NIOSH Skin Notation Profiles

Nitroglycerin

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

Nitroglycerin
[CAS No. 55-63-8]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
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DHHS (NIOSH) Publication No. 2011–147

April 2011

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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 nitroglycerin (CAS No. 55-63-8). 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
CIB	Current Intelligence Bulletin
cm^2	square centimeter(s)
cm/hr	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
(FATAL)	subnotation of SK: SYS indicating chemicals are highly or extremely toxic and may be potentially lethal or life-threatening following exposure of the skin
GHS	Globally Harmonized System of Classification and Lebeling of Chemicals
GPMT	guinea pig maximization test
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
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
log K_{OW}	base-10 logarithm of a substance's octanol–water partition
m^3	cubic meter(s)
mg	milligram(s)
$mg/cm^2/hr$	milligram(s) per square centimeter per hour
mg/hr	milligram(s) per hour
mg/mL	milligram(s) per milliliter
mg/kg/day	milligram(s) per kilogram body weight per day
mg/m^3	milligram(s) per cubic meter
MW	molecular weight
NIOSH	National Institute for Occupational Safety and Health
$nmol/cm^2/hr$	namomoles per square centimeter per hour
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
OEL	occupational exposure limit

OSHA	Occupational Safety and Health Administration
REL	recommended exposure limit
RF	retention factor
SEN	skin notation indicating the potential for immune-mediated reactions following exposure of the skin
SI ratio	ratio of skin dose to inhalation dose
SK	skin notation
S_W	solubility
SYS	skin notation indicating the potential for systemic toxicity following exposure of the skin
TTSs	transcutaneous therapeutic systems
USEPA	United States Environmental Protection Agency

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.

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. Other NIOSH personnel, in particular Heinz Ahlers, J.D., Eric Esswein, M.Sc., Charles L. Geraci, Ph.D., Thomas J. Lentz, Ph.D., Richard Niemeier, Ph.D., and Angie Shepherd, contributed to its development by providing technical reviews and comments. The basis for this document was a report contracted by NIOSH and prepared by Bernard Gadagbui, Ph.D., and Andrew Maier, Ph.D. (*Toxicology Excellence for Risk Assessment [TERA]*).

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

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

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

Division of Surveillance, Hazard Evaluations, and Field Studies
Todd Niemeier, M.Sc.
Aaron Sussell, Ph.D.
Loren Tapp, M.D.

Education and Information Division
Ralph Zumwalde, M.Sc.

Health Effects Laboratory Division
Fredrick H. Frasch, Ph.D.
Michael Luster, Ph.D.
Anna Shvedova, Ph.D.
Paul Siegel, Ph.D.

The authors thank Seleen Collins, Gino Fazio, and Vanessa B. Williams for their editorial support and contributions to the design and layout of this document. Clerical and information resources support in preparing this document was provided by Devin Baker, Daniel Echt, and Barbara Landreth.

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

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1 Introduction

1.1 General Substance Information

Chemical: Nitroglycerin

CAS No: 55–63–8

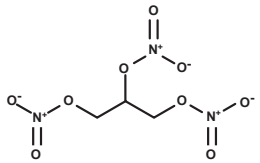
Synonyms:

Glyceryl Trinitrate; NG; 1,2,3-Propanetriol Trinitrate; Trinitroglycerin

Molecular weight (MW): 227.09

Molecular formula: $C_3H_5N_3O_9$

Structural formula:



Uses:
Nitroglycerin is an organic nitrate ester substance used primarily in the production of explosives and as a vasodilating pharmaceutical agent [NIOSH 1978].

1.2 Purpose

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

1.3 Overview of SK Assignment for Nitroglycerin

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

2 Systemic Toxicity from Skin Exposure (SK: SYS)

Numerous studies following human dermal exposure to nitroglycerin were identified. A

Table 1. Summary of the SK assignment for nitroglycerin

Skin Notation	Critical Effect	Data Available
SK: SYS (FATAL)	Circulatory/vascular effects (development of vascular tolerance); developmental effects	Sufficient human and animal data
SK: DIR (IRR)	Skin irritation	Sufficient human and animal data
SK: SEN	Skin sensitization	Limited human and animal data

nitroglycerin transdermal system is extensively used to prevent and treat angina pectoris (suffocating chest pain); the rate of release of nitroglycerin is linearly dependent upon the area of the applied system [Novartis Pharmaceutical Corporation 2000]. Although the percent dermal absorption of nitroglycerin was not included in the reports of any of these studies, there is evidence that the substance is absorbed through the skin of humans following dermal exposure. This evidence is measurements of nitroglycerin concentration in the blood of exposed workers or the onset of systemic effects following use of nitroglycerin in transdermal systems or as ointment in the treatment of chest pain. For example, Schwartz [1946] reported that nitroglycerin was readily absorbed through the intact human skin in amounts sufficient to cause vasodilation. Several studies have revealed increases in blood nitroglycerin levels in humans following application of the substance in ointment or nonointment transdermal systems, indicating that nitroglycerin is dermally absorbed [Wester et al. 1959; Blumenthal et al. 1977; Sved et al. 1981; Colfer et al. 1982; Muller et al. 1982; Iafrate et al. 1983; McAllister et al. 1986]. Gjesdal et al. [1985] and Sivertsen [1984] measured nitroglycerin concentrations in the plasma of 12 volunteers before and during the production of gun powder. The reported results included detection of a higher nitroglycerin concentration in the cubital vein than in the femoral vein in exposed workers, suggesting significant local absorption of nitroglycerin through the skin of the hands and arms despite the use of protective clothing. Crandell et al. [1929] estimated a human skin permeability coefficient of 1.1×10^{-2} centimeter per hour (cm/hr). The potential of nitroglycerin 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 4.97 was calculated for nitroglycerin. 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.

Quantitative estimates of dermal absorption have been provided in several animal studies. Wester et al. [1959] reported that nitroglycerin was readily absorbed through the skin of rhesus monkeys; the absolute bioavailability was reported to be 56.6% following topical application in an ointment. Kikkoji et al. [1991] reported a permeability coefficient for nitroglycerin of 20×10^{-3} cm/hr when it is applied as an aqueous solution and 1.6×10^{-3} cm/hr when

it is applied as an ointment. Those authors used a full-thickness hairless mouse skin in vitro. These investigators also reported a steady-state flux of 154 nanomoles per square centimeter per hour (nmol/cm^2/hr)—corresponding to 0.04 milligram per square centimeter per hour (mg/cm^2/hr)—in the mouse following application of nitroglycerin in ointment formulation. The available findings from in vivo and in vitro studies in both humans and animals show that nitroglycerin can be absorbed through the skin.

No dermal lethal concentration (LD_{Lo}) for humans has been identified. No reliable dermal LD_{50} value (the dose resulting in 50% mortality in the exposed population) has been identified for experimental animals, precluding adequate evaluation of the potential for acute dermal toxicity.

Several epidemiologic studies were identified [Schwartz 1946; Bresler 1949; Hanlon and Fredrick 1966; Lund et al. 1968; Lange et al. 1972; Hogstedt and Andersson 1979] that revealed results such as mortality and chronic vascular effects (i.e., headache, blood pressure changes, chest pain, and electroencephalographic changes) in workers exposed to nitroglycerin. However, these studies involved both inhalation and dermal exposures. Robinson et al. [2001] reported effects on systemic vascular tone, as evidenced by decreased diastolic blood pressure and pulse pressure and increased heart rate following topical application of 2% nitroglycerin ointment. These investigators indicated that the cardiovascular responses did not cause unexpected side effects, except that three of four volunteers had headaches after the experiments. For treatment of chest pain, Novartis Pharmaceutical Corporation [2000] suggested a starting dose of nitroglycerin between 0.2 mg/hr and 0.4 milligram per hour (mg/hr); doses between 0.4 mg/hr and 0.8 mg/hr [corresponding to approximately 0.06 to 0.14 milligram per kilogram per day (mg/kg/day) for a 70-kg person] showed continued effectiveness for 10 to 12 hours daily for at least one month (the longest period studied) of intermittent administration. This implies that the no-observed-adverse-effect level (NOAEL) ranges between 0.06 and 0.14 mg/kg/day in humans and that dermal doses higher than the therapeutic doses are likely to result in systemic (cardiovascular) effects. Because the therapeutic doses and the rabbit NOAEL are much lower than the critical dermal NOAEL value of 1000 mg/kg/day that identifies chemical substances with the potential for repeated-dose dermal toxicity [NIOSH 2009], nitroglycerin is considered systemically available and can cause systemic effects following dermal exposure.

Immediate removal of workers from long-term exposures to nitroglycerin has resulted in life-threatening health effects and deaths [NIOSH 1978; Hogstedt and Andersson 1979]. Workers subchronically or chronically exposed to nitroglycerin develop a tolerance to effects of the vasodilating action of the substance, resulting in a semipermanently altered health state characterized by blood pressure changes and compensatory vasoconstriction [NIOSH 1978; Abrams 1980]. Withdrawal from exposure to the vasodilating agent (i.e., on a weekend or holiday leave) has been associated with angina pectoris and death caused by continued vascular tolerance in the absence of the nitroglycerin [NIOSH 1978]. Because of the potential for sudden death, removal from exposure should not be abrupt.

No standard toxicity or specialty studies evaluating biological system/function–specific effects (including reproductive effects and immunotoxicity) in humans following dermal exposure to nitroglycerin

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

Organization	Carcinogenic designation
NIOSH [2005]	None
NTP [2009]	None
USEPA [2010]	Group D: Not classifiable as to human carcinogenicity
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.

were identified. Novartis Pharmaceutical Corporation [2000] indicated that in a teratology study, nitroglycerin topically applied to rats at doses up to 80 mg/kg/day and to rabbits at doses up to 240 mg/kg/day did not result in toxic effects on dams or fetuses. However, ProStrakan [2007] reported that nitroglycerin was fetotoxic (causing decreased birth weights) in rats after in utero exposure during fetal development at dermal dosages above 28 mg/kg/day, indicating that nitroglycerin is a developmental toxicant with a NOAEL of 28 mg/kg/day. Table 2 summarizes carcinogenic designations by multiple governmental and nongovernmental organizations for nitroglycerin.

Taken together, the available toxicokinetic data from studies of humans and animals **[Wester et al. 1959; Gjesdal et al. 1985; McAllister et al. 1986; Kikkoji et al. 1991*]** and from the pharmaceutical use of nitroglycerin **[Novartis Pharmaceutical Corporation 2000]** are sufficient to conclude that nitroglycerin can penetrate the skin and be absorbed in sufficient amounts to cause circulatory, vascular, gastrointestinal, or kidney effects, death, or fetal effects. In addition, sufficient evidence is available to indicate that abrupt withdrawal of workers from long-term exposure to nitroglycerin may result in deaths because of continued vascular tolerance **[NIOSH 1978; Hogstedt and Andersson 1979; Abrams 1980]**. Therefore, on the basis of the data for this assessment, nitroglycerin is assigned the SK: SYS (FATAL) notation.

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

No data on corrosivity of nitroglycerin from in vitro tests with human or animal skin models or on skin integrity with cadaver skin were identified. However, several case reports have noted skin irritation reactions (irritant contact dermatitis) as cutaneous side effects in patients exposed to nitroglycerin transcutaneous therapeutic systems (TTSs) or patches [Muller et al. 1982; Fischer and Tyler 1985; Kapoor et al. 1985; Schrader et al. 1986; Carmichael and Foulds 1989; Vaillant et al. 1990; Kounis et al. 1996]. These reactions are mostly in the form of burning,

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

pruritus, and erythema that appear in the area of the patch placement. Nitroglycerin was a very mild skin irritant in rabbits [Lee et al. 1975]. The structure-activity relationship model, Deductive Estimation of Risk from Existing Knowledge (DEREK™) for Windows, predicted nitroglycerin to be negative for skin irritation.

Case reports **[Vaillant et al. 1990; Kounis et al. 1996]** demonstrate that prolonged and repeated dermal exposure to nitroglycerin ointment or transdermal nitroglycerin products can result in irritant contact dermatitis. Although the irritant symptoms observed could possibly reflect other ingredients in the ointments or factors related to the conditions of dosing in the clinical studies, animal studies **[Lee et al. 1975]** provide supporting evidence that nitroglycerin itself is mildly irritating to rabbit skin. Therefore, on the basis of the data for this assessment, nitroglycerin is assigned the SK: DIR (IRR) notation.

4 Immune-mediated Responses (SK: SEN)

Several studies were identified that evaluated the potential of nitroglycerin to cause skin sensitization. Vaillant et al. [1990] reported a prospective study in which 33 patients using transdermal nitroglycerin for more than 7 days tested negative in patch tests with nitroglycerin, even though 5 patients (15%) had adverse reactions (burning sensation, sweating, itching, severe erythema, and erythematous vesicular lesions). Kounis et al. [1996] assessed cutaneous reactions to nitroglycerin in a study involving continuous and intermittent use of three different commercially available nitroglycerin TTSs by 320 subjects. Four (1.2%) of these subjects developed localized and remote skin reactions. Three of the four subjects were patch-tested and had positive reactions to both a nitroglycerin solution [0.2 milligram per milliliter (mg/mL)] and a nitroglycerin ointment (concentration not reported). Other case reports described individuals who presented with or without dermatitis from topical use of a nitroglycerin TTS or nitroglycerin ointment and developed allergic reactions when patch-tested with nitroglycerin, nitroglycerin delivered in TTS, or nitroglycerin solutions [Sausker and Frederick 1978; Zugerman et al. 1979; Hendricks and Dec 1979; Rosenfeld and White 1984; Fischer and Tyler 1985; Topaz and Abraham 1987; Silvestre et al. 1991; Kanerva et al. 1991; Torres et al. 1992; Kounis et al. 1996; Machet et al. 1999; Perez-Calderon et al. 2002]. Aquilina et al. [2002] reported a single case of cross-sensitive contact reaction to nitroglycerin (applied in a transdermal patch) following intravenous therapy with isosorbide dinitrate. Nitroglycerin was also reported to cause moderate skin sensitization in one guinea pig maximization test (GPMT) [Lee et al. 1975]. DEREK™ predicted nitroglycerin to be negative for skin sensitization.

Although nitroglycerin yielded negative patch-test results in some prospective studies [Vaillant 1990; Velez et al. 1992; Stanford and Georgouras 1996], findings from patch tests in humans presenting with or without dermatitis after use of topical or transdermal nitroglycerin products **[Sausker and Frederick 1978; Zugerman et al. 1979; Hendricks and Dec 1979; Rosenfeld and White 1984; Fischer and Tyler 1985; Topaz and Abraham 1987; Silvestre et al. 1991; Kanerva et al. 1991; Torres et al. 1992; Kounis et al. 1996; Machet et al. 1999; Perez-Calderon et al. 2002]** and from a GPMT **[Lee et al. 1975]** provide limited evidence that prolonged and repeated contact with nitroglycerin may cause allergic contact

dermatitis or other immune-mediated responses. Therefore, on the basis of the data for this assessment, nitroglycerin is assigned the SK: SEN notation.

5 Summary

The available toxicokinetic data from studies of both humans and animals **[Wester et al. 1959; Gjesdal et al. 1985; McAllister et al. 1986; Kikkoji et al. 1991]** indicate that nitroglycerin can be absorbed through the skin. The wealth of data relating to therapeutic use of topically applied nitroglycerin indicate that such application of nitroglycerin induces systemic effects such as circulatory or vascular changes and death **[Novartis Pharmaceutical Corporation 2000]**. Developmental studies indicated that nitroglycerin is fetotoxic (causing decreased birth weights) for rats. Available data indicate that abrupt withdrawal of workers from long-term nitroglycerin exposure may result in deaths due to continued vascular tolerance **[NIOSH 1978; Hogstedt and Andersson 1979; Abrams 1980]**. Sufficient data are available from human experience **[Vaillant et al. 1990; Kounis et al. 1996]** and standard animal studies **[Lee et al. 1975]** to demonstrate that dermal exposures to nitroglycerin can cause mild skin irritation. Although the incidence of skin sensitization in humans appears to be rare (given the extensive use of nitroglycerin for prevention and treatment of suffocating chest pain), the findings in human patch tests **[Sausker and Frederick 1978; Zugerman et al. 1979; Hendricks and Dec 1979; Rosenfeld and White 1984; Fischer and Tyler 1985; Topaz and Abraham 1987; Silvestre et al. 1991; Kanerva et al. 1991; Torres et al. 1992; Kounis et al. 1996; Machet et al. 1999; Perez-Calderon et al. 2002]** and one GPMT **[Lee et al. 1975]** provide limited evidence that prolonged and repeated use of nitroglycerin can cause allergic contact dermatitis. Therefore, on the basis of the data for this assessment, nitroglycerin is assigned the notation **SK: SYS (FATAL)-DIR (IRR)-SEN**.

Table 3 summarizes the skin hazard designations for nitroglycerin previously issued by NIOSH and other organizations. The equivalent dermal designations for nitroglycerin, according to the Global Harmonized System (GHS) of Classification and Labeling of Chemicals, are Acute Toxicity Category 1 (Hazard statement: Fatal in contact with the skin) and a Category 2 Repeated Exposure Toxicant (Hazard statement: May cause damage to organs through prolonged or repeated exposure) [European Parliament 2008].

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

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption
OSHA [2010]	[skin]: Based on potential contribution to overall exposure by the cutaneous route, including the mucous membranes and the eyes, either by airborne exposure or, more particularly, direct contact with the substance
ACGIH [2001]	[skin]: Based on the potential for dermal absorption and subsequent systemic toxicity
EC [2010]	R27: Very toxic in contact with skin

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 Nitroglycerin

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for nitroglycerin. 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 nitroglycerin

Variables used in calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path(K_{psc})	cm/hr	0.00093
Permeation coefficient of the protein fraction of the stratum corneum (K_{pol})	cm/hr	1.008×10^{-5}
Permeation coefficient of the watery epidermal layer (K_{aq})	cm/hr	0.16590
Molecular weight (MW)*	amu	227
Base-10 logarithm of its octanol–water partition coefficient (log K_{OW})*	None	1.62
Calculated skin permeation coefficient (K_p)	cm/hr	0.00094
Skin dose		
Water solubility (S_W)*	mg/cm^3	1.38
Calculated skin permeation coefficient (K_p)	cm/hr	0.00094
Estimated skin surface area (palms of hand)	cm^2	360
Exposure time	hr	8
Calculated skin dose	mg	3.73
Inhalation dose		
Occupational exposure limit (OEL)†	mg/m^3	0.1
Inhalation volume	m^3	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	0.75
Skin dose–to–inhalation dose (SI) ratio	None	4.97

*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 nitroglycerin. The calculated SI ratio was 4.97. On the basis of these results, nitroglycerin is predicted to represent a skin absorption hazard.

Appendix References

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DHHS (NIOSH) Publication No. 2011–147

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