NIOSH Skin Notation Profile

Cyclohexanol

SK

ID^{SK}

[~~SK~~]

SYS

SYS (FATAL)

DIR

DIR (IRR)

DIR (COR)

SEN

Centers for Disease Control and Prevention
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NIOSH Skin Notation Profile

Cyclohexanol

Naomi L. Hudson

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Centers for Disease Control and Prevention
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Suggested Citation

NIOSH [2020]. NIOSH skin notation profile: cyclohexanol. By Hudson NL. 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. 2021-101.

DHHS (NIOSH) Publication No. 2021-101

DOI: https://doi.org/10.26616/NIOSHPUB2021101

October 2020

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 cyclohexanol. 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

ACGIH®	American Conference of Governmental Industrial Hygienists
AMU	atomic mass unit
ATSDR	Agency for Toxic Substances and Disease Registry
CIB	Current Intelligence Bulletin
ChE	cholinesterase
cm^2	square centimeter(s)
cm/hr	centimeter(s) per hour
COR	subnotation of SK: COR indicating the potential for a chemical to be corrosive to the skin following exposure
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
FATAL	subnotation of SK: SYS, indicating the potential for the chemical to be fatal during dermal absorption
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
GPMT	guinea pig maximization test
hr	hour(s)
IARC	International Agency for Research on Cancer
$ID^{(SK)}$	skin notation indicating that a chemical has been evaluated, but insufficient data exist to accurately assess the hazards of skin exposure
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
LOAEL	lowest-observed-adverse-effect level
log K_{OW}	base-10 logarithm of a substance's octanol–water partition
M	molar
m^3	cubic meter(s)
mg	milligram(s)
mg/cm^3	milligram(s) per cubic centimeter
mg/kg	milligram(s) per kilogram body weight
mg/min	milligram(s) per minute
mL	milliliter(s)
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
~~**SK**~~	skin notation indicating that the reviewed data did not identify a health risk associated with skin exposure
S_W	solubility in water
SYS	skin notation indicating the potential for systemic toxicity following exposure of the skin
US EPA	United States Environmental Protection Agency
w/v	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.

Acknowledgments

This document was developed by the Division of Science Integration (Paul Schulte, Ph.D., Director). Naomi Hudson, Dr.P.H., was the project officer for this document. 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.

Special appreciation is expressed to the following individuals for serving as independent, external reviewers:

- Shane Que Hee, Ph.D., Professor, Environmental Health Sciences Director, UCLA Industrial Hygiene Program Director, UCLA Fielding School of Public Health, Los Angeles, CA
- M. Cecilia Aguila, D.V.M., Division of Human Food Safety, FDA, Center for Veterinary Medicine, Rockville, MD

Special appreciation is expressed to the following individuals for serving as internal reviewers by use of an Intergovernmental Personnel Agreement:

- Ronald E. Baynes, D.V.M., Ph.D., College of Veterinary Medicine, North Carolina State University, Raleigh, NC
- Youcheng Liu, M.D., Sc.D., M.P.H., M.S., University of North Texas Health Science Center, Fort Worth, TX

The following individuals contributed to the development or improvement of the skin notation profiles:

- G. Frank Gerberick, Ph.D., The Procter and Gamble Company, Cincinnati, OH
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- Jennifer Sahmel, M.Sc., CIH, ChemRisk, Boulder, CO
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1 Introduction

1.1 General Substance Information

Chemical: Cyclohexanol

CAS No: 108-93-0

Molecular weight (*MW*): 100.2

Molecular formula: $C_6H_{11}OH$

Structural formula:

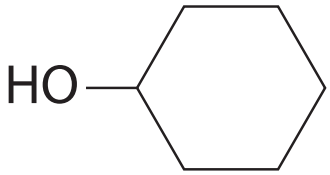

Image: National Center for Biotechnology Information [2020]

Synonyms: Anol, Cyclohexyl alcohol, Hexahydrophenol, Hexalin, Hydralin, Hydroxycyclohexane

Uses: With a melting point of 25.93 °C, cyclohexanol can be a solid or a viscous liquid at 25 °C. Some producers use a mixture containing 2.25% methanol to keep cyclohexanol in a liquid state [HSDB 2011]. Cyclohexanol is used primarily as a chemical intermediate in the manufacturing of nylon, as a stabilizer, and a homogenizer for soap and detergent; an estimated >500 to 1 billion pounds (390 million kilograms) of the substance was produced in 2002 [HSDB 2019].

1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with cyclohexanol and (2) the rationale behind the hazard-specific skin notation (SK) assignment for cyclohexanol. 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 cyclohexanol. A search of all available relevant literature was conducted through January 2020 to identify information on cyclohexanol 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 in humans, animals, or appropriate modeling systems that are relevant to assessing the effects of dermal exposure to cyclohexanol. 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

Cyclohexanol 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 cyclohexanol: **SK: SYS-DIR (IRR)**. Table 1 provides an overview of the critical effects and data used to develop the SK assignment for cyclohexanol.

Table 1. Summary of the SK assignment for cyclohexanol

Skin notation	Critical effect	Available data
SK: SYS	Central nervous and/or peripheral system effects (tremors, narcosis, hypothermia); acute toxicity	Sufficient animal data
SK: DIR(IRR)	Skin irritancy	Sufficient animal data

2 Systemic Toxicity from Skin Exposure (SK: SYS)

No *in vivo* or *in vitro* toxicokinetic studies were identified in humans or animals that evaluated dermal exposure to cyclohexanol. Walker et al. [2003] estimated a skin absorption rate of 6.10×10^{-3} centimeters per hour (cm/h) for cyclohexanol based on a quantitative structure-activity relationship prediction. The potential of cyclohexanol to pose a skin absorption hazard was also evaluated using the NIOSH [2009] predictive algorithm for estimating and evaluating the health hazards of dermal exposure to chemical substances. Based on this algorithm, the ratio of skin dose to inhalation dose (the SI ratio) of 0.34 was calculated for cyclohexanol. An SI ratio of ≥0.1 indicates that skin absorption may significantly contribute to the overall body burden of a substance [NIOSH 2009]; therefore, cyclohexanol is considered to be a skin absorption hazard following dermal exposure.

No estimated dermal lethal dose (LD_{Lo}) in humans was identified. The dermal LD_{50} (lethal dose in 50% of exposed animals) values in rabbits were reported to be greater than 501 milligrams per kilogram body weight (mg/kg) but less than 794 mg/kg [Monsanto 1978]. Because the reported acute dermal LD_{50} value for rabbits is lower than the critical dermal LD_{50} value of 2,000 mg/kg that identifies chemical substances with the potential for acute dermal toxicity [NIOSH 2009], cyclohexanol is considered acutely toxic following dermal exposure.

No epidemiological studies, human case reports, or subchronic/chronic toxicity studies in animals were identified that evaluated the potential of cyclohexanol to cause systemic effects following dermal exposure. Treon et al. [1943] applied 10 milliliters (mL) (in two 5 mL portions at 0.5-hour intervals) of cyclohexanol for one hour a day for 10 days to the clipped abdominal skin of rabbits. Treon et al. [1943] reported that the second and successive dose of cyclohexanol resulted in narcosis, central nervous system effects such as tremor, athetoid movement (inability to maintain body parts in a stable position), and hypothermia, which became more marked with successive exposures. Hypothermia and narcosis were observed in rabbits that received 35 to 130 mL (approximately 29 to 130 grams/animal) of cyclohexanol applied to the clipped skin of the abdomen in 5-mL portions at 20-minute intervals for a total of 160 minutes to 9 hours, in addition to involuntary jerking and twitching of the forelegs and chest muscles in the rabbit given the highest dose. The animals receiving the highest dose of cyclohexanol died [Treon et al. 1943]. These results indicate that high doses of liquid cyclohexanol applied to the skin can result in tremors, narcosis, hypothermia, and death.

No standard toxicity or specialty studies were identified that evaluated biological system/function specific effects (including reproductive and developmental effects and immunotoxicity) following dermal exposure to cyclohexanol.

No epidemiological studies or animal studies were identified that evaluated the potential of cyclohexanol to be a carcinogen following dermal exposure. Table 2 summarizes the carcinogenic designations of multiple governmental and nongovernmental organizations for cyclohexanol.

Table 2. Summary of the carcinogenic designations for cyclohexanol by governmental and nongovernmental organizations

Organization	Carcinogenic designation
NIOSH [2005]	No designation
NTP [2014]	No designation
US EPA [2020]*	No designation
European Parliament [2008]	No GHS designation
IARC [2012]	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; NTP = National Toxicology Program; US EPA = United States Environmental Protection Agency.
*Date accessed

Although no toxicokinetic data were identified that estimated the percent dermal absorption of cyclohexanol in humans or animals, the mathematical model predicts that cyclohexanol may be absorbed through the skin following dermal exposure. Acute and repeat-dose [Monsanto 1978; Treon et al. 1943] toxicity studies with rabbits provide limited data indicating that cyclohexanol can be absorbed through the skin and may be acutely toxic and produce central nervous and/or peripheral nervous systems effects (tremors, narcosis, hypothermia) including death at high doses. Therefore, this assessment assigns a skin notation of SK: SYS for cyclohexanol.

3 Direct Effects on Skin (SK: DIR)

No human or animal *in vivo* studies on corrosivity or *in vivo* tests for corrosivity using human or animal skin models or *in vitro* tests of skin integrity using cadaver skin were identified. Limited skin irritation tests were identified in animals for cyclohexanol. Mild irritation was observed at 24 and 72 hours in a skin irritation test after 0.5 mL of undiluted cyclohexanol was applied to the skin of rabbits for 24 hours [Monsanto 1978]. Skin began to flake off after seven to ten days, but there was no corrosivity reported [Monsanto 1978]. Smyth et al. [1962] also reported mild irritation following application of cyclohexanol to clipped rabbit skin, with an irritation score of 2 out of 6 (where 1 is no irritation and 6 is necrosis). Repeated cutaneous application of cyclohexanol at high doses (10 mL of cyclohexanol for 10 days for a total of 94.4 g/kg) to the skin of rabbits resulted in slight local erythema, localized ulcers, and thickening of the skin [Treon et al. 1943]. Animals that received smaller doses of cyclohexanol (35-130 mL) experienced local erythema of the skin [Treon et al. 1943].

Using human keratinocytes, Muller-Decker et al. [1994] measured *in vitro* proinflammatory eicosanoid and interleukin 1-alpha (IL-1α) release as indicators of skin irritancy. Cyclohexanol was observed to induce a delayed (greater than 4 hour) stimulation of arachidonic acid release, leading the authors to estimate a half-maximum stimulation concentration (SC_{50}) of 2.8 to 3.2 x 10^{-2} molar (M). A 10-fold stimulatory (ED_{10}) concentration of IL-1α was observed at a dose of 5.3 x 10^{-2} M of cyclohexanol [Muller-Decker et al. 1994]. These mechanistic studies support the in vivo studies that suggest that cyclohexanol has the potential to cause skin irritation.

The structure activity relationship model, DEREK®, predicted cyclohexanol to be negative

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

for skin irritation, indicating that the chemical does not have structural alerts for skin irritation.

Although DEREK® predicted cyclohexanol to be negative for skin irritation, skin irritation tests in rabbits [**Treon et al. 1943; Smyth et al. 1962; Monsanto 1978**] and the *in vitro* data using human keratinocytes [**Muller-Decker et al. 1994**] indicate that cyclohexanol has the potential to cause mild skin irritation, including localized ulcers and thickening of the skin at high doses. Therefore, this assessment assigns an SK: DIR(IRR) notation for cyclohexanol.

4 Immune-mediated Responses (SK: SEN)

No occupational exposure studies or diagnostic patch tests in humans or predictive tests (guinea pig maximization tests, Buehler test, murine local lymph node assays, etc.) that evaluated the potential of the cyclohexanol to cause skin sensitization were identified. The structure activity relationship model, DEREK®, predicted cyclohexanol to be negative for skin sensitization, indicating that the chemical does not have structural alerts for skin sensitization.

Lack of case reports or diagnostic patch tests in humans or predictive tests in animals precludes adequate evaluation of the skin sensitization potential of cyclohexanol. Therefore, this assessment does not assign an SK: SEN notation for cyclohexanol.

5 Summary

Although no toxicokinetic data were identified that estimated the percent dermal absorption of cyclohexanol in humans or animals, the mathematical model predicts that cyclohexanol may be absorbed through the skin following dermal exposure. Acute and repeat-dose [**Monsanto 1978; Treon et al. 1943**] toxicity studies with rabbits provide limited data indicating that cyclohexanol can be absorbed through the skin and may be acutely toxic and produce central nervous and/or peripheral nervous systems effects (tremors, narcosis, hypothermia), including death at high doses. Results from a skin irritation test in rabbits [**Smyth et al. 1962; Monsanto 1978**] and in vitro data using human keratinocytes [**Muller-Decker et al. 1994**] provide evidence that cyclohexanol has the potential to cause skin irritation, including the potential to cause localized ulcers and thickening of the skin at high doses. No case reports or diagnostic patch tests in humans or predictive tests in animals were identified upon which the skin sensitization potential of cyclohexanol can be evaluated. Therefore, this assessment assigns a composite skin notation of **SK: SYS-DIR (IRR)** for cyclohexanol.

Table 3 summarizes the skin hazard designations for cyclohexanol issued by NIOSH and other organizations. The equivalent dermal designation for cyclohexanol according to the Globally Harmonized System (GHS) of classification and labeling of chemicals is Skin

Table 3. Summary of the previously issued skin hazard designations for cyclohexanol from NIOSH and other organizations

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Based on the potential for dermal absorption
OSHA [2018]*	No designation
ACGIH® [2001]	[skin] Based on the studies with rabbits in which narcosis, tremors, hypothermia, and death ensued following dermal application of cyclohexanol

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

Irritation Category 2 (Causes skin irritation) [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 Cyclohexanol

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for cyclohexanol. 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, 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 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 [cm^2]).

Equation 2: Determination of Skin Dose

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

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 (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

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

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 cyclohexanol. The calculated SI ratio was 0.34. On the basis of these results, cyclohexanol is predicted to represent a skin absorption hazard.

Appendix References

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

Variables used in calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path *(k_{psc})*	cm/hr	0.0043
Permeation coefficient of the protein fraction of the stratum corneum *(k_{pol})*	cm/hr	1.5178×10^{-5}
Permeation coefficient of the watery epidermal layer *(k_{aq})*	cm/hr	0.2498
Molecular weight *(MW)*[*]	amu	100.16
Base-10 logarithm of its octanol–water partition coefficient *(Log K_{ow})*[*]	None	1.23
Calculated skin permeation coefficient *(k_p)*	cm/hr	0.00427
Skin dose		
Water solubility *(S_w)*[*]	mg/cm^3	42
Calculated skin permeation coefficient *(k_p)*	cm/hr	0.00427
Estimated skin surface area (palms of hands)[§]	cm^2	360
Exposure time	hr	8
Calculated skin dose	mg	516.21
Inhalation dose		
Occupational exposure limit (OEL)[†]	mg/m^3	200
Inhalation volume	m^3	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	1500
Skin dose–to–inhalation dose (SI) ratio	**None**	**0.3441**

[*]Variables identified from NLM [ND].
[†]The OEL used in calculation of the SI ratio for cyclohexanol was the NIOSH recommended exposure limit (REL) [NIOSH 2005].
[§]Hayes WA [2008]. Principles and methods of toxicology. 5th ed. New York: Informa Healthcare USA.

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DHHS (NIOSH) Publication No. 2021-101
DOI: https://doi.org/10.26616/NIOSHPUB2021101