



# *Current Intelligence Bulletin 61*

## **A Strategy for Assigning New NIOSH Skin Notations**



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Centers for Disease Control and Prevention  
National Institute for Occupational Safety and Health





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## Foreword

The National Institute for Occupational Safety and Health (NIOSH) has estimated that workplace skin diseases account for 15%–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. Skin exposures to chemicals can cause a wide array of injuries and illness including contact dermatitis, immune-mediated responses, and irreversible damage to the skin. Despite the relatively high incidence of contact dermatitis and other workplace skin diseases, the impact and risk of skin contact with chemicals and other hazardous agents are not well known, hampering the recognition and prevention of these disorders. Additionally, skin contact represents a significant route of exposure for chemicals that have the potential to be percutaneously absorbed and subsequently cause systemic effects including, but not limited to, acute toxicity, cancers, neurotoxicity, and effects on the reproductive system.

NIOSH has long recognized the hazards of skin contact with chemicals in the workplace and 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 established to promote the identification and control of skin 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, through its Immunological and Dermal Cross-Sector Program, continues to investigate methods for protecting workers from hazardous skin exposures and for reducing the prevalence of occupational skin diseases.

NIOSH skin notations are hazard warnings used worldwide to alert workers and employers to the health risks of skin 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 skin exposures to chemicals. This new strategy is a form of hazard identification that advances our understanding of the hazards posed by skin exposures to chemicals. Such improved understanding will enable us to implement better risk management practices and controls for the prevention of workplace skin diseases

and other occupational diseases where skin exposure may contribute to disease development.

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## Executive Summary

For more than 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 hazards of skin 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 definition, a NIOSH skin notation may be assigned to a chemical only if that substance has been scientifically determined to be dermally absorbed. The current, widespread practice of using a skin notation to indicate that a substance poses other health effects, such as skin irritation, following any kind of skin exposure is inaccurate and misleading.

### Difficulties with Assigning Current NIOSH Skin Notations

NIOSH adopted the skin notations 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 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 skin irritation and corrosion, thereby causing confusion about what types of risk-management practices should be undertaken to prevent skin exposure.
3. The NIOSH skin notation does not reflect the contemporary state of scientific knowledge or recommendations made in NIOSH criteria documents since the 1988 Permissible Exposure Limit update.

### New Strategy for Assigning NIOSH Skin Notations

This document, *Current Intelligence Bulletin (CIB) 61: A Strategy for Assigning New NIOSH Skin Notations*, 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 do the following:

- Ensure that the assigned skin notations reflect the contemporary state of scientific knowledge
- Provide transparency behind the assignment process
- Communicate the hazards of chemical exposures of the skin
- 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 that are highly or extremely toxic and may be potentially lethal or life-threatening following exposures of the skin 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 or life-threatening following acute contact with the skin. Substances identified to cause direct effects (i.e., damage or destruction) to the skin limited to or near the point of contact are labeled SK: DIR, and those resulting in skin irritation and corrosion at the point of contact are labeled as SK: DIR (IRR) and SK: DIR (COR), respectively. The SK: SEN notation is used for substances identified as causing or contributing to allergic contact dermatitis (ACD) or other immune-mediated responses, such as airway hyper reactivity (asthma). Candidate chemicals may be assigned more than one skin notation when they are identified to cause multiple effects resulting from skin exposure. For example, if a chemical is identified as corrosive and also contributes to systemic toxicity, it will be labeled as SK: SYS-DIR (COR). When scientific data for a chemical indicate that skin exposure does not produce systemic, direct, or sensitizing effects, the compound will be assigned the notation (SK). The ID<sup>(SK)</sup> notation is assigned to indicate that insufficient data on the health hazards associated with skin exposure to a substance exist at the time of the review to determine whether the chemical has the potential to act as a systemic, direct, or sensitizing agent. The ND notation indicates that a chemical has not been evaluated by the strategy outlined in this CIB and that the health hazards associated with skin exposure are unknown.

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 to chemicals relies on a critical assessment of the following:

- A substance's physicochemical properties
- Reports of human exposures and health effects
- Empirical data from in vivo and in vitro laboratory testing



- Considerations provided by computational techniques, such as predictive algorithms (e.g., QSAR) and mathematical models (e.g., skin permeation)

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 that incorporates the current scientific database on workplace chemicals and dermal toxicity. The new system warns 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 hazard communication and the associated risk management process. The new strategy outlined in this CIB also corresponds with the classification strategy adopted in the *Globally Harmonized System of Classification and Labeling of Chemicals* (GHS) developed by the United Nations (see Appendix G.2). This CIB will be updated as new scientific data becomes available.

Historically, skin notations have been published in the *NIOSH Pocket Guide to Chemical Hazards*. This practice will continue with the NIOSH skin notation assignments for each evaluated chemical being integrated as they become available. A support document called a *Skin Notation Profile* (see Appendix F) will be developed for each evaluated chemical. The *Skin Notation Profile* for a chemical will provide information supplemental to the skin notation, including a summary of all relevant data used to aid in determining the hazards associated with skin exposures.

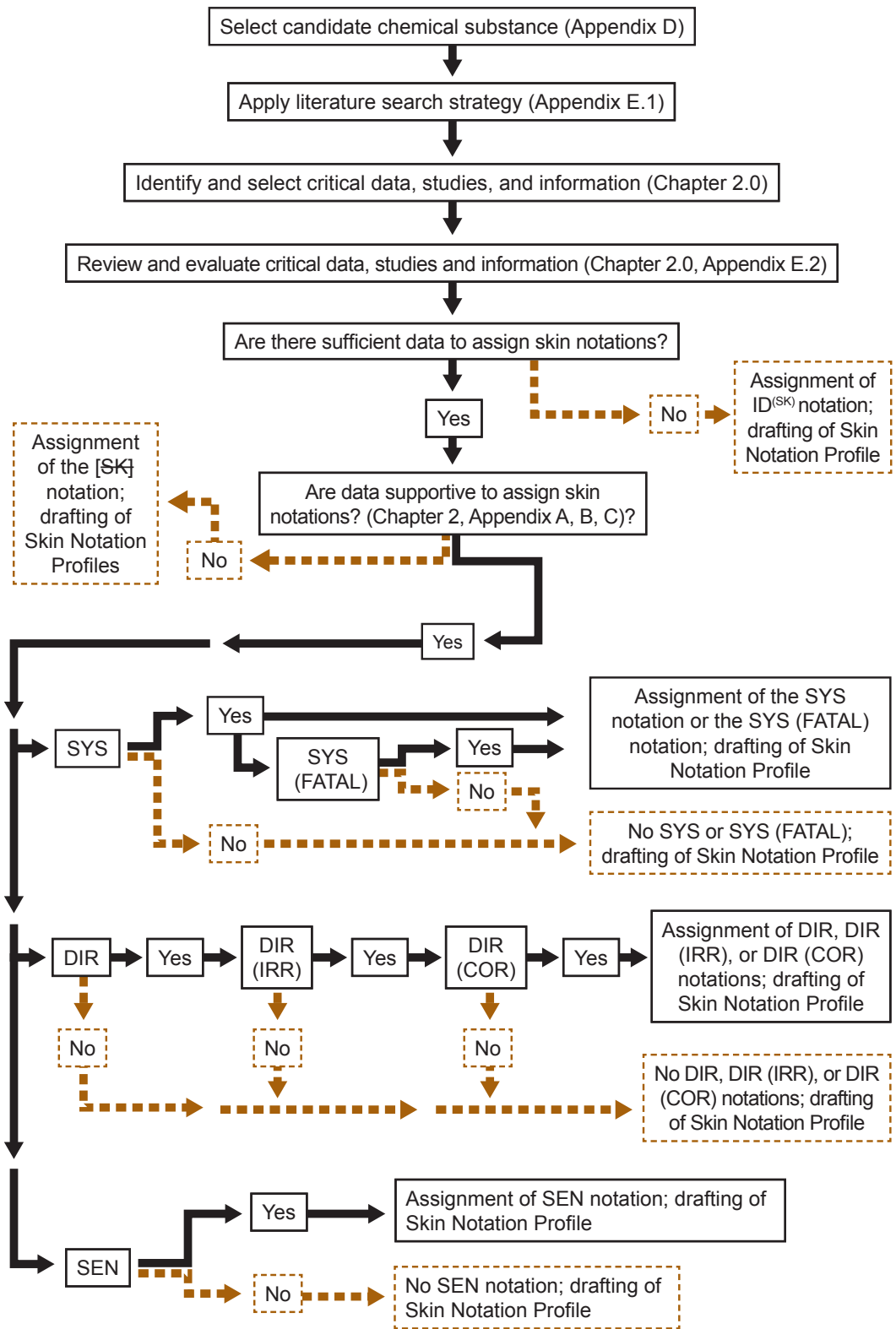


Figure 1. Decision tree for assigning new NIOSH skin notations

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## Abbreviations

ACD	allergic contact dermatitis
ACGIH	American Conference of Governmental Industrial Hygienists
CIB	Current Intelligence Bulletin
cm	centimeter(s)
cm <sup>2</sup>	square centimeter(s)
cm/hr	centimeter(s) per hour
(COR)	subnotation of SK: DIR indicating the potential for a chemical to be corrosive following exposure of the skin
CFR	Code of Federal Regulations
DEREK™	Deductive Estimation of Risk from Existing Knowledge
DIR	skin notation indicating the potential for direct effects to the skin following contact with a chemical
EC	European Commission
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECVAM	European Centre for the Validation of Alternative Methods
(FATAL)	subnotation of SK: SYS indicating chemicals are highly or extremely toxic and may be potentially lethal or life threatening following exposure of the skin
g	gram(s)
g/kg	gram(s) per kilograms of animal body weight
g/kg-day	gram(s) per kilograms of animal body weight per day
GHS	Globally Harmonized System of Classification and Labeling of Chemicals
hr	hour(s)
IARC	International Agency for Research on Cancer

ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
ICSC	International Chemical Safety Cards
ID <sup>(SK)</sup>	skin notation indicating that a chemical has been evaluated, but insufficient data exist to accurately assess the hazards of skin exposure
(IRR)	subnotation of SK: DIR indicating the potential for a chemical to be a skin irritant following exposure to the skin
K <sub>aq</sub>	coefficient in the watery epidermal layer
kg	kilogram(s)
K <sub>OW</sub>	octanol-water partition coefficient
K <sub>p</sub>	skin permeation coefficient
K <sub>pol</sub>	coefficient in the protein fraction of stratum corneum
K <sub>p<sub>sc</sub></sub>	permeation coefficient in the lipid fraction of stratum corneum
LD <sub>50</sub>	lethal dose 50% by skin, oral, and intradermal routes
LLNA	local lymph node assay
LOAEL	lowest-observed-adverse-effect level
LOEL	lowest-observed-effect level
m	meter(s)
m <sup>2</sup>	squared meter(s)
m <sup>3</sup>	cubic meter(s)
MEST	mouse ear swelling test
µg/cm <sup>2</sup>	microgram of a substance/ squared centimeter
mg	milligram(s)
mg/cm <sup>3</sup>	milligram(s) of a dissolved substance/cubic centimeter meter of solute
mg/cm <sup>3</sup> /hr	milligram(s) of a dissolved substance/cubic centimeter meter of solute/hour
mg/kg	milligram(s) of a substance/kilograms animal body weight
mg/kg-day	milligram(s) of a substance/kilograms animal body weight as a daily dose



mg/m <sup>3</sup>	milligram(s) of a substance per cubic meter of air
MW	molecular weight
ND	notation used to indicate that a chemical has not been evaluated by the strategy outlined in this CIB, and that the health risks associated with skin exposure are unknown.
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
QSAR	quantitative structure-activity relationship
QSPR	quantitative structure-permeability relationship
RF	retention factor
RTECS	Registry of Toxic Effects of Chemical Substances
R-phrases	risk phrases
SAR	structure-activity relationship
SI ratio	ratio of the skin dose to the inhalation dose
SEN	skin notation indicating the potential for immune-mediated reactions following exposure of the skin
SK	skin notation
<del>SK</del>	skin notation indicating that the reviewed data did not identify a health risk associated with skin exposure
SYS	skin notation indicating the potential for systemic toxicity following exposure of the skin
S <sub>w</sub>	water solubility
TER	transcutaneous electrical resistance assay
U.S. EPA	U.S. Environmental Protection Agency

## Glossary

**Absorption**—The transport of a chemical from the outer surface of the skin into both the skin and systemic circulation (including penetration, permeation, and resorption).

**Acute**—Contact with a chemical that occurs once or for only a short period of time.

**Cancer**—Any one of a group of diseases that occurs when cells in the body become abnormal and grow or multiply out of control.

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

**Cutaneous (percutaneous)**—Referring to the skin.

**Dermal**—Referring to the skin.

**Dermal contact**—Contact with (touching) the skin.

**Dermatosis**—A disease or disorder of the skin.

**Direct effects**—Localized non-immune mediated adverse health effects to the skin occurring at or near the point of contact, including corrosion, primary irritation, changes in skin pigmentation, and reduction/disruption of the skin barrier integrity, following skin exposure to chemicals.

**Immune-mediated responses**—Responses mediated by the immune systems including allergic responses.

**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 skin exposure to a photo reactive chemical and subsequent exposure to sunlight.

**Phototoxicity**—The elicitation or increase of a toxic response after skin exposure to a photo reactive chemical and subsequent exposure to sunlight.

**Sensitization**—A specific immune-mediated response that develops following exposure to a chemical, which, upon re-exposure, can lead to allergic contact dermatitis (ACD) or other immune-mediated diseases such as asthma, depending on the site and route of re-exposure.

**Substance**—A chemical.

**Systemic effects**—Systemic toxicity associated with skin absorption of chemicals after exposure of the skin.

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# A Strategy for Assigning New NIOSH Skin Notations

## 1 Introduction

The skin<sup>\*</sup> is the largest organ of the human body and accounts for more than 10% of the body's mass. It enables the body to readily interact with the environment and also serves as a general defense system. It also represents a potentially significant exposure pathway for many chemicals because of the large surface area [1.5–2.0 squared meters (m<sup>2</sup>)] available for contact to any one of the innumerable potentially toxic substances in the workplace. The health and economic impacts of such exposures are not fully understood because of the inherent difficulties in differentiating between the contribution of dermal absorption of a chemical and other routes of entry (i.e., inhalation and ingestion) to total body burden and subsequent onset of a specific disease or disorder. Additionally, less attention is often given to characterizing occupational and environmental exposures of the skin to chemicals than is given to other exposure pathways. These limitations potentially leave exposed workers susceptible to a wide spectrum of adverse health outcomes including dermatoses, systemic toxicity, and, in extreme cases, death.

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* to alert workers and employers to the potential of skin absorption [NIOSH 2005]. This skin notation was adopted by NIOSH in its testimony on the Occupational Safety and Health Administration (OSHA) Proposed Rule on Air Contaminants (Permissible Exposure Limit update) on August 1, 1988 [NIOSH 1988]. Despite the usefulness of the notation [skin] as a risk management tool, it provides little guidance about a chemical other than warning of its possible absorption through the skin.

The assignment of skin notations has several inconsistencies and limitations:

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 CFR 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. A single skin notation assigned to a chemical was often used to warn of serious dermal effects other than systemic toxicity—effects such as irritation, corrosion, and sensitization. According to its

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<sup>\*</sup>The terms dermal, cutaneous, and percutaneous refer to the skin. These terms are used interchangeably within this document.

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

3. The skin notation does not reflect the contemporary state of scientific knowledge or include recommendations made

in NIOSH criteria document since the 1988 Permissible Exposure Limit update project. For example, the criteria document for ethylene glycol monomethyl ether, ethylene glycol monoethyl ether, and their acetates recommends that skin exposures to these chemicals be avoided because of their ability to be readily absorbed by the skin [NIOSH 1991]. However, none of these chemicals has been assigned a skin notation.



## 2 Assigning Skin Notations

The *Current Intelligence Bulletin (CIB) 61: A Strategy for Assigning New NIOSH Skin Notations* provides an updated and formalized strategy for the assignment of skin notations capable of distinguishing among systemic, direct, and sensitizing effects caused by exposures of the skin to chemicals. The strategic framework outlined within this document is a form of hazard identification that has been designed to accomplish the following:

1. Ensure that the assigned skin notations reflect the contemporary state of scientific knowledge
2. Provide transparency to the assignment process
3. Communicate the hazards of chemical exposures of the skin
4. 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 hazard from skin 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 subnotation of SYS, indicates that a chemical is highly or extremely toxic, and may be potentially lethal or life-threatening following skin exposures.

- **DIR** indicates non-immune mediated direct effect(s) of a chemical on the skin at or near the point of contact, including corrosion, primary irritation, bleaching (blanching), staining, and reduction/disruption of the skin barrier integrity.
  - **(IRR)**, a subnotation of DIR, indicates that a chemical is a skin irritant.
  - **(COR)**, a subnotation of DIR, indicates that a chemical is a corrosive.
- **SEN** indicates that skin exposure to a chemical may cause or contribute to the onset of allergic contact dermatitis (ACD) or other immune-mediated responses, such as airway hyper reactivity (asthma).
- **SK** indicates that the reviewed data identified no health hazard associated with skin exposure and did not support assignment of the SYS, DIR, or SEN notation.
- **ID<sup>(SK)</sup>** indicates that insufficient data were available at time of evaluation to determine the hazards associated with dermal contact to a candidate chemical substance.
- **ND** indicates that a chemical has not been evaluated by the improved skin notation strategy, and the health hazards associated with skin exposure are unknown.

The new system also permits the assignment of several skin notations for a chemical when multiple skin hazards exist. For example, if health data indicate that the chemical causes systemic toxicity when absorbed by the skin and is also corrosive, the notation assigned to the chemical would be SK: SYS-DIR (COR). The skin notations may be modified or additional skin notations may be added when improved scientific data on test methods and increased understanding about the toxicological mechanisms of skin injuries become available.

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 subnotation under the DIR notation and acute lethality a subnotation 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 skin exposures to chemicals and should not be used to infer toxic potency for evaluated chemicals. Other issues associated with skin notations include their application to chemical mixtures, the health effects of contaminants within neat substances, and isomeric variations of a chemical. Because of the complexity of assessing the hazards of chemical interactions associated with complex mixtures or because of the presence of contaminants, the skin notations are intended to apply to neat chemicals 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 nonspecified isomeric forms of the chemical (see Appendix G.1).

The new skin notations will be included within future NIOSH publications, including the *NIOSH Pocket Guide to Chemical Hazards*. Future versions of the *NIOSH Pocket Guide to Chemical Hazards* will have the skin notation assignments for each evaluated substance [e.g., SK: SYS-DIR (COR)] and an overview of the new skin notations. A separate publication called a *Skin Notation Profile* (see Appendix F) will provide an in-depth summary of the

relevant data used to aid in determining the hazards associated with skin exposures.

## 2.1 Criteria for Assigning Skin Notations

The critical step in assigning skin notations to a chemical is determining its *hazard potential*—that is, its potential for causing adverse health effects as a result of skin exposure. This determination involves a health hazard identification process that assesses the following:

- Scientific data on the physicochemical properties of a chemical
- Human exposures and health effects
- Empirical data from *in vivo* and *in vitro* laboratory testing
- The use of computational techniques, including predictive algorithms [e.g., quantitative structure-activity relationships (QSAR)] and mathematical models that describe a selected process (e.g., skin permeation) using analytical or numerical methods.

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.

Computational techniques, such as mathematical models and predictive algorithms, represent alternative methods to expensive *in vivo* and *in vitro* toxicity testing methods. These approaches are increasingly applied to estimate the potential of chemicals to act as skin irritants and sensitizers and their potential to be absorbed (i.e., skin permeation). The performance and reliability of these computational techniques remain unclear. For this reason, predications from computational techniques,



**Figure 2.** Hierarchy of evaluated scientific data

such as QSARs and the skin dose to inhalation dose ratio (SI ratio) (see Appendix B), should not be used as the primary basis for the assignment of a skin notation. Instead, they are intended only to serve as additional supportive data sources when limited data are available for the assignment of skin notations. As the computational techniques become more reliable and validated, NIOSH will reassess their use

within the assignment of skin notations. If it is determined that the computational techniques accurately predict the effects of skin exposures to chemicals, they may become a primary basis for the assignment of skin notations.

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]. Appendix G.2 contains supplemental information on the harmonization of the NIOSH skin notations with GHS.

## 2.2 SYS

The SYS notation is assigned to chemicals that are absorbed through the skin and contribute to systemic toxicity. The (FATAL) subnotation is assigned to chemicals identified as highly or extremely toxic and potentially lethal or life-threatening following skin exposure. The following are examples of adverse systemic effects that human and animal data have shown to be associated with skin exposures to chemicals with the assignment of the SYS notation or its subnotation (FATAL):

- Cardiotoxicity
- Carcinogenesis and photocarcinogenesis (excluding cancers of the skin) (see Appendix G.3)
- Hematotoxicity
- Hepatotoxicity
- Histopathological changes
- Immunotoxicity
- Lethality

- Neurotoxicity
- Nephrotoxicity
- Reproductive and developmental effects

Systemic immune-mediated responses associated with exposures of the skin to chemicals are not assigned the SYS notation despite being systemic effects. These immune-mediated responses would be assigned the SEN notation if supportive data are identified, and they are addressed within Section 2.4.

Standardized and widely accepted research protocols exist for using animals to test the systemic toxicity of skin exposures to chemicals:

- Protocols for testing chemicals developed by the Organization for Economic Cooperation and Development (OECD) and European Centre for the Validation of Alternative Methods
- Health effects testing guidelines developed by the U.S. Environmental Protection Agency (U.S. EPA) Office of Prevention, Pesticides, and Toxic Substances
- Protocols established by the National Toxicology Program (NTP) for determining the prechronic toxicity and chronic toxicity/carcinogenesis of toxic substances

Experimental toxicity studies using these protocols frequently result in 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:

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

- Data from experimental animal studies indicate—
  - Systemic effects occurred from skin exposures.
  - Fatalities or health effects in exposed animals were not associated with skin damage by the chemical or the vehicle containing the chemical.
  - Skin exposure results for animals included data on acute toxicity, repeat-dose toxicity, subchronic toxicity, chronic toxicity, carcinogenicity, or biologic system/function-specific effects.

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

- Studies of scientific merit that followed protocols other than those previously identified and demonstrated systemic effects from skin exposure to a chemical. The protocols may be modifications of the standardized protocols with variations in the evaluation procedures, or they may be designs allowing for examination of health endpoints other than those the standardized protocols allow for. 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 with skin absorption or potential systemic toxicity 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
- If no acceptable-quality empirical data exist for systemic effects from skin 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 toxicokinetics 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 alternative routes of exposure and skin exposures.

Both conditions must be satisfied to assign a SYS notation.

- When no acceptable-quality empirical data exist on the systemic effects of skin exposure, the potential for dermal absorption and consequent systemic toxicity of the chemical may be mathematically estimated via computational techniques. To mathematically determine the risk for systemic toxicity (e.g., predictive algorithm), the following information is needed: (1) skin permeation rate, (2) chemical dose calculated to be absorbed through skin (skin dose), (3) 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) 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 skin 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. The results of the predictive algorithm should not be used as the sole basis of the assignment of a SYS notation.

Table 2.2 provides an overview for the assignment of the SYS notation based on the criteria outlined within this section, in addition to Appendices A and B. Variables considered for the assignment of the SYS notation within this model include systemic toxicity associated with skin exposures and 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.

### 2.3 DIR

Direct effects are non-immune mediated adverse health effects resulting in damage or destruction of the skin localized at or near the point of contact. 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



**Table 2.2. Overview for the assignment of the SYS notation**

		Systemic toxicity		
		Yes	No	No data
Dermal absorption	Yes	SYS*	SYS <sup>†</sup>	SYS <sup>‡</sup>
	No	SYS	SYS	SYS
	No data	SYS	SYS	No assignment <sup>§</sup>

\*Indicates categories where the SYS notation would be assigned

<sup>†</sup>Indicates categories where the SYS notation would not be assigned

<sup>‡</sup>Assignment of the SYS notation is based on criteria outlined in NIOSH [2009]

<sup>§</sup>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.

in experimental animal studies are frequently used as indicators of skin irritation. Along with these reports, *in vitro* studies have shown that chemical contact with the skin may reduce the skin's integrity as a barrier to penetration. Semiquantitative 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 immune-mediated 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 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 subnotations:

- Carcinogenesis and photocarcinogenesis of the skin (see Appendix G.3)
- 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

A chemical will be assigned the (IRR) subnotation when the reviewed data indicate that exposure of the skin to the substance causes reversible adverse effects, including inflammation, dryness, or redness with minor pain or discomfort, at or near the point of contact. The (COR) subnotation will be assigned when a chemical is known to cause irreversible

adverse effects accompanied by pain or discomfort, such as tissue lesions or blisters, and burns of varying degrees at or near the point of contact. Skin irritants that are identified to cause corrosion will be assigned only the SK: DIR (COR) notation to ensure that the most hazards endpoint is recognized.

Immune-mediated responses of the skin associated with exposures of the skin to chemicals, such as ACD and allergic urticaria, are not assigned the DIR notation. These immune-mediated responses would be assigned the SEN notation if data are supportive and are addressed within Section 2.4.

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

- 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. The effects consist of the following:
  - 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
  - Chloracne caused by chemicals such as halogenated aromatic hydrocarbons
  - Defatting/drying of skin
  - Skin cancer at or near the point of contact

Predictive patch tests conducted on human volunteers (e.g., the acute dermal irritation study in human volunteers) may also yield information about acute or cumulative irritation of human skin [OECD 1997]. Such information will be considered when assigning skin notations.

- 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 skin exposure to chemicals. Appendix A describes protocols and the criteria that can be used for deriving SK: DIR notations.
- Relevant scientific data not generated using the study protocols previously described 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.
- 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 alternative methods 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 corrosivity potential of acidic or alkaline chemicals on the skin. 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

Skin exposure to a chemical may cause or contribute to the onset of ACD or other immune-mediated responses, such as airway hyper reactivity (asthma). Occupationally, the most commonly recognized immune-mediated responses following skin exposure is ACD. For ACD, the skin-sensitizing potential of the chemical is typically evaluated by two endpoints—the immunologic induction of sensitization and the elicitation of ACD. The SEN notation may be assigned to the following types of immune-mediated responses caused by or contributed to exposures of the skin:

- ACD
- Systemic allergic reactions
- Immune-mediated respiratory diseases

Immune-mediated responses are commonly associated with two immune mechanisms: the immediate hypersensitivity response (which, in a previously sensitized person, normally occurs within minutes of exposure) and the delayed hypersensitivity response (which occurs 24–72 hours following exposure). Immediate responses are primarily mediated by immunoglobulin E antibodies when the chemical-specific antibodies in systemic circulation contact antigens such as exogenous proteinaceous molecules. In the immediate hypersensitivity reaction, the respiratory tract, in addition to the skin, may respond after dermal exposure to the causative agent. Delayed hypersensitivity response 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.

Results of animal and human studies support a link between exposures of the skin to certain chemical allergens, systemic sensitization, and the subsequent development of lung allergic responses following inhalational exposures [Kimber 1996; Beck and Leung 2000; Tinkle et al. 2003; Day et al. 2006; Bello et al. 2007; Kreiss 2007; Redlich and Herrick 2008; Pauluhn 2008]. Animal studies in several species have shown that skin exposure to isocyanates followed by inhalational challenge is highly effective at inducing asthmatic lung responses. [Bello et al. 2007; Pauluhn 2008]. Human studies, although more limited, suggest a similar role following skin exposure to certain sensitizing chemicals [Beck et al. 2000; Day et al. 2006; Kreiss et al. 2007; Redlich et al. 2008]. Despite

decreased inhalation exposures to isocyanates and beryllium within various occupational settings, immune-mediated respiratory diseases associated with these compounds continue to occur, frequently in settings with opportunities for skin exposure [Bello et al. 2007; Kreiss et al. 2007; Redlich et al. 2008]. Together, the human and animal data suggest that skin contact with certain chemical allergens may contribute to the development of immune-mediated respiratory diseases, such as asthma or chronic beryllium disease [Bello et al. 2007; Kreiss et al. 2007; Redlich et al. 2008].

In laboratory testing, chemical 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 immune-mediated response include the following [ECETOC 2002]:

- Analytical or descriptive epidemiologic studies
- Observational case reports from health surveillance programs and/or poison control centers
- Clinical studies

**Note**—The main purpose of clinical tests with human volunteers is to confirm the safety of test materials or preparations rather than to identify skin sensitization hazards.

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

- Credible evidence indicates the occurrence of ACD or sensitization as a result of chemical exposure of 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 findings. Information about human immune-mediated 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:
  - Studies in which sensitization is evident from valid clinical investigations (e.g., patch testing or antigen-specific immune responses, such as antibody responses or lymphocyte proliferation)
  - Confirmed case reports describing several subjects in more than one independent study
  - Epidemiologic evidence establishing a causal relationship between exposure and sensitization

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

- Animal data indicate the potential for ACD or other immune-mediated responses associated with skin exposure. Such animal data include the guinea pig sensitization tests identifying sensitization or ACD, LLNA, mouse ear swelling test, and relevant animal models of asthma. Appendix A describes protocols and criteria that can be used in assigning the SEN notation.

- Scientific data other than those previously described may be used to demonstrate sensitization as a result of skin exposure to a chemical. Such protocols include those that 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 antigen-mediated responses following skin exposure.
- When no empirical data of acceptable quality exist, the occurrence of ACD or other immune-mediated responses as a result of skin exposure to a chemical, information from the SAR-based analysis, and other computational techniques can be used as alternative methods 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 and 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 skin exposure and assigning the SEN notation.

## 2.5 SK

The SK notation is assigned to indicate that a chemical underwent a critical assessment, based on the criteria described above, of the scientific data and was not identified as a systemic, direct, or sensitizing health risk from skin exposure. It should be noted that for a

chemical to be assigned the SK notation, the scientific data must be classified as *sufficient* based on the criteria outlined in Appendix E.

## 2.6 ID<sup>(SK)</sup>

The ID<sup>(SK)</sup> notation indicates that insufficient data exist on the health hazards associated with skin exposures to a substance to determine if the chemical has the potential to act as a systemic, direct, or sensitizing agent. Assignment of this notation will be determined through an assessment of a chemical's creditable scientific data identified during an extensive search of published literature (see Appendix E). Chemicals designated with the ID<sup>(SK)</sup> notation may represent a significant health hazard following contact with the skin, and proper controls should be applied to prevent or minimize occupational exposures. Despite the absence of sufficient data to assign the SYS, DIR, or SEN notation, a Skin Notation Profile (see Appendix F) will be drafted for all chemicals assigned ID<sup>(SK)</sup> to document that the substance has been previously evaluated.

## 2.7 ND

The ND notation signifies that a chemical has not been evaluated by the strategy outlined in this CIB, and the associated health hazards of skin exposure are unknown. The ND notation will be included within future NIOSH publications, including the *NIOSH Pocket Guide to Chemical Hazards*.

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# APPENDIX A • Protocols Used in Studies of Health Effects from Skin 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 skin 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 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 skin 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 the terms penetration, permeation, and resorption. Experimental techniques used to estimate the potential for absorption include *in vivo* and *in vitro* toxicity studies and computational techniques.

*In vivo* and *in vitro* test methods have been developed to estimate both the rate and percentage of an applied dose of a substance absorbed (i.e., penetration or permeation) through the skin [OECD 2004a,b,c; IPCS 2006]. *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 skin penetration, permeation, and resorption of test chemicals [OECD 2004a; OECD 2004c; IPCS 2006]. *In vitro* dermal absorption tests generally rely on the application of a radiolabelled 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; U.S. EPA 2004; OECD 2004b]. In both *in vivo* and *in vitro* experimental studies, the applied dose and the vehicle may directly influence the absorption of the substance across the skin.

Computational techniques, such as QSARs and QSPR, have been developed to offer a relatively inexpensive method for determining skin penetration of chemicals [Moss et al. 2002; Riviere and Brooks 2005; IPCS 2006]. The predictive

algorithms use the physicochemical properties (i.e., molecular weight, solubility, pH) of a test substance to estimate the potential biologic effects or transport properties within a biologic system [Moss et al. 2002; Riviere and Brooks 2005; OECD 2004a; IPCS 2006].

The results of dermal absorption tests are frequently presented as the estimated or predicted percentage (%) of the applied dose absorbed. To differentiate between low and high dermal absorption, a 10% absorption rate has been selected as the critical 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 to contribute to systemic dose.

### A.1.2 Acute toxicity

Acute toxicity testing examines the mortality of test animals after single, short-term exposures to a toxic chemical [OECD 1987; U.S. EPA 1998a]. Typically, the test chemical is applied to the skin and remains in place for 24 hours. The animals are then observed for 14 days. The results of acute toxicity tests are presented as the dose that is lethal to 50% of the exposed animals ( $LD_{50}$ ) following application of the chemical to the skin, with observations of behavioral/clinical abnormalities and pathologic findings from gross necropsy. If the  $LD_{50}$  values are consistently lower than the critical cutoff value of 2000 milligrams of a substance/kilograms animal body weight (mg/kg), 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 toxicity. This value corresponds with the upper  $LD_{50}$  limit for establishing a chemical as *harmful* 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  $LD_{50}$  values are consistently lower than the critical cutoff value of 200 mg/kg of animal body weight, the chemical is potentially lethal or life-threatening following acute exposures of the skin 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 (see Appendix G.2.).

### A.1.3 Repeat-dose toxicity

Repeat-dose toxicity testing examines the toxic effect(s) of repeated exposure of the skin to a chemical for 21 or 28 days [OECD 1981a; U.S. 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 critical 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 NOAEL value of 1000 mg/kg-day reflects the dose selected in the standardized limit tests to identify chemicals with the potential for repeat-dose toxicity following contact with the



skin. 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 for comparison with the critical cutoff value of 1000 mg/kg-day.

#### **A.1.4 Subchronic toxicity**

Subchronic toxicity testing examines the cumulative toxic effect(s) from continuous or repeated exposure of the skin to a chemical for at least 90 days [OECD 1981b; U.S. 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 critical 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 NOAEL value of 1000 mg/kg-day reflects the dose selected in the standardized limit tests to identify chemicals with the potential for subchronic toxicity following contact with the skin. 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 critical cutoff value of 1000 mg/kg-day.

#### **A.1.5 Chronic toxicity**

Chronic toxicity testing examines the cumulative toxic effect(s) of continuous or repeated exposure of a chemical to the skin for at least 12 months [OECD 1981c; U.S. 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 critical cutoff value of 1000 mg/kg-day, the chemical is considered systemically toxic following skin exposure and is assigned the SYS notation. The critical cutoff value of 1000 mg/kg-day reflects the dose selected in the standardized limit tests to identify chemicals with the potential for chronic toxicity following contact of the skin. 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 exposure of the skin to a chemical for 18–24 months [OECD 1981d; U.S. EPA 1998e]. The test period constitutes a substantial portion of the lifespan 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 and for gross organ lesions and tissue histopathology at necropsy. Carcinogenicity from skin exposure to a chemical may be studied and reported jointly with chronic toxicity following exposures of the skin [OECD 1981e; U.S. 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 dermal absorption and subsequent exposure to sunlight) [NIH 2002a; OECD 2004d]. If a candidate chemical 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 exposures of the skin on organ systems or biologic functions**

Several types of tests allow for the examination of the destruction or disruption of target organ systems and/or biologic functions from skin exposure to chemicals. Examples include (1) prenatal development toxicity (maternal and fetal toxicity) testing [U.S. EPA 1998g; NTP 2001b; OECD 2001a], (2) two-generation reproduction and fertility effects testing [U.S. EPA 1998h; OECD 2001b], and (3) immunotoxicity (suppression of the immune system) testing [U.S. EPA 1998i]. Ideally, a NOAEL is identified and reported for the studied effect(s). If the NOAEL for selected endpoint(s) is lower than 1000 mg/kg-day, the chemical is considered systemically toxic by the dermal route and assigned the SYS notation. The critical 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 biologic functions following contact with the skin. In the event that a NOAEL cannot be identified within reviewed toxicological data, a LOAEL, LOEL, or NOEL may be substituted when available for comparison to the critical cutoff value of 1000 mg/kg-day.

### **A.1.8 Assignment of the SYS notation based on alternative exposure pathways**

Toxicity data associated with alternative exposure pathways (i.e., ingestion, inhalation, and injection) 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 alternative exposure pathways are as follows:

1. No quality dermal toxicity data were identified.
2. Toxicokinetics data clearly demonstrate 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.
4. The critical systemic endpoint(s) is independent of the route of exposure.

## **A.2 Experimental protocols for investigating direct effects of skin 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 [U.S. EPA 1998j; OECD 2002a], a single dose of the test chemical

is applied to the skin of albino rabbits, normally for 4 hours unless corrosion is observed. The animals are examined for signs of erythema and edema, and the responses are scored at intervals over 72 hours. 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 with minor pain or discomfort of the skin is considered an irritant and is assigned the (IRR) notation. The (COR) subnotation will be assigned when a chemical is known to cause irreversible adverse effects accompanied by pain or discomfort, such as tissue lesions or blisters, and burns of varying degrees at or near the point of contact.

### **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 corrosivity of chemicals. The following methods have been standardized by the OECD as guidelines for testing of chemicals and 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® [NIH 1999a]
- The human skin models [OECD 2004e], including EPISKIN™ and EpiDerm™ [NIH 2002b]
- The rat skin transcutaneous electrical resistance (TER) assay [NIH 2002b; OECD 2004f]

The Corrositex® assay evaluates the pH-sensitive destruction of a reconstituted, collagen-based bio barrier and determines the corrosivity potential by measuring the time required for the test material to pass through the bio barrier 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 hours and 1 hour, respectively [Fentem et al. 1998; U.S. 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 at least a 35% decrease in cell viability. In EpiDerm™, the substance is classified as corrosive if it induces at least a 50% decrease in relative cell viability after 3 minutes of exposure or at least an 85% decrease after 60 minutes. The TER assay measures the reduction of inherent TER on the skin of young rats caused by 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 exposure of the skin to a chemical for 18–24 months [OECD 1981d; U.S. 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 skin exposure to a chemical may be studied and reported jointly with chronic toxicity of the skin [OECD 1981e; U.S. EPA 1998f; NTP 2001a]. If skin 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, chemicals identified as being capable of causing photocarcinogenesis when topically applied in conjunction with exposure to sunlight will be included within this category [NIH 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 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 skin 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 and the Buehler test [OECD 1992; U.S. 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 10–14 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 hours 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 local lymph node assay**

The murine LLNA has been peer-reviewed by ICCVAM and the NICEATM panel and recommended for regulatory acceptance [NIH 1999b]. OECD [2002b] and U.S. EPA [2003] have adopted this assay as a standard test method for evaluating the skin sensitization potential for 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 deoxyribonucleic acid (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 greater than or equal to 3 and is supported by a fitting dose-response relationship.



### A.3.3 Identifying skin sensitization potential with the mouse ear swelling test

The mouse ear swelling test (MEST) [Gad et al. 1986; Thorne et al. 1991a,b] is accepted by OECD [1992] and U.S. 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-hour intervals for 2–3 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 [U.S. EPA 2003] before the substance is considered a nonsensitizer.

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# APPENDIX B • Algorithm for estimating skin absorption and systemic toxicity and suggested application for assigning SYS notations

## B.1 Algorithm for estimating and evaluating skin exposure hazards

Appendix B presents a predictive algorithm for estimating and evaluating the health hazards of skin 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
3. Evaluating whether the chemical poses a skin exposure hazard.

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 biologic 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 QSPR or QSAR.

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 U.S. EPA [69 Fed. Reg.<sup>†</sup> 22402 (2004)]. These methods typically measure the

<sup>†</sup>Federal Register. See Fed. Reg. in references.

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 [U.S. 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 as follows:

$$K_p = \frac{1}{\frac{1}{K_{psc}} + \frac{1}{K_{pol}} + \frac{1}{K_{aq}}}$$

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

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

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

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

Exercising caution is important when a QSPR is used in the derivation of  $K_p$ . Many of the empirical QSPRs, which are constrained by the experimental data used in the development and validation, are subject to limitations in the types of chemicals to which the models may apply. These QSPRs may not provide reliable  $K_p$  estimates for inorganic substances, ionized substances, very high-MW chemicals, small hydrophilic molecules, or highly volatile substances. 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 substances 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. Also, 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 substances 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 biologic 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  $K_p$  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 hours to unprotected skin on both palms (a surface area of 360 cm<sup>2</sup>),

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

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 hours, an inhalation volume of 10 m<sup>3</sup> in 8 hours, and a factor of 75% for the retention of the airborne substance in the lungs during respiration (retention factor, RF),

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

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%–100% [European Chemicals Bureau 2003], and the default RF of 0.75 is selected to avoid underestimating skin absorption as a significant route of biologic uptake because 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 with systemic bioavailability lower than the default value (e.g., because of the extensive metabolism of substances in the lungs or accumulation in the blood leading to 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 dermal 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 greater than or equal to 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 of at least 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, SI ratios were calculated for 108 chemicals; all chemicals had assigned NIOSH skin notations, and the literature suggested them to be agents of systemic toxicity following skin exposure. Approximately 76% of the examined substances had SI ratios greater than 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 substances predicted to have an SI ratio less than 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 substances having an SI ratio greater than 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 semiquantitative 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 hour could exceed 10% of the amount absorbed by inhalation when airborne concentrations are at the OEL for 8 hours. The defaults of the exposed skin surface area, the air volume inhaled in 8 hours, and the respiratory RF in the ECETOC algorithm are 2000 cm<sup>2</sup>, 10 m<sup>3</sup>, and 50%, respectively. The SI ratio calculated in the algorithm proposed for recommending the NIOSH SK: SYS notations (SI ratio<sub>NIOSH</sub>) can be modified to derive an SI ratio according to the method proposed by the ECETOC (SI ratio<sub>ECETOC</sub>). A comparison between the SI ratio<sub>NIOSH</sub> and the SI ratio<sub>ECETOC</sub> reveals that

$$\text{SI ratio}_{\text{ECETOC}} = \text{SI ratio}_{\text{NIOSH}} \times [2000 \text{ cm}^2 (\text{hands and arms}) \div 360 \text{ cm}^2 (\text{palms})] \times (1 \text{ hr} \div 8 \text{ hr}) \times [75\% (\text{default RF in NIOSH algorithm}) \div 50\% (\text{default RF in ECETOC algorithm})] = \text{SI ratio}_{\text{NIOSH}} \times 1.04$$

This comparison shows that for any chemical where the modeling approach may be 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 skin exposure are based on essentially the same level of skin absorption.

In view of these findings, dermal 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 greater than 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 to serve as a hazard identification tool for determining whether skin exposure to a chemical agent is inherently capable of provoking systemic toxicity and is supportive of 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-based analysis

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

In *A Sequential Testing Strategy for Dermal Irritation and Corrosion*, the supplement to the *OECD Guideline for Testing of Chemicals 404* [OECD 2002], 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 methods alternative to biologic 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 ( $\leq 2.0$  or  $\geq 11.5$ ) (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 the outlined predictive models [Worth et al. 1998]:

- $\text{pH} \leq 2.0$  or  $\geq 11.5$
- $\text{pH} - (\text{acid reserve} \div 6) \leq 1$  or
- $\text{pH} + (\text{alkali reserve} \div 12) \geq 14.5$

where the acid reserve of a substance is the amount in 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 in grams 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 mixtures based on a series of structure-activity rules (also known as structural rules or structural alerts). These rules describe the substructures 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 guinea pig maximization test conducted for 294 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 discussed the DEREK™ skin sensitization rule base as an alternative to skin sensitization testing. The Workshop recommended that QSAR predictions and expert systems serve as screens for identifying positive substances [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,  $\beta$ -lactams, aldehydes, epoxides, and quaternary ammonium cation.

These structural alerts will be used to evaluate substances for their potential as skin sensitizers when no human or biologic 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 through three primary pathways:

1. When recognized as existing occupational hazards or associated with potential emerging issues
2. When nominated by interested parties, including NIOSH stakeholders, other governmental agencies, and the public
3. When listed in the *NIOSH Pocket Guide to Chemical Hazards*.

Chemicals identified as emerging issues, existing as occupational hazards, or nominated for evaluation will be assessed by NIOSH based on the availability of quality data that clearly outline the hazards 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.2).

## D.2 Selecting and prioritizing candidate chemicals found within the *NIOSH Pocket Guide to Chemical Hazards*

The *NIOSH Pocket Guide to Chemical Hazards* lists 142 chemicals assigned the skin notation

[skin], which indicates the potential for dermal absorption. These substances have been selected to be the first evaluated through the strategic framework outlined in this CIB. As part of this process, a hierarchal ranking scheme that applies a binominal hazard-ranking approach has been developed to aid in the ranking of the many candidate chemicals. Parameters addressed within the hierarchal scheme of prioritizing the candidate chemicals include the following:

- Potential health hazards
- Potential for occupational exposure
- Annual production volume
- OELs recommended by both governmental and nongovernmental organizations.

An array of information resources containing data related to the outlined parameters were assessed to aid in ranking the chemicals to be classified according to the new strategy. The following information resources were applied within this scheme:

### ATSDR Toxicological Profiles (ToxProfiles)

[www.atsdr.cdc.gov/toxpro2.html](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)

[www.cdc.gov/noes/](http://www.cdc.gov/noes/)

**NIOSHTIC-2**

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

**NIOSH Immediately Dangerous to Life and Health (IDLH) Values**

[www.cdc.gov/niosh/idlh/idlh-1.html](http://www.cdc.gov/niosh/idlh/idlh-1.html)

**NIOSH International Chemical Safety Card (ICSC)**

[www.cdc.gov/niosh/ipcs/nicstart.html](http://www.cdc.gov/niosh/ipcs/nicstart.html)

**NIOSH Pocket Guide to Chemical Hazards**

[www.cdc.gov/niosh/npg/](http://www.cdc.gov/niosh/npg/)

**NIOSH Registry of Toxic Effects of Chemical Substances (RTECS)**

[www.cdc.gov/niosh/rtecs/rteccas1.html](http://www.cdc.gov/niosh/rtecs/rteccas1.html)

**NIOSH Recommendations for Occupational Safety and Health, Compendium of Policy Documents and Statements**

[www.cdc.gov/niosh/pubs/all\\_date\\_desc\\_nopubnumbers.html](http://www.cdc.gov/niosh/pubs/all_date_desc_nopubnumbers.html)

**NIOSH Skin Exposures and Effects Topic Page**

[www.cdc.gov/niosh/topics/skin/](http://www.cdc.gov/niosh/topics/skin/)

**OSHA Permissible Exposure Limits**

[www.osha.gov/SLTC/pel/](http://www.osha.gov/SLTC/pel/)

**U.S. EPA High Production Volume Information System (HPV)**

[www.epa.gov/hpvis/](http://www.epa.gov/hpvis/)

The 142 chemicals previously assigned the notation [skin] by NIOSH were systematically assigned a score from 0–7 to determine which substances posed the greatest potential occupational health hazard based on the parameters outlined in Table D.1. The scores for 15 chemicals are illustrated within Table D.2. The hierarchal ranking scheme may be modified in the future to aid NIOSH in prioritizing (1) chemicals listed within the *NIOSH Pocket Guide to Chemical Hazards* that do not have the notation [skin] and (2) chemicals nominated for evaluation from stakeholders, governmental agencies, and public interest groups.

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

<b>Parameter</b>	<b>Definition and scoring</b>
OEL potency	If OEL is < 1 mg/m <sup>3</sup> , 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.

(Continued)

**Table D.1 (Continued). Definition scoring of parameters applied with hierarchal ranking scheme**

<b>Parameter</b>	<b>Definition and scoring</b>
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 potential to expose > 75,000 workers, assign score of 1; if not, assign score of 0.
RTECS or risk phrases (R-phrases)	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 15 candidate chemicals**

<b>Chemical</b>	<b>CAS no.</b>	<b>OEL* Potency</b>	<b>CAN<sup>†</sup></b>	<b>R/DT<sup>‡</sup></b>	<b>IRR/COR<sup>§</sup></b>	<b>SEN<sup>¶</sup></b>	<b>HPV<sup>**</sup></b>	<b>Exposure potential</b>	<b>Skin hazard<sup>††</sup></b>	<b>Overall score</b>
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
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

(Continued)



**Table D.2 (Continued). Example of the application of the hierarchal ranking scheme ranking of 15 candidate chemicals**

<b>Chemical</b>	<b>CAS no.</b>	<b>OEL* potency</b>	<b>CAN†</b>	<b>R/DT‡</b>	<b>IRR/ COR§</b>	<b>SEN¶</b>	<b>HPV**</b>	<b>Expo- sure po- tential</b>	<b>Skin hazard††</b>	<b>Overall score</b>
Diethylenetri- amine	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
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-Dichloropro- pene	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

\*OEL = Occupational Exposure Limits

†CAN = Carcinogen

‡R/DT = Reproductive and Development Toxicant

§IRR/COR = Irritant/Corrosive

¶SEN = sensitizer

\*\*HPV = High Production Volume Chemical

††Skin Hazard = Based on information provided by RTECS and EU risk phrases

# 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) physical and chemical properties of candidate substances, (2) human health effects associated with exposures to substances, (3) reported results of in vivo and in vitro toxicity testing, and (4) estimates of chemical toxicokinetics and toxicity based on computational techniques. The primary sources of information reviewed during the literature search are peer-reviewed journals, domestic and international governmental agencies reports, reference books, private industry reports, and 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:

**European Inventory of Existing Commercial chemical Substances (EINICS)**

<http://ecb.jrc.it/esis/index.php?PGM=ein>

**EMBASE**

[www.embase.com/](http://www.embase.com/)

**Extension Toxicology Network (EXTOXNET)**

<http://extoxnet.orst.edu/pips/ghindex.html>

**Haz-Map: Occupational Exposure to Hazardous Agents (Haz-Map)**

[www.nlm.nih.gov/pubs/factsheets/hazmap.html](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>

**NIOSH Registry of Toxic Effects of Chemical Substances (RTECS)**

[www.cdc.gov/niosh/rtecs/](http://www.cdc.gov/niosh/rtecs/)

**NIOSHTIC-2**

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

**National Toxicology Program Report on Carcinogens (NTP)**

<http://ehis.niehs.nih.gov/roc/>

**OSH References Collection**

<http://ccinfoweb.ccohs.ca/bibliographic/search.html>

**PubMed**

[www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed](http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed)

**Toxicology Literature 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 (U.S. EPA) Substance Registry Services**  
[www.epa.gov/srs/](http://www.epa.gov/srs/)

**Web of Science**  
[http://thomsonreuters.com/products\\_services/scientific/Web\\_of\\_Science](http://thomsonreuters.com/products_services/scientific/Web_of_Science)

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

The following published books, technical documents, and Web sites represent common sources used during the derivation of the new NIOSH skin notations:

**Agency for Toxic Substances and Disease Registry (ATSDR) Public Health Statements (PHS) Web site**  
[www.atsdr.cdc.gov/phshome.html](http://www.atsdr.cdc.gov/phshome.html)

**ATSDR TOXFAQS Web site**  
[www.atsdr.cdc.gov/toxfaq.html](http://www.atsdr.cdc.gov/toxfaq.html)

**ATSDR Toxicological Profiles Web site**  
[www.atsdr.cdc.gov/toxpro2.html](http://www.atsdr.cdc.gov/toxpro2.html)

**American Conference of Governmental Industrial Hygienists (ACGIH)**

**Documentation of the Threshold Limit Values (TLV) for Chemical Substances and Physical Agents**

**American Industrial Hygiene Association (AIHA) Workplace Environmental Exposure Levels Guide (WEEL) Web site**  
[www.aiha.org/webapps/taxonomy/documentrepository/erpgweels/7d11ed78-37da-4ce1-99f2-763603376151.pdf](http://www.aiha.org/webapps/taxonomy/documentrepository/erpgweels/7d11ed78-37da-4ce1-99f2-763603376151.pdf)

**California Environmental Protection Agency (CalEPA) Health Reports Web site**  
[www.calepa.ca.gov/Publications/](http://www.calepa.ca.gov/Publications/)

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

**European Commission Risk Assessment Reports Web site**  
[http://ec.europa.eu/health/ph\\_risk/risk\\_en.htm](http://ec.europa.eu/health/ph_risk/risk_en.htm)

**Hamilton and Hardy's Industrial Toxicology**

**Health and Safety Executive (HSE) Publications Web site**  
[www.hse.gov.uk/pubns/index.htm](http://www.hse.gov.uk/pubns/index.htm)

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

**International Programme on Chemical Safety (IPCS) Web site**  
[www.inchem.org/](http://www.inchem.org/)

**Merck Index**

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

**NIOSH International Chemical Safety Cards (ICSC)**  
[www.cdc.gov/niosh/ipcs/nicstart.html](http://www.cdc.gov/niosh/ipcs/nicstart.html)

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

**NIOSH Publications Web site**  
[www.cdc.gov/niosh/pubs/all\\_date\\_desc\\_nopubnumbers.html](http://www.cdc.gov/niosh/pubs/all_date_desc_nopubnumbers.html)

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

**New Jersey Right to Know Hazardous Substances Fact Sheets Web site web.**

[doh.state.nj.us/rtkhsfs/indexfs.aspx](http://doh.state.nj.us/rtkhsfs/indexfs.aspx)

**Occupational and Exposure Exposures of the Skin to Chemicals (OEESC)**

**Conference Abstracts**

[http://inside.mines.edu/outreach/cont\\_ed/oeesc/](http://inside.mines.edu/outreach/cont_ed/oeesc/)

[www.cdc.gov/niosh/topics/skin/OEESC2/index.html](http://www.cdc.gov/niosh/topics/skin/OEESC2/index.html)

[www.oeesc2009.pwp.blueyonder.co.uk/OEESC/Abstracts.html](http://www.oeesc2009.pwp.blueyonder.co.uk/OEESC/Abstracts.html)

**Patty's Industrial Hygiene and Toxicology**

**Proctor and Hughes' Chemical Hazards of the Workplace**

**OSHA Publications Web site**

[www.osha.gov/](http://www.osha.gov/)

**U.S. EPA Web site**

[www.epa.gov/](http://www.epa.gov/)

**U.S. National Technical Information Service (NTIS) Web site**

[www.ntis.gov/](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>

### E.1.2 Search terms

Literature searches are conducted by NIOSH technical informational specialist for a candidate chemical based on the substance's Chemical Abstract Services Number (CAS No.), chemical nomenclature, common names, and synonyms. Additional terminology used during the literature search can be located in Table E.1.

### 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

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

Acne*	Epicutaneous*	Keratoacanthoma	QSAR
Allerg*	Epiderm*	Keratoderma	QSPR
Apocrine	Episkin	Keratosis	Radiodermatitis
Argyria	Erythema	Leukoderma	Rash*
Atopic	Exanthema	Lichenoid	Redness
Blister*	Exfoliat*	Miliaria	Sebaceous
Burn	Fingernail*	Mucocutaneous	Sensitizer
Callosity	Follicle*	Neurodermat*	Skin
Cancer*	Gangren*	Onychomyco*	Skin Diseases
Corrosion	Granuloma	Pain	Skin Irritancy Tests
Crositex*	Hirsut*	Pallor	Skin Physiology

(Continued)

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

Cutaneous	Hyperhidrosis*	Panniculitis	Skin Tests
Cutis	Hyperpigment*	Papulosquamous	Stratum Corneum
Cyst	Hypertricho*	Paronychia	Structure Activity Relationship
Cystic	Hypopigment*	Patch Test*	Sunburn
Cysts	Hypotricho*	Photoallerg	Sweat
Skin*	Inflammation	Photosensitiv*	Ulcer*
Dermatitis	Immune	Phototoxic*	Urticaria
Dermato*	Intertrigo	Porphyria*	Vacciniforme
Dermis	Intraskin*	Prurigo	Vesiculobullous
Eccrine	Irritat*	Prurit*	Xeroderma
Ectoderm*	Jaundice	Psoriasis	
Eczema*	Keloid	Purpura	

\*Indicates truncated terms used within the literature search

scheme relies on a case-by-case analysis of the assembled data using a weight-of-evidence approach. Other general considerations used to evaluate the assembled data include:

- 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, European Centre for the Validation of Alternative Methods, U.S. EPA, or NTP)?
- Were the exposure conditions and the studies' reported findings described in detail?
- Should any other available information be considered?

Based on the results of this qualitative classification scheme, the data sets are classified as

sufficient, limited, or insufficient. These rankings are intended to aid in assessing the overall quality and completeness of the assembled data sets. Data sets classified as sufficient are those that include human and/or animal toxicity studies conducted according to standardized protocols and that provide in-depth descriptions of the exposure conditions and study findings. Data sets classified as limited via the qualitative ranking scheme contain either human and/or animal studies conducted by nonstandardized protocols or contain incomplete descriptions of the exposure conditions and study findings. Data sets classified as insufficient include studies that primarily either did not apply standard protocols or did not provide an in-depth description of the exposure conditions or study findings. Data sets that receive the insufficient ranking will not be used as the basis for the NIOSH skin notation.

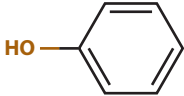
# APPENDIX F • Example of Assigning New NIOSH Skin Notations and Format of the Skin Notation Profile

This appendix documents the assignment of skin notations based on the scientific criteria outlined in this document. This profile contains a proposed skin notation assignment and supporting documentation for phenol (CAS No.108-95-2). It should be noted that the presented information is intended to serve only as an illustration of the strategy outlined in this CIB to assess the hazards of skin contact with phenol. The proposed skin notation assignment should not be construed as official NIOSH policy.

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)

<b>Synonyms:</b> Carbolic acid, monohydroxybenzene, hydroxybenzene, benzenol, phenylic acid, phenyl hydroxide, benzophenol, phenyl hydrate, phenylic alcohol, monophenol, phenic acid, oxybenzene	<b>Structure:</b> 
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### Skin Notation for Phenol: SK: SYS-DIR (COR)

This documentation for skin notation assignments is limited to an assessment of the potential health effects following skin 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, repeat-dose, and chronic toxicity, carcinogenicity, and biologic-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 skin exposure to phenol. This toxicological review is intended to provide brief documentation of the rationale in support of the SK assignments for this chemical, which were based on the logic outlined in *CIB #61: A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009]. Table F.1 provides a summary of the assigned skin notations for phenol, and data supporting these notations are summarized below.

- This section outlines (1) background information on phenol, (2) briefly discusses the application of the literature search (Appendix E.1), and (3) summarizes the skin notations assigned to phenol. Table F.1 includes the identification of critical effects associated with each assigned skin notation, and a description of the quality



**Table F.1. Skin notation for phenol**

<b>Supporting data for phenol skin notation</b>		
<b>Skin notations</b>	<b>Critical effects</b>	<b>Available data</b>
SK: SYS	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

and type of data used to determine the skin notation assignment for phenol (Appendix E.2).

## F.2 Systemic toxicity from skin exposure

Toxicokinetic studies of phenol have been identified. Dermal absorption of phenol by human subjects has been reported to range from 4%–23% of the applied dose, depending 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 g/L from a 2 mL reservoir) applied directly to the forearm (15.6 cm<sup>2</sup>) was found to be concentration-dependent, with the rate ranging from 0.079 mg/cm<sup>2</sup>/hr at the low concentration to 0.301 mg/cm<sup>2</sup>/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 µg/cm<sup>2</sup> phenol on 13 cm<sup>2</sup> 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 skin exposure [Piotrowski 1971]. In a whole-body skin exposure study in which unclothed and lightly clothed volunteers were exposed to phenol vapors at concentrations from 1.3–6.5 ppm for 6 hours, but were breathing clean air by mask, reported that absorption increased proportionately with air concentration [Piotrowski 1971]. 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%–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 rats 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. **Brooks and Riviere [1996]** considered a recent study that evaluated dermal absorption of phenol in acetone and water under nonoccluded and occluded applications using isolated perfused porcine skin. The authors reported 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  $\mu\text{g}/\text{cm}^2$ ) compared to the high-dose (40  $\mu\text{g}/\text{cm}^2$ ), suggesting saturation of absorption or other nonlinear kinetics under some conditions of exposure. Depending on the solvent and dose, Brooks and Riviere [1996] reported that dermal absorption ranged from 9.24%–14.62% under occluded conditions at the low dose and 2.90%–5.45% under non-occluded 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 g/L to 40 g/L, and a value of 0.169 cm/hr 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 dermal absorption. Results from animal studies in vivo and studies using 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 [2009] predictive algorithm for estimating and evaluating the health hazards of skin exposure to substances.

Based on this algorithm, the ratio of the skin dose to the inhalation dose (SI ratio) of 11 was calculated for phenol. This ratio is significantly higher than the SI ratio of greater than or equal to 0.1 indicating that skin absorption may substantially contribute to the overall body burden of a chemical. For this reason, phenol is considered to be absorbed through the skin following dermal contact. The result from the predictive algorithm supports the results from human and animal studies in vivo and from in vitro studies.

- **Application of Appendix A.1.1: Dermal absorption.** The results of studies using human subjects have reported that dermal absorption of phenol range from 4%–23% of the applied dose. The studies indicate that phenol may be readily absorbed in liquid or vapor forms. Animal studies using different protocols report dermal absorption range from 9%–85% of the applied dose in multiple species. For this reason, phenol is identified as having a high potential to be absorbed following contact with the skin in liquid and vapor forms.

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, e.g., 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<sub>50</sub> values (the dose resulting in 50% mortality in the exposed animals) range from 0.5 mL/kg body weight to 0.68 mL/kg (corresponding to 669–1,500 mL/kg body weight) [**Conning and Hayes 1970; Brown et al. 1975**] in rats under

both occlusive and nonocclusive conditions and 1400 mg/kg in rabbits [Vernot et al. 1977]. The Conning and Hayes [1970] study reported severe muscular tremors, twitching, generalized convulsions with loss of consciousness, and prostration occurring within 10 minutes of skin exposure to phenol in water; subjects developed severe hemoglobinuria from 45–90 minutes. Brown et al. [1975] reported hematuria and convulsions as clinical signs of phenol toxicity. Because the reported acute dermal LD<sub>50</sub> values for the rat and rabbit are both lower than the critical dermal LD<sub>50</sub> value of 2 g/kg body weight that identifies substances with the potential for acute dermal toxicity [NIOSH 2009], phenol is considered systemically toxic by the acute dermal route.

- **Application of Appendix A.1.2: Evaluation of acute toxicity of exposures of the skin.** The reported LD<sub>50</sub> of 414–1400 mg/kg body weight did not exceed the critical cutoff value of 2000 mg/kg body weight. For this reason, phenol is assigned the SYS notation.

Quantitative information on doses that cause systemic effects during repeated occupational exposures is lacking. However, doses chronic to humans (unspecified) may result in neurologic damage [Merliss 1972]. A number of repeat-dose animal studies have been identified in which show systemic effects following skin exposure to phenol. **Deichmann et al. [1950]** exposed the tail of rabbits to aqueous phenol solutions of 1.18%–7.12% in water (reported as 64–380 mg/kg by the International Program for Chemical Safety IPCS [1994]) for 5 hr/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. Identified in this study were a NOAEL of 64 mg/kg-day and a LOAEL of 130 mg/kg-day to protect against

occasional mild tremors and skin irritation. **Boutwell and Bosch [1959]** conducted a study in mice involving skin painting of 25 microliter (μL) of a 5% [1.25 milligram (mg)] phenol or a 10% (2.5 mg phenol) in benzene per application, twice weekly for 52 weeks. The high dose (10%) caused decreased body weight (average body weight at the 20th week for the group dosed 10% was 35.0 g compared with 38.9 g at the 5% level of phenol) and decreased survival (24/30 mice survived at the end of 52 weeks compared with 30/30 at the 5% level of phenol at the 20th week). The resulting doses were reported as 41.7 and 83.3 mg/kg/treatment [ATSDR 2006]. The potential skin and systemic effects of the benzene solvent were not investigated in this study; however, the effect levels of 18 mg/kg-day from the Boutwell and Bosch study [1959] 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 1000 mg/kg for repeat-dose toxicity. This NOAEL identifies substances with the potential for subchronic dermal toxicity [NIOSH 2009]. Therefore, phenol is considered to be systemically toxic following repeated dermal exposure.

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

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

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

Although a literature search identified no epidemiologic studies that allowed for evaluation of the carcinogenic potential of phenol, 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 (i.e., 9,10-dimethyl-1,2-benzanthracene). These studies are inadequate for the evaluation of the carcinogenic potential of phenol because of the following:

- The short duration of exposures applied in the studies [32 weeks (Salaman and Glendenning 1957), 12 months or 52 weeks (Salaman and Glendenning 1957; Boutwell and Bosch 1959)]
- The lack of appropriate controls [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 exposure pathways alternative to the skin. NIOSH [2006] does not classify phenol as a potential occupational carcinogen. The U.S. EPA states that the data regarding the carcinogenicity of phenol through the ingestion, inhalation, and dermal routes *are inadequate for an assessment of human carcinogenic potential* [U.S. EPA 2002]. The American Conference of Governmental Industrial Hygienists (ACGIH) has assigned an A4 (not classifiable as a human carcinogen) notation to phenol [ACGIH 2001]. IARC has classified phenol as *not classifiable as to its carcinogenicity to humans* (Group 3) [IARC 2007].

- **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 the 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, skin



exposure to liquid phenol or concentrated phenol vapor caused 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 solid or liquid phenol [Brown et al. 1975; Conning and Hayes 1970]. The effects of phenol on the skin have been attributed to its ability 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™, predicts that phenol is nonirritating to the skin, which indicates 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 skin 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 an SK: DIR (COR) notation for phenol.

- **Application of Appendix A.2: Experimental protocols for investigating direct effects of skin exposure and derived criteria for assigning the SK: DIR notations.** Sufficient evidence in the forms of numerous human and animal studies was identified that clearly demonstrated phenol's ability to cause direct effects including inflammation, discoloration, eczema,

redness, edema, and necrosis of the skin and underlying tissues. Based upon this evidence, phenol has been assigned both the DIR and (COR) subnotations.

## F.4 Sensitization

Few 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]. The Magnussen and Kligman skin sensitization test in guinea pigs also gave negative results for phenol [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 skin 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 skin 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 (e.g., central nervous system effects, effects on body weight and survival) following skin 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 and that 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 upon contact with the skin and corrosive by the European Commission (EC) [2007]. ACGIH [2001], NIOSH [2006], and OSHA [2007] have also assigned a skin notation to the chemical. The classifications assigned by these organizations are indicated in Table F.2. Based on the scheme developed by NIOSH [2009] to coordinate the skin notations with the GHS, the equivalent GHS classification for phenol would most likely be Dermal Category 3 acute toxicant (200 mg/kg body weight < LD<sub>50</sub> < 1000 mg/kg body weight) and Category 1 Skin Corrosive.

**Table F.2. Summary of skin hazard designations beyond NIOSH**

Organization	Skin hazard designations
NIOSH <sup>‡</sup> [2006]	Skin notation—potential for skin and eye irritation and dermal absorption
OSHA <sup>§</sup> [2007]	Skin notation—indicates that the cutaneous route of exposure (including mucous membranes and eyes) contributes to overall exposure
ACGIH <sup>†</sup> [2001]	Skin notation—phenol, as a vapor, liquid, or solid, can penetrate the intact skin causing systemic effects
EC* [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

<sup>‡</sup>NIOSH = National Institute for Occupational Safety and Health

<sup>§</sup>OSHA = Occupational Safety and Health Administration.

<sup>†</sup>ACGIH = American Conference of Governmental Industrial Hygienists

\*EC = European Commission, Joint Research Center, Institute for Health and Consumer Protection



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**Note**—(\*) cited in text; (†) represent additional resources of interest not cited within text

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## APPENDIX G • Supplemental information

### G.1 Contaminants and isomers

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

1. A chemical that is unintentionally present within a neat substance or mixture having a concentration less than 1.0% or
2. A chemical that is recognized as a potential carcinogen present within a neat substance or mixture having a concentration less than 0.1% [29 CFR 1910.1200 (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 because of the potential for the contaminant to represent a unique occupational hazard. If a contaminant is deemed to represent a substantial health hazard for workers following contact of the skin, it may be independently evaluated to determine whether assignment of skin notations is appropriate.

Isomers are molecules that exhibit unique physical structures, despite having the same elementary composition and weight. Variations within the chemical properties of isomers of a molecule may result in substantial 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 of Classification and Labeling of Chemicals

GHS is an international classification and labeling system for chemicals adopted by the U.N. 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 and specifying what information should be included on labels of hazardous chemicals and material safety data sheets. The GHS criteria outlines a similar strategy as presented in this CIB for the classification and labeling of chemicals to warn against the health risks of skin exposures, including systemic toxicity, skin irritation or corrosivity, and sensitization [UNECE 2005]. The strategy outlined in this CIB has been purposely designed to correspond with GHS to encourage harmonization between the two systems. Table G.2 has been included to illustrate the harmonization of 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.

It should be noted that in some cases the NIOSH skin notation assignments and hazard statements found on labels and material safety data sheets prepared in accordance with the GHS may vary because of differences associated with (1) professional judgment and interruption of reviewed data and (2) deviations between the criteria outlined in the NIOSH and GHS strategies. The classification of hazards associated with skin exposures to chemicals under the NIOSH and GHS strategies relies heavily on the use of professional judgment

during the evaluation of the scientific data and subsequent assignment of the hazard designations. For this reason, differences in the interruption of the reviewed data may result in discrepancies for a particular substance. An additional reason that potential differences may occur is because of variations in the criteria outlined in this CIB and the GHS, such as the numeric cutoff values applied to assess critical effects in animal studies. Although the strategy outlined in this CIB has been designed to harmonize with GHS, differences between the NIOSH skin notation assignment and hazard statements developed using the GHS strategy can be reasonably anticipated.

**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)	Dermal Category 1: Symbol: Skull and Crossbones Signal word: Danger Hazard Statement: Fatal in contact with skin (Criteria: LD <sub>50</sub> < 50)  OR  Dermal Category 2: Symbol: Skull and Crossbones Signal word: Danger Hazard Statement: Fatal in contact with skin (Criteria: 50 < LD <sub>50</sub> < 200)	SK: SYS (FATAL) (Criteria: LD <sub>50</sub> < 200)

(Continued)

**Table G.2 (Continued). 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) (Continued)	Dermal Category 3: Symbol: Skull and Crossbones Signal word: Danger Hazard Statement: Toxic in contact with skin (Criteria: $200 < LD_{50} < 1000$ )  OR  Dermal Category 4: Symbol: Exclamation mark Signal word: Warning Hazard Statement: Harmful in contact with skin (Criteria: $1000 < LD_{50} < 2000$ )	SK: SYS (Criteria: $200 < LD_{50} < 2000$ )
	Dermal Category 5: Symbol: No symbol Signal word: Warning Hazard Statement: May be harmful in contact with skin (Criteria: $2000 < LD_{50} < 5000$ )	No equivalent assignment
Direct effects of the skin	Skin Corrosion Category 1: Symbol: Corrosion Signal word: Danger Hazard Statement: Causes severe skin burns and eye damage	SK: DIR (COR)
	Skin Irritation Category 2: Symbol: Exclamation mark Signal word: Warning Hazard Statement: Causes skin irritation	SK: DIR (IRR)
	Skin Irritation Category 3: Symbol: No symbol Signal word: Warning Hazard Statement: May be harmful in contact with skin	SK: DIR
Skin Sensitization	Skin Sensitization Category 1: Symbol: Exclamation mark Signal word: Warning Hazard Statement: May cause an allergic skin reaction	SK: SEN



### G.3 Cancer

Cancer refers to any one of a group of diseases that occurs when cells in the body become abnormal and grow or multiply out of control. Exposure of the skin to some chemicals has been demonstrated to contribute to the development of (1) cancers within internal organ systems beyond the point of contact and (2) cancers of the skin at or near the point of contact. To ensure consistency in the assignment of the skin notations, the following paradigm has been developed:

- Cancers occurring within an internal organ system or tissue beyond the point of contact are defined as systemic effects and warrant the assignment of the SYS notation.
- Cancers occurring at or near the point of contact on the skin are defined as direct effects and warrant the assignment of the DIR notation.

The weight-of-evidence approach described within this CIB will be applied to assess the potential for a chemical to act as a carcinogen following exposures of the skin and the subsequent assignment of the SYS and DIR notations when appropriate. In addition, the Skin Notation Profiles (see Appendix F) will summarize the data associated with carcinogenic potential of a chemical, including cancer designations provided by NIOSH, NTP, U.S. EPA, IARC, and ACGIH.

### G.4 Nanoparticles and the skin

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

(i.e., nanotubes and fullerenes), metal-based materials (i.e., quantum dots, metal oxides, nanogold, and nanosilver), nanocomposites, and dendrimers. Because of their small size and relatively large surface area, engineered nanoparticles may have chemical, physical, and biologic properties distinctly different from and greater than fine particles of similar chemical composition [NIOSH 2009]. 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 hazards of skin exposures to nanoparticles. The results from *in vitro* studies using primary or cultured human skin cells show that single-walled and multi-walled carbon nanotubes are able to enter cells and cause the release of proinflammatory 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 fullerenes to penetrate the stratum corneum by passive diffusion and to induce inflammatory response and cytotoxicity within skin fibroblasts 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 hazards of exposing skin to the different forms of nanoparticles are unclear. For this reason, skin notations derived from neat substances or mixtures with similar chemical composition to a specific form of nanoparticles may not be applicable because of the different physicochemical properties and toxic potential. As new data become available, the skin notations and supporting documentation will address the 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: Managing the Health and Safety Concerns with Engineered Nanomaterials* [NIOSH 2009].

## References

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# Notes

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