# NIOSH Skin Notation Profile

## Cyclohexanone

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

## Cyclohexanone

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

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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 cyclohexanone. 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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# Contents

# Abbreviations

| | |
|---|---|
| **ACGIH®** | American Conference of Governmental Industrial Hygienists |
| **AMU** | atomic mass unit |
| **ATSDR** | Agency for Toxic Substances and Disease Registry |
| **CIB** | Current Intelligence Bulletin |
| **$cm^2$** | square centimeter(s) |
| **cm/hr** | centimeter(s) per hour |
| **cm/s** | centimeter(s) per second |
| **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 |
| **g** | gram(s) |
| **g/L** | gram(s)/liter |
| **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 |
| **IPCS** | International Program for Chemical Safety |
| **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 |
| **LLNA** | local lymph node assay |
| **LOAEL** | lowest-observed-adverse-effect level |
| **log $K_{OW}$** | base-10 logarithm of a substance's octanol–water partition |
| **M** | molarity |
| **$m^3$** | cubic meter(s) |
| **MEST** | mouse ear swelling test |
| **mg** | milligram(s) |
| **$mg/cm^2/hr$** | milligram(s) per square centimeter per hour |
| **mg/kg** | milligram(s) per kilogram body weight |

| | |
|---|---|
| **mg/m³** | milligram(s) per cubic meter |
| **mL** | milliliter(s) |
| **mL/kg** | milliliter(s) per kilogram body weight |
| **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 |
| **ppm** | parts per million |
| **PVC** | polyvinyl chloride |
| **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 |
| **µg** | microgram(s) |
| **µg/cm²** | microgram(s) per square centimeter |
| **µg/cm²/hr** | microgram(s) per square centimeter per hour |
| **µL** | microliter(s) |
| **µmol** | micromole(s) |
| **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.

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# 1 Introduction

## 1.1 General Substance Information

**Chemical:** Cyclohexanone

**CAS No:** 108-94-1

**Molecular weight (*MW*):** 98.2

**Molecular formula:** $C_6H_{10}O$

**Structural formula:**

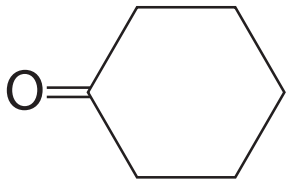

Image: National Center for Biotechnology Information [2020]

**Synonyms:** Anone; Cyclohexyl ketone; Pimelic ketone.

**Uses:** Cyclohexanone is an organic compound used as a solvent in multiple applications including metal degreasing; an estimated 1.1 billion pounds (500 million kilograms) of the compound was used in 1994 [Bingham et al. 2001].

## 1.2 Purpose

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

Cyclohexanone is potentially capable of causing numerous adverse health effects following skin contact. A critical review of available data has

**Table 1. Summary of the SK assignment for cyclohexanone**

| Skin notation | Critical effect | Available data |
|---|---|---|
| SK: DIR (COR) | Skin irritation | Sufficient animal data |

resulted in the following SK assignment for cyclohexanone: SK: DIR (COR). Table 1 provides an overview of the critical effects and data used to develop the SK assignment for cyclohexanone.

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

Limited toxicokinetic data following dermal exposure to cyclohexanone were identified. Mraz et al. [1994] assessed the percutaneous absorption of cyclohexanone in an experiment in which three human volunteers immersed one hand in pure solvent for 30 minutes. These authors calculated the permeation rate of cyclohexanone through the skin to be 0.037 to 0.069 (mean, 0.056) milligrams per square centimeter per hour (mg/cm$^2$/hr) [Mraz et al. 1994]. Dennerlein et al. [2013] reported a mean penetration rate of 257.2-375.6 micrograms per square centimeter per hour (µg/cm$^2$/hr) (corresponding to 0.26-0.38 mg/cm$^2$/hr) in excised abdominal human skin in exposure chambers treated with 50 microliters (µl) cyclohexanone for 4 hours. The potential of cyclohexanone 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, a ratio of the skin dose to the inhalation dose (SI ratio) of 0.24 was calculated for cyclohexanone. An SI ratio of ≥0.1 indicates that skin absorption may significantly contribute to the overall body burden of a substance [NIOSH 2009]; therefore, cyclohexanone is considered to be absorbed through the skin following dermal exposure. Additional information on the SI ratio and the variables used in its calculation are included in the appendix.

No estimated dermal lethal dose ($LD_{Lo}$) for humans was identified. A dermal $LD_{50}$ value (lethal doses in 50% of exposed animals) of 1 milliliter per kilogram [mL/kg] (corresponding to 950 milligrams per kilogram [mg/kg]) has been reported in rabbits [Smyth et al. 1969; Union Carbide Corporation 1967]. Eastman Kodak Company [1978] and EI du Pont de Nemours and Company (DuPont) [1983a] reported dermal $LD_{50}$ values of 10 to 20 mL/kg (corresponding to 9,500 to 19,000 mg/kg) in rabbits and guinea pigs. Because the reported acute dermal $LD_{50}$ values for rabbits were conflicting and the $LD_{50}$ value in guinea pigs was higher than the critical dermal $LD_{50}$ value of 2,000 mg/kg body weight that identifies chemical substances with the potential for acute toxicity [NIOSH 2009], cyclohexanone is not considered acutely toxic following dermal exposure.

No epidemiological studies or human case reports were identified that evaluated the potential of cyclohexanone to cause systemic effects following dermal exposure. No chronic dermal toxicity studies for cyclohexanone were identified in animals.

Repeat-dose studies have been conducted in guinea pigs and rats [Industrial Health Foundation, Inc. 1983; Rengstorff et al. 1972] that indicate dermal exposure to cyclohexanone may lead to formation of cataracts and lens vacuoles in the eye. Rengstorff et al. [1972] reported formation of cataracts/lens vacuoles in the eyes of guinea pigs when dermally exposed to cyclohexanone 3 times a week for 3 weeks. The guinea pigs were examined every 30 days for 6 months [Rengstorff et al. 1972]. Union Health Foundation, Inc. [1983] exposed guinea pigs to 0.5 mL of vehicle (saline) control, a 2% solution of cyclohexanone in saline (volume/volume), neat liquid cyclohexanone, or neat dimethyl sulfoxide (DMSO) (as positive control) to the shaven backs three times a week for 3 weeks (corresponding to 0, 17.4, or 872 mg cyclohexonone/kg-day in males, and 0, 19.16, or 971 mg cyclohexonone/kg-day in females, based on the individual body weights provided). All of the animals and positive controls were observed for 6 months. Clinical observations and mortality checks were conducted twice daily during the treated and untreated phases of the study, body weights were measured weekly on all animals, and ophthalmoscopic examinations were conducted monthly on all animals throughout the study [Industrial Health Foundation, Inc. 1983]. Only the eyes were processed for

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

| Organization | Carcinogenic designation |
|---|---|
| NIOSH [2005] | No designation |
| NTP [2014] | No designation |
| US EPA [2014] | No designation |
| European Parliament [2008] | No GHS designation |
| IARC [2012] | Category 3: Not classifiable as to its carcinogenicity in humans |
| ACGIH® [2003] | A3: Confirmed animal carcinogen with unknown relevance to humans |

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.

histopathological evaluation. Industrial Health Foundation, Inc. [1983] reported that dermal exposure to cyclohexanone did not affect body weights or hematology parameters but caused ophthalmoscopic changes (vacuoles, which varied from subtle to marked involvement of the lens) as well as histopathologic changes (formation of vacuoles in the cells of the lens) in all treated groups, including the saline controls. From these findings, the Industrial Health Foundation, Inc. [1983] concluded that the vacuolar changes were spontaneous in guinea pigs and that they were not related to dermal exposure to (neat) cyclohexanone or the positive control material, DMSO. A limited number of systemic endpoints evaluated in these studies preclude determination of the potential of cyclohexanone to affect systemic toxicity following dermal exposure.

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 cyclohexanone.

No studies were identified that evaluated the potential of cyclohexanone to be a carcinogen following exposure by the dermal route. Table 2 summarizes the carcinogenic designation of governmental and nongovernmental organizations.

The mathematical model predicted that cyclohexanone is considered to be absorbed through the skin following dermal exposure. However, acute toxicity studies in rabbits and guinea pigs [Union Carbide Corporation 1967; Smyth et al. 1969; Eastman Kodak Company 1978; EI du Pont de Nemours and Company (DuPont) 1983a] indicate that cyclohexanone is not acutely toxic. While no epidemiological studies, human case reports, or animal chronic dermal toxicity studies were identified, repeat-dose studies [Rengstorff et al. 1972; Industrial Health Foundation, Inc. 1983] evaluated limited systemic endpoints and ophthalmologic and histopathologic changes in the eye, and these studies indicated no treatment-related systemic effects or other effects on the eye. Based on the limited information available in this assessment, a skin notation of SK: SYS is not assigned for cyclohexanone.

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

No human or animal in vivo studies on corrosivity or in vitro tests for corrosivity using human or animal skin models or in vitro tests of skin integrity using cadaver skin were identified. Gupta et al. [1979] reported

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

concentration-dependent irritation in occlusive conditions in rabbits, in which 12.4% to 99% of cyclohexanone in cottonseed oil was applied to the skin. Concentrations of 99% cyclohexanone were severely irritating, 49.5% was moderately irritating, 24.5% was mildly irritating, and 12.4% was very slightly/questionably irritating [Gupta et al. 1979]. Union Carbide [1982] applied two samples of 0.5 mL (471 mg) cyclohexanone under a 1.0 to 1.5 square inch ($in^2$) patch to the clipped skin of rabbits for 4 hours and observed for 72 hours post-application. The first sample caused necrosis in 5 of 6 rabbits, moderate erythema in 2 rabbits, and minor to moderate edema in 4 rabbits [Union Carbide 1982]. However, the second sample of cyclohexanone produced minor to moderate erythema in 3 rabbits and minor edema in 1 rabbit [Union Carbide 1982]. Eastman Kodak Company [1978] reported that cyclohexanone was moderately irritating to the skin of guinea pigs, but details of the study were not available for evaluation. In the repeat-dose dermal toxicity studies in which guinea pigs were exposed to 0.5 mL of neat cyclohexanone three times per week for 3 weeks, the Industrial Health Foundation Inc. [1983] reported skin irritation at the application site when guinea pigs and rats received 2% cyclohexanone or neat cyclohexanone for 3-13 weeks. The structure activity relationship model, DEREK®, predicted cyclohexanone to be negative for skin irritation.

Irritation tests in rabbits and guinea pigs [**Gupta et al. 1979; Union Carbide 1982; Industrial Health Foundation Inc. 1983; Eastman Kodak Company 1978**] indicate that high concentrations of cyclohexanone or repeated dermal exposures are mildly to severely irritating to the skin, with the potential to cause necrosis. Therefore, this assessment assigns a skin notation of SK: DIR (COR) for cyclohexanone.

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

The potential of cyclohexanone to cause skin sensitization has been evaluated in a number of studies. In humans, a diagnostic patch test by Pazzaglia et al. [2003] revealed that concentrations as low as 1% cyclohexanone elicited irritation in a woman with frequent occupational interaction with neat cyclohexanone in a factory making polyvinyl chloride (PVC) fluid therapy bags. Sanmartin and de la Cuadra [1992] reported a case in which a woman manufacturing PVC fluidotherapy bags presented with pruriginous allergic contact dermatitis (a chronic, inflammatory skin disease characterized by pale-red papules and intense itching). Patch testing with 1% cyclohexanone resin in petrolatum was negative, but 10% aqueous cyclohexanone produced a slight erythamatous reaction, which was confined to the patch test application zone after 2 days, indicating the potential to cause skin irritation and not skin sensitization [Sanmartin and de la Cuadra 1992]. Bruze et al. [1988] reported five cases of allergic contact dermatitis in individuals handling various paints, and patch testing revealed the individuals were allergic to cyclohexanone resin present in the paints.

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

| Organization | Skin hazard designation |
|---|---|
| NIOSH [2005] | [skin]: based on the potential for dermal absorption |
| OSHA [2018]* | No designation |
| ACGIH® [2003] | [skin]: based on the dermal $LD_{50}$ data |

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

Allergic responses were observed at doses as low as 0.001% (weight/volume, or w/v), and negative results were noted in 20 control patients who were tested with the cyclohexanone resin in petrolatum at 1% w/v [Bruze et al. 1988]. However, when Bruze et al. [1988] conducted Guinea Pig Maximization Tests (GPMTs), following identification of people with contact allergies to cyclohexanone resin, none of the guinea pigs had a positive response to cyclohexanone alone. These results indicate that the sensitizers responsible for the contact allergy to cyclohexanone resin may be the monomers and dimers formed when cyclohexanone is condensed in the production of the resin [Bruze et al. 1988]. Gad et al. [1986] evaluated the potential of cyclohexanone to cause delayed-type hypersensitivity by the dermal route in humans (details of the test not reported) and conducted the Mouse Ear Swelling Test (MEST) and GPMT, but no evidence of skin sensitization was found. In the MEST, induction and challenge with 100% cyclohexanone produced no sensitization in the animals, but a swelling of 102% suggested that the test material was irritating [Gad et al. 1986]. The structure activity relationship model, DEREK®, predicted cyclohexanone to be negative for skin sensitization.

The available data indicate that cyclohexanone resin formulation may cause allergic contact dermatitis in humans [Bruze et al. 1988; Pazzaglia et al. 2003]; however, results from predictive tests in animals (GPMTs and MESTs) indicated that cyclohexanone alone is not a skin sensitizer [Gad et al. 1986; Bruze et al. 1988]. On the basis of the available data, a skin notation of SK: SEN is not assigned for cyclohexanone.

# 5 Summary

The mathematical model predicted that cyclohexanone is considered to be absorbed through the skin following dermal exposure. However, acute toxicity studies in rabbits and guinea pigs [Union Carbide Corporation 1967; Smyth et al. 1969; Eastman Kodak Company 1978; EI du Pont de Nemours and Company (DuPont) 1983a] indicate that cyclohexanone is not acutely toxic. While no epidemiological studies, human case reports, or animal chronic dermal toxicity studies were identified, repeat-dose studies [Rengstorff et al. 1972; Industrial Health Foundation, Inc. 1983] evaluated limited systemic endpoints and ophthalmologic and histopathologic changes in the eye, and these studies indicated no treatment-related systemic effects or other effects on the eye. Irritation tests in rabbits and guinea pigs **[Gupta et al. 1979; Union Carbide 1982; Industrial Health Foundation Inc. 1983; Eastman Kodak Company 1978]** indicate that high concentrations of cyclohexanone or repeated dermal exposures are mildly to severely irritating to the skin with the potential to cause necrosis. The available data indicate that cyclohexanone resin may cause allergic contact dermatitis in humans [Bruze et al. 1988; Pazzaglia et al. 2003]; however, results from predictive tests in animals (GPMTs and MESTs) indicated that cyclohexanone itself is not a skin sensitizer [Gad et al. 1986; Bruze et al. 1988]. Based on the available information, this assessment assigns a composite skin notation of SK: DIR (COR) for cyclohexanone.

Table 3 summarizes the skin hazard designations for cyclohexanone issued by NIOSH and other organizations. There were no equivalent dermal designations for cyclohexanone according to the Globally Harmonized System (GHS) of classification and labeling 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 Cyclohexanone

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for cyclohexanone. 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 cyclohexanone. The calculated SI ratio was 0.24. On the basis of these results, cyclohexanone is predicted to represent a skin absorption hazard.

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

| Variables used in calculation | Units | Value |
|---|---|---|
| **Skin permeation coefficient** | | |
| Permeation coefficient of stratum corneum lipid path *($k_{psc}$)* | cm/hr | 0.0025 |
| Permeation coefficient of the protein fraction of the stratum corneum *($k_{pol}$)* | cm/hr | $1.5329 \times 10^{-5}$ |
| Permeation coefficient of the watery epidermal layer *($k_{aq}$)* | cm/hr | 0.2523 |
| Molecular weight *(MW)*[†] | amu | 98.2 |
| Base-10 logarithm of its octanol–water partition coefficient *(Log $K_{ow}$)*[*] | None | 0.81 |
| Calculated skin permeation coefficient *($k_p$)* | cm/hr | 0.00249 |
| **Skin dose** | | |
| Water solubility *($S_w$)*[*] | mg/cm$^3$ | 25 |
| Calculated skin permeation coefficient *($k_p$)* | cm/hr | 0.00249 |
| Estimated skin surface area (palms of hands)[§] | cm$^2$ | 360 |
| Exposure time | hr | 8 |
| Calculated skin dose | mg | 179.3418 |
| **Inhalation dose** | | |
| Occupational exposure limit (OEL)[δ] | mg/m$^3$ | 100 |
| Inhalation volume | m$^3$ | 10 |
| Retention factor (RF) | None | 0.75 |
| Inhalation dose | mg | 750 |
| **Skin dose–to–inhalation dose (SI) ratio** | **None** | **0.2391** |

[*]Variables identified from NLM [ND].
[†]Variables identified from the NPG [2005].
[δ]The OEL used in calculation of the SI ratio for cyclohexanone 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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