NIOSH Skin Notation Profiles

Phosdrin

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

Phosdrin

[CAS No. 7786-34-7]

Naomi L. Hudson and G. Scott Dotson

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

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NIOSH [2015]. NIOSH skin notation profile: Phosdrin. By Hudson NL, Dotson GS. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2015-226.

DHHS (NIOSH) Publication No. 2015-226

September 2015

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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 2009-147]. 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 (such as skin permeation) by means of analytical or numerical methods.

This *Skin Notation Profile* provides the SK assignments and supportive data for phosdrin. 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.

John Howard, M.D.
Director, National Institute for
Occupational Safety and Health
Centers for Disease Control and Prevention

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Contents

Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
AChE	acetylcholinesterase
Amu	atomic mass unit
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
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
(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
REL	recommended exposure limit
RBC	red blood cells
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
US EPA	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
µg/min/cm²	microgram(s) per minute per square centimeter
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.

Acknowledgments

This document was developed by the Education and Information Division (Paul Schulte, Ph.D., Director). G. Scott Dotson, Ph.D., was the project officer for this document, assisted in great part by Naomi Hudson, Dr.P.H., M.P.H., H. Fredrick Frasch, Ph.D., and Anna Shvedova, Ph.D. The basis for this document was a report (*Toxicology Excellence for Risk Assessment [TERA]*) contracted by NIOSH and prepared by Bernard Gadagbui, Ph.D., and Andrew Maier, Ph.D.

For their contribution to the technical content and review of this document, special acknowledgment is given to the following NIOSH personnel:

Denver Field Office
Eric Esswein, M.Sc.

Division of Applied Research and Technology
Clayton B'Hymer, Ph.D.
John Snawder, Ph.D.
Mark Toraason, Ph.D.

Division of Respiratory Disease Studies
Gregory A. Day, Ph.D.
Aleksander Stefaniak, Ph.D.

Division of Surveillance, Hazard Evaluations, and Field Studies
Matt Dahm, M.Sc.
Todd Niemeier, M.Sc.
Aaron Sussell, Ph.D.
Loren Tapp, M.D.

Education and Information Division
Devin Baker, M.Ed.
Charles L. Geraci, Ph.D.
Thomas J. Lentz, Ph.D.
Richard Niemeier, Ph.D.
Ralph Zumwalde, M.Sc.

Health Effects Laboratory Division
Stacey Anderson, Ph.D.
Vic Johnson, Ph.D.
Michael Luster, Ph.D.
Paul Siegel, Ph.D.
Berran Yucesoy, Ph.D.

National Personal Protective Technology Laboratory
Heinz Ahlers, J.D., M.Sc.
Angie Shepherd

For their contribution to the technical content and review of this document, special acknowledgment is given to the following CDC personnel:

Office of Surveillance, Epidemiology and Laboratory Services/Epidemiology and Analysis Program Office

Barbara Landreth, M.A.

In addition, special appreciation is expressed to the following individuals for serving as independent, external reviewers and providing comments that contributed to the development or improvement of this document:

John Herbold, D.V.M., Ph.D., M.P.H., San Antonio, TX

Youcheng Liu, M.D., Sc.D., M.P.H., M.S., University of North Texas Health Science Center, Fort Worth, TX

G. Frank Gerberick, Ph.D., The Procter and Gamble Company, Cincinnati, OH

Dori Germolec, Ph.D., National Toxicology Program, National Institute for Environmental Health Sciences, Research Triangle, NC

Ben Hayes, M.D., Ph.D., Division of Dermatology, Vanderbilt School of Medicine, Nashville, TN

Jennifer Sahmel, M.Sc., CIH, ChemRisk, Boulder, CO

James Taylor, M.D., Industrial Dermatology, The Cleveland Clinic, Cleveland, OH

1 Introduction

1.1 General Substance Information:

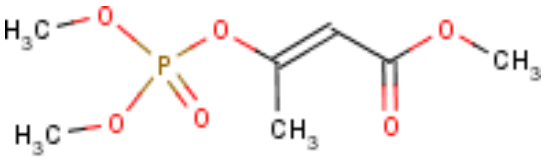
Chemical: Phosdrin

CAS No: 7786-34-7

Molecular weight (*MW*)**:** 224.2

Molecular formula: $C_7H_{13}PO_6$

Structural formula:



Synonyms: 2-Carboxymethoxy-1-methylvinyl dimethyl phosphate, Dimethyl-1-carbomethoxy-1- propen-2-yl phosphate, mevinphos (note: the commercial product is a mixture of the cis- & trans-isomers)

Uses: Phosdrin is an organophosphorus compound used primarily as an insecticide [HSDB 2005].

1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with phosdrin and (2) the rationale behind the hazard-specific skin notation (SK) assignment for phosdrin. 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 phosdrin. A literature search was conducted through October 2014 to identify information on phosdrin, 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 phosdrin.

1.3 Overview of SK Assignment

Phosdrin is potentially capable of causing adverse health effects following skin contact. A critical review of available data has resulted in the following SK assignment for phosdrin: **SK: SYS (FATAL)**. Table 1 provides an overview of the critical effects and data used to develop the SK assignment for phosdrin.

Table 1. Summary of the SK assignment for phosdrin

Skin notation	Critical effect	Available data
SK: SYS (FATAL)	Acetylcholinesterase (AChE) inhibition; acute toxicity	Sufficient human and animal data

2 Systemic Toxicity from Skin Exposure (SK: SYS)

No toxicokinetic studies in humans were identified that estimated the degree of absorption of phosdrin through the skin following dermal exposure. However, Schellenberger et al. [1965] reported a dermal absorption rate in rabbits of 1.4 micrograms per minute per square centimeter (μg/min/cm^2), as estimated from cholinesterase inhibition slopes after 30 milligrams per kilogram body weight (mg/kg) of undiluted phosdrin was applied to a 2.54 square centimeter (cm^2) surface area. They noted a dermal absorption rate of 7.8 μg/min/cm^2 for phosdrin in the presence of dimethyl sulfoxide (DMSO). The authors concluded that phosdrin was readily absorbed through the skin following dermal exposure. Studies in animals indicate the potential for phosdrin to be absorbed through the skin (that is, absorption of greater than 10%) following dermal exposure. The potential of phosdrin to pose a skin absorption hazard was 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 299.7 was calculated for phosdrin. An SI ratio of ≥0.1 indicates that skin absorption may significantly contribute to the overall body burden of a substance [NIOSH 2009]; therefore, phosdrin 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 phosdrin. Dermal LD_{50} values (lethal doses in 50% of exposed animals) were reported to range from 4.2 mg/kg in female rats to 4.7 mg/kg in male rats when phosdrin was applied to their shaven skin for 24 hours under occlusive conditions [Gaines 1960]. Edson [1960] reported an LD_{50} value of 90 mg/kg in the rat with application under occlusive conditions for 24 hours. A dermal LD_{50} value of 33.8 mg/kg was reported for the male rabbit [Kodama et al. 1954], whereas Skinner and Kilgore [1982a] reported an LD_{50} value of 12 mg/kg when mevinphos (phosdrin) in acetone was applied to the hind feet of muzzled mice. The acute dermal LD_{50} values for phosdrin in rats, mice, and rabbits are lower than the critical dermal LD_{50} value of 200 mg/kg that identifies chemical substances that are fatal at relatively low doses following acute dermal exposure [NIOSH 2009]. This finding indicates that phosdrin is systemically available and can be fatal following dermal exposure.

No epidemiological studies and no repeated-dose, subchronic, or chronic toxicity studies in animals were identified that evaluated the potential for phosdrin to cause systemic effects following dermal exposure. However, several cases of occupational poisoning with mevinphos (phosdrin) have been reported. These cases reported systemic symptoms and signs characteristic of organophosphate poisoning, including nausea, vomiting, dizziness, muscle weakness, headache, abdominal pain, sweating, excessive salivation, chest pain, and shortness of breath [California Department of Public Health (California DPH) 1958; Bell et al 1968; NIOSH 1984; Midtling et al. 1985; Coye et al 1986, 1987]. California DPH [1958] reported 19 occupational cases of systemic phosdrin poisoning, primarily in farm workers and foremen. Midtling et al. [1985] reported an event involving a group of 16 cauliflower workers poisoned by residues of phosdrin and another organophosphate insecticide, phosphamidon. Postexposure determinations of erythrocyte cholinesterase (ChE) levels indicated that the erythrocyte activity was significantly inhibited in 10 of the workers, and erythrocyte ChE levels did not reach a plateau until an average of 66 days after exposure [Midtling et al. 1985]. Most subjects continued to report blurred vision, headache, weakness, or anorexia even after the ChE leveled off, but the most severe symptoms resolved after 28 days [Midtling et al. 1984]. NIOSH [1984] and Coye et al. [1986, 1987] reported similar findings in several cases

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

Organization	Carcinogenic designation
NIOSH [2005]	No designation
NTP [2014]	No designation
US EPA	No designation
European Parliament [2008]	No GHS designation
IARC [2012]	No designation
ACGIH [2003]	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.

in which agricultural workers with a history of exposure to mevinphos (phosdrin) or mevinphos and phosphamidon presented with cholinergic symptoms but without baseline cholinesterase values. Plasma or erythrocyte (red blood cell, or RBC) ChE values in some of the subjects were above the lower limit of the laboratory normal range [Coy 1986, 1987]. Sequential post exposure determinations of ChE analyses indicated that plasma ChE was inhibited by an average of 16% and RBC ChE by 6% [NIOSH 1984; Coye et al. 1986]. Jauhialnen et al. [1992] reported that RBC acetylcholinesterase (AChE) was inhibited by 18% to 26% and plasma pseudocholinesterase activity by 15% to 29% in greenhouse workers exposed to mevinphos during spraying operations and during plant handling and harvesting of the flowers in eight greenhouses. In greenhouses, the main route of exposure to mevinphos is dermal [Kangas et al. 1993]. Other case reports involving phosdrin poisoning include those of Brachfeld and Zavon [1965], Bell et al. [1968], Savage et al. [1971], and Reichert et al. [1978]. These occupational exposure studies indicate the potential for phosdrin to cause cholinesterase inhibition following dermal exposure.

No standard toxicity or specialty studies were identified that evaluated the biological system/function–specific effects (including reproductive and developmental effects and immunotoxicity) for phosdrin following dermal exposure.

No epidemiological studies or animal bioassays were identified that evaluated the potential for phosdrin to be a carcinogen following dermal exposure. Table 2 summarizes carcinogenic designations for phosdrin by multiple governmental and nongovernmental organizations.

Toxicokinetic data on rabbits [Schellenberger et al. 1965] and results of a mathematical model indicate that phosdrin has the potential to be absorbed through the skin and become systemically available. Acute toxicity data on rats and mice [**Kodama et al. 1954; Edson 1960; Gaines 1960; Skinner and Kilgore 1982a**][*] and several occupational exposure datasets [**California DPH 1958; NIOSH 1984; Midtling et al. 1985; Coye et al. 1986, 1987; Jauhialnen et al. 1992**] provide sufficient evidence that phosdrin has the potential to be acutely toxic; may cause systemic toxicity, including ChE inhibition; and is potentially fatal following dermal exposure. Therefore, on the basis of the data for this assessment, phosdrin is assigned the SK: SYS (FATAL) notation.

3 Direct Effects on Skin (SK: DIR)

No human or animal studies for corrosivity of phosdrin, *in vitro* tests for corrosivity using human or animal skin models, or *in vitro* tests

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

of skin integrity using cadaver skin were identified. Additionally, no standard irritation studies in animals were identified that evaluated the potential for phosdrin to cause direct skin effects following dermal exposure. NIOSH investigated a group of 44 workers exposed to phosdrin in a lettuce field and found that 5 (17.2%) of the workers reported skin irritation [NIOSH 1984]; however, the degree and extent of irritation were not provided. Therefore, because of the paucity of data for this assessment, phosdrin is not assigned the SK: DIR (IRR) notation.

4 Immune-mediated Responses (SK: SEN)

No occupational exposure studies or diagnostic (human patch) tests, predictive tests in animals (for example, guinea pig maximization tests, Buehler tests, murine local lymph node assays, or mouse ear swelling tests), or any other studies were identified that evaluated the potential of the substance to cause skin sensitization. Therefore, on the basis of the data for this assessment, phosdrin is not assigned the SK: SEN notation

5 Summary

Toxicokinetic data available on rabbits [Schellenberger et al. 1965] and results of a mathematical model indicate that phosdrin has the potential to be absorbed through the skin and become systemically available. Acute toxicity data on rats and mice [**Kodama et al. 1954; Edson 1960; Gaines 1960; Skinner and Kilgore 1982a**] and several occupational exposure datasets [**California DPH 1958; NIOSH 1984; Midtling et al. 1985; Coye et al. 1986, 1987; Jauhialnen et al. 1992**] provide sufficient evidence that phosdrin has the potential to be acutely toxic; may cause systemic toxicity, including ChE inhibition; and is potentially fatal following dermal exposure. No studies were identified that investigated the potential of the substance to cause skin irritation under occupational exposure or in standard skin irritation tests in animals. There were no diagnostic (human patch) tests or predictive tests in animals that evaluated the skin sensitization potential of phosdrin. Therefore, on the basis of these assessments, phosdrin is assigned a composite skin notation of **SK: SYS (FATAL)**.

Table 3 summarizes the skin hazard designations for phosdrin previously issued by NIOSH and other organizations. The equivalent dermal designation for phosdrin, according to the Globally Harmonized System (GHS) for the 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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Note: Asterisks (*) denote sources cited in text; daggers (†) denote additional resources.

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Table 3. Summary of previous skin hazard designations for phosdrin

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption; prevent skin contact
OSHA [2014]*	[skin]: Potential for dermal absorption
ACGIH [2003]	[skin]: Highly toxic following dermal exposure in animals

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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Appendix: Calculation of the SI Ratio for Phosdrin

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for phosdrin. Although the SI ratio is considered in the determination of a substance's hazard potential following skin contact, it is intended to serve only 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 its 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)

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

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

$$\text{Skin dose} = k_p \times S_w \times \text{Exposed skin surface area} \times \text{Exposure time}$$
$$= k_p\,(\text{cm/hour}) \times S_w\,(\text{mg/cm}^3) \times 360\ \text{cm}^2 \times 8\ \text{hours}$$

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

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

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 phosdrin. The calculated SI ratio was 299.7. On the basis of these results, phosdrin is predicted to represent a skin absorption hazard.

Appendix References

NIOSH [2005]. NIOSH pocket guide to chemical hazards. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2005–149, http://www.cdc.gov/niosh/npg/.

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

Variables used in calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path (k_{psc})	cm/hr	0.0001
Permeation coefficient of the protein fraction of the stratum corneum (k_{pol})	cm/hr	1.015×10^{-5}
Permeation coefficient of the watery epidermal layer (k_{aq})	cm/hr	0.167
Molecular weight (MW)*	amu	224.15
Base-10 logarithm of its octanol–water partition coefficient ($Log\ K_{ow}$)*	None	0.13
Calculated skin permeation coefficient (k_p)	cm/hr	0.0001
Skin dose		
Water solubility (S_w)*	mg/cm^3	600
Calculated skin permeation coefficient (k_p)	cm/hr	0.0001
Estimated skin surface area (palms of hands)	cm^2	360
Exposure time	hr	8
Calculated skin dose	mg	224.8
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**	**299.7**

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

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DHHS (NIOSH) Publication No. 2015-226

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