Skin Notation (SK) Profile

Nitrobenzene

[CAS No. 98-95-3]

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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 (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 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 (e.g., skin permeation) by means of analytical or numerical methods.

This *Skin Notation Profile* provides the SK assignments and supportive data for nitrobenzene. 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
ATSDR	Agency for Toxic Substances and Disease Registry
CIB	Current Intelligence Bulletin
cm^2	squared centimeter(s)
cm/hour	centimeter(s) per hour
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 for Labelling and Classification of Chemicals
IARC	International Agency for Research on Cancer
(IRR)	subnotation of SK: DIR indicating the potential for a chemical to be a skin irritant following exposure to the skin
kaq	coefficient in the watery epidermal layer
k_p	skin permeation coefficient
kpol	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
log K_{OW}	base-10 logarithm of a substance's octanol–water partition
M	molarity
m^3	cubic meter(s)
mg	milligram(s)
mg/kg	milligram(s) per kilogram body weight
mg/m^3	milligram(s) per cubic meter
mL	milliliter(s)
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
USEPA	United States Environmental Protection Agency
µg	microgram(s)

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$\mu g/cm^2$	microgram(s) per square centimeter

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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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Acknowledgments

This document was developed by the Education and Information Division (Paul Schulte, Ph.D., Director). G. Scott Dotson, Ph.D., was the project officer for this document, assisted in great part by Naomi Hudson, Dr.P.H., Paul Siegel, Ph.D., and John Snawder, Ph.D. The basis for this document was a report (*Toxicology Excellence for Risk Assessment [TERA]*) contracted by NIOSH and prepared by Bernard Gadagbui, Ph.D., and Andrew Maier, Ph.D.

For their contribution to the technical content and review of this document, special acknowledgment is given to the following NIOSH personnel:

Denver Field Office
Eric Esswein, M.Sc.

Division of Applied Research and Technology
Clayton B'Hymer, Ph.D.
Mark Toraason, Ph.D.

Division of Respiratory Disease Studies
Gregory A. Day, Ph.D.
Aleksander Stefaniak, Ph.D.

Division of Surveillance, Hazard Evaluations, and Field Studies
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Todd Niemeier, M.Sc.
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Office of Surveillance, Epidemiology and Laboratory Services/Epidemiology and Analysis Program Office
Barbara Landreth, M.A.

In addition, special appreciation is expressed to the following individuals for serving as independent, external reviewers and providing comments that contributed to the development or improvement of this document:

- G. Frank Gerberick, Ph.D., The Procter and Gamble Company, Cincinnati, Ohio
- Dori Germolec, Ph.D., National Toxicology Program, National Institute for Environmental Health Sciences, Research Triangle, North Carolina
- Ben Hayes, M.D., Ph.D., Division of Dermatology, Vanderbilt School of Medicine, Nashville, Tennessee
- Jennifer Sahmel, M.Sc., CIH, ChemRisk, Boulder, Colorado
- James Taylor, M.D., Industrial Dermatology, The Cleveland Clinic, Cleveland, Ohio

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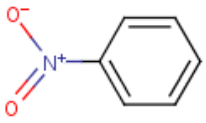
1.0 Introduction

1.1 General Substance Information:

Chemical: Nitrobenzene
CAS No: 98-95-3
Molecular weight (*MW*): 123.1
Molecular formula: $C_6H_5NO_2$
Structural formula:



Synonyms: Nitrobenzol

Uses: Nitrobenzene is used primarily as a chemical intermediate of aniline and similar compounds [ATSDR 1990]. Additional applications of nitrobenzene include as a solvent in petroleum eefining, in the manufacture of cellulose ethers and acetate, and in the synthesis of other organic compounds including acetaminophen [ATSDR 1990].

1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with nitrobenzene and (2) the rationale behind the hazard-specific skin notation (SK) assignment for nitrobenzene. 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 nitrobenzene. A literature search was conducted through September 2012 to identify information on nitrobenzene, 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 nitrobenzene.

1.3 Overview of SK Assignment

Nitrobenzene 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

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nitrobenzene: **SK: SYS**. Table 1 provides an overview of the critical effects and data used to develop the SK assignment for nitrobenzene.

Table 1. Summary of the SK Assignment for nitrobenzene

Skin Notation	Critical Effect	Available Data
SK: SYS	Hepatic, and neurological effects	Sufficient human and animal data

2.0 Systemic Toxicity from Skin Exposure (SK: SYS)

Several toxicokinetic studies following dermal exposure to nitrobenzene were identified. Feldman and Maibach [1970] reported dermal absorption of 1.5% of the applied dose after 4 micrograms per square centimeter (μg/cm^2), a total of 52 micrograms (μg), of nitrobenzene in acetone solvent was applied to an unoccluded 13-cm^2 circular area of the forearm of a human volunteer for 24 hours. Bronaugh and Maibach [1985] reported dermal absorption of 4.2% of the applied dose following a single application to the monkey abdominal skin *in vivo*. The limited absorption observed in these studies could be attributed to the small amounts applied in acetone solvent to an unoccluded site. Piotrowski [1967] investigated the uptake of nitrobenzene vapors via multiple exposure routes in human volunteers. Test subjects were repeatedly exposed via the inhalation or dermal routes to concentrations of nitrobenzene vapors ranging from 5 to 30 micrograms per liter (μg/L). The magnitude of exposure was determined via urinary p-nitrophenol, a primary metabolite of nitrobenzene. Piotrowski [1967] reported that a dressed worker exposed for 6-hours (hr) to nitrobenzene vapors at a concentration of 5 μg/L would have an estimated dermal absorption of 7 milligrams (mg)/day, whereas the18 mg/day is estimated via the inhalation route. The findings of this study indicate that the dermal absorption of nitrobenzene vapors was approximately half of the absorption via the lungs, but still contributes substantially to total dose.

Bronaugh and Maibach [1985] reported dermal absorption *in vitro* of 7.8% (human skin) and 6.2% (monkey skin) of the applied dose. *In vitro* skin penetration studies indicated that approximately 8 and 41% of the applied dose penetrated the abdominal skin of humans under open conditions and evaporation-prevented conditions, respectively [Bronaugh and Maibach 1985]. The potential of nitrobenzene to pose a 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 1.03 was calculated for nitrobenzene. An SI ratio of ≥0.1 indicates that skin absorption may significantly contribute to the overall body burden of a substance [NIOSH 2009]; therefore, nitrobenzene 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.

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While no dermal lethal concentration (LD_{Lo}) for humans has been identified, the reported dermal LD_{50} values (the dose resulting in 50% mortality in the exposed animals) for rabbits was 760 milligrams per kilogram body weight (mg/kg) [Harton and Rawl 1976]. Because the reported acute dermal LD_{50} value for rabbits is lower than the critical dermal LD_{50} value of 2000 mg/kg body weight that identifies chemical substances with the potential for acute dermal toxicity [NIOSH 2009], nitrobenzene is acutely toxic following dermal exposure.

No epidemiology studies were identified that evaluated toxic effects of nitrobenzene in exposed workers. In a case report by Ikeda and Kita [1964], a worker who was exposed to nitrobenzene for 17 months developed severe methemoglobinemia with hepatic and neurological effects. No quantitative estimate of the dermal dose or the contribution of inhalation exposure was provided. Matsumaru and Yoshida [1959] reported that prolonged application of nitrobenzene (15 to 89 days) to the skin of rabbits caused damage to the liver and brain. However, the experimental design, lack of information on the dose of nitrobenzene applied, and the use of only one animal per group precludes use of information from this study in assessing the dermal effects of the substance.

No standard toxicity or specialty studies evaluating biological system/function specific effects (including reproductive and developmental effects and immunotoxicity) following dermal exposure to nitrobenzene were identified in humans. There is insufficient data available to evaluate the carcinogenicity potential of nitrobenzene following dermal exposure. Table 2 summarizes carcinogenic designations of multiple governmental and nongovernmental organizations for nitrobenzene.

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

Organization	Carcinogenic designation
NIOSH [2005]	No designation
NTP [2011]	Reasonably anticipated to be a human carcinogen
USEPA [2009]	Likely to be carcinogenic to humans
GHS [European Parliament 2008]	Carcinogenicity Category 2: Suspected of causing cancer
IARC [2012]	Group 2B: Probably carcinogenic to humans
EC [2012]*	R40: Limited evidence of a carcinogenic effect
ACGIH [2001]	Confirmed animal carcinogen with unknown relevance to humans

ACGIH = American Conference of Governmental Industrial Hygienists; EC = European Commission, Joint Research, Institute for Health and Consumer Protection; GHS = Globally Harmonized System for Labelling and Classification of Chemicals; 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.

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

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Taken together, data from the toxicokinetic studies in humans *in vivo* **[Piotrowski 1967; Feldman and Maibach 1970]** [*] and *in vitro* studies **[Feldmann and Maibach 1970; Bronaugh and Maibach 1985]**, acute dermal toxicity studies **[Harton and Rawl 1976]**, and human case reports **[**e.g., **Ikeda and Kita 1964]** demonstrate that nitrobenzene is absorbed through the skin, is systemically available and is toxic. Therefore, on the basis of the data for this assessment, nitrobenzene is assigned the SK: SYS notation.

3.0 Direct Effects on Skin (SK: DIR)

No human or animal *in* vivo studies for corrosivity for nitrobenzene or *in vitro* tests for corrosivity using human or animal skin models or *in vitro* tests for skin integrity using cadaver skin were identified. In a study by E.I. du Pont de Nemours and Company [1977], rabbits administered 0.5 milliliter (mL) nitrobenzene to 1.5 square inches of skin under occlusion exhibited no corrosivity. No information is available to suggest that nitrobenzene is a skin irritant based on occupational exposure experience. No controlled exposure studies in humans were identified that assessed skin irritation. In animals, nitrobenzene was reported not to irritate rabbit skin [Spielman et al. 1991]. The structure activity relationship model, Deductive Estimation of Risk from Existing Knowledge (*DEREK*) for Windows, predicted nitrobenzene to be negative for skin irritation, indicating that the substance does not have structural alerts for skin irritation.

There is limited information upon which to base the potential of nitrobenzene to cause skin irritation in humans. Acute dermal irritation studies in animals [Spielman et al. 1991] show that nitrobenzene is not a significant skin irritant. Therefore, on the basis of the data for this assessment, nitrobenzene is not assigned the SK: DIR notation.

4.0 Immune-mediated Responses (SK: SEN)

No epidemiological or human studies were identified for skin sensitization potential of nitrobenzene. In a standard ear-flank skin sensitization test in guinea pigs, nitrobenzene dissolved in dimethyl formamide failed to cause sensitization when applied daily to the outer surface of the ears (0.1 mL per ear per day; 10%) for three days, followed by a range of concentrations of solutions (0.2 mL) of the test material on the clipped flank [Stevens 1967]. *DEREK* predicted nitrobenzene to be negative as a skin sensitizer. Therefore, on the basis of the data for this assessment, nitrobenzene is not assigned the SK: SEN notation.

5.0 Summary

The available data in human *in vivo* studies **[Piotrowski 1967; Feldman and Maibach 1970; Bronaugh and Maibach 1985]** and supporting *in vitro* studies **[Feldmann and Maibach 1970; Bronaugh and Maibach 1985]**, acute dermal toxicity studies in animals **[Harton and Rawl 1976]**, and human case reports **[**e.g., **Ikeda and Kita 1964]** demonstrate that nitrobenzene is

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

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absorbed through the skin. Nitrobenzene is systemically available and can cause methemoglobinemia and hepatic and neurological effects in humans **[Ikeda and Kita 1964]**. The available studies show that nitrobenzene is not a skin irritant or a skin sensitizer. Therefore, this assessment assigns the skin notations of SK: SYS for nitrobenzene. Therefore, on the basis of these assessments, nitrobenzene is assigned a composite skin notation of **SK: SYS**.

Table 3 summarizes the skin hazard designations for nitrobenzene previously issued by NIOSH and other organizations. The equivalent dermal designation for nitrobenzene, according to the Global Harmonization System (GHS) of Classification and Labelling of Chemicals, is Acute Toxicity Category 3 (Hazard statement: Toxic in contact with the skin) [European Parliament 2008]. In addition, nitrobenzene has been classified as a Reproductive Toxicity Category 2 (Hazard Statement: Suspected of damaging fertility) [European Parliament 2008].

Table 3. Summary of previous skin hazard designations for nitrobenzene

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption; prevent skin contact
OSHA [2012]*	[skin]: Prevent skin contact.
ACGIH [2001]	[skin]: Based on the acute and chronic systemic toxicity of topical nitrobenzene in air.
EC [2012]*	R24: Toxic in contact with skin

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.
*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 Nitrobenzene

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for nitrobenzene. 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 *kp* 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 outlined in Table A1. Other model-based estimates of k_p may also be used [NIOSH 2009].

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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 squared centimeters [cm^2]).

Equation 2: Determination of Skin Dose

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

Inhalation dose = OEL $\times$ Inhalation volume $\times$ RF
= 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.

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Calculation

Table A1 summarizes the data applied in the previously described equations to determine the SI ratio for nitrobenzene. The calculated SI ratio was 1.03. On the basis of these results, nitrobenzene is predicted to represent a skin absorption hazard.

Table A1. Summary of Data used to Calculate the SI Ratio for nitrobenzene

Variables Used in Calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path(k_{psc})	cm/hour	6.611×10^{-3}
Permeation coefficient of the protein fraction of the stratum corneum (k_{pol})	cm/hour	1.3690×10^{-5}
Permeation coefficient of the watery epidermal layer (k_{aq})	cm/hour	0.2532
Molecular weight (MW)[a]	amu	123.1
Base-10 logarithm of its octanol–water partition coefficient (Log K_{ow})[a]	None	1.85
Calculated skin permeation coefficient (k_p)	cm/hour	6.4358×10^{-3}
Skin dose		
Water solubility (S_w)[a]	mg/cm^3	2.09
Calculated skin permeation coefficient (k_p)	cm/hour	6.4358×10^{-3}
Estimated skin surface area (palms of hand)	cm^2	360
Exposure time	hour	8
Calculated skin dose	mg	38.78
Inhalation Dose		
Occupational exposure limit (OEL)[b]	mg/m^3	5
Inhalation volume	m^3	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	37.5
Skin dose–to–inhalation dose (SI) ratio	None	1.03

[a]Variables identified from SRC [2009].
[b]The OEL used in calculation of the SI ratio for nitrobenzene was the NIOSH recommended exposure limit (REL) [NIOSH 2005].

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Appendix References

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