)

California Environmental Protection Agency (CalEPA) Health Reports
(http://www.calepa.ca.gov/Publications/)

Cassarett and Doull's Toxicology: The Basic Science of Poisons

European Commission Risk Assessment Reports
(http://ec.europa.eu/health/ph_risk/risk_en.htm)

Hamilton and Hardy's Industrial Toxicology

Health and Safety Executive (HSE) Publications
(http://www.hse.gov.uk/pubns/index.htm)

International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans
(http://monographs.iarc.fr)

International Programme on Chemical Safety (IPCS)
(http://www.inchem.org/)

Merck Index

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) Scientific Reports
(http://www.nicnas.gov.au/)

NIOSH ICSC
(http://www.cdc.gov/niosh/ipcs/nicstart.html)

NIOSH Pocket Guide to Chemical Hazards
(http://www.cdc.gov/niosh/npg/)

NIOSH RTECS
(http://www.cdc.gov/niosh/rtecs/rteccas1.html)

NIOSH Recommendations for Occupational Safety and Health, Compendium of Policy Documents and Statements
(http://www.cdc.gov/niosh/pubs/all_date_desc_nopubnumbers.html)

New Jersey Right to Know Hazardous Substances Fact Sheets
(http://web.doh.state.nj.us/rtkhsfs/indexfs.aspx)

Patty's Industrial Hygiene and Toxicology

Proctor and Hughes' Chemical Hazards of the Workplace

US EPA Health Effects Documents
(http://www.epa.gov/)

U.S. National Technical Information Services (NTIS)
(http://www.ntis.gov/)

U.S. National Toxicology Program (NTP) Study Reports
(http://ntp.niehs.nih.gov/ntpweb/index.cfm?objectid=7DA86165-BDB5-82F8-F7E4FB36737253D5)

US Occupational Safety and Health Administration (OSHA) Publications (http://www.osha.gov/)

E.1.2 Search terms

Literature searches are conducted for a candidate chemical based on the compound's Chemical Abstract Services Number (CAS#), chemical nomenclature, common names and synonyms. Additional terminology used during the literature search can be located in Table E.1.

Table E.1 Terminology applied during the search for critical scientific data on each candidate chemical substance

Acne	Follicle	Paronychia e
Apocrine	Gangrene	Photosensitive
Argyria	Granuloma	Phototoxicity
Atopic	Hirsute	Porphyria
Blister	Hyperhidrosis	Prurigo
Burn	Hyperpigment	Prurit
Callosity	Hypertricho	Psoriasis
Cancer	Hypopigment	Purpura
Corrosion	Hypotricho	QSAR
Crositex	Inflammation	Radiodermatitis
Cutaneous	Intertrigo	Rash
Cutis	Intradermal	Redness
Cyst	Irritant	Sebaceous
Cystic	Jaundice	Skin
Cysts	Keloid	Skin Diseases
Dermal	Keratoacanthoma	Skin Irritancy Tests
Dermatitis	Keratoderma	Skin Physiology
Dermato	Keratosis	Skin Tests
Eccrine	Lichenoid	Stratum Corneum
Ectoderm	Miliaria	Structure Activity Relationship
Eczema	Mucocutaneous	Sunburn
Epiderm	Neurodermat	Sweat
Episkin	Onychomyco	Ulcer
Erythema	Pain	Urticaria
Exanthema	Pall	Vacciniforme
Exfoliate	Panniculitis	Vesiculobullous
Fingernail	Papulosquamous	Xeroderma

• E.2 Evaluation of data

A qualitative classification scheme has been developed to aid in the evaluation of data sets identified through the literature search. This scheme relies on a case-by-case analysis of the assembled data sets based on a weight-of-evidence approach, in addition to the following general considerations:

- How many studies were identified?
- Were the identified studies peer-reviewed?
- Were the identified data generated using standardized protocols (e.g., guidelines established by OECD, REACH, US EPA, or NTP)?
- Were the exposure conditions and the studies' reported findings described in detail?
- Was additional information provided which should be taken consideration?

Based on the results of this qualitative classification scheme, the data sets are classified as either 1) *sufficient*, 2) *limited*, or 3) *insufficient*. Data sets classified as *sufficient* are those determined to include human and/or animal toxicity studies conducted following standardized protocols, in addition to providing in-depth descriptions of the exposure conditions and study findings. Data sets classified as *limited* via the qualitative ranking scheme are identified to contain few human and/or animal studies conducted following standardized protocols, incomplete descriptions of the exposure conditions and study findings, or studies conducted by non-standardized protocols. Data sets classified as *insufficient* are those determined to include studies that primarily did not apply standard protocols, in-depth descriptions of the exposure conditions and study findings.

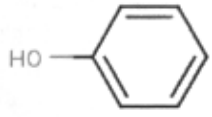
Data sets that receive the *insufficient* ranking should not be used as the basis for the NIOSH skin notation.

APPENDIX F: Example of Assigning the New NIOSH Skin Notations and Format of the Skin Notation Profile

This appendix documents the assignment of skin notations based on the scientific criteria outlined in this document. This profile contains the skin notations and supporting documentation for phenol [CAS No.108-95-2]. Each section of this appendix contains a brief summary highlighting the rationale for assigning or not assigning the various skin notations. References that are bold indicate primary studies.

• F.1 Chemical background information and introduction

Skin Notation Profile for Phenol [CAS No. 108-95-2]

Synonyms:	**Structure:**
Carbolic acid, monohydroxybenzene, hydroxybenzene, benzenol, phenylic acid, phenyl hydroxide, benzophenol, phenyl hydrate, phenylic alcohol, monophenol, phenic acid, oxybenzene	

Skin Notation for Phenol:SK: SYS(FATAL)-DIR(COR)

This documentation for skin notation assignments is limited to an assessment of the potential health effects following dermal exposure or the potential for direct skin injuries from phenol. A literature search was conducted through November 2006 to identify potential health effects information on phenol toxicokinetics,

acute, repeated-dose, and chronic toxicity, carcinogenicity, and biological system/function specific effects (including reproductive and developmental effects and immunotoxicity), irritation, and sensitization. Information was considered from studies in humans, animals, or appropriate modeling systems that are relevant to dermal exposure to phenol. This toxicological review is intended to provide brief documentation of the rationale in support of the skin notation assignments for this chemical. Assignments were made based on the approach described in the National Institute for Occupational Safety and Health [NIOSH 2008] Skin Notation Strategy Document. The following table provides the assigned skin notations for phenol, and data supporting these notations are summarized below. Table F.1 provides the assigned skin notations for phenol, and data supporting these notations are summarized below.

Table F.1 Skin Notation for Phenol

Supporting Data for Phenol Skin Notation		
Skin Notations	**Critical Effects**	**Available Data**
SK: SYS (FATAL)	Central nervous system effects, Respiratory depression, cardiac arrest, body weight changes, decreased survival.	Sufficient human and animal data
SK: DIR(COR)	Skin corrosivity	Sufficient human and animal data

- *This section outlines 1) background information on phenol, 2) briefly discusses the application of the literature search (Appendix E.1), and 3) a summary of the skin notations assigned to phenol. The summary includes the critical effects identified during the assignment of the skin notation, in addition to classifying the quantity and quality of the data set used to draft the profile (Appendix E.2).*

• F.2 Systemic toxicity from dermal exposure

Toxicokinetic studies of phenol have been identified. Dermal absorption of phenol by human subjects has been reported to range from 4 to 23% of the applied dose, with the extent of the dermal absorption, dependent on the period of exposure and the concentration of phenol [Feldman and Maibach 1970; Piotrowski 1971; Roberts et al. 1977; Baranowska-Dutkiewicz 1981]. In male volunteers, the rate of absorption of an aqueous phenol solution [2.5, 5.0, or 10.0 gallons per liter (g/L)] from a 2 milliliter (mL) reservoir applied directly to the forearm [15.6 square centimeters (cm^2)] was found to be concentration-dependent, with the rate ranging from 0.079 milligrams per square centimeter per hour (mg/cm^2/hour) at the low concentration to 0.301 mg/cm^2/hr at the high concentration [Baranowska-Dutkiewicz 1981]. In this study, the total amount of phenol absorbed – but not the rate of absorption – at the low concentration increased with time, with 12.6% and 22.7% of the applied dose absorbed in 30 and 60 minutes, respectively. Feldman and Maibach [1970] reported the degree of dermal absorption as 4.4% of the administered dose following a single topical application of 4 microgram (µg) phenol/cm^2 on 13 cm^2 of the unprotected ventral forearm of human adults. Phenol vapors are also reported to readily penetrate the skin with absorption efficiency equal to that of inhalation, thus contributing to the total dermal exposure [Piotrowski 1971]. In a whole-body skin exposure study in which lightly clothed and unclothed volunteers were exposed to phenol vapors at concentrations from 1.3 to 6.5 ppm for 6 hours, but were breathing

clean air by mask, Piotrowski [1971] reported that absorption increased proportionately with air concentration. These studies generally demonstrated that phenol can be absorbed through the human skin.

The potential of phenol to be absorbed through the skin has also been evaluated in laboratory animals. Hughes and Hall [1997] reported a 120-hour cumulative dermal absorption of 66% to 80% in young rats (29-day-old female rat). In an earlier study, the same authors [Hughes and Hall 1995] reported that approximately 85% of the dose of phenol was absorbed in 72 hours in 90-day-old female rat after dermal administration of phenol. *In vitro* studies using laboratory animal tissues also indicate that phenol is absorbed through the skin. For example, in an *in vitro* system using dermatomed rat skin, Hughes et al. [1993] reported a 72-hour dermal absorption of phenol of 95% of the applied dose. In a recent study that evaluated dermal absorption of phenol in acetone and water under nonoccluded and occluded applications using isolated perfused porcine skin, Brooks and Riviere [1996] found absorption, penetration into tissues, and total recoveries of phenol to be greater under occluded than nonoccluded conditions and that for each solvent, the absorption percentage was higher with the low-dose (4 $\mu g/cm^2$) compared to the high-dose (40 $\mu g/cm^2$) phenol, suggesting saturation of absorption or other non-linear kinetics under some conditions of exposure. Depending on the solvent and dose, Brooks and Riviere [1996] reported that dermal absorption ranged from 9.24% to 14.62% under occluded conditions at the low dose and 2.90% to 5.45% under nonoccluded

condition. *In vitro* permeability coefficients for phenol were found to increase with increasing concentration of aqueous phenol applied to mouse skin [Behl et al. 1983], with a 12-fold increase in mean coefficient (0.007–0.085 cm/hour) resulting from doubling the concentration from 20 to 40 g/L, and a value of 0.169 cm/hour noted when 60 g/L was applied [Behl et al. 1983]. The authors concluded that phenol concentrations exceeding 20 g/L may destroy a diffusion barrier normally provided by the intact stratum corneum, permitting increased percutaneous absorption. Results from animal studies in vivo and studies utilizing animal skin *in vitro* also demonstrated that phenol is absorbed through the skin of animals. The potential of phenol to pose a skin absorption hazard was also evaluated using the NIOSH [2008] predictive algorithm for estimating and evaluating the health hazards of dermal exposure to chemical substances. Based on this algorithm, the ratio of the skin dose to the inhalation dose (SI ratio) of 11 was calculated for phenol. Because this ratio is significantly higher than the SI ratio of greater than or equal to 0.1 that indicates that skin absorption may significantly contribute to the overall body burden of a chemical [NIOSH 2008], phenol is considered to be absorbed through the skin following dermal exposure. The result from the predictive algorithm supports the results from human and animal studies *in vivo* and from the *in vitro* studies.

Several case reports of humans dermally exposed to varying doses of phenol have been identified [Griffiths 1973; Soares and Tift 1982; Lewin and Cleary 1982; Turtle and Dolan 1922; Foxall et al. 1989]. In these reports, accidental exposure of phenol to intact skin or intentional (therapeutic) application of phenol

to the skin has resulted in fatalities (from, for example, respiratory depression and cardiac arrest), but the doses were not known with any accuracy, precluding estimation of a lethal dermal dose for humans. In animals, the dermal LD_{50} values (the dose resulting in 50% mortality in the exposed animals) range from 0.5 milliliter per kilogram body weight (mL/kg) to 0.68 mL/kg (corresponding to 669 to 1500 milligram per kilogram body weight, mg/kg) [Conning and Hayes 1970; Brown et al. 1975] in rats under both occlusive and non-occlusive conditions and 1400 mg/kg in rabbits [Vernot et al. 1977]. In the Corning and Hayes [1970] study, severe muscular tremors, twitching, generalized convulsions with loss of consciousness and prostration were reported within 10 minutes, and severe hemoglobinuria between 45 minutes and 90 minutes of dermal exposure to phenol in water. Brown et al. [1975] reported hematuria and convulsions as clinical signs of phenol toxicity. Because the reported acute dermal LD_{50} values for the rat and rabbit are both lower than the critical dermal LD_{50} value of 2 g/kg body weight that identifies chemical substances with the potential for acute dermal toxicity [NIOSH 2008], phenol is considered systemically toxic by the acute dermal route.

- *Application of Appendix A.1.2: Evaluation of acute dermal toxicity. The reported LD_{50} ranged from 414 mg/kg to 1400 mg/kg animal body weight did not exceed the numerical cutoff value of 2000 mg/kg animal body weight. For this reason, phenol is assigned the SYS notation. Multiple case studies were identified that reported workers' death following accidental exposure to phenol which supports the assigning of the SYS (FATAL) notation.*

Quantitative information on doses that cause systemic effects during repeated occupational exposures is lacking. However, chronic doses (unspecified) to

humans may result in neurological damage [Merliss 1972]. A number of repeated-dose studies have been identified in animals that evaluated systemic effects following dermal exposure to phenol. For example, Deichmann et al. [1950] exposed the tail of rabbits to aqueous phenol solutions of 1.18 to 7.12% in water (reported as 64 to 380 mg/kg by the International Program for Chemical Safety IPCS, 1994) for 5 h/day, 5 days/week, for a total of 18 days. Dose-related systemic effects (tremors, death) were observed at 130 mg phenol/kg and above. A No-Observed-Adverse-Effect-Level (NOAEL) of 64 mg/kg-day and a Lowest-Observed-Adverse-Effect-Level (LOAEL) of 130 mg/kg-day to protect against occasional mild tremors and skin irritation were identified in this study. Boutwell and Bosch [1959] conducted a study in mice involving skin painting of 25 microliters (µL) of a 5% (1.25 mg phenol) or a 10% (2.5 mg phenol) in benzene per application, twice weekly for 52 weeks. The high dose caused decreased body weight (average body weight at the 20^{th} week was 35.0 g compared to 38.9 g at the 5% level of phenol) and decreased survival (24/30 mice survived compared to 30/30 at the 5% level of phenol at the 20^{th} week). The resulting doses were reported as 41.7 and 83.3 mg/kg/treatment [Agency for Toxic Substances and Disease Registry, ATSDR, 2006]. Although the potential dermal and systemic effects of the benzene solvent was not investigated in this study, the effect levels of 18 mg/kg-day from the Boutwell and Bosch [1959] study and 130 mg/kg-day identified in the shorter duration study by Deichmann et al. [1950] together indicate the potential for effects at doses significantly lower than the critical dermal NOAEL value of 1 g/kg for repeat-dose toxicity that identifies

chemical substances with the potential for subchronic dermal toxicity [NIOSH 2008]. Therefore, phenol is considered to be systemically toxic following repeated dermal exposure.

- *Application of Appendix A.1.3: Evaluation of repeated-dose dermal toxicity. The doses reported in the reviewed studies ranging from 18 to 130 mg/kg-day did not exceed the numerical cutoff value of 1000 mg/kg-day animal body weight. For this reason, phenol would be assigned the SYS notation.*

No standard toxicity or specialty studies evaluating biological system/function specific effects (including reproductive and developmental effects and immunotoxicity) following dermal exposure to phenol were identified in humans or animals.

- *Application of Appendix A.1.7: Toxic effects of dermal exposures on organ systems or biological functions. No evidence was identified that evaluated the effects of phenol on organ systems or biological functions. The SYS notation would not be assigned to phenol based on the criteria outlined in this section.*

Although no epidemiological studies that evaluated the potential of phenol to be carcinogenic were identified, a limited number of studies in animals involving repeated application of phenol in benzene [Boutwell and Bosch 1959] or in acetone [Salaman and Glendenning 1957; Wynder and Hoffman 1961] in two-stage carcinogenicity protocols in mice indicated that phenol has promoting activity. Studies conducted by Boutwell and Bosch [1959] in several strains of mice also suggested that phenol in benzene or dioxane is a tumor promoter and possibly a complete carcinogen (i.e., having both promoting and initiating activity). In the latter study, phenol elicited skin tumors in mice even in the absence of a tumor initiating agent, 9,10-dimethyl-1,2-benzanthracene. These

studies are inadequate for the evaluation of the carcinogenicity potential of phenol due to the short duration (32 weeks [Salaman and Glendenning 1957] and 12 months or 52 weeks [Salaman and Glendenning 1957; Boutwell and Bosch 1959]), the lack of appropriate controls [e.g., Salaman and Glendenning 1957], and/or the use of vehicles (dioxane, benzene) that are skin irritants and/or defatting agents. Other agencies or organizations have also evaluated the potential of phenol to be a carcinogen following non-dermal exposure routes. NIOSH [2006] does not classify phenol as a potential occupational carcinogen. The United States Environmental Protection Agency [US EPA 2002] states that the data regarding the carcinogenicity of phenol via the oral, inhalation, and dermal exposure routes *are inadequate for an assessment of human carcinogenic potential*. The American Conference of Governmental Industrial Hygienists [ACGIH 2001] has assigned an A4 (not classifiable as a human carcinogen) notation to phenol. The International Agency for Research on Cancer [IARC 2007] has classified phenol as *not classifiable as to its carcinogenicity to humans* (Group 3).

- *Application of Appendix A.1.6: Evaluation of carcinogenicity of phenol. No evidence was identified that would support identifying phenol as a carcinogen or the subsequent assignment of the SYS notation.*

Identified human **[Feldman and Maibach 1970; Piotrowski 1971; Baranowska-Dutkiewicz 1981]** and animal **[Behl et al. 1983; Hughes and Hall 1995; Brooks and Riviere 1996]** toxicokinetic data, acute dermal toxicity studies **[Conning and Hayes 1970; Brown et al. 1975; Vernot et al. 1977]**, and repeat-

dose studies **[Deichmann et al. 1950; Boutwell and Bosch 1959]** are sufficient to demonstrate the potential for phenol to be dermally absorbed and systemically toxic. Systemic toxicity includes effects on the central nervous system, body weight changes, and decreased survival. Therefore, this assessment concludes that sufficient human and animal data exist to assign a SK: SYS notation for phenol.

• F.3 Direct effect(s) on the skin

The available information indicates that phenol is corrosive to the skin. For example, dermal exposure to liquid phenol or concentrated phenol vapor causes corrosive effects including tissue death (necrosis) in humans [Schmidt and Maibach 1981; Horch et al. 1994], rats [Conning and Hayes 1970], mice [Patrick et al. 1985], and pigs [Pullin et al. 1978; Hunter et al.1992]. Other effects, such as erythema, inflammation, discoloration, eczema, redness, and severe edema have been reported on contact of the skin with the solid or liquid phenol [Brown et al. 1975; Conning and Hayes 1970]. The effects of phenol on the skin have been attributed to its property to impair the barrier function of the stratum corneum and produce coagulation necrosis by denaturing and precipitating proteins. Although the structure activity relationship model, DEREK predicted that phenol is non-irritating to the skin, indicating that the chemical does not have structural alerts for skin irritation, several studies in humans and animals show that phenol is corrosive to the skin or is a skin irritant depending on the concentration.

Reports of necrosis and chemical burns in humans **[Schmidt and Maibach 1981; Horch et al. 1994]** and animals **[Conning and Hayes 1970; Pullin et al. 1978; Patrick et al. 1985; Hunter et al. 1992]** following direct contact with undiluted phenol or concentrated solutions are sufficient to demonstrate the corrosivity of phenol. More diluted solutions are more likely to be irritating to the skin. Therefore, this assessment assigns a SK: DIR (COR) notation for phenol.

- *Application of Appendix A.2 Experimental protocols for investigating direct effects of dermal exposure and derived criteria for assigning the SK: DIR notations. Sufficient evidence in the forms of numerous human and animal studies were identified that clearly demonstrated phenol's ability to cause direct effects including inflammation, discoloration, eczema, redness, edema, in addition to necrosis of the skin and underlying tissues. Based upon this evidence, phenol has been assigned both the DIR and (COR) notations.*

• F.4 Sensitization

A limited number of studies have been identified that evaluated the potential of phenol to cause skin sensitization in both humans and animals. In one study using 24 volunteers, phenol produced negative results in skin sensitization tests [Kligman 1966]. Phenol also gave negative results in the Magnussen and Kligman skin sensitization test in guinea pigs [Itoh 1982]. Predictions using structure activity relationship models provide some information regarding this endpoint. Based on the chemical structure, phenol is predicted by DEREK® as negative for sensitization, indicating that the chemical does not have structural alerts for skin sensitization. This prediction of negative sensitization potential is

consistent with the absence of published reports of sensitization in workers handling phenol and the limited empirical evidence.

The limited information available indicates that phenol is not likely to be a skin sensitizer. Therefore, this assessment does not assign a SK: SEN notation for phenol.

- *Application of Appendix A.3 Experimental protocols for investigating sensitization from dermal exposure and derived criteria for Assigning the SK: SEN Notations and Appendix C.2 Using structural alerts implemented in the DEREK™ expert system to identify sensitizers. This section reviews the assembled data set for phenol to assess the potential for sensitization following dermal exposures. The identified data set provided insufficient information to assign the SEN notation. This decision is supported by the inclusion of the DEREK™ negative prediction for phenol to cause sensitization.*

• F.5 Summary

There is sufficient information from toxicokinetics **[Feldman and Maibach 1970; Piotrowski 1971; Baranowska-Dutkiewicz 1981]**, acute dermal toxicity studies **[Conning and Hayes 1970; Brown et al. 1975; Vernot et al. 1977],** and repeat-dose dermal toxicity studies **[Deichmann et al. 1950; Boutwell and Bosch 1959]** to indicate that phenol is absorbed through the skin and is acutely toxic and induces systemic effects (for example, central nervous system effects, effects on body weight and survival) following dermal exposure. Information from human experience **[Merliss 1972; Schmidt and Maibach 1981; Horch et al. 1994]** and animal studies **[Conning et al. 1970; Pullin et al. 1978; Patrick et al. 1985; Hunter et al. 1992]** is sufficient to demonstrate that phenol is corrosive, while more dilute solutions are irritating to the skin. The limited information

available indicates that phenol is not a skin sensitizer. Therefore, this assessment recommends the composite skin notation of SK: SYS-DIR(COR) for phenol. Phenol has also been classified as being harmful and toxic in contact with the skin as well as corrosive by the European Union [2007]. ACGIH [2001], NIOSH [2006], and OSHA (Occupational Safety and Health Administration) [2007] have also assigned a skin notation to the chemical. The classifications assigned by these organizations are indicated in the table below. The classifications assigned by these organizations are indicated in Table F.2. Based on the scheme developed by NIOSH to coordinate the skin notations with the GHS, the equivalent GHS classification for phenol would most likely be considered an acute toxicant (200 mg/kg body weight < LD_{50} < 1000 mg/kg body weight), in addition to an irritant and corrosive agent.

Table F.2: Summary of Skin Hazard Designations beyond NIOSH

Organization	Dermal Classification
EU [2007]	R21 – Harmful: danger of serious damage to health by prolonged contact with skin
	R24 – Toxic in contact with skin
	R34 – Corrosive: Causes burns
	C – Corrosive
ACGIH [2001]	Skin notation - phenol, as a vapor, liquid, or solid, can penetrate the intact skin causing systemic effects.
NIOSH [2006]	Skin notation – potential for skin and eye irritation and dermal absorption
OSHA [2007]	Skin notation – indicates that the cutaneous route of exposure (including mucous membranes and eyes) contributes to overall exposure

EU - European-Union; ACGIH - American Conference of Governmental Industrial Hygienists; NIOSH – National Institute for Occupational Safety and Health; OSHA – Occupational Safety and Health Administration.

- **Appendix F References**

Note: References identified with a (*) are citied within Skin Notation Profile; References not identified with a (*) represent additional resources not citied within the Skin Notation Profile

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APPENDIX G: Supplemental information

• G.1 Contaminants and isomers

Skin notations are intended to provide warning and the salient facts about the adverse health effects associated with dermal exposures to a neat chemical or mixture. Commercial-grade compounds may contain a contaminant, which has been defined as:

1. A chemical that is unintentionally present within a neat substance or mixture in concentrations less than 1.0% (<1.0%) [OSHA 2005], or
2. A chemical that is recognized as a potential carcinogen present within a neat substance or mixture in concentrations less than 0.1% (<0.1%) [OSHA 2005].

Contaminants may be discussed within the supporting documentation for a specific compound, but the skin notations apply solely to the neat substance or mixture due to the potential for the contaminant to represent a unique occupational hazard. If a contaminant is deemed to represent a substantial health risk for workers following contact of the skin, it may be independently evaluated to determine if assignment of skin notations is appropriate.

Isomers are molecules that exhibit unique physical structures, despite consisting of the same elementary composition and weight. Variations within the chemical

properties of isomers of a molecule may result in significant differences in toxic potency. Unless otherwise noted, skin notations derived for a chemical that displays isomerism apply strictly to the structural arrangements specified within the supporting documentation of the compound.

• G.2 Globally Harmonized System (GHS) of Classification and Labeling of Chemicals

GHS is an international classification and labeling system for chemicals adopted by the United Nation (UN) in 2003 to ensure their safe use, transport and disposal [UNECE 2005]. The GHS criteria for the classification of chemicals is based on health (toxicological), physical (flammability) and environmental hazards, as well as specifying what information should be included on labels of hazardous chemicals and safety data sheets. The GHS criteria outline a similar strategy as presented in this CIB for the classification and labeling of chemicals to warn against the health risks of dermal exposures including systemic toxicity, skin irritation, or corrosivity, and sensitization [UNECE 2005]. Table G.2 has been included to aid in harmonizing the GHS classification system and the new NIOSH skin notations for acute systemic toxicity (lethality), direct effects of the skin and sensitization. The GHS assignment will be included within the skin notation profiles to support the assignment of the new NIOSH skin notations.

Table G.2 Coordination of the GHS classification system and the new NIOSH skin notations

Health Hazard	GHS Assignment (mg/kg body weight)	NIOSH Assignment (mg/kg body weight)
Acute systemic toxicity (Lethality)	Symbol: Skull and Crossbones Signal word: Danger Dermal: Fatal in contact with skin (Criteria: LD_{50} < 200)	SK: SYS (FATAL) (Criteria: LD_{50} < 200)
	Symbol: Skull and Crossbones Signal word: Danger Dermal: Toxic in contact with skin (Criteria: 200 < LD_{50} < 1000)	SK: SYS (Criteria: 100 < LD_{50} < 2000)
	Symbol: Exclamation mark Signal word: Warning Dermal: Harmful in contact with skin (Criteria: 1000 < LD_{50} < 2000)	SK: SYS (Criteria: 200 < LD_{50} < 1000)
	Symbol: No symbol Signal word: Warning Dermal: May be harmful in contact with skin (Criteria: 2000 < LD_{50} < 5000)	No equivalent assignment
Direct effects of the skin	Symbol: Corrosion Signal word: Danger Dermal: Causes severe skin burns and eye damage	SK: DIR (COR)
	Symbol: Exclamation mark Signal word: Warning Dermal: Causes skin irritation	SK: DIR (IRR)
	Symbol: No symbol Signal word: Warning Dermal: May be harmful in contact with skin	SK: DIR
Sensitization	Symbol: Exclamation mark Signal word: Warning Dermal: May cause an allergic skin reaction	SK: SEN

• G.3 Nanotechnology and dermal toxicity

Nanotechnology is a system of innovative methods to control and manipulate matter at near-atomic scale (1 to 100 nanometers) to produce new materials, structures, and devices. Examples of nanoparticles include carbon-based materials (i.e. nanotubes and fullereness), metal-based materials (i.e. quantum

dots, metal oxides, nanogold, and nanosilver), nanocomposites, and dendrimers. Because of their small size and large surface area, engineered nanoparticles may have chemical, physical, and biological properties distinctly different from and greater than fine particles of similar chemical composition [NIOSH 2007]. These variations may result in unique health hazards for workers employed to manufacture or use products containing nanomaterials.

Limited information is currently available to accurately assess the health risks of dermal exposures to nanoparticles. The results from *in vitro* studies using primary or cultured human skin cells report the ability of single-walled and multi-walled carbon nanotubes to enter cells and cause the release of pro-inflammatory cytokines, oxidative stress, and decreased viability [Shvedova et al. 2003; Monteiro-Riviere et al. 2005]. More recent studies have reported the ability of quantum dots and fullereness to penetrate the stratum corneum by passive diffusion, in addition to inducing inflammatory response and cytotoxicity within dermal fibroblast and keratinocytes [Sayes et al. 2005; Ryman-Rasmussen et al. 2006]. Factors, including size, shape, water solubility, and surface coating, may directly affect a nanoparticle's potential to penetrate the skin [Sayes et al. 2004; Ryman-Rasmussen et al. 2006].

The occupational health risks posed by dermal exposures to the different forms of nanoparticles are unclear. For this reason, skin notations derived from neat chemical substances or mixtures with similar chemical composition to a specific

form of nanoparticles may be not be applicable due to the different physiochemical properties and toxic potential. As new data become available, the skin notations and supporting documentation will address the dermal toxic potential of nanoparticles when warranted. Additional information and guidance on safe work practices associated with nanoparticles can be found within the NIOSH document, *Approaches to Safe Nanotechnology: an Information Exchange with NIOSH* [NIOSH 2007].

• Appendix G References

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