NIOSH Skin Notation Profiles

Chlordane and Technical Grade Chlordane

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

Chlordane and Technical Grade Chlordane
[CAS No. 57-74-9; 12789-03-6]

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

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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 chlordane. 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
Amu	atomic mass unit
ATSDR	Agency for Toxic Substances and Disease Registry
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
HCCPD	hexachlorocyclopentadiene
hr	hour(s)
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	molarity
m^3	cubic meter(s)
mg	milligram(s)
$mg/cm^2/hr$	milligram(s) per square centimeter per hour
mg/kg	milligram(s) per kilogram body weight
mg/m^3	milligram(s) per cubic meter
mL	milliliter(s)
mL/kg	milliliter(s) per kilogram body weight
MW	molecular weight
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
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
µCi	microcurie
µg	microgram(s)
µg/cm²	microgram(s) per square centimeter
µg/m³	microgram(s) per cubic meter
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

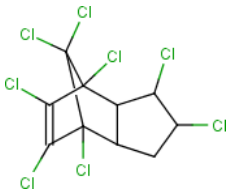
Chemical: Chlordane

CAS No: 57-74-9; 12789-03-6

Molecular weight (*MW*): 409.8

Molecular formula: $C_{10}H_6Cl_8$

Structural formula:



Synonyms: Chlordan, Chlordano, 1,2,4,5,6,7,8,8-Octachloro-3a,4,7,7a-tetrahydro-4,7-methanoindane

Uses: Chlordane historically was used as a pesticide, but all commercial uses of the substance were canceled in the United States [53 Fed. Reg. 11798 (1988)]. No information was available to determine the volume of chlordane currently produced in the United States.

1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with chlordane and (2) the rationale behind the hazard-specific skin notation (SK) assignment for chlordane. 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 chlordane. A literature search was conducted through October 2014 to identify information on chlordane (57-74-9; 12789-03-6), 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 chlordane.

1.3 Overview of SK Assignment

Chlordane is potentially capable of causing numerous adverse health effects following skin contact. Chlordane (57-74-9) refers to a mixture of chlordane isomers (*cis* and *trans*) and

Table 1. Summary of the SK assignment for chlordane

Skin notation	Critical effect	Available data
SK: SYS	Hepatotoxicity	Limited human and animal data

other compounds, and technical chlordane (12789-03-6) is a mixture of chlordane and chlordane-related compounds [McGaughy et al. 1997]. Technical chlordane has a lower percentage of *cis* and *trans* isomers and a larger percentage of other compounds than chlordane (57-74-9) [McGaughy et al. 1997]. This review applies to chlordane (57-74-9) and technical chlordane (12789-03-6). The available data identified are based on technical chlordane, unless otherwise specified. A critical review of available data has resulted in the following SK assignment for chlordane (57-74-9; 12789-03-6): **SK: SYS**. Table 1 provides an overview of the critical effects and data used to develop the SK assignment for chlordane.

2 Systemic Toxicity from Skin Exposure (SK: SYS)

Limited toxicokinetic data were identified on the degree of absorption of chlordane through the skin following dermal exposure. Percutaneous absorption in rhesus monkeys administered 1 microcurie (μCi) ^{14}C-chlordane (57-74-9) to 12 square centimeters (cm^2) of abdominal skin for 24 hours (hr) was determined by the ratio of urinary excretion following topical application to that following intravenous administration; the reported absorption was 4.2% when the substance was applied in soil medium and 6.0% when applied in acetone [Wester et al. 1992]. In an *in vitro* study using cadaver skin, 500 micromoles (μm) ^{14}C-chlordane was applied for 24 hours. The percent of chlordane absorbed in the skin was 0.34% of the dose when applied in soil and 10.8% when applied in an acetone vehicle [Wester et al. 1992]. Other studies have measured detectable levels of chlordane and its metabolites in the blood of non–occupationally exposed individuals whose homes were treated with chlordane and who had detectable levels of the substance on their skin [Hirai and Tomokuni 1993a, 1993b, 1995]. Weschler and Nazaroff [2012] reported that air-to-skin contact with chlordane in indoor air may contribute to total uptake in the body. The potential of chlordane 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 0.0018 was calculated for chlordane. An SI ratio of ≥0.1 indicates that skin absorption may significantly contribute to the overall body burden of a substance [NIOSH 2009]; therefore, chlordane is not considered to be absorbed through the skin following dermal exposure. Additional information on the SI ratio and on the variables used in its calculation is included in the appendix.

No estimate of the human dermal lethal dose (LD_{Lo}) was identified for chlordane. Dermal LD_{50} values (lethal doses in 50% of exposed animals) of technical grade chlordane in xylene were reported as 840 milligrams per kilogram body weight (mg/kg) and 690 mg/kg of technical grade chlordane in xylene for male rats and female rats, respectively [Gaines 1969]. Also, the reported LD_{50} value for female rats treated with undiluted technical grade chlordane was 530 mg/kg [Gaines 1969]. Application of 50 mg chlordane in cottonseed oil to the skin of rats was lethal to all after daily application for 3 days, whereas identical application in ethyl alcohol caused no lethality [Ambrose et al. 1953]. The dermal LD_{50} values reported indicate that the vehicle in which chlordane was administered influenced its toxicity. Because the reported acute dermal LD_{50} values for rats are lower than the critical dermal LD_{50} value of 2000 mg/kg that identifies chemical substances with the potential for acute dermal toxicity [NIOSH 2009], chlordane is considered acutely toxic following dermal exposure.

No epidemiological studies were identified that investigated the potential of chlordane

to cause systemic effects following repeated or prolonged dermal exposure. Princi and Spurbeck [1951] conducted an occupational exposure study of 34 pesticide workers involved from 1 to 3 years in the manufacture and formulation of chlorinated hydrocarbons, including chlordane, aldrin, and dieldrin. Twenty two of the workers were directly exposed during the manufacturing process; however, the workers were exposed mainly by inhalation to total chlorinated hydrocarbon air concentrations of up to 10 milligrams per cubic meter (mg/m^3) and to an unspecified amount by dermal contact [Princi and Spurbeck 1951]. The authors observed no evidence of any adverse effects on the central nervous system (CNS), the liver, the kidneys, or the hematopoietic system.

Repeat-dose and subchronic dermal toxicity studies in animals were identified. In a repeated-dose study, Frings and O'Tousa [1950] administered 0.01 milliliter (mL) of 2% chlordane solution in odorless kerosene (corresponding to 7.4 milligrams per kilograms per day [mg/kg-day]) or 0.04 mL of 2% wettable powder suspension of chlordane (corresponding to 29.6 mg/kg-day) to the skin of female mice daily, 5 days per week, for 20 weeks; another group of animals received no treatment and served as the control group. The incidence of seizures rose steadily in the kerosene-chlordane group, reaching 45% after 6 weeks. No increase in the incidence of seizures was observed in mice treated with the chlordane wettable powder until 9 weeks, when incidence of seizures reached 50% [Frings and O'Tousa 1950]. Decreased survival was observed in the kerosene-chlordane group (3 of the 16 animals died) [Frings and O'Tousa 1950]. Histological examination of the liver, the only organ evaluated, revealed liver necrosis in both chlordane-treated groups [Frings and O'Tousa 1950]. The Agency for Toxic Substances and Disease Registry (ATSDR) [1994] noted that the chlordane used in the Frings and O'Tousa [1950] study was an "early" production chlordane that contained significant amounts of the reaction intermediate hexachlorocyclopentadiene (HCCPD), in contrast to the more highly purified "later" production chlordane. Therefore, it is unclear whether the neurological and liver effects, as well as the decreased survival, were due to chlordane alone or with HCCPD. To assess this, the potential of HCCPD to elicit these responses was evaluated. No repeated dermal toxicity studies were identified that evaluated the potential of HCCPD to cause neurological or liver effects or decreased survival. However, subchronic gavage bioassays with HCCPD in mice and rats [Adbo et al. 1984] indicated that HCCPD caused liver and kidney effects, although no seizures or neurological effects were reported at the highest oral dose of 150 mg/kg-day in rats or 300 mg/kg-day in mice.

Moreover, other (more recent) oral toxicity studies have observed hepatic effects in animals exposed to chlordane. Among these studies, Khasawinah and Grutsch [1989a, 1989b] identified hepatic effects after feeding rats 25 ppm of chlordane for 130 weeks. The overall data suggest that chlordane itself, and not HCCPD, is likely the cause of the decreased survival, seizures, and liver effects at the dermal dose of 7.4 or 29.6 mg/kg-day observed in the Frings and O'Tousa [1950] dermal toxicity study. The lowest dose in this study (7.4 mg/kg-day) can be regarded as the LOAEL, without a NOAEL being identified. Therefore, this assessment concludes that chlordane has the potential to be systemically available and may cause hepatic effects and decreased survival, with a NOAEL 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].

No standard toxicity or specialty studies were identified that evaluated the potential for chlordane to cause biological system/function–specific effects (including reproductive and developmental effects and immunotoxicity) following dermal exposure. In a 90-day subchronic skin painting study, Datta et al. [1977] exposed male guinea pigs to 0 or 168 mg/kg-day chlordane in 1 mL of acetone on their shaved abdomens under unoccluded

conditions. No symptoms of insecticide poisoning or significant changes in the activity of acetylcholinesterase in the blood and brain were reported; however, histopathological examination of the testes showed mild degenerative changes. Although no other dermal studies have identified the testes as a target organ, alterations in reproductive-related behavior in male rats as a consequence of an oral chlordane exposure have been reported [Cassidy et al. 1994]. Although these results are supportive of the findings of Datta et al. [1977] that chlordane has potential functional reproductive effects, no multigenerational reproductive studies were available to confirm these effects.

Studies that evaluated the potential for chlordane to be carcinogenic following dermal exposure were identified. In a population-based case-control study of white male farmers by Cantor et al. [1992], the risk of non-Hodgkins lymphoma was significantly elevated (odds ratio [OR], 1.7; 95% confidence interval [CI], 1.0–1.5] with use of protective clothing or equipment (versus an OR of 2.2 and 95% CI of 1.2–4.2 without protective clothing or equipment) in 55 men who handled chlordane, compared with 68 controls. However, subjects may have been simultaneously exposed to other chemicals. Following a cross-sectional epidemiological investigation of the health status of 261 people from 85 private households previously treated with chlordane for termite control, Menconi et al. [1988] reported a statistically significant increase in the incidence of unspecified skin neoplasms. The population was exposed to indoor air levels of chlordane up to >5 micrograms per cubic meters ($\mu g/m^3$); however, the dermal contribution to the exposure was not quantified [Menconi et al. 1988]. Table 2 summarizes carcinogenic designations of multiple governmental and nongovernmental organizations for chlordane.

Although the predictive mathematical model (see Appendix) did not indicate that the chemical can be absorbed through the skin, limited toxicokinetic data [Wester et al. 1992] were identified that indicate chlordane has the potential to be absorbed through the skin. The acute dermal toxicity data from rats **[Gaines 1969]**[*] and repeated-dose studies **[Frings and O'Tousa 1950]**, with support from oral toxicity studies [Khasawinah and Grutsch 1989a, 1989b], provide evidence that chlordane is absorbed through the skin, is systemically available, and has the potential to cause neurological and liver effects and decreased survival. Therefore, on the basis of the data for this assessment, chlordane is assigned the SK: SYS notation.

3 Direct Effects on Skin (SK: DIR)

No human or animal *in vivo* studies for corrosivity of chlordane, *in vitro* tests for corrosivity using human or animal skin models, or *in vitro* tests of skin integrity using cadaver skin were identified. Datta et al. [1977] reported hyperkeratinization and cellular degeneration (such as vacuolization and a multinucleated condition in cells of the malpighian layer) in the skin of guinea pigs, without any changes being observed in the dermis after exposure to a mixture of chlordane (67 mg/kg-day) and acetone through dermal painting for 90 days. Ambrose et al. [1953] observed no local reactions in rats topically treated with 273 mg/kg-day chlordane in ethyl alcohol for 4 days.

Despite the extensive worker experience, no controlled studies were identified that evaluated direct skin effects of chlordane in humans. The few cases of skin irritation observed during occupational exposure involved a mixture of chlordane and oils, but not chlordane alone. No severe skin reactions were reported in the available repeated-dose dermal studies, but some effects were noted by Datta et al. [1977]. No standard skin irritation tests were identified for chlordane. There is no compelling evidence that chlordane is a potent skin irritant; however, the available data from animals are insufficient to adequately evaluate the potential for chlordane to cause direct

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

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

Organization	Carcinogenic designation
NIOSH [2005]	Potential occupational carcinogen
NTP [2014]	No designation
US EPA [2012]	B2: Probable human carcinogen
European Parliament [2008]	Carcinogenicity Category 2: Suspected of causing cancer
IARC [2012]	2B: Possibly carcinogenic to humans
ACGIH [2007]	A3: Confirmed animal carcinogen with unknown relevance to humans

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.
†All designations are for chlordane, CAS No. 57-74-9, except for the US EPA [2012] designations, which is for technical grade chlordane, CAS No. 12789-03-6.

skin effects following repeated dermal exposures. Therefore, on the basis of the data for this assessment, chlordane is not assigned the SK: DIR (IRR) notation.

4 Immune-mediated Responses (SK: SEN)

No human patch tests or predictive tests in animals (for example, 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. Following a 90-day study in which guinea pigs were topically treated with chlordane in acetone, Datta et al. [1977] reported that there was no evidence of sensitization. However, it is not clear whether the protocol used could have effectively detected a sensitization response.

The limited data identified did not specifically indicate that chlordane has the potential to cause skin sensitization in humans. In addition, the lack of predictive tests in animals precludes adequate evaluation of the skin sensitization potential of chlordane. Therefore, on the basis of the data for this assessment, chlordane is not assigned the SK: SEN notation.

5 Summary

Although the predictive mathematical model (see Appendix) did not indicate that the chemical can be absorbed through the skin, limited toxicokinetic data [Wester et al. 1992] were identified that provide evidence of the potential of chlordane to be absorbed through the skin following dermal exposure. Evidence was identified from data on acute dermal toxicity in rats **[Gaines 1969]** and from repeated-dose studies **[Frings and O'Tousa 1950]**, with support from oral toxicity studies [Khasawinah and Grutsch 1989a, 1989b], to indicate that chlordane is absorbed through the skin, is systemically available and toxic, and has the potential to cause neurological and liver effects and decreased survival. Insufficient data were available to adequately evaluate the potential for chlordane to cause direct skin effects or skin sensitization. Therefore, on the basis of these assessments, chlordane is assigned a composite skin notation of **SK: SYS**.

Table 3 summarizes the skin hazard designations for chlordane previously issued by NIOSH and other organizations. The equivalent dermal designations for chlordane, according to the Globally Harmonized System (GHS) for the Classification and Labelling

Table 3. Summary of previous skin hazard designations for chlordane[*]

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption; prevent skin contact
OSHA [2014][†]	[skin]: Potential for dermal absorption
ACGIH [2007]	[skin]: Based on the significant toxicity, including death, from dermal exposure of animals and humans

ACGIH = American Conference of Governmental Industrial Hygienists; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration.
[*]All designations are for chlordane, CAS No. 57-74-9.
[†]Date accessed

of Chemicals, is Acute Toxicity Category 4 (Hazard statement: Harmful in contact with the skin) [European Parliament 2008].

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

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Appendix: Calculation of the SI Ratio for Chlordane

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for chlordane. 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 chlordane. The calculated SI ratio was 0.0018. On the basis of these results, chlordane is not predicted to represent a skin absorption hazard.

Appendix References

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

Variables used in calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path *(k_{psc})*	cm/hr	0.0652
Permeation coefficient of the protein fraction of the stratum corneum *(k_{pol})*	cm/hr	7.5036×10^{-6}
Permeation coefficient of the watery epidermal layer *(k_{aq})*	cm/hr	0.1235
Molecular weight *(MW)*[*]	amu	409.78
Base-10 logarithm of its octanol–water partition coefficient *(Log K_{ow})*[*]	None	6.16
Calculated skin permeation coefficient *(k_p)*	cm/hr	0.04268
Skin dose		
Water solubility *(S_w)*[*]	mg/cm^3	5.6×10^{-5}
Calculated skin permeation coefficient *(k_p)*	cm/hr	0.04268
Estimated skin surface area (palms of hands)	cm^2	360
Exposure time	hr	8
Calculated skin dose	mg	0.0069
Inhalation Dose		
Occupational exposure limit (OEL)[†]	mg/m^3	0.5
Inhalation volume	m^3	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	3.75
Skin dose–to–inhalation dose (SI) ratio	**None**	**0.0018**

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

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