NIOSH Skin Notation Profiles

2-Butoxyethanol (BE)

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

2-Butoxyethanol (BE)
[CAS No. 111–76–2]

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

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Foreword

As the largest organ of the body, the skin performs multiple critical functions, such as serving as the primary barrier to the external environment. For this reason, the skin is often exposed to potentially hazardous agents, including chemicals, which may contribute to the onset of a spectrum of adverse health effects ranging from localized damage (e.g., irritant contact dermatitis and corrosion) to induction of immune-mediated responses (e.g., allergic contact dermatitis and pulmonary responses), or systemic toxicity (e.g., neurotoxicity and hepatoxicity). Understanding the hazards related to skin contact with chemicals is a critical component of modern occupational safety and health programs.

In 2009, the National Institute for Occupational Safety and Health (NIOSH) published *Current Intelligence Bulletin (CIB) 61: A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009–147]. This document provides the scientific rationale and framework for the assignment of multiple hazard-specific skin notations (SK) that clearly distinguish between the systemic effects, direct (localized) effects, and immune-mediated responses caused by skin contact with chemicals. The key step within assignment of the hazard-specific SK is the determination of 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 2-butoxyethanol (BE; CAS No. 111–76–2). In particular, this document evaluates and summarizes the literature describing the substance's hazard potential and its assessment according to the scientific rationale and framework outlined in CIB 61. In meeting this objective, this *Skin Notation Profile* intends to inform the audience—mostly occupational health practitioners, researchers, policy- and decision-makers, employers, and workers in potentially hazardous workplaces—so that improved risk-management practices may be developed to better protect workers from the risks of skin contact with the chemical of interest.

John Howard, M.D.
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Contents

Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
ATSDR	Agency for Toxic Substances and Disease Registry
BE	2-Ethoxyethanol
CIB	Current Intelligence Bulletin
cm^2	square centimeter(s)
cm/hr	centimeter(s) per hour
cm/s	centimeter(s) per second
DEREK™	Deductive Estimation of Risk from Existing Knowledge
DIR	skin notation indicating the potential for direct effects to the skin following contact with a chemical
EC	European Commission
EEC	European Economic Communities
g	gram(s)
GHS	Globally Harmonized System of Classification and Labeling of Chemicals
GPMT	guinea pig maximization test
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
LOAEL	lowest-observed-adverse-effect level
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
$mg/cm^2/min$	milligram(s) per square centimeter per minute
mg/kg	milligram(s) per kilogram body weight
mg/kg/day	milligram(s) per kilogram body weight per day
mg/mL	milligram(s) per milliliter
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
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
USEPA	United States Environmental Protection Agency
µg/cm^2	microgram(s) per square centimeter
µL	microliter(s)

Glossary

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

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

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

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

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

Dermal—Referring to the skin.

Dermal contact—Contact with (touching) the skin.

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

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

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

Substance—A chemical.

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

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1 Introduction

1.1 General Substance Information

Chemical: 2-Butoxyethanol (BE)

CAS No: 111–76–2

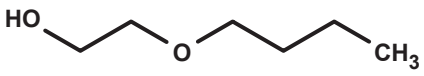
Synonyms:

BE; Butyl oxitol; Ethylene Glycol Monobutyl Ether; EGBE

Molecular weight (MW): 118.17

Molecular formula: $C_6H_{14}O_2$

Structural formula:



Uses:
2-Butoxyethanol (BE) is an organic compound used primarily as a solvent and chemical intermediate [ATSDR 1998].

1.2 Purpose

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

1.3 Overview of SK Assignment for BE

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

2 Systemic Toxicity from Skin Exposure (SK: SYS)

Several toxicokinetic studies following dermal exposure to BE were identified, and significant percutaneous absorption has been demonstrated in humans and animals in vivo and through human and animal skin in vitro. Jakasa et al. [2004] reported greater percutaneous absorption of BE as an aqueous solution than as a neat substance, after six male volunteers were dermally exposed for 4 hours on the volar forearm, over an area of 40 square centimeters (cm^2). After exposure to a 50% solution (BE dissolved in water), a 90% solution, or neat BE, the time-weighted

Table 1. Summary of the SK assignment for BE

Skin notation	Critical effect	Data available
SK: SYS	Hemoglobinuria (and other blood effects)	Limited human data; sufficient animal data
SK: DIR (IRR)	Skin irritation	Limited human data; sufficient animal data

average dermal fluxes from a 24-hours cumulative period were 1.34, 0.92, and 0.26 milligram per square centimeter per hour (mg/cm^2/hr), respectively. Kezic et al. [2004] also reported an average dermal flux of 3.5 mg/cm^2/hr, based on free or total butoxyethanoic acid appearing in the urine of volunteers following dermal exposure to 50% of the substance in water, under the same conditions as in the study of Jakasa et al. (2004). In vivo permeability coefficients (K_p) of 1.75×10^{-3} and 0.88×10^{-3} centimeter per hour (cm/hr) for 50% and 90% aqueous solutions of BE, respectively, have been reported for humans [Jakasa et al. 2004], and K_p of 0.3×10^{-3}, 0.84×10^{-3}, and 1.82×10^{-3} cm/hr for neat, 80%, and 40% aqueous solutions of BE have been reported for guinea pigs [Johanson and Fernstrom 1988]. The human K_p values for BE were estimated to be 2 cm/hr and 4 cm/hr, respectively, for normal temperature and relative humidity (23oC and 29%) and elevated temperature and humidity (33oC and 71%) [Corley et al. 1997]. Following in vitro studies of human skin exposed to either an aqueous solution of BE [3 milligrams per milliliter (mg/mL)] or undiluted BE, Wilkinson and Williams [2002] reported higher apparent K_p values with the aqueous solution [dose, 200 microliters (µL); L; K_p, 64.3 mg/cm^2/hr] than with undiluted BE [dose, 10.5 µL; K_p, 30.8 mg/cm^2/hr]. Johanson et al. [1988] reported percutaneous uptake of neat liquid BE at a rate of 0.83–11.33 milligram per square centimeter per minute (mg/cm^2/min), based on measured blood levels in 12 experiments involving five volunteers, who had two or four fingers exposed to the neat substance for 2 hours. Sufficient data are available from toxicokinetic studies in both humans and animals [Bartnik et al. 1987; Sabourin et al. 1992, 1993; Jakasa et al. 2004] to demonstrate that BE is absorbed through the skin following dermal exposure.

In in vivo percutaneous absorption studies in rats, Bartnik et al. [1987] estimated dermal absorption of 25% to 29% of the applied topical dose, calculated on the basis of urinary excretion of radioactivity following topical and subcutaneous administration of BE. In that study, 200 milligrams per kilograms body weight (mg/kg) of BE in water was applied to a 12-cm^2 area of shaved rat skin under occlusive conditions. Sabourin et al. [1992, 1993] reported dermal absorption values of 21% to 25% of the applied dose, based on measurements of excretion of ^{14}C, following 72-hours dermal application of BE in acetone ranging in concentration from 53.2 to 472.7 mg/kg to shaved rat skin under semiocclusive conditions.

In in vitro percutaneous studies of dorsal skin of hairless rats, dorsal domestic pig skin, and human skin from the flexus side of the arm, Bartnik et al. [1987] found that dermal absorption increases with time of exposure and that absorption is greater under semiocclusive conditions than under nonocclusive conditions. Using undiluted (100%) BE, Bartnik et al. [1987] reported time-course absorption (percent of applied radioactivity) of 19.4% (after 1 hour), 66.7% (after 6 hours), and

94.3% (after 16 hours) in rat skin under semiocclusive conditions. The authors reported that only 5.6% of the applied does was absorbed after 1 hour in hairless rat skin under nonocclusive conditions, while 11.2% of the applied dose was absorbed after 6 hours in pig skin under semiocclusive conditions. The results of the study indicate that dermal uptake of BE varies based on exposure scenario (nonoccluded vs. occluded) and type of skin (rat vs. pig) used within the experiment.

When the substance was diluted in water, a 10% concentration applied to 100 micrograms per square centimeter (µg/cm^2) of the skin under semiocclusive conditions for 1 hour resulted in dermal absorption of 17.3% (human), 17.7% (pig), and 43.3% (rat). Under nonocclusive conditions, the same concentration applied to the same area of skin yielded absorption of 6.9% (human), 8.6% (pig), and 11.0% (rat). For absorption of BE through human abdominal epidermis in an in vitro system [Dugard et al. 1984], a rate of 0.2 mg/cm^2/hr was reported.

Corley et al. [1997], using physiologically based pharmacokinetic modeling, reported dermal absorption of 15% to 27% of the total uptake of BE vapors (50 parts per million [ppm] for 2 hours) for worst-case exposure scenarios (no clothing and exposure of 100% of the total body surface) and 4.4% to 8.4% for more realistic exposures (25% of the surface area, such as parts of both arms and head). The potential of BE to pose a skin absorption hazard was also evaluated with a predictive algorithm for estimating and evaluating the health hazards of dermal exposure to substances [NIOSH 2009]. The evaluation method compares an estimated chemical 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 27.7 was calculated for BE. 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.

Although no dermal lethal concentration (LD_{Lo}) for humans has been identified, the reported values for dermal LD_{50} (the dose resulting in 50% mortality in the exposed population) of undiluted BE ranged from 0.11 to 0.56 milligrams per kilogram body weight (mL/kg), which corresponded to 99 to 505 mg/kg [Carpenter et al. 1956; Duprat and Gradiski 1979] under occlusive conditions and 2.0 mL/kg (1,804 mg/kg) under nonocclusive conditions [Carpenter et al. 1956] for rabbits. A value of 1.59 mL/kg to 2.52 mL/kg (corresponding to 1434 to 2271 mg/kg) was reported for rats (Union Carbide Corporation 1972). Because the reported acute dermal LD_{50} values for rabbits are generally lower than the critical dermal LD_{50} value of 2000 mg/kg body weight that identifies chemical substances with the potential for acute dermal toxicity [NIOSH 2009], BE is considered acutely toxic following dermal exposure.

No chronic toxicity studies of dermal exposure in humans or animals were identified. However, a 13-week, subchronic dermal toxicity study was conducted in rabbits under the sponsorship of the Wil Research Laboratories [1983]. The animals were treated with BE at dose levels of 10, 50, or 150 milligrams per kilogram body weight per day (mg/kg/day) through the topical application of approximately 1 milliliter (mL) of 2.8%, 14.3%, or 42.8% aqueous solution, respectively, for 6 hours

a day for 5 days/week. In that study, the highest dose of 150 mg/kg/day elicited no systemic effects and, hence, was regarded as the no-observed-adverse-effect level (NOAEL). In a shorter study (Union Carbide Corporation 1980b) that formed the basis for the subchronic study, rabbits were administered 1 mL of a 100%, 50%, 25%, or 5% solution of BE (reported by Tyler [1984] as 360, 180, 90, and 18 mg/kg/day) under an occlusive condition for 6 hours a day, 5 days/week, for nine applications over 11 days; this was followed by a 14-day observation period. The undiluted BE (at 360 mg/kg/day) caused significant decreases in the rate of body weight gain, decreases in erythrocyte count and hemoglobin concentration, and an increase in the mean corpuscular hemoglobin value for the females; it caused hemoglobinuria in both males and females. Hemoglobinuria was also noted in females exposed to the 50% aqueous dilution (180 mg/kg/day), indicating that this was the lowest-observed-adverse-effect level (LOAEL) in the short-term study. From these studies, a NOAEL of 150 mg/kg/day can be derived, with a LOAEL of 180 mg/kg/day to protect against hemoglobinuria and other blood effects at higher doses.

No epidemiological or case reports that evaluated reproductive or developmental toxicity following dermal exposure to BE were identified. No standard toxicity or specialty studies of biological system/function specific effects (including reproductive effects and immunotoxicity) following dermal exposure to BE were identified in animals. However, a study by Hardin et al. [1984] indicated that BE did not induce embryotoxic, fetotoxic, or teratogenic effects in rats dermally exposed four times/day to 0.12 mL/application (0.48 mL/day) of undiluted BE at 2.5-hr intervals on gestation days 7 to 16, followed by a 5-day postexposure period prior to death. The dose is calculated as 1880 mg/kg/day, based on the average body weight of 230 grams (g) computed from body weights reported by the authors on 4 days between gestation days 5 and 17 inclusive. There were no effects on body weight or body weight gain, gravid uterus weight, extragestational weight, or extragestational weight gain in treated animals, in comparison with controls. The same investigators reported that dermal exposure to 0.35 mL/application four times a day (corresponding to 5490 mg/kg/day) resulted in burgundy-colored urine by the end of the first treatment day, whereas continued treatment elicited ataxia, progressing to moderate to marked inactivity; rough hair coats with dark stains around the muzzle and anogenital area; and then death in 10 of 11 rats. Based on the results of Hardin et al. [1984], the NOAEL for developmental effects was approximately 1880 mg/kg/day.

No epidemiological or case reports that evaluated the potential of BE to cause cancer following dermal exposure to BE were identified. However, Jacobs et al. [1984] reported a dermal carcinogenicity study in mice in which a hair dye formulation containing 10% BE was applied to the clipped skin (0.5 mL/application) three times weekly for 20 months. There were no statistically significant differences in the incidence of pulmonary adenomas or hepatic hemangiomas between treated and control groups. There are insufficient data to evaluate the carcinogenicity of BE following dermal exposure. Table 2 provides a summary of carcinogenic designations from multiple governmental and nongovernmental organizations for BE. Taken together, findings of toxicokinetic studies in human and animals *in vivo* and *in vitro* **[Bartnik et al. 1987; Sabourin et al. 1992,**

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

Organization	Carcinogenic designation
NIOSH [2005]	None
NTP [2009]	None
USEPA [2009]	Group C: Possible human carcinogen
IARC [2006]	Group 3: Not classifiable as to carcinogenicity to humans
EC [2010]	None
ACGIH [2003]	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.

1993; Jakasa et al. 2004*] and findings of systemic toxicity studies **[Carpenter et al. 1956; Union Carbide Corporation 1972; Duprat and Gradiski 1979; Union Carbide Corporation 1980b]**, supported by the results of mathematical modeling, are sufficient to conclude that BE is absorbed through the skin, is systemically available, and has the potential to cause hemoglobinuria (and other blood effects and body weight changes). Therefore, on the basis of the data for this assessment, BE is assigned the **SK: SYS** notation.

3 Direct Effects on Skin (SK: DIR)

The literature search yielded no data on the corrosivity of BE or data from in vitro tests for corrosivity in human or animal skin models or for skin integrity in cadaver skin. However, skin irritation was observed in a repeated-insult patch test conducted in over 200 volunteers with a 10% aqueous (volume/volume) solution of BE. This concentration was selected by the investigators [Greenspan et al. 1995] to simulate the highest concentration used in cosmetic products and because higher concentrations may be irritating. In that study, the substance caused few signs of irritation, only within the first 24 hours, but 25% of the volunteers had slight or definite erythema after multiple applications. During the challenge phase, the investigators observed slight erythema in only 7 and 12 of 200 subjects during the 48-hours and 72-hours evaluations, respectively, and only 1 of the 200 had definite irritation at the 72-hours evaluation.

A number of studies have evaluated the skin irritation potential of BE in experimental animals. In a primary skin irritation test, Union Carbide Corporation (1972) concluded that the chemical is a slight skin irritant in rabbits. In a recent study, Zissu [1995] compared the skin irritation potential of the substance by using the Draize protocol and the European Economic Communities (EEC) method. With the Draize protocol, the undiluted substance was severely irritating to rabbit skin, whereas with the EEC method, it was irritating. However, earlier studies in rabbits yielded mixed results. In an acute study in which rabbits were administered

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

0.08 to 0.25 mL/kg to the skin, Duprat and Gradiski [1979] reported that irritation and necrosis were time-dependent but not dose-dependent. However, Jacobs et al. [1984] reported that 0.5 mL of the test material (5%–50% in sweet almond oil), applied to the skin of rabbits for 4 hours under occlusion, was not irritating to the skin. The structure-activity relationship model (Deductive Estimation of Risk from Existing Knowledge, or DEREK™, for Windows) predicted BE to be negative for skin irritation.

Taken together, the positive results from the human repeat-insult patch test **[Greenspan et al. 1995]** and from the clinical studies in experimental animals **[Union Carbide Corporation 1972; Duprat and Gradiski 1979; Zissu 1995]** sufficiently demonstrate that BE is a mild to moderate skin irritant. Therefore, on the basis of the data for this assessment, BE is assigned the SK: DIR (IRR) notation.

4 Immune-mediated Responses (SK: SEN)

No case reports have indicated, on the basis of occupational exposure, that BE is a skin sensitizer. However, one study evaluated the potential of BE to cause skin sensitization or photosensitization in humans. Greenspan et al. [1995] conducted a repeat-insult patch test with more than 200 volunteers, using a 10% aqueous solution of BE. Those investigators found no evidence of skin sensitization elicited by BE. In guinea pigs, the potential for BE to be a skin sensitizer was investigated in the Magnusson and Kligman skin sensitization test [Zissu 1995]. However, the authors concluded that the substance did not elicit a positive skin response in excess of that seen in control animals. DEREK™ predicted BE to be negative for skin sensitization.

A limited number of studies in humans and animals concerning the potential of BE to cause skin sensitization were identified. However, the negative results in the human repeat-insult patch study [Greenspan et al. 1995] and the guinea pig maximization test [Zissu 1995] are sufficient to demonstrate that BE is not a skin sensitizer in humans or animals. Therefore, on the basis of the data for this assessment, BE is not assigned the SK: SEN notation.

5 Summary

Sufficient information was available from human and animal dermal toxicokinetic studies in vivo and in vitro **[Bartnik et al. 1987; Sabourin et al. 1992, 1993; Jakasa et al. 2004]** and from dermal toxicity studies **[Carpenter et al. 1956; Duprat and Gradiski 1979]** to demonstrate that BE is absorbed through the skin, is systemically available, and can elicit systemic effects such as hemoglobinuria (and other blood effects and changes in body weight). Positive results from the single human repeat-insult patch test **[Greenspan et al. 1995]** and from the clinical studies in experimental animals **[Union Carbide Corporation 1972; Duprat and Gradiski 1979; Zissu 1995]** sufficiently demonstrate that BE is a mild to moderate skin irritant. Although a limited number of human and animal studies were identified concerning the potential of the substance to be a skin sensitizer, negative results in the human repeat-insult patch study [Greenspan et al. 1995], and the guinea pig maximization test [Zissu 1995] are sufficient to demonstrate that BE is not likely to be a skin sensitizer in humans or animals. Therefore, on the basis of these assessments, BE is assigned a composite skin notation of **SK: SYS-DIR (IRR)**.

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

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption
OSHA [2009]	[skin]: Potential for dermal absorption
ACGIH [2003]	None
EC [2010]	R21: Harmful if in contact with skin R38: Irritating to 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.

Table 3 summarizes the skin hazard designations for BE previously issued by NIOSH and other organizations. The equivalent dermal designations for BE, according to the Global Harmonization System (GHS) of Classification and Labelling of Chemicals, are Acute Toxicity Category 4 (Hazard statement: Harmful in contact with the skin) and Skin Irritation Category 2 (Hazard statement: Causes skin irritation) [European Parliament 2008].

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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 BE

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This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for BE. 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 (Kp)

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

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 BE

Variables used in calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path(K_{psc})	cm/hr	0.00173
Permeation coefficient of the protein fraction of the stratum corneum (K_{pol})	cm/hr	1.39717×10^{-5}
Permeation coefficient of the watery epidermal layer (K_{aq})	cm/hr	0.22995
Molecular weight (MW)*	amu	118
Base-10 logarithm of its octanol–water partition coefficient (log K_{OW})*	None	0.83
Calculated skin permeation coefficient (K_p)	cm/hr	0.00173
Skin dose		
Water solubility (S_W)*	mg/cm^3	1000
Calculated skin permeation coefficient (K_p)	cm/hr	0.00173
Estimated skin surface area (palms of hand)	cm^2	360
Exposure time	hr	8
Calculated skin dose	mg	4987.87
Inhalation dose		
Occupational exposure limit (OEL)†	mg/m^3	24
Inhalation volume	m^3	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	180
Skin dose–to–inhalation dose (SI) ratio	None	27.7

*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

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

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

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 BE. The calculated SI ratio was 27.7. On the basis of these results, BE is predicted to represent a skin absorption hazard.

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