NIOSH Skin Notation Profile

Cyclonite

SK

ID^{SK}

[~~SK~~]

SYS

SYS (FATAL)

DIR

DIR (IRR)

DIR (COR)

SEN

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NIOSH Skin Notation Profile

Cyclonite

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Centers for Disease Control and Prevention
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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 cyclonite. 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
cm²	square centimeter(s)
cm/hr	centimeter(s) per hour
CNS	central nervous system
COR	subnotation of SK: COR indicating the potential for a chemical to be corrosive to the skin following exposure
DIR	skin notation indicating the potential for direct effects to the skin following contact with a chemical
DMSO	Dimethyl sulfoxide
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	molarity
m³	cubic meter(s)
mg	milligram(s)
mg/cm³	milligram(s) per cubic centimeter
mg/kg	milligram(s) per kilogram body weight
mg/min	milligram(s) per minute
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
µg/cm²	micrograms per square centimeter
µL	microliter

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

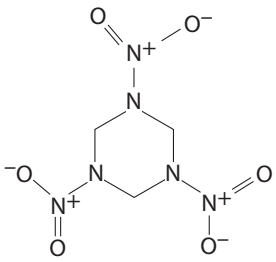
Chemical: Cyclonite

CAS No: 121-82-4

Molecular weight (*MW*): 222.2

Molecular formula: $C_3H_6N_6O_6$

Structural formula:



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Synonyms: Cyclotrimethylene-trinitramine; Hexogen; Hexahydro-1,3,5-trinitro-1,3,5-triazine; RDX; 1,3,5-Trinitro-1,3,5-triazacyclohexane.

Uses: Cyclonite is used primarily as a component of highly explosive materials and as a rodenticide [ATSDR 1995]. It is a white powder of melting point 205.5°C [National Center for Biotechnology Information 2020]. An estimated 16 million pounds (7.3 million kilograms) of cyclonite were produced in 1984.

1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with cyclonite and (2) the rationale behind the hazard-specific skin notation (SK) assignment for cyclonite. 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 cyclonite. A search of all available relevant literature was conducted through January 2018 to identify information on cyclonite 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 cyclonite. 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

Cyclonite is potentially capable of causing adverse effects following skin contact. A critical review of available data has resulted in the following SK assignment for cyclonite: **SK: DIR(IRR)**.

Table 1. Summary of the SK assignment for cyclonite

Skin notation	Critical effect	Available data
SK: DIR(IRR)	Skin irritation	Limited animal data

Table 1 provides an overview of the critical effects and data used to develop the SK assignment for cyclonite.

2 Systemic Toxicity from Skin Exposure (SK: SYS)

In vitro studies were identified in which percutaneous absorption of cyclonite was determined from acetone or soil. Reifenrath et al. [2002] applied approximately 10 micrograms per square centimeter (μg/cm^2) of 14C-radiolabeled cyclonite in 5 microliters (μL) of acetone or in 10 milligrams per square centimeter (mg/cm^2) of soil to excised pigskin for 24 hours. Percutaneous absorptions of 1.8%, 1.2%, and 8% of the applied dose were reported for the high-carbon soil, low-carbon soil, and acetone, respectively. Reddy et al. [2008] measured dermal absorption in acetone (10 μL) or in soils (10 mg) using excised human skin in Teflon flow-through diffusion cells. Cyclonite was applied to the epidermal surface and was allowed to transverse the skin and dissolved in a reservoir of receptor fluid that maintained contact with the dermal surface. Reddy et al. [2008] reported that only 2.5 ± 1.8% of cyclonite in acetone was recovered in receptor fluid and 2.6 ± 1.1% and 1.4 ± 0.41% from high and low carbon soil, respectively. The potential of cyclonite 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. The evaluation method compares an estimated chemical dose accumulated in the body from skin absorption to an estimated dose from respiratory absorption associated with a reference occupational exposure limit (OEL). Based on this algorithm, the ratio of skin dose to inhalation dose (the SI ratio) of 0.002 was estimated. An SI ratio of ≥0.1 indicates that skin absorption may significantly contribute to the overall body burden of a substance [NIOSH 2009]; therefore, cyclonite is not 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.

No estimate of the human dermal lethal dose (LD_{Lo}) was identified for cyclonite. The dermal LD_{50} (the dose resulting in 50% mortality in the exposed animals) for guinea pigs was above 2000 mg/kg [McNamara et al. 1974]. MacNamara et al. [1974] reported no death in guinea pigs following a single dermal exposure to 316 to 2000 milligrams per kilogram body weight (mg/kg); 2000 mg/kg is the critical dermal LD_{50} value that identifies chemical substances with the potential for acute dermal toxicity [NIOSH 2009].

No animal chronic or subchronic toxicity studies were identified that reported adverse systemic effects following dermal exposure to cyclonite. However, a repeated-dose toxicity study was identified in rabbits and beagles [McNamara et al. 1974]. In rabbits, 0.1 or 1.0 milliliter (mL) of 33% RDX (cyclonite) in dimethyl sulfoxide (DMSO) [corresponding to 16.5 and 165 milligrams per kilogram body weight per day (mg/kg-day) of cyclonite, respectively], 7.5% cyclonite in cyclohexanone (3.75 and 37.5 mg/kg-day of cyclonite, respectively), or 5.4% cyclonite in acetone (2.7 and 27 mg/kg-day of cyclonite) was applied to the shaved skin under a polyethylene sleeve, 5 days/week for 4 weeks [McNamara et al. 1974]. Control animals received applications of 0.1 or 1.0 mL of the solvents alone [McNamara et al. 1974]. Two rabbits from each dose group and one control rabbit from each solvent group were sacrificed for pathological examination at 7 days (2 days after the 5th dose), 14 days (2 days after the 10th dose), and 28 days (2 days after the 20th dose). Signs of posterior leg weakness or posterior leg paralysis (possibly attributed to broken backs) were observed in three animals [McNamara et al. 1974]. No gross defects, lesions, microscopic abnormalities in organs, or changes in blood component values were noted in rabbits that died or were killed following repeated topical applications of cyclonite either in the three solvent groups or the solvents alone [McNamara et al. 1974]. For dogs, topical application of 480 mg/kg for 3 consecutive days to the clipped back did not produce consistent noticeable changes in physiological parameters [electroencephalograph (EEG), respiratory and heart

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

Organization	Carcinogenic designation
NIOSH [2005]	No designation
NTP [2014]	No designation
US EPA [2018]	Suggestive evidence of carcinogenic potential
ECHA [2020]	No GHS designation
IARC [2012]	No designation
ACGIH® [2001]	A4: Not classifiable as a human carcinogen

ACGIH® = American Conference of Governmental Industrial Hygienists; ECHA = European Chemicals Agency; 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.

rates, electrocardiograph (EKG), and gross hyperreflexia (overactive or over-responsive reflexes)] [McNamara et al. 1974]. Neither a No Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect Level (LOAEL) could be identified. McNamara et al. [1974] indicated that cyclonite was not dermally absorbed in rabbits, guinea pigs, or dogs, as evidenced by lack of systemic effects in guinea pigs, unchanged blood component values in rabbits, and lack of physiological responses in dogs following a single or repeated topical exposure.

No epidemiological studies were identified that evaluated the potential for cyclonite to cause systemic effects following dermal exposure. However, Kaplan et al. [1965] reported five cases of illness in workers handling RDX (i.e., cyclonite) in its finely powdered form in an explosives plant. The workers were reported to be exposed via inhalation, ingestion, and dermal routes, but the relative contribution by each route was unknown. Exposure to cyclonite resulted in loss of consciousness with, without, or followed by convulsions, and in some cases, stupor, nausea and vomiting, dizziness, and weakness, were also reported [Kaplan et al. 1965]. These results indicate the potential for cyclonite to cause central nervous system (CNS) effects; however, the dermal contribution is unknown.

No standard toxicity or specialty studies evaluating biological system function–specific effects (including reproductive and developmental effects and immunotoxicity) following dermal exposure to cyclonite were identified. No epidemiological studies or animal bioassays were identified that evaluated the potential for cyclonite to be carcinogenic following dermal exposure. Table 2 summarizes the carcinogenic designations for cyclonite from governmental and non-governmental organizations.

No *in vivo* toxicokinetic data were identified that estimated the degree of absorption of cyclonite through human or animal skin following dermal exposure. *In vitro* toxicokinetic data identified from animals [Reifenrath et al. 2002; Reddy et al. 2008], with support from a model prediction, indicate that cyclonite has a limited potential for skin absorption (absorption of less than 10% of the applied dose) whether applied in acetone or in soil. Five case reports identified health effects such as stupor, nausea and vomiting, dizziness, and weakness in workers exposed to powdered cyclonite [Kaplan et al. 1965]; however, the route of exposure is unknown and could have occurred via inhalation and ingestion in addition to the dermal route. Acute toxicity studies indicated that the LD_{50} for cyclonite was greater than

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

2000 mg/kg for guinea pigs [McNamara et al. 1974], which is above the critical value that identifies chemicals with the potential for acute dermal toxicity. Single- and repeat-dose toxicity studies in rabbits and dogs found no gross or microscopic abnormalities [McNamara et al. 1974]. Based on the acute toxicity data, this assessment does not assign an SK: SYS notation for cyclonite.

3 Direct Effects on Skin (SK: DIR)

No human or animal *in vivo* studies on corrosivity of cyclonite or *in vitro* tests for corrosivity using human or animal skin models or in vitro tests of skin integrity using cadaver skin were identified. No occupational exposure studies were identified that evaluated the potential of cyclonite to cause skin irritation. In a study that tested the irritant action of cyclonite on human skin, von Oettingen et al. [1949] reported no signs of irritation when 1 square centimeter (cm^2) of the forearm of a man was covered with an unspecified amount of dry cyclonite under cellophane and adhesive tape for 48 hours.

McNamara et al. [1974] conducted a study where cyclonite was topically applied at a single dose or at multiple doses (5 days/week for 4 weeks) of 33% [weight/volume, (w/v)] cyclonite dissolved in DMSO (165 mg/kg-day), 7.5% cyclonite in cyclohexanone (37.5 mg/kg-day), or 5.4% of cyclonite in acetone (27 mg/kg-day) to the skin of rabbits under a polyethylene sleeve for 24 h/day [McNamara et al. 1974]. Microscopic examination of the dosed area of animals after exposure revealed that cyclonite, in all three solvents, caused dermatitis that persisted for as long as 30 days, with 33% cyclonite in DMSO causing the most pronounced effect. McNamara et al. [1974] also reported that application of 316 to 2,000 mg/kg cyclonite (33% w/v) in DMSO to the clipped skin of guinea pigs produced no skin irritation at 316 to 510 mg/kg, but slight erythema was observed at higher doses of 1,000 mg/kg and 2,000 mg/kg. In dogs, repeated applications of cyclonite in DMSO caused slight erythema and desquamation during the second and third week of application of DMSO alone or in combination with cyclonite.

One study involving humans indicated that dry cyclonite was not a skin irritant [von Oettingen et al. 1949]. However, in animals, evidence from single and repeat-dose studies using different solvents indicate that cyclonite is irritating to the skin following repeated exposures in rabbits and at doses of 1000 mg/kg or greater in guinea pigs [**McNamara et al. 1974**]. Therefore, based on the data, this assessment assigns an SK: DIR (IRR) notation for cyclonite.

4 Immune-mediated Responses (SK: SEN)

No occupational exposure studies or diagnostic (human patch) tests were identified that investigated the skin sensitization potential of cyclonite. The sensitization potential of cyclonite in DMSO, acetone, or cyclohexanone has been investigated in guinea pigs. McNamara et al. [1974] applied intradermal

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

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption
OSHA [2018]	[skin]: Potential for dermal absorption
ACGIH® [2001]	[skin]: Based on a report that skin absorption was a possible route of entry that led to CNS effects in cyclonite-exposed munitions workers

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

injection/topical application, intradermal/intradermal injections, topical/topical applications or topical application/intradermal injection of cyclonite for sensitization and challenge. In the sensitization phase, animals were topically or intradermally exposed to 0.5 mL of 33% cyclonite in pure or technical grade DMSO, 7.5% in cyclohexanone, or 5.4% in acetone, 3 times a week for 3 weeks, followed by 2 weeks of rest [McNamara et al. 1974]. The guinea pigs were then challenged topically or intradermally with a predetermined maximum sub-effective level of cyclonite [1:1 (volume/volume)] solvent-saline mixtures (intradermal) and polyethylene glycol (topical) [McNamara et al. 1974]. No evidence of skin sensitization was reported [McNamara et al 1974].

No diagnostic (human patch) tests were identified that evaluated the potential of cyclonite to cause skin sensitization. A skin sensitization study in guinea pigs [McNamara et al. 1974] found no evidence of the potential of cyclonite to cause skin sensitization. Therefore, the SK: SEN notation is not assigned to cyclonite.

5 Summary

No *in vivo* toxicokinetic data were identified that estimated the degree of absorption of cyclonite through human or animal skin following dermal exposure. *In vitro* toxicokinetic data identified from animals [Reifenrath et al. 2002; Reddy et al. 2008], with support from a model prediction, indicate that cyclonite has a limited potential for skin absorption (absorption of less than 10% of the applied dose) whether applied in acetone or in soil. Five case reports identified CNS effects in workers exposed to powdered cyclonite [Kaplan et al. 1965]; however, the route of exposure is unknown and could have occurred via inhalation and ingestion in addition to the dermal route of exposure. Acute toxicity studies indicated that the LD_{50} for cyclonite was greater than 2000 mg/kg for guinea pigs [McNamara et al. 1974], and single and repeat-dose toxicity studies in rabbits and dogs found no gross or microscopic abnormalities [McNamara et al. 1974]. One study involving humans indicated that dry cyclonite was not a skin irritant [von Oettingen et al. 1949]. However, in animals, evidence from single and repeat-dose studies using different solvents indicate that cyclonite is irritating to the skin following repeated exposures in rabbits and at doses of 1000 mg/kg or greater in guinea pigs [**McNamara et al. 1974**]. No diagnostic (human patch) tests were identified that evaluated the potential of cyclonite to cause skin sensitization. A skin sensitization study in guinea pigs [McNamara et al. 1974] found no evidence of the potential of cyclonite to cause skin sensitization. Based on the available data, this assessment assigns a composite skin notation of SK: DIR(IRR) for cyclonite.

Table 3 summarizes the skin hazard designations for cyclonite previously issued by NIOSH and other organizations. There were no equivalent dermal designations for cyclonite, according to the Globally Harmonized System (GHS) of Classification and Labelling of Chemicals [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 Cyclonite

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for cyclonite. 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 cyclonite. The calculated SI ratio was 0.002. On the basis of these results, cyclonite is predicted not to represent a skin absorption hazard.

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

Variables used in calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path *(k_{psc})*	cm/hr	0.000349
Permeation coefficient of the protein fraction of the stratum corneum *(k_{pol})*	cm/hr	1.01921×10^{-5}
Permeation coefficient of the watery epidermal layer *(k_{aq})*	cm/hr	0.167744
Molecular weight *(MW)*	amu	222.12
Base-10 logarithm of its octanol–water partition coefficient *(Log K_{ow})*[*]	None	0.87
Calculated skin permeation coefficient *(k_p)*	cm/hr	0.000358276
Skin dose		
Water solubility *(S_w)*[*]	mg/cm^3	0.03008
Calculated skin permeation coefficient *(k_p)*	cm/hr	0.000358276
Estimated skin surface area (palms of hands)[§]	cm^2	360
Exposure time	hr	8
Calculated skin dose	mg	0.902752639
Inhalation dose		
Occupational exposure limit (OEL)[†]	mg/m^3	1.5
Inhalation volume	m^3	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	11.25
Skin dose–to–inhalation dose (SI) ratio	**None**	**0.002758898**

[*]Variables identified from NLM [ND].
[†]The OEL used in calculation of the SI ratio for cyclonite 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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