NIOSH Skin Notation Profiles

Nonane

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

NIOSH Skin Notation (SK) Profile

Nonane
[CAS No. 111–84–2]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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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 (e.g., irritant contact dermatitis and corrosion) to induction of immune-mediated responses (e.g., allergic contact dermatitis and pulmonary responses), or systemic toxicity (e.g., neurotoxicity and hepatoxicity). Understanding the hazards related to skin contact with chemicals is a critical component of modern occupational safety and health programs.

In 2009, the National Institute for Occupational Safety and Health (NIOSH) published *Current Intelligence Bulletin (CIB) 61: A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009–147]. This document provides the scientific rationale and framework for the assignment of multiple hazard-specific skin notations (SK) that clearly distinguish between the systemic effects, direct (localized) effects, and immune-mediated responses caused by skin contact with chemicals. The key step within assignment of the hazard-specific SK is the determination of a substance's hazard potential, or its potential for causing adverse health effects as a result of skin exposure. This determination entails a health hazard identification process that involves use of the following:

- Scientific data on the physicochemical properties of a chemical
- Data on human exposures and health effects
- Empirical data from in vivo and in vitro laboratory testing
- Computational techniques, including predictive algorithms and mathematical models that describe a selected process (e.g., skin permeation) by means of analytical or numerical methods.

This *Skin Notation Profile* provides the SK assignment and supportive data for nonane (CAS No. 111–84–2). In particular, this document evaluates and summarizes the literature describing the substance's hazard potential and its assessment according to the scientific rationale and framework outlined in CIB 61. In meeting this objective, this *Skin Notation Profile* intends to inform the audience—mostly occupational health practitioners, researchers, policy- and decision-makers, employers, and workers in potentially hazardous workplaces—so that improved risk-management practices may be developed to better protect workers from the risks of skin contact with the chemical of interest.

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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
GHS	Globally Harmonized System of Classification and Labeling of Chemicals
IARC	International Agency for Research on Cancer
IL-1α	interleukin-α
(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
JP-8	Jet Propellant 8
log K_{OW}	base-10 logarithm of a substance's octanol–water partition
m^3	cubic meter(s)
MCP-1	monocyte chemotactic
mg	milligram(s)
mg/m^3	milligram(s) per cubic meter
MRI	magnetic resonance imaging
MW	molecular weight
NIOSH	National Institute for Occupational Safety and Health
NTP	National Toxicology Program
OEL	occupational exposure limit
OSHA	Occupational Safety and Health Administration
REL	recommended exposure limit
RF	retention factor
SEN	skin notation indicating the potential for immune-mediated reactions following exposure of the skin
SI ratio	ratio of skin dose to inhalation dose

SK	skin notation
S_W	solubility
SYS	skin notation indicating the potential for systemic toxicity following exposure of the skin
TEWL	transepidermal water loss
TNF-α	tumor necrosis factor-α
USEPA	United States Environmental Protection Agency
μg/cm²/hr	microgram(s) per square centimeter per hour
μL	microliter(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 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: Nonane

CAS No: 111–84–2

Synonyms:

n-Nonane, Nonyl Hydride

Molecular weight (MW): 128.26

Molecular formula: $CH_3(CH_2)_7CH_3$

Structural formula:

Uses:
Nonane is an aliphatic hydrocarbon used primarily as an organic solvent and as a component of fuels [HSDB 2010].

1.2 Purpose

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

1.3 Overview of SK Assignment for Nonane

Nonane is potentially capable of causing adverse health effects following skin contact. A critical review of available data has resulted in the following SK assignment for nonane: **SK: DIR (IRR)**. Table 1 provides an overview of the critical effects and data used to develop the SK assignment for nonane.

2 Systemic Toxicity from Skin Exposure (SK: SYS)

A few toxicokinetic studies were identified that evaluated the potential for pure nonane or nonane in a mixture of other aliphatic and aromatic hydrocarbons to penetrate the skin following dermal application. For example, in an in vitro study, Babu et al. [2004a] applied 15 microliters (µL) of nonane to rat skin repeatedly (every 2 hours for 8 hours per day for 4 days) under nonocclusive conditions. The majority of nonane was retained in the stratum corneum; concentrations in the epidermis and dermis were minimal. The potential of nonane to pose a

Table 1. Summary of the SK assignment for nonane

Skin notation	Critical effect	Data available
SK: DIR (IRR)	Skin irritation	Limited human and animal data

skin absorption hazard was also evaluated, with use of a predictive algorithm for estimating 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 1.51×10^{-5} was calculated for nonane. An SI ratio of ≥0.1 indicates that a chemical is capable of producing systemic toxicity from skin exposure [NIOSH 2009]. Additional information on the SI ratio and the variables used in its calculation are included in the appendix.

Using the Jet Propellant 8 (JP-8), which contains a mixture of hundreds of aliphatic and aromatic hydrocarbons (including nonane), Kanikkannan et al. [2001a] noted steady-state fluxes of 0.4765 and 0.6370 micrograms per square centimeter per hour (μg/cm²/hr) for nonane in vitro across pig ear skin and human skin, respectively; the corresponding permeability coefficients were 5.410×10^{-5} cm/hr and 7.239×10^{-5} cm/hr. In another in vitro study, Kanikkannan et al. [2001b] reported steady-state fluxes of 0.395 to 0.477 μg/cm²/hr for nonane in three jet fuels across pig ear skin. An in vitro study conducted by McDougal et al. [2000] with JP-8 also showed low flux of nonane (0.384 μg/cm²/hr) across rat skin. Kerosene, which also contains nonane and several other hydrocarbons (alkanes, cycloalkanes, benzene and substituted benzene, and naphthalene and substituted naphthalenes), increased the permeability of tritiated water through the skin [Schumann et al. 2004], but this effect cannot be attributed to nonane alone. Taken together, these penetration studies with nonane alone or in mixtures such as JP-8 indicate that the amount of nonane that can be absorbed through the skin and become available systemically may be limited.

No acute dermal toxicity studies, repeat-dose studies, subchronic dermal toxicity studies, or chronic dermal toxicity studies of nonane were identified. In addition, the literature search revealed no standard toxicity or specialty studies evaluating biological systemic/function (including reproductive/developmental toxicity or immunotoxicity) and no epidemiological investigations or experimental animal studies evaluating the potential for nonane to induce carcinogenicity. Table 2 provides a summary of carcinogenic designations from multiple governmental and nongovernmental organizations for nonane.

The paucity of data relating to the dermal absorption and lack of dermal acute and repeat-dose toxicity studies prevents an adequate evaluation of the systemic hazards of nonane following skin contact. Therefore, on the basis of this assessment, nonane is not assigned a SK: SYS notation.

3 Direct Effect(s) on Skin (SK: DIR)

No data on the corrosive potential of nonane were identified, although several skin irritation studies were. In a skin irritation study conducted according to standard protocol,

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

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

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; EC = European Commission, Joint Research, Institute for Health and Consumer Protection; IARC = International Agency for Research on Cancer; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; USEPA = United States Environmental Protection Agency.

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

Jacobs et al. [1987] found nonane to be irritating to rabbit skin after 4 hours of contact and irritating to human skin at the limit concentration of 50% (weight by volume, w/v), a concentration reported by the investigators as the dilution of a nonirritating solvent below which a marked decrease in irritation or no irritation would be expected. Other studies also indicated that nonane has the potential to disrupt the stratum corneum barrier function (indicated by an increase in transepidermal water loss, or TEWL) and to cause erythema and edema. For example, using TEWL and erythema as indications of rat skin irritation, Babu et al. studied the effect of 1-hr occlusive application of nonane (230 µL) [Babu et al. 2004b] and repeated nonocclusive application of low-level nonane (15 µL every 2 hours; 8 hours per day for 4 days) [Babu et al. 2004a]. The applications resulted in significant increase in TEWL and erythema during the dermal exposure period, indicating that nonane was irritating to the rat skin. Babu et al. [2004a, 2004b] also reported increased expression of cytokine and chemokine molecular markers (interleukin-α [IL-1α], tumor necrosis factor-α [TNF-α], monocyte chemotactic protein-1 [MCP-1] of irritant response in the skin and blood and activation of the transcription factor NFκB (responsible for regulating the expression of genes involved in controlling inflammatory responses) in the skin following dermal exposure to nonane. Ramapuram et al. [2004] also investigated the skin effects of nonane in rats, by using TEWL, expression of molecular markers (IL-1α, TNF-α, and MCP-1), and magnetic resonance imaging (MRI). The authors compared results for nonane with those for dodecane and noted that the flux and deposition of nonane in the skin layers (stratum corneum, epidermis, and dermis) was significantly lower than for dodecane, although nonane caused higher TEWL than dodecane. Compared with the MRI of controls, MRI of nonane-treated skin showed significantly higher signal intensities in the epidermis, dermis, hair follicles, and lipid regions of the skin and higher cytokine and chemokine expression in the skin. Other studies (e.g., Schumann et al. [2004]) have also indicated that kerosene (containing nonane and several other hydrocarbons) has a deleterious effect on the barrier function of the skin, significantly reducing the ability of the skin to protect against loss of internal water.

In vivo studies using minipigs indicated that a single dermal application of pure nonane or JP-8 also resulted in an increase in TEWL, a non-statistically-significant decrease in skin moisture content, and slight (with pure nonane) or moderate (with JP-8) erythema and edema [Kanikkannan et al. 2001a]. The skin irritation potential of nonane observed by these investigators was greater than that of toluene, which is commonly used as a positive irritant control in the evaluation of protective creams in contact dermatitis. Other studies with JP-8 also showed that prolonged or repeated JP-8 contact with the skin also causes irritation, but it is not entirely clear which component(s) caused the irritation [Baker et al. 1999; Kinkead et al. 1992; Wolfe et al. 1996; McDougal et al. 2000]. The structure activity relationship model, Deductive Estimation of Risk from Existing Knowledge (DEREK™) for Windows, predicted nonane not to be a skin irritant.

The available irritation data on rabbits **[Jacobs et al. 1987*]**, rats **[Babu et al. 2004a, 2004b]**, and minipigs **[Kanikkannan et al. 2001a]** are sufficient to conclude that nonane causes skin irritation. Therefore, on the basis of the data for this assessment, nonane is assigned the SK: DIR (IRR) notation.

4 Immune-mediated Responses (SK: SEN)

No evidence of the skin sensitization potential of nonane following dermal exposure was identified. The jet fuel JP-8, which contains nonane (1.1% on a weight–by-weight basis), was reported to be a weak sensitizer [Kinkead et al. 1992]. Predictions using structure-activity relationship models provide some information regarding this endpoint. DEREK™ predicted nonane to be negative for sensitization. These predictions of negative or weak activity are consistent with the absence of published reports of sensitization in workers handling nonane. Therefore, on the basis of the data for this assessment, nonane is not assigned the SK: SEN notation.

5 Summary

The paucity of data relating to the dermal absorption and lack of dermal acute and repeat-dose toxicity studies prevents an adequate evaluation of the systemic hazards of nonane following skin contact. Sufficient irritation data on rabbits **[Jacobs et al. 1987]**, rats **[Babu et al. 2004a, 2004b]**, and minipigs **[Kanikkannan et al. 2001b]** were identified to conclude that nonane causes skin irritation, but it is not likely to be corrosive. Data are insufficient to assess the sensitization potential of nonane, although model prediction indicates that the chemical does not have structural alerts for skin sensitization. Therefore, on the basis of this assessment, nonane is assigned a composite skin notation of **SK: DIR (IRR).**

Table 3 summarizes the skin hazard designations for nonane previously issued by NIOSH and other organizations. A dermal designation for nonane, according to the Globally Harmonized System (GHS) of Classification and Labeling of Chemicals, was not located [European Parliament 2008]. The scheme developed by NIOSH to coordinate the SK assignments with the GHS classifications would most likely result in nonane being assigned the designation Skin Irritation Category 2 (Hazard statement: Causes skin irritation) [UNECE 2007; NIOSH 2009].

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

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

Organization	Skin hazard designation
NIOSH [2005]	None
OSHA [2009]	None
ACGIH [2001]	None
EC [2010]	None

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; EC = European Commission, Joint Research, Institute for Health and Consumer Protection; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration.

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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 Nonane

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for nonane. Although the SI ratio is considered in the determination of a substance's hazard potential following skin contact, it is intended only to serve as supportive data during the assignment of the NIOSH SK. An in-depth discussion on the rationale and calculation of the SI ratio can be found in Appendix B of the *Current Intelligence Bulletin (CIB) 61: A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009].

Overview

The SI ratio is a predictive algorithm for estimating and evaluating the health hazards of skin exposure to substances. The algorithm is designed to evaluate the potential for a substance to penetrate the skin and induce systemic toxicity [NIOSH 2009]. The goals for incorporating this algorithm into the proposed strategy for assigning the SYS notation are as follows:

1. Provide an alternative method to evaluate substances for which no clinical reports or animal toxicity studies exist or for which empirical data are insufficient to determine systemic effects.
2. Use the algorithm evaluation results to determine whether a substance poses a skin absorption hazard and should be labeled with the SYS notation.

The algorithm evaluation includes three steps: (1) determining a skin permeation coefficient (K_p) for the substance of interest, (2) estimating substance uptake by the skin and respiratory absorption routes, and (3) evaluating whether the substance poses a skin exposure hazard.

The algorithm is flexible in the data requirement and can operate entirely on the basis of the physicochemical properties of a substance and the relevant exposure parameters. Thus, the algorithm is independent of the need for biologic data. Alternatively, it can function with both the physicochemical properties and the experimentally determined permeation coefficient when such data are available and appropriate for use.

The first step in the evaluation is to determine the K_p for the substance to describe the transdermal penetration rate of the substance [NIOSH 2009]. The K_p, which represents the overall diffusion of the substance through the stratum corneum and into the blood capillaries of the dermis, is estimated from the compound's molecular weight (MW) and base-10 logarithm of its octanol–water partition coefficient (log K_{OW}). In this example, K_p is determined for a substance with use of Equation 1. A self-consistent set of units must be used, such as cm/hr, outlined in Table A1 Other model-based estimates of K_p may also be used [NIOSH 2009].

Equation 1: Calculation of Skin Permeation Coefficient (K_p)

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

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

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

Variables used in calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path(K_{psc})	cm/hr	1.24774
Permeation coefficient of the protein fraction of the stratum corneum (K_{pol})	cm/hr	1.34126×10^{-5}
Permeation coefficient of the watery epidermal layer (K_{aq})	cm/hr	0.22075
Molecular weight (MW)*	amu	128.26
Base-10 logarithm of its octanol–water partition coefficient (log K_{OW})*	None	5.65
Calculated skin permeation coefficient (K_p)	cm/hr	0.18756
Skin dose		
Water solubility (S_W)*	mg/cm^3	0.00022
Calculated skin permeation coefficient (K_p)	cm/hr	0.18756
Estimated skin surface area (palms of hand)	cm^2	360
Exposure time	hr	8
Calculated skin dose	mg	0.12
Inhalation dose		
Occupational exposure limit (OEL)†	mg/m^3	1050
Inhalation volume	m^3	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	7875
Skin dose–to–inhalation dose (SI) ratio	None	1.51×10^{-5}

*Variables identified from SRC [2009].
†The OEL used in calculation of the SI ratio was the NIOSH-recommended exposure limit (REL) [NIOSH 2005].

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 cm^2).

Equation 2: Determination of Skin Dose

$$\text{Skin dose} = K_p \times S_W \times \text{Exposed skin surface area} \times \text{Exposure time}$$

$$= K_p(cm/hr) \times S_W\ (mg/cm^3) \times 360\ cm^2 \times 8\ \text{hours}$$

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

$$\text{Inhalation dose} = \text{OEL} \times \text{Inhalation volume} \times \text{RF}$$

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

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 nonane. The calculated SI ratio was 1.51×10^{-5}. On the basis of these results, nitroglycerin is not predicted to represent a skin absorption hazard.

Appendix References

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