NIOSH Skin Notation Profiles

Tetraethyl pyrophosphate (TEPP)

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

Tetraethyl pyrophosphate (TEPP)

[CAS No. 107-49-3]

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 (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 pyrophosphate (TEPP). 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.
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Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
AChE	acetylcholinesterase
ALD	approximate lethal dose
Amu	atomic mass unit
ATSDR	Agency for Toxic Substances and Disease Registry
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)
(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
L liter(s)	
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
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
TEPP	tetraethyl pyrophosphate
US EPA	United States Environmental Protection Agency
L/kg	microliter(s) per kilogram

Glossary

Absorption—The transport of a chemical from the outer surface of the skin into both the skin and systemic circulation (including penetration, permeation, and resorption).

Acute exposure—Contact with a chemical that occurs once or for only a short period of time.

Cancer—Any one of a group of diseases that occur when cells in the body become abnormal and grow or multiply out of control.

Contaminant—A chemical that is (1) unintentionally present within a neat substance or mixture at a concentration less than 1.0% or (2) recognized as a potential carcinogen and present within a neat substance or mixture at a concentration less than 0.1%.

Cutaneous (or percutaneous)—Referring to the skin (or through the skin).

Dermal—Referring to the skin.

Dermal contact—Contact with (touching) the skin.

Direct effects—Localized, non-immune-mediated adverse health effects on the skin, including corrosion, primary irritation, changes in skin pigmentation, and reduction/disruption of the skin barrier integrity, occurring at or near the point of contact with chemicals.

Immune-mediated responses—Responses mediated by the immune system, including allergic responses.

Sensitization—A specific immune-mediated response that develops following exposure to a chemical, which, upon re-exposure, can lead to allergic contact dermatitis (ACD) or other immune-mediated diseases such as asthma, depending on the site and route of re-exposure.

Substance—A chemical.

Systemic effects—Systemic toxicity associated with skin absorption of chemicals after exposure of the skin.

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1 Introduction

1.1 General Substance Information

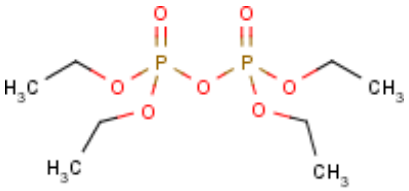
Chemical: Tetraethyl pyrophosphate (TEPP)

CAS No: 107-49-3

Molecular weight (*MW*)**:** 290.2

Molecular formula: $[(CH_3CH_2O)_2PO]_2O$

Structural formula:



Synonyms: Ethyl pyrophosphate; Tetron® diphosphoric acid tetraethyl ester; ethyl pyrophosphate; tetra-phosphoric acid tetraethyl ester; tetraethyl ester diphosphonic acid; O,O,O¢,O¢-tetraethyl pyrophosphate; diphosphoric acid tetraethyl ester; bis-O,O-diethylphosphoric anhydride; pyrophosphoric acid, tetraethyl ester

Uses: Tetraethyl pyrophosphate (TEPP) is an organophosphate compound used as a broad-spectrum pesticide. An estimated 100,000 pounds (45,000 kilograms) of TEPP were produced in the United States in 1972 [HSDB 2009]. No more-recent production data were identified during this assessment.

1.2 Purpose

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

1.3 Overview of SK Assignment

TEPP 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 TEPP: **SK: SYS (FATAL)**. Table 1 provides

Table 1. Summary of the SK assignment for TEPP

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

an overview of the critical effects and data used to develop the SK assignment for TEPP.

2 Systemic Toxicity from Skin Exposure (SK: SYS)

No toxicokinetic studies in humans or animals were identified that estimated the degree of TEPP absorption through the skin following dermal exposure. The potential of TEPP 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 686.5 was calculated for TEPP. An SI ratio of ≥0.1 indicates that skin absorption may significantly contribute to the overall body burden of a substance [NIOSH 2009]; therefore, TEPP 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 TEPP. An acute dermal LD_{50} value (the lethal dose in 50% of exposed animals) of 2.4 milligrams per kilogram body weight (mg/kg) has been reported for rats [Gaines 1969]. E.I. du Pont de Nemours and Company [1977a, 1977b] reported approximate lethal doses (ALDs) ranging from <17 microliters per kilogram (µL/kg) (corresponding to 20 mg/kg) of TEPP in acetone to 130 mg/kg of TEPP in unknown material in rabbits. Because the reported acute dermal LD_{50} value for rats and the ALD for 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], TEPP is considered to be absorbed through the skin, systemically available, and potentially fatal following dermal exposure.

No epidemiological studies or occupational exposure studies were identified that investigated the potential of TEPP to cause systemic effects following dermal exposure. However, two case reports [Faust 1949; Reeder and Whittier 1961] were identified that indicate that TEPP has the potential to cause organophosphate poisoning via acetylcholinesterase (AChE) inhibition in humans, following dermal exposure. Faust [1949] reported a worker who was exposed to a pesticide solution containing 20% TEPP and 30% other related (ethyl) phosphates diluted in water (0.21 liters [L] to 3.78 L) that leaked during application. The worker also ingested some of the pesticide solution because he sliced fruit and ate without washing his hands [Faust 1949]. Within 3 hours, symptoms of organophosphate poisoning, including loss of vision, tightness of the chest, cramping, and vomiting developed [Faust 1949]. Reeder and Whittier [1961] reported that two workers wearing protective clothing and respirators absorbed TEPP through their skin after prolonged contact of their perspiration-soaked clothing with a mixture of TEPP and agricultural dusting powders. According to the study authors, 10 times the amount of TEPP was mistakenly added to the dusting powders, and although the actual amount to which the workers were exposed was not quantified, the product mixture was reported to contain an unusually high amount of TEPP [Reeder and Whittier 1961]. Within hours, the workers reported symptoms of organophosphate poisoning, including nausea, weakness, and dizziness [Reeder and Whittier 1961]. These studies indicate that overexposure to TEPP or prolonged exposure to low doses of the chemical can result in systemic effects consistent with organophosphate poisoning via AChE inhibition.

No repeated-dose, subchronic, or chronic toxicity studies in animals were identified that evaluated the systemic effects of TEPP following dermal exposure. No specialty studies were identified for TEPP that evaluated biological

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

Organization	Carcinogenic designation
NIOSH [2005]	No designation
NTP [2014]	No designation
US EPA [2014]	No designation
European Parliament [2008]	No GHS designation
IARC [2012]	No designation
ACGIH [2007]	No data on which to assign a carcinogenicity notation

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.

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

Although no toxicokinetic data were identified that estimated the degree of absorption of TEPP through the skin following dermal exposure, the mathematical model predicted that TEPP was absorbed through the skin. Acute toxicity studies in rats and rabbits **[Gaines 1969; E.I. du Pont de Nemours and Company 1977a, 1977b**[*] and two case reports **[Faust 1949; Reeder and Whittier 1961]** indicate that TEPP is absorbed through skin, is systemically available, has the potential to cause AChE inhibition, and can be potentially fatal following dermal exposure. Therefore, on the basis of the data for this assessment, TEPP is assigned the SK: SYS (FATAL) notation.

3 Direct Effects on Skin (SK: DIR)

No human or animal *in vivo* studies for corrosivity of TEPP, *in vitro* tests for corrosivity using human or animal skin models, or *in vitro* tests of skin integrity using cadaver skin were identified. No occupational studies or case reports and no standard skin irritation tests in animals were identified that evaluated the potential of TEPP to cause direct skin effects. However, E.I. du Pont de Nemours and Company [1977a, 1977b] noted slight irritation at the application site when 0.14 mL/kg (corresponding to 168 mg/kg) of TEPP in unknown solution and 0.10 mL/kg (corresponding to 120 mg/kg) of 10% TEPP in acetone were applied to the shaved back and trunk of rabbits in occluded conditions in acute skin absorption tests. However, acetone has been noted as a mild skin irritant after long periods of exposure [Smyth et al. 1962]. Therefore, the data [E.I. du Pont de Nemours and Company 1977a, 1977b] are insufficient to assign TEPP the SK: DIR notation.

4 Immune-mediated Responses (SK: SEN)

No occupational exposure studies or diagnostic (human patch) tests, 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 TEPP to cause skin sensitization. Lack of these studies precludes adequate evaluation of TEPP as a potential

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

skin sensitizer. Therefore, on the basis of the data for this assessment, TEPP is not assigned the SK: SEN notation.

5 Summary

No toxicokinetic data were identified that estimated the degree of absorption of TEPP through the skin following dermal exposure; however, the mathematical model predicted that TEPP was dermally absorbed. Acute toxicity studies in rats **[Gaines 1969; E.I. du Pont de Nemours and Company 1977a, 1977b]** and two case reports **[Faust 1949; Reeder and Whittier 1961]** indicate that TEPP is systemically available, may cause systemic effects (such as AChE inhibition, including fatality), and is potentially fatal following dermal exposure. No occupational exposure studies or case reports and no standard skin irritation tests were identified that evaluated the potential of TEPP to cause direct skin effects. Slight skin irritation was noted in acute toxicity tests in rabbits [E.I. du Pont de Nemours and Company 1977a, 1977b]; however the vehicle used in these studies, acetone, has been noted to be a mild irritant. Therefore, these data are insufficient to assign the SK: DIR notation. In addition, no diagnostic (human) patch tests or predictive tests in animals were identified that evaluated the potential of TEPP to cause skin sensitization. Therefore, on the basis of these assessments, TEPP is assigned a composite skin notation of **SK: SYS (FATAL)**.

Table 3 summarizes the skin hazard designations for TEPP previously issued by NIOSH and other organizations. The equivalent dermal designation for TEPP, 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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Table 3. Summary of previous skin hazard designations for TEPP

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption; prevent skin contact
OSHA [2014]*	[skin]: Potential for dermal absorption
ACGIH [2007]	[skin]: Based on the high level of toxicity seen in animals following either single or repeated dose

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

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Appendix: Calculation of the SI Ratio for TEPP

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for TEPP. 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 TEPP. The calculated SI ratio was 686.5. On the basis of these results, TEPP is predicted to represent a skin absorption hazard.

Appendix References

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

Variables used in calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path(k_{psc})	cm/hr	8.052×10^{-5}
Permeation coefficient of the protein fraction of the stratum corneum (k_{pol})	cm/hr	8.917×10^{-6}
Permeation coefficient of the watery epidermal layer (k_{aq})	cm/hr	0.1468
Molecular weight *(MW)*[*]	amu	290.19
Base-10 logarithm of its octanol–water partition coefficient *(Log* K_{ow}*)*[*]	None	0.45
Calculated skin permeation coefficient (k_p)	cm/hr	8.984×10^{-5}
Skin dose		
Water solubility (S_w)[*]	mg/cm^3	0.148
Calculated skin permeation coefficient (k_p)	cm/hr	8.984×10^{-5}
Estimated skin surface area (palms of hands)	cm^2	360
Exposure time	hr	8
Calculated skin dose	mg	257.4
Inhalation dose		
Occupational exposure limit (OEL)	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**	**686.5**

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

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