NIOSH Skin Notation Profiles

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

This page intentionally left blank.

NIOSH Skin Notation (SK) Profile

Parathion
[CAS No. 56-38-2]

Naomi L. Hudson and G. Scott Dotson

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

Disclaimer

Mention of any company or product does not constitute endorsement by the National Institute for Occupational Safety and Health (NIOSH). In addition, citations to websites external to NIOSH do not constitute NIOSH endorsement of the sponsoring organizations or their programs or products. Furthermore, NIOSH is not responsible for the content of these websites.

Ordering Information

To receive this document or information about other occupational safety and health topics, contact NIOSH:

Telephone: 1-800-CDC-INFO (1-800-232-4636)
TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov

Or visit the NIOSH website: **www.cdc.gov/niosh**

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

Suggested Citation

NIOSH [2015]. NIOSH skin notation profile: Parathion. By Hudson NL, Dotson GS. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2015-232.

DHHS (NIOSH) Publication No. 2015-232

September 2015

SAFER • HEALTHIER • PEOPLE™

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 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.

John Howard, M.D.
Director, National Institute for
Occupational Safety and Health
Centers for Disease Control and Prevention

This page intentionally left blank.

Contents

Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
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
GHS	Globally Harmonized System for Classification and Labelling of Chemicals
GPMT	guinea pig maximization test
IARC	International Agency for Research on Cancer
(IRR)	subnotation of SK: DIR indicating the potential for a chemical to be a skin irritant following exposure to the skin
k_{aq}	coefficient in the watery epidermal layer
k_p	skin permeation coefficient
k_{pol}	coefficient in the protein fraction of the stratum corneum
k_{psc}	permeation coefficient in the lipid fraction of the stratum corneum
LD_{50}	dose resulting in 50% mortality in the exposed population
LD_{Lo}	dermal lethal dose
LLNA	local lymph node assay
LOAEL	lowest-observed-adverse-effect level
log K_{OW}	base-10 logarithm of a substance's octanol–water partition
m^3	cubic meter(s)
mg	milligram(s)
mg/cm^2/hr	milligram(s) per square centimeter per hour
mg/kg	milligram(s) per kilogram body weight
mg/m^3	milligram(s) per cubic meter
mL	milliliter(s)
mL/kg	milliliter(s) per kilogram body weight
MW	molecular weight
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
OEL	occupational exposure limit
OSHA	Occupational Safety and Health Administration

REL	recommended exposure limit
RF	retention factor
SEN	skin notation indicating the potential for immune-mediated reactions following exposure of the skin
SI	ratio ratio of skin dose to inhalation dose
SK	skin notation
S_w	solubility in water
SYS	skin notation indicating the potential for systemic toxicity following exposure of the skin
US EPA	United States Environmental Protection Agency
µg	micrograms
µg/cm²	micrograms per square centimeter
µg/cm²/hr	micrograms per square centimeter per hour
w/v	weight per volume

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.

Acknowledgments

This document was developed by the Education and Information Division (Paul Schulte, Ph.D., Director). G. Scott Dotson, Ph.D., was the project officer for this document, assisted in great part by Naomi Hudson, Dr.P.H., M.P.H., Vic Johnson, Ph.D., and Loren Tapp, M.D. The basis for this document was a report (*Toxicology Excellence for Risk Assessment [TERA]*) contracted by NIOSH and prepared by Bernard Gadagbui, Ph.D., and Andrew Maier, Ph.D.

For their contribution to the technical content and review of this document, special acknowledgment is given to the following NIOSH personnel:

Denver Field Office
Eric Esswein, M.Sc.

Division of Applied Research and Technology
Clayton B'Hymer, Ph.D.
John Snawder, Ph.D.
Mark Toraason, Ph.D.

Division of Respiratory Disease Studies
Gregory A. Day, Ph.D.
Aleksander Stefaniak, Ph.D.

Division of Surveillance, Hazard Evaluations, and Field Studies
Matt Dahm, M.Sc.
Todd Niemeier, M.Sc.
Aaron Sussell, Ph.D.
Loren Tapp, M.D.

Education and Information Division
Devin Baker, M.Ed.
Charles L. Geraci, Ph.D.
Thomas J. Lentz, Ph.D.
Richard Niemeier, Ph.D.
Ralph Zumwalde, M.Sc.

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

National Personal Protective Technology Laboratory
Heinz Ahlers, J.D., M.Sc.
Angie Shepherd

For their contribution to the technical content and review of this document, special acknowledgment is given to the following CDC personnel:

Office of Surveillance, Epidemiology and Laboratory Services/Epidemiology and Analysis Program Office

Barbara Landreth, M.A.

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

John Herbold, D.V.M., Ph.D., M.P.H., San Antonio, TX

Shane Stephen Que Hee, M.Sc., Ph.D., University of California at Los Angeles, School of Public Health, Los Angeles, CA

G. Frank Gerberick, Ph.D., The Procter and Gamble Company, Cincinnati, OH

Dori Germolec, Ph.D., National Toxicology Program, National Institute for Environmental Health Sciences, Research Triangle, NC

Ben Hayes, M.D., Ph.D., Division of Dermatology, Vanderbilt School of Medicine, Nashville, TN

Jennifer Sahmel, M.Sc., CIH, ChemRisk, Boulder, CO

James Taylor, M.D., Industrial Dermatology, The Cleveland Clinic, Cleveland, OH

1 Introduction

1.1 General Substance Information:

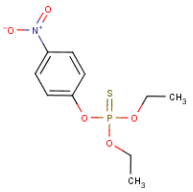
Chemical: Parathion

CAS No: 56-38-2

Molecular weight (*MW*): 291.3

Molecular formula: $(C_2H_5O)_2P(S)OC_6H_4NO_2$

Structural formula:



Synonyms: O,O-Diethyl-O(p-nitrophenyl) phosphorothioate; diethyl parathion; ethyl parathion; parathion-ethyl

Uses: Parathion is a pesticide and acaracide whose use is restricted to certain crops, including corn, soybeans, and wheat [Storm 2001].

1.2 Purpose

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

1.3 Overview of SK Assignment

Parathion is potentially capable of causing adverse health effects following skin contact. A critical review of available data has resulted

Table 1. Summary of the SK assignment for parathion

Skin notation	Critical effect	Available data
SK: SYS (FATAL)	Cholinesterase (ChE) inhibition	Limited human data and sufficient animal data

in the following SK assignment for parathion: **SK: SYS (FATAL)**. Table 1 provides an overview of the critical effects and data used to develop the SK assignment for parathion.

2 Systemic Toxicity from Skin Exposure (SK: SYS)

Several *in vivo* studies were identified that reported dermal absorption of parathion in humans and animals. In humans, 8.6% to 9.7% of the applied parathion dose was dermally absorbed when 4 micrograms (µg) of parathion in acetone was applied per square centimeter (cm^2) to the forearm of volunteers for 24 hours [Maibach et al. 1971; Feldmann and Maibach 1974]. Carver and Riviere [1989] applied parathion at a concentration of 1 milligram per kilogram of body weight (mg/kg) in ethanol solution on the shaved abdomen of pigs under nonocclusive conditions and reported dermal absorption of 6.7%. In another study, Shah and Guthrie [1983] investigated the dermal uptake of parathion in rats. Following the application of 4 micrograms per square centimeter (µg/cm^2) of parathion in 0.1 mL solution of acetone on the shaved backs of the test animals under nonocclusive conditions, the authors estimated absorption of 95% to 99% of the applied dose. Qiao et al. [1993] reported *in vivo* percutaneous absorption of 29.28% to 48.82% of the applied dose (depending on location of topical application) when 300 µg of parathion was applied onto four skin sites (7.5 cm^2) at a surface concentration of 40 µg/cm^2 on weanling swine under occlusive conditions; the percutaneous absorption was 7.47% to 25.00% under nonocclusive conditions. Knaak et al. [1984] investigated the dermal uptake of parathion in rats. Parathion (363 µg in 20 µl acetone) was applied to the backs of the rats under nonoccluded conditions. The authors reported dermal absorption of 57.0% to 59.2% of the applied dose, with rates of 0.33 µg/cm^2 per hour over an observation period of 120 hours. In another study with pigs, 15% to 30% of dermally applied parathion (at a concentration of 100 mg/kg) was absorbed when administered in dimethylsulfoxide or octanol, whereas only 4% to 5% was absorbed when applied in macragol, indicating the influence of vehicle on dermal absorption [Gyrd-Hansen and Rasmussen 1993].

In vitro studies indicate that parathion is absorbed through the skin. Shehata-Karam et al. [1988] reported a mean penetration of 78.6% of the applied parathion dose, 38 µg/cm^2, through fresh human newborn foreskin mounted in a diffusion cell system after 48 hours. Chang and Riviere [1991, 1993] reported percutaneous absorption ranging from 4.9% to 27.43% (4 µg/cm^2) and 0.5% to 2.2% (400 µg/cm^2) of parathion in 10 µL ethanol applied over an 8-hour period to excised skin from weanling pigs. The *in vitro* study used a flow-through diffusion cell system. *In vitro* model absorption studies of isolated perfused porcine skin flaps created from abdominal skin revealed estimated percutaneous absorptions of 4.5% [Chang et al. 1994a] and 6.4% [Williams et al. 1990] of the applied dose. These data indicate a lower absorption than in *in vitro* studies utilizing human newborn foreskin and weanling pig skin.

In vitro studies have shown that using a variety of conditions, including different solvents and the atmosphere (occluded vs. nonoccluded), affected dermal absorption of parathion [van der Merwe and Riviere 2005, 2006; van der Merwe et al. 2006]. Boudry et al. [2008] compared three experimental skin models, including human abdominal and pig ear *in vitro* models and the HuSki (human skin grafted on a nude mouse) *in vivo* model. Differences in dermal absorption were noted when ethanol vs. acetone was used as a solvent, and variation was also noted between the human and pig skin *in vitro* models as well as the HuSki model [Bourdy et al. 2008]. Chang and Riviere [1991] reported that the percentage of absorption was decreased with higher doses, indicating saturation, and that absorption was increased by high relative humidity and elevated temperatures. Absorption of lower doses appeared to be more

sensitive to environmental changes [Chang and Riviere 1991]. In a later study, Chang et al. [1994b] showed that increasing the air temperature, percent relative humidity, or perfusate flow produced a significant increase in parathion dermal absorption through porcine skin *in vitro*. These studies are important in evaluating occupational situations where elevated temperature, blood flow, and skin moisture might increase absorption potential. Miller and Kasting [2010] investigated the dermal absorption of radiolabeled parathion within an *in vitro* model using occluded and nonoccluded conditions. Human cadaver skin mounted in modified Franz diffusion cells were treated with a parathion and acetone solution for 76 hours with the following doses: 0.4, 4.0, 41, and 117 μg/cm^2 [Miller and Kasting 2010]. After 76 hours at the four treatment levels, approximately 19% to 31% of the applied doses were recovered under the nonoccluded conditions, whereas approximately 31% to 56% of the applied doses were recovered under the occluded conditions [Miller and Kasting 2010]. Concentrations for occluded cells were approximately threefold higher than for nonoccluded cells at the three lowest treatment levels [Miller and Kasting 2010]. Moody et al. [2007] reported that 32% of parathion was absorbed in an *in vitro* model using fresh excised breast and leg skin specimens, although the skin was washed with soap 30 minutes post-exposure.

The potential of 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 0.73 was calculated for 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, 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.

Although no human dermal lethal concentration (LD_{LO}) estimates were identified, the reported dermal LD_{50} values (the doses resulting in 50% mortality in the exposed animals) were 6.8 mg/kg in rats dermally exposed to parathion mixed in xylene and 21 mg/kg in rats dermally exposed to a solution with a 1:1:2 ratio of acetone: ethanol: peanut oil in a volume of 2.5 mL/kg [Gaines 1960; Pasquet et al. 1976]. Puga and Rodrigues [1996] reported dermal LD_{50} values of 310 mg/kg and 242 mg/kg in rats following application of 20% (weight/volume; w/v) of parathion in arol and xylene, respectively, indicating the influence of the vehicle on parathion toxicity. Because the reported acute dermal LD_{50} values in rats are lower than the critical cutoff dermal LD_{50} value of 200 mg/kg that identifies chemical substances with the potential to be fatal at low doses [NIOSH 2009], parathion is considered acutely fatal following dermal exposure.

No epidemiological or repeated-dose studies in animals were identified that evaluated the potential of parathion to cause systemic toxicity after dermal exposure. One case report was identified in which repeated exposure to parathion manifested in cholinergic symptoms and changes in ChE activity prior to death [Grob et al. 1949]. No standard toxicity or specialty studies evaluating biological system/function–specific effects (including reproductive effects and immunotoxicity) following dermal exposure to parathion were identified. 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]. However, other agencies and organizations

have evaluated its potential as a carcinogen following other routes of exposure. Table 2 summarizes carcinogenic designations for parathion by multiple governmental and nongovernmental organizations.

Toxicokinetic studies of humans *in vivo* [Maibach et al. 1971; Feldmann and Maibach 1974]indicate that approximately 9% to 10% of the parathion dose is absorbed through the skin, whereas the substance is absorbed to a greater extent (up to 99%) through the skin of some animals *in vivo* [Shah and Guthrie 1983; Knaak et al., 1984; Carver and Riviere 1989; Gyrd-Hansen and Rasmussen 1993; Qiao et al., 1993] and *in vitro* studies [Shehata-Karam et al., 1988; Chang and Riviere 1991, 1993; van der Merwe and Riviere 2005, 2006; van der Merwe et al. 2006; Moody et al. 2007; Boudry et al. 2008; Miller and Kasting 2010]. Acute dermal toxicity studies suggest that parathion is acutely toxic, with the potential to be fatal following acute dermal exposure **[Gaines 1960; Pasquet et al. 1976]**[*], and this is supported by the case report describing a human fatality following repeated dermal exposure to parathion **[Grob et al. 1949]**. Therefore, on the basis of the data for this assessment, parathion is assigned the SK: SYS (FATAL) notation.

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

3 Direct Effects on Skin (SK: DIR)

No human or animal *in vivo* studies for corrosivity of parathion, *in vitro* tests for corrosivity using human or animal skin models, or *in vitro* tests of skin integrity using cadaver skin were identified. No studies evaluating the skin-irritating potential of parathion in humans were identified. An examination of the skin of guinea pigs exposed daily to 1 mL solution (approximately 1290 mg) of parathion in 50% ethanol for 5 to 15 days did not show dermatitis or other visible signs of irritation, but an examination using a microscope revealed progressive pathological lesions ranging from hyperkeratinization of the epidermal layer and thickening of the stratum corneum, proliferation of mononuclear cells in the dermis, swelling and fusing of collagen and reticular fibers, proliferation of connective tissues around hair follicles and sebaceous glands, and thickening of the wall of the blood vessel and mild perivascular inflammatory infiltrate in the dermis [Dikshith and Datta 1972]. The structure–activity relationship model, Deductive Estimation of Risk from Existing Knowledge (*DEREK*) for Windows, predicted parathion to be negative for skin irritation, indicating that the substance does not have structural alerts for skin irritation.

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

Organization	Carcinogenic designation
NIOSH [2005]	No designation
NTP [2014]	No designation
US EPA [2012]	Group C: Possible human carcinogen
European Parliament [2008]	No GHS designation
IARC [2012]	Group 3: Not classifiable as to its carcinogenicity to humans
ACGIH [2003]	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.

Table 3. Summary of previous skin hazard designations for parathion

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption
OSHA [2014]*	[skin]
ACGIH [2003]	[skin]: Dermal exposures in humans have been associated with clinical signs of response up to and including death.

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

No occupational case reports or human studies were identified that evaluated the potential of parathion to cause skin irritation in humans. No standard skin irritation tests were available for review. A repeated-dose study [Dikshith and Datta 1972] indicated that parathion has the potential to cause skin damage, but the damage was revealed only on microscopic examination. Therefore, on the basis of the data for this assessment, parathion is not assigned the SK: DIR (IRR) notation.

4 Immune-mediated Responses (SK: SEN)

No occupational exposure studies, diagnostic tests in humans, or predictive tests in animals were located that investigated the skin-sensitization potential of parathion. The structure–activity relationship model, *DEREK* for Windows, predicted the skin-sensitization potential of the substance, which is probably due to the presence of alkyl ester of phosphoric or phosphonic acid. The lack of diagnostic and/or predictive tests precludes adequate evaluation of the potential of parathion to cause skin sensitization. Therefore, on the basis of the data for this assessment, parathion is not assigned the SK: SEN notation.

5 Summary

The available toxicokinetic data from both humans and animals in *in vivo* studies [Maibach et al. 1971; Feldmann and Maibach 1974; Shah and Guthrie 1983; Knaak et al. 1984; Carver and Riviere 1989; Gyrd-Hansen and Rasmussen 1993; Qiao et al. 1993] and *in vitro* studies [Shehata-Karam et al., 1988; Chang and Riviere 1991, 1993; van der Merwe and Riviere 2005, 2006; van der Merwe et al. 2006; Moody et al. 2007 Boudry et al. 2008; Miller and Kasting 2010] and from acute dermal toxicity studies in animals **[Gaines 1960; Pasquet et al. 1976]**, supported by the case report describing a human fatality following repeated dermal exposure to parathion **[Grob et al. 1949]**,provide sufficient evidence that parathion can penetrate the skin and be absorbed in sufficient quantities to be fatal following acute dermal exposure. Although no standard skin irritation tests were identified, a repeated-dose study [Dikshith and Datta 1972] indicated that parathion has the potential to cause skin irritation and skin damage, but the damage was revealed only on microscopic examination. Therefore, on the basis of these assessments, parathion is assigned a composite skin notation of **SK: SYS (FATAL)**.

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

*ACGIH [2003]. Parathion. In: Documentation of threshold limit values and biological exposure indices, 7th ed., vol. 3. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

†Arterberry JD, Durham WF, Elliott JW, Wolfe HR [1961]. Exposure to parathion: measurement by blood cholinesterase level and urinary p-nitrophenol excretion. Arch Environ Health *3*:476–485.

*Boudry I, Blanck O, Cruz C, Blanck M, Vallet V, Bazire A, Capt A, Josse D, Lallement G [2008]. Percutaneous penetration and absorption of parathion using human and pig skin models in vitro and human skin grafted onto nude mouse skin model in vivo. J Appl Toxicol *28*(5):645–657.

*Carver MP, Riviere JE [1989]. Percutaneous absorption and excretion of xenobiotics after topical and intravenous administration to pigs. Fund Appl Toxicol *13*:714–722.

*Chang SK, Riviere JE [1991]. Percutaneous absorption of parathion in vitro in porcine skin: Effects of dose, temperature, humidity and perfusate composition on absorptive flux. Fund Appl Toxicol *17*:494–504.

*Chang SK, Riviere JE [1993]. Effect of humidity and occlusion on the percutaneous absorption of parathion in vitro. Pharm Res *10*(1):152–155.

*Chang SK, Williams PL, Dauterman WC, Riviere JE [1994a]. Percutaneous absorption, dermatopharmacokinetics and related biotransformation studies of carbaryl, lindane, malathion, and parathion in isolated perfused porcine skin. Toxicology volume *91*(issue 3): pages 269–280.

*Chang SK, Brownie C, Riviere JE [1994b]. Percutaneous absorption of topical parathion through porcine skin: in vitro studies on the effect of environmental perturbations. J Vet Pharmacol Ther *17*(6):434–439.

*Dennis LK, Lynch CF, Sandler DP, Alavanja MCR [2010]. Pesticide use and cutaneous melanoma in pesticide applicators in the agricultural health study. Environ Health Perspect *118*:812–817.

*Dikshith TSS, Datta KK [1972]. Effect of parathion on the skin of guinea-pigs. Experientia *28*(2):169–171.

*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/LexUriServ.do?uri=OJ:L:2008:353:0001:1355:EN:PDF.

*Feldmann RJ, Maibach HI [1974]. Percutaneous penetration of some pesticides and herbicides in man. Toxicol Appl Pharmacol *28*(1):126–132.

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

*Grob D, Garlick WL, Merrill GG, Freimuth HC [1949]. Death due to parathion, and anticholinesterase insecticide. Ann Intern Med *31*:899–904.

*Gyrd-Hansen N, Rasmussen F [1993]. Percutaneous absorption of organophosphorus insecticides in pigs: the influence of difference vehicles. J Vet Pharmacol Ther *16*:174–180.

†Hatcher RL, Wiseman JS [1969]. Epidemiology of pesticide poisoning in the Lower Rio Grande Valley in 1968. Tex Med *65*:40–43.

*HSDB [2009]. Parathion. In: HSDB (Hazardous Substances Data Bank), http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB.

*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.

†Kay K, Monkman L, Windish JP, Doherty T, Pare J, Racicot C [1952]. Parathion exposure and cholinesterase response of Quebec apple growers. AMA Arch Ind Hyg Occup Med *6*(3):252–262.

*Knaak JB, Yee K, Ackerman CR, et al. [1984]. Percutaneous absorption and dermal dose–cholinesterase response studies with parathion and carbaryl in the rat. Toxicol Appl Pharmacol *76*:252–263.

*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.

*Moody RP, Akram M, Dickson E, Chu I [2007]. In vitro dermal absorption of methyl salicylate, ethyl parathion, and malathion: first responder safety. J Toxicol Environ Health A *70*(12):985–999.

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

*NIOSH [2005]. 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/npgd0479.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]. OSHA occupational chemical database, http://www.osha.gov/chemicaldata/chemResult.html?recNo=413.

*Pasquet J, Mazuret A, Fournel J, Koenig FH. [1976].Acute oral and percutaneous toxicity of phosalone in the rat, in comparison with azinphosmethyl and parathion. Toxicol Appl Pharmacol *37*(1):85–92.

*Puga FR, Rodrigues MALaR [1996]. Evaluation of the role of formulation on parathion toxicity. Ecotoxicol Environ Safety *35*:38–40.

*Qiao GL, Chang SK, Riviere JE [1993]. Effects of anatomical site and occlusion on the percutaneous absorption and residue pattern of 2,6-(ring-14C)parathion *in vivo* in pigs. Toxicol Appl Pharmacol *122*:131–138.

†Roudabush RL, Terhear CJ, Fassett DW, Dziuba SP [1965]. Comparative acute effects of some chemicals on the skin of rabbits and guinea pigs. Toxicol Appl Pharmacol *7*:559–565.

*Shah PV, Guthrie FE [1983]. Percutaneous penetration of three insecticides in rats: a comparison of two methods for in vivo determination. J Invest Dermatol *80*(4):291–293.

*Shehata-Karam H, Monteiro-Riviere NA, Guthrie FE [1988]. In vitro penetration of pesticides through human newborn foreskin. Toxicol Lett *40*(3):233–239.

*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]. Parathion. In: Integrated risk information system, http://www.epa.gov/ncea/iris/subst/0327.htm.

*van der Merwe D, Brooks JD, Gehring R, Baynes RE, Monteiro-Riviere JE [2006]. A physiologically based pharmacokinetic model of organophosphate dermal absorption. Toxicol Sci *89*(1):188–204.

*van der Merwe D, Riviere JE [2005]. Comparative studies on the effects of water, ethanol and water/ethanol mixtures on chemical partitioning into porcine stratum corneum and silastic membrane. Toxicol In Vitro *19*(1):69–77.

*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*(4):198–206.

*Williams PL, Carver MP, Riviere JE [1990]. A physiological relevant pharmacokinetic model of xenobiotic percutaneous absorption utilizing the isolated perfused porcine skin flap (IPPSF). J Pharm Sci *79*:305–311.

Appendix: Calculation of the SI Ratio for Parathion

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for parathion. Although the SI ratio is considered in the determination of a substance's hazard potential following skin contact, it is intended to serve only as supportive data during the assignment of the NIOSH SK. An in-depth discussion on the rationale and calculation of the SI ratio can be found in Appendix B of the *Current Intelligence Bulletin (CIB) 61: A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009].

Overview

The SI ratio is a predictive algorithm for estimating and evaluating the health hazards of skin exposure to substances. The algorithm is designed to evaluate the potential for a substance to penetrate the skin and induce systemic toxicity [NIOSH 2009]. The goals for incorporating this algorithm into the proposed strategy for assigning SYS notation are as follows:

1. Provide an alternative method to evaluate substances for which no clinical reports or animal toxicity studies exist or for which empirical data are insufficient to determine systemic effects.
2. Use the algorithm evaluation results to determine whether a substance poses a skin absorption hazard and should be labeled with the SYS notation.

The algorithm evaluation includes three steps:

1. determining a skin permeation coefficient (k_p) for the substance of interest,
2. estimating substance uptake by the skin and respiratory absorption routes, and
3. evaluating whether the substance poses a skin exposure hazard.

The algorithm is flexible in the data requirement and can operate entirely on the basis of the physicochemical properties of a substance and the relevant exposure parameters. Thus, the algorithm is independent of the need for biologic data. Alternatively, it can function with both the physicochemical properties and the experimentally determined permeation coefficient when such data are available and appropriate for use.

The first step in the evaluation is to determine the k_p for the substance to describe its transdermal penetration rate [NIOSH 2009]. The k_p, which represents the overall diffusion of the substance through the stratum corneum and into the blood capillaries of the dermis, is estimated from the compound's molecular weight (MW) and base-10 logarithm of its octanol–water partition coefficient (log K_{OW}). In this example, k_p is determined for a substance with use of Equation 1. A self-consistent set of units must be used, such as 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)

$$k_p = \frac{1}{\frac{1}{k_{psc} + k_{pol}} + \frac{1}{k_q}}$$

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 parathion. The calculated SI ratio was 0.73. On the basis of these results, parathion is predicted to represent a skin absorption hazard.

Appendix References

NIOSH [2005]. 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/npgd0479.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.

SRC [2009]. Interactive PhysProp database demo. Research Triangle Park, NC: 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 parathion

Variables used in calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path *(k_{psc})*	cm/hr	0.0091
Permeation coefficient of the protein fraction of the stratum corneum *(k_{pol})*	cm/hr	8.9×10^{-6}
Permeation coefficient of the watery epidermal layer *(k_{aq})*	cm/hr	0.1465
Molecular weight *(MW)*[*]	amu	291.3
Base-10 logarithm of its octanol–water partition coefficient *($Log\ K_{ow}$)*[*]	None	3.83
Calculated skin permeation coefficient *(k_p)*	cm/hr	0.0086
Skin dose		
Water solubility *(S_w)*[*]	mg/cm^3	0.011
Calculated skin permeation coefficient *(k_p)*	cm/hr	0.0086
Estimated skin surface area (palms of hands)	cm^2	360
Exposure time	hr	8
Calculated skin dose	mg	0.2728
Inhalation dose		
Occupational exposure limit (OEL)[†]	mg/m^3	0.05
Inhalation volume	m^3	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	0.375
Skin dose–to–inhalation dose (SI) ratio	**None**	**0.7274**

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

This page intentionally left blank.

Delivering on the Nation's promise: safety and health at work for all people through research and prevention

To receive NIOSH documents or more information about occupational safety and health topics, contact NIOSH at

1-800-CDC-INFO (1-800-232-4636)
TTY: 1-888-232-6348
CDC-INFO: www.cdc.gov/info

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

DHHS (NIOSH) Publication No. 2015-232

SAFER • HEALTHIER • PEOPLE™