NIOSH Skin Notation Profiles

2 Diethylaminoethanol
NIOSH Skin Notation (SK) Profiles

2-Diethylaminoethanol
[CAS No. 100-37-8]
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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 (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
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## Abbreviations

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

1.1 General Substance Information

Chemical: 2-Diethylaminoethanol (2-DAE)

CAS No: 100-37-8

Molecular weight (MW): 117.2

Molecular formula: \((\text{C}_2\text{H}_5\text{NCH}_2\text{CH}_2\text{OH})\)

Structural formula:

\[
\begin{align*}
\text{H}_3\text{C} & \text{N} \text{CH}_2\text{CH}_2\text{OH} \\
\text{H}_3\text{C} & \text{CH}
\end{align*}
\]

Synonyms:

2-DAE; Diethylaminoethanol; 2-Diethylaminoethyl alcohol; N,N-Diethylthanolamine; 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/cm²) 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
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 and Development (OECD) guidelines for skin corrosion were not identified.

<table>
<thead>
<tr>
<th>Skin notation</th>
<th>Critical effect</th>
<th>Available data</th>
</tr>
</thead>
<tbody>
<tr>
<td>SK: SYS</td>
<td>Acute toxicity</td>
<td>Limited animal data</td>
</tr>
<tr>
<td>SK: DIR (COR)</td>
<td>Skin corrosion</td>
<td>Sufficient animal data</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Organization</th>
<th>Carcinogenic designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIOSH [2005]</td>
<td>No designation</td>
</tr>
<tr>
<td>NTP [2011]</td>
<td>No designation</td>
</tr>
<tr>
<td>USEPA [2014]</td>
<td>No designation</td>
</tr>
<tr>
<td>European Parliament [2008]</td>
<td>No designation</td>
</tr>
<tr>
<td>IARC [2012]</td>
<td>No designation</td>
</tr>
<tr>
<td>EC [2014]†</td>
<td>No designation</td>
</tr>
<tr>
<td>ACGIH [2001]</td>
<td>No designation</td>
</tr>
</tbody>
</table>

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 systematically toxic in humans were limited to models of human skin penetration based on physico-chemical properties [Fiserova-Bergerova...
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-diethylaminoethal 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].

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

<table>
<thead>
<tr>
<th>Organization</th>
<th>Skin hazard designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIOSH [2005]</td>
<td>[skin]: Potential for dermal absorption</td>
</tr>
<tr>
<td>OSHA [2014]*</td>
<td>[skin]: Potential for dermal absorption</td>
</tr>
<tr>
<td>ACGIH [2001]</td>
<td>[skin]: Based on reported dermal LD&lt;sub&gt;50&lt;/sub&gt; in rabbits</td>
</tr>
<tr>
<td>EC [2014]*</td>
<td>R21: Harmful if in contact with skin</td>
</tr>
<tr>
<td></td>
<td>R34: Causes burns</td>
</tr>
</tbody>
</table>

*Date accessed

References


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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 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 (\(k_p\))**

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

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 \(\left(S_w\right)\) 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**

\[
\text{Skin dose} = K_p \times S_w \times \text{Exposed skin surface area} \times \text{Exposure time} = K_p (\text{cm/hour}) \times S_w (\text{mg/cm}^3) \times 360 \text{ cm}^2 \times 8 \text{ hours}
\]

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**

\[
\text{Inhalation dose} = \text{OEL} \times \text{Inhalation volume} \times \text{RF} = \text{OEL (mg/m}^3) \times 10 \text{ m}^3 \times 0.75
\]

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**

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