Skin Notation (SK) Profile

Tetramethyl lead (TML)

[CAS No. 75-74-1]

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 tetramethyl lead (TML). 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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Contents

Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
ALD	approximate lethal dose
ATSDR	Agency for Toxic Substances and Disease Registry
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
EDB	ethylene dibromide
GHS	Globally Harmonized System for Classification and Labelling of Chemicals
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
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
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
TML	tetramethyl 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.

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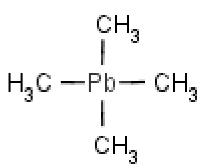
1.0 Introduction

1.1 General Substance Information:

Chemical: Tetramethyl lead (TML)
CAS No: 75-74-1
Molecular weight (*MW*): 267.3
Molecular formula: $Pb(CH_3)_4$
Structural formula:



Synonyms: Lead tetramethyl; Tetramethylplumbane; TML; Alkyllead; Organolead

Uses: TML is an organic lead compound historically used as a octane booster (i.e., antiknock additive) for gasoline of premium and aviation grades [ACGIH 2001]. This substance is no longer used in large volumes commercially.

1.2 Purpose

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

1.3 Overview of SK Assignment for TML

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

Table 1. Summary of the SK Assignment for TML

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

2.0 Systemic Toxicity from Skin Exposure (SK: SYS)

No toxicokinetic studies following dermal exposure to TML have been identified in humans or animals. The potential of TML 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 2.76 was calculated for TML. An SI ratio of ≥0.1 indicates that skin absorption may significantly contribute to the overall body burden of a substance [NIOSH 2009]; therefore, TML 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 human dermal lethal dose (LD_{Lo}) or dermal LD_{50} values (the dose resulting in 50% mortality in the exposed animals) were identified for TML. E.I. du Pont de Nemours and Company [1959, 1991] reported an approximate lethal dose (ALD) (i.e., the lowest dose which causes mortality) of 6,203 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. A minimum lethal dose (MLD) value of 2.0 milliliters per kilogram (mL/kg) of bodyweight (mL/kg) (corresponding to 4,000 milligrams per kilogram of bodyweight (mg/kg)) for rabbits was identified [Akatsuka K 1973]. The ALD and MLD values for rabbits indicate that TML was absorbed through the skin following dermal exposure and is lethal in concentrations greater 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 or occupational studies or case reports, nor repeat-dose, subchronic or chronic toxicity studies in animals were identified that evaluated the potential for TML to cause systemic effects following dermal exposure. Schepers [1964] has indicated that virtually identical effects could be induced by the oral, cutaneous, and inhalation routes of exposure to TML, based on studies that compared the severity and distribution of lesions cumulatively induced by separate but comparable repeated dosage studies, following each route of exposure. Based on this finding and the results of the model prediction that TML can be absorbed through the skin, the potential of the substance to induce systemic toxicity was evaluated following repeated or prolonged exposure via other routes. In a 20-week study conducted by Schepers [1964], tetramethyl lead administered to rats in peanut oil by gavage at 0.001 or 1.08 milligrams per kilogram body weight (mg/kg) 5 days/week, caused cytoplasmic degeneration and vacuolation of the liver and neuronal damage at the low dose while animals exposed to the higher dose exhibited similar but more severe histopathologies. A Lowest Observed Adverse Effect Level (LOAEL) of 0.001 mg/kg-day, the lowest dose tested, can be determined from this study. Because this LOAEL observed in this study is very low, this assessment concludes that TML has the potential to be systemically available and may cause similar effects (liver and neuronal damage), with a NOAEL that is likely to be lower or equal to the critical dermal NOAEL value of 1000 mg/kg-day that identifies chemical substances with the potential for repeated-dose dermal toxicity [NIOSH 2009].

No standard toxicity or specialty studies were identified that evaluated biological system/function specific effects (including reproductive and developmental effects and immunotoxicity) following dermal exposure to TML. No epidemiological studies or animal bioassays were identified that evaluated the carcinogenic potential of TML following dermal exposure. No other organizations or agencies have classified TML as a carcinogen by other routes of exposure. Table 2 summarizes carcinogenic designations of multiple governmental and nongovernmental organizations for TML.

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

Organization	Carcinogenic designation
NIOSH [2005]	No designation
NTP [2014]	No designation
European Parliament [2008]	No GHS designation
USEPA [2015]	No designation
IARC [2012]	No designation
EC [2013]†	No designation
ACGIH [2001]	No designation

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.

No toxicokinetic data were identified that estimated the degree of absorption of TML following dermal exposure, although a model predicted TML to be absorbed following skin contact. No acute toxicity studies were identified that reported LD_{50} values for TML, however an ALD of 6,203 mg/kg [E.I. du Pont de Nemours and Company 1959, 1991] and a MLD of 4000 mg/kg were identified [Akatsuka 1973]. No epidemiological or occupational exposure studies or case reports and no repeat-dose, subchronic, or chronic studies in animals were identified that evaluated the potential of TML to cause systemic effects following dermal exposure. Given the results of the model prediction and because virtually identical effects could be induced by the oral, cutaneous, and inhalation routes of exposure to

TML **[Schepers 1964]** [1], the potency of the substance was evaluated following repeated or prolonged exposure via alternative exposure routes (i.e., oral) in animals. TML caused liver and neuronal damage in rats in an oral exposure study **[Schepers 1964]** at low doses, indicating that the potential exists for dermal exposure to result in similar effects observed in this study. Therefore, on the basis of the data for this assessment, TML is assigned the SK: SYS notation.

3.0 Direct Effects on Skin (SK: DIR)

No human or animal *in vivo* studies on corrosivity of TML 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 occupational studies or case reports and no standard skin irritation tests in animals were identified that evaluated the potential of TML to cause direct skin effects. Lack of these studies precludes adequate evaluation of the potential of TML to cause skin irritation in humans or animals. Therefore, on the basis of the data for this assessment, TML is not assigned the SK: DIR notation.

4.0 Immune-mediated Responses (SK: SEN)

No occupational exposure studies or diagnostic (human patch) patch tests or 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. Lack of these studies precludes adequate evaluation of TML as a potential skin sensitizer. Therefore, on the basis of the data for this assessment, TML is not assigned the SK: SEN notation.

5.0 Summary

No toxicokinetic data were identified that estimated the degree of absorption of TML following dermal exposure. A model predicted TML to be absorbed following skin contact. No acute toxicity studies that reported LD_{50} values for TML were identified. However, an ALD of 6,203 mg/kg [E.I. du Pont de Nemours and Company 1959, 1991] and a MLD of 4,000 were identified, indicating that TML can be absorbed by the skin but ALD and MLD identified are above the critical dermal LD_{50} value of 2000 mg/kg body weight that identifies chemical substances with the potential for acute dermal toxicity. Additionally, no epidemiological or occupational exposure studies or case reports nor repeated-dose, subchronic, or chronic studies in animals were identified that evaluated the potential of TML to cause systemic effects following dermal exposure. Based on the results of the model prediction and because virtually identical effects were produced by the oral, cutaneous, and inhalation routes of exposure to TML [Schepers 1964], the potency of the substance was evaluated following repeated or prolonged exposure via other exposure routes (i.e., oral) in animals. TML at very low doses caused liver and neuronal damage in rats in an oral exposure study **[Schepers 1964]**, indicating that the potential exists for dermal exposure to cause similar effects as observed in the oral study. No epidemiological investigations or experimental animal studies were identified that evaluated the potential for TML to

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

cause direct skin effects or skin sensitization. Therefore, on the basis of these assessments, TML is assigned a composite skin notation of **SK: SYS**.

Table 3 summarizes the skin hazard designations for TML previously issued by NIOSH and other organizations. No Globally Harmonized System (GHS) of classification and labeling of chemicals dermal classification for TML was located [European Parliament 2008]

Table 3. Summary of previous skin hazard designations for TML

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption
OSHA [2013]*	[skin]: Potential for dermal absorption
ACGIH [2001]	[skin]: Potential for dermal 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.

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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 TML

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for TML. 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 TML. The calculated SI ratio was 2.76. On the basis of these results, TML is predicted to represent a skin absorption hazard.

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

Variables Used in Calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path(k_{psc})	cm/hour	3.6713×10^{-3}
Permeation coefficient of the protein fraction of the stratum corneum (k_{pol})	cm/hour	9.2909×10^{-6}
Permeation coefficient of the watery epidermal layer (k_{aq})	cm/hour	0.1529
Molecular weight (MW)*	amu	267.3
Base-10 logarithm of its octanol–water partition coefficient (Log K_{ow})*	None	297
Calculated skin permeation coefficient (k_p)	cm/hour	
Skin dose		
Water solubility (S_w)*	mg/cm^3	0.15
Calculated skin permeation coefficient (k_p)	cm/hour	3.5941×10^{-3}
Estimated skin surface area (palms of hand)	cm^2	360
Exposure time	hour	8
Calculated skin dose	mg	1.5527
Inhalation Dose		
Occupational exposure limit (OEL)†	mg/m^3	0.075
Inhalation volume	m^3	100
Retention factor (RF)	None	0.75
Inhalation dose	mg	0.5625
Skin dose–to–inhalation dose (SI) ratio	None	2.76

*Variables identified from SRC [ND].

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

Appendix References

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