

NIOSH Skin Notation Profiles

2 Diethylaminoethanol

SKK

ID^{SK}

[SK]

SYS

SYS (FATAL)

DIR

DIR (IRR)

DIR (COR)

SEN

NIOSH Skin Notation (SK) Profiles

2-Diethylaminoethanol

[CAS No. 100-37-8]

This document is in the public domain and may be freely copied or reprinted.

Disclaimer

Mention of any company or product does not constitute endorsement by the National Institute for Occupational Safety and Health (NIOSH). In addition, citations to websites external to NIOSH do not constitute NIOSH endorsement of the sponsoring organizations or their programs or products. Furthermore, NIOSH is not responsible for the content of these websites.

Ordering Information

To receive this document or information about other occupational safety and health topics, contact NIOSH:

Telephone: 1-800-CDC-INFO (1-800-232-4636)
TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov

or visit the NIOSH website: www.cdc.gov/niosh

For a monthly update on news at NIOSH, subscribe to *NIOSH eNews* by visiting www.cdc.gov/niosh/eNews.

Suggested Citation

NIOSH [2014]. NIOSH skin notation profiles: 2-diethylaminoethanol By Hudson NL, Dotson GS. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2014-140.

DHHS (NIOSH) Publication No. 2014-140

August 2014

SAFER • HEALTHIER • PEOPLE™

Foreword

As the largest organ of the body, the skin performs multiple critical functions, such as serving as the primary barrier to the external environment. For this reason, the skin is often exposed to potentially hazardous agents, including chemicals, which may contribute to the onset of a spectrum of adverse health effects ranging from localized damage (e.g., irritant contact dermatitis and corrosion) to induction of immune-mediated responses (e.g., allergic contact dermatitis and pulmonary responses), or systemic toxicity (e.g., neurotoxicity and hepatotoxicity). Understanding the hazards related to skin contact with chemicals is a critical component of modern occupational safety and health programs.

In 2009, the National Institute for Occupational Safety and Health (NIOSH) published *Current Intelligence Bulletin (CIB) 61: A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009-147]. This document provides the scientific rationale and framework for the assignment of multiple hazard-specific skin notations (SK) that clearly distinguish between the systemic effects, direct (localized) effects, and immune-mediated responses caused by skin contact with chemicals. The key step within assignment of the hazard-specific SK is the determination of the hazard potential of the substance, or its potential for causing adverse health effects as a result of skin exposure. This determination entails a health hazard identification process that involves use of the following:

- Scientific data on the physicochemical properties of a chemical
- Data on human exposures and health effects
- Empirical data from *in vivo* and *in vitro* laboratory testing
- Computational techniques, including predictive algorithms and mathematical models that describe a selected process (e.g., skin permeation) by means of analytical or numerical methods.

This *Skin Notation Profile* provides the SK assignments and supportive data for 2-diethylaminoethanol (2-DAE). In particular, this document evaluates and summarizes the literature describing the hazard potential of the substance and its assessment according to the scientific rationale and framework outlined in CIB 61. In meeting this objective, this Skin Notation Profile intends to inform the audience—mostly occupational health practitioners, researchers, policy- and decision-makers, employers, and workers in potentially hazardous workplaces—so that improved risk-management practices may be developed to better protect workers from the risks of skin contact with the chemicals of interest.

John Howard, M.D.
Director, National Institute for
Occupational Safety and Health
Centers for Disease Control and Prevention

Contents

Foreword	iii
Abbreviations	vi
Glossary	viii
Acknowledgments	ix
1 Introduction	1
1.1 General Substance Information	1
1.2 Purpose	1
1.3 Overview of SK Assignment	1
2 Systemic Toxicity from Skin Exposure (SK: SYS)	1
3 Direct Effects on Skin (SK: DIR)	2
4 Immune-mediated Responses (SK: SEN)	3
5 Summary	3
References	4
Appendix: Calculation of the SI Ratio	7
Overview	7
Appendix References	8

Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
CIB	Current Intelligence Bulletin
cm ²	square centimeter(s)
cm/hour	centimeter(s) per hour
2-DAE	2-diethylaminoethanol
<i>DEREK</i>	Deductive Estimation of Risk from Existing Knowledge
DIR	skin notation indicating the potential for direct effects to the skin following contact with a chemical
EC	European Commission
GHS	Globally Harmonized System for Classification and Labelling of Chemicals
g/L	grams per liter
GPMT	guinea pig maximization test
IARC	International Agency for Research on Cancer
(IRR)	subnotation of SK: DIR indicating the potential for a chemical to be a skin irritant following exposure to the skin
k_{aq}	coefficient in the watery epidermal layer
k_p	skin permeation coefficient
k_{pol}	coefficient in the protein fraction of the stratum corneum
k_{psc}	permeation coefficient in the lipid fraction of the stratum corneum
LD ₅₀	dose resulting in 50% mortality in the exposed population
LD _{Lo}	dermal lethal dose
LLNA	local lymph node assay
LOAEL	lowest-observed-adverse-effect level
log K _{OW}	base-10 logarithm of a substance's octanol–water partition
M	molarity
m ³	cubic meter(s)
mg	milligram(s)
mg/cm ²	milligram(s) per square centimeter
mg/kg	milligram(s) per kilogram body weight
mg/m ³	milligram(s) per cubic meter
mL/kg	milliliter(s) per kilogram body weight
MW	molecular weight
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
OEL	occupational exposure limit
OSHA	Occupational Safety and Health Administration
REL	recommended exposure limit
RF	retention factor

SEN	skin notation indicating the potential for immune-mediated reactions following exposure of the skin
SI ratio	ratio of skin dose to inhalation dose
SK	skin notation
S _w	solubility
SYS	skin notation indicating the potential for systemic toxicity following exposure of the skin
USEPA	United States Environmental Protection Agency

Glossary

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

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

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

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

Cutaneous (or percutaneous)—Referring to the skin (or through the skin).

Dermal—Referring to the skin.

Dermal contact—Contact with (touching) the skin.

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

Immune-mediated responses—Responses mediated by the immune system, including allergic responses.

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

Substance—A chemical.

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

Acknowledgments

This document was developed by the NIOSH Education and Information Division (Paul Schulte, Ph.D., Director). G. Scott Dotson, Ph.D., was the project officer for this document, assisted in great part by Naomi Hudson, Dr.P.H., MPH, Todd Niemeier, M.Sc., and Berran Yucesoy, Ph.D. The basis for this document was a report (*Toxicology Excellence for Risk Assessment [TERA]*) contracted by NIOSH and prepared by Bernard Gadagbui, Ph.D., and Andrew Maier, Ph.D.

For their contribution to the technical content and review of this document, special acknowledgment is given to the following NIOSH personnel:

Denver Field Office

Eric Esswein, M.Sc.

Division of Applied Research and Technology

Clayton B'Hymer, Ph.D.

John Snawder, Ph.D.

Mark Toraason, Ph.D.

Division of Respiratory Disease Studies

Gregory A. Day, Ph.D.

Aleksander Stefaniak, Ph.D.

Division of Surveillance, Hazard Evaluations, and Field Studies

Matt Dahm, M.Sc.

Aaron Sussell, Ph.D.

Loren Tapp, M.D.

Education and Information Division

Devin Baker, M.Ed.

Charles L. Geraci, Ph.D.

Thomas J. Lentz, Ph.D.

Richard Niemeier, Ph.D.

Sudha Pandalai, M.D., Ph.D.

Health Effects Laboratory Division

Stacey Anderson, Ph.D.

H. Fredrick Frasch, Ph.D.

Vic Johnson, Ph.D.

Michael Luster, Ph.D.

Anna Shvedova, Ph.D.

Paul Siegel, Ph.D.

National Personal Protection Technology Laboratory

Heinz Ahlers, M.Sc.

Angie Shephard

For their contribution to the technical content and review of this document, special acknowledgment is given to the following CDC personnel:

Office of Surveillance, Epidemiology and Laboratory Services/Epidemiology and Analysis Program Office

Barbara Landreth, M.A.

In addition, special appreciation is expressed to the following individuals for serving as independent, external reviewers and providing comments that contributed to the development or improvement of this document:

Phil Bigelow, B.Sc., M.H.Sc., Ph.D., University of Waterloo, School of Public Health and Health Systems, Waterloo, ON, Canada

Youcheng Liu, M.D., Sc.D., M.P.H., M.S., University of North Texas Health Science Center, Fort Worth, TX

G. Frank Gerberick, Ph.D., The Procter and Gamble Company, Cincinnati, OH

Dori Germolec, Ph.D., National Toxicology Program, National Institute for Environmental Health Sciences, Research Triangle, NC

Ben Hayes, M.D., Ph.D., Division of Dermatology, Vanderbilt School of Medicine, Nashville, TN

Jennifer Sahmel, M.Sc., CIH, ChemRisk, Boulder, CO

James Taylor, M.D., Industrial Dermatology, The Cleveland Clinic, Cleveland, OH

1 Introduction

1.1 General Substance Information

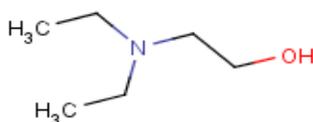
Chemical: 2-Diethylaminoethanol (2-DAE)

CAS No: 100-37-8

Molecular weight (MW): 117.2

Molecular formula: $(C_2H_5)_2NCH_2CH_2OH$

Structural formula:



Synonyms:

2-DAE; Diethylaminoethanol; 2-Diethylaminoethyl alcohol; N,N-Diethylethanolamine; Diethyl-(2-hydroxyethyl)amine; 2-Hydroxytriethylamine

Uses:

2-DAE is used primarily as a chemical intermediate and as an emulsifying agent, in addition during the extraction of hydrogen sulfide and carbon dioxide from natural gas. [ACGIH 2001].

1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with 2-DAE and (2) the rationale behind the hazard-specific skin notation (SK) assignment for 2-DAE. The SK assignment is based on the scientific rationale and logic outlined in the *Current Intelligence Bulletin (CIB) 61: A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009]. The summarized information and health hazard assessment are limited to an evaluation of the potential health effects of dermal exposure to 2-DAE. A literature search was conducted through April 2014 to identify information on 2-DAE, including but not limited to data relating to its toxicokinetics, acute toxicity, repeated-dose systemic toxicity, carcinogenicity, biological system/function-specific effects (including reproductive and developmental effects and immunotoxicity), irritation, and sensitization. Information was considered from studies of humans, animals, or appropriate modeling systems that are relevant to assessing the effects of dermal exposure to 2-DAE.

1.3 Overview of SK Assignment

2-DAE is potentially capable of causing numerous adverse health effects following skin contact. A critical review of available data has resulted in the following SK assignment for 2-DAE: **SK: SYS-DIR (COR)**. Table 1 provides an overview of the critical effects and data used to develop the SK assignment for 2-DAE.

2 Systemic Toxicity from Skin Exposure (SK: SYS)

No quantitative estimates of absorption of 2-DAE were identified following dermal exposure in humans or animals. However, based on the physical properties of a saturated aqueous 2-DAE solution, Fiserova-Bergerova [1990] estimated a dermal penetration rate of 3.44 milligrams per square centimeter (mg/cm^2) for human skin, with the rate described as being high. 2-DAE was also predicted to have significant skin absorption and potential toxicity through human skin based on a physico-chemical model of skin penetration [Guy and Potts 1993]. Some evidence for dermal

Table 1. Summary of the SK assignment for 2-DAE

Skin notation	Critical effect	Available data
SK: SYS	Acute toxicity	Limited animal data
SK: DIR (COR)	Skin corrosion	Sufficient animal data

absorption of 2-DAE in humans is provided by two case reports that indicated that workers who were likely exposed repeatedly through both inhalation and dermal routes to 2-DAE developed nausea, vomiting, dizziness, chest tightness and/or headache [NIOSH 1981, 1983]. The potential of 2-DAE to pose a skin absorption hazard could not be evaluated by the predictive algorithm for estimating and evaluating the health hazards of dermal exposure to substances [NIOSH 2009]. The evaluation method compares an estimated dose accumulated in the body from skin absorption with an estimated dose from respiratory absorption associated with a reference occupational exposure limit. Additional information on the SI ratio and the variables used in its calculation are included in the appendix.

While no dermal lethal dose (LD_{Lo}) for humans has been identified, the reported dermal LD_{50} value (the dose resulting in 50% mortality in the exposed animals) was reported as 1.0 milliliters per kilogram bodyweight (mL/kg) (corresponding to 892 milligrams per kilogram body weight, mg/kg) for the guinea pig [Smyth and Carpenter 1944]. The LD_{50} value is lower than the critical dermal LD_{50} value of 2000 mg/kg body weight that identifies chemical substances with the potential for acute dermal toxicity [NIOSH 2009]. Therefore, 2-DAE is acutely toxic following dermal exposure.

No epidemiological studies in workers following dermal exposure or dermal repeat-dose, subchronic, or chronic toxicity studies in animals were identified that evaluated the systemic toxic effects of 2-DAE. No repeat-dose studies were identified in humans or animals that evaluated standard biological system or function specific effects (including

reproductive and developmental effects and immunotoxicity) following dermal exposure to 2-DAE. No epidemiology studies or standard rodent cancer bioassays that evaluated the potential of 2-DAE to be carcinogenic following dermal exposure were identified. Table 2 summarizes carcinogenic designations of multiple governmental and nongovernmental organizations for 2-DAE.

Although information from human evidence is limited, modeled skin penetration rates for human skin [Fiserova-Bergerova 1990; Guy and Potts 1993]^{*} and an acute dermal toxicity study in animals [Smyth and Carpenter 1944] provide evidence that 2-DAE is absorbed through the skin, systemically available, and acutely toxic. Therefore, on the basis of the data for this assessment, 2-DAE is assigned the SK: SYS notation.

3 Direct Effects on Skin (SK:DIR)

No human or animal *in vivo* studies on corrosivity of 2-DAE or *in vitro* tests for corrosivity using human skin models or *in vitro* tests of skin integrity using cadaver skin were identified. However, skin irritation or dermatitis was reported in two case reports following exposure to 2-DAE [NIOSH 1981, 1983]. In one of these reports, NIOSH [1981] suggested that a condensation or reaction product of 2-DAE present in the air was responsible for the primary irritation of exposed skin, and the response possibly involved a phototoxic skin reaction. Studies conducted according to the Organization for Economic Cooperation

^{*}References in **bold** text indicate studies that serve as the basis of the SK assignments.

Table 2. Summary of the carcinogenic designations* for 2-DAE by numerous governmental and nongovernmental organizations

Organization	Carcinogenic designation
NIOSH [2005]	No designation
NTP [2011]	No designation
USEPA [2014]	No designation
European Parliament [2008]	No designation
IARC [2012]	No designation
EC [2014] [†]	No designation
ACGIH [2001]	No designation

ACGIH = American Conference of Governmental Industrial Hygienists; EC = European Commission, Joint Research, Institute for Health and Consumer Protection; IARC = International Agency for Research on Cancer; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; USEPA = United States Environmental Protection Agency.

*The listed cancer designations were based on data from nondermal (such as oral or inhalation) exposure rather than dermal exposure.

[†]Date accessed

and Development (OECD) Guideline 404 indicated that 2-DAE was corrosive to the skin of rabbits. For example, in two studies 2-DAE applied to shaved skin of rabbits under occlusive or semi-occlusive conditions for 1 hour or 4 hours was corrosive to the skin [Potokar et al. 1985; Union Carbide, 1990]. Smyth and Carpenter [1944] observed necrosis, edema and erythema when 2-DAE was applied to the skin of a rabbit. Corrosivity of 2-DAE to the skin is expected since the pH measured at 20°C was 11.5 [100 grams per liter (g/L)] [OECD 2002]. The structure activity relationship model, Deductive Estimation of Risk from Existing Knowledge (*DEREK*) for Windows, predicted 2-DAE to be a skin irritant.

Based on case reports of skin irritation following accidental dermal exposure to 2-DAE in humans [NIOSH 1981, 1983], and corrosivity observed in experimental animals [Smyth and Carpenter 1944; Potokar et al. 1985; Union Carbide, 1990], this assessment concludes that undiluted 2-DAE is corrosive to the skin. The diluted substance produced concentration-related irritation effects when evaluated in rabbits. Therefore, on the basis of the data for this assessment, 2-DAE is assigned the SK: DIR (COR) notation.

4 Immune-mediated Responses (SK: SEN)

Occupational exposure experiences or standard studies in humans that involved skin sensitization following dermal exposure to 2-DAE were not identified. However, the substance was not a skin sensitizer in guinea pig sensitization tests performed according to the Magnusson and Kligman method [Nakamura et al. 1994; Leung and Blaszcak 1998]. *DEREK* predicted 2-DAE to be negative regarding skin sensitization potential.

Based on the negative responses from two guinea pig maximization tests [Nakamura et al. 1994; Leung and Blaszcak 1998], sufficient data exist to conclude that the substance is not a skin sensitizer. Therefore, on the basis of the data for this assessment, 2-DAE is not assigned the SK: SEN notation.

5 Summary

Studies that evaluated the potential of 2-DAE to be absorbed through the skin or to be systemically toxic in humans were limited to models of human skin penetration based on physico-chemical properties [Fiserova-Bergerova

Table 3. Summary of previous skin hazard designations for 2-DAE

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption
OSHA [2014]*	[skin]: Potential for dermal absorption
ACGIH [2001]	[skin]: Based on reported dermal LD ₅₀ in rabbits
EC [2014]*	R21: Harmful if in contact with skin R34: Causes burns

ACGIH = American Conference of Governmental Industrial Hygienists; EC = European Commission, Joint Research, Institute for Health and Consumer Protection; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration.

*Date accessed

1990; Guy and Potts 1993]. However, these predictions are supported by an acute dermal toxicity study [Smyth and Carpenter 1944]; therefore, this assessment assigns a skin notation of SK: SYS for 2-DAE. Taken together, there is limited data in humans and animals to demonstrate that 2-DAE is absorbed through the skin, is systemically available, and is acutely toxic. Based on case reports of skin irritation following accidental dermal exposure to 2-DAE in humans [NIOSH 1981, 1983] and corrosivity observed in experimental animals [Smyth and Carpenter 1944; Potokar et al. 1985; Union Carbide, 1990], sufficient information exists to conclude that 2-diethylaminoethanol is corrosive, and that dilute solutions of the substance may irritate the skin. No standard studies conducted in humans were identified that evaluated the potential of the substance to be a skin sensitizer. However, guinea pig maximization tests [Nakamura et al. 1994; Leung and Blaszcak 1998] show that 2-DAE was not a skin sensitizer. Therefore, on the basis of these assessments, 2-DAE is assigned a composite skin notation of **SK: SYS-DIR (COR)**.

Table 3 summarizes the skin hazard designations for 2-DAE previously issued by NIOSH and other organizations. The equivalent dermal designations for 2-DAE, according to the Global Harmonization System (GHS) of Classification and Labeling of Chemicals, are Acute Toxicity Category 4 (Hazard statement:

Harmful in contact with the skin) and Skin Corrosion Category 1B (Hazard statement: Causes severe skin burns and eye damage) [European Parliament 2008].

References

- ACGIH (American Conference of Governmental Industrial Hygienists) [2001]. 2-diethylaminoethanol. In: Documentation of threshold limit values and biological exposure indices 7th ed., Vol. 1. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.
- EC (European Commission) [ND]. 2-diethylaminoethanol. In: EINECS (European Inventory of Existing Commercial Chemical Substances), <http://esis.jrc.ec.europa.eu/>. Accessed: 04-30-14.
- European Parliament, Council of the European Union [2008]. Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJEU, Off J Eur Union L353:1–1355 [<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:353:0001:1355:EN:PDF>]. Accessed: 04-30-14.
- Fiserova-Bergerova V, Pierce JT, and Droz PO. [1990]. Dermal absorption potential of industrial chemicals: Criteria for skin notation. *Am J Ind Med* 17(5):617–636.
- Guy RH, Potts RO [1993]. Penetration of industrial chemicals across the skin: a predictive model. *Am J Ind Med* 23(5):711–719.

- IARC (International Agency for Research on Cancer) [2012]. Agents reviewed by the IARC monographs. In: IARC monographs on the evaluation of carcinogenic risks to humans [<http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php>]. Accessed: 04-30-14.
- Leung HW, Blaszcak DL [1998]. The skin Sensitization potential of four alkylalkanolamines. *Vet Hum Toxicol* 40: 65 – 67.
- Nakamura A, Momma J, Sekiguchi H, Nodat T, Yamano T, Kaniwa MA, Kojima S, Tsuda M, and Kurokawa Y. [1994]. A new protocol and criteria for quantitative determination of sensitization potencies of chemicals by guinea pig maximization test. *Contact Dermatitis* 31: 72-85.
- NIOSH [1981]. Health hazard evaluation report: Boehringer Ingelheim Ltd., Ridgefield CT. Cincinnati, OH: Department of Health and Human Services, Centers for Disease Control, National Institute for Occupational Safety and Health, NIOSH HETA Report No. 81-247-958.
- NIOSH [1983]. Health hazard evaluation report: Johnson Museum, Cornell, NY. Cincinnati, OH: Department of Health and Human Services, Centers for Disease Control, National Institute for Occupational Safety and Health, NIOSH HETA Report No. 83-020-1351.
- NIOSH [2005]. 2-Diethylaminoethanol. In: NIOSH pocket guide to chemical hazards. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2005-149, <http://www.cdc.gov/niosh/npg/>. Accessed: 04-30-14.
- NIOSH [2009]. Current intelligence bulletin 61: a strategy for assigning new NIOSH skin notations. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2009-147, <http://www.cdc.gov/niosh/docs/2009-147/pdfs/2009-147.pdf>. Accessed: 05-29-13.
- NTP [2011]. Report on Carcinogens. Twelfth Edition; U.S. Department of Health and Human Services, Public Health Service. National Toxicology Program, [<http://ntp.niehs.nih.gov/ntp/roc/twelfth/roc12.pdf>]. Accessed 04-30-14.
- OECD (Organization for economic co-operation and development) [2002]. SIDS initial assessment profile. In: inChem, <http://www.inchem.org/documents/sids/sids/DIETHYLAMINOETHAN.pdf>. Accessed: 04-30-14.
- OSHA [ND]. 2-diethylaminoethanol. In: OSHA/EPA occupational chemical database, <http://www.osha.gov/chemicaldata/chemResult.html?recNo=11>. Accessed: 04-30-14.
- Potokar M, Grundler OJ, Heusener A, Jung R, Mürmann P, Schöbel C, Suberg H, and Zechel HJ [1985]. Studies on the design of animal tests for the corrosiveness of industrial chemicals. *Food Chem Toxicol* 23:615–617.
- Smyth HF, and Carpenter CP [1944]. The place of range-finding test in the industrial toxicology laboratory. *J Ind Hyg Toxicol* 26:269–273.
- Union Carbide [1990]. Diethylethanolamine Primary skin irritancy studies in the rabbit. Export, PA: Union Carbide Corporation, Bushy Run Research Center. On file with the U.S. Environmental Protection Agency under TSCA Section 8e. Project Report 53-21.
- USEPA (United States Environmental Protection Agency) [2011]. Integrated Risk Information System (IRIS), <http://www.epa.gov/ncea/iris/>. Accessed: 04-30-14.

This page intentionally left blank.

Appendix: Calculation of the SI Ratio

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for 2-DAE. Although the SI ratio is considered in the determination of a substance's hazard potential following skin contact, it is intended only to serve as supportive data during the assignment of the NIOSH SK. An in-depth discussion on the rationale and calculation of the SI ratio can be found in Appendix B of the *Current Intelligence Bulletin (CIB) 61: A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009].

Overview

The SI ratio is a predictive algorithm for estimating and evaluating the health hazards of skin exposure to substances. The algorithm is designed to evaluate the potential for a substance to penetrate the skin and induce systemic toxicity [NIOSH 2009]. The goals for incorporating this algorithm into the proposed strategy for assigning SYS notation are as follows:

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

The algorithm evaluation includes three steps:

1. Determining a skin permeation coefficient (k_p) for the substance of interest.
2. Estimating substance uptake by the skin and respiratory absorption routes.
3. Evaluating whether the substance poses a skin exposure hazard.

The algorithm is flexible in the data requirement and can operate entirely on the basis of the physicochemical properties of a substance and the relevant exposure parameters. Thus,

the algorithm is independent of the need for biologic data. Alternatively, it can function with both the physicochemical properties and the experimentally determined permeation coefficient when such data are available and appropriate for use.

The first step in the evaluation is to determine the k_p for the substance to describe the transdermal penetration rate of the substance [NIOSH 2009]. The k_p , which represents the overall diffusion of the substance through the stratum corneum and into the blood capillaries of the dermis, is estimated from the compound's molecular weight (MW) and base-10 logarithm of its octanol-water partition coefficient ($\log K_{ow}$). In this example, k_p is determined for a substance with use of Equation 1. Other model-based estimates of k_p may also be used [NIOSH 2009].

Equation 1: Calculation of Skin Permeation Coefficient (k_p)

$$k_p = \frac{1}{\frac{1}{k_{psc} + k_{pol}} + \frac{1}{k_a}}$$

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

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

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

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

The second step is to calculate the biologic mass uptake of the substance from skin absorption (skin dose) and inhalation (inhalation dose) during the same period of exposure. The skin dose is calculated as a mathematical product of the k_p , the water solubility (S_w) of

the substance, the exposed skin surface area, and the duration of exposure. Its units are milligrams (mg). Assume that the skin exposure continues for 8 hours to unprotected skin on the palms of both hands (a surface area of 360 square centimeters [cm²]).

Equation 2: Determination of Skin Dose

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

The inhalation dose (in mg) is derived on the basis of the occupational exposure limit (OEL) of the substance—if the OEL is developed to prevent the occurrence of systemic effects rather than sensory/irritant effects or direct effects on the respiratory tract. Assume a continuous exposure of 8 hours, an inhalation volume of 10 cubic meters (m³) inhaled air in 8 hours, and a factor of 75% for retention of the airborne substance in the lungs during respiration (retention factor, or RF).

Equation 3: Determination of Inhalation Dose

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

The final step is to compare the calculated skin and inhalation doses and to present the result as a ratio of skin dose to inhalation dose (the SI ratio). This ratio quantitatively indicates (1) the significance of dermal absorption as a route of occupational exposure to the substance and (2) the contribution of dermal uptake to systemic toxicity. If a substance has an SI ratio greater than or equal to 0.1, it is considered a skin absorption hazard.

Appendix References

NIOSH [2009]. Current intelligence bulletin 61: a strategy for assigning new NIOSH skin notations. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2009-147, <http://www.cdc.gov/niosh/docs/2009-147/pdfs/2009-147.pdf>. Accessed: 04-30-14.

This page intentionally left blank.

This page intentionally left blank.

This page intentionally left blank.



***Delivering on the Nation's promise:
safety and health at work for all people
through research and prevention***

To receive NIOSH documents or more information about occupational safety and health topics, contact NIOSH at

1-800-CDC-INFO (1-800-232-4636)

TTY: 1-888-232-6348

E-mail: cdcinfo@cdc.gov

or visit the NIOSH website at **www.cdc.gov/niosh**.

For a monthly update on news at NIOSH, subscribe to *NIOSH eNews* by visiting **www.cdc.gov/niosh/eNews**.

DHHS (NIOSH) Publication No. 2014-140

SAFER • HEALTHIER • PEOPLE™