NIOSH Skin Notation Profiles

Parathion
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NIOSH Skin Notation (SK) Profile

Parathion
[CAS No. 56-38-2]

Naomi L. Hudson and G. Scott Dotson
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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 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
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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
cm²   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
m³   cubic meter(s)
mg   milligram(s)
mg/cm²/hr milligram(s) per square centimeter per hour
mg/kg  milligram(s) per kilogram body weight
mg/m³  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
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>REL</td>
<td>recommended exposure limit</td>
</tr>
<tr>
<td>RF</td>
<td>retention factor</td>
</tr>
<tr>
<td>SEN</td>
<td>skin notation indicating the potential for immune-mediated reactions following exposure of the skin</td>
</tr>
<tr>
<td>SI</td>
<td>ratio ratio of skin dose to inhalation dose</td>
</tr>
<tr>
<td>SK</td>
<td>skin notation</td>
</tr>
<tr>
<td>$S_w$</td>
<td>solubility in water</td>
</tr>
<tr>
<td>SYS</td>
<td>skin notation indicating the potential for systemic toxicity following exposure of the skin</td>
</tr>
<tr>
<td>US EPA</td>
<td>United States Environmental Protection Agency</td>
</tr>
<tr>
<td>$\mu g$</td>
<td>micrograms</td>
</tr>
<tr>
<td>$\mu g/cm^2$</td>
<td>micrograms per square centimeter</td>
</tr>
<tr>
<td>$\mu g/cm^2/hr$</td>
<td>micrograms per square centimeter per hour</td>
</tr>
<tr>
<td>w/v</td>
<td>weight per volume</td>
</tr>
</tbody>
</table>
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:** Parathion

**CAS No:** 56-38-2

**Molecular weight** \((MW): 291.3\)

**Molecular formula:** \((C_2H_5O)_2P(S)OC_6H_4NO_2\)

**Structural formula:**

![Structural formula of Parathion]

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

**Uses:** Parathion is a pesticide and acaricide 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>
<thead>
<tr>
<th>Table 1. Summary of the SK assignment for parathion</th>
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<tbody>
<tr>
<td>Skin notation</td>
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<tr>
<td>SK: SYS (FATAL)</td>
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</table>
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 (cm²) 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/cm²) 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 cm²) at a surface concentration of 40 µg/cm² 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/cm² 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 dimethylsuloxide or octanol, whereas only 4% to 5% was absorbed when applied in macrogol, 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/cm², 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/cm²) and 0.5% to 2.2% (400 µg/cm²) 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/cm² [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 (LD₅₀) estimates were identified, the reported dermal LD₅₀ 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 LD₅₀ 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 LD₅₀ values in rats are lower than the critical cutoff dermal LD₅₀ 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 non-governmental organizations.

Toxicokinetic studies of humans in vivo [Mai-bach 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.

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

<table>
<thead>
<tr>
<th>Organization</th>
<th>Carcinogenic designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIOSH [2005]</td>
<td>No designation</td>
</tr>
<tr>
<td>NTP [2014]</td>
<td>No designation</td>
</tr>
<tr>
<td>European Parliament [2008]</td>
<td>No GHS designation</td>
</tr>
<tr>
<td>IARC [2012]</td>
<td>Group 3: Not classifiable as to its carcinogenicity to humans</td>
</tr>
<tr>
<td>ACGIH [2003]</td>
<td>A4: Not classifiable as a human carcinogen</td>
</tr>
</tbody>
</table>

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.
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 [Mai-bach 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].

Table 3. Summary of previous skin hazard designations for parathion

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

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

*Date accessed.

References

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


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 ($k_p$)**

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

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**

Skin dose = $k_p \times S_w \times$ Exposed skin surface area $\times$ Exposure time

= $k_p$ (cm/hour) $\times$ $S_w$ (mg/cm$^3$) $\times$ 360 cm$^2$ $\times$ 8 hours

The inhalation dose (in mg) is derived on the basis of the occupational exposure limit (OEL) of the substance—if the OEL is developed to prevent the occurrence of systemic effects rather than sensory/irritant effects or direct effects on the respiratory tract. Assume a continuous exposure of 8 hours, an inhalation volume of 10 cubic meters (m$^3$) inhaled air in 8 hours, and a factor of 75% for retention of the airborne substance in the lungs during respiration (retention factor, or RF).

**Equation 3: Determination of Inhalation Dose**

Inhalation dose = $OEL \times$ Inhalation volume $\times$ RF

= $OEL$ (mg/m$^3$) $\times$ 10 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**


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

<table>
<thead>
<tr>
<th>Variables used in calculation</th>
<th>Units</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin permeation coefficient</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permeation coefficient of stratum corneum lipid path ( (k_{psc}) )</td>
<td>cm/hr</td>
<td>0.0091</td>
</tr>
<tr>
<td>Permeation coefficient of the protein fraction of the stratum corneum ( (k_{prot}) )</td>
<td>cm/hr</td>
<td>( 8.9 \times 10^{-6} )</td>
</tr>
<tr>
<td>Permeation coefficient of the watery epidermal layer ( (k_{aq}) )</td>
<td>cm/hr</td>
<td>0.1465</td>
</tr>
<tr>
<td>Molecular weight ( (MW) )</td>
<td>amu</td>
<td>291.3</td>
</tr>
<tr>
<td>Base-10 logarithm of its octanol–water partition coefficient ( (\log K_{ow}) )</td>
<td>None</td>
<td>3.83</td>
</tr>
<tr>
<td>Calculated skin permeation coefficient ( (k_{p}) )</td>
<td>cm/hr</td>
<td>0.0086</td>
</tr>
<tr>
<td><strong>Skin dose</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water solubility ( (S) )</td>
<td>mg/cm³</td>
<td>0.011</td>
</tr>
<tr>
<td>Calculated skin permeation coefficient ( (k_{p}) )</td>
<td>cm/hr</td>
<td>0.0086</td>
</tr>
<tr>
<td>Estimated skin surface area (palms of hands)</td>
<td>cm²</td>
<td>360</td>
</tr>
<tr>
<td>Exposure time</td>
<td>hr</td>
<td>8</td>
</tr>
<tr>
<td>Calculated skin dose</td>
<td>mg</td>
<td>0.2728</td>
</tr>
<tr>
<td><strong>Inhalation dose</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupational exposure limit (OEL) (^\dagger)</td>
<td>mg/m³</td>
<td>0.05</td>
</tr>
<tr>
<td>Inhalation volume</td>
<td>m³</td>
<td>10</td>
</tr>
<tr>
<td>Retention factor (RF)</td>
<td>None</td>
<td>0.75</td>
</tr>
<tr>
<td>Inhalation dose</td>
<td>mg</td>
<td>0.375</td>
</tr>
<tr>
<td><strong>Skin dose–to–inhalation dose (SI) ratio</strong></td>
<td>None</td>
<td>0.7274</td>
</tr>
</tbody>
</table>

\(^\dagger\)Variables identified from SRC [ND].

\(^\dagger\)The OEL used in calculation of the SI ratio for parathion was the NIOSH recommended exposure limit (REL) [NIOSH 2005].
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