NIOSH Skin Notation Profiles

Morpholine

SK

ID^{SK}

[~~SK~~]

SYS

SYS (FATAL)

DIR

DIR (IRR)

DIR (COR)

SEN

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

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NIOSH Skin Notation (SK) Profile

Morpholine

[CAS No. 110-91-8]

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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 morpholine. 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
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
DEREK	Deductive Estimation of Risk from Existing Knowledge
DIR	skin notation indicating the potential for direct effects to the skin following contact with a chemical
EC	European Commission
g	gram(s)
g/L	gram(s)/liter
GHS	Globally Harmonized System for Classification and Labelling of Chemicals
GPMT	guinea pig maximization test
hr	hour(s)
IARC	International Agency for Research on Cancer
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
LSE	living skin equivalent
M	molarity
m^3	cubic meter(s)
mg	milligram(s)
mg/cm^2/hr	milligram(s) per square centimeter per hour
mg/kg	milligram(s) per kilogram body weight
mg/m^3	milligram(s) per cubic meter
mL	milliliter(s)
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
REL	recommended exposure limit
RF	retention factor
SEN	skin notation indicating the potential for immune-mediated reactions following exposure of the skin
SI ratio	ratio of skin dose to inhalation dose
SK	skin notation
S_W	solubility 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)

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:

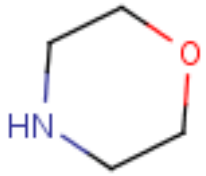
Chemical: Morpholine

CAS No: 110-91-8

Molecular weight (*MW*)**:** 87.1

Molecular formula: C_4H_9ON

Structural formula:



Synonyms: Diethylene imidoxide; Diethylene oximide; Tetrahydro-1,4-oxazine; Tetrahydro-p-oxazine

Uses: Morpholine is used primarily as a rubber accelerator, boiler water additive, and solvent. An estimated 44 million pounds of the chemical was used in 1992 [HSDB 2014]. Morpholine is also used as a solvent for resins, waxes, casein, and dyes; as an optical brightener for detergents; as a corrosion inhibitor; for the preservation of book paper; and as an organic intermediate (catalysts, antioxidants, pharmaceuticals, bactericides, etc.) [HSDB 2014].

1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with morpholine and (2) the rationale behind the hazard-specific skin notation (SK) assignment for morpholine. 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 morpholine. A literature search was conducted through May 2016 to identify information on morpholine, including but not limited to data relating to its toxicokinetics, acute toxicity, repeated-dose systemic toxicity, carcinogenicity, biological system/function–specific effects (including reproductive and developmental effects and immunotoxicity), irritation, and sensitization. Information was considered from studies of humans, animals, or appropriate modeling systems that are relevant to assessing the effects of dermal exposure to morpholine. 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

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

2 Systemic Toxicity from Skin Exposure (SK: SYS)

No data on toxicokinetic effects following dermal exposure to morpholine were identified. The potential of morpholine to pose a skin absorption hazard was also evaluated, with use of a predictive algorithm for estimating

Table 1. Summary of the SK assignment for morpholine

Skin notation	Critical effect	Available data
SK: SYS	Liver, kidney, spleen	Sufficient animal data
SK: DIR (COR)	Skin corrosivity	Sufficient animal data

and evaluating the health hazards of dermal exposure to substances [NIOSH 2009]. The evaluation method compares an estimated dose accumulated in the body from skin absorption and an estimated dose from respiratory absorption associated with a reference occupational exposure limit. On the basis of this algorithm, a ratio of the skin dose to the inhalation dose (SI ratio) of 1.76 was calculated for morpholine. An SI ratio of ≥0.1 indicates that skin absorption may significantly contribute to the overall body burden of a substance [NIOSH 2009]; therefore, morpholine has the potential to be absorbed through the skin and to become available systemically following dermal exposure. Additional information on the SI ratio and the variables used in its calculation are included in the appendix.

No human dermal lethal dose (LD_{Lo}) estimates were identified. A minimum lethal dose in guinea pigs of 0.9 grams per kilogram body weight (g/kg; 900 milligrams per kilogram body weight [mg/kg]) was reported [Shea 1939]. The reported dermal LD_{50} value (the dose resulting in 50% mortality in the exposed animals) was 0.5 milliliters per kilogram (mL/kg; corresponding to 503.5 mg/kg) in the rabbit [Smyth et al. 1954]. Because the reported acute dermal LD_{50} value for rats and the minimum lethal dose for guinea pigs were lower than the critical dermal LD_{50} value of 2,000 mg/kg that identifies chemical substances with the potential for acute toxicity [NIOSH 2009], morpholine is considered acutely toxic following dermal exposure.

No epidemiological studies or human case reports or repeated-dose, subchronic, or chronic dermal toxicity studies in animals were identified. However, Shea [1939] reported a dermal toxicity study in rabbits exposed to diluted (aqueous) morpholine and guinea pigs exposed to undiluted morpholine at a dosage of 900 mg/kg-day for up to 2 weeks. In that study, all animals died before the eleventh dose (rabbits) or thirteenth dose (guinea pigs) dose. In rabbits, morpholine caused necrosis of the liver with congestion and cloudy swelling, an abnormal amount of secretion into kidney tubules, and congestion of the spleen [Shea 1939]. In guinea pigs, morpholine caused small hemorrhagic areas on the liver and necrosis of kidney tubules [Shea [1939]. Although no prolonged dermal exposure studies were identified, the Shea [1939] study suggests the potential for effects at doses lower than the critical dermal No-Observed-Adverse-Effect-Level (NOAEL) value of 1000 mg/kg for repeat-dose toxicity that identifies chemical substances with the potential for repeated-dose dermal toxicity [NIOSH 2009]. Therefore, morpholine is considered to be systemically toxic, causing liver, kidney, and spleen effects, following repeated 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 morpholine. No studies were identified that evaluated the potential of morpholine to be a carcinogen in humans or animals following dermal exposure. Table 2 summarizes carcinogenic designations of multiple governmental and nongovernmental organizations for morpholine.

Although no toxicokinetic data were identified to evaluate the potential of morpholine to be absorbed through the skin, data from an acute dermal toxicity study in rabbits **[Smyth et al. 1954]** and from a short-term dermal toxicity study in guinea pigs and rabbits **[Shea 1939]** are sufficient to suggest that morpholine can be absorbed by the skin, become systemically available, and be toxic, with the potential to cause liver, kidney, and spleen effects following

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

Organization	Carcinogenic designation
NIOSH [2005]	No designation
NTP [2014]	No designation
US EPA [2017]	No designation
European Parliament [2008]	No GHS designation
IARC [2012]	Group 3: Not classifiable as to its carcinogenicity to humans
ACGIH [2001]	A4: Not classifiable as carcinogenic 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.

* The listed cancer designations were based on data from nondermal (such as oral or inhalation) exposure since studies using the dermal route of exposure were unavailable.

repeated exposure. Therefore, on the basis of the data for this assessment, morpholine is assigned the SK: SYS notation.

3 Direct Effects on Skin (SK: DIR)

Only one study was identified that reported the potential of morpholine to have direct effects on human skin. Shea [1939] reported that undiluted morpholine applied to the human fingertip caused cracking of the cuticle and epithelium of the nail bed and burning sensations. Evidence of skin corrosivity of morpholine is well-documented in experimental animals. Occluded topical application of 900 mg/kg of the undiluted or un-neutralized morpholine as a single dose or the same dose of diluted morpholine applied daily for up to 2 weeks caused necrosis of the skin, inflammation, edema, and severe burning in rabbits [Shea 1939]. Guinea pigs receiving occluded, daily topical application of 900 mg/kg undiluted morpholine for up to 2 weeks also exhibited edema and necrosis of the skin [Shea 1939]. Smyth [1954] reported that topical application of 0.001 mL of undiluted morpholine [corresponding to 1 mg] resulted in skin necrosis in rabbits within 24 hours. Wang and Suskind [1988] reported 0.1-g applications of 0.5, 2, 5 and 10% morpholine concentrations produced no irritation when applied to 1.5 square centimeters (cm^2) of the shaved skin of guinea pigs under occlusive conditions.

Evidence of direct skin effects of morpholine in humans and animals is also provided by *in vitro* studies. Gay et al. [1992] applied morpholine to living skin equivalent (LSE), collagen-fibroblast lattice from which human epidermal keratinocytes form a stratified epidermis. Concentrations greater than 1% morpholine (by weight) were required to produce inflammation, indicative of irritation in both rabbit and human LSE. In a similar study conducted by van de Sandt and Rutten [1995], rabbit cell cultures administered 5% morpholine solution exhibited no changes. The structure-activity relationship model, Deductive Estimation of Risk from Existing Knowledge (*DEREK*) for Windows [Sanderson and Earnshaw 1991], predicted morpholine to be negative for skin irritation.

On the basis of the results of the studies that evaluated the direct effects of undiluted morpholine in animals **[Shea 1939; Smyth 1954]**, there is sufficient information to indicate that morpholine is corrosive to the skin. Therefore, on the basis of the data for this assessment, morpholine is assigned the SK: DIR (COR) notation.

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

4 Immune-mediated Responses (SK: SEN)

No evidence was identified in human studies to suggest that morpholine has the potential to produce skin sensitization. Animal data were limited to a single study. In a modified Buehler test [Wang and Suskind 1988], 10 guinea pigs were administered 0.1 g morpholine in 5% petrolatum under occlusion on clipped napes for 1 hour, 3 days/week, for 2 weeks. Two weeks after the final dose, the guinea pigs were challenged with 0.1, 0.5, and 2% morpholine concentrations, and no sensitization was observed; however, Wang and Suskind [1988] reported cross-sensitization reactions when animals were initially sensitized with 4,4-dithiodimorpholine (DTDM) or morpholinyl-mercaptobenzothiazole (MMBT) and then challenged with morpholine. The structure-activity relationship model, *DEREK* for Windows [Sanderson and Earnshaw 1991], predicted morpholine to be negative for skin sensitization.

The modified Buehler test identified suggests that morpholine is not a skin sensitizer but can cross-react with structurally similar chemicals. However, this information is considered insufficient as the basis for assigning a SK-SEN notation for morpholine. Therefore, morpholine is not assigned the SK: SEN notation.

5 Summary

No toxicokinetic data were identified to evaluate the potential of morpholine to be absorbed through the skin. However, data from an acute dermal toxicity study in rabbits **[Smyth et al. 1954]** and from a short-term dermal toxicity study in guinea pigs and rabbits **[Shea 1939]** are sufficient to indicate that morpholine has the potential to be absorbed through the skin, be systemically available and toxic, and cause liver, kidney, and spleen effects following repeated exposure. Available studies in animals indicate that undiluted morpholine is corrosive to the skin **[Shea 1939; Smyth 1954]**. Results from a modified Buehler test suggest that morpholine is not likely to cause skin sensitization but can cross-react with structurally similar chemicals. Therefore, on the basis of these assessments, morpholine is assigned a composite skin notation of **SK: SYS-DIR (COR)**.

Table 3 summarizes the skin hazard designations for morpholine previously issued by NIOSH and other organizations. The equivalent dermal designation for morpholine, according to the Globally Harmonized System (GHS) for the Classification and Labelling of Chemicals, is Acute Toxicity Category 4 (Harmful in contact with the skin) and Skin Corrosion Category 1B (Causes severe skin burns and eye damage) [European Parliament 2008].

Table 3. Summary of previous skin hazard designations for morpholine

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption
OSHA [2017]*	[skin]: Potential for dermal absorption
ACGIH [2001]	[skin]: Based on report of human dermal penetration and a dermal LD_{50} for 24-hour skin contact of 0.5 mL/kg in rats

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

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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 Morpholine

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for morpholine. 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 [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_p)

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

where k_{psc} is the permeation coefficient in the lipid fraction of the stratum corneum, k_{pol} is the coefficient in the protein 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 morpholine. The calculated SI ratio was 1.76. On the basis of these results, morpholine 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 morpholine

Variables used in calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path(k_{psc})	cm/hr	0.0003
Permeation coefficient of the protein fraction of the stratum corneum (k_{pol})	cm/hr	1.628×10^{-5}
Permeation coefficient of the watery epidermal layer (k_{aq})	cm/hr	0.2679
Molecular weight (MW)*	amu	87.1
Base-10 logarithm of its octanol–water partition coefficient (Log K_{ow})*	None	-0.86
Calculated skin permeation coefficient (k_p)	cm/hr	0.0003
Skin dose		
Water solubility (S_w)*	mg/cm^3	1000
Calculated skin permeation coefficient (k_p)	cm/hr	0.0003
Estimated skin surface area (palms of hand) §	cm^2	360
Exposure time	hr	8
Calculated skin dose	mg	921.2
Inhalation Dose		
Occupational exposure limit (OEL)†	mg/m^3	70
Inhalation volume	m^3	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	525
Skin dose–to–inhalation dose (SI) ratio	**None**	**1.755**

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