

# NIOSH Skin Notation Profile

Diethylenetriamine (DETA)

SKK

ID<sup>SK</sup>

[SK]

**SYS**

SYS (FATAL)

DIR

DIR (IRR)

**DIR (COR)**

**SEN**



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# NIOSH Skin Notation Profile

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## Diethylenetriamine (DETA)

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Naomi L. Hudson

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## 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 (such as irritant contact dermatitis and corrosion) to induction of immune-mediated responses (such as allergic contact dermatitis and pulmonary responses) or systemic toxicity (such as 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 (such as skin permeation) by means of analytical or numerical methods.

This *Skin Notation Profile* provides the SK assignments and supportive data for diethylenetriamine. 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.

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## Abbreviations

<b>ACGIH®</b>	American Conference of Governmental Industrial Hygienists
<b>AMU</b>	atomic mass unit
<b>ATSDR</b>	Agency for Toxic Substances and Disease Registry
<b>CIB</b>	Current Intelligence Bulletin
<b>cm<sup>2</sup></b>	squared centimeter(s)
<b>cm/hr</b>	centimeter(s) per hour
<b>cm/s</b>	centimeter(s) per second
<b>COR</b>	subnotation of SK: COR indicating the potential for a chemical to be a skin corrosive following exposure to the skin
<b>DEREK</b>	Deductive Estimation of Risk from Existing Knowledge
<b>DETA</b>	diethylenetriamine
<b>DIR</b>	skin notation indicating the potential for direct effects to the skin following contact with a chemical
<b>FATAL</b>	subnotation of SK: SYS, indicating the potential for the chemical to be fatal during dermal absorption
<b>g</b>	gram(s)
<b>g/L</b>	gram(s)/liter
<b>GHS</b>	Globally Harmonized System for Classification and Labelling of Chemicals
<b>GPMT</b>	guinea pig maximization test
<b>hr</b>	hour(s)
<b>IARC</b>	International Agency for Research on Cancer
<b>ID(SK)</b>	skin notation indicating that a chemical has been evaluated, but insufficient data exist to accurately assess the hazards of skin exposure
<b>IPCS</b>	International Program for Chemical Safety
<b>IRR</b>	subnotation of SK: DIR indicating the potential for a chemical to be a skin irritant following exposure to the skin
<b><math>k_{aq}</math></b>	coefficient in the watery epidermal layer
<b><math>k_p</math></b>	skin permeation coefficient
<b><math>k_{pol}</math></b>	coefficient in the protein fraction of the stratum corneum
<b><math>k_{psc}</math></b>	permeation coefficient in the lipid fraction of the stratum corneum
<b>LD<sub>50</sub></b>	dose resulting in 50% mortality in the exposed population
<b>LD<sub>Lo</sub></b>	dermal lethal dose
<b>LLNA</b>	local lymph node assay
<b>LOAEL</b>	lowest-observed-adverse-effect level
<b>log <math>K_{ow}</math></b>	base-10 logarithm of a substance's octanol–water partition
<b>M</b>	molarity
<b>m<sup>3</sup></b>	cubic meter(s)
<b>mg</b>	milligram(s)
<b>mg/cm<sup>2</sup>/hr</b>	milligram(s) per square centimeter per hour
<b>mg/kg</b>	milligram(s) per kilogram body weight



<b>mg/m<sup>3</sup></b>	milligram(s) per cubic meter
<b>mL</b>	milliliter(s)
<b>mL/kg</b>	milliliter(s) per kilogram body weight
<b>MW</b>	molecular weight
<b>NIOSH</b>	National Institute for Occupational Safety and Health
<b>nmol/cm<sup>2</sup>/hr</b>	nanomoles per square centimeter per hour
<b>NOAEL</b>	no-observed-adverse-effect level
<b>NTP</b>	National Toxicology Program
<b>OEL</b>	occupational exposure limit
<b>OSHA</b>	Occupational Safety and Health Administration
<b>ppm</b>	parts per million
<b>REL</b>	recommended exposure limit
<b>RF</b>	retention factor
<b>SEN</b>	skin notation indicating the potential for immune-mediated reactions following exposure of the skin
<b>SI ratio</b>	ratio of skin dose to inhalation dose
<b>SK</b>	skin notation
<b>SK</b>	skin notation indicating that the reviewed data did not identify a health risk associated with skin exposure
<b>S<sub>w</sub></b>	solubility in water
<b>SYS</b>	skin notation indicating the potential for systemic toxicity following exposure of the skin
<b>US EPA</b>	United States Environmental Protection Agency
<b>µg</b>	microgram(s)
<b>µg/cm<sup>2</sup></b>	microgram(s) per square centimeter
<b>µg/cm<sup>2</sup>/hr</b>	microgram(s) per square centimeter per hour
<b>µL</b>	microliter(s)
<b>µmol</b>	micromole(s)
<b>w/v</b>	weight/volume

## 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 occur 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.

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# 1 Introduction

## 1.1 General Substance Information

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**Chemical:** Diethylenetriamine

**CAS No:** 111-40-0

**Molecular weight (MW):** 103.2

**Molecular formula:**  $(\text{NH}_2\text{CH}_2\text{CH}_2)_2\text{NH}$

**Structural formula:**

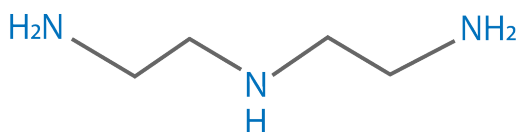


Image by National Center for Biotechnology Information [2020]

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**Synonyms:** DETA; Aminoethyl-ethanediamine; 2,2'-Diaminodiethylamine; N-(2-Aminoethyl)-1,2-ethanediamine; Bis(2-aminoethyl)amine

**Uses:** Diethylenetriamine (DETA) is used as an additive in asphalt, chelating agents, corrosion inhibitors, drainage aids, epoxy curing agents, fabric softeners, and fuel.

## 1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with diethylenetriamine (DETA) and (2) the rationale behind the hazard-specific skin notation (SK) assignment for DETA. 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 DETA and the potential for direct skin injuries from DETA. A search of all available relevant literature was conducted through January 2018 to identify DETA dermal absorption, 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 DETA. The criteria for the search strategy, evaluation, and selection of data are described in Appendix E in the aforementioned *CIB 61* [NIOSH 2009].

## 1.3 Overview of SK Assignment for Diethylenetriamine (DETA)

DETA 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 DETA: SK: SYS-DIR(COR)-SEN. Table 1 provides an overview of the critical effects and data used to develop the SK assignment for DETA.

**Table 1. Summary of the SK assignment for diethylenetriamine (DETA)**

Skin notation	Critical effect	Available data
SK: SYS	Acute toxicity	Sufficient
SK: DIR(COR)	Skin corrosivity	Sufficient animal data
SK: SEN	Skin allergy, cross-sensitization	Sufficient human and animal data

## 2 Systemic Toxicity from Skin Exposure (SK: SYS)

No data from human or animal toxicokinetic studies that evaluated dermal absorption of DETA were identified. However, a study evaluating permeation of risedronate (RIS) through skin extracted from hairless mice looked at RIS dissolved in DETA [Nam et al. 2011]. The study authors found that RIS alone had a penetration rate as low as 4.13 micrograms per square centimeters ( $\mu\text{g}/\text{cm}^2$ ) and the solution containing RIS and DETA at molar ratios of 1:1 and 1:2 had a penetration rate of 511.21  $\mu\text{g}/\text{cm}^2$  and 504.73  $\mu\text{g}/\text{cm}^2$ , respectively. However, Nam et al. [2011] did not evaluate the penetration rate of DETA alone. The potential of DETA to pose a skin absorption hazard was evaluated by means of the NIOSH [2009] predictive algorithm for estimating and evaluating the health hazards of dermal exposure to chemical substances. On the basis of this algorithm, a ratio of skin dose to inhalation dose (SI ratio) of 4.93 was calculated for DETA. Because this ratio is significantly higher than the SI ratio of  $\geq 0.1$  that indicates that skin absorption may significantly contribute to the overall body burden of a chemical [NIOSH 2009], DETA is considered to be a skin absorption hazard following dermal exposure. Additional information on the SI ratio and the variables used in its calculation are included in the appendix.

Although no dermal lethal dose ( $\text{LD}_{10}$ ) values for humans were identified, the dermal  $\text{LD}_{50}$  (the dose resulting in 50% mortality in the

exposed population) values have been reported for rabbits and guinea pigs.  $\text{LD}_{50}$  values of 0.707 milliliter per kilogram body weight (mL/kg) (corresponding to 675.19 milligrams/kg [mg/kg]) [Union Carbide Corporation 1977] and 1.09 mL/kg (corresponding to 1040.95 mg/kg) [Smyth et al. 1949] were reported for rabbits, and 170 mg/kg were reported for guinea pigs [Smyth and Carpenter 1944]. Because  $\text{LD}_{50}$  values for rabbits and guinea pigs are below the critical  $\text{LD}_{50}$  value of 2000 mg/kg that identifies chemical substances with potential for acute dermal toxicity [NIOSH 2009], DETA is considered acutely toxic by the dermal route.

No epidemiological studies that evaluated the potential of DETA to cause systemic effects have been identified. No standard toxicity studies have evaluated biological system/function-specific effects of DETA (including reproductive effects, developmental effects, and immunotoxicity) following dermal exposure. However, a chronic study designed primarily to evaluate tumorigenicity has been conducted. In a study of male mice exposed dermally for their lifetime to 25 microliters ( $\mu\text{L}$ ) of a 5% aqueous solution of DETA (corresponding to 1.25 mg/day of high-purity [HP] grade [96.77% purity]) or the commercial preparation (90.8% purity) for 3 days per week applied on the shaved back, DePass et al. [1987] observed no evidence of skin tumors or internal tumors. Limited animal data show that DETA is not carcinogenic. Table 2 summarizes the carcinogenic designations from NIOSH and other governmental and nongovernmental organizations.

**Table 2. Summary of the carcinogenic designations for diethylenetriamine (DETA) by governmental and nongovernmental organizations**

Organization	Carcinogenic designation
NIOSH [2005]	No designation
US EPA [1988]	No designation
NTP [2011]	No designation
European Parliament [2008]	No GHS designation
IARC [2009]	No designation
ACGIH* [2001]	No designation

ACGIH\* = American Conference of Governmental Industrial Hygienists; GHS = Globally Harmonized System for Classification and Labelling of Chemicals; IARC = International Agency for Research on Cancer; NIOSH = National Institute for Occupational Safety and Health; US EPA = United States Environmental Protection Agency.

Although no toxicokinetic studies of humans or animals have involved estimating the extent of dermal absorption of DETA, a mathematical algorithm predicted its potential to be absorbed through the skin. Sufficient information was identified from acute toxicity studies [**Smyth and Carpenter 1944; Smyth et al. 1949; Union Carbide Corporation 1977**] to show that DETA is absorbed through the skin and is acutely toxic. Therefore, DETA is assigned the SK: SYS notation.

### 3 Direct Effects on Skin (SK: DIR)

One study evaluated the effects of occupational exposure to ethylene amines, including DETA. In that study, Dernehl [1951] reported skin irritation, including dermatitis, erythema, and edema in 34% of 35 workers exposed to ethylene amines at a manufacturing plant. A majority of these workers had recurring episodes that became progressively more severe, but these reactions ceased when the workers were transferred to other units [Dernehl 1951]. Several studies using standard skin irritation test protocols in animals have evaluated the potential of DETA to cause skin corrosivity or irritation. Hine et al. [1958] reported that a single application of DETA to rabbit skin for 24 hours under patches of gauze or a repeated application to the skin for 1 hour per day for 2 days was corrosive to the skin. Another study reported that

the concentrated material applied to the shaved abdomen of rabbits for 1 to 3 minutes produced minimal skin irritation, whereas application for 6 to 12 minutes resulted in complete destruction of the skin, and a 1% aqueous solution applied repeatedly to the ears and shaven abdomens of rabbits for 10 days produced only slight irritation [Dow Chemical Company 1951]. Undiluted DETA was reported to be corrosive to the skin of rabbits following nonoccluded application [Union Carbide Corporation 1977; Smyth et al. 1949], and 0.5 mL of undiluted DETA for 24 hours under occlusion was corrosive to rabbit skin [American Cyanamid Company 1969]. A 10% dilution of DETA in distilled water was corrosive to the skin of rabbits [Union Carbide Corporation 1977]. Studies conducted by the structure-activity relationship model (Deductive Estimation of Risk from Existing Knowledge, or *DEREK*, for Windows) predicted DETA to be negative for skin irritation.

Dernehl [1951] reported the effects of occupational exposure to ethylene amines, including skin irritation, dermatitis, erythema, and edema. Sufficient animal data [**Smyth et al. 1949; Dow Chemical Company 1951; Hine et al. 1958; American Cyanamid Company 1969; Union Carbide Corporation 1977**] were identified to demonstrate that DETA is corrosive to the skin.

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

More-dilute solutions are likely to cause skin irritation. Therefore, on the basis of the data for this assessment, DETA is assigned the notation SK-DIR(COR).

## 4 Immune-mediated Responses (SK: SEN)

Data from studies of volunteers are sufficient to indicate that dermal exposure to DETA can result in sensitization. Kligman [1966] conducted a maximization test and reported extreme sensitization in 21 of 25 volunteers patch-tested with DETA at a concentration of 10% at both induction and challenge. Booth et al. [1962] conducted a prophetic patch test on 200 volunteers to evaluate the health hazards of Elcide 75, which is used in industrial cutting oils and contains DETA as a coupling agent. Patch tests revealed positive reactions in two subjects [Booth et al. 1962]. Upon further testing, one of the two workers reacted to 0.009% DETA, and the investigators concluded that the chemical has sensitizing properties [Booth et al. 1962]. Ormerod et al. [1989] reported allergy in 10 of 800 patients due to oil-based drilling mud, a complex mixture containing amines in emulsifiers. Patch-testing of these 10 patients yielded a positive reaction to DETA (0.5% in petrolatum) in five patients and cross-reactivity between ethylenediamine, DETA, and triethylenetriamine in nine patients. Kydd [1960] reported that standard patch tests resulted in positive reactions, ranging from light to moderate, in 9 of 50 volunteers. However, the 9 volunteers did not have reactions when the patch was re-applied, but 8 different volunteers had reactions to DETA ranging from light to moderate. One study showed no skin sensitization reaction in humans [Key et al. 1961].

Several guinea-pig maximization tests (GPMTs) revealed sensitization reactions. Thorgeirsson [1978] reported positive reactions in 93% of the animals patch-tested with a 2% solution after dermal exposure to 0.5% aqueous DETA solutions for 2 weeks. In another GPMT, Union Carbide Chemicals [1990] noted positive reactions in 16 of 20 guinea pigs exposed to HP

DETA (98.8% pure) and in 11 of 20 guinea pigs exposed to commercial-grade DETA (90.8% pure). Leung and Auletta [1997] reported that 80% of 20 guinea pigs had positive responses when 5% aqueous DETA solutions were used for intradermal induction, 50% solutions were used for epicutaneous induction, and 25% solutions were used for epicutaneous challenge. Basketter et al. [1994] conducted a murine local lymph node assay (LLNA) with DETA and reported skin sensitization. Union Carbide Chemicals [1990] reported that commercial-grade DETA induced cross-sensitization to the structurally similar amines ethylenediamine-UHP, diethylenetriamine-HP, aminoethylpiperazine, triethylenetetramine, aminoethylethanolamine, and tetraethylenepentamine, as well as probable slight cross-sensitization to piperazine. The structure-activity relationship model, DEREK, predicted DETA to be positive for skin sensitization, indicating that the chemical has structural alerts for skin sensitization.

There is sufficient evidence from diagnostic patch tests in humans [Booth et al. 1962; Kligman 1966; Ormerod 1989] and from predictive tests in animals (GPMTs and murine LLNAs) [Thorgeirsson 1978; Union Carbide Chemicals 1990; Basketter et al. 1994; Leung and Auletta 1997] to demonstrate that exposure to DETA causes skin sensitization. Therefore, DETA is assigned the notation SK-SEN.

## 5 Summary

Although there were no toxicokinetic studies that estimated the extent of dermal absorption of DETA identified in humans or animals, acute dermal toxicity studies [Smyth and Carpenter 1944; Smyth et al. 1949; Union Carbide Corporation 1977] sufficiently demonstrate that DETA is absorbed through the skin and is acutely toxic. A limited number of human studies were identified that evaluated the potential of DETA to cause direct skin effects. However, sufficient evidence is provided by animal data [Smyth et al. 1949; Dow Chemical Company 1951; Hine et al. 1958; American Cyanamid Company 1969; Union Carbide Corporation 1977] to



**Table 3. Summary of previous skin hazard designations for diethylenetriamine (DETA)**

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Corrosive to the skin; repeated or prolonged contact may cause skin sensitization
ACGIH* [2001]*	[skin]: [skin]: Based on the LD <sub>50</sub> values for guinea pigs and rabbits following dermal application. Recommendation of a sensitizer (SEN) notation is deferred until additional evidence becomes available linking exposure and sensitization.
OSHA [2018]*	None

ACGIH\* = American Conference of Governmental Industrial Hygienists; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration.

\*Year accessed

demonstrate that DETA is corrosive to the skin at high concentrations, whereas more-dilute solutions are likely to cause skin irritation. Information from diagnostic patch tests in humans [Booth et al. 1962; Kligman 1966; Ormerod 1989] and from predictive tests in animals (GPMTs and murine LLNAs) [Thorgeirssen 1978; Union Carbide Chemicals 1990; Basketter et al. 1994; Leung and Aulette 1997] is sufficient to show that exposure to DETA causes skin sensitization and can induce cross-sensitization with structurally similar amines. On the basis of the available data, a composite skin notation of SK-SYS-DIR(COR)-SEN is assigned to DETA.

Table 3 summarizes the skin hazard designations for DETA previously issued by NIOSH and other organizations. The equivalent dermal designations for DETA, according to the Globally Harmonized System (GHS) for Classification and Labelling of Chemicals, are Acute Toxicity Category 4 (Hazard statement: Harmful in contact with the skin), Skin Corrosion Category 1B (Hazard statement: Causes severe skin burns and eye damage), and Skin Sensitization Category 1 (May cause an allergic skin reaction) [European Parliament 2008].

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**Note:** Asterisks (\*) denote sources cited in text; daggers (†) denote additional resources.

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## Appendix: Calculation of the SI Ratio for Diethylenetriamine (DETA)

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for diethylenetriamine (DETA). Although the SI ratio is considered in the determination of a substance's hazard potential following skin contact, it is intended to serve only 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, and
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 its transdermal penetration rate [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. A self-consistent set of units must be used, such as centimeters per hour (cm/hr), outlined in Table A1. Other model-based estimates of  $k_p$  may also be used [NIOSH 2009].

### Equation 1: Calculation of Skin Permeation Coefficient ( $k_{aq}$ )

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

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

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

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

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

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 [ $\text{cm}^2$ ]).

#### Equation 2: Determination of Skin Dose

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

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 ( $\text{m}^3$ ) 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

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

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.

## Calculation

Table A1 summarizes the data applied in the previously described equations to determine the SI ratio for DETA. The calculated SI ratio was 4.93. On the basis of these results, DETA is predicted to represent a skin absorption hazard.

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**Table A1. Summary of data used to calculate the SI ratio for diethylenetriamine (DETA)**

Variables used in calculation	Units	Value
<b>Skin permeation coefficient</b>		
Permeation coefficient of stratum corneum lipid path ( $k_{psc}$ )	cm/hr	0.000364
Permeation coefficient of the protein fraction of the stratum corneum ( $k_{pot}$ )	cm/hr	$1.015 \times 10^{-5}$
Permeation coefficient of the watery epidermal layer ( $k_{aq}$ )	cm/hr	0.246129
Molecular weight ( $MW$ ) <sup>*</sup>	amu	103.17
Base-10 logarithm of its octanol–water partition coefficient ( $Log K_{ow}$ ) <sup>*</sup>	None	-2.13
Calculated skin permeation coefficient ( $k_p$ )	cm/hr	0.0000514
<b>Skin dose</b>		
Water solubility ( $S_w$ ) <sup>*</sup>	mg/cm <sup>3</sup>	1000
Calculated skin permeation coefficient ( $k_p$ )	cm/hr	0.000054
Estimated skin surface area (palms of hands) <sup>§</sup>	cm <sup>2</sup>	360
Exposure time	hr	8
Calculated skin dose	mg	147.91
<b>Inhalation dose</b>		
Occupational exposure limit (OEL) <sup>†</sup>	mg/m <sup>3</sup>	4
Inhalation volume	m <sup>3</sup>	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	30
<b>Skin dose–to–inhalation dose (SI) ratio</b>	<b>None</b>	<b>4.93</b>

<sup>\*</sup>Variables identified from NLM [ND].

<sup>†</sup>The OEL used in calculation of the SI ratio for diethylenetriamine was the NIOSH recommended exposure limit (REL) [NIOSH 2005].

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