NIOSH Skin Notation Profiles

1-Bromopropane

SK

ID[SK]

[~~SK~~]

SYS

SYS (FATAL)

DIR

DIR (IRR)

DIR (COR)

SEN

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

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NIOSH Skin Notation (SK) Profile

1-Bromopropane

[CAS No. 106-94-5]

Naomi L. Hudson and G. Scott Dotson

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 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 (SKs) 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 1-bromopropane (1-BP). 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.

John Howard, M.D.
Director, National Institute for
Occupational Safety and Health
Centers for Disease Control and Prevention

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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/hr	centimeter(s) per hour
cm/s	centimeter(s) per second
DEREK	Deductive Estimation of Risk from Existing Knowledge
DIR	skin notation indicating the potential for direct effects to the skin following contact with a chemical
EC	European Commission
g	gram(s)
g/L	gram(s)/liter
GHS	Globally Harmonized System for Classification and Labelling of Chemicals
GPMT	guinea pig maximization test
hr	hour(s)
IARC	International Agency for Research on Cancer
IPCS	International Program for Chemical Safety
(IRR)	subnotation of SK: DIR indicating the potential for a chemical to be a skin irritant following exposure to the skin
k_{aq}	coefficient in the watery epidermal layer
k_p	skin permeation coefficient
k_{pol}	coefficient in the protein fraction of the stratum corneum
k_{psc}	permeation coefficient in the lipid fraction of the stratum corneum
LD_{50}	dose resulting in 50% mortality in the exposed population
LD_{Lo}	dermal lethal dose
LLNA	local lymph node assay
LOAEL	lowest-observed-adverse-effect level
log K_{OW}	base-10 logarithm of a substance's octanol–water partition
M	molarity
m^3	cubic meter(s)
mg	milligram(s)
$mg/cm^2/hr$	milligram(s) per square centimeter per hour
mg/kg	milligram(s) per kilogram body weight
mg/m^3	milligram(s) per cubic meter
mL	milliliter(s)
mL/kg	milliliter(s) per kilogram body weight
MW	molecular weight
NIOSH	National Institute for Occupational Safety and Health
$nmol/cm^2/hr$	nanomoles 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
ppm	parts per million
REL	recommended exposure limit
RF	retention factor
SEN	skin notation indicating the potential for immune-mediated reactions following exposure of the skin
SI ratio	ratio of skin dose to inhalation dose
SK	skin notation
S_W	solubility in water
SYS	skin notation indicating the potential for systemic toxicity following exposure of the skin
USEPA	United States Environmental Protection Agency
µg	microgram(s)
µg/cm^2	microgram(s) per square centimeter
µg/cm^2/hr	microgram(s) per square centimeter per hour
µL	microliter(s)
µmol	micromole(s)

Glossary

Absorption—The transport of a chemical from the outer surface of the skin into both the skin and systemic circulation (including penetration, permeation, and resorption).

Acute exposure—Contact with a chemical that occurs once or for only a short period of time.

Cancer—Any one of a group of diseases that occur when cells in the body become abnormal and grow or multiply out of control.

Contaminant—A chemical that is (1) unintentionally present within a neat substance or mixture at a concentration less than 1.0% or (2) recognized as a potential carcinogen and present within a neat substance or mixture at a concentration less than 0.1%.

Cutaneous (or percutaneous)—Referring to the skin (or through the skin).

Dermal—Referring to the skin.

Dermal contact—Contact with (touching) the skin.

Direct effects—Localized, non-immune-mediated adverse health effects on the skin, including corrosion, primary irritation, changes in skin pigmentation, and reduction/disruption of the skin barrier integrity, occurring at or near the point of contact with chemicals.

Immune-mediated responses—Responses mediated by the immune system, including allergic responses.

Sensitization—A specific immune-mediated response that develops following exposure to a chemical, which, upon re-exposure, can lead to allergic contact dermatitis (ACD) or other immune-mediated diseases such as asthma, depending on the site and route of re-exposure.

Substance—A chemical.

Systemic effects—Systemic toxicity associated with skin absorption of chemicals after exposure of the skin.

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Charles L. Geraci, Ph.D.
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Health Effects Laboratory Division

Stacey Anderson, Ph.D.
H. Fredrick Frasch, Ph.D.
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1 Introduction

1.1 General Substance Information:

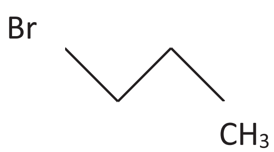
Chemical: 1-Bromopropane (1-BP)

CAS No: 106-94-5

Molecular weight (*MW*): 123.00

Molecular formula: $CH_3CH_2CH_2Br$

Structural formula:



Synonyms: 1-BP; N-Propyl bromide; nPB; Propyl bromide; n-Propyl bromide; Propane, 1-bromo

Uses: 1-Bromopropane (1-BP) is used primarily as a solvent in vapor degreasing and cold cleaning operations, as well as adhesive and coating spray applications [USEPA 2003]. An estimated 8.2 million pounds (3.8 million kilograms) of 1-BP was used in the United States in 2002 [NTP 2004].

1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with 1-BP and (2) the rationale behind the hazard-specific skin notation (SK) assignment for 1-BP. 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 1-BP and the potential for direct skin injuries from 1-BP. A literature search was conducted through June 2017 to identify 1-BP 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 1-BP. The criteria for the search strategy, evaluation, and selection of data are described in Appendix E in *CIB 61: A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009].

1.3 Overview of SK Assignment

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

2 Systemic Toxicity from Skin Exposure (SK: SYS)

There were no toxicokinetic studies involving humans identified; however an *in vitro* dermal penetration study was identified. Frasch et al. [2011] used heat-separated epidermal membranes from Caucasian female breasts or abdominal skin samples with 3 different dosing

Table 1. Summary of the SK assignment for 1-BP

Skin notation	Critical effect	Available data
SK: SYS	Neurotoxicity; reproductive and developmental toxicity	Animal toxicity data from studies of alternative exposure routes (inhalation, oral, and subcutaneous injection)
SK: DIR(IRR)	Skin irritation	Sufficient animal data

regimens. The skin samples were dosed with 10 microliters per square centimeter (μL/cm^2), equivalent to 13.5 milligrams per square centimeter (mg/cm^2), in an non occluded environment to simulate splash exposures. The samples had a transient exposure (10 minutes of exposure where 1-BP was applied to donor compartments in an occluded environment to an infinite dose of 1-BP, 179 ± 78 micrograms per square centimeter (μg/cm^2)), or were exposed to an infinite dose of 1-BP in an occluded environment for 3 hours [Frasch et al. 2011]. The authors noted that the total amount of 1-BP absorbed from the 13.5 mg/cm^2 dose was 22 μg/cm^2, corresponding to an average penetration of 0.16% of the applied dose [Frasch et al. 2011]. The total amount of 1-BP absorbed from transient and infinite exposures was 179 μg/cm^2, and 1,322 μg/cm^2, respectively [Frasch et al. 2011]. These data indicate that 1-BP has the potential for substantial dermal penetration dependent of type and duration of exposure. The potential of 1-BP to pose a skin absorption hazard has also been evaluated with use of a predictive algorithm for estimating and evaluating the health hazards of dermal exposure to chemical substances [NIOSH 2009]. The evaluation method compares the chemical dose accumulated in the body from skin absorption and the 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) calculated for 1-BP by 8.43. An SI ratio of ≥0.1 indicates that skin absorption may significantly contribute to the overall body burden of a substance [NIOSH 2009]; therefore, 1-BP has the potential to be absorbed through the skin and to become available systemically following dermal exposure. Additional information on the SI ratio can be found in the appendix.

No dermal lethal doses (LD_{Lo}) of 1-BP for humans have been identified. Only one acute dermal toxicity study was identified, in which 1-BP (2,000 milligrams per kilogram body weight [mg/kg]; 99.3% purity) was applied to the shaved dorsal skin of rats under semi-occlusive wrap for 24 hours [Elf Atochem 1995a]. In this study, no clinical signs of toxicity were observed, and the authors concluded that the dermal LD_{50} (the dose resulting in 50% mortality in the exposed population) was higher than 2,000 mg/kg, indicating that 1-BP is not acutely toxic upon dermal exposure. However, 1-BP is highly volatile, and the use of semi-occlusive instead of occlusive wrap is likely to have resulted in evaporation of the chemical, leading to a less-than-optimal exposure period.

Because of a paucity of toxicokinetic and toxicity data concerning skin exposures to 1-BP, a review of data associated with alternative exposure pathways (e.g., inhalation, oral, and subcutaneous injections) was conducted. Numerous studies of rats revealed systemic effects, including neurotoxicity, hepatotoxicity, hematotoxicity, reproductive toxicity, and developmental toxicity, attributed to the inhalation of airborne 1-BP below 1,000 parts per million (ppm) [ClinTrials Bioresearch 1997; Ichihara et al. 2000a, b; WIL Research Laboratories 2001; Wang et al. 2002, 2003; Yamada et al. 2003; NTP 2004; Banu et al. 2007; Fueta et al. 2007]. Anderson et al. [2010] reported significant decreases in the spleen IgM responses to sheep red blood cells in mice (125-500 ppm) and rats

Table 2. Summary of the carcinogenic designations for 1-BP* by numerous governmental and nongovernmental organizations

Organization	Carcinogenic designation
NIOSH	No designation
NTP [2014]	Reasonably anticipated to be a human carcinogen
European Parliament [2008]	No GHS designation
USEPA [2015]	No designation
IARC [2012]	No designation
ACGIH [2014]	A3, Confirmed animal carcinogen with unknown relevance to humans

ACGIH = American Conference of Governmental Industrial Hygienists; GHS = Globally Harmonized System for Classification and Labelling of Chemicals; IARC = International Agency for Research on Cancer; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; 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.

(1000 ppm) after whole body inhalation exposure to 1-BP for 10 weeks. Lee et al. [2005, 2007] treated mice with a single dose of 1-BP at levels of 200, 500, and 1,000 mg/kg via the oral route. At 500- and 1000-mg/kg treatment levels, the authors reported a significant increase in relative liver weight and changes in liver enzyme levels [Lee et al. 2005, 2007]. In another investigation, Zhao et al. [1999] treated rats with daily injections of 1-BP at treatment levels of 3.7 millimoles (mmol)/kg (corresponding to 455 mg/kg) and 11.0 mmol/kg (corresponding to 1,353 mg/kg) for 20 days. At both treatment levels, neurotoxic effects were reported.

There were no human epidemiological studies or repeated-dose (subchronic or chronic) studies in animals that evaluated the potential of 1-BP to cause systemic toxicity following dermal exposure were identified. However, occupational (presumably a combination of dermal and respiratory) exposure to 1-BP resulted in neuropathy in a male worker after he was exposed for 2 months to a degreasing solvent (containing 95.5% 1-BP, less than 0.5% butylene oxide, less than 2.5% 1,3-dioxolane, and less than 0.25% nitromethane) [Sclar 1999]. In addition, central nervous system effects were noted in a cohort of workers who had sprayed an adhesive (containing 70% 1-BP, 0.3% 1,2-epoxybutane, 10% styrene-butadiene rubber, and 20% rosin ester) without proper personal protective equipment in a poorly ventilated area for 30 to 40 hours a week for 3 months [Beck and Caravati 2003]. Other case reports also detailed nervous system effects [Ichihara et al. 2002, 2004a, 2004b; Majersik et al. 2007; Raymond and Ford 2007]. Hanley et al. [2006] assessed occupational exposures to 1-BP through air sampling and urinary testing for bromide (Br-) concentrations (a known biomarker of 1-BP exposure) in workers employed as either adhesive sprayers or nonsprayers at foam-fabricating plants that used a spray adhesive containing 1-BP during the manufacture of polyurethane seat cushions. One of the reported findings included a lower than expected correlation between urinary Br- concentration and time-weighted average (TWA) for sprayers, where the mean urinary Br- concentrations for sprayers were approximately 4 times greater than non-sprayers. The authors stated that this disparity may be due to the absorption of 1-BP by the skin when the sprayers handled the wet adhesive with bare hands. The results of Hanley et al. [2006] indicate that 1-BP may be absorbed via the skin, thus contributing to the systemic dose.

No standard toxicity or specialty studies evaluating biological system/function–specific effects (including reproductive and developmental effects and immunotoxicity) following dermal exposure to 1-BP were identified. Table 2 summarizes the carcinogenic designations for 1-BP from NIOSH and other governmental and nongovernmental organizations.

The mathematical model predicted that 1-BP was absorbed by the skin. Additionally, there was an *in vitro* dermal penetration study identified that indicates that 1-BP has the potential for substantial dermal penetration dependent on type and duration of exposure [Frasch et al. 2011]. Studies of workers exposed to 1-BP indicate that the solvent may be absorbed by the skin and contribute to systemic toxicity, but the results of these investigations are confounded by the inhalation of 1-BP vapors [Sclar 1999; Ichihara et al. 2002, 2004a, 2004b; Beck and Caravati 2003; NTP 2004; Hanley et al. 2006; Majersik et al. 2007; Raymond and Ford 2007]. A review of animal toxicity data from several non-dermal exposure routes indicated that 1-BP is capable of inducing a range of systemic effects, including neurotoxicity, hepatotoxicity, hematotoxicity, reproductive toxicity, and developmental toxicity in a dose-response manner **[ClinTrials Bioresearch 1997; Zhao et al. 1999; Ichihara et al. 2000a, 2000b; WIL Research Laboratory 2001; Wang et al. 2002, 2003; Lee et al. 2005, 2007; Banu et al. 2007; Fueta et al. 2007]**. Therefore, on the basis of these data, 1-BP is assigned the SK: SYS notation.

3 Direct Effects on Skin (SK: DIR)

No evidence of skin corrosivity of 1-BP, no *in vitro* tests for corrosivity in human or animal skin models, and no *in vitro* tests of skin integrity using cadaver skin were identified. Frasch et al. [2011] evaluated the corrosivity of 1-BP using the EpiDerm human reconstructed epidermis model. Using this model, a chemical is classified as corrosive to skin if the cell viability after a 3 minute exposure is less than 50% and less than 15% after a one hour exposure [Frasch et al. 2011]. Frasch et al. [2011] found that after the 3 minute exposure, the viability for cells exposed to 1-BP was 101% compared to the water-exposed control and a one hour exposure of 1-BP had a cell viability of 22%, indicating that 1-BP is not considered corrosive to the skin.

No studies on the skin-irritating potential of 1-BP in humans were identified, but there is limited evidence that the substance is a skin irritant in animals. Using a Draize scale, Jacobs et al. [1987] reported 1-BP was a skin irritant, and observed a limit concentration (defined as the highest tested concentration at which the mean erythema score remains below 2) for skin irritation of 50% for 1-BP solution in sweet almond oil in rabbits. In another test, performed according to the chemical testing guidelines of the Organization for Economic Co-operation and Development (OECD), topical application of 1-BP to rabbit skin produced erythema and edema and complete regeneration of the skin occurred within 8 days [Pálovics 2004]. Pálovics [2004] also tested the irritation potential of 1-BP on the chorioallantoic membrane of hen's egg according to the ECVAM/INVITTIX Protocol. In this test, local application of 1-BP caused copious hemorrhage and moderate lysis of blood vessels in the chorioallantoic membrane, indicating severe irritation after exposure to 1-BP; however, this procedure is typically used to evaluate ocular irritancy [Pálovics 2004]. Although rats administered 2,000 mg/kg 1-BP covered by a semi-occlusive dressing for 24 hours exhibited no cutaneous reaction [Elf Atochem 1995a], use of the semi-occlusive rather than occlusive wrap in this study was likely to result in less-than-optimal exposure. This may explain the lack of irritation observed by those investigators. The structure–activity relationship model (Deductive Estimation of Risk from Existing Knowledge, or *DEREK*, for Windows) predicted 1-BP to be negative for skin irritation.

A study using the EpiDerm human reconstructed epidermis model [Frasch et al. 2011]

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

Table 3. Summary of previous skin hazard designations for 1-BP

Organization	Skin hazard designation
NIOSH [2005]	No designation
OSHA [2017][*]	No designation
ACGIH [2014]	No designation

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

indicated that 1-BP is not corrosive to the skin following exposure to 1-BP. Two *in vivo* tests conducted with standard methods **[Jacobs et al. 1987; Pálovics 2004]** provide sufficient evidence that 1-BP is irritating to the skin of rabbits. Therefore, on the basis of the findings for this assessment, 1-BP is assigned a skin notation of SK: DIR (IRR).

4 Immune-mediated Responses (SK: SEN)

No diagnostic human patch tests that evaluated the potential of 1-BP to cause skin sensitization were identified. However, one study evaluated the skin sensitization potential of 1-BP with use of the guinea pig maximization test. In this study, Elf Atochem [1995b] intradermally injected 0.1 ml of 1-BP solution at a concentration of 25% on day 1, and applied 0.5ml of 1-BP in occlusive conditions to the skin of guinea pigs for 48 hours on day 8. A challenge dose of 0.5 ml 1-BP was given on day 12 on the left flank in occlusive conditions for 24 hours [Elf Atochem 1995b]. The investigators did not observe any cutaneous reactions that can be attributed to the sensitization potential of 1-BP [Elf Atochem 1995b]. *DEREK* predicted 1-BP to have skin sensitization potential. However, because of the absence of human data and the negative study in animals, a skin notation of SK: SEN is not assigned to 1-BP.

5 Summary

The mathematical model predicted that 1-BP was absorbed by the skin. Additionally, there was an *in vitro* dermal penetration study identified that indicates that 1-BP has the potential for substantial dermal penetration dependent on type and duration of exposure [Frasch et al. 2011]. A review of the available literature indicates that 1-BP is capable of inducing a wide array of adverse systemic health effects, including neurotoxicity, hepatotoxicity, hematotoxicity, reproductive toxicity, and developmental toxicity, regardless of exposure route **[ClinTrials Bioresearch 1997; Zhao et al. 1999; Ichihara et al. 2000a, 2000b; WIL Research Laboratory 2001; Wang et al. 2002, 2003; Lee et al. 2005, 2007; Banu et al. 2007; Fueta et al. 2007]**. Although the exact systemic hazards associated with skin contact and absorption of 1-BP are unknown, 1-BP is assigned the SK: SYS notation; this notation is based on the recognition of adverse health effects in test animals exposed via the inhalation, oral, and subcutaneous injection routes. Although a study using the EpiDerm human reconstructed epidermis model [Frasch et al. 2011] indicated that 1-BP is not corrosive to the skin following exposure to 1-BP, two *in vivo* tests, conducted with standard methods **[Jacobs et al. 1987; Pálovics 2004]**, provide sufficient evidence that 1-BP is irritating to the skin of rabbits. Although no human patch tests that evaluated the sensitization potential of 1-BP were identified, one guinea pig maximization test [Elf Atochem 1995b] showed that the substance is not a skin sensitizer. Therefore, on the basis of this assessment, 1-BP is assigned the composite skin notation **SK: SYS-DIR (IRR)**.

Table 3 summarizes the skin designations for 1-BP from NIOSH and other organizations. The equivalent skin designation for 1-BP from the

Globally Harmonized System (GHS) of Classification and Labelling is Reproductive Category 1B (Presumed human reproductive toxicant) and Skin Irritation Category 2 (Causes skin irritation) [European Parliament 2008].

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Appendix: Calculation of the SI Ratio for 1-Bromopropane

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for 1-BP. Although the SI ratio is considered in the determination of a substance's hazard potential following skin contact, it is intended only to serve as supportive data during the assignment of the NIOSH SK. An in-depth discussion on the rationale and calculation of the SI ratio can be found in Appendix B of the *Current Intelligence Bulletin (CIB) 61: A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009].

Overview

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

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

The algorithm evaluation includes three steps:

1. determining a skin permeation coefficient (k_p) for the substance of interest,
2. estimating substance uptake by the skin and respiratory absorption routes, and
3. evaluating whether the substance poses a skin exposure hazard.

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

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

$$\boldsymbol{k}_p = \frac{1}{\dfrac{1}{\boldsymbol{k}_{psc} + \boldsymbol{k}_{pol}} + \dfrac{1}{\boldsymbol{k}_{aq}}}$$

where k_{psc} is the permeation coefficient in the lipid fraction of the stratum corneum, k_{pol} is the coefficient in the protein fraction of the stratum corneum, and k_{aq} is the coefficient in the watery epidermal layer. These components are individually estimated by

$$\log k_{psc} = -1.326 + 0.6097 \times \log K_{ow} - 0.1786 \times MW^{0.5}$$
$$k_{pol} = 0.0001519 \times MW^{-0.5}$$
$$k_{aq} = 2.5 \times MW^{-0.5}$$

The second step is to calculate the biologic mass uptake of the substance from skin absorption (skin dose) and inhalation (inhalation dose) during the same period of exposure. The skin dose is calculated as a mathematical product of the k_p, the water solubility (S_W) of the substance, the exposed skin surface area, and the duration of exposure. Its units are milligrams (mg). Assume that the skin exposure continues for 8 hours to unprotected skin on the palms of both hands (a surface area of 360 square centimeters [cm^2]).

Equation 2: Determination of Skin Dose

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

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^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

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

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 (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 1-BP. The calculated SI ratio was 8.43. On the basis of these results, 1-BP is predicted to represent a skin absorption hazard.

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Table A1. Summary of data used to calculate the SI ratio for 1-BP

Variables used in calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path(k_{psc})	cm/hr	0.00941
Permeation coefficient of the protein fraction of the stratum corneum (k_{pol})	cm/hr	1.3696×10^{-6}
Permeation coefficient of the watery epidermal layer (k_{aq})	cm/hr	0.22542
Molecular weight (MW)*	amu	123
Base-10 logarithm of its octanol–water partition coefficient (Log K_{ow})*	None	2.1
Calculated skin permeation coefficient (k_p)	cm/hr	0.00904575
Skin dose		
Water solubility (S_w)*	mg/cm^3	2.45
Calculated skin permeation coefficient (k_p)	cm/hr	0.00904575
Estimated skin surface area (palms of hand)§	cm^2	360
Exposure time	hr	8
Calculated skin dose	mg	63.8268
Inhalation Dose		
Occupational exposure limit (OEL)†	mg/m^3	1.01
Inhalation volume	m^3	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	7.575
Skin dose–to–inhalation dose (SI) ratio	**None**	**8.42598**

*Variables identified from SRC [ND].
†The OEL used in calculation of the SI ratio for 1-BP was the ACGIH threshold limit value (TLV) [ACGIH 2014].
§Hayes, Wallace A [2008]. Principles and Methods of Toxicology. Fifth Edition. Informa Healthcare USA, Inc. New York, NY.

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