

Skin Notation (SK) Profile

Ethyl p-nitrophenyl phenylphosphorothioate (EPN)

[CAS No. 2104-64-5]

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 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 (e.g., skin permeation) by means of analytical or numerical methods.

This *Skin Notation Profile* provides the SK assignments and supportive data for EPN. 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

Foreword	iii
Abbreviations	v
Glossary	vii
Acknowledgments	viii
1.0 Introduction	1
1.1 General Substance Information	1
1.2 Purpose	1
1.3 Overview of SK Assignment	2
2.0 Systemic Toxicity from Skin Exposure (SK: SYS)	2
3.0 Direct Effects on Skin (SK: DIR)	4
4.0 Immune-mediated Responses (SK: SEN)	5
5.0 Summary	5
References	6
Appendix: Calculation of the SI Ratio for EPN	8
Overview	8
Calculation	10
Appendix References	11

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Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
ATSDR	Agency for Toxic Substances and Disease Registry
CIB	Current Intelligence Bulletin
cm ²	squared 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
g	gram(s)
g/L	gram(s)/liter
GHS	Globally Harmonized System for Classification and Labelling of Chemicals
GPMT	guinea pig maximization test
hr	hour(s)
IARC	International Agency for Research on Cancer
IPCS	International Program for Chemical Safety
(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/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

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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 in water
SYS	skin notation indicating the potential for systemic toxicity following exposure of the skin
USEPA	United States Environmental Protection Agency
μg	microgram(s)
$\mu\text{g}/\text{cm}^2$	microgram(s) per square centimeter
$\mu\text{g}/\text{cm}^2/\text{hr}$	microgram(s) per square centimeter per hour
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

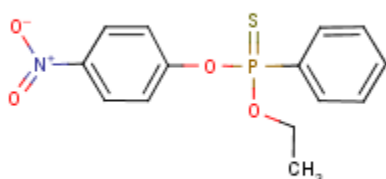
Chemical: Ethyl p-nitrophenyl phenylphosphorothioate (EPN)

CAS No: 2104-64-5

Molecular weight (MW): 323.3

Molecular formula: C₁₄H₁₄O₄NSP

Structural formula:



Synonyms: o-Ethyl-o-p-nitrophenyl phenylphosphonothioate, Ethyl p-nitrophenyl benzenethiophosphonate

Uses: EPN is an insecticide and acaricide no longer registered for use in the United States [Storm 2001].

1.2 Purpose

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

1.3 Overview of SK Assignment

EPN may potentially be capable of causing numerous adverse health effects following skin contact. A critical review of available data has resulted in the following SK assignment for EPN: **SK: SYS (FATAL)**. Table 1 provides an overview of the critical effects and data used to develop the SK assignment for EPN.

Table 1. Summary of the SK Assignment for EPN

Skin Notation	Critical Effect	Available Data
SK: SYS (FATAL)	Neurotoxicity	Sufficient animal data

2.0 Systemic Toxicity from Skin Exposure (SK: SYS)

Limited toxicokinetic data following dermal exposure to EPN were identified. Although no data were identified for humans, a series of studies conducted by Abou-Donia et al. [1983a; 1983d, 1983e] evaluated absorption of EPN in cats and hens. After a single non-occluded dermal application of 20 milligrams per kilogram of body weight (mg/kg) of uniformly phenyl-labeled [¹⁴C] EPN in 0.1 milliliter (mL) acetone to the clipped skin of cats, most of the radioactivity was excreted in the urine (29.9%), only 3.2% was recovered in the feces, and no radioactivity was detected in expired air [Abou-Donia 1983d]. When cats were administered 0.5 mg/kg [¹⁴C] EPN dermally for 10 consecutive days, 62% of the cumulative dose was recovered in the urine, 10% in the feces, and no radioactivity was detected in the expired air [Abou-Donia et al 1983e]. In hens administered 0.5 mg/kg [0.56 micro Curie per dose (μCi/dose)] of [¹⁴C] EPN dermally for 10 consecutive days, a total of 65% of the cumulative dose was excreted in the combined urinary and fetal excrement 15 days after the last dose, and no radioactivity was detected in the expired air [Abou-Donia et al. 1983a]. These toxicokinetic studies indicate that EPN is absorbed through the skin following dermal exposure of cats and hens. The potential of EPN 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 0.049 was calculated for EPN. An SI ratio of ≥ 0.1 indicates that skin absorption may significantly contribute to the overall body burden of a substance [NIOSH 2009]; therefore, EPN 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 estimated dermal lethal dose (LD_{Lo}) for humans was identified. Dermal LD₅₀ values (lethal doses in 50% of exposed animals) of 230 and 25 mg/kg have been reported for male and female rats, respectively [Gaines 1969]. In cats, Abou-Donia et al. [1983b] reported an LD₅₀ of 45 mg/kg. In rabbits, Hodge et al. [1954] reported a dermal lethal range of 30 to 50 mg/kg in males and of 90 to 150 mg/kg in females and Dupont Chemical [1980] and Dupont de Nemours [1980c] reported an LD₅₀ of 296 to 312 mg/kg for intact skin and 218 to 467 mg/kg for abraded skin in rabbit,. Because the reported acute dermal LD₅₀ values for cats, rabbits and female rats are lower than the critical dermal LD₅₀ value of 200 mg/kg body

weight that identifies chemical substances that are fatal at relatively low doses following acute dermal exposure [NIOSH 2009], EPN is considered fatal after acute dermal exposure.

No epidemiological or occupational exposure studies or chronic toxicity studies in animals were identified following dermal exposure to EPN. However, two subchronic (90-day) studies that evaluated the potential of EPN to induce neurotoxicity in animals following dermal exposure were identified [Abou-Donia et al. 1983b, c]. Cats administered 0.5 to 2.0 mg/kg-day EPN topically for 90 days exhibited significant weight loss during treatment, cats receiving 0.5 mg/kg-day exhibited mild ataxia, while cats that received 1.0 mg/kg-day exhibited severe ataxia [Abou-Donia et al. 1983b]. Abou-Donia et al. [1983c] also administered dermal doses of 0.01 to 10.0 mg/kg of EPN (85%) on the back of the neck of hens for 90 days. Spinal cord lesions were observed at 0.5 mg/kg-day and above in cats [Abou-Donia et al. 1983b], and similar neurotoxic effects at doses of 2.5 mg/kg and above were observed in hens [Abou-Donia et al. 1983c]. Significant weight loss was observed at 1.0 to 10.0 mg/kg EPN at the onset of ataxia, with the loss increasing after development of paralysis [Abou-Donia et al. 1983c]. All hens treated with 0.01 to 10 mg/kg EPN exhibited signs of delayed neurotoxicity, with the onset and severity of neurologic dysfunction being dose-dependent [Abou-Donia et al. 1983c]. Brain cholinesterase activity at 2.5 mg/kg and above and plasma butylcholinesterase activity at 0.01 mg/kg and above were significantly inhibited compared to controls when these activities were measured 30 days after the dermal application [Abou-Donia et al. 1983c]. Hens' exposure to 0.01 to 10 mg/kg showed histological changes in the spinal cord, such as degeneration of axons and myelin, which were more severe and frequent in hens that survived longer [Abou-Donia et al. 1983c]. However, it is important to note that although the investigators noted neurotoxicity in animals dermally exposed to EPN, Abou-Donia et al. [1983c] reported different concentrations in the abstract than in the methods. Francis et al [1985] reported ataxia in one egg-laying hen after daily dermal dosing of as little as 1.3 mg/kg for up to 90 days. Higher doses caused similar effects that progressed to death [Francis et al. 1985]. The reported dermal subchronic LOAEL of 0.01 mg/kg-day based on histological changes in the spinal cord of hens [Abou-Donia et al. 1983c], of which similar effects were seen in subchronic studies in cats [Abou-Donia et al. 1983b], is lower than the critical dermal subchronic NOAEL of 1,000 mg/kg-day that identifies chemical substances with the potential for subchronic dermal toxicity [NIOSH 2009]. Based on these findings, EPN is considered systemically toxic following dermal exposure with dose-dependent effects on the nervous system that vary in severity, including lethality.

No additional specialty studies evaluating biological systemic/function (including reproductive/developmental toxicity or immunotoxicity) were identified following dermal exposure. No studies were identified that evaluated the potential of EPN to be a carcinogen in humans or animals following exposure by the dermal route. Table 2 summarizes carcinogenic designations of multiple governmental and nongovernmental organizations for EPN.

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

Organization	Carcinogenic designation
NIOSH [2005]	No designation
NTP [2011]	No designation
USEPA [2015]	No designation
European Parliament [2008]	No GHS designation
IARC [2012]	No designation
EC [2013]*	No designation
ACGIH [2001]	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.

Although the mathematical model did not predict EPN to be absorbed through the skin following dermal exposure, toxicokinetic data in cats [**Abou-Donia et al. 1983a; 1983d, 1983e**]¹, acute toxicity studies in rats [**Gaines 1969**], rabbits [**Hodge et al 1954**], and cats [**Abou-Donia et al. 1983b**] and sub-chronic toxicity studies in hens and cats [**Abou-Donia et al. 1983b, 1983c**] indicate EPN is absorbed through skin, is systemically available and has the potential to cause systemic effects, including fatality, following dermal exposure. Therefore, on the basis of the data for this assessment, EPN is assigned the SK: SYS (FATAL) notation.

3.0 Direct Effects on Skin (SK: DIR)

No human or animal *in vivo* studies that evaluated the corrosivity of EPN 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 case reports or clinical studies evaluating the potential of EPN to cause skin irritation were identified. E.I. Du Pont de Nemours [1980a] reported mild irritation when rabbits were exposed to 500 mg/kg of a mixture of EPN and 0,0-dimethyl 0-(4-nitrophenyl) phosphorothioate on clipped intact and abraded skin using the Draize procedure. Similar results were seen when E.I. Du Pont de Nemours [1980b] applied 0.5 ml a mixture of EPN and penyl-0-ethyl, 0-(4-nitrophenyl) ester on clipped intact and abraded skin using the Draize procedure. Exposure to these mixtures containing EPN caused fatalities in some of the rabbits [E.I. Du Pont de Nemours 1980a, b].

Although the E.I. Dupont de Nemours [1980a, b] studies indicate that EPN is a mild skin irritant, the animals were exposed to mixtures of EPN, and there is insufficient data that EPN alone can cause skin irritation. Therefore, this assessment does not assign a SK: DIR notation for EPN.

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

4.0 Immune-mediated Responses (SK: SEN)

No studies were identified that evaluated skin sensitization following dermal exposure to EPN. No reports of sensitization in humans, or predictive tests (for example, guinea pig maximization tests, Buehler tests, murine local lymph node assays, mouse ear swelling tests) or other tests that evaluated the potential of EPN to cause skin sensitization in animals were identified. Lack of data precludes adequate evaluation of the sensitization potential of EPN. Therefore, on the basis of the data for this assessment, EPN is not assigned the SK: SEN notation.

5.0 Summary

Although the mathematical model did not predict EPN to be absorbed through the skin following dermal exposure, toxicokinetic data in cats [Abou-Donia et al. 1983a; 1983d, 1983e], acute toxicity studies in rats [Gaines 1969], rabbits [Hodge et al 1954], and cats [Abou-Donia et al. 1983b], and sub-chronic studies identified in hens and cats [Abou-Donia et al. 1983b, 1983c] indicate EPN is absorbed through skin, is systemically available and has the potential to cause systemic effects, including fatality following dermal exposure. No *in vivo* or *in vitro* studies in humans or animals that evaluated the potential of EPN to cause direct skin effects or skin sensitization were identified. Therefore, on the basis of these assessments, EPN is assigned a composite skin notation of **SK: SYS (FATAL)**.

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

Organization	Skin hazard designation
NIOSH [2005]	[skin]: potential for dermal absorption
OSHA [2015]*	[skin]: potential for dermal absorption
ACGIH [2003]	[skin]: Based on low doses applied to rabbit skin that produced lethality
EC [2013]*	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.

References

- Abou-Donia MB, Abdel-Kader HM, Abou-Donia SA [1983a]. Tissue distribution, elimination, and metabolism of *o*-ethyl *o*-nitrophenyl phenylphosphonothionate in hens following daily dermal doses. *J Amer Coll Toxicol* 2(6): 391-404.
- Abou-Donia MB, Graham DG, Kinnes CG. [1983b]. Sensitivity of the Cat to Delayed Neurotoxicity Induced by *o*-Ethyl *o*-4-Nitrophenyl Phenylphosphonothioate. *Toxicol Appl Pharmacol* 68: 54-65.
- Abou-Donia MB, Graham DG, Makkawy H, Abdo KM. [1983c]. Effect of Subchronic Dermal Application of *o*-Ethyl *o*-4-Nitrophenyl Phenylphosphonothioate on Producing Neurotoxicity in Hens. *Neurotoxicology* 4(2): 247-260.
- Abou-Donia MB, Kinnes CG, Abdo KM, and Bjornsson D. [1983d]. Physiological Disposition and Metabolism of *o*-Ethyl-*o*-4-Nitrophenyl Phenylphosphonothioate in Male Cats Following a Single Dermal Administration. *Drug Metabolism and Disposition* 11(1): 31-36.
- Abou-Donia MB, Sivarajah K, Abou-Donia A. [1983e]. Disposition, elimination and metabolism of *o*-ethyl *o*-4-nitrophenyl phenylphosphonothioate after subchronic dermal application in male cats. *Toxicology* 26: 93-111
- ACGIH (American Conference of Governmental Industrial Hygienists) [2003]. *EPN Documentation of Threshold Limit Values and Biological Exposure Indices*. 7th Ed. Cincinnati, OH.
- Dupont Chemical [1980]. Initial submission: Acute dermal toxicity of phosphonothioic acid, phenyl-,*o*-ethyl *o*-(nitrophenyl)ester with *o*,*o*-dimethyl *o*-(4-nitrophenyl)*with cover letter dated 082092. OTS No. 0570800.
- EC (European Commission) [2011]. *O-ethyl O-4-nitrophenyl phenylphosphonothioate*. In: *EINICS (European Inventory of Existing Commercial Chemical Substances)*, <http://ecb.jrc.ec.europa.eu/esis/index.php?GENRE=CASNO&ENTREE=2104-64-5>. [Accessed](#): 08-14-13.
- E.I. Dupont de Nemours [1980a]. Initial submission: Skin irritation test with EPN4-E in rabbits for EPA pesticide registration with cover letter dated 061592 and attachments. OTS No. 0540536.
- E.I. Dupont de Nemours [1980b]. Initial submission: Skin irritation test with EPN-MP3-3 in rabbits for EPA pesticide registration with cover letter dated 061592 and attachments. OTS No. 0540516.
- E.I. Dupont de Nemours [1980c]. Initial submission: An acute skin absorption LD50 test with EPN in rabbits with cover sheets and letter dated 082092. OTS No. 0543804.

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://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:353:0001:1355:EN:PDF>. Accessed: 01-28-15.

Francis BM, Metcalf RL, Hansen LG. [1985]. Toxicity of Organophosphorus Esters to Laying Hens After Oral and Dermal Administration. *J. Environ Sci. Health B20(1)*, 73-95.

Gaines TB. [1969]. Acute Toxicity of Pesticides. *Toxicology and Applied Pharmacology 14*: 513-534.

Hodge HC, Maynard EA, Hurwitz L, DiStefano V, Downs WI, Jones CK, Blanchet HJ. [1954]. Studies of the Toxicity and of the enzyme kinetics of ethyl p-nitrophenyl thionobenzene phosphate (EPN). *J Pharmacol Exp Ther 112*: 29-39.

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: 01-28-15.

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/npgd0211.html>. Accessed: 01-28-15.

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: 01-28-15.

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: 01-28-15.

OSHA [ND]. EPN. In: OSHA Occupational chemical database, <https://www.osha.gov/chemicaldata/chemResult.html?recNo=309>. [Accessed](#): 01-28-15.

Storm JE [2001]. EPN. In: Bingham E, Cohrssen B, Powell CH (Eds.), *Patty's toxicology and industrial hygiene 5th ed.*, Vol. 7. New York: John Wiley and Sons pp. 836-842.

USEPA [2015]. Intergrated Risk Information System: ethyl p-nitrophenyl phenylphosphorothioate (EPN). In: Intergrated Risk Information System, <http://www.epa.gov/iris/>. Accessed: 01-28-15.

Appendix: Calculation of the SI Ratio for EPN

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for EPN. 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 centimeters per hour (cm/hr), 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

$$\begin{aligned}\log k_{psc} &= -1.326 + 0.6097 \times \log K_{ow} - 0.1786 \times MW^{0.5} \\ k_{pol} &= 0.0001519 \times MW^{-0.5} \\ k_{aq} &= 2.5 \times MW^{-0.5}\end{aligned}$$

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

$$\begin{aligned}\text{Skin dose} &= k_p \times S_w \times \text{Exposed skin surface area} \times \text{Exposure time} \\ &= k_p(\text{cm/hr}) \times S_w(\text{mg/cm}^3) \times 360 \text{ cm}^2 \times 8 \text{ hr}\end{aligned}$$

The inhalation dose (in mg) is derived on the basis of the occupational exposure limit (OEL) of the substance—if the OEL is developed to prevent the occurrence of systemic effects rather than sensory/irritant effects or direct effects on the respiratory tract. Assume a continuous exposure of 8 hours, an inhalation volume of 10 cubic meters (m^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

$$\begin{aligned}\text{Inhalation dose} &= \text{OEL} \times \text{Inhalation volume} \times \text{RF} \\ &= \text{OEL}(\text{mg/m}^3) \times 10 \text{ m}^3 \times 0.75\end{aligned}$$

The final step is to compare the calculated skin and inhalation doses and to present the result as a ratio of skin dose to inhalation dose (the SI ratio). This ratio quantitatively indicates (1) the significance of dermal absorption as a route of occupational exposure to the substance and (2) the contribution of dermal uptake to systemic toxicity. If a substance has an SI ratio greater than or equal to 0.1, it is considered a skin absorption hazard.

Calculation

Table A1 summarizes the data applied in the previously described equations to determine the SI ratio for EPN. The calculated SI ratio was 0.049. On the basis of these results, EPN is not predicted to represent a skin absorption hazard.

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

Variables Used in Calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path (k_{psc})	cm/hr	0.0238
Permeation coefficient of the protein fraction of the stratum corneum (k_{poi})	cm/hr	8.445×10^{-6}
Permeation coefficient of the watery epidermal layer (k_{aq})	cm/hr	0.139
Molecular weight (MW) [*]	amu	323.31
Base-10 logarithm of its octanol–water partition coefficient ($\text{Log } K_{ow}$) [*]	None	4.78
Calculated skin permeation coefficient (k_p)	cm/hr	0.0203
Skin dose		
Water solubility (S_w) [*]	mg/cm ³	0.0031
Calculated skin permeation coefficient (k_p)	cm/hr	0.0203
Estimated skin surface area (palms of hand)	cm ²	360
Exposure time	hr	8
Calculated skin dose	mg	0.1822
Inhalation Dose		
Occupational exposure limit (OEL) [†]	mg/m ³	0.5
Inhalation volume	m ³	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	3.75
Skin dose–to–inhalation dose (SI) ratio	None	0.0486

^{*}Variables identified from SRC [ND].

[†]The OEL used in calculation of the SI ratio for EPN 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: 01-28-15.

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: 01-28-15.

SRC [2009]. Interactive PhysProp database demo <http://esc.syrres.com/fatepointer/webprop.asp?CAS=2104645>. Accessed: 01-28-15.

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