Skin Notation (SK) Profile

Tetraethyl Lead (TEL)

[CAS No. 78-00-2]

Department of Health and Human Services
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

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 Web sites 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 Web sites.

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
Or visit the NIOSH Web site: www.cdc.gov/niosh

For a monthly update on news at NIOSH, subscribe to *NIOSH eNews* by visiting www.cdc.gov/niosh/eNews.

Suggested Citation

NIOSH [20XX]. NIOSH skin notation profile: Tetraethyl lead. 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. XXX

DHHS (NIOSH) Publication No. XXX

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 lead (TEL). 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

Contents

Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
CIB	Current Intelligence Bulletin
cm^2	squared centimeter(s)
cm/hour	centimeter(s) per hour
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
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/kg	milligram(s) per kilogram body weight
mg/m^3	milligram(s) per cubic meter
mL	milliliter(s)
MLD	minimum lethal dose
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
TEL	tetraethyl lead
USEPA	United States Environmental Protection Agency

Glossary

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

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

Approximate Lethal Dose—The lowest dose which causes mortality.

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.

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. MPH, Heinz Ahlers, M.Sc., and Aaron Sussell, 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.
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.
Sudha Pandalai. M.D., Ph.D.

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

National Personal Protection Technology Laboratory
Heinz Ahlers, M.Sc.
Angie Shephard

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.

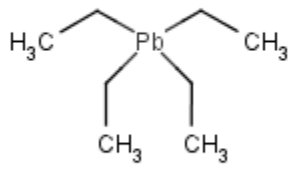
In addition, special appreciation is expressed to the following individuals for serving as independent, external reviewers and providing comments that contributed to the development or improvement of this document:

- 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

1.0 Introduction

1.1 General Substance Information:

Chemical: Tetraethyl Lead
CAS No: 78-00-2
Molecular weight (*MW*): 323.5
Molecular formula: $Pb(C_2H_5)_4$
Structural formula:



Synonyms: Lead tetraethyl; TEL; Tetraethylplumbane

Uses: Tetraethyl lead (TEL) was historically used as an additive to fuel as an antiknock agent; currently, the substance is used during the manufacturing of other metals [HSDB 2008].

1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with TEL and (2) the rationale behind the hazard-specific skin notation (SK) assignment for TEL. 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 TEL. A literature search was conducted through January 2013 to identify information on TEL, 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 TEL.

1.3 Overview of SK Assignment

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

Table 1. Summary of the SK Assignment for TEL

Skin Notation	Critical Effect	Available Data
SK: SYS	Hepatotoxicity; Hemotoxicity	Limited animal data

2.0 Systemic Toxicity from Skin Exposure (SK: SYS)

No studies were identified that provided quantitative estimates of dermal absorption of TEL in humans or animals following dermal exposure. However, evidence of dermal absorption after topical application was provided by Kehoe and Thamann [1931] who uniformly spread 0.75 milliliter (mL) of TEL over an area of 25 square centimeters (cm^2) on the abdominal skin of rabbits. The authors reported an accumulation of 1.06 to 4.41 milligrams (mg) of lead in the carcass of the test animals, corresponding to exposure durations of 0.5 to 6 hours, respectively. Laug and Kunze [1948] noted that 90 to 95% of tetraethyl lead evaporated before it could be absorbed by the skin; however, using lead content of the kidney as an index for dermal absorption, the authors reported a hundredfold increase in the kidney lead concentration following application of TEL to shaved skin of rats. These authors also noted that scarifying the skin enhanced absorption [Laug and Kunze 1948]. The potential of TEL 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 0.01 was calculated for TEL. An SI ratio of ≥0.1 indicates that skin absorption may significantly contribute to the overall body burden of a substance [NIOSH 2009]; therefore, TEL is not 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 dermal lethal dose (LD_{Lo}) of TEL in humans has been identified. However, approximate lethal dose (ALD) (i.e., the lowest dose which causes mortality) and minimum lethal dose (MLD) values were identified. E.I. du Pont de Nemours and Company [1959, 1991] reported an ALD of 1500 and 2250 milligrams per kilogram body weight (mg/kg) when TML was applied to the skin of male albino rabbits in a mixture of toluene and ethylene dibromide (EDB). However, the authors reported the clinical signs preceding death were indicative of EDB poisoning. MLD values of 1.5 milliliters per kilogram of bodyweight (mL/kg) (corresponding to 2475 mg/kg [Akatsura 1973] and 0.7 mL/kg (corresponding to 1157 mg/kg) in adult rabbits [Kehoe 1927] have been reported. Akatsura [1973] reported

hyperglycemia, marked reduction in body weight, porphyrinuria, and marked reduction in liver function following dermal application of TEL to the rabbits. Although no dermal LD_{50} values (the dose resulting in 50% mortality in the exposed animals) were identified in animals, the ALD and MLD values for rabbits indicate that TEL was absorbed through the skin following dermal exposure. However, the data are insufficient to determine if TEL is lethal in concentrations less than the critical dermal LD_{50} value of 2000 mg/kg body weight that identifies chemical substances with the potential for acute dermal toxicity [NIOSH 2009].

No epidemiological studies, case reports or occupational exposure studies or repeat-dose, subchronic or chronic toxicity studies in animals were identified following dermal exposure to TEL. No standard toxicity or specialty studies evaluating biological system/function specific effects (including reproductive and developmental effects and immunotoxicity) following dermal exposure to TEL were identified. No epidemiological studies or animal bioassays were identified that evaluated the carcinogenic potential of TEL following dermal exposure. No other organizations or agencies have classified TEL as a carcinogen by other routes of exposure. Table 2 summarizes carcinogenic designations of multiple governmental and nongovernmental organizations for TEL.

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

Organization	Carcinogenic designation
NIOSH [2005]	No designation
NTP [2014]	No designation
USEPA [2014]	No designation
European Parliament [2008]	No GHS designation
IARC [2012]	Group 3: Not classifiable as to carcinogenicity to humans
EC [2013]†	No designation
ACGIH [2001]	Group 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; 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.
*The listed cancer designations were based on data from nondermal (such as oral or inhalation) exposure since studies using the dermal route of exposure were unavailable.
†Date accessed.

Although the predictive mathematical model (see Appendix) did not indicate that the chemical can be absorbed through the skin, sufficient data exist from toxicokinetic **[Kehoe and Thamann 1931**; **Laug and Kunze 1948]**[1] and acute toxicity **[Kehoe 1927; Akatsura 1973]** data that demonstrate that the chemical is absorbed through the skin and is systemically available**.** Although limited, evidence suggests that TEL was absorbed by the skin and may cause hyperglycemia, marked reduction in body weight, porphyrinuria, and marked reduction in liver function was observed at high doses. Therefore, on the basis of the data for this assessment, TEL is assigned the SK: SYS notation.

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

3.0 Direct Effects on Skin (SK: DIR)

No human or animal *in vivo* studies on corrosivity or *in vitro* tests for corrosivity using human or animal skin models or *in vitro* tests of skin integrity using cadaver skin were identified. No reliable studies that specifically evaluated the potential of TEL to cause skin irritation were identified. In an acute toxicity study, E.I. du Pont de Nemours and Company [1959, 1991] reported skin irritation at every dose of TEL tested; however it is unknown if the irritation was due to TEL or EDB since clinical signs preceding death were indicative of EDB poisoning There are insufficient data to determine skin irritation; therefore, on the basis of the data for this assessment, TEL is not assigned the SK: DIR notation.

4.0 Immune-mediated Responses (SK: SEN)

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

5.0 Summary

Although the predictive mathematical model (see Appendix) did not indicate that the chemical can be absorbed through the skin, toxicokinetic **[Kehoe and Thamann 1931**; **Laug and Kunze 1948]** and acute toxicity **[Kehoe 1927]** data indicate tetraethyl lead demonstrated the ability to be absorbed through the skin and has the potential to cause hyperglycemia, marked reduction in body weight, porphyrinuria, and marked reduction in liver function at high doses. No reliable information was identified upon which to evaluate the potential of TEL to cause skin irritation/corrosion or skin sensitization. Therefore, on the basis of these assessments, TEL is assigned a composite skin notation of **SK: SYS**.

Table 3 summarizes the skin hazard designations for TEL previously issued by NIOSH and other organizations. No dermal designation based on the Globally Harmonized System (GHS) of Classification and Labelling of Chemicals was identified for TEL [European Parliament 2008].

Table 3. Summary of previous skin hazard designations for TEL

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption
OSHA [2015]*	[skin]: Potential for dermal absorption
ACGIH [2001]	[skin]: Based on systemic toxicity following percutaneous absorption.
EC [2013]*	No designation

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.

References

ACGIH (American Conference of Governmental Industrial Hygienists) [2001]. Tetraethyl lead. In: Documentation of threshold limit values and biological exposure indices 7th ed., Vol. 3. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

Akatsuka K [1973]. Tetraalkyl lead poisoning. Sangyo Igaku (Japanese Journal of Industrial Health) *15*:366.

EC (European Commission) [ND]. Tetraethyllead. In: EINICS (European Inventory of Existing Commercial Chemical Substances), http://esis.jrc.ec.europa.eu/. Accessed: 01-24-13.

E.I. du Pont de Nemours and Company [1959]. Preliminary comparative toxicity studies with tetramethyl lead and tetraethyl lead. Newark, DE: E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Medical Research Project #MR-476, Report #20-59. On file with the U.S. Environmental Protection Agency under TSCA Section 8D. OTS #0555601. Document # 88-920010199.

E.I. du Pont de Nemours and Company [1991]. Follow-up information: Concerning the enclosed summary from Haskell Laboratory on tetraethyl lead and tetramethyl lead with attachments. Newark, DE: E.I. du Pont de Nemours and Company. On file with the U.S. Environmental Protection Agency under TSCA Section 8D. OTS #0533656-1. Document # 89-92000023.

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, labeling 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 . Accessed: 01-23-15.

HSDB (Hazardous Substances Data Bank) [2008]. Tetraethyl lead. In: HSDB (Hazardous Substances Data Bank), http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~NjKI4B:1. Accessed: 01-23-15.

IARC (International Agency for Research on Cancer) [2012]. Agents reviewed by the IARC monographs. In: IARC monographs on the evaluation of carcinogenic risks to humans, http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php. Accessed: 01-23-15.

Kehoe RA [1927]. On the toxicity of tetraethyl lead and inorganic lead salts. J. Lab. Clin. Med. *7*: 554-560.

Kehoe RA, Thamann F [1931]. The behavior of lead in the animal organism. II. Tetraethyl lead. Am. J. Hyg. *13*: 478-498.

Laug EP, Kunze FM [1948]. The penetration of lead through the skin. J. Ind. Hyg. Toxicol. *30*: 256-259.

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/. Accessed: 01-23-15.

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. Accessed: 01-23-15.

NTP [2014]. Report on Carcinogens. Thirteenth Edition; U.S. Department of Health and Human Services, Public Health Service. National Toxicology Program, http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html. Accessed: 01-23-15.

OSHA [ND]. Tetraethyl lead, as Pb. In: OSHA/EPA occupational chemical database, http://www.osha.gov/chemicaldata/chemResult.html?recNo=666. Accessed: 01-24-13.

USEPA [2014]. Integrated Risk Information System: tetraethyl lead. In: Integrated Risk Information System, http://www.epa.gov/ncea/iris/subst/0109.htm. Accessed: 01-23-15.

Appendix: Calculation of the SI Ratio for TEL

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for TEL. 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 k_p 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 squared centimeters [cm^2]).

Equation 2: Determination of Skin Dose

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

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 TEL. The calculated SI ratio was 0.01. On the basis of these results, TEL is not predicted to represent a skin absorption hazard.

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

Variables Used in Calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path(k_{psc})	cm/hour	9.8×10^{-3}
Permeation coefficient of the protein fraction of the stratum corneum (k_{pol})	cm/hour	8.446×10^{-6}
Permeation coefficient of the watery epidermal layer (k_{aq})	cm/hour	1.39×10^{-2}
Molecular weight (MW)*	amu	323.44
Base-10 logarithm of its octanol–water partition coefficient (Log K_{ow})*	None	4.15
Calculated skin permeation coefficient (k_p)	cm/hour	9.2×10^{-3}
Skin dose		
Water solubility (S_w)*	mg/cm^3	2.9×10^{-4}
Calculated skin permeation coefficient (k_p)	cm/hour	9.2×10^{-3}
Estimated skin surface area (palms of hand)	cm^2	360
Exposure time	hour	8
Calculated skin dose	mg	1.36×10^{-2}
Inhalation Dose		
Occupational exposure limit (OEL)†	mg/m^3	0.075
Inhalation volume	m^3	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	0.5625
Skin dose–to–inhalation dose (SI) ratio	None	0.01

*Variables identified from SRC [ND].

†The OEL used in calculation of the SI ratio for TEL was the NIOSH recommended exposure limit (REL) [NIOSH 2005].

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/. Accessed: 01-23-15.

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. Accessed: 01-23-15.

SRC [2009]. Interactive PhysProp database demo, http://esc.syrres.com/fatepointer/webprop.asp?CAS=78002. Accessed: 01-23-15.