



# Abstract

Industrial hygienists have traditionally relied on inhalation-based exposure guidance (occupational exposure limits or OELs) for assessing risks to worker health. These OELs do not directly account for potential skin exposures. To warn workers of potential impacts of dermal contact, skin notations are assigned for chemicals that can be absorbed through the skin. NIOSH has developed an improved strategy for assigning these skin notations. This new strategy was developed to address limitations associated with the current skin notations and to provide a systematic approach for assigning such notations. The new system relies on a weight-of evidence approach based on the findings of an extensive review of reports of human exposure and health effects, empirical data from animal toxicity studies and considerations provided by mathematical models. The modeling component includes both skin absorption estimation as well as structure-activity predictions for skin irritation and sensitization. Benefits of the new system include improved consistency in skin notation assignments through the use of more fully-defined criteria, and the inclusion of information that distinguishes between systemic and point-of-contact health effects associated with dermal exposure to chemicals. Additionally, the strategy has been designed to improve the use of skin notations beyond their historical interpretation by providing supplemental information on the potential for point-of-contact effects, which enhances efforts to protect workers' health. Scientific and data interpretation issues associated with the application of this revised methodology have been identified in its application for over 20 case-study chemicals. Key issues have centered on assessing adequacy of data sets and the definition of cut-off points and criteria for assessing "significant" dermal absorption and systemic toxicity.

# Introduction

Skin notations have been used worldwide to alert workers and employers to the potential health effects of dermal exposures to chemicals. The NIOSH Pocket Guide to Chemical Hazards currently lists 142 chemicals with a skin notation represented by the symbol "[skin]" [www.cdc.gov/niosh/npg/]. This notation indicates only that a chemical may be dermally absorbed; it does not identify the potential for systemic toxicity following absorption or provide a warning when the chemical can cause direct effects to the skin or act as a sensitizer. NIOSH has developed criteria to address these shortcomings and allow assignment of improved skin notations that will provide additional warnings about potential health effects from dermal exposures to chemicals (Tables 1).

# Limitations of the Current NIOSH Skin Notation

- The current NIOSH skin notation indicates only that a chemical may be dermally absorbed, may contribute to systemic toxicity, and thus may affect the interpretation of airborne exposure limits.
- No guidance or warnings are provided for chemicals that have direct effects on the skin (e.g., irritation or corrosion) or are skin sensitizers.
- Because only one skin notation is available, users have often assumed that it also refers to chemicals that are not systemically toxic but have direct effects on the skin or are skin sensitizers.
- Current skin notations were adopted for many chemicals after the 1988 update of the Occupational Safety and Health Administration (OSHA) permissible exposure limits (PELs) [www.cdc.gov/niosh/pel88/pelstart.html]. The current skin notations do not include skin exposure precautions recommended by NIOSH since that time.

## Advantages of the Improved NIOSH Skin Notation Strategy

The new skin notation strategy improves the current strategy by doing the following:

- 1. Standardizing the assignment of skin notations
- 2. Providing warnings when a chemical has direct effects on the skin or is a skin sensitizer
- 3. Assessing current scientific knowledge about dermal exposure to chemicals in the workplace
- 4. Distinguishing between systemic, direct, and sensitization effects by using multiple skin notations
- 5. Combining the improved skin notations to accommodate the presence of multiple skin hazards









following

# Deriving Skin Notations Based on the Improved Strategy Developed by the National Institute for **Occupational Safety and Health** Dotson GS<sup>1</sup>, Gadagbui BK<sup>2</sup>, Kroner O<sup>2</sup>, Nance P<sup>2</sup>, Lentz TJ<sup>1</sup>, Maier A<sup>2</sup>

# Approach

The improved skin notation strategy relies on a weight-of-evidence approach based on data from the

- 1. Critical evaluation of the following data to determine the health risks associated with dermal con-
- tact with chemicals: a) Dermal absorption (human case reports, in vivo human/animal and in vitro studies)
- b) Acute dermal toxicity
- c) Repeat-dose (21 or 28 days), subchronic (90 days), or chronic (at least 12 months) dermal toxicity; dermal carcinogenicity (18 – 28 months); developmental, reproductive, immunologic dermal toxicity, etc.
- d) Primary skin irritation
- i. Human case reports
- ii. In vivo animal tests for acute irritancy and corrosivity
- iii.In vitro tests for corrosivity using human or animal skin models
- iv. In vitro tests of skin integrity using cadaver skin e) Skin sensitization
- i.Human case reports
- ii.Allergic contact dermatitis (ACD) with guinea pig tests
- iii. Murine lymph node assay (LLNA)
- iv. Mouse ear swelling test (MEST)

f) Use of predictive algorithm for evaluating potential health hazards of a chemical for which no data or insufficient data exist to determine systemic effects from dermal exposure g) Use of Structural alerts (e.g., DEREK Expert System) to identify sensitizers in absence of human or biological testing data

. Application of hierarchical approach to evaluate the weight of evidence (Figure 1). Assignment of the improved skin notation on the basis of the evaluation

# Criteria for Assigning Skin Notation for a Chemical

rmal absorption	>10%	high potential to be dermally absorbed and significantly contributing to sys- temic dose.	
ute dermal toxicity	LD50 < 2 g/kg	reflects the dose selected in standard- ized limit tests to identify chemical sub- stances with the potential for acute der- mal toxicity	
stemic dermal toxicity Repeat-dose, Subchronic, Chronic, eproductive, Developmental, nmunotoxicity, etc.)	NOAEL < 1 g/kg-day	reflects the dose selected in the stan- dardized limit tests to identify chemical substances with the potential for re- peated-, dose or subchronic dermal toxicity	
ect dermal effects	Irritant	chemical induces reversible inflamma-	
	Corrosive	chemical that causes irreversible tissue - lesions at the site of contact	
n sensitization	Positive response in diagnostic Patch testing and predictive tests (GPMT, Buehler, murrine LLNA, MEST, etc)	Potential for skin allergy	
thematical models	Ratio of the skin dose to the Inhalation dose (SI ratio ≥0.1)	ratio quantitatively indicates (a) signifi- cance of percutaneous absorption as a route of occupational exposure to the substance and (b) the contribution of	

Structural Alerts Implemented in the skin irritation/sensitization DEREK Expert System

supportive evidence of skin irritation or allergy in humans

the dermal uptake to systemic effect





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# Table 1. Skin notations used by the improved NIOSH skin notation strategy

### Skin Notation

### Hazard Category



Systemic toxicity from dermal absorption

Direct effect(s) on the skin, including corrosion, primary irritation, reduction/ disruption of the dermal barrier integrity

A subcategory of SK-DIR assigned when a chemical substance is identified as corrosive

Allergic contact dermatitis (ACD) or sensitization of skin, mucous membranes, or airways due to dermal exposure

### Key Issues Addressed in the Improved Skin Notations

- Criteria for assessing "significant" dermal absorption]
- Cut-off points for systemic effects level
- Adequacy of data sets
- Role of modeling versus empirical data - Role of kinetic data versus dermal toxicity data
- Direct skin effects:
- -Concentration-dependence responses where concentrated solutions are corrosive while diluted solutions – the form in which a chemical is sold – is irritating to the skin. Skin sensitization:
- -cross-reactivity
- -irritant versus allergic responses in patch tests
- Extrapolation of systemic toxicity from non-dermal routes of exposures

# Results

Table 2 shows skin notations for a series of case-study chemicals based on the improved NIOSH skin notation strategy. These notations are compared to the current NIOSH skin notations.

		NIOSH Current	Improved	
Chemical	CASRN	Notation	Notation	Basis
Acrylamide	79-06-1	[Skin]	SK-SYS-DIR-SEN	Limited – sufficient human data; sufficient animal
Acrylic acid	79-10-7	[Skin]	SK-SYS-DIR(COR)	Limited human and sufficient ani- mal data
Acrylonitrile	107-13-1	[Skin]	SK-SYS-DIR-SEN	Limited – sufficient human data; sufficient animal data
Bisphenol A	80-05-7	-	SK-DIR-SEN	Limited – sufficient human and ani- mal data
Carbaryl	63-25-2	-	SK-SYS-DIR-SEN	Limited human and animal data
o-Cresol	95-48-7	-	SK-SYS-DIR(COR)-SEN	Sufficient human and animal data; limited human data for sensitization
1,3-dichloropropene	542-75-6	[Skin]	SK-SYS-DIR(COR)-SEN	Limited – sufficient human and ani- mal data
Dichlorvos	62-73-7	[Skin]	SK-SYS-DIR-SEN	Sufficient human and animal data; limited human data for sensitization
Dimethylamine borane	74-94-2	-	SK-SYS	Limited human data
Diethylenetriamine	111-40-0	-	SK-SYS-DIR(COR)-SEN	Limited—sufficient animal data; suf- ficient human data for sensitization
Dimethyl sulfate	111-40-0	[Skin]	SK-SYS-DIR(COR)-SEN	Limited—sufficient human and ani- mal data; only limited data for sen- sitization
2,4-Dinitrotoluene	121-14-2	[Skin]	SK-SYS-DIR	Limited animal data
Epichlorohydrin	106-89-8	-	SK-SYS-DIR(COR)-SEN	Limited animal data; sufficient hu- man data for sensitization
2-Ethoxyethanol	110-80-5	[Skin]	SK-SYS	Limited human and animal data
Glutaraldehyde	111-30-8	-	SK-SYS-DIR(COR)-SEN	Limited – sufficient human and ani- mal data
Heptachlor	76-44-8	[Skin]	SK-SYS	Sufficient human and animal data
Hydrazine	302-01-2	-	SK-SYS-DIR(COR)-SEN	Sufficient human and animal data; only sufficient human data for sen- sitization
2- Mercaptobenzothiazole	149-30-4	-	SK-DIR-SEN	Sufficient human and animal data
Methyl isocyanate	624-83-9	[Skin]	SK-SYS-DIR(COR)-SEN	Limited animal data
Nonane	111-84-2	-	SK-DIR	Limited human and animal data
Phenol	108-95-2	[Skin]	SK-SYS-DIR(COR)	Sufficient human and animal data
<i>p</i> -Phenylene diamine	106-50-3	[Skin]	SK-DIR-SEN	Sufficient human and animal data
Phenylhydrazine	100-63-0	[Skin]	SK-SYS-DIR-SEN	Limited - sufficient human and ani- mal data
Trichloroethylene	79-01-6	_	SK-DIR	Limited human and animal data

# Conclusions

The improved NIOSH skin notation strategy:

- allows for a focused and thorough assessment of the data on the adverse health effects of der-
- mal exposure and absorption of chemicals in occupational settings.
- provides clear and consistent skin notations resulting from clearly defined criteria
- provides skin notations that distinguish between the type of hazard posed by a chemical following dermal exposure (systemic, direct, corrosive, and sensitizing)
- identifies the skin as an important target organ for many chemicals
- Enables assignment of multiple notations when a chemical may produce more than one type
- of adverse effect to better communicate skin hazards to workers
- Identifies the need for periodic evaluation of data to update the skin notations

# **References and Disclaimer**

References are available on request from G. Scott Dotson at scott.dotson@cdc.hhs.gov.

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