Skin Notation (SK) Profile

Tetraethyl dithionopyrophosphate (TEDP)

[CAS No. 3689-24-5]

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 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.

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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
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
(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)
$mg/cm^2/hr$	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
SYS	skin notation indicating the potential for systemic toxicity following exposure of the skin
TEDP	tetraethyl dithionopyrophosphate
USEPA	United States Environmental Protection Agency
µg	microgram(s)
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 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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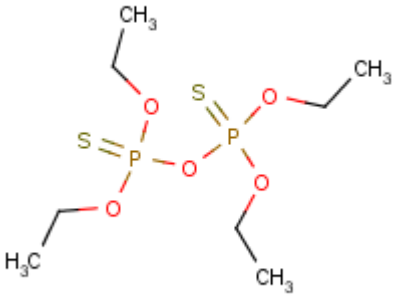
1.0 Introduction

1.1 General Substance Information

Chemical: Tetraethyl dithionopyrophosphate (TEDP)
CAS No: 3689-24-5
Molecular weight (*MW*): 322.3
Molecular formula: $[(CH_3CH_2O)_2PS]_2O$
Structural formula:



Synonyms: Dithion®; Bladafum®; Sulfotep; Tetraethyl dithionopyrophosphate; Tetraethyl dithiopyrophosphate; Thiotepp®

Uses: TEDP is a restricted-use organophosphate compound approved only for the use as an insecticide within commercial greenhouses [USEPA 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 2012 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)-DIR (IRR)**. 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	Sufficient animal data
SK: DIR (IRR)	Skin irritation	Limited 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 TEDP absorption through the skin following dermal. The potential of TEDP 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 0.43 was calculated for TEDP. An SI ratio of ≥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 the variables used in its calculation are included in the appendix.

No estimate of the human dermal lethal dose (LD_{Lo}) was identified for TEDP. Dermal LD_{50} (the dose resulting in 50% mortality in the exposed animals) values reported 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 repeat-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 evaluating biological system/function specific effects (including reproductive and developmental effects and immunotoxicity) were identified 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.

Table 2. Summary of the carcinogenic designations for TEDP 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.

Although no *in vivo* or *in vitro* toxicokinetic data were identified for humans or animals that evaluated the potential of TEDP to be absorbed through the skin following dermal exposure, the weight of evidence from acute toxicity data in animals **[Scientific Associates 1950; Kimmerle and Klimmer 1974]**[1], supported by a model prediction, indicate that TEDP is absorbed through the skin, is systemically available, and can be fatal following dermal exposure. No epidemiological or occupational exposure studies and no repeated-dose or long-term dermal exposure studies in animals were identified that evaluated the potential of TEDP to cause systemic effects, but acute dermal toxicity

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

studies, with support from inhalation and oral studies, indicate that TEDP has the potential to cause ChE inhibition following repeated or prolonged dermal exposure. Therefore, on the basis of the data for this assessment, TEDP 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 TEDP 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 the acute dermal toxicity study conducted by Scientific Associates [1950], application of 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 on the skin of rats as evidence by mild redness without edema or other untoward visual reactions. In rabbits, Kimmerle and Klimmer [1974] reported that application of cotton pads treated with 100 mg of TEDP to the skin inside the auricles of two rabbits under adhesive bandage for 24 hr 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_{50} in rabbits was twice that of rats suggesting that there might be a species difference in dose response.

Limited data identified from an acute dermal toxicity study **[Scientific Associates 1950]** indicate that TEDP has the potential to cause skin irritation on prolonged contact with the skin. Therefore, on the basis of the data for this assessment, TEDP is assigned the SK: DIR (IRR) notation.

4.0 Immune-mediated Responses (SK: SEN)

No occupational exposure studies or diagnostic (human patch) tests, and no 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.

5.0 Summary

Although no *in vivo* or *in vitro* toxicokinetic data were identified for humans or animals that evaluated the potential of TEDP to be absorbed through the skin following dermal exposure, the weight of evidence from acute toxicity data in animals **[Scientific Associates 1950; Kimmerle and Klimmer 1974]**, supported by a model prediction, indicate that TEDP is absorbed through the skin, is systemically available, and can be fatal following dermal exposure. Although no epidemiological studies, occupational

exposure studies or case reports, and no repeated-dose or long-term dermal exposure studies in animals were identified that evaluated the potential of TEDP to cause systemic effects, 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. Limited data identified from an acute dermal toxicity study **[Scientific Associates 1950]** indicate that TEDP has the potential to cause skin irritation on prolonged contact with the skin. 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)-DIR (IRR)**.

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 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 TEDP

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption; prevent skin contact
OSHA [2012]*	[skin]: Potential for dermal absorption
ACGIH [2005]	[skin]: Based on symptoms of organophosphate poisoning seen following dermal contact with relatively low doses to 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 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 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 $\times$ Exposure time
= k_p(cm/hr) $\times$ S_w (mg/cm^3) $\times$ 360 cm^2 $\times$ 8 hr

The inhalation dose (in mg) is derived on the basis of the occupational exposure limit (OEL) of the substance—if the OEL is developed to prevent the occurrence of systemic effects rather than sensory/irritant effects or direct effects on the respiratory tract. Assume a continuous exposure of 8 hours, an inhalation volume of 10 cubic meters (m^3) inhaled air in 8 hours, and a factor of 75% for retention of the airborne substance in the lungs during respiration (retention factor, or RF).

Equation 3: Determination of Inhalation Dose

Inhalation dose = OEL × Inhalation volume × RF
= OEL (mg/m^3) × 10 m^3 × 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 TEDP. The calculated SI ratio was 0.43. On the basis of these results, TEDP is predicted to represent a skin absorption hazard.

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

Variables Used in Calculation	Units	Value
Skin permeation coefficient		
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	8.481×10^{-6}
Permeation coefficient of the watery epidermal layer (k_{aq})	cm/hr	0.1393
Molecular weight (MW)[a]	amu	322.32
Base-10 logarithm of its octanol–water partition coefficient (Log K_{ow})[a]	None	3.99
Calculated skin permeation coefficient (k_p)	cm/hr	0.0075
Skin dose		
Water solubility (S_w)[a]	mg/cm^3	0.03
Calculated skin permeation coefficient (k_p)	cm/hr	0.0075
Estimated skin surface area (palms of hand)	cm^2	360
Exposure time	hr	8
Calculated skin dose	mg	0.65
Inhalation Dose		
Occupational exposure limit (OEL)[b]	mg/m^3	0.2
Inhalation volume	m^3	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	1.5
Skin dose–to–inhalation dose (SI) ratio	None	0.434

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

Appendix References

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