Reuss, Vicki A. (CDC/NIOSH/EID)

From: Dragon, Karen E. (CDC/NIOSH/EID)
Sent: Wednesday, December 17, 2008 10:37 AM
To: NIOSH Docket Office (CDC)
Subject: FW: Review of NIOSH document: Skin notation strategy
Attachments: 02. Draft- CIB-Skin NotationRedlichEdits.doc; ATT1857298.htm

Diane: I am forwarding this to the docket e-mail so that we have everything in the folder for this docket. I will give to Vicki to input into the system under 153. I printed off only the pages in the document that had comments on it from Thanks, Karen

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From: Dotson, G. Scott (CDC/NIOSH/EID)
Sent: Friday, December 05, 2008 11:19 AM
To: Dragon, Karen E. (CDC/NIOSH/EID)
Subject: FW: Review of NIOSH document: Skin notation strategy

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From:
Sent: Thursday, December 04, 2008 1:54 PM
To: Dotson, G. Scott (CDC/NIOSH/EID)
Subject: Re: Review of NIOSH document: Skin notation strategy

Most apologize for delay.
once start making some edits - can do more harm than good. Not as bad as look as I included some "editorial" comments / explanations.
Of course may want to ignore some (more than some).
You'll probably have some questions - correct wording on some of this is bit awkward - want to include chemicals like isocyanates which clearly sensitizing and cause asthma - but in humans the role of skin not as well proved as in animals - for obvious reasons.
definition of "sensitization", "sensitizing effect" bit tricky. not quite sure what's best to use.
don't hesitate to call. i'm around rest of this week and next week.
problem is current criteria that exist (eg Kimber 2003 reference you cite are for contact allergens not a chemical like isocyanates that can cause systemic sensitization after skin exposure - proven at least in critters).
Did NOT meant to be critical as doc is great - just trying make it technically more accurate re immunology - but not easy to do.

Also - another "technical" detail - definition allergy, allergic reaction. wikipedia has it correct - quickest source.
"allergy" refers to IgE mediated (type I). (bee sting, asthma, hives etc).
immune-mediated more general - includes Type IV.
But "allergy" gets used more broadly.

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

National Institute for Occupational Safety and Health, 2008
Draft 09/02/08

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DHHS (NIOSH) Publication No. 2008–XXX

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Foreword

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

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

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

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

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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 dermal exposures to chemicals. This new strategy is a form of hazard identification that advances our understanding of the risks posed by dermal exposures to chemicals. Such improved understanding will enable us to implement better risk management practices and controls for the prevention of workplace skin diseases and other occupational diseases where skin exposure

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may contribute to disease development, such as immune-mediated asthma or chronic beryllium disease. *(would include the "may")*

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Christine Branche, Ph.D., M.S.P.H.
Acting Director, National Institute for Occupational Safety and Health
Centers for Disease Control and Prevention

Executive Summary

For 20 years, the occupational safety and health community has relied on skin notations from the National Institute for Occupational Safety and Health (NIOSH) to warn workers about the health risks of 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 current definition, a NIOSH skin notation may be assigned to a chemical only if that substance has been scientifically determined to be dermally absorbed. The currently widespread practice of using a skin notation to indicate that a substance poses other health effects following skin exposure is inaccurate and misleading.

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Difficulties with Assigning Current NIOSH Skin Notations

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

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

New Strategy for Assigning NIOSH Skin Notations

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

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

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

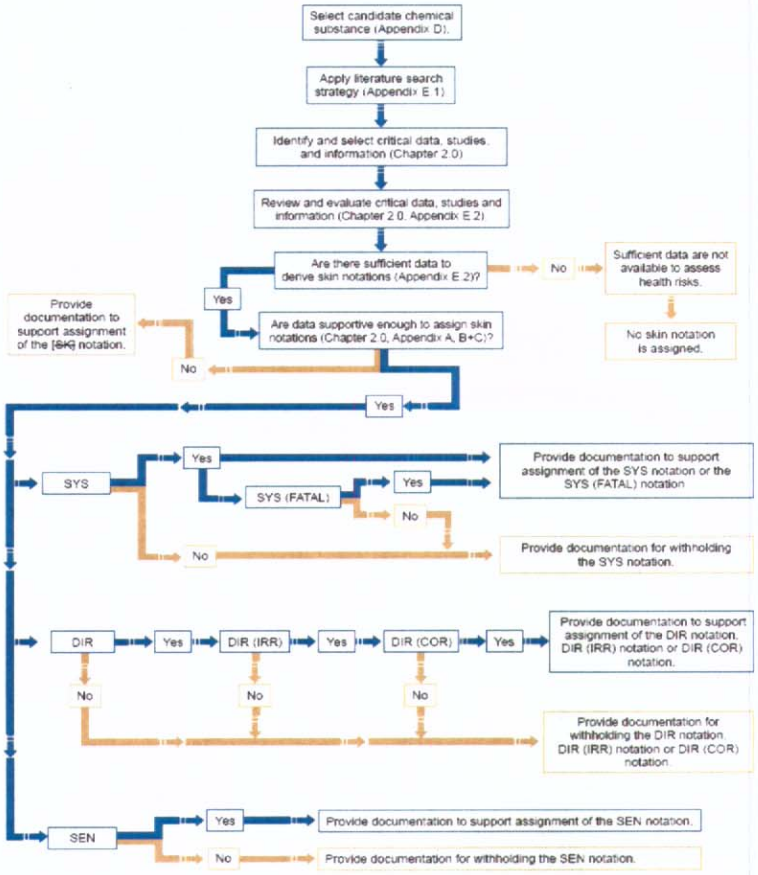
NIOSH skin notations relies on a critical assessment of data on the physiochemical properties of chemicals as well as reports of human exposures and health effects, empirical data from *in vivo* and *in vitro* laboratory testing, and considerations provided by predictive algorithms and mathematical models.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

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

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

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

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



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Abbreviations

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

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

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

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

Glossary

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

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

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

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

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

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

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

Sensitizing effects: Skin exposure leading to sensitization, which can result in ACD following re-exposure of the skin, or other immune-mediated diseases such as asthma, depending on the site of re-exposure. Or Systemic immune response induced by exposure to a substance, which upon further exposure can lead to ACD or other immune-mediated diseases such as asthma, depending on the site of exposure.
Might omit "sensitizing effects" and define instead
"Sensitization" - a specific immune response that develops following exposure to an antigenic chemical or substance. *or add* (and upon re-exposure can lead to ACD or other immune-mediated diseases such as asthma, depending on the site / route of re-exposure.) *Less may be more here -short definition of sensitization as there are different definitions used in different settings.*

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Deleted: mucous membranes, or airways

Deleted: including allergic contact dermatitis (ACD), following dermal exposure to chemicals.

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

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1.0 Introduction

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

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

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

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

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

2.0 Assigning Skin Notations

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

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

- **DIR** Indicates direct effect(s) of a chemical on the skin, including corrosion, primary irritation, bleaching (blanching), staining, and reduction/disruption of the dermal barrier integrity.
    - **(IRR)** A subcategory of SK: DIR assigned when a chemical is identified as a dermal irritant.
    - **(COR)** A subcategory of DIR assigned when a chemical is identified as a corrosive.
- **SEN** Indicates that skin exposure to a chemical may cause systemic sensitization and allergic contact dermatitis (ACD), and /or may contribute to other allergic diseases such as asthma following inhalational exposure.

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Deleted: or sensitization of skin, mucous membranes, or airways.

~~SK~~ Indicates that sufficient data were identified and evaluated for a chemical that did not identify a health risk associated with dermal exposure and did

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

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

and may not provide adequate warnings about unique hazards of the non-specified isomeric forms of the chemical (See Appendix G.1).

2.1 Criteria for Assigning Skin Notations

The critical step in assigning skin notations to a chemical is determining its "hazard potential"—that is, it's potential for causing adverse health effects as a result of skin exposure. This determination involves a health hazard identification process that assesses the following: (1) scientific data on the physiochemical properties of a chemical, (2) human exposures and health effects, (3) empirical data from *in vivo* and *in vitro* laboratory testing, and (4) the use of predictive algorithms such as quantitative structure-activity relationships (QSARs) and mathematical models that describe a selected process (e.g., skin permeation) using analytical or numerical methods. A weight-of-evidence approach is applied when available data are inconsistent. Figure 2 illustrates the hierarchy of scientific data used for assigning skin notations.

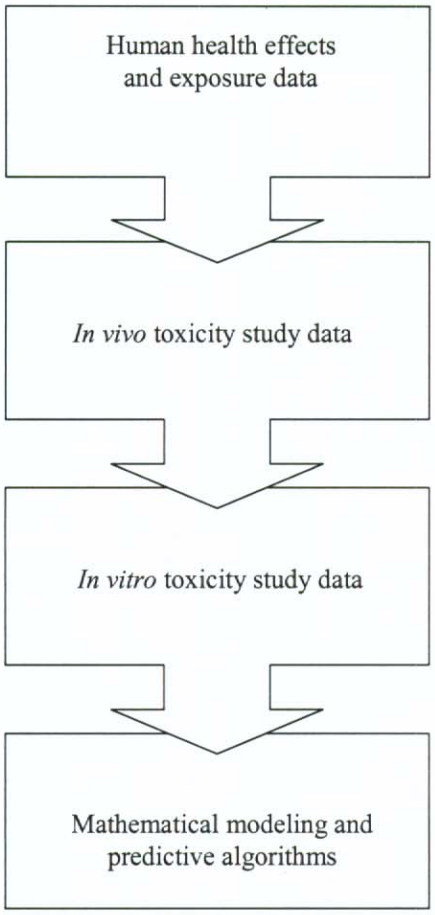

Figure 2: Hierarchy of evaluated scientific data

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

2.2 SYS

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

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

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

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

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

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

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

B Data from experimental animal studies indicate the following:

- Systemic effects occurred from dermal exposures.
- Fatalities or health effects in exposed animals were not associated with skin damage by the chemical or the vehicle containing the chemical.

Deleted: Dermal

- Skin exposure results for animals included data on acute toxicity, repeated-dose toxicity, subchronic toxicity, chronic toxicity, carcinogenicity, or biological system/function-specific effects.

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

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

- Investigation of the relevant toxicokinetics and potential toxic effects of metabolic transformation(s) of chemicals following skin absorption
- Examination of the adverse effects of chemical mixtures whose skin absorption or potential systemic toxicity is different from the level anticipated for individual components of the mixture because of synergistic effects
- Investigation of altered skin permeability characteristics of toxic components resulting from the presence of a solvent or vehicle in a chemical preparation.

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

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

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

Both conditions must be satisfied to assign a SYS notation.

E When no acceptable-quality empirical data exist on the systemic effects of dermal exposure, the potential for dermal absorption and consequent systemic toxicity of the chemical may be mathematically estimated. To mathematically determine the risk for systemic toxicity (e.g., predictive algorithm), the following information is needed: (1) the skin permeation rate, (2) the chemical dose calculated to be absorbed through skin (skin dose), (3) a reference dose representing the threshold of acceptable body accumulation (a chemical dose to be absorbed via inhalation during the same period of exposure), and (4) a comparison of the skin dose to the reference dose (which indicates the significance of skin absorption and its potential contribution to systemic toxicity).

Appendix B presents an algorithm that can be used for determining the potential for systemic toxicity. When the predictive algorithm is used as

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

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

Table 2.2 Paradigm for the assignment of the SYS notation

Systemic Toxicity		
Yes		

			No	
				No Data
Dermal Absorption	Yes	SYS†	~~SYS~~‡	SYS¥
	No	SYS	~~SYS~~	

				~~SYS~~
	No Data	SYS	~~SYS~~	No assignment[‡]

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

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

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

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

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

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

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

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

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

2.3 DIR

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

SK: DIR. Chemicals that are identified as irritants would be identified with the subnotation (IRR) [i.e., SK: DIR (IRR)]. Additionally, chemicals that cause necrosis of skin tissues or destruction of stratum corneum following skin exposure would also receive the subnotation (COR) [i.e., SK: DIR (COR)]. The

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

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

Parameter	Definition and scoring

OEL Potency	If OEL is < 1 mg/m3, assign score of 1; if not, assign score of 0.
Sensitizer	If identified as a sensitizer, assign score of 1; if not, assign score of 0.
HPV Chemical	If identified as a HPV chemical, assign score of 1; if not, assign score of 0.
Exposure Potential	If identified within NOES data as having > 75,000 potential workers exposures, assign score of 1; if not, assign score of 0.

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

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

Chemical	CAS No.	OEL[1] Potency	CAN[2]	R/DT[3]	IRR/ COR[4]	SEN[5]	HPV[6]	Exposure Potential	Skin Hazard[7]	Overall Score

Epichlorohydrin	106-89-8	0	0.5	0.5	1	1	1	1	1	6

Dichlorvos	62-73-7	1	0.5	0.5	0.5	1	1	0	1	5.5

Phenol	108-95-2	0	0	0.5	1	0	1	1	1	4.5

o-Cresol	95-48-7	1	0	0	1	0	1	0	1	4

Captafol	2425-06-1	1	0.5	0.5	0.5	1	0	0	0	3.5

Isophorone diisocyanate	4098-71-9	1	0	0	0.5	1	1	0	0	3.5

o-Dinitrobenzene	528-29-0	1	0	0.5	0	0	1	0	1	3.5

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

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

Chemical Hazards that do not have the skin notation [skin] and 2) chemicals nominated for evaluation from stakeholders, governmental agencies and public interest groups.

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

E.1 Literature Search

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

E.1.1 Primary sources

E.1.1.1 Electronic databases

The following databases are searched:

Chemical Identification (ChemID)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Hamilton and Hardy's Industrial Toxicology

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

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

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

Merck Index

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

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

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

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

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

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

Patty's Industrial Hygiene and Toxicology

Proctor and Hughes' Chemical Hazards of the Workplace

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

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

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

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

E.1.2 Search terms

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

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

Acne	Follicle	Paronychia e

Apocrine	Gangrene	Photosensitive
Corrosion	Hypotricho	QSAR

Crositex	Inflammation	Radiodermatitis
Epiderm	Neurodermat	Sweat

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Episkin	Onychomyco	Ulcer
Fingernail	Papulosquamous	Xeroderma

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Per email - would add additional search terms related to allergy, sensitization, lung diseases etc.

E.2 Evaluation of data

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

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

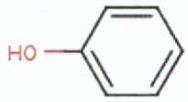
Based on the results of this qualitative classification scheme, the data sets are classified as either 1) *sufficient*, 2) *limited*, or 3) *insufficient*. Data sets classified as *sufficient* are those determined to include human and/or animal toxicity studies conducted following standardized protocols,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

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

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

F.1 Chemical background information and introduction

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

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

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

This documentation for skin notation assignments is limited to an assessment of the potential health effects following dermal exposure or the potential for direct skin injuries from phenol. A literature search was conducted through November 2006 to identify potential health effects information on phenol toxicokinetics, acute, repeated-dose, and chronic toxicity, carcinogenicity, and biological system/function specific effects (including reproductive and developmental effects and immunotoxicity), irritation, and sensitization. Information was considered from studies in humans, animals, or appropriate modeling systems that are relevant to dermal exposure to phenol. This toxicological review is intended to provide brief documentation of the rationale in support of the skin notation assignments for this chemical. Assignments were made based on the approach described in the National Institute for Occupational Safety and Health [NIOSH 2008] Skin Notation Strategy Document. The following table provides the assigned skin notations for phenol, and data supporting these notations are summarized below. Table F.1 provides the assigned skin notations for phenol, and data supporting these notations are summarized below.

Table F.1 Skin Notation for Phenol

Supporting Data for Phenol Skin Notation

Skin Notations	Critical Effects	Available Data
SK: DIR(COR)	Skin corrosivity	Sufficient human and animal data

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

F.2 Systemic toxicity from dermal exposure

- *Application of Appendix A.1.2. Toxic effects of dermal exposure on organ systems or biological functions. No evidence was identified that evaluated the effects of phenol on organ systems or biological functions. The SYS notation would not be assigned to phenol based on the criteria outlined in this section.*

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

Toxicokinetic studies of phenol have been identified. Dermal absorption of phenol by humans has been reported to range from 4 to 23% of the applied dose, with the extent of dermal absorption dependent on the period of exposure and the concentration of phenol [Feldman and Maibach 1970; Piotrowski 1971; Roberts et al. 1977; Baranowska-Dutkiewicz 1981]. In male volunteers, the rate of absorption of aqueous phenol solutions [2.5, 5.0, or 10 grams per liter (g/L)] applied to the forearm [35.8 square centimeters (cm^2)] was concentration-dependent, with the rate ranging from 0.079 milligrams per square centimeter per hour (mg/cm^2/hour) at the low concentration to 0.301 mg/cm^2/hr at the high concentration [Baranowska-Dutkiewicz 1981]. In this study, the total amount of phenol absorbed – but not the rate of absorption – at the low concentration

Although no epidemiological studies that evaluated the potential of phenol to be carcinogenic were identified, a limited number of studies involving repeated application of phenol in benzene (mL) [illegible] applied directly to the [illegible] [Boutwell and Bosch 1959; Salaman and Glendenning 1957; Wynder and Hoffman 1961]

stage carcinogenicity protocols in mice indicated that phenol has promoting activity. Studies conducted by Boutwell and Bosch [1959] in several strains of mice also suggested that phenol in benzene or dioxane is a tumor promoter and possibly a complete carcinogen (i.e., having both promoting and initiating activity). In the latter study, phenol elicited skin tumors in mice even in the absence of a tumor initiating agent, 9,10-dimethyl-1,2-benzanthracene. These studies are inadequate for the evaluation of the carcinogenicity potential of phenol due to the short duration (32 weeks [Salaman and Glendenning 1957] and 12 months or 52 weeks [Salaman and Glendenning 1957; Boutwell and Bosch 1959]), the lack of appropriate controls [e.g., Salaman and Glendenning 1957], and/or the use of vehicles (dioxane, benzene) that are skin irritants and/or defatting agents. Other agencies or organizations have also evaluated the potential of phenol to be a carcinogen following non-dermal exposure routes. NIOSH [2006] does not classify phenol as a potential occupational carcinogen. The United States Environmental Protection Agency [US EPA 2002] states that the data regarding the carcinogenicity of phenol via the oral, inhalation, and dermal exposure routes *are inadequate for an assessment of human carcinogenic potential.* The American Conference of Governmental Industrial Hygienists [ACGIH 2001] has assigned an A4 (not classifiable as a human carcinogen) notation to phenol. The International Agency for Research on Cancer [IARC 2007] has classified phenol as *not classifiable as to its carcinogenicity to humans* (Group 3).

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

Identified human **[Feldman and Maibach 1970; Piotrowski 1971; Baranowska-Dutkiewicz 1981]** and animal **[Behl et al. 1983; Hughes and Hall 1995; Brooks and Riviere 1996]** toxicokinetic data, acute dermal toxicity studies **[Conning and Hayes 1970; Brown et al. 1975; Vernot et al. 1977]**, and repeat-dose studies **[Deichmann et al. 1950; Boutwell and Bosch 1959]** are sufficient to demonstrate the potential for phenol to be dermally absorbed and systemically toxic. Systemic toxicity includes effects on the central nervous system, body weight changes, and decreased survival. Therefore, this assessment concludes that sufficient human and animal data exist to assign a SK: SYS notation for phenol.

F.3 Direct effect(s) on the skin

The available information indicates that phenol is corrosive to the skin. For example, dermal exposure to liquid phenol or concentrated phenol vapor causes corrosive effects including tissue death (necrosis) in humans [Schmidt and Maibach 1981; Horch et al. 1994], rats [Conning and Hayes 1970], mice [Patrick et al. 1985], and pigs [Pullin et al. 1978; Hunter et al.1992]. Other effects, such as erythema, inflammation, discoloration, eczema, redness, and severe edema have been reported on contact of the skin with the solid or liquid phenol [Brown et al. 1975; Conning and Hayes 1970]. The effects of phenol on the skin have been attributed to its property to impair the barrier function of the stratum

corneum and produce coagulation necrosis by denaturing and precipitating proteins. Although the structure activity relationship model, DEREK predicted that phenol is non-irritating to the skin, indicating that the chemical does not have structural alerts for skin irritation, several studies in humans and animals show that phenol is corrosive to the skin or is a skin irritant depending on the concentration.

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

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

F.4 Sensitization

A limited number of studies have been identified that evaluated the potential of phenol to cause skin sensitization in both humans and animals. In one study using 24 volunteers, phenol produced negative results in skin sensitization tests [Kligman 1966]. Phenol also gave negative results in the Magnussen and

Kligman skin sensitization test in guinea pigs [Itoh 1982]. Predictions using structure activity relationship models provide some information regarding this endpoint. Based on the chemical structure, phenol is predicted by DEREK® as negative for sensitization, indicating that the chemical does not have structural alerts for skin sensitization. This prediction of negative sensitization potential is consistent with the absence of published reports of sensitization in workers handling phenol and the limited empirical evidence.

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

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

F.5 Summary

There is sufficient information from toxicokinetics **[Feldman and Maibach 1970; Piotrowski 1971; Baranowska-Dutkiewicz 1981]**, acute dermal toxicity studies **[Conning and Hayes 1970; Brown et al. 1975; Vernot et al. 1977],** and repeat-dose dermal toxicity studies **[Deichmann et al. 1950; Boutwell and Bosch 1959]** to indicate that phenol is absorbed through the skin and is acutely toxic and induces systemic effects (for example, central nervous system effects,

effects on body weight and survival) following dermal exposure. Information from human experience **[Merliss 1972; Schmidt and Maibach 1981; Horch et al. 1994]** and animal studies **[Conning et al. 1970; Pullin et al. 1978; Patrick et al. 1985; Hunter et al. 1992]** is sufficient to demonstrate that phenol is corrosive, while more dilute solutions are irritating to the skin. The limited information available indicates that phenol is not a skin sensitizer. Therefore, this assessment recommends the composite skin notation of SK: SYS-DIR(COR) for phenol. Phenol has also been classified as being harmful and toxic in contact with the skin as well as corrosive by the European Union [2007]. ACGIH [2001], NIOSH [2006], and OSHA (Occupational Safety and Health Administration) [2007] have also assigned a skin notation to the chemical. The classifications assigned by these organizations are indicated in the table below. The classifications assigned by these organizations are indicated in Table F.2. Based on the scheme developed by NIOSH to coordinate the skin notations with the GHS, the equivalent GHS classification for phenol would most likely be considered an acute toxicant (200 mg/kg body weight < LD_{50} < 1000 mg/kg body weight), in addition to an irritant and corrosive agent.

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

Organization	Dermal Classification
EU [2007]	R21 – Harmful: danger of serious damage to health by

	R24 – Toxic in contact with skin
	R34 – Corrosive: Causes burns
	C – Corrosive

ACGIH [2001]	Skin notation - phenol, as a vapor, liquid, or solid, can penetrate the intact skin causing systemic effects.
NIOSH [2006]	Skin notation – potential for skin and eye irritation and dermal

	and dermal absorption
OSHA [2007]	Skin notation – indicates that the cutaneous route of exposure (including mucous membranes and eyes) contributes to overall exposure

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

*Soares ER, Tift JP [1982]. Phenol poisoning: Three fatal cases. J Forensic Sci 27(3):729-731.

*Turtle WRM, Dolan T [1922]. A case of rapid and fatal absorption of carbolic acid through the skin. Lancet 2: 1273-1274.

Union Carbide Corporation [1948]. Skin absorption and irritation – phenol. OTS0515564. Doc#:86-870001402.

*ACGIH (American Conference of Governmental Industrial Hygienists) [2001]. Documentation of the threshold limit values and biological exposure indices, Phenol. 7th ed. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

* ATSDR (Agency for Toxic Substances and Disease Registry) [2006]. Toxicological Profile for Phenol (Draft for Public Comment). U.S. Department of Health and Human Services. Agency for Toxic Substances and Disease

Appendix F References

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

Union Carbide Corporation [1949]. Acute toxicity of phenol. OTS0515567. Doc#: 86-870001405.

* U.S. EPA (United States Environmental Protection Agency) [2002]. Toxicological Review of Phenol. Integrated Risk Information System (IRIS). United States Environmental Protection Agency. Available at www.epa.gov/iris

*Vernot EH, MacEwen JD, Haun CC, Kinkead ER [1977]. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxicol Appl Pharmacol 42:417-424. [

*Wynder E, Hoffman D. [1961]. A study of tobacco carcinogenesis. VIII. The role of acidic fractios as promoters. Cancer 14:1306-1315.

APPENDIX G: Supplemental information

G.1 Contaminants and isomers

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

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

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

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

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

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

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

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

Health Hazard	GHS Assignment (mg/kg body weight)	NIOSH Assignment (mg/kg body weight)

Acute systemic toxicity (Lethality)	Symbol: Skull and Crossbones Signal word: Danger Dermal: Fatal in contact with skin (Criteria: LD_{50} < 200)	SK: SYS (FATAL) (Criteria: LD_{50} < 200)

	Symbol: Exclamation mark Signal word: Warning Dermal: Harmful in contact with skin (Criteria: 1000 < LD_{50} < 2000)	SK: SYS (Criteria: 200 < LD_{50} < 2000)

	Symbol: No symbol Signal word: Warning Dermal: May be harmful in contact with skin (Criteria: 2000 < LD_{50} < 5000)	No equivalent assignment
	Symbol: Exclamation mark Signal word: Warning Dermal: Causes skin irritation	SK: DIR (IRR)

	Symbol: No symbol Signal word: Warning Dermal: May be harmful in contact with skin	SK: DIR

G.3 Nanotechnology and dermal toxicity

Nanotechnology is a system of innovative methods to control and manipulate matter at near-atomic scale (1 to 100 nanometers) to produce new materials, structures, and devices. Examples of nanoparticles include carbon-based materials (i.e. nanotubes and fullereness), metal-based materials (i.e. quantum dots, metal oxides, nanogold, and nanosilver), nanocomposites, and dendrimers. Because of their small size and large surface area, engineered nanoparticles may have chemical, physical, and biological properties distinctly different from and greater than fine particles of similar chemical composition [NIOSH 2007]. These variations may result in unique health hazards for workers employed to manufacture or use products containing nanomaterials.

Limited information is currently available to accurately assess the health risks of dermal exposures to nanoparticles. The results from *in vitro* studies using primary or cultured human skin cells report the ability of single-walled and multi-walled carbon nanotubes to enter cells and cause the release of pro-inflammatory cytokines, oxidative stress, and decreased viability [Shvedova et al. 2003; Monteiro-Riviere et al. 2005]. More recent studies have reported the ability

of quantum dots and fullereness to penetrate the stratum corneum by passive diffusion, in addition to inducing inflammatory response and cytotoxicity within dermal fibroblast and keratinocytes [Sayes et al. 2005; Ryman-Rasmussen et al. 2006]. Factors, including size, shape, water solubility, and surface coating, may directly affect a nanoparticle's potential to penetrate the skin [Sayes et al. 2004; Ryman-Rasmussen et al. 2006].

The occupational health risks posed by dermal exposures to the different forms of nanoparticles are unclear. For this reason, skin notations derived from neat chemical substances or mixtures with similar chemical composition to a specific form of nanoparticles may be not be applicable due to the different physiochemical properties and toxic potential. As new data become available, the skin notations and supporting documentation will address the dermal toxic potential of nanoparticles when warranted. Additional information and guidance on safe work practices associated with nanoparticles can be found within the NIOSH document, *Approaches to Safe Nanotechnology: an Information Exchange with NIOSH* [NIOSH 2007].

Appendix G References

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