NIOSH Skin Notation Profiles

Disulfoton

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

Disulfoton

[CAS No. 297-04-4]

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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 disulfoton. 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)
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
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/cm²	microgram(s) per square centimeter
µg/cm²/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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1 Introduction

1.1 General Substance Information:

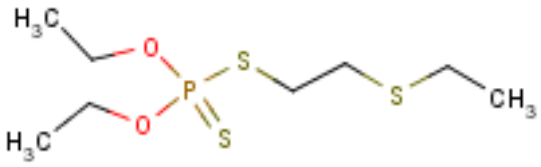
Chemical: Disulfoton

CAS No: 298-04-4

Molecular weight (*MW*)**:** 274.41

Molecular formula: $C_8H_{19}O_2PS_3$

Structural formula:



Synonyms: O,O-Diethyl S-2-(ethylthio)-ethyl phosphorodithioate

Uses: Disulfoton is used primarily as an organophosphate pesticide; approximately 5.5 million pounds (2.5 million kilograms) of disulfoton were used in 1974 [HSDB 2010].

1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with disulfoton and (2) the rationale behind the hazard-specific skin notation (SK) assignment for disulfoton. 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 disulfoton. A literature search was conducted through June 2017 to identify information on disulfoton, 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 disulfoton. 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

Disulfoton 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 disulfoton: **SK: SYS (FATAL)**. Table 1 provides an overview of the critical effects and data used to develop the SK assignment for disulfoton.

2 Systemic Toxicity from Skin Exposure (SK: SYS)

Studies of the human health effects of disulfoton were limited to occupational exposure studies with potential for both dermal and inhalation exposures. Wolfe et al. [1978] calculated a potential dermal exposure of workers to disulfoton

Table 1. Summary of the SK assignment for disulfoton

Skin notation	Critical effect	Available data
SK: SYS(FATAL)	Cholinesterase inhibition	Sufficient animal and limited human data

in fertilizer mixing plants that ranged from 0.1 milligram per hour (mg/hour) to 10.5 mg/hour with a mean value of 2.0 mg/hour of work activity, and respiratory values ranged from 0.001 to 0.036 mg/hour with a mean of 0.009 mg/hour during both wet and dry conditions. These data indicate that there is higher exposure by the dermal route [Wolfe et al. 1978]. At the highest exposure, these investigators estimated a potential dermal absorption value of around 34.4% dose per 8-hour day, indicating that relatively high exposure can occur [Wolfe et al. 1978]. Brokopp et al. [1981] measured metabolites of disulfoton in urine samples from volunteers who worked in a disulfoton formulating plant. The workers were exposed to disulfoton for the first 25 weeks of the study and phorate for the remaining 10 weeks. The pesticide formulators were exposed to differing amounts of disulfoton throughout the 25 week study period. While the presence of urinary disulfoton metabolites were detected in the workers, it is uncertain how much was absorption through the skin and how much was inhalation exposure [Brokopp et al. 1981]. The potential of disulfoton 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 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 0.837 was calculated for disulfoton. An SI ratio of ≥0.1 indicates that skin absorption may significantly contribute to the overall body burden of a substance [NIOSH 2009]; therefore, disulfoton has the potential to be absorbed through the skin and to become available systemically following dermal exposure. Additional information on the SI ratio and the variables used in its calculation are included in the appendix.

No dermal lethal doses (LD_{Lo}) of disulfoton in humans have been identified. However, LD_{50} values (the dose resulting in 50% mortality in exposed animals) have been reported. These values ranged from 2.3 to 15.9 milligrams per kilogram (mg/kg) for male and female rats [Gaines 1969; Bayer AG 1978]. A higher LD_{50} value of 0.285 milliliters per kilogram (mL/kg) [corresponding to 324.9 mg/kg] in rats was reported for a liquid formulation containing 65.7% disulfoton [Weil et al. 1971]. Because the reported acute dermal LD_{50} values for disulfoton are lower than the critical cutoff dermal LD_{50} value of 200 mg/kg body weight that identifies chemical substances with the potential to be fatal at low doses [NIOSH 2009], disulfoton is considered acutely fatal following dermal exposure.

No clinical human health effects data were identified for chronic exposure to disulfoton. However, one occupational exposure study evaluated effects of disulfoton. Wolfe et al. [1978] conducted a 9-week study in which employees in a fertilizer-pesticide mixing plant were exposed to mean disulfoton doses calculated to be 0.11 to 2.0 mg/hour (dermal) and 0.009 to 0.325 mg/hour (inhalation) for wet and dry mix operations, respectively. A decrease of 22.8% of erythrocyte cholinesterase activity was reported from week 2 to week 9 in employees engaged in dry mix operations who were exposed dermally to doses as high as 0.23 mg/kg-day (dermal) and 0.04 mg/kg-day (inhalation) of disulfoton [Wolfe et al. 1978]. No depression of cholinesterase activity was observed in employees involved in wet mix operations [Wolfe et al. 1978]. Savage

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

Organization	Carcinogenic designation
NIOSH [2005]	No designation
NTP [2014]	No designation
USEPA [2017]	No designation
European Parliament [2008]	No GHS designation
IARC [2012]	No designation
ACGIH [2002]	A4- Not classifiable as a human carcinogen

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, since studies using the dermal route of exposure were unavailable.

et al. [1971] noted signs of disulfoton toxicity evidenced by weakness, fatigue, cyanosis, and severe depression of cholinesterase activity, and high concentration of disulfoton in the serum of a farmer exposed to unspecified dose of the substance through a contaminated glove.

No repeat-dose, subchronic, or chronic toxicology studies were identified in animals. No studies were identified that evaluated the reproductive or developmental toxicity potential in humans or animals after dermal exposure to disulfoton. No standard toxicity or specialty studies evaluating biological system/function specific effects (including reproductive and developmental effects and immunotoxicity) following dermal exposure to disulfoton were identified. No studies were identified that evaluated the carcinogenic potential in humans or animals from dermal exposure to disulfoton. Table 2 summarizes carcinogenic designations of multiple governmental and nongovernmental organizations for disulfoton.

Taken together, there is sufficient information from dermal absorption studies [Wolfe et al. 1978; Brokopp et al. 1981], acute dermal toxicity studies **[Gaines 1969; Bayer AG 1978]***, and the occupational exposure studies **[Wolfe et al. 1978; Savage et al. 1971]** to demonstrate that disulfoton is absorbed through the skin, is acutely toxic and potentially fatal, and can cause cholinesterase inhibition. Therefore, on the basis of the data for this assessment, disulfoton is assigned the SK: SYS (FATAL) notation.

3 Direct Effects on Skin (SK: DIR)

No human or animal *in vivo* studies on corrosivity of disulfoton or *in vitro* tests for corrosivity using human or animal skin models or *in vitro* tests of skin integrity using cadaver skin were identified. The U.S. EPA [2008] waived dermal irritation studies because disulfoton was too toxic to test in standard irritation assays. The structure-activity relationship model, Deductive Estimation of Risk from Existing Knowledge (*DEREK*) for Windows, predicted disulfoton to be negative for skin irritation.

The absence of reliable standard irritation tests precludes adequate evaluation of the skin irritation potential of disulfoton. Therefore, on the basis of the data for this assessment, disulfoton is not assigned the SK: DIR (IRR) notation.

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

Table 3. Summary of previous skin hazard designations for disulfoton

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Based on potential for skin absorption
OSHA [2017]*	No designation
ACGIH [2002]	[skin]: Disulftoton was highly toxic by the dermal route in animals and produced organophosphate poisoning in workers

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

4 Immune-mediated Responses (SK: SEN)

Although no studies were identified that evaluated the potential of disulfoton to cause skin sensitization in humans or animals, the U.S. EPA [2008] waived dermal sensitization studies because disulfoton was too toxic to test. The structure activity relationship model, *DEREK* for Windows, predicted disulfoton to be negative for skin sensitization.

The absence of sensitization data precludes adequate evaluation of the skin sensitization potential of disulfoton. Therefore, on the basis of the data for this assessment, disulfoton is not assigned the SK: SEN notation.

5 Summary

The available data in both humans and animals indicate that disulfoton is absorbed through skin, is systemically available, acutely toxic and potentially fatal following acute dermal exposure **[Gaines 1969; Bayer AG 1978]**, and can cause cholinesterase inhibition following prolonged exposure to the skin **[Savage 1971; Wolfe et al. 1978]**. Insufficient data precludes the assessment of skin irritation and sensitization potential of disulfoton. Therefore, on the basis of these assessments, disulfoton is assigned a composite skin notation of **SK: SYS (FATAL)**.

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

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Appendix: Calculation of the SI Ratio for Disulfoton

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

$$k_p = \frac{1}{\frac{1}{k_{psc} + k_{pol}} + \frac{1}{k_{aq}}}$$

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

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

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

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

The final step is to compare the calculated skin and inhalation doses and to present the result as a ratio of skin dose to inhalation dose (the SI ratio). This ratio quantitatively indicates (1) the significance of dermal absorption as a route of occupational exposure to the substance and (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 disulfoton. The calculated SI ratio was 0.837. On the basis of these results, disulfoton is predicted to represent a skin absorption hazard.

Appendix References

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

Variables used in calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path(k_{psc})	cm/hr	0.0147
Permeation coefficient of the protein fraction of the stratum corneum (k_{pol})	cm/hr	9.1698×10^{-6}
Permeation coefficient of the watery epidermal layer (k_{aq})	cm/hr	0.151
Molecular weight (MW)*	amu	274.41
Base-10 logarithm of its octanol–water partition coefficient (Log K_{ow})*	None	4.02
Calculated skin permeation coefficient (k_p)	cm/hr	0.013
Skin dose		
Water solubility (S_w)*	mg/cm^3	0.016
Calculated skin permeation coefficient (k_p)	cm/hr	0.013
Estimated skin surface area (palms of hand)	cm^2	360
Exposure time	hr	8
Calculated skin dose	mg	0.628
Inhalation Dose		
Occupational exposure limit (OEL)†	mg/m^3	0.1
Inhalation volume	m^3	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	0.75
Skin dose–to–inhalation dose (SI) ratio	**None**	**0.837**

*Variables identified from SRC [ND].
†The OEL used in calculation of the SI ratio for disulfoton was the NIOSH recommended exposure limit (REL) [NIOSH 2005].

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