NIOSH Skin Notation Profiles

1,3-Dichloropropene (1,3-D)

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) Profiles

1,3-Dichloropropene (1,3-D)
[CAS No. 542-75-6]

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 1,3-dichloropropene (1,3-D; CAS No. 542–75–6). In particular, this document evaluates and summarizes the literature describing the substance's hazard potential and its assessment according to the scientific rationale and framework outlined in CIB 61. In meeting this objective, this Skin Notation Profile intends to inform the audience—mostly occupational health practitioners, researchers, policy- and decision-makers, employers, and workers in potentially hazardous workplaces—so that improved risk-management practices may be developed to better protect workers from the risks of skin contact with the chemical of interest.

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Contents

Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
CIB	Current Intelligence Bulletin
cm^2	squared centimeter(s)
cm/hr	centimeter(s) per hour
1,3-D	1,3-dichloropropene
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
GHS	Globally Harmonized System of Classification and Labeling of Chemicals
IARC	International Agency for Research on Cancer
(IRR)	subnotation of SK: DIR indicating the potential for a chemical to be a skin irritant following exposure to the skin
K_{aq}	coefficient in the watery epidermal layer
K_p	skin permeation coefficient
K_{pol}	coefficient in the protein fraction of the stratum corneum
K_{psc}	permeation coefficient in the lipid fraction of the stratum corneum
LD_{50}	dose resulting in 50% mortality in the exposed population
LD_{Lo}	dermal lethal dose
log K_{OW}	base-10 logarithm of a substance's octanol–water partition coefficient
m^3	cubic meter(s)
mg	milligram(s)
mg/kg	milligram(s) per kilogram body weight
mg/m^3	milligram(s) per cubic meter
MW	molecular weight
NIOSH	National Institute for Occupational Safety and Health
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

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: 1,3-Dicholoropropene (1,3-D)

CAS No.: 542–75–6

Synonyms:

1,3-D; Telone; 3-Chloroallyl chloride; DCP; 1,3-Dichloro-1-propene; 1,3-Dichloropropylene; 3-Chloropropenyl chloride; 1,3-Dichloropropylene; Trilone; Tri-Form

Molecular weight (MW): 110.98

Molecular formula: $C_3H_4C_{12}$

Structural formula:

Use:

1,3-D is a restricted-use pesticide applied as a soil fumigant for parasitic nematodes; commercially available formulations of the pesticide are a mixture of approximately equal proportions of the *cis*- and *trans*-isomers of 1,3-D [USEPA 1998; ATSDR 2008]. In addition, 1,3-D is used as an organic solvent and chemical intermediate during the manufacturing of 3,3-dichloro-1-propene and other pesticides [NTP 2005; ATSDR 2008].

1.2 Purpose

This *Skin Notation Profile* presents (1) a brief summary of technical data associated with skin contact with 1,3-D and (2) the rationale behind the hazard-specific skin notation (SK) assignment for 1,3-D. 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 1,3-D. A literature search was conducted through July 2010 to identify information on 1,3-D, 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 1,3-D.

1.3 Overview of SK Assignment for 1,3-D

1,3-D 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 1,3-D: **SK: SYS-DIR (IRR)-SEN**. Table 1 provides an overview of the critical effects and data used to develop the SK assignment for 1,3-D. The following section provides additional detail about the potential health hazards of skin contact with 1,3-D and the rationale behind the SK assignment.

Table 1. Summary of the SK Assignment for 1,3-D

Skin notation	Critical effect	Data available
SK: SYS	Neurotoxicity	Limited human data; sufficient animal data
SK: DIR (IRR)	Skin irritation	Sufficient animal data
SK: SEN	Skin allergy	Limited human data; sufficient animal data

2 Systemic Toxicity from Skin Exposure (SK: SYS)

No studies were identified regarding the absorption of 1,3-D in liquid form after dermal exposures in humans or animals. The ability of 1,3-D vapor to be readily absorbed through the skin has been demonstrated by detection of the metabolite cis-1,3-D/mercapturic acid in urine of volunteers exposed to *cis*-1,3-D vapor on the forearm skin at a concentration of 86 milligrams per cubic meter (mg/m^3), or 19 parts per million (ppm), for 45 minutes [Kezic et al. 1996]. According to Kezic et al. [1996], dermal absorption of 1,3-D vapor would account for 2% to 5% of absorption from inhalation in a whole-body-exposure scenario. The potential of 1,3-D 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 2.2 was calculated for 1,3-D. 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 dose (LD_{Lo}) has been established for humans, the following values for dermal LD_{50} (the dose resulting in 50% mortality in the exposed population) have been reported for commercial pesticide formulations containing 1,3-D: a range of 333 milligrams per kilogram body weight (mg/kg) to 504 mg/kg for rabbits [Dow Chemical USA 1975, Dow Chemical Company 1987a] and a value of 1200 mg/kg for rats [Dow Chemical Company 1986]. The clinical signs of toxicity reported in these studies included incoordination (ataxia), lethargy, and salivation. Because the reported LD_{50} values for rats and rabbits are below the critical LD_{50} value of 2000 mg/kg that identifies substances with potential for acute dermal toxicity [NIOSH 2009], 1,3-D is considered systemically available and can be neurotoxic following acute dermal exposure.

No epidemiological studies were identified that evaluated the potential of 1,3-D to cause systemic effects following dermal exposure. Additionally, no information was identified about the potential systemic effects in animals following repeat-dose (21-day or 28-day), subchronic (90-day), or chronic (at least 12-month) dermal exposure to any of the isomers of 1,3-D. No standard toxicity or specialty studies of biological system or function–specific effects (including reproductive and developmental effects and immunotoxicity) following dermal exposure to dichloropropene were identified. In addition, no studies were located regarding cancer in humans after dermal exposure to 1,3-D or

Table 2. Summary of the carcinogenic designations* for 1,3-D by numerous governmental and nongovernmental organizations

Organization	Carcinogenic designation
NIOSH [2005]	Potential occupational carcinogen
NTP [2005]	Reasonably anticipated to be a human carcinogen
USEPA [2010]	Group B2: Probable human carcinogen (based on sufficient evidence of carcinogenicity in animals)
IARC [1999]	Group 2B: Possibly carcinogenic to humans
EC [2010]	No designation
ACGIH [2005]	Group A3: Confirmed animal carcinogen with unknown relevance to humans

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.

*The listed cancer designations were based on data from nondermal (such as oral or inhalation) exposure rather than dermal exposure.

any other dichloropropene isomers. Table 2 summarizes carcinogenic designations of multiple governmental and nongovernmental organizations for 1,3-D.

The limited dermal toxicokinetic data on humans **[Kezic et al. 1996]*** demonstrate that 1,3-D vapor has the potential to be absorbed through the skin. The results from acute dermal toxicity studies of animals **[Dow Chemical USA 1975, Dow Chemical Company 1986, 1987a]** are sufficient to demonstrate that 1,3-D is systemically available and can be neurotoxic. Therefore, on the basis of the data for this assessment, 1,3-D is assigned the SK: SYS notation.

3 Direct Effects on Skin (SK: DIR)

A literature search revealed no data on corrosivity of 1,3-D; no *in vitro* tests for either corrosivity (with use of human or animal skin models) or skin integrity (with use of cadaver skin); and no tests in humans to evaluate the potential of 1,3-D to be a skin irritant. However, a primary skin irritation test [Dow 1987b] indicated that 1,3-D caused slight to moderate erythema and edema when 0.5 milliliter of the undiluted substance was applied under occlusion to the skin of rabbits for 4 hours. Skin irritation was also noted in acute dermal toxicity studies in the rat and rabbit [Dow Chemical USA 1975, Dow Chemical Company 1986, 1987b]. The structure activity relationship model, Deductive Estimation of Risk from Existing Knowledge (DEREK™) for Windows, predicted 1,3-D to be negative for skin irritation.

Van Duuren et al. [1979] conducted an initiation-promotion study of cis-1,3-D dermal exposure in mice. The authors concluded that 1,3-D was not a tumor initiator and did not induce skin tumors in mice (1) after a single topical application of 122 milligrams (mg), followed by repeated applications of the tumor promoter phorbol myristate acetate, for at least 428 days or (2) after topical application of 122 mg three times weekly for at least 440 days.

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

Data from primary skin irritation tests and acute dermal toxicity studies in animals [Dow Chemical USA 1975, Dow Chemical Company 1986, 1987b] are sufficient to demonstrate that 1,3-D causes skin irritation. Therefore, on the basis of the data for this assessment, 1,3-D is assigned the SK: DIR (IRR) notation.

4 Immune-mediated Responses (SK: SEN)

The potential of 1,3-D to cause skin sensitization following repeated or prolonged exposure has been demonstrated in case reports and animal studies. The results of diagnostic patch tests suggest that 1,3-D has the potential to cause skin sensitization in humans [van Joost and de Jong 1988; Bousema et al. 1991; Vozza et al. 1996; Corazza et al. 2003]. Delayed-type hypersensitivity was noted in four workers involved in the production or use of pesticides containing 1,3-D. The workers developed dermatitis with erythema and itching vesicles 3 weeks after exposure [van Joost and de Jong 1988; Bousema et al. 1991; Vozza et al. 1996; Corazza et al. 2003]. Skin allergic reactions have also been demonstrated in 4 of 10 [Dow Chemical USA 1983] and 9 of 10 [Dow Chemical Company 1987c] guinea pigs in maximization tests. DEREK™ predicted 1,3-D to be a plausible skin sensitizer.

Diagnostic patch tests in humans **[van Joost and de Jong 1988; Bousema et al. 1991; Vozza et al. 1996; Corazza et al. 2003]** have provided limited data indicating that 1,3-D is a skin sensitizer. However, results from guinea pig maximization tests **[Dow Chemical USA 1983, Dow Chemical Company 1987c]** have provided sufficient evidence that 1,3-D elicits allergic contact dermatitis in animals. Therefore, on the basis of the data for this assessment, 1,3-D is assigned the SK: SEN notation.

5 Summary

Data from a dermal toxicokinetic study using human volunteers demonstrate absorption of 1,3-D vapor through the skin **[Kezic et al. 1996]**. Acute dermal toxicity studies **[Dow Chemical USA 1975, Dow Chemical Company 1986, 1987a]** have provided sufficient evidence that 1,3-D is absorbed through the skin and can cause systemic effects such as neurotoxicity. Data from animal studies are sufficient to demonstrate that 1,3-D has the potential to cause skin irritation **[Dow Chemical USA 1975, Dow Chemical Company 1986, 1987b]**. Whereas the results of diagnostic patch tests suggest that 1,3-D has the potential to cause skin sensitization in humans **[Van Joost and de Jong 1988; Bousema et al. 1991; Vozza et al. 1996; Corazza et al. 2003]**, results of guinea pig maximization tests **[Dow Chemical USA 1983, Dow Chemical Company 1987c]** provide sufficient evidence that 1,3-D elicits allergic contact dermatitis in humans and animals. Therefore, on the basis of these assessments, 1,3-D is assigned a composite skin notation of **SK: SYS-DIR (IRR)-SEN.**

Table 3 summarizes the skin hazard designations for 1,3-D previously issued by NIOSH and other organizations. The equivalent dermal designations for 1,3-D, according to the Globally Harmonized System of Classification and Labeling of Chemicals (GHS), are Acute Toxicity Category 4 (Hazard statement: Harmful in contact with the skin), Skin Irritation Category 2 (Hazard statement: Causes skin irritation), and Skin Sensitization Category 1 (Hazard statement: May cause an allergic skin reaction) [European Parliament 2008].

Table 3. Summary of the previously issued skin hazard designations for 1,3-D

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption; prevent skin contact
OSHA	None assigned
ACGIH [2005]	[skin]: Based on evidence of skin penetration of 1,3-D, with subsequent mortality, in treated rabbits
EC [2010]	R21: Harmful if in contact with skin
	R38: Irritating to skin
	R43: May cause sensitization by skin contact

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; EC = European Commission, Joint Research, Institute for Health and Consumer Protection; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration.

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Note: Asterisks (*) denote sources cited in text; daggers (†) denote additional resources.

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Appendix: Calculation of the SI atio for 1,3-D

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for 1,3-D. 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 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 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

Table A1. Summary of data used to calculate the SI ratio for 1,3-D

Variables used in calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path(K_{psc})	cm/hr	0.01087
Permeation coefficient of the protein fraction of the stratum corneum (K_{pol})	cm/hr	1.4497×10^{-5}
Permeation coefficient of the watery epidermal layer (K_{aq})	cm/hr	0.23732
Molecular weight (MW)*	amu	110.97
Base-10 logarithm of its octanol–water partition coefficient (Log K_{OW})*	None	2.04
Calculated skin permeation coefficient (K_p)	cm/hr	0.01041
Skin dose		
Water solubility (S_W)*	mg/cm^3	2.8
Calculated skin permeation coefficient (K_p)	cm/hr	0.01041
Estimated skin surface area (palms of hand)	cm^2	360
Exposure time	hr	8
Calculated skin dose	mg	83.95
Inhalation Dose		
Occupational exposure limit (OEL)†	mg/m^3	5
Inhalation volume	m^3	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	37.5
Skin dose–to–inhalation dose (SI) ratio	None	2.24

*Variables identified from SRC [2009].

†The OEL used in calculation of the SI ratio for 1,3-D was the NIOSH recommended exposure limit (REL) [NIOSH 2005].

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 squared centimeters [cm^2]).

Equation 2: Determination of Skin Dose

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

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

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

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

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 1,3-D. The calculated SI ratio was 2.24. On the basis of these results, 1,3-D is predicted to represent a skin absorption hazard.

Appendix References

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