NIOSH Skin Notation Profiles

Methyl Parathion

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

Methyl Parathion
[CAS No. 298-00-0]

Naomi L. Hudson and G. Scott Dotson

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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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 methyl parathion. 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
AChE	acetylcholinesterase
Amu	atomic mass unit
ATSDR	Agency for Toxic Substances and Disease Registry
ChE	cholinesterase
CIB	Current Intelligence Bulletin
cm^2	square centimeter(s)
cm/hr	centimeter(s) per hour
cm/s	centimeter(s) per second
DEREK	Deductive Estimation of Risk from Existing Knowledge
DIR	skin notation indicating the potential for direct effects to the skin following contact with a chemical
EC	European Commission
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 substances octanol–water partition
M	molarity
m^3	cubic meter(s)
mg	milligram(s)
mg/kg	milligram(s) per kilogram body weight
mg/kg-day	milligram(s) per kilogram of body weight per day
mg/m^3	milligram(s) per cubic meter
mL	milliliter(s)
mL/kg	milliliter(s) per kilogram body weight

MW	molecular weight
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
OEL	occupational exposure limit
OSHA	Occupational Safety and Health Administration
ppm	parts per million
REL	recommended exposure limit
RF	retention factor
SEN	skin notation indicating the potential for immune-mediated reactions following exposure of the skin
SI	ratio ratio of skin dose to inhalation dose
SK	skin notation
S_w	solubility in water
SYS	skin notation indicating the potential for systemic toxicity following exposure of the skin
US EPA	United States Environmental Protection Agency
µg	microgram(s)
µL	microliter(s)
µmol	micromole(s)

Glossary

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

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

Cancer—Any one of a group of diseases that 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:

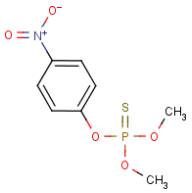
Chemical: Methyl Parathion

CAS No: 298-00-0

Molecular weight (*MW*)**:** 263.2

Molecular formula: $(CH_3O)_2P(S)OC_6H_4NO_2$

Structural formula:



Synonyms: Azophos®, O,O-Dimethyl-O-p-nitrophenylphosphorothioate, Parathion methyl

Uses: Methyl parathion is an organophosphate compound used as an insecticide, primarily on farm crops such as cotton [ATSDR 2001].

1.2 Purpose

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

1.3 Overview of SK Assignment

Methyl parathion 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 methyl parathion: **SK: SYS**

Table 1. Summary of the SK assignment for methyl parathion

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

(FATAL). Table 1 provides an overview of the critical effects and data used to develop the SK assignment for methyl parathion.

2 Systemic Toxicity from Skin Exposure (SK: SYS)

There are limited toxicokinetic data for estimating the degree of dermal absorption of methyl parathion in humans. Muttray et al. [2010] investigated acute effects of methyl parathion on the human central nervous system in a study of 23 male winegrowers. The winegrowers sprayed between 150 and 1420 grams (g) (median, 450 g) of methyl parathion for 50 minutes, with the volume and concentration of methyl parathion depending on the amount of active ingredient needed per hectare. Although the winegrowers wore protective clothing, the authors reported that most exposures were to the face and hands [Muttray et al. 2010]. Estimated dermal exposure ranged from 2 micrograms (µg) to 12 milligrams (mg), depending on the amount of personal protective equipment worn. A maximum of 22 µg was measured via inhalation in this study, indicating that dermal exposure to methyl parathion exceeded inhalation exposure [Muttray et al. 2010]. Cholinesterase activity did not decrease in serum or in erythrocytes [Muttray et al. 2010]. Several *in vivo* studies assessed dermal kinetics of methyl parathion in animals. Abu-Qare et al. [2000a] applied 10 milligrams per kilogram body weight (mg/kg) of radiolabeled methyl parathion, in 0.1 milliliters (mL) of acetone, to 1 square centimeter (cm^2) of clipped skin on the unoccluded necks of pregnant rats at 14 to 18 days of gestation. About 50% of the dose remained at the site of application after 1 hour (hr) of application and 3% after 96 hours. By the end of the 96th hour, 91% of the applied dose was excreted in the urine, with only 3% of the radioactivity recovered in the feces, indicating that the test material was well absorbed through the skin [Abu-Qare et al. 2000a]. In another study also using pregnant rats, Abu-Qare and Abou-Donia [2000b] reported that a single dermal dose at 14 to 18 days of gestation resulted in 30% of the total radiolabel dose being excreted in the urine within 4 hours; 50% of the dose was recovered in the urine by 24 hours and 90% by 96 hours. Kramer et al. [2002] reported the dermal absorption coefficient of approximately 0.41 per hour (hr^{-1}) following dermal administration of 6.25 to 25 mg/kg methyl parathion dissolved in propylene glycol. Concentrations of the test material peaked within 12 to 26 hours, followed by a dose-dependent decline [Kramer et al. 2002].

The observations in the animal studies are supported by *in vitro* and predictive methods. Sartorelli et al. [1997] evaluated skin penetration of methyl parathion in acetone and in the form of a commercial formulation using human skin *in vitro*. The authors reported the percentages of the applied dose absorbed after 24 and 48 hours to be 5.20% and 8.99%, respectively, for the test material dissolved in acetone, versus 1.35% and 3.58% for the commercial formulation. Van der Merwe and Riviere [2006] reported a permeability rate from 4×10^{-5} to 4.92×10^{-3} cm/hr, depending on the solvent used. Maibach et al. [1971] reported regional variation of percutaneous absorption in the body, noting that penetration in the abdomen and dorsum of the hand were twice that on the forearm. The potential of methyl parathion 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 0.235 was calculated for methyl parathion. An SI ratio of ≥0.1 indicates that skin absorption may significantly contribute to the overall body burden of a substance [NIOSH 2009]; therefore, methyl parathion 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}) of methyl parathion was identified, but dermal LD_{50} values (lethal doses in 50% of exposed animals) were identified for animals. The LD_{50} value for methyl parathion dissolved in xylene and applied to the backs of male and female rats was reported to be 67 mg/kg [Gaines 1960]. In another study, the LD_{50} value for methyl parathion dissolved in acetone and applied to the hind foot of mice was 1200 mg/kg [Skinner and Kilgore 1982a]. The reported acute dermal LD_{50} value for methyl parathion in rats is lower than the critical dermal LD_{50} value of 200 mg/kg that identifies chemical substances that are potentially fatal at relatively low doses following dermal exposure [NIOSH 2009]. Methyl parathion, therefore, is considered potentially fatal following acute dermal exposure.

No epidemiological studies were identified that provided adequate data to evaluate the dose-response associated with methyl parathion–induced effects following dermal exposure. Several occupational exposure studies [Nemec et al. 1968; Ware et al. 1975; Wolff et al. 1992] reported cholinesterase (ChE) inhibition and associated symptoms, the known toxic mode of action of organophosphate pesticides including methyl parathion. However, exposure durations were short or dermal doses were not quantified.

No chronic dermal toxicity studies in animals were identified. In a repeated-dose study, Zhu et al. [2001] topically applied 0, 0.1, or 1 mg/kg per day (mg/kg-day) of methyl parathion to rats for 28 days. Methyl parathion treatment at 0.1 mg/kg was not associated with a reduction in ChE activity; however, the 1 mg/kg-day dose resulted in 50% inhibition of blood ChE activity within the first 7 days and caused impairment of both motor function and memory, with the inhibition remaining sustained over the course of treatment. Because a specific cut-off of 20% for inhibition of acetylcholinesterase (AChE) is used routinely to differentiate between adverse and nonadverse effects [Solecki et al. 2005], a no-observed-adverse-effect level (NOAEL) of 0.1 mg/kg-day can be derived from this study, with a lowest-observed-adverse-effect level (LOAEL) of 1 mg/kg-day, based on inhibition of ChE activity and impairment of motor function and memory. Although no chronic dermal toxicity studies were identified, Ma et al. [2003] investigated the effects of methyl parathion on the cholinergic neurotransmitter system in the brain of rats in a subchronic dermal exposure study. In this study, female rats were exposed to 0, 0.1, or 1.0 mg/kg-day methyl parathion to 1 cm^2 of shaved skin on the back of the neck for 95 days. AChE activity was examined histochemically in rat brain regions, and 0.1 mg/kg-day methyl parathion produced statistically significant inhibition of AChE (85% of control) in caudate-putamen and thalamic nuclei, whereas 1.0 mg/kg-day caused statistically significant inhibition (36% to 74% of control) in most brain regions, including the caudate-putamen, thalamic nuclei, hippocampal formation, and brain stem [Ma et al. 2003]. The lowest dose tested in this study (0.1 mg/kg-day) can be regarded as the LOAEL, without a NOAEL being identified. Because the rat NOAELs and LOAELs observed in repeated-dose and subchronic studies, respectively, are much lower than the critical dermal NOAEL value of 1000 mg/kg-day that identifies chemical substances with the potential for repeated-dose dermal toxicity [NIOSH 2009], methyl parathion is considered systemically available and able to cause systemic effects (ChE inhibition) and central nervous system effects following dermal exposure.

No specialty studies evaluating biological system/function–specific effects (including reproductive and developmental effects and immunotoxicity) following dermal exposure to methyl parathion were identified. However, Abu-Qare et al. [2000a] detected radioactivity in the fetal tissue following application of 10 mg/kg of radiolabeled methyl parathion to the clipped skin of pregnant rats at 14 to 18 days of gestation. Although the study was not designed to evaluate developmental effects following dermal exposure to methyl

parathion, the results indicate the potential of the test material to cross the placenta and be potentially available to the fetus following dermal exposure.

There were limited data for evaluating the carcinogenic potential of parathion following dermal exposure. In one study, parathion (ethyl or methyl) was associated with cutaneous melanoma in a cohort of 24,704 pesticide applicators who completed the Agricultural Health Study (11 of 709 study participants exposed to ≥56 exposure days with an odds ratio of 2.4 and confidence interval: 1.3-4.4, p=0.003) [Dennis et al. 2010]. The authors also noted that increased exposure to parathion coincided with increased risk of cutaneous melanoma (p = 0.003) [Dennis et al. 2010]. Table 2 summarizes carcinogenic designations for methyl parathion by multiple governmental and nongovernmental organizations.

The available toxicokinetic data from studies of methyl parathion absorption in humans [Muttray et al. 2010] and rats [Abu-Qare et al. 2000a, 2000b; Kramer et al. 2002] and from *in vitro* studies [Sartorelli et al. 1997; Van der Merwe and Riviere 2006] indicate that methyl parathion can be absorbed through the skin. Acute toxicity studies in mice and rats **[Gaines 1960]**[*], occupational exposure studies **[Nemec et al. 1968; Ware et al. 1975; Wolff et al. 1992]**, and repeated-dose and subchronic toxicity studies in rats **[Zhu et al. 2001; Ma et al. 2003]** provide sufficient evidence that methyl parathion has the potential to cause systemic effects, including ChE inhibition, and central nervous system effects following dermal exposure. Therefore, on the basis of the data for this assessment, methyl parathion is assigned the SK: SYS (FATAL) notation.

3 Direct Effects on Skin (SK: DIR)

No human or animal *in vivo* studies for corrosivity of methyl parathion, *in vitro* tests for corrosivity using human skin models, or *in vitro* tests of skin integrity using cadaver skin were identified. No standard skin irritation tests in animals were identified. The reports on acute toxicity [Gaines 1960] and repeated-dose studies [Zhu et al. 2001; Ma et al. 2003] did not note whether dermal effects were observed at the site of application. Lack of data precludes adequate evaluation of the potential of methyl parathion to be a skin irritant. Therefore, on the basis of the data for this assessment, methyl parathion is not assigned the SK: DIR (IRR) notation.

4 Immune-mediated Responses (SK: SEN)

Occupational exposure reports or studies investigating the skin sensitization potential of methyl parathion in humans were not identified. Reports from diagnostic (human patch) tests were limited to a single study that reported allergic dermatitis in reaction to a skin patch test in 1 of 294 volunteers (of which 107, 36, and 151 were agricultural, ex-agricultural, and nonagricultural workers, respectively) [Lisi et al. 1987]. Sharma and Kaur [1990] observed no skin sensitization when 30 farmers with contact dermatitis and 20 control subjects were patch tested with a series of locally used pesticides, including methyl parathion. No predictive tests in animals (such as guinea pig maximization tests, murine local lymph node assays, or mouse ear swelling tests) or any other studies that evaluated the potential of the substance to cause skin sensitization were identified.

The information available indicates that methyl parathion is not likely to be a skin sensitizer. Therefore, on the basis of the data for this assessment, methyl parathion is not assigned the SK: SEN notation.

5 Summary

The available toxicokinetic data from studies of methyl parathion absorption in humans [Muttray et al. 2010] and rats [Abu-Qare et al. 2000a, 2000b; Kramer et al. 2002] and from

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

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

Organization	Carcinogenic designation
NIOSH [2005]	No designation
NTP [2014]	No designation
US EPA [2012]	No designation
European Parliament [2008]	No GHS designation
IARC [2014]	Group 3: Not classifiable as to carcinogenicity to humans
ACGIH [2001]	A4: Not classifiable as a human carcinogen

ACGIH = American Conference of Governmental Industrial Hygienists; GHS = Globally Harmonized System for Classification and Labelling; IARC = International Agency for Research on Cancer; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; US EPA = United States Environmental Protection Agency.
*The listed cancer designations were based on data from nondermal (such as oral or inhalation) exposure rather than dermal exposure.

in vitro studies [Sartorelli et al. 1997; Van der Merwe and Riviere 2006] indicate that methyl parathion can be absorbed through the skin. Acute toxicity studies in rats **[Gaines 1960]**, occupational exposure studies **[Nemec et al. 1968; Ware et al. 1975; Wolff et al. 1992]**, and repeated-dose and subchronic toxicity studies in rats **[Zhu et al. 2001; Ma et al. 2003]** indicate the potential to cause systemic effects, including ChE inhibition, central nervous system effects, and lethality. No standard skin irritation tests were identified to evaluate the potential of methyl parathion to be a skin irritant. Human diagnostic patch tests indicate that methyl parathion is not likely to be a skin sensitizer. Therefore, on the basis of these assessments, methyl parathion is assigned a composite skin notation of **SK: SYS (FATAL)**.

Table 3 summarizes the skin hazard designations for methyl parathion previously issued by NIOSH and other organizations. The equivalent dermal designation for methyl parathion, according to the Globally Harmonized System (GHS) for the Classification and Labelling of Chemicals, is Acute Toxicity Category 3 (Hazard statement: Toxic in contact with the skin) [European Parliament 2008].

References

Note: Asterisks (*) denote sources cited in text; daggers (†) denote additional resources.

*Abu-Qare AW, Abdel-Rahman AA, Kishk AM, Abou-Donia MB [2000a]. Placental transfer and pharmacokinetics of a single dermal dose of [14C] methyl parathion in rats. Toxicol Sci *53*:5–12.

*Abu-Qare AW, Abou-Donia MB [2000b]. Urinary excretion of metabolites following a single dermal dose of [^{14}C]methyl parathion in pregnant rats. Toxicology *150*:119–127.

*ACGIH [2001]. Methyl parathion. In: Documentation of threshold limit values and biological exposure indices, 7th ed., vol. 2. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

*ATSDR [2001]. Methyl parathion. Atlanta: U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, http://www.atsdr.cdc.gov/tfacts48.pdf.

*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, labelling 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/LexUriServdo?uri=OJ:L:2008:353:0001:1355:EN:PDF.

*Gaines TB [1960]. The acute toxicity of pesticides to rats. Toxicol Appl Pharmacol *2*:88–99.

*Gaines TB [1969]. Acute toxicity of pesticides. Toxicol Appl Pharmacol *4*:515–534.

†Galal EE, Latif MA, Kandil A, et al. [1975]. The percutaneous cardiac toxicokinesis of anticholinesterase insecticides. J Drug Res *7*:29–43.

Table 3. Summary of previous skin hazard designations for methyl parathion

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption; prevent skin contact
OSHA [2014]*	No designation
ACGIH [2001]	[skin]: Based on human experience as well as the systemic toxicity and dermal LD_{50} values reported among rats administered methyl parathion via topical application

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

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

*Kramer RE, Wellman SE, Rockhold RW, Baker RC [2002]. Pharmacokinetics of methyl parathion: a comparison following single intravenous, oral or dermal administration. J Biomed Sci *9*:311–320.

*Lisi P, Caraffini S, Assalve D [1987]. Irritation and sensitization potential of pesticides. Contact Dermatitis *17*:212–218.

*Ma T, Kramer RE, Baker RC, Fan LW, Ho IK [2003]. Effects of chronic dermal exposure to nonlethal doses of methyl parathion on brain regional acetylcholinesterase and muscarinic cholinergic receptors in female rats. J Neurosci Res *71*:138–145.

*Maibach HI, Feldmann RJ, Milby TH, Serat WF [1971]. Regional variation in percutaneous penetration in man. Arch Environ Health *23*:208–211.

*Miller MA, Kasting GM [2010]. Toward a better understanding of pesticide dermal absorption: Diffusion model analysis of parathion absorption in vitro and in vivo. J Toxicol Environ Health A *73*:284–300.

†Namba T, Nolte CT, Jackrel J, Grob D [1971]. Poisoning due to organophosphate insecticides. Am J Med *50*:475–492.

*Muttray A, BŠcker G, Jung D, Hill G, Letzel S [2006]. External and internal exposure of winegrowers spraying methyl parathion. Toxicol Lett *162*:219–224.

*Nemec SJ, Adkisson PL, Dorough HW [1968]. Methyl parathion adsorbed on the skin and blood cholinesterase levels of persons checking cotton treated with ultra-low-volume sprays. J Econ Entomol *61*:1740–1742.

*NIOSH [2005]. Methyl parathion. In: 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.

*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.

*NTP [2014]. Report on carcinogens, 13th ed. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program, http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html.

*OSHA [ND]. Methyl parathion. In: OSHA occupational chemical database, http://www.osha.gov/chemicaldata/chemResult.html?recNo=341.

*Sartorelli P, Aprea C, Bussani R, Novelli MT, Orsi D, Sciarra G [1997]. In vitro percutaneous penetration of methyl-parathion from a commercial formulation through the human skin. Occup Environ Med *54*:524–525.

*Sharma VK, Kaur S [1990]. Contact sensitization by pesticides in farmers. Contact Dermatitis *23*:77–80.

*Skinner CS, Kilgore WW [1982a]. Acute dermal toxicities of various organophosphate insecticides in mice. J Toxicol Environ Health *9*:491–497.

*Skinner CS, Kilgore WW [1982b]. Application of a dermal self-exposure model to worker reentry. J Toxicol Environ Health *9*:461–481.

*Solecki R, Davies L, Dellarco V, Dewhurst I, van Raaij M, Tritscher A [2005]. Guidance on setting of acute reference dose (RfD) for pesticides. Food Chem Toxicol *43*:1569–1593.

*Storm JE [2001]. Organophosphorus compounds. In: Bingham E, Cohrssen B, Powell CH, eds. Patty's toxicology, 5th ed., vol. 7. New York: John Wiley & Sons.

*US EPA [2012]. Methyl parathion. In: Integrated risk information system, http://www.epa.gov/ncea/iris/subst/0174.htm.

*van der Merwe D, Riviere JE [2006]. Cluster analysis of the dermal permeability and stratum corneum/solvent partitioning of ten chemicals in twenty-four chemical mixtures in porcine skin. Skin Pharmacol Physiol *19*:198–206.

†Ware GW, Morgan DP, Estesen BJ, et al. [1973]. Establishment of reentry intervals for organophosphate-treated cotton fields based on human data. I. Ethyl- and methyl parathion. Arch Environ Contam Toxicol *1*:48–59.

†Ware GW, Morgan DP, Estesen BJ, et al. [1974]. Establishment of reentry intervals for organophosphate-treated cotton fields based on human data. II. Asodrin, ethyl and methyl parathion. Arch Environ Contam Toxicol *2*:117–129.

*Ware GW, Morgan DP, Estesen BJ, et al. [1975]. Establishment of reentry intervals for organophosphate-treated cotton fields based on human data. III. 12 to 17 hours post-treatment to monocrotophos, ethyl- and methyl parathion. Arch Environ Contam Toxicol *3*:289–306.

*Wolff MS, McConnell R, Cedillo L, Rivera M [1992]. Dermal levels of methyl-parathion, organochlorine pesticides, and acetylcholinesterase among formulators. Bull Environ Contam Toxicol *48*:671–678.

*Zhu H, Rockhold RW, Baker RC, Kramer RE, Ho IK [2001]. Effects of single or repeated dermal exposure to methyl parathion on behavior and blood cholinesterase activity in rats. J Biomed Sci *8*:467–474.

Appendix: Calculation of the SI Ratio for Methyl Parathion

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for methyl parathion. Although the SI ratio is considered in the determination of a substances 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)
2. for the substance of interest,
3. estimating substance uptake by the skin and respiratory absorption routes, and
4. 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 methyl parathion. The calculated SI ratio was 0.235. On the basis of these results, methyl parathion is predicted to represent a skin absorption hazard.

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/.

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.

SRC [2009]. Interactive PhysProp database demo. North Syracuse, NY: SRC, Inc., http://www.srcinc.com/what-we-do/databaseforms.aspx?id=386.

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

Variables used in calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path *(k_{psc})*	cm/hr	0.0033
Permeation coefficient of the protein fraction of the stratum corneum *(k_{pol})*	cm/hr	9.363×10^{-6}
Permeation coefficient of the watery epidermal layer *(k_{aq})*	cm/hr	0.1541
Molecular weight *(MW)*[*]	amu	263.21
Base-10 logarithm of its octanol–water partition coefficient *(Log K_{ow})*[*]	None	2.86
Calculated skin permeation coefficient *(k_p)*	cm/hr	0.0033
Skin dose		
Water solubility *(S_w)*[*]	mg/cm^3	0.0377
Calculated skin permeation coefficient *(k_p)*	cm/hr	0.0033
Estimated skin surface area (palms of hands)	cm^2	360
Exposure time	hr	8
Calculated skin dose	mg	0.3531
Inhalation dose		
Occupational exposure limit (OEL)[†]	mg/m^3	0.2
Inhalation volume	m^3	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	1.5
Skin dose–to–inhalation dose (SI) ratio	**None**	**0.2354**

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

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