

NIOSH Skin Notation Profiles

2-Ethoxyethanol (EE)

SKK

ID^{SK}

[SK]

SYS

SYS (FATAL)

DIR

DIR (IRR)

DIR (COR)

SEN

NIOSH Skin Notation (SK) Profile

2-Ethoxyethanol (EE)

[CAS No. 110–80–5]

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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 a substance's hazard potential, 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 assignment and supportive data for 2-ethoxyethanol (EE; CAS No. 110–80–5). In particular, this document evaluates and summarizes the literature describing the substance's hazard potential 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 chemical of interest.

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Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
CIB	Current Intelligence Bulletin
cm ²	square centimeter(s)
cm/hr	centimeter(s) per hour
DEREK™	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
EE	2-ethoxyethanol
g/kg	gram(s) per kilogram body weight
GHS	Globally Harmonized System of Classification and Labeling of Chemicals
GPMT	guinea pig maximization test
IARC	International Agency for Research on Cancer
IPCS	International Program for Chemical Safety
IUCID	International Uniform Chemical Information Database
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 _{p_{sc}}	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
LOAEL	lowest-observed-adverse-effect level
log K _{OW}	base-10 logarithm of a substance's octanol–water partition
m ³	cubic meter(s)
mg	milligram(s)
mg/cm ² /hr	milligram(s) per square centimeter per hour
mg/kg	milligram(s) per kilogram body weight
mg/m ³	milligram(s) per cubic meter
mL	milliliter(s)
MW	molecular weight
NIOSH	National Institute for Occupational Safety and Health
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.

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1 Introduction

1.1 General Substance Information

Chemical: 2-Ethoxyethanol (EE)

CAS No: 110–80–5

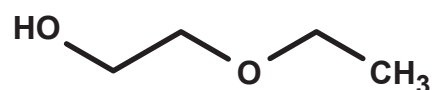
Synonyms:

EE; 2-EE; EGEE; Ethylene Glycol Mzonoethyl Ether; Ethyl Cello-solve; Ethylglycol

Molecular weight (MW): 90

Molecular formula: C₄H₁₀O₂

Structural formula:



Uses:

2-Ethoxyethanol (EE) is an organic compound used primarily as a chemical intermediate and solvent [Boatman and Knaak 2001].

1.2 Purpose

This *Skin Notation Profile* presents (1) a brief summary of technical data associated with skin contact with EE and (2) the rationale behind the hazard-specific skin notation (SK) assignment for EE. 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 EE. A literature search was conducted through July 2010 to identify information on EE, 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 EE.

1.3 Overview of SK Assignment for EE

EE is potentially capable of causing multiple toxic effects following skin contact. A critical review of available data has resulted in the following SK assignment for EE: **SK: SYS**. Table 1 provides an overview of the critical effects and data used to develop the SK assignment for EE.

2 Systemic Toxicity from Skin Exposure (SK: SYS)

Toxicokinetic studies following dermal exposure to EE were identified. In a study involving healthy volunteers, Kezic et al. [1997] noted that vaporized and liquid EE were readily absorbed, with uptake through the skin estimated to be 42% following a 45-minute combined inhalation and dermal exposure (with the assumption that the whole body surface was exposed to vapor). Those investigators reported permeability coefficients (K_p) of 19 centimeters per hour (cm/hr) following dermal exposure of an area of 1000 square centimeter (cm²) on the forearm and hand to the vapor for 45 minutes and

Table 1. Summary of the SK assignment for EE

Skin notation	Critical effect	Data available
SK: SYS	Teratogenicity, developmental toxicity, reproductive toxicity	Limited human and animal data

0.7 milligrams per square centimeter per hour (mg/cm²/hr) when an area of 27 cm² (forearm) was exposed to the liquid for 15 minutes. Lockley et al. [2002] reported absorption of 8% of the administered dose in human skin in vitro. Larese Filon et al. [1999] and Wilkinson and Williams [2002] also reported a high potential for skin absorption of EE in vitro by human skin or by full-thickness or dermatomed human breast skin. A dermal in vitro penetration rate of 0.80 mg/cm²/hr has been measured experimentally in human skin [Dugard 1984; Larese Filon et al. 1999].

In rats, Sabourin et al. [1992] noted dermal absorption of approximately 20% to 27% of the nonocclusive administered dose. Lockley et al. [2002] reported absorption of 25% of the dose when radiolabeled EE was administered to occluded rat skin in vivo. When administered in vitro to split rat skin, absorption was 22% under occlusion and 20% without occlusion. The study by Lockley et al. [2002] indicated that the in vitro rat results most accurately predicted absorption through rat skin in vivo and that penetration through rat skin was greater than through human skin in vitro. The investigators also noted that systemic exposure after skin contact is likely to be to the parent material. By extrapolation of the in vitro data for human and rat skin, Lockley et al. [2002] suggested that the dermal absorption of EE at the same dose in humans would be approximately one-third of that in rats in vivo. The available absorption data demonstrate that the substance is systemically available following dermal exposure in humans.

The potential of EE to pose a skin absorption hazard was also evaluated by means of a predictive algorithm for estimating and evaluating the health hazards of dermal exposure to substances [NIOSH 2009]. The evaluation method compares an estimated chemical dose accumulated in the body from skin absorption and an estimated dose from respiratory absorption associated with a reference occupational exposure limit. On the basis of this algorithm, a ratio of the skin dose to the inhalation dose (SI ratio) of 132.66 was calculated for EE. An SI ratio of ≥ 0.1 indicates that a chemical is capable of producing systemic toxicity from skin exposure [NIOSH 2009]. Additional information on the SI ratio and the variables used in its calculation are included in the appendix.

No information was identified regarding acute toxicity of EE in humans following dermal exposure. However, with regard to animals, the dermal LD₅₀ value (the dose resulting in 50% mortality in the exposed population) for rabbits was 3900 milligrams per kilogram body weight (mg/kg) under occlusive conditions in one study [Daughtrey et al. 1984] and ranged from 2511 mg/kg to 4950 mg/kg in another [Eastman Kodak Company 1992]. Because the reported acute dermal LD₅₀ value for the rabbit is greater than the critical dermal LD₅₀ value of 2000 mg/kg body weight that identifies a chemical substance with the potential for acute dermal toxicity [NIOSH 2009], EE is not considered to be systemically toxic by the acute dermal route.

No data regarding the health effects caused by chronic or subchronic dermal exposures to EE in humans were identified. A series of cross-sectional and environmental studies were identified that investigated occupational exposures of shipyard painters to EE and other glycol ethers [Sparer et al. 1988; Welch and Cullen 1988; Welch et al. 1988]. In the first study, Welch and Cullen [1988] reported various hematological effects (i.e., anemia, granulocytopenia, and low polymorphonuclear leukocyte count) among exposed workers. Welch et al. [1988] indicated that male workers experienced effects of the reproductive system, including increased frequency of reduced sperm counts and decreased testicular size. Those studies provided estimates of airborne concentrations of glycol ether compounds including EE. Despite providing no estimates of dermal exposures, the authors concluded that skin contact was a significant exposure pathway for glycol ethers. It should also be noted that the adverse effects noted in the studies cannot be exclusively linked to EE and do not provide evidence that glycol ethers may cause systemic toxicity that target the male reproductive system and the hematological system.

Dermal repeated-dose toxicity studies [Hardin et al. 1982, 1984; Ryan et al. 1988] in animals indicate that EE induced adverse teratogenic, developmental, and reproductive effects. Hardin et al. [1982] observed a significant increase in resorptions, significant decrease in number of live fetuses per litter, significant decrease in fetal body weight, and significant increase in the incidence of visceral malformations (predominantly of the cardiovascular system) and skeletal variations in rats dermally exposed four times per day to 0.25 or 0.50 milliliter (mL) applications of EE (corresponding to 1 mL/day or 2 mL/day) during gestation days 7 to 16, followed by

a 5-day postexposure period. The International Uniform Chemical Information Database (IUCID) [ECB 2000] reported the doses as 3445 milligram per kilogram body weight per day (mg/kg/day) and 6889 mg/kg/day. Because maternal toxicity (ataxia toward the end of the treatment period and a significant decrease in body weight gain in the last half of gestation) was observed only at the high dose, a LOAEL of 3445 mg/kg/day for developmental effects can be established in the absence of maternal toxicity. In a later teratogenicity study by Hardin et al. [1984], in which EE was used as a positive control in rats, dermal application of 0.25 mL of EE four times daily—reported as 3875 mg/kg/day [ECB 2000]—on gestation days 7 to 16 resulted in similar toxicity; manifestations were a decrease in body weight in dams associated with completely resorbed litters, a significant decrease in fetal body weights, and a significant increase in visceral malformations and skeletal variations, in comparison with negative control animals. EE was also used as a positive control in another dermal teratogenicity study. In that study, conducted by Ryan et al. [1988], EE caused developmental effects, as evidenced by reduced fetal body weight, cardiovascular defects, delayed skeletal development, and skeletal malformations in rats when 0.1 mL of the chemical (calculated to be equivalent to 93 mg/kg/day) was applied to the skin on gestation days 6 to 15. The developmental studies available demonstrate that EE is a dermal teratogen and that a developmental LOAEL of 93 mg/kg/day [Ryan et al. 1988] can be established for the chemical.

No long-term study, standard reproductive toxicity study, or specialty studies evaluating function-specific effects (including reproductive toxicity and immunotoxicity) or carcinogenicity study following dermal exposure to EE was identified. Table 2

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

Organization	Carcinogenic designation
NIOSH [2005]	None
NTP [2009]	None
USEPA [2009]	None
IARC [2009]	None
EC [2010]	None
ACGIH [2001]	None

Abbreviations: 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.

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

provides a summary of carcinogenic designations from multiple governmental and nongovernmental organizations for EE.

Review of available data indicates that EE is absorbed, systemically available, and potentially toxic. In particular, the reviewed studies provide sufficient evidence to determine that EE may cause teratogenic, developmental, and reproductive effects following repeated skin contact [**Hardin et al. 1982, 1984; Ryan et al. 1988***]. Therefore, on the basis of the data for this assessment, EE is not assigned the SK: SYS notation.

3 Direct Effects on Skin (SK: DIR)

No data on corrosivity of EE or in vitro tests for corrosivity with human or animal skin models or for skin integrity with cadaver skin were identified. Skin irritation studies produced inconsistent results, depending on the standard protocol used in assessing the irritation potential. EE applied under an occlusive wrap to depilated abdominal skin of rabbits at doses up to 3.8 grams per kilogram (g/kg) and to guinea pigs at doses up to 18.6

g/kg for 24 hours produced only slight irritation, according to the Draize scale [Eastman Kodak Company 1981, 1992]. Zissu [1995] reported EE to be nonirritating to rabbits after using the European Economic Community (EEC) test method, but the investigator did not evaluate this chemical with the Draize protocol of 24 hours versus 4 hours occlusion, as in the EEC method. The structure activity relationship model, Deductive Estimation of Risk from Existing Knowledge (DEREK™) for Windows, predicted EE to be a skin irritant.

The available information demonstrates that EE produces only a very mild skin irritation at very high doses or following prolonged and repeated dermal exposure. Therefore, on the basis of the data for this assessment, EE is not assigned the SK: DIR notation.

4 Immune-mediated Responses (SK: SEN)

No evidence of the potential of EE to cause skin sensitization in humans has been identified. Zissu [1995] did not observe delayed cutaneous hypersensitivity (i.e., cell-mediated sensitization) in the

*References in **bold** text indicate studies that served as the basis of the SK assignment.

Table 3. Summary of the previously issued skin hazard designations for EE

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption
OSHA [2009]	[skin]: Potential for dermal absorption
ACGIH [2001]	[skin]: Based on the potential to be absorbed through rabbit skin
EC [2010]	R21: Harmful if in contact with skin

Abbreviations: 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.

guinea pig maximization test (GPMT) when the chemical was tested at sensitization and challenge concentrations of 10%. DEREK™ does not predict EE to be a skin sensitizer. Therefore, on account of the data for this assessment, EE is not assigned the SK: SEN notation.

5 Summary

The available toxicokinetic data demonstrate that EE is dermally absorbed in humans and animals following both in vitro and in vivo exposure, although the extent of absorption is lesser in humans than in animals. Available data indicate that EE is absorbed, systemically available, and potentially toxic. In particular, the reviewed studies provide sufficient evidence to determine that EE may cause teratogenic, developmental, and reproductive effects following repeated skin contact [Hardin et al. 1982, 1984; Ryan et al. 1988]. The substance is not identified as a skin irritant or sensitizer in humans or animals. Therefore, on the basis of these assessments, EE is assigned a composite skin notation of **SK: SYS**.

Table 3 summarizes the skin hazard designations for EE previously issued by NIOSH and other organizations. The equivalent dermal designation for EE, according to the Globally Harmonized System (GHS) of Classification and Labeling of Chemicals, is Acute Toxicity Category

4 (Hazard statement: Harmful in contact with the skin). EE has been identified as a Category 1B Reproductive toxicant (Hazard statements: May damage fertility; May damage the unborn child) [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 EE

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for EE. 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 the 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 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. A self-consistent set of units must be used, such as 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_p)

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

where K_{psc} is the permeation coefficient in the lipid fraction of the stratum corneum, K_{pol} is the coefficient in the protein

Table A1. Summary of data used to calculate the SI ratio for EE

Variables used in calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path (K_{psc})	cm/hr	0.00061
Permeation coefficient of the protein fraction of the stratum corneum (K_{pol})	cm/hr	1.6001×10^{-5}
Permeation coefficient of the watery epidermal layer (K_{aq})	cm/hr	0.26335
Molecular weight (MW)*	amu	90
Base-10 logarithm of its octanol–water partition coefficient ($\log K_{OW}$)*	None	-0.32
Calculated skin permeation coefficient (K_p)	cm/hr	0.00062
Skin dose		
Water solubility (S_W)*	mg/cm ³	1000
Calculated skin permeation coefficient (K_p)	cm/hr	0.00062
Estimated skin surface area (palms of hand)	cm ²	360
Exposure time	hr	8
Calculated skin dose	mg	1790.93
Inhalation dose		
Occupational exposure limit (OEL)†	mg/m ³	1.8
Inhalation volume	m ³	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	14
Skin dose–to–inhalation dose (SI) ratio	None	132.66

*Variables identified from SRC [2009].

†The OEL used in calculation of the SI ratio was the NIOSH-recommended exposure limit (REL) [NIOSH 2005].

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 cm²).

Equation 2: Determination of Skin Dose

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

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

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

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 EE. The calculated SI ratio was 132.66. On the basis of these results, EE is predicted to represent a skin absorption hazard.

Appendix References

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