NIOSH Skin Notation Profile

Dioxane

SK

ID^{SK}

[~~SK~~]

SYS

SYS (FATAL)

DIR

DIR (IRR)

DIR (COR)

SEN

Centers for Disease Control and Prevention
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NIOSH Skin Notation Profile

Dioxane

[CAS No. 123-91-1]

Naomi L. Hudson

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 (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]. 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 dioxane. 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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Contents

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)
COR	subnotation of SK: DIR indicating the potential for a chemical to be corrosive to the skin following exposure
DIR	skin notation indicating the potential for direct effects to the skin following contact with a chemical
DMBA	dimethylbenzanthracene
FATAL	subnotation of SK: SYS indicating the potential for the chemical to be fatal during dermal absorption
GHS	Globally Harmonized System for Classification and Labelling of Chemicals
IARC	International Agency for Research on Cancer
ID^{SK}	skin notation indicating that a chemical has been evaluated, but insufficient data exist to accurately assess the hazards of skin exposure
IRR	subnotation of SK: DIR indicating the potential for a chemical to be a skin irritant following exposure to the skin
LD_{50}	dose resulting in 50% mortality in the exposed population
LD_{Lo}	dermal lethal dose
LOAEL	lowest-observed-adverse-effect level
M	molarity
mg	milligram(s)
mg/kg	milligram(s) per kilogram
mg/kg-day	milligrams per kilogram a day
µL	microliter(s)
MW	molecular weight
ng	nanograms
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
SEN	skin notation indicating the potential for immune-mediated reactions following exposure of the skin
SK	skin notation
~~SK~~	skin notation indicating that the reviewed data did not identify a health risk associated with skin exposure
SYS	skin notation indicating the potential for systemic toxicity following exposure of the skin
TPA	12-*O*-tetradecanoylphorbol-13-acetate

µg/cm²	micrograms per square centimeter
µg/cm²/h	micrograms per square centimeter per hour
U.S. EPA	United States Environmental Protection Agency

Glossary

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

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

Cancer—Any one of a group of diseases that 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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1 Introduction

1.1 General Substance Information

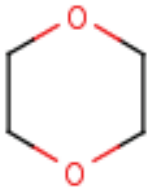
Chemical: Dioxane

CAS No: 123-91-1

Molecular weight (*MW*): 88.1

Molecular formula: $C_4H_8O_2$

Structural formula:



General substance information was obtained from NIOSH [2007].

Synonyms: Diethylene dioxide; Diethylene ether; Dioxan; p-Dioxane; 1,4-Dioxane

Uses: Dioxane is an aromatic compound used primarily as an organic solvent and as a stabilizer for chlorinated solvents; greater than 1 million pounds of dioxane were produced in 2002 [HSDB 2021].

1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with dioxane and (2) the rationale behind the hazard-specific skin notation (SK) assignment for dioxane. 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 dioxane. A literature search was conducted through March 2021 to identify information on dioxane dermal absorption, 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 in humans, animals, or appropriate modeling systems that are relevant to assessing the effects of dermal exposure to dioxane. The criteria for the search strategy, evaluation, and selection of data are described in Appendix E in the aforementioned *CIB 61* [NIOSH 2009].

1.3 Overview of SK Assignment for Dioxane

Dioxane is potentially capable of causing numerous adverse health effects following skin contact. A critical review of the available data has resulted in the following SK assignment for dioxane: **SK: SYS**. Table 1 provides an

Table 1. Summary of the SK assignment for dioxane

Skin notation	Critical effect	Available data
SK: SYS	Renal and hepatic effects	Limited animal data

overview of the critical effects and data used to develop the SK assignment for dioxane.

2 Systemic Toxicity From Skin Exposure (SK: SYS)

No human studies were identified that estimated the absorption of dioxane following dermal exposure. However, limited toxicokinetic data following dermal exposure to dioxane were identified in animals. In a skin-penetration study in monkeys, each animal received non-occluded applications of 4 micrograms per square centimeter (µg/cm^2) of ^{14}C-dioxane in methanol or in skin lotion on 3 to 15 cm^2 of the forearm for 24 hours (h) [Marzulli et al. 1981]. Twenty-four hours after treatment, 2.3% and 3.4% of the respective doses had penetrated the skin [Marzulli et al. 1981]. In an *in vitro* study, Bronaugh [1982] measured absorption of dioxane applied to excised human abdominal epidermis in diffusion cells. When administered in an unspecified lotion under occlusion for 205 minutes, 3.2% of the applied dose of dioxane was absorbed, compared to 0.30% absorption when the skin was non-occluded. Bronaugh [1982] also evaluated percutaneous absorption of dioxane under occlusion in three different vehicles. Fluxes of dioxane were reported as 0.36 nanograms per square centimeter per hour (ng/cm^2/h) in water, 0.23 ng/cm^2/h in an unspecified lotion, and 0.94 ng/cm^2/h in isopropyl myristate, with respective permeability constants of 4.3×10^{-4}, 2.7×10^{-4}, and 11.2×10^{-4} centimeters per hour (cm/h) [Bronaugh 1982]. In a later study, Dennerlein et al. [2013] reported a flux of 1,116.8–1,483.4 micrograms per square centimeter per hour (µg/cm^2/h) for excised human skin in diffusion cell exposure chambers treated with 50 microliters (µl) of dioxane. In a later study, Dennerlein et al. [2015] reported that 2% of dioxane that penetrated the skin was found in the epidermis/dermis and 98% was detected in the receptor fluid.

No dermal lethal dose (LD_{Lo}) estimates in humans or acute animal dermal LD_{50} (the dose resulting in 50% mortality in the exposed animals) for dioxane were identified.

No epidemiological studies following prolonged dermal exposure to dioxane were identified. A single case report where a worker was exposed to dioxane for one week before developing an acute illness leading to his death was reported by Johnstone [1959]. In this report, it was indicated that the worker used liquid dioxane to keep his hands free of glue, and that the worker kept the bucket between his knees. In postmortem examinations, it was noted that the liver and kidneys exhibited necrosis, the worker suffered from bronchopneumonia, and in the nervous system there was focal malacia that was secondary to anoxia and cerebral edema [Johnstone 1959].

In animals, a sub-chronic study was identified in which Fairley et al. [1934] administered 10 drops of 1:4 solution of dioxane and water to the clipped and non-occluded skin of four rabbits and 5 drops to the skin of four guinea pigs. The applications continued twice a day for 5 days of the week and once on the sixth day of the week, and no application the seventh day (11 applications/week). Animals were euthanized in pairs from day 49 to day 101. The doses were calculated to be approximately 57 milligrams per kilogram body weight a day (mg/kg-day) for rabbits and 143 mg/kg-day for guinea pigs [ATSDR 2007]. Progressive damage to the kidney (renal cortical cell degeneration and hemorrhages in both species) and liver (patchy cell degeneration in guinea pigs and rabbits and vascular congestion in rabbits only) was observed upon microscopic examination of treated animals euthanized on days 49, 66, 77, and 101 [Fairley et al. 1934]. Other routes of exposure (oral, inhalation, and intravenous injection) were also examined in this study and indicate that the effects are not route specific. Fairley et al. [1934] observed renal and hepatic effects similar to those observed following dermal exposure. Changes in the kidney and liver were seen in a later study conducted by Stott et al. [1981], where rats received repeated doses of 0, 10, or 100 mg dioxane via drinking water 7 days a week for 11 weeks. Stott et al. [1981] reported that repeated dosing

Table 2. Summary of the carcinogenic designations for dioxane by governmental and nongovernmental organizations

Organization	Carcinogenic designation
NIOSH [2007]	Potential occupational carcinogen
NTP [2016]	Reasonably anticipated to be a human carcinogen
U.S. EPA [2021]	Likely human carcinogen
ECHA [2022]	Carcinogenic
IARC [2012]	2B: Possibly carcinogenic to humans
ACGIH® [2018]	A3: Confirmed animal carcinogen with unknown relevance to humans

ACGIH® = American Conference of Governmental Industrial Hygienists; ECHA = European Chemicals Agency; IARC = International Agency for Research on Cancer; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; U.S. EPA = United States Environmental Protection Agency.

of dioxane for 11 weeks at tumorigenic doses (an average of 1,000 mg/kg per day) caused an increase in liver weight and a hepatocellular swelling; however, dioxane did not cause a significant degree of hepatic cytotoxicity as a single acute dose. The observed effects following repeated dermal exposures were at doses less than the critical dermal no-observed-adverse-effect level (NOAEL) value of 1,000 mg/kg-day, which identifies chemical substances with the potential for repeated dermal toxicity [NIOSH 2009]. Therefore, dioxane has the potential to become systemically available and cause toxicity following dermal exposure.

No standard toxicity or specialty studies evaluating biological systemic/function of dioxane were identified (including reproductive/developmental toxicity or immunotoxicity).

The carcinogenicity and tumor initiation and promotion abilities of dioxane have been evaluated in experimental animals following dermal application. King et al. [1973] applied 0.2 milliliter (mL) of a solution of dioxane in acetone three times per week to skin of mice for 60 weeks. No increase in tumors was observed; however, when 50 µg of dimethylbenzanthracene (DMBA) was applied prior to the application of dioxane at an unspecified concentration, neoplastic lesions of the skin, lungs, and kidneys were reported [King et al. 1973]. Dioxane was not an initiator when Bull et al. [1986] applied doses of 1,000 mg/kg dioxane to female mice prior to topical application of 1 µg of 12-*O*-tetradecanoylphorbol-13-acetate (TPA) three times per week for 20 weeks. Although data were not adequate to determine the potential of dioxane to be carcinogenic following dermal exposure, other agencies or organizations have evaluated the carcinogenic potential of the substance via other routes. Table 2 summarizes the carcinogenic designations for dioxane by numerous governmental and nongovernmental organizations.

Toxicokinetic data suggest that dioxane has limited absorption following dermal exposure. The results of the repeat-dose toxicity study **[Fairley et al. 1934]**[*] indicate that the substance is absorbed through the skin and can cause hepatic and renal effects and was supported by a case report **[Johnstone 1959]** where a worker had extensive dermal exposure and upon post-mortem examination liver and kidney necroses were identified. Similar effects that were observed in animals after inhalation and oral exposures **[Fairley et al. 1934; Stott 1981]** indicate that these effects are not route specific. The data indicate that dioxane may cause systemic effects such as hepatic and renal toxicity following dermal exposure. Therefore, dioxane is assigned a SK: SYS notation.

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

3 Direct Effects on Skin (SK: DIR)

No human or animal *in vivo* studies on corrosivity or *in vitro* tests for corrosivity using human or animal skin models or in vitro tests of skin integrity using cadaver skin for dioxane were identified. One case study of skin irritation following dioxane exposure in humans was identified. Sonneck [1964] reported a case who received first and second degree burns from an explosion caused by isoprene. After the worker recovered and returned to work, she experienced inflammatory skin changes on the upper extremities and to a lesser extent on the face following transfer to the dioxane distillation division of her workplace. After 4 weeks of leave due to the skin inflammation, the patient resumed her work but had a relapse after a few days. On the right limb, the skin disorder showed a stripe-shaped formation around the previously burned areas of the skin, which showed slight pigment changes. These consisted of flat or somewhat hemispherical, slightly reddish or skin-colored lichenoid papules, which formed a relatively narrow strip. It is unknown if there were any other chemical exposures or how much the integrity of the skin was compromised following the skin burns.

A limited number of skin irritation studies were identified in animals. Fairley et al. [1934] reported no signs of skin irritation when 10 drops of 1:4 solution of dioxane and water were applied to the clipped and non-occluded skin of rabbits and 5 drops were applied to the skin of guinea pigs. The applications continued twice a day for 5 days of the week and once on the sixth day of the week, and no application the seventh day (i.e., 11 applications/week) for up to 101 days. Nelson [1951] reported erythema with superficial scaling that cleared within a few days in rabbits following application of dioxane on the clipped skin of the trunk. In a standard irritation test using rats and mice, single non-occluded applications of greater than 800 mg/kg of dioxane at concentrations greater than 80% to the shaved skin were required to produce moderate or severe irritation [Sekizawa et al. 1994].

The structure activity relationship model DEREK® predicted dioxane to be negative for skin irritation. This is supported by the standard irritation tests in rabbits, rats, and mice [Fairley et al. 1934; Sekizawa et al. 1994]. A single occupational case reporting irritation following potential exposure to dioxane was identified. However it is unknown if there were any other chemical exposures or how much the integrity of the skin was compromised following the skin burns [Sonneck 1964]. Based on this assessment, dioxane is not assigned a skin notation of SK: DIR.

4 Immune-mediated Responses (SK: SEN)

No predictive tests (guinea pig maximization tests, Buehler test, murine local lymph node assays, etc.) that evaluated the potential of the dioxane to cause skin sensitization were identified. Evidence of skin sensitization in humans is limited to a single study. In a case report, Fregert [1974] described a man who had a positive reaction in a patch test to a solution of 0.5% dioxane in water after developing dermatitis from daily exposure to a dioxane containing solvent for 3 years. The structure activity relationship model DEREK® predicted dioxane to be negative for skin sensitization indicating that the chemical does not have a structural alert for sensitization.

Although a case report for a worker exposed to dioxane [Fregert 1974] indicates that dioxane may have sensitization potential, the paucity of data precludes adequate evaluation of the sensitizing potential for dioxane. Therefore, dioxane is not assigned the SK: SEN notation.

5 Summary

Results of a repeat-dose toxicity study **[Fairley et al. 1934]** indicate that the substance is absorbed through the skin and can cause hepatic and renal effects. This was supported by a case report **[Johnstone 1959]** where a worker had extensive dermal exposure and upon post-mortem

examination liver and kidney necroses were identified. Similar effects were observed in animals after inhalation and oral exposures [**Fairley et al. 1934; Stott 1981**] indicating that these effects are not route specific. The structure activity relationship model DEREK® predicted dioxane to be negative for skin irritation. This is supported by the standard irritation tests in rabbits, rats, and mice [Fairley et al. 1934; Sekizawa et al. 1994]. A single human case was reported with skin effects, however, it is unknown if there were any other chemical exposures or how much the integrity of the skin was compromised following the skin burns [Sonneck 1964]. Although an occupational case report [Fregert 1974] indicates that dioxane may have sensitization potential, the paucity of data precludes adequate evaluation of the sensitizing potential for dioxane. Based on this assessment, dioxane is assigned a composite skin notation of SK: SYS.

Table 3 summarizes the previously issued skin hazard designations for dioxane issued by NIOSH and other organizations.

Table 3. Summary of the previously issued skin hazard designations for dioxane from NIOSH and other organizations

Organization	Skin hazard designation
NIOSH [2007]	No designation
OSHA [2018]*	[Skin]: based on the potential for skin absorption.
ACGIH [2018]	[Skin]: based on rapid absorption following application to the skin of rabbits and guinea pigs.

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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