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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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Foreword

1

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

10

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

21

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

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

12
13 NIOSH skin notations are hazard warnings used worldwide to alert workers and
14 employers to the health risks of dermal exposures to chemicals in the workplace.
15 This Current Intelligence Bulletin (CIB) provides the rationale for assigning new
16 NIOSH skin notations. The new system reflects the current state of scientific
17 knowledge and involves critical evaluation of scientific data so that scientists can
18 assign multiple skin notations that distinguish between the systemic, direct, and
19 sensitizing effects of dermal exposures to chemicals. This new strategy is a form
20 of hazard identification that advances our understanding of the risks posed by
21 dermal exposures to chemicals. Such improved understanding will enable us to
22 implement better risk management practices and controls for the prevention of
23 workplace skin diseases.

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

- 1 Christine Branche, Ph.D., M.S.P.H.
- 2 Acting Director, National Institute for Occupational Safety and Health
- 3 Centers for Disease Control and Prevention
- 4

Executive Summary

1
2 For 20 years, the occupational safety and health community has relied on skin
3 notations from the National Institute for Occupational Safety and Health (NIOSH)
4 to warn workers about the health risks of dermal exposures to chemicals. These
5 notations have proved to be useful risk management tools for occupational health
6 professionals concerned about protecting workers from injuries and illnesses
7 caused by skin contact with chemicals. However, according to the current
8 definition, a NIOSH skin notation may be assigned to a chemical only if that
9 substance has been scientifically determined to be dermally absorbed. The
10 currently widespread practice of using a skin notation to indicate that a substance
11 poses other health effects from dermal exposure is inaccurate and misleading.

12

13 • **Difficulties with Assigning Current NIOSH Skin** 14 **Notations**

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

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

14 • **New Strategy for Assigning NIOSH Skin Notations**

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

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

22

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1 The new skin notation strategy is a form of health hazard identification that
2 standardizes the method for deriving skin notations. Assignment of the new
3 NIOSH skin notations relies on a critical assessment of data on the
4 physiochemical properties of chemicals as well as reports of human exposures
5 and health effects, empirical data from *in vivo* and *in vitro* laboratory testing, and
6 considerations provided by predictive algorithms and mathematical models. A
7 weight-of-evidence approach is applied in evaluating the quality and constituency
8 of the scientific data when conflicting findings are reported. Figure 1 illustrates an
9 overview of the process used to assign skin notations.

10

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

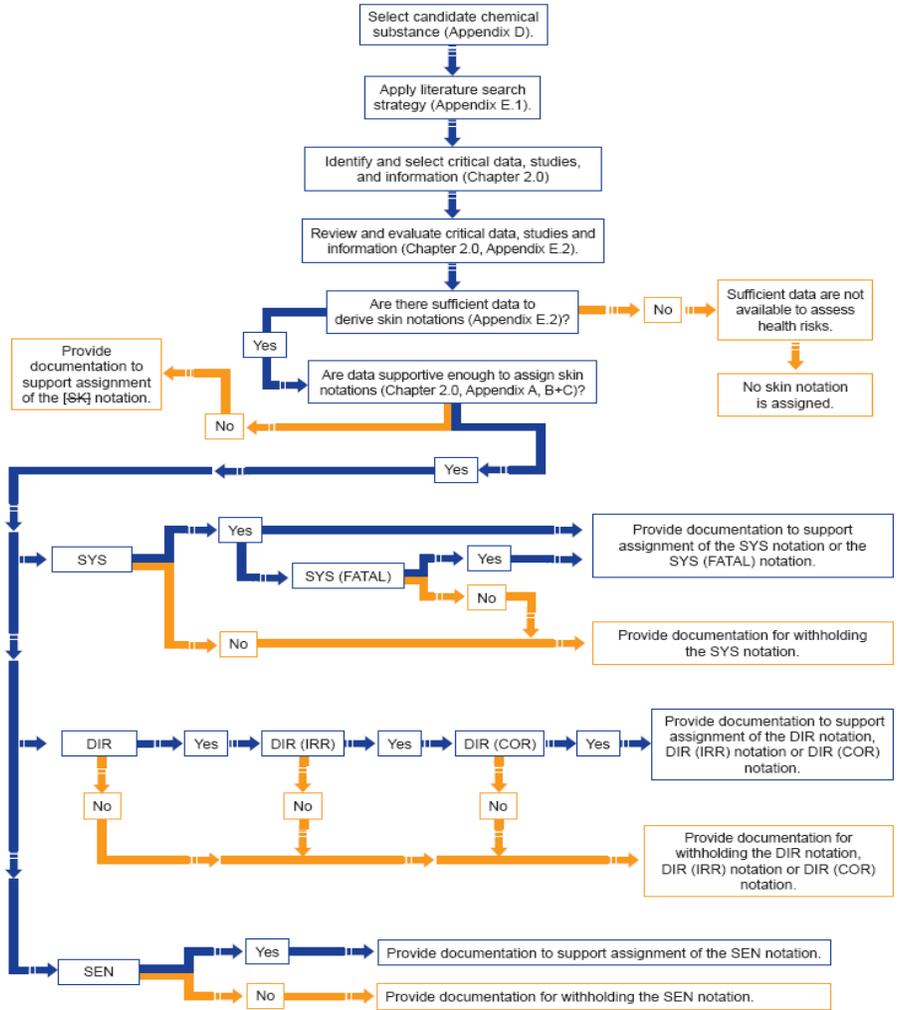
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- 1 A support document called a Skin Notation Profile will be developed for each
- 2 chemical evaluated via the strategic framework and scientific rationale presented
- 3 within this CIB. The Skin Notation Profile will summarize all relevant data used to
- 4 aid in determining the hazards associated with dermal exposures to the
- 5 evaluated chemical.

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1 **Figure 1:** Decision tree for assigning the new NIOSH skin notations
2



3

Contents

1		
2	Disclaimer	ii
3	Ordering Information	ii
4	Foreword	iii
5	Executive Summary	vi
6	• <i>Difficulties with Assigning Current NIOSH Skin Notations</i>	<i>vi</i>
7	• <i>New Strategy for Assigning NIOSH Skin Notations</i>	<i>vii</i>
8	Contents	xii
9	Glossary	xix
10	Acknowledgements	xx
11	1.0 Introduction	1
12	2.0 Assigning Skin Notations	3
13	• <i>2.1 Criteria for Assigning Skin Notations</i>	<i>5</i>
14	• <i>2.2 SYS</i>	<i>7</i>
15	• <i>2.3 DIR</i>	<i>13</i>
16	• <i>2.4 SEN</i>	<i>16</i>
17	• <i>2.5 SK</i>	<i>21</i>
18	References	23
19	APPENDIX A: Protocols Used in Studies of Health Effects from Dermal Exposure and the	
20	Determination of Criteria Derived for Assigning Skin Notations	25
21	• <i>A.1 Experimental protocols for investigating systemic effects of dermal exposure and derived criteria</i>	
22	<i>for assigning the SYS notations</i>	<i>25</i>
23	A.1.1 Dermal absorption.....	25
24	A.1.2 Acute dermal toxicity	27
25	A.1.3 Repeated-dose dermal toxicity	28
26	A.1.4 Subchronic dermal toxicity	29
27	A.1.5 Chronic dermal toxicity.....	29
28	A.1.6 Carcinogenicity	30
29	A.1.7 Toxic effects of dermal exposures on organ systems or biological functions	31
30	A.1.8 Assignment of the SYS notation based on nondermal routes of exposures	32
31	• <i>A.2 Experimental protocols for investigating direct effects of dermal exposure and derived criteria for</i>	
32	<i>assigning the DIR notations</i>	<i>33</i>
33	A.2.1 <i>In vivo</i> animal tests for acute irritancy and corrosivity	33
34	A.2.2 <i>In vitro</i> tests for corrosivity using human or animal skin models	33
35	A.2.3 Carcinogenicity	35
36	A.2.4 <i>In vitro</i> tests of skin integrity using human donor skin	36

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

1	• A.3 Experimental protocols for investigating sensitization from dermal exposure and derived criteria	
2	for assigning the SEN Notation.....	36
3	A.3.1 Identifying skin sensitization or ACD with guinea pig test methods.....	36
4	A.3.2 Identifying skin sensitization potential with the murine LLNA.....	37
5	A.3.3 Identifying skin sensitization potential with the mouse ear swelling test (MEST).....	37
6	• Appendix A References.....	39
7	APPENDIX B: Algorithm for estimating dermal absorption and systemic toxicity and suggested	
8	application for assigning SYS notations.....	44
9	• B.1 Algorithm for estimating and evaluating dermal exposure hazards.....	44
10	B.1.1 Step 1: Determining the skin permeation coefficient.....	45
11	B.1.2 Step 2: Estimating chemical uptake from skin and inhalation exposures.....	48
12	B.1.3 Step 3: Evaluating the skin exposure hazard.....	50
13	• B.2 Criterion for assigning the SYS notations.....	50
14	• Appendix B References.....	54
15	APPENDIX C: Identifying skin corrosives and sensitizers using physicochemical properties and	
16	structure activity relationship (SAR)-based analysis.....	56
17	• C.1 Using pH and acid/alkali reserve to identify skin corrosives.....	56
18	• C.2 Using structural alerts implemented in the DEREK™ expert system to identify sensitizers.....	57
19	• Appendix C References.....	59
20	APPENDIX D: Selecting and Prioritizing Candidate Chemicals.....	60
21	• D.1 Selecting Chemicals for Evaluation.....	60
22	• D.2 Selecting and Prioritizing Candidate Chemicals found within the NIOSH Pocket Guide to	
23	Chemical Hazards.....	60
24	APPENDIX E: Guidelines and Criteria for the Search Strategy, Evaluation, and Selection of	
25	Supporting Data Used for the Assignment of Skin Notations.....	65
26	• E.1 Literature Search.....	65
27	E.1.1 Primary sources.....	65
28	E.1.2 Search terms.....	69
29	• E.2 Evaluation of data.....	70
30	APPENDIX F: Example of Assigning the New NIOSH Skin Notations and Format of the Skin	
31	Notation Profile.....	72
32	• F.1 Chemical background information and introduction.....	72
33	• F.2 Systemic toxicity from dermal exposure.....	74
34	• F.3 Direct effect(s) on the skin.....	81
35	• F.4 Sensitization.....	82
36	• F.5 Summary.....	83
37	• Appendix F References.....	85
38	APPENDIX G: Supplemental information.....	89

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

1	• <i>G.1 Contaminants and isomers</i>	89
2	• <i>G.2 Globally Harmonized System (GHS) of Classification and Labeling of Chemicals</i>	90
3	• <i>G.3 Nanotechnology and dermal toxicity</i>	91
4	• <i>Appendix G References</i>	94

Abbreviations

1		
2		
3	ACD	Allergic Contact Dermatitis
4		
5	BgVV	German Federal Institute for Health Protection of Consumers and Veterinary Medicine
6		
7		
8	CFR	Code of Federal Regulations
9		
10	CIB	Current Intelligence Bulletin
11		
12	cm	centimeter(s)
13		
14	cm ²	square centimeters
15		
16	cm/hr	centimeter(s) per hour
17		
18	(COR)	Subcategory of SK: DIR indicating the potential for a chemical to be corrosive following dermal exposure
19		
20		
21	DEREK™	Deductive Estimation of Risk from Existing Knowledge
22		
23	DERP	Dermal Exposure Research Program
24		
25	DNA	deoxyribonucleic acid
26		
27	ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
28		
29	ECVAM	European Centre for the Validation of Alternative Methods
30		
31	EU	European Union
32		
33	(FATAL)	Subcategory of SK: SYS indicating chemicals are highly or extremely toxic and may be potentially lethal or life threatening following acute dermal exposures
34		
35		
36		
37	g	gram(s)
38		
39	g/kg	grams per kilograms of animal body weight
40		
41	GHS	Globally Harmonized System of Classification and Labeling of Chemicals
42		
43		
44	GPMT	guinea pig maximization test

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1	hr	hour(s)
2		
3	ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
4		
5		
6	ICSC	International Chemical Safety Cards
7		
8	(IRR)	Subcategory of SK: DIR indicating the potential for a chemical to be a dermal irritant
9		
10		
11	K_{aq}	Coefficient in the watery epidermal layer
12		
13	kg	kilogram(s)
14		
15	K_{OW}	Octanol-water partition coefficient
16		
17	K_p	Skin permeation coefficient
18		
19	K_{pol}	Coefficient in the protein fraction of stratum corneum
20		
21	K_{psc}	Permeation coefficient in the lipid fraction of stratum corneum
22		
23	LD_{50}	Lethal dose 50% by dermal, oral, and intradermal routes
24		
25	LLNA	Local Lymph Node Assay
26		
27	LOAEL	Lowest-observed-adverse-effect level
28		
29	LOEL	Lowest-observed-effect level
30		
31	m	meter(s)
32		
33	m^3	cubic meter(s)
34		
35	MEST	Mouse Ear Swelling Test
36		
37	mg/kg-day	milligrams/kilograms animal body weight as a daily dose
38		
39	mg/m^3	milligrams per cubic meter of air
40		
41	min	minute(s)
42		
43	MW	molecular weight
44		
45	NICEATM	NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
46		

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1		
2	NIOSH	National Institute for Occupational Safety and Health
3		
4	NOAEL	No-observed-adverse-effect level
5		
6	NOEL	No-observed-effect level
7		
8	NTP	National Toxicology Program
9		
10	OECD	Organization for Economic Cooperation and Development
11		
12	OEL	Occupational Exposure Limit
13		
14	OSHA	Occupational Safety and Health Administration
15		
16	PEL	Permissible Exposure Limit
17		
18	QSARs	Quantitative structure-activity relationships
19		
20	QSPRs	Quantitative structure-permeability relationships
21		
22	REACH	Registration, Evaluation, Authorization and Restriction of Chemicals
23		
24	REL	Recommended Exposure Limit
25		
26	RF	Retention factor
27		
28	RTECS	Registry of Toxic Effects of Chemical Substances
29		
30	R-Phrases	Risk phrases
31		
32	SAR	Structure-activity relationships
33		
34	SI Ratio	Ratio of the skin dose to the inhalation dose
35		
36	SK	Skin notation
37		
38	SK	Skin notation indicating that the reviewed data did not identify a health risk associated with dermal exposure
39		
40		
41	SK: DIR	Skin notation indicating the potential for direct effects to the skin
42		
43	SK: SEN	Skin notation indicating the potential for sensitization of skin
44		
45	SK: SYS	Skin notation indicating the potential for systemic toxicity
46		

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1	S _w	water solubility
2		
3	TER	Transcutaneous Electrical Resistance assay
4		
5	TEWL	Trans-epidermal water loss from the stratum corneum
6		
7	US EPA	United States Environmental Protection Agency

Glossary

1

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

6

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

10

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

15

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

19

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

23

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

27

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

30

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

34

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

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1
2 Rolland BerryAnn
3 Nadia S. El-Ayouby, Ph.D.

4
5 **Office of the Director (OD)**

6
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Draft Document (D26) - Current Intelligence Bulletin (CIB): A Strategy for
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Travis M. Parsons, M.Sc., Occupational Safety and Health Division, Laborers' Health & Safety Fund of North America

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Peter J. Robinson, Ph.D., Principal Scientist, Air Force Research Laboratory, Mantech Environmental Technology Inc.

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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*

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

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

6 3. *Skin notations assigned after the 1988 PEL update project do not include*
7 *the skin exposure precautions made in NIOSH criteria documents.* For
8 example, the criteria document for ethylene glycol monomethyl ether,
9 ethylene glycol monoethyl ether and their acetates, recommends that
10 dermal exposures with these chemicals should be avoided due to their
11 ability to be readily absorbed by the skin [NIOSH 1991]. However, none
12 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

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

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

14

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

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

3

4 It should be noted that the strategy and skin notations outlined in this CIB are not
5 intended to provide a risk-based exposure value for dermal exposures to
6 chemicals, and should not be used to infer toxic potency for evaluated chemicals.

7 Other issues associated with the skin notations include their application to
8 chemical mixtures, the health effects of contaminants within neat substances and
9 isomeric variations of a chemical. Due to the complexity of assessing the
10 hazards of chemical interactions associated with complex mixtures or due to the
11 presence of contaminants, the skin notations are intended to apply to neat
12 compounds and may not be health protective against additional effects
13 associated with complex mixtures (See Appendix G.1). Also, assigned skin
14 notations are applicable only to the specified forms of an evaluated compound
15 and may not provide adequate warnings about unique hazards of the non-
16 specified isomeric forms of the chemical (See Appendix G.1).

17

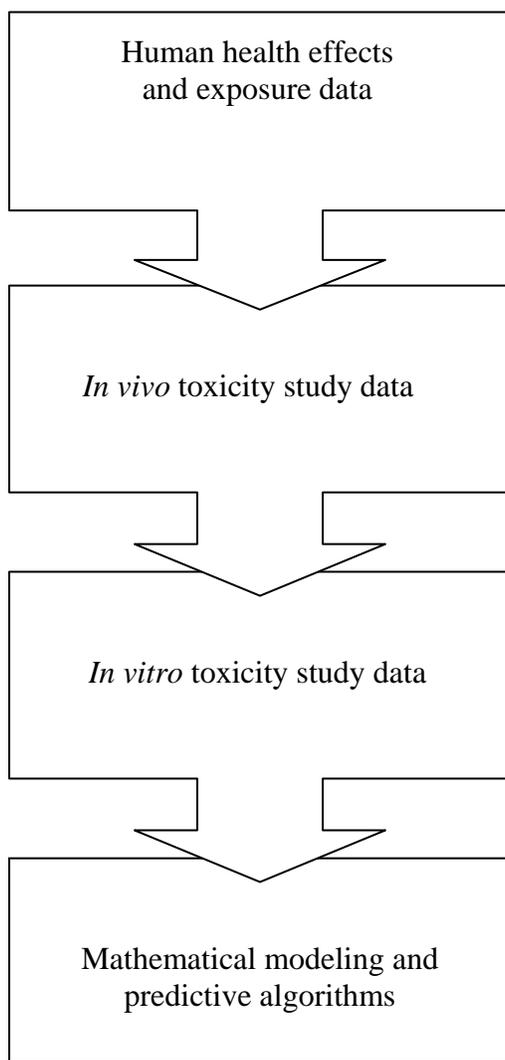
18 • **2.1 Criteria for Assigning Skin Notations**

19 The critical step in assigning skin notations to a chemical is determining its
20 “hazard potential”—that is, it’s potential for causing adverse health effects as a
21 result of skin exposure. This determination involves a health hazard
22 identification process that assesses the following: (1) scientific data on the

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

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

8



9

1 **Figure 2:** Hierarchy of evaluated scientific data

2

3 The following sections discuss the skin notation assignments in each category.

4 Exceptions to this approach are also described. This strategy for assigning skin

5 notations has been developed to correspond with the classification strategy

6 adopted in the *Globally Harmonized System of Classification and Labeling of*

7 *Chemicals* (GHS) developed by the United Nations [UNECE 2005].

8 • **2.2 SYS**

9 The SYS notation is assigned to chemicals that are absorbed through the skin

10 and contribute to systemic toxicity. Chemicals that are identified as highly or

11 extremely toxic and may be potentially lethal or life threatening following acute

12 dermal exposures would also receive the subnotation (FATAL) [i.e., SK: SYS

13 (FATAL)]. The following are examples of adverse systemic effects that have

14 been associated with dermal exposures to chemicals through the use of human

15 and animal data that require the assignment of the SYS notation or its

16 subnotation (FATAL):

- 17 • Cardiotoxicity
- 18 • Carcinogenesis and photocarcinogenesis (excluding cancers of the skin)
- 19 • Hematotoxicity
- 20 • Hepatotoxicity
- 21 • Histopathological changes
- 22 • Immunotoxicity
- 23 • Lethality

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

- 1 • Neurotoxicity
- 2 • Nephrotoxicity
- 3 • Reproductive and developmental effects

4

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

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

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

19

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

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

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

4 B Data from experimental animal studies indicate the following:

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

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

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

- 1 • Investigation of the relevant toxicokinetics and potential toxic
 - 2 effects of metabolic transformation(s) of chemicals following skin
 - 3 absorption
 - 4 • Examination of the adverse effects of chemical mixtures whose
 - 5 skin absorption or potential systemic toxicity is different from the
 - 6 level anticipated for individual components of the mixture because
 - 7 of synergistic effects
 - 8 • Investigation of altered skin permeability characteristics of toxic
 - 9 components resulting from the presence of a solvent or vehicle in
 - 10 a chemical preparation.
- 11 D If no acceptable-quality empirical data exist for systemic effects from
- 12 dermal exposure to a chemical, systemic toxicity data may be extrapolated
- 13 from toxicity data associated with other routes of exposure (such as oral
- 14 and inhalation) when
- 15 —quality dermal kinetics data demonstrate the ability of a chemical to
- 16 be absorbed by the skin, and
- 17 —a direct link can be determined between the health effects caused by
- 18 the alternative routes of exposure and dermal exposures.
- 19 Both conditions must be satisfied to assign a SYS notation.
- 20 E When no acceptable-quality empirical data exist on the systemic effects of
- 21 dermal exposure, the potential for dermal absorption and consequent
- 22 systemic toxicity of the chemical may be mathematically estimated. To
- 23 mathematically determine the risk for systemic toxicity (e.g., predictive

1 algorithm), the following information is needed: (1) the skin permeation
2 rate, (2) the chemical dose calculated to be absorbed through skin (skin
3 dose), (3) a reference dose representing the threshold of acceptable body
4 accumulation (a chemical dose to be absorbed via inhalation during the
5 same period of exposure), and (4) a comparison of the skin dose to the
6 reference dose (which indicates the significance of skin absorption and its
7 potential contribution to systemic toxicity).

8
9 Appendix B presents an algorithm that can be used for determining the
10 potential for systemic toxicity. When the predictive algorithm is used as
11 the basis for identification, a positive result indicates that a chemical is
12 capable of producing systemic toxicity from dermal exposure and should
13 be assigned the SYS notation. If the predictive algorithm indicates no
14 potential for systemic toxicity from dermal absorption, the chemical should
15 be further evaluated with accepted tests.

16
17 Table 2.2 provides a paradigm for the assignment of the SYS notation based on
18 the criteria outlined within this section, in addition to Appendixes A and B.
19 Variables considered for the assignment of the SYS notation within this model
20 include 1) systemic toxicity associated with dermal exposures of the skin and 2)
21 dermal absorption. Table 2.2 illustrates when the assignment of the SYS
22 notation is appropriate based on the results of the critical review of all relevant
23 scientific data.

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

1

1 **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 [±]

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

8 • **2.3 DIR**

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

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

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

- 6 • Carcinogenesis and photocarcinogenesis at the site of chemical contact
- 7 • Changes in pigmentation including bleaching (blanching) and staining of
8 the skin
- 9 • Chloracne
- 10 • Compromise of the skin barrier integrity
- 11 • Corrosion
- 12 • Defatting or drying of skin
- 13 • Irritant contact dermatitis
- 14 • Phototoxicity

15

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

- 18 A Credible evidence indicates that immediate, prolonged, or repeated
19 contact of skin with the chemical produces direct effects on the skin of
20 exposed workers. The direct effects reported were based on incidents of
21 worker exposures and consist of primary irritation, including irritant contact
22 dermatitis (macroscopically manifested as erythema and edema),
23 corrosion (manifested as ulceration, visible necrosis of epidermis/dermis,

1 bleeding, eschar formation, and discoloration), changed pigmentation
2 including bleaching (blanching) and staining of the skin, chloracne caused
3 by chemicals such as halogenated aromatic hydrocarbons,
4 defatting/drying of skin, and skin cancer at the site of contact. Information
5 about acute or cumulative irritation of human skin may also be available
6 from the results of predictive patch tests conducted on human volunteers
7 (e.g., the acute dermal irritation study in human volunteers [OECD 1997]).

8 Such information will be considered when assigning skin notations.

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

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

1 impairment of skin tissues, disintegration of skin components (e.g.,
2 defatting and discoloration), or the presence of neoplastic lesions or
3 tumors in the epidermis and dermis in association with changes in the
4 transdermal penetration of chemicals.

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

19

20 • **2.4 SEN**

21 Immune-mediated reactions associated with exposures of the skin to chemicals
22 encompass a wide spectrum of dermal disorders and systemic allergic
23 responses, including respiratory sensitization, airway hyperactivity and mucosal

1 inflammation. Occupationally, the most common and significant reaction is
2 allergic contact dermatitis (ACD). For ACD, the skin-sensitizing potential of the
3 chemical is typically evaluated by two endpoints—the immunological induction of
4 sensitization and the elicitation of ACD.

5
6 Findings reported within multiple published studies support a link between
7 exposures of the skin to certain chemical allergens and the induction and/or
8 elicitation of systemic allergic responses, including respiratory sensitization,
9 airway hyperactivity and mucosal inflammation (Kimber et al., 1996; Beck et al.,
10 2000; Tinkle, et al., 2003; Day et al. 2006; Bello et al., 2007; Kreiss et al., 2007;
11 Redlich et al., 2008). For example, despite decreased inhalation exposures to
12 isocyanates and beryllium within various occupational settings, immune-
13 mediated respiratory diseases associated with these compounds continue to
14 persist (Bello et al., 2007; Kreiss et al., 2007; Redlich et al., 2008). The results of
15 these investigations point to skin contact with certain chemical allergens as
16 having a potentially significant role within the onset of immune-mediated
17 respiratory diseases (Bello et al., 2007; Kreiss et al., 2007; Redlich et al., 2008).
18 The exact mechanisms responsible for immune-mediated systemic responses
19 following dermal exposures are not fully understood. It has been theorized that
20 one possible pathway involves the absorption of a chemical allergen across the
21 stratum corneum, its subsequent penetration of the epidermis and the initiation
22 and/or elicitation of an immune-mediated response associated with dendrite cells
23 (Kimber 1996). Regardless of the mechanism, dermal exposures to chemical

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

3

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

- 23
- Allergic Contact Dermatitis (ACD)

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

- 1 • Delayed hypersensitivity response (Type IV)
- 2 • Immediate hypersensitivity response (Type I)
- 3 • Photosensitization

4

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

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

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

16

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

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

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

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

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

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

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

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

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

20 • **2.5 SK**

21 The ~~SK~~ notation is assigned to indicate that a chemical underwent a critical
22 assessment of the scientific data and was not identified as a systemic, direct, or

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

- 1 sensitizing health risk from dermal exposure based on the criteria described
- 2 above for the assignment of the SYS, DIR, and SEN notations. It should be
- 3 noted that for a chemical to receive the SK notation the scientific data must be
- 4 classified as *sufficient* based on the criteria outlined in Appendix E.2).
- 5
- 6

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

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

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

A.1.1 Dermal absorption

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

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1

2 In addition to predictive models, *in vitro* and *in vivo* test methods have been
3 developed to estimate the rate of absorption (of one or more of its phases) of
4 chemicals through the skin [OECD 2004 a, b, c; WHO 2006]. *In vitro* dermal
5 absorption tests generally rely on the application of a radiolabeled test substance
6 to a sample of nonviable or metabolically active excised skin suspended between
7 two chambers of a diffusion cell, and are used to measure the rates of
8 penetration and permeation [Bronaugh and Stewart 1985; US EPA 2004; OECD
9 2004b]. *In vivo* studies use a physiologically and metabolically active system in
10 the form of human volunteers or test animals, such as rats, to assess the dermal
11 penetration, permeation and resorption of test chemicals [OECD 2004a; OECD
12 2004c; WHO 2006]. Predictive algorithms and mathematical models, such as
13 quantitative structure-permeability relationships (QSPR), have been developed to
14 offer a relatively inexpensive method for determining dermal penetration of
15 chemicals [Moss et al. 2002; Riviere and Brooks 2005; WHO 2006]. The
16 predictive algorithms utilize the physiochemical properties (i.e. molecular weight,
17 solubility, pH) of a test substance to estimate the potential biological effects or
18 transport properties within a biological system [Moss et al. 2002; Riviere and
19 Brooks 2005; OECD 2004a; WHO 2006]. The results of dermal absorption tests
20 are frequently presented as the estimated or predicted percentage (%) of the test
21 substance dermally absorbed. To differentiate between low and high dermal
22 absorption, a 10% absorption rate has been selected as the cutoff value. This
23 value corresponds to OECD guidelines [OECD 2004a], and is based on

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

6

7 **A.1.2 Acute dermal toxicity**

8 Acute dermal toxicity testing examines the mortality of test animals after single,
9 short-term exposures to a toxic chemical [OECD 1987; US EPA 1998a].

10 Typically, the test chemical is applied to the skin and remains in place for 24 hr.
11 The animals are then observed for 14 days. The results of acute toxicity tests are
12 presented as the dermal dose that is lethal for 50% of the exposed animals
13 (LD_{50}), with observations of behavioral/clinical abnormalities and pathological
14 findings from gross necropsy. If the LD_{50} values are consistently lower than the
15 numeric cutoff value of 2000 mg/kg of animal body weight, the chemical is
16 considered systemically toxic by the dermal route and is assigned the SYS
17 notation. The critical value of 2000 mg/kg for the dermal LD_{50} reflects the dose
18 selected in standardized limit tests to identify chemicals with the potential for
19 acute dermal toxicity. This value corresponds with the upper dermal LD_{50} limit for
20 establishing a chemical as a “harmful” substance in the general classification and
21 labeling requirements for chemicals in member countries of the OECD [Council
22 of the European Communities 1992] and by GHS [UNECE 2005].

23

1 If the LD₅₀ values are consistently lower than the numeric cutoff value of 200
2 mg/kg of animal body weight, the chemical is potentially lethal following acute
3 dermal exposures and is assigned the (FATAL) notation. This value is consistent
4 with the numeric cutoff value used by GHS to identify chemicals capable of
5 causing death following contact with the skin.

6

7 **A.1.3 Repeated-dose dermal toxicity**

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

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

3

4 **A.1.4 Subchronic dermal toxicity**

5 Subchronic toxicity testing examines the cumulative toxic effect(s) from
6 continuous or repeated exposure to a toxic chemical for at least 90 days [OECD
7 1981b; US EPA 1998c]. The animals are observed for behavioral/clinical
8 abnormalities during the study. At the end of the study, they are examined for
9 gross organ lesions, hematology, clinical chemistry, ophthalmology, and
10 histopathology. Test results often include the NOAEL for the most sensitive
11 endpoint(s) selected from all evaluated health effects. If the NOAEL for a
12 selected endpoint is lower than the numeric cutoff value of 1000 mg/kg-day, the
13 chemical is considered systemically toxic by the dermal route and is assigned the
14 SYS notation. The critical dermal NOAEL value of 1000 mg/kg-day reflects the
15 dose selected in the standardized limit tests to identify chemicals with the
16 potential for subchronic dermal toxicity. If a creditable NOAEL is not identified
17 within the reviewed toxicological data, a LOAEL, LOEL or NOEL may be
18 substituted when available for comparison to the selected cutoff value of 1000
19 mg/kg-day.

20

21 **A.1.5 Chronic dermal toxicity**

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

1 1981c; US EPA 1998d]. The animals are observed for behavioral/clinical
2 abnormalities during the study. They are evaluated using hematology, clinical
3 chemistry, urinalysis, and ophthalmology during and at the end of the study. At
4 necropsy, they are examined for gross organ lesions and tissue histopathology.
5 Test results often include the NOAEL for the most sensitive endpoint(s) selected
6 from all evaluated health effects. If the NOAEL for a selected endpoint is lower
7 than the numeric cutoff value of 1000 mg/kg-day, the chemical is considered
8 systemically toxic by the dermal route and is assigned the SYS notation. The
9 critical dermal NOAEL value of 1000 mg/kg-day reflects the dose selected in the
10 standardized limit tests to identify chemicals with the potential for chronic dermal
11 toxicity. If a creditable NOAEL is not identified within the reviewed toxicological
12 data, a LOAEL, LOEL or NOEL may be substituted when available for
13 comparison to the selected cutoff value of 1000 mg/kg-day.

14

15 **A.1.6 Carcinogenicity**

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

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

10

11 **A.1.7 Toxic effects of dermal exposures on organ systems or biological** 12 **functions**

13 Several types of tests examine the destruction or disruption of target organ
14 systems and/or biological functions from dermal exposure to chemicals.
15 Examples include (1) prenatal development toxicity (maternal and fetal toxicity)
16 testing [US EPA 1998g; NTP 2001b; OECD 2001a] and (2) two-generation
17 reproduction and fertility effects testing [US EPA 1998h; OECD 2001b], and (3)
18 immunotoxicity (suppression of the immune system) testing [US EPA 1998i].
19 Ideally, a no-observed-adverse-effect level (NOAEL) is identified and reported for
20 the studied effect(s). If the NOAEL for a selected endpoint is lower than 1000
21 mg/kg-day, the chemical is considered systemically toxic by the dermal route and
22 assigned the SYS notation. The critical dermal cutoff value of 1000 mg/kg-day
23 reflects the dose selected in the standardized limit tests used to identify
24 chemicals that are potentially toxic to organs or biological functions. In the event
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1 that a NOAEL can not be identified within reviewed toxicological data, a lowest-
2 observed-adverse-effect level (LOAEL) may be substituted when available for
3 comparison to the selected cutoff value of 1000 mg/kg-day.

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

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

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

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

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

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

19

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

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

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

- 5 • Corrositex® [NTP 1999a]
- 6 • The human skin models [OECD 2004e], including EPISKIN™ and
7 EpiDerm™ [NTP 2002b]
- 8 • The rat skin transcutaneous electrical resistance (TER) assay [NTP
9 2002b; OECD 2004f]

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

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

5

6 **A.2.3 Carcinogenicity**

7 Carcinogenicity testing examines the development of neoplastic lesions on skin
8 as a result of long-term dermal exposure to a chemical for 18 to 24 months
9 [OECD 1981d; US EPA 1998e]. The test period constitutes a major portion of the
10 life span of test animals. The animals are observed for behavioral/clinical
11 abnormalities during the study. They are investigated for clinical pathology during
12 and at the end of the study. They are also examined for gross organ lesions and
13 tissue histopathology at necropsy. Carcinogenicity from dermal exposure to a
14 chemical may be studied and reported jointly with chronic dermal toxicity [OECD
15 1981e; US EPA 1998f; NTP 2001a]. If dermal exposure to a chemical induces a
16 statistically significant increase in the incidence of neoplastic lesions or tumors in
17 test animals, it is considered to be a potential skin carcinogen and is assigned
18 the DIR notation. Additionally, toxicants identified as being capable of causing
19 photocarcinogenesis when topically applied in conjugation with exposure to
20 sunlight will also be included within this category [NTP 2002a; OECD 2004d].

21

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

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

7

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

11

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

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

1

2 **A.3.2 Identifying skin sensitization potential with the murine LLNA**

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

16

17 **A.3.3 Identifying skin sensitization potential with the mouse ear swelling** 18 **test (MEST)**

19

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

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

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1 **APPENDIX B: Algorithm for estimating**
2 **dermal absorption and systemic toxicity and**
3 **suggested application for assigning SYS**
4 **notations**

5
6 • **B.1 Algorithm for estimating and evaluating dermal**
7 **exposure hazards**

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

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

19
20 The algorithm evaluation includes three steps: (1) determining a skin permeation
21 coefficient for the chemical; (2) estimating chemical uptake by the dermal and
22 respiratory absorption routes; and (3) evaluating whether the chemical poses a

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

9

10 **B.1.1 Step 1: Determining the skin permeation coefficient**

11

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

18

19 Experimentally, the permeation of chemicals through human skin can be
20 determined *in vitro* using diffusion cell techniques such as those described in the
21 protocols standardized by OECD [2004a,b] and US EPA [69 Fed. Reg.
22 22402(2004)]. These methods typically measure the diffusion of a test
23 substance into and across the excised skin (which consists of epidermal
24 membranes or split-thickness skin) to a fluid reservoir; they report the K_p as a

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

12

13 As an example to demonstrate the determination of K_p by predictive QSPRs, the
14 revised Robinson model is presented here for its mathematical descriptors and
15 operation. The revised Robinson model has been shown to be among the
16 QSPRs that provide reasonable K_p estimates when compared with the
17 experimentally derived values [Wilschut et al. 1995; Vecchia and Bunge 2003].

18 The revised Robinson model estimates K_p based on the molecular weight of a
19 chemical (MW, representing the molecular size) and the logarithm of its octanol-
20 water partition coefficient ($\log K_{OW}$, representing the hydrophobicity). This model
21 is mathematically expressed:

22

23

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

1

2

3 where K_{psc} is the permeation coefficient in the lipid fraction of the stratum
4 corneum, K_{pol} is the coefficient in the protein fraction of the stratum corneum, and
5 K_{aq} is the coefficient in the watery epidermal layer. These components are
6 individually estimated by

$$7 \log K_{psc} = -1.326 + 0.6097 \times \log K_{OW} - 0.1786 \times MW^{0.5}$$

$$8 K_{pol} = 0.0001519 \times MW^{-0.5}$$

$$9 K_{aq} = 2.5 \times MW^{-0.5}$$

10

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

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

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

5
6 Step 2 in the evaluation (as initially proposed by the Toxic Substances Control
7 Act Interagency Testing Committee [Walker et al. 1996]) is to calculate the
8 biological uptake of the chemical from skin absorption (skin dose) and inhalation
9 (inhalation dose) during the same period of exposure. The inhalation dose
10 represents a critical presence of the examined substance in the body. Beyond
11 this dose, bioaccumulation of the substance is a cause for concern for health
12 effects. The skin and inhalation doses provide quantifiable measures for
13 absorption of the chemical by different routes. These doses serve as the basis
14 for determining whether the substance constitutes a skin absorption hazard.

15
16 The skin dose is calculated as a mathematical product of the K_p acquired in Step
17 1, the water solubility (S_w) of the chemical, the exposed skin surface area, and
18 the duration of exposure. In the calculation, the transdermal flux of the
19 substance is assumed to originate from a saturated aqueous solution. Assuming
20 that the skin exposure continues for 8 hr and occurs to the unprotected skin on
21 both palms (a surface area of 360 cm^2),

22
23 Skin dose = $K_p \times S_w \times \text{Exposed skin surface area} \times \text{Exposure time}$
24 = $K_p \text{ (cm/hr)} \times S_w \text{ (mg/cm}^3\text{)} \times 360 \text{ (cm}^2\text{)} \times 8 \text{ (hr)}$

1

2 The inhalation dose is derived on the basis of the occupational exposure limit
3 (OEL) of the substance—if the OEL is developed to prevent the occurrence of
4 systemic effects rather than sensory/irritant effects or direct effects on the
5 respiratory tract. Assuming a continuous exposure of 8 hr, an inhalation volume
6 of 10 m³ in 8 hr, and a factor of 75% for the retention of the airborne substance in
7 the lungs during respiration (retention factor, RF),

8

$$\begin{aligned} 9 \text{ Inhalation dose} &= \text{OEL} \times \text{Inhalation volume} \times \text{RF} \\ 10 &= \text{OEL (mg/m}^3\text{)} \times 10 \text{ (m}^3\text{)} \times 0.75 \end{aligned}$$

11

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

1 **B.1.3 Step 3: Evaluating the skin exposure hazard**

2 The final step is to compare the calculated skin and inhalation doses and to
3 present the result as a ratio of skin dose to inhalation dose (the SI ratio). This
4 ratio quantitatively indicates (1) the significance of percutaneous absorption as a
5 route of occupational exposure to the substance and (2) the contribution of
6 dermal uptake to systemic toxicity. If a chemical has an SI ratio ≥ 0.1 , it is
7 considered a skin absorption hazard.

8
9 • **B.2 Criterion for assigning the SYS notations**

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

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

1 • The OELs used to calculate inhalation dose were initially developed with a
2 small safety margin compared with the OELs for compounds having an SI
3 >0.1.

4 • The health effects basis for skin notations may not be adequate.

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

9

10 This criterion agrees with the findings from similar research conducted by other
11 international occupational safety and health organizations. One example is the
12 proposal of the European Centre for Ecotoxicology and Toxicology of Chemicals
13 (ECETOC) to recommend skin notations based on a semi-quantitative approach
14 [ECETOC 1998]. The algorithm proposed by ECETOC is similar to the one
15 intended for assigning NIOSH SK:SYS notations. The ECETOC algorithm
16 determines the skin exposure hazard posed by a chemical agent by comparing
17 its dermal uptake to its systemic absorption from inhalation. ECETOC concluded
18 that a skin notation should be assigned to a chemical when the amount of
19 chemical absorbed by both hands and forearms in 1 hr could exceed 10% of the
20 amount absorbed by inhalation when airborne concentrations are at the OEL for
21 8 hr. The defaults of the exposed skin surface area, the air volume inhaled in 8
22 hr, and the respiratory RF in the ECETOC algorithm are 2,000 cm², 10 m³, and
23 50%, respectively. The SI ratio calculated in the algorithm proposed for

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

$$\begin{aligned} 5 \text{ SI Ratio}_{\text{ECETOC}} &= \text{SI Ratio}_{\text{NIOSH}} \times [2,000 \text{ cm}^2 \text{ (hands/arms)} \div 360 \text{ cm}^2 \text{ (palms)}] \\ 6 &\quad \times [1 \text{ hr} \div 8 \text{ hrs}] \times [75\% \text{ (default RF in NIOSH algorithm)} \div \\ 7 &\quad \div 50\% \text{ (default RF in ECETOC algorithm)}] \\ 8 &= \text{SI Ratio}_{\text{NIOSH}} \times 1.04 \end{aligned}$$

9

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

16

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

23

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

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

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

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

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

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

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

- 4 • The pH of a chemical is ≤ 2.0 or ≥ 11.5 .
- 5 • $\text{pH} - \text{acid reserve}/6 \leq 1$ or
- 6 • $\text{pH} + \text{alkali reserve}/12 \geq 14.5$

7 where the acid reserve of a substance is the amount (grams) of sodium
8 hydroxide required to bring 100 g of a test substance (in a 10% solution or
9 suspension) to a pH of 4, and the alkali reserve is the amount of sulfuric acid
10 required to bring 100 g of a test substance to a pH of 10. (See Young et al.
11 [1988] for details about the generation and use of acid/alkali reserve
12 measurements.)

13

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

16
17 The knowledge-based DEREK™ expert system contains algorithms to predict
18 the toxicity of chemical substances based on a series of structure-activity rules
19 (also known as structural rules or structural alerts). These rules or alerts describe
20 the sub-structures of chemical molecules potentially responsible for adverse
21 health effects [Ridings et al. 1996]. As part of the DEREK™ expert system
22 architecture, a rule base for identifying potential contact allergens was derived
23 using results of the GPMT conducted for 294 chemical substances classified as
24 strong or moderate sensitizers [Barratt et al. 1994]. The rule base initially

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

7

8 Zinke et al. [2002] assessed the effectiveness of these structural alerts for
9 identifying the skin-sensitizing properties of chemicals. The researchers
10 evaluated the 40 originally published structural alerts against a database
11 developed in the German Federal Institute for Health Protection of Consumers
12 and Veterinary Medicine (BgVV). The BgVV database contained data submitted
13 under its procedure for notification about new chemicals within the European
14 Union and data on the skin-sensitization potentials of 1,039 substances [Zinke et
15 al. 2002]. Zinke et al. [2002] reported that among the structural alerts examined,
16 eight could be used to identify contact allergens without further refinement.

17 These alerts are for acid halides, acid anhydrides, isocyanates, isothiocyanates,
18 β -lactams, aldehydes, epoxides, and quaternary ammonium cation.

19

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

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

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39

APPENDIX D: Selecting and Prioritizing Candidate Chemicals

• D.1 Selecting Chemicals for Evaluation

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

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

One hundred forty-two chemicals listed in the *NIOSH Pocket Guide to Chemical Hazards* have been previously assigned the skin notation [skin] which indicates the potential for dermal absorption. These compounds have been selected to be the first group of compounds to be evaluated via the strategic framework outlined

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

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

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

13
14 European Inventory of Existing Commercial chemical Substances
15 (EINICS) (<http://ecb.jrc.it/esis/index.php?PGM=ein>)

16
17 National Occupational Exposure Survey (NOES)
18 (<http://www.cdc.gov/noes/>)

19
20 NIOSHTIC-2
21 (<http://www2a.cdc.gov/nioshtic-2/advsearch2.asp>)

22
23 NIOSH Immediately Dangerous to Life and Health (IDLH) Values
24 (<http://www.cdc.gov/niosh/idlh/idlh-1.html>)

25
26 NIOSH International Chemical Safety Card (ICSC)
27 (<http://www.cdc.gov/niosh/ipcs/nicstart.html>)

28
29 NIOSH Pocket Guide to Chemical Hazards
30 (<http://www.cdc.gov/niosh/npq/>)

31
32 NIOSH Registry of Toxic Effects of Chemical Substances (RTECS)
33 (<http://www.cdc.gov/niosh/rtecs/rteccas1.html>)

34
35 NIOSH Recommendations for Occupational Safety and Health,
36 Compendium of Policy Documents and Statements

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

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2
3 NIOSH Skin Exposures and Effects Topic Page

4 [\(<http://www.cdc.gov/niosh/topics/skin/>\)](http://www.cdc.gov/niosh/topics/skin/)

5
6 OSHA Permissible Exposure Limits

7 [\(<http://www.osha.gov/SLTC/pel/>\)](http://www.osha.gov/SLTC/pel/)

8
9 US EPA High Production Volume Information System (HPV)

10 [\(<http://www.epa.gov/hpvis/>\)](http://www.epa.gov/hpvis/)

11
12
13 The 142 chemicals previously assigned the [skin] notation by NIOSH were
14 systematically assigned a score ranging from 0 to 7 to determine which
15 substances posed the greatest potential occupational health hazard based on the
16 parameters outlined in Table D.1. The scores for 30 chemicals are illustrated
17 within Table D.2.

18
19 **Table D.1 Definition scoring of parameters applied with hierarchal ranking**
20 **scheme**
21

Parameter	Definition and scoring
OEL Potency	If OEL is < 1 mg/m ³ , assign score of 1; if not, assign score of 0.
Carcinogen	If identified as a carcinogen, assign score of 0.5; if not, assign score of 0.
Reproductive/ Development Toxicant	If identified as a reproductive or development toxicant, assign score of 0.5; if not, assign score of 0.
Irritant/Corrosive	If identified as a corrosive, assign score of 1; if identified as an irritant only, assign score of 0.5; if identified as neither, assign score of 0.
Sensitizer	If identified as a sensitizer, assign score of 1; if not, assign score of 0.
HPV Chemical	If identified as a HPV chemical, assign score of 1; if not, assign score of 0.

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

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.

1

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

4

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

5

6

7

8

9

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

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

- 1 The hierarchal ranking scheme presented in this section of the CIB may be
- 2 modified in the future to aid NIOSH in prioritizing 1) chemicals listed within the
- 3 Pocket Guide to Chemical Hazards that do not have the skin notation [skin] and
- 4 2) chemicals nominated for evaluation from stakeholders, governmental agencies
- 5 and public interest groups.
- 6

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)

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

- 1 (<http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?CHEM>)
- 2
- 3 European Inventory of Existing Commercial chemical Substances
- 4 (EINICS) (<http://ecb.jrc.it/esis/index.php?PGM=ein>)
- 5
- 6 EMBASE
- 7 (<http://www.embase.com/>)
- 8
- 9 Extension Toxicology Network (EXTOXNET)
- 10 <http://extoxnet.orst.edu/pips/ghindex.html>
- 11
- 12 Haz-Map: Occupational Exposure to Hazardous Agents (Haz-Map)
- 13 (<http://www.nlm.nih.gov/pubs/factsheets/hazmap.html>)
- 14
- 15 Hazardous Substances Data Bank (HSDB)
- 16 (<http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>)
- 17
- 18 Integrated Risk Information System (IRIS)
- 19 (<http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?IRIS>)
- 20
- 21 International Toxicity Estimates for Risk (ITER)
- 22 (<http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?iter>)
- 23
- 24 MICROMEDEX
- 25 (<http://intra-apps.cdc.gov/scripts/elib.pl?url=http://csi.micromedex.com>)
- 26
- 27 NIOSH Registry of Toxic Effects of Chemical Substances (RTECS)
- 28 (<http://www.cdc.gov/niosh/rtecs/>)
- 29
- 30 NIOSHTIC-2
- 31 (<http://www2a.cdc.gov/nioshtic-2/advsearch2.asp>)
- 32
- 33 National Toxicology Program Report on Carcinogens (NTPA)
- 34 (<http://ehis.niehs.nih.gov/roc/>)
- 35
- 36 OSH References Collection
- 37 (<http://ccinfoweb.ccohs.ca/bibliographic/search.html>)
- 38
- 39 Public Medline (PubMed)
- 40 (<http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed>)
- 41
- 42 Toxicology Information Online (TOXLINE) database from the U.S. National
- 43 Library of Medicine's TOXNET ([http://toxnet.nlm.nih.gov/cgi-](http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE)
- 44 [bin/sis/htmlgen?TOXLINE](http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE))
- 45

1 U.S. Environmental Protection Agency (US EPA) Substance Registry
2 System
3 (<http://www.epa.gov/srs/>)
4

5 Web of Science
6 (<http://publisorperish.nih.gov/>)
7

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

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

12
13 Agency for Toxic Substance and Disease Registry (ATSDR) Public Health
14 Statements (PHSs)
15 (<http://www.atsdr.cdc.gov/phshome.html>)
16

17 ATSDR Toxicological Frequently Asked Questions (TOXFAQS)
18 (<http://www.atsdr.cdc.gov/toxfaq.html>)
19

20 ATSDR ToxProfiles
21 (<http://www.atsdr.cdc.gov/toxpro2.html>)
22

23 American Conference of Government and Industrial Hygienists (ACGIH)
24 Documentation of the Threshold Limit Values (TLV) for Chemical
25 Substances and Physical Agents
26

27 American Industrial Hygiene Association (AIHA) Workplace Environmental
28 Exposure Limits (WEELs)
29 ([http://www.aiha.org/webapps/taxonomy/documentrepository/erpgweels/7
30 d11ed78-37da-4ce1-99f2-763603376151.pdf](http://www.aiha.org/webapps/taxonomy/documentrepository/erpgweels/7d11ed78-37da-4ce1-99f2-763603376151.pdf))
31

32 California Environmental Protection Agency (CalEPA) Health Reports
33 (<http://www.calepa.ca.gov/Publications/>)
34

35 Cassarett and Doull's Toxicology: The Basic Science of Poisons
36

37 European Commission Risk Assessment Reports
38 (http://ec.europa.eu/health/ph_risk/risk_en.htm)
39

40 Hamilton and Hardy's Industrial Toxicology
41

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

- 1 Health and Safety Executive (HSE) Publications
- 2 (<http://www.hse.gov.uk/pubns/index.htm>)
- 3
- 4 International Agency for Research on Cancer (IARC) Monographs on the
- 5 Evaluation of Carcinogenic Risks to Humans
- 6 (<http://monographs.iarc.fr>)
- 7
- 8 International Programme on Chemical Safety (IPCS)
- 9 (<http://www.inchem.org/>)
- 10
- 11 Merck Index
- 12
- 13 National Industrial Chemicals Notification and Assessment Scheme
- 14 (NICNAS) Scientific Reports
- 15 (<http://www.nicnas.gov.au/>)
- 16
- 17 NIOSH ICSC
- 18 (<http://www.cdc.gov/niosh/ipcs/nicstart.html>)
- 19
- 20 NIOSH Pocket Guide to Chemical Hazards
- 21 (<http://www.cdc.gov/niosh/nppl/>)
- 22
- 23 NIOSH RTECS
- 24 (<http://www.cdc.gov/niosh/rtecs/rteccas1.html>)
- 25
- 26 NIOSH Recommendations for Occupational Safety and Health,
- 27 Compendium of Policy Documents and Statements
- 28 (http://www.cdc.gov/niosh/pubs/all_date_desc_nopubnumbers.html)
- 29
- 30 New Jersey Right to Know Hazardous Substances Fact Sheets
- 31 (<http://web.doh.state.nj.us/rtkhsfs/indexfs.aspx>)
- 32
- 33 Patty's Industrial Hygiene and Toxicology
- 34
- 35 Proctor and Hughes' Chemical Hazards of the Workplace
- 36
- 37 US EPA Health Effects Documents
- 38 (<http://www.epa.gov/>)
- 39
- 40 U.S. National Technical Information Services (NTIS)
- 41 (<http://www.ntis.gov/>)
- 42
- 43 U.S. National Toxicology Program (NTP) Study Reports
- 44 (<http://ntp.niehs.nih.gov/ntpweb/index.cfm?objectid=7DA86165-BDB5-82F8-F7E4FB36737253D5>)
- 45
- 46

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

1 US Occupational Safety and Health Administration (OSHA) Publications
2 (<http://www.osha.gov/>)
3

4 **E.1.2 Search terms**

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

9
10 **Table E.1 Terminology applied during the search for critical scientific data**
11 **on each candidate chemical substance**
12

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

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Fingernail	Papulosquamous	Xeroderma
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1 • **E.2 Evaluation of data**

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

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

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

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

- 1 protocols, in-depth descriptions of the exposure conditions and study findings.
- 2 Data sets that receive the *insufficient* ranking should not be used as the basis for
- 3 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.

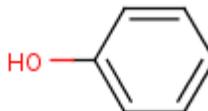
• F.1 Chemical background information and introduction

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

Synonyms:

Carbolic acid, monohydroxybenzene, hydroxybenzene, benzenol, phenylic acid, phenyl hydroxide, benzophenol, phenyl hydrate, phenylic alcohol, monophenol, phenic acid, oxybenzene

Structure:



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

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

14

15 **Table F.1 Skin Notation for Phenol**

16

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

17

18

19

20

- *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*

1 *includes the critical effects identified during the assignment of the skin*
2 *notation, in addition to classifying the quantity and quality of the data set*
3 *used to draft the profile (Appendix E.2).*
4

5 • **F.2 Systemic toxicity from dermal exposure**

6
7 Toxicokinetic studies of phenol have been identified. Dermal absorption of phenol
8 by human subjects has been reported to range from 4 to 23% of the applied
9 dose, with the extent of the dermal absorption, dependent on the period of
10 exposure and the concentration of phenol [Feldman and Maibach 1970;
11 Piotrowski 1971; Roberts et al. 1977; Baranowska-Dutkiewicz 1981]. In male
12 volunteers, the rate of absorption of an aqueous phenol solution [2.5, 5.0, or 10.0
13 gallons per liter (g/L)] from a 2 milliliter (mL) reservoir applied directly to the
14 forearm [15.6 square centimeters (cm²)] was found to be concentration-
15 dependent, with the rate ranging from 0.079 milligrams per square centimeter per
16 hour (mg/cm²/hour) at the low concentration to 0.301 mg/cm²/hr at the high
17 concentration [Baranowska-Dutkiewicz 1981]. In this study, the total amount of
18 phenol absorbed – but not the rate of absorption – at the low concentration
19 increased with time, with 12.6% and 22.7% of the applied dose absorbed in 30
20 and 60 minutes, respectively. Feldman and Maibach [1970] reported the degree
21 of dermal absorption as 4.4% of the administered dose following a single topical
22 application of 4 microgram (µg) phenol/cm² on 13 cm² of the unprotected ventral
23 forearm of human adults. Phenol vapors are also reported to readily penetrate
24 the skin with absorption efficiency equal to that of inhalation, thus contributing to
25 the total dermal exposure [Piotrowski 1971]. In a whole-body skin exposure

1 study in which lightly clothed and unclothed volunteers were exposed to phenol
2 vapors at concentrations from 1.3 to 6.5 ppm for 6 hours, but were breathing
3 clean air by mask, Piotrowski [1971] reported that absorption increased
4 proportionately with air concentration. These studies generally demonstrated
5 that phenol can be absorbed through the human skin.

6

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

1 [1996] reported that dermal absorption ranged from 9.24% to 14.62% under
2 occluded conditions at the low dose and 2.90% to 5.45% under nonoccluded
3 condition. *In vitro* permeability coefficients for phenol were found to increase with
4 increasing concentration of aqueous phenol applied to mouse skin [Behl et al.
5 1983], with a 12-fold increase in mean coefficient (0.007–0.085 cm/hour)
6 resulting from doubling the concentration from 20 to 40 g/L, and a value of 0.169
7 cm/hour noted when 60 g/L was applied [Behl et al. 1983]. The authors
8 concluded that phenol concentrations exceeding 20 g/L may destroy a diffusion
9 barrier normally provided by the intact stratum corneum, permitting increased
10 percutaneous absorption. Results from animal studies *in vivo* and studies utilizing
11 animal skin *in vitro* also demonstrated that phenol is absorbed through the skin of
12 animals. The potential of phenol to pose a skin absorption hazard was also
13 evaluated using the NIOSH [2008] predictive algorithm for estimating and
14 evaluating the health hazards of dermal exposure to chemical substances. Based
15 on this algorithm, the ratio of the skin dose to the inhalation dose (SI ratio) of 11
16 was calculated for phenol. Because this ratio is significantly higher than the SI
17 ratio of greater than or equal to 0.1 that indicates that skin absorption may
18 significantly contribute to the overall body burden of a chemical [NIOSH 2008],
19 phenol is considered to be absorbed through the skin following dermal exposure.
20 The result from the predictive algorithm supports the results from human and
21 animal studies *in vivo* and from the *in vitro* studies.

22
23 Several case reports of humans dermally exposed to varying doses of phenol
24 have been identified [Griffiths 1973; Soares and Tift 1982; Lewin and Cleary

1 1982; Turtle and Dolan 1922; Foxall et al. 1989]. In these reports, accidental
2 exposure of phenol to intact skin or intentional (therapeutic) application of phenol
3 to the skin has resulted in fatalities (from, for example, respiratory depression
4 and cardiac arrest), but the doses were not known with any accuracy, precluding
5 estimation of a lethal dermal dose for humans. In animals, the dermal LD₅₀
6 values (the dose resulting in 50% mortality in the exposed animals) range from
7 0.5 milliliter per kilogram body weight (mL/kg) to 0.68 mL/kg (corresponding to
8 669 to 1500 milligram per kilogram body weight, mg/kg) [Conning and Hayes
9 1970; Brown et al. 1975] in rats under both occlusive and non-occlusive
10 conditions and 1400 mg/kg in rabbits [Vernot et al. 1977]. In the Conning and
11 Hayes [1970] study, severe muscular tremors, twitching, generalized convulsions
12 with loss of consciousness and prostration were reported within 10 minutes, and
13 severe hemoglobinuria between 45 minutes and 90 minutes of dermal exposure
14 to phenol in water. Brown et al. [1975] reported hematuria and convulsions as
15 clinical signs of phenol toxicity. Because the reported acute dermal LD₅₀ values
16 for the rat and rabbit are both lower than the critical dermal LD₅₀ value of 2 g/kg
17 body weight that identifies chemical substances with the potential for acute
18 dermal toxicity [NIOSH 2008], phenol is considered systemically toxic by the
19 acute dermal route.

20

- 21 • *Application of Appendix A.1.2: Evaluation of acute dermal toxicity. The*
22 *reported LD₅₀ ranged from 414 mg/kg to 1400 mg/kg animal body weight*
23 *did not exceed the numerical cutoff value of 2000 mg/kg animal body*
24 *weight. For this reason, phenol is assigned the SYS notation. Multiple*
25 *case studies were identified that reported workers' death following*
26 *accidental exposure to phenol which supports the assigning of the SYS*
27 *(FATAL) notation.*

1
2 Quantitative information on doses that cause systemic effects during repeated
3 occupational exposures is lacking. However, chronic doses (unspecified) to
4 humans may result in neurological damage [Merliss 1972]. A number of
5 repeated-dose studies have been identified in animals that evaluated systemic
6 effects following dermal exposure to phenol. For example, Deichmann et al.
7 [1950] exposed the tail of rabbits to aqueous phenol solutions of 1.18 to 7.12% in
8 water (reported as 64 to 380 mg/kg by the International Program for Chemical
9 Safety IPCS, 1994) for 5 h/day, 5 days/week, for a total of 18 days. Dose-related
10 systemic effects (tremors, death) were observed at 130 mg phenol/kg and above.
11 A No-Observed-Adverse-Effect-Level (NOAEL) of 64 mg/kg-day and a Lowest-
12 Observed-Adverse-Effect-Level (LOAEL) of 130 mg/kg-day to protect against
13 occasional mild tremors and skin irritation were identified in this study. Boutwell
14 and Bosch [1959] conducted a study in mice involving skin painting of 25
15 microliters (μL) of a 5% (1.25 mg phenol) or a 10% (2.5 mg phenol) in benzene
16 per application, twice weekly for 52 weeks. The high dose caused decreased
17 body weight (average body weight at the 20th week was 35.0 g compared to 38.9
18 g at the 5% level of phenol) and decreased survival (24/30 mice survived
19 compared to 30/30 at the 5% level of phenol at the 20th week). The resulting
20 doses were reported as 41.7 and 83.3 mg/kg/treatment [Agency for Toxic
21 Substances and Disease Registry, ATSDR, 2006]. Although the potential dermal
22 and systemic effects of the benzene solvent was not investigated in this study,
23 the effect levels of 18 mg/kg-day from the Boutwell and Bosch [1959] study and
24 130 mg/kg-day identified in the shorter duration study by Deichmann et al. [1950]

1 together indicate the potential for effects at doses significantly lower than the
2 critical dermal NOAEL value of 1 g/kg for repeat-dose toxicity that identifies
3 chemical substances with the potential for subchronic dermal toxicity [NIOSH
4 2008]. Therefore, phenol is considered to be systemically toxic following
5 repeated dermal exposure.

- 6
- 7 • Application of Appendix A.1.3: Evaluation of repeated-dose dermal
8 toxicity. *The doses reported in the reviewed studies ranging from 18 to*
9 *130 mg/kg-day did not exceed the numerical cutoff value of 1000 mg/kg-*
10 *day animal body weight. For this reason, phenol would be assigned the*
11 *SYS notation.*

12

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

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

22

23 Although no epidemiological studies that evaluated the potential of phenol to be
24 carcinogenic were identified, a limited number of studies in animals involving
25 repeated application of phenol in benzene [Boutwell and Bosch 1959] or in
26 acetone [Salaman and Glendenning 1957; Wynder and Hoffman 1961] in two-
27 stage carcinogenicity protocols in mice indicated that phenol has promoting
28 activity. Studies conducted by Boutwell and Bosch [1959] in several strains of
29 mice also suggested that phenol in benzene or dioxane is a tumor promoter and
30 possibly a complete carcinogen (i.e., having both promoting and initiating

1 activity). In the latter study, phenol elicited skin tumors in mice even in the
2 absence of a tumor initiating agent, 9,10-dimethyl-1,2-benzanthracene. These
3 studies are inadequate for the evaluation of the carcinogenicity potential of
4 phenol due to the short duration (32 weeks [Salaman and Glendenning 1957]
5 and 12 months or 52 weeks [Salaman and Glendenning 1957; Boutwell and
6 Bosch 1959]), the lack of appropriate controls [e.g., Salaman and Glendenning
7 1957], and/or the use of vehicles (dioxane, benzene) that are skin irritants and/or
8 defatting agents. Other agencies or organizations have also evaluated the
9 potential of phenol to be a carcinogen following non-dermal exposure routes.
10 NIOSH [2006] does not classify phenol as a potential occupational carcinogen.
11 The United States Environmental Protection Agency [US EPA 2002] states that
12 the data regarding the carcinogenicity of phenol via the oral, inhalation, and
13 dermal exposure routes *are inadequate for an assessment of human*
14 *carcinogenic potential*. The American Conference of Governmental Industrial
15 Hygienists [ACGIH 2001] has assigned an A4 (not classifiable as a human
16 carcinogen) notation to phenol. The International Agency for Research on
17 Cancer [IARC 2007] has classified phenol as *not classifiable as to its*
18 *carcinogenicity to humans* (Group 3).

- 19
- 20 • Application of Appendix A.1.6: Evaluation of carcinogenicity of phenol. No
21 evidence was identified that would support identifying phenol as a
22 carcinogen or the subsequent assignment of the SYS notation.
- 23
24

25 Identified human [**Feldman and Maibach 1970; Piotrowski 1971; Baranowska-**
26 **Dutkiewicz 1981**] and animal [**Behl et al. 1983; Hughes and Hall 1995;**

1 **Brooks and Riviere 1996]** toxicokinetic data, acute dermal toxicity studies
2 **[Conning and Hayes 1970; Brown et al. 1975; Vernet et al. 1977]**, and repeat-
3 dose studies **[Deichmann et al. 1950; Boutwell and Bosch 1959]** are sufficient
4 to demonstrate the potential for phenol to be dermally absorbed and systemically
5 toxic. Systemic toxicity includes effects on the central nervous system, body
6 weight changes, and decreased survival. Therefore, this assessment concludes
7 that sufficient human and animal data exist to assign a SK: SYS notation for
8 phenol.

9

10 • **F.3 Direct effect(s) on the skin**

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

1 that phenol is corrosive to the skin or is a skin irritant depending on the
2 concentration.

3

4 Reports of necrosis and chemical burns in humans [**Schmidt and Maibach**
5 **1981; Horch et al. 1994**] and animals [**Conning and Hayes 1970; Pullin et al.**
6 **1978; Patrick et al. 1985; Hunter et al. 1992**] following direct contact with
7 undiluted phenol or concentrated solutions are sufficient to demonstrate the
8 corrosivity of phenol. More diluted solutions are more likely to be irritating to the
9 skin. Therefore, this assessment assigns a SK: DIR (COR) notation for phenol.

10

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

19 • **F.4 Sensitization**

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

1 alerts for skin sensitization. This prediction of negative sensitization potential is
2 consistent with the absence of published reports of sensitization in workers
3 handling phenol and the limited empirical evidence.

4

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

8

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

18 • **F.5 Summary**

19 There is sufficient information from toxicokinetics [**Feldman and Maibach 1970;**
20 **Piotrowski 1971; Baranowska-Dutkiewicz 1981**], acute dermal toxicity studies
21 [**Conning and Hayes 1970; Brown et al. 1975; Vernet et al. 1977**], and repeat-
22 dose dermal toxicity studies [**Deichmann et al. 1950; Boutwell and Bosch**
23 **1959**] to indicate that phenol is absorbed through the skin and is acutely toxic
24 and induces systemic effects (for example, central nervous system effects,
25 effects on body weight and survival) following dermal exposure. Information from
26 human experience [**Merliss 1972; Schmidt and Maibach 1981; Horch et al.**
27 **1994**] and animal studies [**Conning et al. 1970; Pullin et al. 1978; Patrick et al.**

1 **1985; Hunter et al. 1992]** is sufficient to demonstrate that phenol is corrosive,
2 while more dilute solutions are irritating to the skin. The limited information
3 available indicates that phenol is not a skin sensitizer. Therefore, this
4 assessment recommends the composite skin notation of SK: SYS-DIR(COR) for
5 phenol. Phenol has also been classified as being harmful and toxic in contact
6 with the skin as well as corrosive by the European Union [2007]. ACGIH [2001],
7 NIOSH [2006], and OSHA (Occupational Safety and Health Administration)
8 [2007] have also assigned a skin notation to the chemical. The classifications
9 assigned by these organizations are indicated in the table below. The
10 classifications assigned by these organizations are indicated in Table F.2. Based
11 on the scheme developed by NIOSH to coordinate the skin notations with the
12 GHS, the equivalent GHS classification for phenol would most likely be
13 considered an acute toxicant ($200 \text{ mg/kg body weight} < LD_{50} < 1000 \text{ mg/kg body}$
14 weight), in addition to an irritant and corrosive agent.

15
16
17

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

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

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

1 EU - European-Union; ACGIH - American Conference of Governmental Industrial Hygienists;
2 NIOSH – National Institute for Occupational Safety and Health; OSHA – Occupational Safety and
3 Health Administration.
4

5 • **Appendix F References**

6 *Note: References identified with a (*) are cited within Skin Notation Profile;*
7 *References not identified with a (*) represent additional resources not cited*
8 *within the Skin Notation Profile*
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APPENDIX G: Supplemental information

• G.1 Contaminants and isomers

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

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

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

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

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

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

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

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

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

5

6 • **G.3 Nanotechnology and dermal toxicity**

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

1 materials (i.e. nanotubes and fullereness), metal-based materials (i.e. quantum
2 dots, metal oxides, nanogold, and nanosilver), nanocomposites, and dendrimers.
3 Because of their small size and large surface area, engineered nanoparticles
4 may have chemical, physical, and biological properties distinctly different from
5 and greater than fine particles of similar chemical composition [NIOSH 2007].
6 These variations may result in unique health hazards for workers employed to
7 manufacture or use products containing nanomaterials.

8
9 Limited information is currently available to accurately assess the health risks of
10 dermal exposures to nanoparticles. The results from *in vitro* studies using
11 primary or cultured human skin cells report the ability of single-walled and multi-
12 walled carbon nanotubes to enter cells and cause the release of pro-
13 inflammatory cytokines, oxidative stress, and decreased viability [Shvedova et al.
14 2003; Monteiro-Riviere et al. 2005]. More recent studies have reported the ability
15 of quantum dots and fullereness to penetrate the stratum corneum by passive
16 diffusion, in addition to inducing inflammatory response and cytotoxicity within
17 dermal fibroblast and keratinocytes [Sayes et al. 2005; Ryman-Rasmussen et al.
18 2006]. Factors, including size, shape, water solubility, and surface coating, may
19 directly affect a nanoparticle's potential to penetrate the skin [Sayes et al. 2004;
20 Ryman-Rasmussen et al. 2006].

21
22 The occupational health risks posed by dermal exposures to the different forms
23 of nanoparticles are unclear. For this reason, skin notations derived from neat

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1 chemical substances or mixtures with similar chemical composition to a specific
2 form of nanoparticles may be not be applicable due to the different
3 physiochemical properties and toxic potential. As new data become available,
4 the skin notations and supporting documentation will address the dermal toxic
5 potential of nanoparticles when warranted. Additional information and guidance
6 on safe work practices associated with nanoparticles can be found within the
7 NIOSH document, *Approaches to Safe Nanotechnology: an Information*
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