

# NIOSH Skin Notation Profiles

## Nicotine

SK

ID<sup>SK</sup>

[SK]

**SYS**

SYS (FATAL)

DIR

**DIR (IRR)**

DIR (COR)

**SEN**

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# NIOSH Skin Notation (SK) Profile

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**Nicotine**

**[CAS No. 54-11-5]**

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**Naomi L. Hudson and G. Scott Dotson**

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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 nicotine. 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

<b>ACGIH</b>	American Conference of Governmental Industrial Hygienists
<b>Amu</b>	atomic mass unit
<b>ATSDR</b>	Agency for Toxic Substances and Disease Registry
<b>CIB</b>	Current Intelligence Bulletin
<b>cm<sup>2</sup></b>	square centimeter(s)
<b>cm/hr</b>	centimeter(s) per hour
<b>cm/s</b>	centimeter(s) per second
<b>DEREK</b>	Deductive Estimation of Risk from Existing Knowledge
<b>DIR</b>	skin notation indicating the potential for direct effects to the skin following contact with a chemical
<b>EC</b>	European Commission
<b>GHS</b>	Globally Harmonized System for Classification and Labelling of Chemicals
<b>GPMT</b>	guinea pig maximization test
<b>GTS</b>	green tobacco sickness
<b>IARC</b>	International Agency for Research on Cancer
<b>(IRR)</b>	subnotation of SK: DIR indicating the potential for a chemical to be a skin irritant following exposure to the skin
<b><math>k_{aq}</math></b>	coefficient in the watery epidermal layer
<b><math>k_p</math></b>	skin permeation coefficient
<b><math>k_{pol}</math></b>	coefficient in the protein fraction of the stratum corneum
<b><math>k_{psc}</math></b>	permeation coefficient in the lipid fraction of the stratum corneum
<b>LD<sub>50</sub></b>	dose resulting in 50% mortality in the exposed population
<b>LD<sub>Lo</sub></b>	dermal lethal dose
<b>LLNA</b>	local lymph node assay
<b>LOAEL</b>	lowest-observed-adverse-effect level
<b>log <math>K_{ow}</math></b>	base-10 logarithm of a substance's octanol–water partition
<b>m<sup>3</sup></b>	cubic meter(s)
<b>mg</b>	milligram(s)
<b>mg/day</b>	milligram(s) per day
<b>mg/cm<sup>2</sup>/hr</b>	milligram(s) per square centimeter per hour
<b>mg/kg</b>	milligram(s) per kilogram body weight
<b>mg/m<sup>3</sup></b>	milligram(s) per cubic meter
<b>mL</b>	milliliter(s)
<b>mL/kg</b>	milliliter(s) per kilogram body weight
<b>MW</b>	molecular weight
<b>ng</b>	nanogram(s)
<b>ng/mL</b>	nanogram(s) per milliliter
<b>ng/mL/m<sup>2</sup></b>	nanogram(s) per milliliter per square meter
<b>NIOSH</b>	National Institute for Occupational Safety and Health



<b>NOAEL</b>	no-observed-adverse-effect level
<b>NTP</b>	National Toxicology Program
<b>OEL</b>	occupational exposure limit
<b>OSHA</b>	Occupational Safety and Health Administration
<b>REL</b>	recommended exposure limit
<b>RF</b>	retention factor
<b>SEN</b>	skin notation indicating the potential for immune-mediated reactions following exposure of the skin
<b>SI</b>	ratio ratio of skin dose to inhalation dose
<b>SK</b>	skin notation
<b>S<sub>w</sub></b>	solubility in water
<b>SYS</b>	skin notation indicating the potential for systemic toxicity following exposure of the skin
<b>TTS</b>	transdermal nicotine-delivery system
<b>US EPA</b>	United States Environmental Protection Agency
<b>µg/L</b>	microgram(s) per liter
<b>µg/cm<sup>2</sup>/hr<sup>1/2</sup></b>	microgram(s) per square centimeter per half hour
<b>µM/cm<sup>2</sup>/hr</b>	micromole(s) per square centimeter per hour

## 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 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:

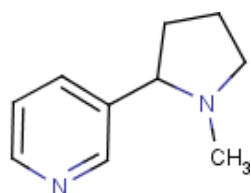
**Chemical:** Nicotin

**CAS No:** 54-11-5

**Molecular weight (MW):** 162.2

**Molecular formula:** C<sub>5</sub>H<sub>4</sub>NC<sub>4</sub>H<sub>7</sub>NCH<sub>3</sub>

**Structural formula:**



**Synonyms:** 3-(1-Methyl-2-pyrrolidyl) pyridine

**Uses:** Nicotine is an alkaloid found within tobacco plants. It is used in medicinal applications and as a pesticide [ACGIH 2001].

## 1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with nicotine and the rationale behind the hazard-specific skin notation (SK) assignment for nicotine. 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 nicotine. A literature search was conducted through September 2014 to identify information on nicotine, 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

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

Skin notation	Critical effect	Available data
SK: SYS	Nervous system effects, cerebrovascular disease, developmental effects including potential pregnancy loss	Sufficient human and animal data
SK: DIR (IRR)	Skin irritation	Sufficient animal data
SK: SEN	Skin allergy	Sufficient human data

systems that are relevant to assessing the effects of dermal exposure to nicotine.

### 1.3 Overview of SK Assignment

Nicotine 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 nicotine: **SK: SYS-DIR (IRR)-SEN**. Table 1 provides an overview of the critical effects and data used to develop the SK assignment for nicotine.

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

Numerous toxicokinetic data were identified that provide evidence of the absorption of nicotine in humans through skin, following dermal exposure. The nicotine transdermal therapeutic system (TTS) is extensively used in treatment of tobacco addiction. In a TTS study that evaluated the potential of nicotine to be absorbed through the skin, 52.5 milligrams (mg) nicotine was applied to the lower 30 square centimeters (cm<sup>2</sup>) of the abdomen of 14 cigarette-abstinent smokers for 24 hours, with deuterium-labeled nicotine infused simultaneously to the TTS application [Benowitz et al. 1991]. The absolute bioavailability, based on the amount of nicotine released from the patch, averaged 76.8%, with a peak rate of absorption occurring between 6 and 12 hours after TTS application. The authors also reported the continued absorption of nicotine after the TTS was removed, which accounted for an average of 10% of the dose [Benowitz et al. 1991]. Other studies measured nicotine and metabolite levels in the blood following dermal exposure. For example, Kongtip et al. [2009] measured the concentration of nicotine residue on the hands of tobacco workers working in the post-curing process and found a linear correlation between the amount of nicotine residue on hands and urine cotinine concentrations. Gorsline et al. [1992] applied nicotine at a dosage of 14 milligrams per day

(mg/day) to the upper back, upper outer arm, and upper chest of 12 smokers and reported that nicotine concentrations in plasma increased rapidly within 2 to 4 hours, reaching peaks of 11 to 14 nanograms per milliliter (ng/mL) at all sites. Using higher doses, Homsy et al. [1997] applied 21-mg nicotine patches to the skin of 18 male smokers for 2 days, measuring maximum nicotine concentrations of 30.2 ng/mL in the plasma.

Dermal exposure to nicotine has also been demonstrated in farmers handling tobacco leaves. In nonsmoking tobacco farmers, Onuki et al. [2003] measured urinary levels of cotinine, a metabolite of nicotine, of 37.0 ng/mL per square meter (ng/mL/m<sup>2</sup>) in farmers not wearing protective gloves and 17.2 ng/mL/m<sup>2</sup> in farmers wearing protective gloves. D'Alesandro et al. [2001] measured peak blood nicotine levels of 3.45 nanograms per liter (ng/L) in a 1-day biological monitoring study of 10 female tobacco harvesters. Urinary nicotine reached a peak value of 158 ng/L at the end of the workday, and plasma cotinine levels averaged approximately 15 ng/L, indicating a daily intake of 1.2 mg nicotine [D'Alesandro et al. 2001].

In *in vitro*, the mean permeation rate (flux) of nicotine from a transdermal patch was reported to be 137.92 micrograms per square centimeter per half hour ( $\mu\text{g}/\text{cm}^2/\text{hr}^{1/2}$ ) in human skin excised from cadavers [Pongjanjajul et al. 2000]. Berner et al. [1990] reported *in vitro* skin fluxes for two donors of 0.24 and 0.49 micromoles per square centimeter per hour ( $\mu\text{M}/\text{cm}^2/\text{hr}$ ) from 1.0% and 5.0% test solutions, respectively. Zorin et al. [1999] measured flux of 82.0  $\mu\text{g}/\text{cm}^2/\text{hr}$  for 100% nicotine in excised human cadaver skin. In addition, the authors observed a dose-dependent increase in flux with aqueous solutions of nicotine. The flux ranged from 88.2 to 1341.5  $\mu\text{g}/\text{cm}^2/\text{hr}$  for 1% to 50% concentrations in water and 6.1 to 12.3  $\mu\text{g}/\text{cm}^2/\text{hr}$  in 8% and 20% ethanol, respectively. Zorin et al. [1999] noted that the permeation rate through the skin is dependent on the pH and the solvent type (water, ethanol, lipids, or phosphate buffer).

Toxicokinetic data from animals were also identified. In mice, Shah et al. [1981] observed that the geometric mean percentage penetration of radiolabeled nicotine (1 mg per kilogram body weight [mg/kg]) increased with duration of exposure, recording values of 5.2% (1 min), 27.9% (5 min), 59.5% (15 min), 71.5% (60 min), and 90.7% (480 min). Matsushima et al. [1995] evaluated dermal absorption of nicotine in dogs and found that topically administered nicotine patches at dosages of 1 to 2 mg/kg for 24 hours resulted in a maximum plasma concentration of 43 ng/mL.

The potential of nicotine 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 997.7 was calculated for nicotine. An SI ratio of  $\geq 0.1$  indicates that skin absorption may significantly contribute to the overall body burden of a substance [NIOSH 2009]; therefore, nicotine is considered to be absorbed through the skin following dermal exposure. Additional information on the SI ratio and the variables used in its calculation are included in the appendix.

No estimated dermal lethal dose ( $LD_{Lo}$ ) values for humans were identified. A dermal  $LD_{50}$  value (lethal dose in 50% of exposed animals) of 285 mg/kg has been reported for rats [Gaines 1969]. Because the reported acute dermal  $LD_{50}$  values for rats are lower than the critical dermal  $LD_{50}$  value of 2,000 mg/kg that identifies chemical substances with the potential for systemic toxicity following acute dermal exposure [NIOSH 2009], nicotine is considered toxic after acute dermal exposure.

Numerous epidemiological studies of dermal exposure to nicotine were identified [Ghosh et al. 1986; Ballard et al. 1995; Arcury et al., 2001, 2003; Trape-Cardoso et al. 2003]. Among

tobacco farmers, contact with green tobacco leaves has been observed to produce green tobacco sickness (GTS), defined as "acute nicotine poisoning due to the transdermal absorption of nicotine," with symptoms including dizziness, headache, nausea, and vomiting [Arcury et al. 2003]. GTS is a self-limiting condition from which workers typically recover within 1 to 3 days [Gehlbach et al. 1974; Ballard et al. 1995; McBride et al. 1998; Arcury et al. 2003; Trape-Cardoso et al. 2005]. The incidence of GTS in tobacco farmers varies with climate and season, with estimates of incidence ranging from 15 to 53% [Ghosh et al. 1986; Trape-Cardoso et al. 2003].

Greenland et al. [1998] conducted a meta-analysis, involving data from 47 reports collected during 35 clinical trials, to estimate the frequency of adverse effects associated with the use of the transdermal nicotine patch. Data for the analysis were synthesized from 41 groups of nicotine patch recipients, totaling 5501 patients (most of the nicotine patch groups used patches containing nicotine in the range of 17 to 25 mg), and 33 groups of placebo recipients, totaling 3752 patients (most used effectively inert patches, whereas 9 groups totaling 1155 patients used "placebo" patches that contained small doses (<1 mg) of nicotine) [Greenland et al. 1998]. Results indicated that the patch was effective as an aid to smoking abstinence, with few adverse cardiovascular outcomes (such as myocardial infarction, stroke, tachycardia, arrhythmia, or angina). However, several minor adverse effects were elevated among the nicotine-patch groups (sleep disturbances, nausea or vomiting, and respiratory symptoms) [Greenland et al. 1998]. In a later study, Gourlay et al. [1999] conducted a cohort study involving 1392 participants to assess the timing, severity, and predictive factors of adverse experiences reported during 24-hour transdermal nicotine therapy. The authors reported that the transdermal nicotine therapy was well tolerated, even if the user smoked concurrently and that the majority of adverse experiences during therapy were mild, with sleep disturbance occurring in 669 (48%) of 1392 participants

[Gourlay et al. 1999]. However, the authors indicated that the sleep disturbance was primarily associated with tobacco withdrawal rather than with nicotine excess from treatment with transdermal nicotine. In a more recent case report, Ang et al. [2005] reported 14 cases of cerebrovascular disease shortly (a mean of 40 days) after use of nicotine replacement therapy; 7 patients were exposed to 10–35 mg nicotine/day and 1 patient was exposed to 2–4 mg nicotine/day, for 4 hours to 3 months. The amount of nicotine the remaining 6 patients were exposed to is unknown. Their findings suggested that prolonged use of the nicotine patches may result in cerebrovascular disease. Lemay et al. [2003] reported complications during repeated-dose nicotine treatment in patients with Parkinson's disease, in which 64% of patients experienced nausea, vomiting, and dizziness after receiving 7 mg nicotine for 11 days, followed by 14 mg for 11 days and then 21 mg for the last 3 days.

Developmental toxicity resulting from dermal nicotine exposure was evaluated by Witschi et al. [1994], who reported that pregnancy failure was 100% among rats administered 3.5 mg nicotine during the entire pregnancy (days 2 through 19) and 50% among rats administered the same amount during the first trimester (days 2 through 7) and when 1.75 mg nicotine was applied during the entire pregnancy to the backs of pregnant rats. Among the rats administered nicotine during gestational days 2 through 19, mean plasma nicotine levels were 43 µg/L in those receiving 1.75 mg/day and 241 µg/L in those receiving 3.5 mg/day. Witschi et al. [1994] concluded that continuous exposure to nicotine early during pregnancy may adversely affect pregnancy outcome in rats. Therefore, the dose of 1.75 mg/kg-day, the lowest dose tested, can be regarded as the lowest-observed-adverse-effect level (LOAEL) on the basis of pregnancy loss, with no NOAEL (no-observed-adverse-effect level) estimated. Because the rat LOAEL and the therapeutic dose for patients receiving nicotine replacement therapy who experience adverse outcomes are lower than the critical dermal NOAEL value of 1000 mg/kg-day that

identifies chemical substances with potential for repeated-dose dermal toxicity [NIOSH 2009], nicotine is considered systemically available and able to cause systemic effects (nervous system symptoms, cerebrovascular disease, and pregnancy loss) following dermal exposure.

Evaluation of the potential carcinogenicity of nicotine following dermal exposure has been limited. In a population-based case-control interview study of pesticide applicators, a statistically significantly increased risk for leukemia was reported for sprayers of nicotine [Brown et al. 1990]. In farmers who applied nicotine at least once, the odds ratio of developing leukemia relative to nonfarmers was 1.6 (confidence interval [CI], 1.0–2.6); the odds ratio increased to 2.0 (CI, 1.2–3.4) in farmers who reported spraying nicotine for more than 20 years [Brown et al. 1990]. Davis et al. [2009] reported that tumor size increased in BALB/c mice when nicotine was administered via intraperitoneal injection or transdermal patches, suggesting that nicotine might facilitate the progression of tumors that are already initiated by tobacco carcinogens. No standard animal cancer bioassays were identified. Table 2 summarizes carcinogenic designations for nicotine by multiple governmental and non-governmental organizations.

Toxicokinetic data on humans *in vivo* [Benowitz et al. 1991; Gorsline et al. 1992; D'Alesandro et al. 2001; Onuki et al. 2003] and *in vitro* [Zorin et al. 1999; Pongjanyajul et al. 2000] and data on animals [Shah et al. 1981; Matsushima et al. 1995] indicate that nicotine is readily absorbed through the skin. Acute dermal toxicity studies [such as **Gaines 1969**]\*, numerous epidemiological data [**Ghosh et al. 1986; Ballard et al. 1995; Arcury et al. 2003; Trape-Cardoso et al. 2003; Ang et al. 2005**], and developmental toxicity data from rats [**Witschi et al. 1994**] indicate nicotine is systemically available and systemically toxic, with the potential to cause a variety of symptoms secondary to nervous

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



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

Organization	Carcinogenic designation
NIOSH [2005]	No designation
NTP [2014]	No designation
US EPA [2014]	No designation
European Parliament [2008]	No GHS designation
IARC [2012]	No designation
ACGIH [2001]	No designation

ACGIH = American Conference of Governmental Industrial Hygienists; GHS = Globally Harmonized System for Classification and Labelling; 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.

system effects, cerebrovascular disease with prolonged exposure, and developmental effects, including pregnancy loss in rats. Therefore, on the basis of the data for this assessment, nicotine is assigned the SK: SYS notation.

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

No human or animal *in vivo* studies for corrosivity of nicotine, *in vitro* tests for corrosivity using human or animal skin models, or *in vitro* tests for skin integrity using cadaver skin were identified. In addition, no standard irritation tests in animals were identified. Several studies reporting local skin reactions to nicotine and nicotine patches were identified. In an evaluation of 1392 patients undergoing transdermal nicotine therapy for smoking, Gourlay et al. [1999] reported erythema in 14.7%, rash in 5.2%, pruritis in 20.8%, irritation in 4.7%, vesicles in 4.9%, and edema in 3.8% of patients. Of pregnant women receiving a nicotine patch for smoking cessation, 23 of 203 women reported a skin reaction at the patch site [Berlin et al. 2014]. Application of 0.2 mL nicotine to the backs of 16 women for 30 min/day for 3 days, by means of Hill Top chambers, produced redness and mild to moderate erythema [Berner et al. 1990]. In 183 smokers undergoing transdermal nicotine therapy, 53% experienced pruritis and 39% developed erythema [Eichelberg et al. 1989]. Bircher et al. [1991] patch-tested 14 volunteers with a

history of adverse reactions to nicotine TTS. When patch-tested with the individual components of the TTS, the authors reported irritation reactions due to occlusion in nine subjects. In the meta-analysis conducted by Greenland et al. [1998], localized skin irritation was reported as one of the several minor adverse effects that was elevated in 25% of patients in the nicotine-patch groups.

As indicated by the dermatitis and irritation observed in humans [Berner et al. 1990; Bircher et al. 1991; Greenland et al. 1998; Gourlay et al. 1999; Berlin et al. 2014], nicotine may be a potential skin irritant. Therefore, on the basis of the data for this assessment, nicotine is assigned the SK: DIR (IRR) notation.

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

Human patch tests and case reports provide evidence of skin sensitization following dermal exposure to nicotine. Case reports of allergic contact dermatitis in individuals using transdermal nicotine patches to relieve smoking withdrawal symptoms are numerous [Eichelberg et al. 1989; Bircher et al. 1991; Farm 1993; Vincenzi et al. 1993; Dwyer and Forsyth 1994]. Among 183 smokers undergoing transdermal nicotine therapy with patches delivering 7.2 to 21.6 mg/d for 8 weeks, 5 (2.6%) exhibited allergic contact dermatitis [Eichelberg et al.

1989]. In two large, randomized, double-blind, multicenter studies, the Transdermal Nicotine Study Group [1991] found that 11 (1.6%) of 664 patients who received transdermal nicotine developed contact sensitization, which was confirmed upon rechallenge. In an evaluation of 14 people who had previously presented with adverse skin reactions from the use of nicotine patches, positive allergic responses to nicotine solutions occurred in 1 person at 1% concentration of, and positive allergic responses were observed in 3 people at a 10% concentration and one person at a 50% concentration. One person had positive allergic response to a 5% concentration of nicotine sulphate [Bircher et al. 1991]. Irritant reactions were reported in the remaining 9 people [Bircher et al. 1991]. Dwyer and Forsyth [1994] reported allergic contact dermatitis from nicotine TTS when an individual was patch tested with nicotine base (5% aqueous and 5% in ethanol). The patient also reacted positively to other components in the patch. Another patient reacted to a nicotine base concentration as low as 3% aqueous solution when patch-tested [Farm 1993]. Vincenzi et al. [1993] reported 5 cases in which erythema or eczematous reactions occurred after use of a nicotine TTS; the cases had positive responses to patch tests with the GIRDCA standard series nicotine base in 1% and 10% aqueous solutions. Goncalo et al. [1990] reported allergic contact dermatitis in a female tobacco plantation worker, who experienced allergic reactions in response to handling greenish or yellowish tobacco leaves, as well as to acetone and ether extracts of green leaf tobacco; however, negative responses were observed for 0.5 and 1% nicotine. No predictive tests (for example, guinea pig maximization tests, Buehler tests, murine local lymph node assays, mouse ear swelling tests) or other tests were identified that evaluated the potential of nicotine to cause skin sensitization in animals.

Several studies of transdermal nicotine patches [Eichelberg et al. 1989; Bircher et al. 1991; Transdermal Nicotine Study Group 1991; Vincenzi et al. 1993; Dwyer and Forsyth 1994] provide sufficient evidence that nicotine can cause allergic contact dermatitis

in humans. Therefore, on the basis of the data for this assessment, nicotine is assigned the SK: SEN notation.

## 5 Summary

Sufficient toxicokinetic data on humans *in vivo* [Benowitz et al. 1991; Gorsline et al. 1992; D'Alesandro et al. 2001; Onuki et al. 2003] and *in vitro* [Zorin et al. 1999; Pongjanyajul et al. 2000] and data on animals [Shah et al. 1981; Matsushima et al. 1995] demonstrate that nicotine is readily absorbed through the skin and is systemically available. Acute dermal toxicity studies [Gaines 1969], epidemiological studies [Ghosh et al. 1986; Ballard et al. 1995; Arcury et al. 2003; Trape-Cardoso et al. 2003; Ang et al. 2005], and developmental toxicity studies in rats [Witschi et al. 1994] indicate that nicotine is systemically available and toxic, with the potential to cause a variety of diverse symptoms secondary to effects on the nervous system, cerebrovascular disease with prolonged exposure, and developmental effects such as pregnancy loss. Dermatitis and irritation observed in humans [Berner et al. 1990; Bircher et al. 1991; Greenland et al. 1998; Gourlay et al. 1999; Berlin et al. 2014] provide sufficient evidence that nicotine has the potential to be a skin irritant. Several studies using transdermal nicotine therapy [Eichelberg et al. 1989; Bircher et al. 1991; Transdermal Nicotine Study Group 1991; Vincenzi et al. 1993; Dwyer and Forsyth 1994] also provide sufficient evidence that nicotine can cause skin sensitization in humans. Therefore, on the basis of these assessments, nicotine is assigned a composite skin notation of **SK: SYS- DIR (IRR)-SEN**.

Table 3 summarizes the skin hazard designations for nicotine previously issued by NIOSH and other organizations. The equivalent dermal designation for nicotine, according to the Globally Harmonized System (GHS) for the Classification and Labelling of Chemicals, is Acute Toxicity Category 1 (Hazard statement: Fatal in contact with the skin) [European Parliament 2008].

**Table 3. Summary of previous skin hazard designations for nicotine**

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption; prevent skin contact
OSHA [2014]*	[skin]: Potential for dermal absorption
ACGIH [2001]	[skin]: Based on percutaneous absorption and systemic toxicity from handling tobacco leaves

ACGIH = American Conference of Governmental Industrial Hygienists; 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 Nicotine

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for nicotine. Although the SI ratio is considered in the determination of a substance's hazard potential following skin contact, it is intended to serve only 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 its 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

$$\begin{aligned} \log k_{psc} &= -1.326 + 0.6097 \times \log k_{ow} - \\ &\quad 0.1786 \times MW^{0.5} \\ k_{pol} &= 0.0001519 \times MW^{0.5} \\ k_{aq} &= 2.5 \times MW^{0.5} \end{aligned}$$

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<sup>2</sup>]).

### Equation 2: Determination of Skin Dose

$$\begin{aligned}\text{Skin dose} &= k_p \times S_w \times \text{Exposed skin surface area} \times \text{Exposure time} \\ &= k_p (\text{cm/hour}) \times S_w (\text{mg/cm}^3) \times \\ &\quad 360 \text{ cm}^2 \times 8 \text{ hours}\end{aligned}$$

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<sup>3</sup>) 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

$$\begin{aligned}\text{Inhalation dose} &= \text{OEL} \times \text{Inhalation volume} \times \text{RF} \\ &= \text{OEL} (\text{mg/m}^3) \times 10 \text{ m}^3 \times 0.75\end{aligned}$$

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

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.

## Calculations

Table A1 summarizes the data applied in the previously described equations to determine the SI ratio for nicotine. The calculated SI ratio was 997.7. On the basis of these results, nicotine is predicted to represent a skin absorption hazard.

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

Variables used in calculation	Units	Value
<b>Skin permeation coefficient</b>		
Permeation coefficient of stratum corneum lipid path ( $k_{psc}$ )	cm/hr	0.0013
Permeation coefficient of the protein fraction of the stratum corneum ( $k_{pol}$ )	cm/hr	$1.1926 \times 10^{-5}$
Permeation coefficient of the watery epidermal layer ( $k_{aq}$ )	cm/hr	0.1963
Molecular weight ( $MW$ ) <sup>†</sup>	amu	162.23
Base-10 logarithm of its octanol–water partition coefficient ( $Log K_{ow}$ ) <sup>†</sup>	None	1.17
Calculated skin permeation coefficient ( $k_p$ )	cm/hr	0.0013
<b>Skin dose</b>		
Water solubility ( $S_w$ ) <sup>†</sup>	mg/cm <sup>3</sup>	1000
Calculated skin permeation coefficient ( $k_p$ )	cm/hr	0.0013
Estimated skin surface area (palms of hands)	cm <sup>2</sup>	360
Exposure time	hr	8
Calculated skin dose	mg	3741.25
<b>Inhalation dose</b>		
Occupational exposure limit (OEL) <sup>†</sup>	mg/m <sup>3</sup>	0.5
Inhalation volume	m <sup>3</sup>	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	3.75
<b>Skin dose–to–inhalation dose (SI) ratio</b>	<b>None</b>	<b>997.7</b>

<sup>†</sup>Variables identified from SRC [ND].

<sup>†</sup>The OEL used in calculation of the SI ratio for nicotine was the NIOSH recommended exposure limit (REL) [NIOSH 2005].



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