Skin Notation (SK) Profile

Phorate

[CAS No. 298-02-2]

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 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 phorate. 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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Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
ATSDR	Agency for Toxic Substances and Disease Registry
ChE	cholinesterase
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
g	gram(s)
g/L	gram(s)/liter
GHS	Globally Harmonized System for Labelling and Classification 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
kaq	coefficient in the watery epidermal layer
k_p	skin permeation coefficient
kpol	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/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
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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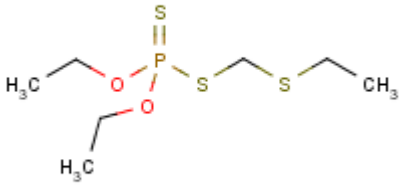
1.0 Introduction

1.1 General Substance Information

Chemical: Phorate
CAS No: 298-02-2
Molecular weight (*MW*): 260.4
Molecular formula: $(C_2H_5O)_2P(S)SCH_2SC_2H_5$
Structural formula:



Synonyms: *O*,*O*-Diethyl S-(ethylthio)methylphosphorodithioate; *O*,*O*-Diethyl S-ethylthiomethylthiothionophosphate; Thimet; Timet; phosphorodithioic acid *O*,*O*-diethyl *S*-[(ethylthio)methyl] ester; diethyl S-((ethylthio)methyl) phosphorodithioate

Uses: Phorate is an organophosphrous compound used primarily as an insecticide [HSDB 2009].

1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with phorate and (2) the rationale behind the hazard-specific skin notation (SK) assignment for phorate. 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 phorate. A literature search was conducted through October 2012 to identify information on phorate, 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 phorate.

1.3 Overview of SK Assignment

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

Table 1. Summary of the SK Assignment for phorate

Skin Notation	Critical Effect	Available Data
SK: SYS (FATAL)	Cholinesterase (ChE) inhibition; acute toxicity	Limited human and sufficient animal data

2.0 Systemic Toxicity from Skin Exposure (SK: SYS)

No toxicokinetic studies were identified in humans or animals that estimated the degree of absorption of phorate following dermal exposure. The potential of phorate 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 3.3 was calculated for phorate. An SI ratio of ≥0.1 indicates that skin absorption may significantly contribute to the overall body burden of a substance [NIOSH 2009]; therefore, phorate is considered to be absorbed through the skin following dermal exposure. Additional information on the SI ratio and the variables used in its calculation are included in the appendix.

No estimate of the human dermal lethal dose (LD_{Lo}) was identified for phorate. Dermal LD_{50} values (lethal doses in 50% of exposed animals) were reported as 2.5 and 6.2 milligrams per kilogram body weight (mg/kg) for female and male rats, respectively [Gaines 1969]. The United States Environmental Protection Agency (USEPA) [2006] reported LD_{50} values of 3.9 and 9.3 mg/kg in female and male rats, respectively, from unpublished data. Edson [1960] reported an acute LD_{50} of 80 mg/kg. Because the dermal LD_{50} values reported for rats are lower than the critical dermal LD_{50} value of 200 mg/kg body weight that identifies chemical substances that are fatal at relatively low doses following acute dermal exposure [NIOSH 2009], phorate is considered fatal after acute dermal exposure.

No repeat-dose, sub-chronic, or chronic toxicity studies in animals were identified that investigated the potential for phorate to elicit systemic toxic effects following dermal exposure. Kashyap et al. [1984] conducted an occupational exposure study, in which a group of 40 pesticide handlers, who were exposed to a combination of pesticides (organochlorines, organophosphates, and carbamates) for periods ranging between 2 and 19 years, were identified and selected as study subjects. Workers were removed from phorate exposure for at least one week, and then allowed to work for 2 weeks in a phorate formulation plant using personal protective equipment, where 10% phorate granules were formulated from technical grade material [Kashyap et al. 1984]. Phorate exposure significantly depressed cholinesterase (ChE) activity; for example, the mean plasma ChE activity was depressed at the end of the first week and second week by 55 and 71% compared to pre-exposure values, respectively. Neurological effects (e.g., headache, giddiness, fatigue), gastrointestinal symptoms (nausea, vomiting, stomachache, etc.), and bradycardia (lowering of heart rate) were observed in 60% of the workers as compared to pre-exposure values [Kashyap et al. 1984]. The gastrointestinal symptoms were more pronounced compared to those of the other systems. Only the plasma ChE activity depression persisted after 10 days following exposure [Kashyap et al. 1984]. Although exposure in this study probably involved both inhalation and dermal routes, and the dermal contribution to the total exposure was not quantified, the primary adverse effects of organophosphates include decreased activity of cholinergic enzymes. Therefore, this assessment concludes that phorate has the potential to cause cholinesterase inhibition, neurotoxicity, and gastrointestinal effects following dermal exposure.

No standard toxicity or specialty studies were identified that evaluated biological system/function specific effects (including reproductive and developmental effects and immunotoxicity) for phorate following dermal exposure. No epidemiological studies or animal bioassays were identified that evaluated the carcinogenic potential for phorate following dermal exposure. Table 2 summarizes carcinogenic designations of multiple governmental and nongovernmental organizations for phorate.

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

Organization	Carcinogenic designation
NIOSH [2005]	No designation
NTP [2011]	No designation
USEPA [2012]	No designation
GHS [European Parliament 2008]	No designation
IARC [2012]	No designation
EC [2012]*	No designation
ACGIH [2005]	A4: Not classifiable as a human carcinogen

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.
*Date accessed.

No studies were identified that estimated the degree of absorption of phorate through the skin following dermal exposure; however, capacity of the compound to penetrate the skin can be inferred from the fact that dermal LD_{50} values have been reported in rats, and is supported by the predictive algorithm for estimating and evaluating the health hazards of dermal exposure to chemical substances [NIOSH 2009]. No epidemiological studies and no animal repeat-dose, subchronic, or chronic toxicity studies were identified that evaluate the potential for phorate to cause systemic effect. However, several acute toxicity studies in rats **[Edson 1960; Gaines 1969]**[1] and an occupational exposure study **[Kashyap et al. 1984]** indicate phorate is highly toxic in contact with skin and has the potential to cause systemic effects including cholinergic inhibition, neurological and gastrointestinal effects, and lethality following dermal exposure. Therefore, on the basis of the data for this assessment, phorate is assigned the SK: SYS (FATAL) notation.

3.0 Direct Effects on Skin (SK: DIR)

No human or animal *in vivo* studies for corrosivity of phorate or *in vitro* tests for corrosivity using human or animal skin models or *in vitro* tests of skin integrity using cadaver skin were identified. In a diagnostic patch test to evaluate the potential for phorate to cause skin sensitization in 350 subjects, consisting of 59 agricultural workers, 17 ex-agricultural workers, and 274 non-agricultural workers, Lisi et al. [1987] reported that 1% phorate produced irritant contact dermatitis in only one of the 274 non-agricultural workers. Lisi et al. [1986] did not observe any skin irritation in a similar study involving 46 subjects. No standard skin irritation tests were identified that investigated the potential for phorate to cause irritant contact dermatitis. The USEPA [2006] has waived primary skin irritation test for phorate probably due to its high acute toxicity.

No standard skin irritation tests were identified that evaluated the potential for phorate to cause skin irritation in animals. Limited number of diagnostic (human patch) tests identified did not indicate that phorate has the potential to cause direct skin effects following dermal exposure. Therefore, on the basis of the data for this assessment, phorate is not assigned the SK: DIR (IRR) notation.

4.0 Immune-mediated Responses (SK: SEN)

Diagnostic (human patch) tests were identified that evaluated the potential for phorate to cause skin sensitization. Lisi et al. [1986] did not observe any allergic reactions when 46 subjects were patch tested to 1% phorate. In another study, Lisi et al. [1987] found only one allergic reaction to 1% phorate when 350 subjects, consisting of 59 agricultural

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

workers, 17 ex-agricultural workers, and 274 non-agricultural, were patch-tested. No predictive tests (guinea pig maximization tests, Buehler test, murine local lymph node assays, etc.) were identified that evaluated the potential for phorate to cause skin sensitization.

While no predictive tests were identified to adequately evaluate the potential for phorate to cause skin sensitization in animals, a limited number of diagnostic (human patch) tests identified indicate that phorate is not likely to pose significant skin sensitization threat in humans. Therefore, on the basis of the data for this assessment, phorate is not assigned the SK: SEN notation.

5.0 Summary

No studies were identified that estimated the degree of absorption of phorate through the skin following dermal exposure; however, capacity of the compound to penetrate the skin can be inferred from the fact that values for the dermal LD_{50} values have been reported in rats, and is supported by the predictive algorithm for estimating and evaluating the health hazards of dermal exposure to chemical substances [NIOSH 2009]. No epidemiological studies and no repeat-dose, subchronic, or chronic toxicity studies in animals were identified that evaluated the potential for phorate to cause systemic effects following dermal exposure. Acute dermal toxicity studies in rats **[Edson 1960; Gaines 1969]** and an occupational exposure study **[Kashyap et al. 1984]** indicated phorate is highly toxic in contact with skin and has the potential to cause systemic effects including ChE inhibition, neurological and gastrointestinal effects, and lethality at low doses following dermal exposure. Although no standard skin irritation tests were identified for animals, limited number of human patch tests did not provide sufficient evidence that phorate can cause direct skin effects. No predictive tests were identified in animals that evaluated the potential of phorate to cause skin sensitization. However, a limited number of diagnostic (human patch) tests identified indicated that phorate is not likely to pose a significant skin sensitization threat to humans. Therefore, on the basis of these assessments, phorate is assigned a composite skin notation of **SK: SYS (FATAL)**.

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

Table 3. Summary of previous skin hazard designations for phorate

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption; prevent skin contact
OSHA [2012]*	None assigned
ACGIH [2001]	[skin]: Based on symptoms of organophosphate poisoning occur

	following dermal contact with low doses of phorate in animals
EC [2012]*	R27: Very toxic in contact with skin

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.
*Date accessed.

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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 Phorate

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for phorate. 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 *kp* 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 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

Skin dose = $k_p \times S_w \times$ Exposed skin surface area × Exposure time
= k_p(cm/hr) × S_w (mg/cm^3) × 360 cm^2 × 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

Inhalation dose = OEL × Inhalation volume × RF

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

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 phorate. The calculated SI ratio was 3.33 On the basis of these results, phorate is predicted to represent a skin absorption hazard.

Table A1. Summary of Data used to Calculate the SI Ratio for phorate

Variables Used in Calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path(k_{psc})	cm/hr	0.0092
Permeation coefficient of the protein fraction of the stratum corneum (k_{pol})	cm/hr	9.414×10^{-6}
Permeation coefficient of the watery epidermal layer (k_{aq})	cm/hr	0.1549
Molecular weight (MW)[a]	amu	260.38
Base-10 logarithm of its octanol–water partition coefficient (Log K_{ow})[a]	None	3.56
Calculated skin permeation coefficient (k_p)	cm/hr	0.0087
Skin dose		
Water solubility (S_w)[a]	mg/cm^3	0.05
Calculated skin permeation coefficient (k_p)	cm/hr	0.0087
Estimated skin surface area (palms of hand)	cm^2	360
Exposure time	hr	8
Calculated skin dose	mg	1.248
Inhalation Dose		
Occupational exposure limit (OEL)[b]	mg/m^3	0.05
Inhalation volume	m^3	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	0.375
Skin dose–to–inhalation dose (SI) ratio	None	3.329

[a]Variables identified from SRC [2009].
[b]The OEL used in calculation of the SI ratio for phorate was the NIOSH recommended exposure limit (REL) [NIOSH 2005].

Appendix References

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