

# NIOSH Skin Notation Profiles

## Tetraethyl dithionopyrophosphate (TEDP)

SK

ID<sup>SK</sup>

{SK}

SYS

SYS (FATAL)

DIR

DIR (IRR)

DIR (COR)

SEN

This page intentionally left blank.

# NIOSH Skin Notation (SK) Profile

---

**Tetraethyl dithionopyrophosphate (TEDP)**  
**[CAS No. 3689-24-5]**

---

Naomi L. Hudson and G. Scott Dotson

**This document is in the public domain and may be freely copied or reprinted.**

## Disclaimer

Mention of any company or product does not constitute endorsement by the National Institute for Occupational Safety and Health (NIOSH). In addition, citations to websites external to NIOSH do not constitute NIOSH endorsement of the sponsoring organizations or their programs or products. Furthermore, NIOSH is not responsible for the content of these websites.

## Ordering Information

To receive this document or information about other occupational safety and health topics, contact NIOSH:

Telephone: 1-800-CDC-INFO (1-800-232-4636)

TTY: 1-888-232-6348

E-mail: [cdcinfo@cdc.gov](mailto:cdcinfo@cdc.gov)

Or visit the NIOSH website: [www.cdc.gov/niosh](http://www.cdc.gov/niosh)

For a monthly update on news at NIOSH, subscribe to *NIOSH eNews* by visiting [www.cdc.gov/niosh/eNews](http://www.cdc.gov/niosh/eNews).

## Suggested Citation

NIOSH [2015]. NIOSH skin notation profile: Tetraethyl dithionopyrophosphate (TEDP). 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. 2015-227.

DHHS (NIOSH) Publication No. 2015-227

September 2015

**SAFER • HEALTHIER • PEOPLE™**

## 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 tetraethyl dithionopyrophosphate (TEDP). 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

This page intentionally left blank.

# Contents

Foreword. . . . .	iii
Abbreviations. . . . .	vi
Glossary . . . . .	viii
Acknowledgments. . . . .	ix
1 Introduction. . . . .	1
1.1 General Substance Information . . . . .	1
1.2 Purpose . . . . .	1
1.3 Overview of SK Assignment. . . . .	1
2 Systemic Toxicity from Skin Exposure (SK: SYS). . . . .	2
3 Direct Effects on Skin (SK: DIR). . . . .	3
4 Immune-mediated Responses (SK: SEN) . . . . .	3
5 Summary . . . . .	3
References. . . . .	4
Appendix: Calculation of the SI Ratio for TEDP . . . . .	6
Overview . . . . .	6
Calculation . . . . .	7
Appendix References . . . . .	7

## Abbreviations

<b>ACGIH</b>	American Conference of Governmental Industrial Hygienists
<b>Amu</b>	atomic mass unit
<b>ATSDR</b>	Agency for Toxic Substances and Disease Registry
<b>ChE</b>	cholinesterase
<b>CIB</b>	Current Intelligence Bulletin
<b>cm<sup>2</sup></b>	square centimeter(s)
<b>cm/hr</b>	centimeter(s) per hour
<b>cm/s</b>	centimeter(s) per second
<b>DEREK</b>	Deductive Estimation of Risk from Existing Knowledge
<b>DIR</b>	skin notation indicating the potential for direct effects to the skin following contact with a chemical
<b>EC</b>	European Commission
<b>GHS</b>	Globally Harmonized System for Classification and Labelling of Chemicals
<b>GPMT</b>	guinea pig maximization test
<b>hr</b>	hour(s)
<b>IARC</b>	International Agency for Research on Cancer
<b>(IRR)</b>	subnotation of SK: DIR indicating the potential for a chemical to be a skin irritant following exposure to the skin
<b><math>k_{aq}</math></b>	coefficient in the watery epidermal layer
<b><math>k_p</math></b>	skin permeation coefficient
<b><math>k_{pol}</math></b>	coefficient in the protein fraction of the stratum corneum
<b><math>k_{psc}</math></b>	permeation coefficient in the lipid fraction of the stratum corneum
<b>LD<sub>50</sub></b>	dose resulting in 50% mortality in the exposed population
<b>LD<sub>Lo</sub></b>	dermal lethal dose
<b>LLNA</b>	local lymph node assay
<b>LOAEL</b>	lowest-observed-adverse-effect level
<b>log <math>K_{ow}</math></b>	base-10 logarithm of a substance's octanol–water partition
<b><math>M</math></b>	molarity
<b>m<sup>3</sup></b>	cubic meter(s)
<b>mg</b>	milligram(s)
<b>mg/cm<sup>2</sup>/hr</b>	milligram(s) per square centimeter per hour
<b>mg/kg</b>	milligram(s) per kilogram body weight
<b>mg/m<sup>3</sup></b>	milligram(s) per cubic meter
<b>mL</b>	milliliter(s)
<b>mL/kg</b>	milliliter(s) per kilogram body weight
<b>MW</b>	molecular weight
<b>NIOSH</b>	National Institute for Occupational Safety and Health
<b>NOAEL</b>	no-observed-adverse-effect level
<b>NTP</b>	National Toxicology Program



<b>OEL</b>	occupational exposure limit
<b>OSHA</b>	Occupational Safety and Health Administration
<b>ppm</b>	parts per million
<b>REL</b>	recommended exposure limit
<b>RF</b>	retention factor
<b>SEN</b>	skin notation indicating the potential for immune-mediated reactions following exposure of the skin
<b>SI</b>	ratio ratio of skin dose to inhalation dose
<b>SK</b>	skin notation
$S_w$	solubility in water
<b>SYS</b>	skin notation indicating the potential for systemic toxicity following exposure of the skin
<b>TEDP</b>	tetraethyl dithionopyrophosphate
<b>US EPA</b>	United States Environmental Protection Agency
<b>µg</b>	microgram(s)
<b>µL</b>	microliter(s)
<b>µmol</b>	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 Frasc, Ph.D., and Vic Johnson, 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.

Michael Luster, Ph.D.

Anna Shvedova, 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

Shane Stephen Que Hee, M.Sc., Ph.D., University of California at Los Angeles, School of Public Health, Los Angeles, CA

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

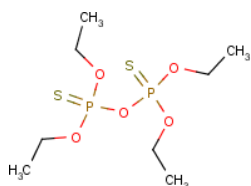
**Chemical:** Tetraethyl dithionopyrophosphate (TEDP)

**CAS No:** 3689-24-5

**Molecular weight (MW):** 322.3

**Molecular formula:**  $[(\text{CH}_3\text{CH}_2\text{O})_2\text{PS}]_2\text{O}$

**Structural formula:**



**Synonyms:** Dithion®; Bladafum®; Sulfotep; Tetraethyl dithiopyrophosphate; Thioptepp®

**Uses:** TEDP is a restricted-use organophosphate compound approved only for use as an insecticide within commercial greenhouses [US EPA 1999].

## 1.2 Purpose

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

## 1.3 Overview of SK Assignment

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

**Table 1. Summary of the SK assignment for TEDP**

Skin notation	Critical effect	Available data
SK: SYS (FATAL)	Acute toxicity; cholinesterase (ChE) inhibition	Limited animal data

## 2 Systemic Toxicity from Skin Exposure (SK: SYS)

No toxicokinetic studies of humans or animals were identified that estimated the degree of TEDP absorption through the skin following dermal exposure. The potential of TEDP 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 0.43 was calculated for TEDP. An SI ratio of  $\geq 0.1$  indicates that skin absorption may significantly contribute to the overall body burden of a substance [NIOSH 2009]; therefore, TEDP is considered to be absorbed through the skin following dermal exposure. Additional information on the SI ratio and on the variables used in its calculation is included in the appendix.

No estimate of the human dermal lethal dose ( $LD_{Lo}$ ) was identified for TEDP. Dermal  $LD_{50}$  values (lethal doses in 50% of exposed animals) ranged from 65 milligrams per kilogram (mg/kg) for male rats exposed for 7 days to 262

mg/kg for male rats exposed for 4 hours (hr) [Kimmerle and Klimmer 1974], and 0.069 milliliters per kilogram (mL/kg) [corresponding to 82 mg/kg] in rats [Scientific Associates 1950]. The weight of evidence indicates that the acute dermal  $LD_{50}$  values in animals are lower than the critical dermal  $LD_{50}$  value of 200 mg/kg that identifies chemical substances with the potential to be fatal at low doses following acute dermal exposure [NIOSH 2009]. Therefore, TEDP can be absorbed through the skin, is systemically available, and can be fatal following dermal exposure.

No epidemiological studies, case reports, or occupational exposure studies and no repeated-dose, subchronic or chronic toxicity studies in animals were identified that evaluated the potential of TEDP to cause systemic effects following dermal exposure. However, dermal contact with TEDP at low levels used in the acute dermal toxicity studies [Kimmerle and Klimmer 1974] resulted in depression of cholinesterase (ChE) activity in peripheral and central nervous systems. This effect is consistent with the known mode of action of organophosphates, including TEDP. Kimmerle and Klimmer [1974] also reported ChE inhibition following oral and inhalation exposures of short-term or longer-term duration, indicating that the effect is not route specific.

No standard toxicity or specialty studies were identified that evaluated biological system/

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

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

function-specific effects (including reproductive and developmental effects and immunotoxicity) following dermal exposure to TEDP. No epidemiological studies or animal bioassays were identified that investigated the carcinogenic potential of TEDP following dermal exposure. Table 2 summarizes carcinogenic designations of multiple governmental and nongovernmental organizations for TEDP.

No *in vivo* or *in vitro* toxicokinetic data from humans or animals were identified with regard to the potential of TEDP to be dermally absorbed; however, the mathematical model predicted that TEDP is absorbed through the skin. Acute toxicity data from animals [**Scientific Associates 1950; Kimmerle and Klimmer 1974**]\* indicate that TEDP is absorbed through the skin, is systemically available, and can be potentially fatal following dermal exposure. Acute dermal toxicity studies, with support from inhalation and oral studies, indicate that TEDP has the potential to cause ChE inhibition following repeated or prolonged dermal exposure [**Kimmerle and Klimmer 1974**]. Therefore, on the basis of the data for this assessment, TEDP is assigned the SK: SYS (FATAL) notation.

### 3 Direct Effects on Skin (SK: DIR)

No human or animal *in vivo* studies for corrosivity of TEDP, *in vitro* tests for corrosivity using human or animal skin models, or *in vitro* tests of skin integrity using cadaver skin were identified. In the acute dermal toxicity study conducted by Scientific Associates [1950], 0.005 to 0.124 mL/kg of TEDP [corresponding to 6 to 148 mg/kg] was applied to rat skin for an unspecified duration and caused slight effects, as evidenced by mild redness without edema or other untoward visible reactions. Kimmerle and Klimmer [1974] reported that application of cotton pads treated with 100 mg of TEDP, underneath adhesive bandages, to the skin inside the auricles of two rabbits for 24 hours

caused no skin effects. However, the amount applied to rats in the Kimmerle and Klimmer [1974] study, up to 100 mg, is much lower than the 500 mg required for a standard skin irritation test. Additionally, the Scientific Associates [1950] found that the oral LD<sub>50</sub> in rabbits was twice that of rats, a finding suggesting that there might be a species difference in dose response.

The limited, conflicting data on direct skin effects [Scientific Associates 1950; Kimmerle and Klimmer 1974] do not allow for adequate evaluation of the potential for TEDP to cause skin irritation. Given these data limitations and inconsistencies, TEDP is not assigned the SK: DIR notation.

## 4 Immune-mediated Responses (SK: SEN)

No occupational exposure studies, 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, TEDP is not assigned the SK: SEN notation.

## 5 Summary

No *in vivo* or *in vitro* toxicokinetic data from humans or animals were identified for evaluating the potential of TEDP to be dermally absorbed; however, the mathematical model predicted that TEDP is absorbed through the skin. Acute toxicity data from animals [**Scientific Associates 1950; Kimmerle and Klimmer 1974**] indicate that TEDP is absorbed through the skin, is systemically available, and can be potentially fatal following dermal exposure. Acute dermal toxicity studies, with support from inhalation and oral studies, indicate that TEDP has the potential to cause ChE inhibition following repeated or prolonged dermal exposure [**Kimmerle and Klimmer 1974**]. The

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



**Table 3. Summary of previous skin hazard designations for TEDP**

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption; prevent skin contact
OSHA [2014]*	[skin]: Potential for dermal absorption
ACGIH [2005]	[skin]: Based on symptoms of organophosphate poisoning seen following dermal contact with relatively low doses to animals

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

\*Date accessed.

limited, conflicting data on direct skin effects [Scientific Associates 1950; Kimmerle and Klimmer 1974] do not allow for adequate evaluation of the potential for TEDP to cause skin irritation. No diagnostic (human patch) tests and no predictive tests in animals were identified that investigated the potential of TEDP to cause skin sensitization. Therefore, on the basis of these assessments, TEDP is assigned a composite skin notation of **SK: SYS (FATAL)**.

Table 3 summarizes the skin hazard designations for TEDP previously issued by NIOSH and other organizations. The equivalent dermal designation for TEDP, 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].

## References

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

- \*ACGIH [2005]. Sulfotep. In: 2015 TLVs and BEIs: threshold limit values for chemical substances and physical agents and biological exposure indices with 7<sup>th</sup> edition documentation. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.
- \*BenDyke R, Sanderson DM, Nakes DN [1970]. Acute toxicity data for pesticides. *World Rev Pest Control* 9:119–127.
- \*European Parliament, Council of the European Union [2008]. Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJEU, Off J Eur Union L353:1–1355, <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:353:0001:1355:EN:PDF>.
- \*IARC [2012]. Agents reviewed by the IARC monographs. In: IARC monographs on the evaluation of carcinogenic risks to humans. Lyon, France: International Agency for Research on Cancer, <http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php>.
- \*Kimmerle G, Klimmer OR [1974]. Acute and sub-chronic toxicity of sulfotep. *Arch Toxicol* 33:1–16.
- \*NIOSH [2005]. TEDP. In: 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/npgd0586.html>.
- \*NIOSH [2009]. Current intelligence bulletin 61: a strategy for assigning new NIOSH skin notations. 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. 2009-147, <http://www.cdc.gov/niosh/docs/2009-147/pdfs/2009-147.pdf>.
- \*NTP [2014]. Report on carcinogens. 13th Edition. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program, <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html>.
- \*OSHA [ND]. TEDP. In: OSHA occupational chemical database, <https://www.osha.gov/chemicaldata/chemResult.html?recNo=362>.
- \*Scientific Associates [1950]. Toxicological investigation of tetraethyl dithionopyrophosphate. By Younger FM. St. Louis, MO: Scientific Associates for the Monsanto Chemical Company. On file



- with the U.S. Environmental Protection Agency under TSCA Section 8D. OTS #0545594.
- \*Storm JE [2001]. Organophosphorus compounds. In: Bingham E, Cohrssen B, Powell CH, eds. *Patty's toxicology and industrial hygiene*, 5th ed. Vol. 7. New York: John Wiley and Sons.
- \*US EPA [1999]. Reregistration eligibility decision (RED): sulfotepp. Washington, DC: United States Environmental Protection Agency, 738 R 99 012.
- \*US EPA [2012]. Tetraethyldithiopyrophosphate. In: Integrated risk information system. Washington, DC: United States Environmental Protection Agency, <http://www.epa.gov/iris/subst/0330.htm>.

## Appendix: Calculation of the SI Ratio for TEDP

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for TEDP. 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 ( $k_p$ )

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

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

$$\log k_{psc} = -1.326 + 0.6097 \times \log k_{ow} - \frac{0.1786 \times MW^{0.5}}{0.1786 \times MW^{0.5}}$$

$$k_{pol} = 0.0001519 \times MW^{-0.5}$$

$$k_{aq} = 2.5 \times MW^{-0.5}$$

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<sup>2</sup>]).

### 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<sup>3</sup>) 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 TEDP. The calculated SI ratio was 0.43. On the basis of these results, TEDP 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/>.
- NIOSH [2009]. Current intelligence bulletin 61: a strategy for assigning new NIOSH skin notations. 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. 2009-147, <http://www.cdc.gov/niosh/docs/2009-147/pdfs/2009-147.pdf>.
- SRC [ND]. Interactive PhysProp database demo, <http://www.srcinc.com/what-we-do/databas-eforms.aspx?id=386>.

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

Variables used in calculation	Units	Value
<b>Skin permeation coefficient</b>		
Permeation coefficient of stratum corneum lipid path ( $k_{psc}$ )	cm/hr	0.0079
Permeation coefficient of the protein fraction of the stratum corneum ( $k_{pol}$ )	cm/hr	$8.481 \times 10^{-6}$
Permeation coefficient of the watery epidermal layer ( $k_{aq}$ )	cm/hr	0.1393
Molecular weight ( $MW$ ) <sup>*</sup>	amu	322.32
Base-10 logarithm of its octanol–water partition coefficient ( $Log K_{ow}$ ) <sup>*</sup>	None	3.99
Calculated skin permeation coefficient ( $k_p$ )	cm/hr	0.0075
<b>Skin dose</b>		
Water solubility ( $S_w$ ) <sup>*</sup>	mg/cm <sup>3</sup>	0.03
Calculated skin permeation coefficient ( $k_p$ )	cm/hr	0.0075
Estimated skin surface area (palms of hands)	cm <sup>2</sup>	360
Exposure time	hr	8
Calculated skin dose	mg	0.65
<b>Inhalation dose</b>		
Occupational exposure limit (OEL) <sup>†</sup>	mg/m <sup>3</sup>	0.2
Inhalation volume	m <sup>3</sup>	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	1.5
<b>Skin dose–to–inhalation dose (SI) ratio</b>	<b>None</b>	<b>0.434</b>

<sup>\*</sup>Variables identified from SRC [ND].

<sup>†</sup>The OEL used in calculation of the SI ratio for TEPP was the NIOSH recommended exposure limit (REL) [NIOSH 2005].

This page intentionally left blank.



***Delivering on the Nation's promise:  
safety and health at work for all people  
through research and prevention***

To receive NIOSH documents or more information about occupational safety and health topics, contact NIOSH at

**1-800-CDC-INFO** (1-800-232-4636)

TTY: 1-888-232-6348

CDC-INFO: [www.cdc.gov/info](http://www.cdc.gov/info)

or visit the NIOSH website at [www.cdc.gov/niosh](http://www.cdc.gov/niosh).

For a monthly update on news at NIOSH, subscribe to *NIOSH eNews* by visiting [www.cdc.gov/niosh/eNews](http://www.cdc.gov/niosh/eNews).

**DHHS (NIOSH) Publication No. 2015-227**

**SAFER • HEALTHIER • PEOPLE™**