Skin Notation (SK) Profile

Heptachlor

[CAS No. 76-44-8]

Department of Health and Human Services
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

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Foreword

As the largest organ of the body, the skin performs multiple critical functions, such as serving as the primary barrier to the external environment. For this reason, the skin is often exposed to potentially hazardous agents, including chemicals, which may contribute to the onset of a spectrum of adverse health effects ranging from localized damage (e.g., irritant contact dermatitis and corrosion) to induction of immune-mediated responses (e.g., allergic contact dermatitis and pulmonary responses), or systemic toxicity (e.g., neurotoxicity and hepatoxicity). Understanding the hazards related to skin contact with chemicals is a critical component of modern occupational safety and health programs.

In 2009, the National Institute for Occupational Safety and Health (NIOSH) published *Current Intelligence Bulletin (CIB) 61 – A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009-147]. This document provides the scientific rationale and framework for the assignment of multiple hazard-specific skin notations (SK) that clearly distinguish between the systemic effects, direct (localized) effects, and immune-mediated responses caused by skin contact with chemicals. The key step within assignment of the hazard-specific SK is the determination of the hazard potential of the substance, or its potential for causing adverse health effects as a result of skin exposure. This determination entails a health hazard identification process that involves use of the following:

- Scientific data on the physicochemical properties of a chemical
- Data on human exposures and health effects
- Empirical data from *in vivo* and *in vitro* laboratory testing
- Computational techniques, including predictive algorithms and mathematical models that describe a selected process (e.g., skin permeation) by means of analytical or numerical methods.

This *Skin Notation Profile* provides the SK assignments and supportive data for heptachlor. 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
ATSDR	Agency for Toxic Substances and Disease Registry
CIB	Current Intelligence Bulletin
cm^2	squared centimeter(s)
cm/hour	centimeter(s) per hour
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
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
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^3	milligram(s) per cubic centimeter
mg/kg	milligram(s) per kilogram body weight
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
USEPA	United States Environmental Protection Agency

Glossary

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

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

Cancer—Any one of a group of diseases that occurs when cells in the body become abnormal and grow or multiply out of control.

Contaminant—A chemical that is (1) unintentionally present within a neat substance or mixture at a concentration less than 1.0% or (2) recognized as a potential carcinogen and present within a neat substance or mixture at a concentration less than 0.1%.

Cutaneous (or percutaneous)—Referring to the skin (or through the skin).

Dermal—Referring to the skin.

Dermal contact—Contact with (touching) the skin.

Direct effects—Localized, non-immune-mediated adverse health effects on the skin, including corrosion, primary irritation, changes in skin pigmentation, and reduction/disruption of the skin barrier integrity, occurring at or near the point of contact with chemicals.

Immune-mediated responses—Responses mediated by the immune system, including allergic responses.

Sensitization—A specific immune-mediated response that develops following exposure to a chemical, which, upon re-exposure, can lead to allergic contact dermatitis (ACD) or other immune-mediated diseases such as asthma, depending on the site and route of re-exposure.
Substance—A chemical.

Systemic effects—Systemic toxicity associated with skin absorption of chemicals after exposure of the skin.

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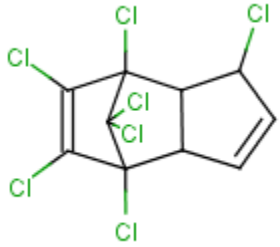
1.0 Introduction

1.1 General Substance Information:

Chemical: Heptachlor
CAS No: 76-44-8
Molecular weight (*MW*): 373.4
Molecular formula: $C_{10}H_5Cl_7$
Structural formula:



Synonyms: 1,4,5,6,7,8,8-Heptachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene, Dicyclopentadiene, 3,4,5,6,7,8,8a-heptachloro-, Heptachlorotetrahydro-4,7-methanoindene, heptachlorodicyclopentadiene, 3-chloro-chlordene

Uses: Heptachlor is an organochlorine pesticide that was used for killing insects in homes, in buildings, and on food crops, but was banned from this use in 1988 [ATSDR 2007]. However, heptachlor is still approved by EPA for killing fire ants that are in buried power transformers [ATSDR 2007].

1.2 Purpose

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

1.3 Overview of SK Assignment

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

Table 1. Summary of the SK Assignment for Heptachlor

Skin Notation	Critical Effect	Available Data
SK: SYS	Acute toxicity	Limited animal data

2.0 Systemic Toxicity from Skin Exposure (SK: SYS)

No specific animal or human toxicokinetic data were identified that estimated the degree of absorption of heptachlor following dermal exposure. A human study was identified where dermal exposure of 29 applicators was evaluated by attaching gauze pads to outer and inner clothing at selected body regions [Kamble et al. 1992]. Hands had the highest amounts of heptachlor that was recovered, followed by ankles and the forearms [Kamble et al. 1992]. Total exposure to heptachlor during subterranean termite treatments was 1.8 micrograms per kilograms per hour (µg/kg/hr). In the absence of quantitative absorption data, the potential of heptachlor to pose a skin absorption hazard was 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 0.007 was calculated for heptachlor. An SI ratio of ≥0.1 indicates that skin absorption may significantly contribute to the overall body burden of a substance [NIOSH 2009]; therefore, heptachlor is not considered to be absorbed through the skin following dermal exposure. Additional information on the SI ratio and the variables used in its calculation are included in the appendix.

No estimate of the lethal dermal dose (LD_{Lo}) for humans has been identified. However, in rats, the reported dermal LD_{50} value (the dose resulting in 50% mortality in the exposed animals) ranged from 195 to 250 milligrams per kilogram body weight (mg/kg) in male and female rats, respectively [Gaines 1960, 1969]. When rabbits were exposed to heptachlor in powder form, the LD_{50} was greater than 2,000 mg/kg [Lehmann 1952]. However, Lehmann [1952] also reported an LD_{50} of less than 20 mg/kg when rabbits were exposed to heptachlor in a solution of dimethyl phthalate, indicating that heptachlor may be more toxic in solution than in powder form. Because the dermal LD_{50} values reported for rats are at or above the critical LD_{50} value of 200 mg/kg body weight that identifies chemical substances with potential to be acutely fatal [NIOSH 2009], heptachlor is considered systemically available and acutely toxic by the dermal route.

No epidemiological studies, clinical case histories, or occupational exposure studies or animal repeat-dose (21-day, 28-day), subchronic (90-day) or chronic (at least 12-month) toxicity studies were

identified for heptachlor following dermal exposure. Absence of these studies precludes detailed evaluation of the potential of heptachlor to cause systemic effects and the dermal dose levels at which these effects can be observed. A study was identified where rabbits received daily application to heptachlor for 14 days [Lehmann 1952]. There were no survivors after 14 doses when rabbits were given 20 mg/kg of heptachlor in a solution of dimethyl phthalate [Lehmann 1952]. No standard toxicity or specialty studies evaluating biological system/function specific effects (including reproductive and developmental effects and immunotoxicity) were identified for heptachlor following dermal exposure.

No epidemiological studies or standard bioassays that evaluated the carcinogenic potential of heptachlor following dermal exposure were identified. However, the carcinogenicity of the chemical has been evaluated following exposure via non-dermal routes. Table 2 summarizes carcinogenic designations of multiple governmental and nongovernmental organizations for heptachlor.

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

Organization	Carcinogenic designation
NIOSH [2005]	Potential occupational carcinogen
NTP [2014]	No designation
USEPA [2014]	B2; probable human carcinogen
European Parliament [2008]	GHS Carcinogenicity Category 2: Suspected of causing cancer
IARC [2012]	Group 2B: Possibly carcinogenic to humans
EC [2013]†	R40: Limited evidence of a carcinogenic effect
ACGIH [2001]	A3: Confirmed animal carcinogen with unknown relevance to humans

ACGIH = American Conference of Governmental Industrial Hygienists; EC = European Commission, Joint Research, Institute for Health and Consumer Protection; GHS = Globally Harmonized System for Classification and Labelling of Chemicals; IARC = International Agency for Research on Cancer; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; USEPA = United States Environmental Protection Agency.

* The listed cancer designations were based on data from nondermal (such as oral or inhalation) exposure since studies using the dermal route of exposure were unavailable.

†Date accessed.

Dermal absorption studies were not identified for heptachlor. Although a mathematical model predicted that the chemical is not likely to be absorbed through the skin, acute dermal toxicity studies in rats **[Gaines 1960, 1969]**[1] show that heptachlor can be absorbed through the skin and can be acutely toxic. Because the reported LD_{50} values were at or below the cutoff value of 200 mg/kg body weight that indicates a substance is acutely fatal, heptachlor is assigned the SK: SYS notation.

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

3.0 Direct Effects on Skin (SK: DIR)

No human or animal *in vivo* studies on the corrosivity of heptachlor or *in vitro* tests for corrosivity using human or animal skin models or *in vitro* tests of skin integrity using cadaver skin were identified.. No primary skin irritation tests were identified. The structure-activity relationship model, Deductive Estimation of Risk from Existing Knowledge (*DEREK*), predicted heptachlor to be negative for skin irritation. Absence of these studies precludes detailed evaluation of the potential of heptachlor to be corrosive or irritating to the skin. Therefore, on the basis of the data for this assessment, heptachlor is not assigned the SK: DIR (IRR) notation.

4.0 Immune-mediated Responses (SK: SEN)

No human diagnostic patch tests or predictive tests in animals (i.e., guinea pig maximization tests, Buehler tests, murine local lymph node assays, or mouse ear swelling tests) were identified that evaluated the potential of heptachlor to be a skin sensitizer. *DEREK* predicted heptachlor to be a plausible skin sensitizer. Although, model predictions are not considered sufficient to assign a SK: SEN notation, they highlight testing for this endpoint as an important data gap. Therefore, on the basis of the data for this assessment, heptachlor is not assigned the SK: SEN notation.

5.0 Summary

No quantitative data on the dermal absorption kinetics of heptachlor were identified. A mathematical model predicted heptachlor is not likely to be absorbed through the skin. However, acute toxicity studies in rats **[Gaines 1960, 1969]** showed that the chemical has the potential to be absorbed through the skin, systemically available, and toxic following acute dermal exposure. No studies were identified that evaluated the potential of heptachlor to be corrosive or irritating to the skin or be a skin sensitizer. A structure-activity relationship model predicted heptachlor to be negative for skin irritation, but a plausible skin sensitizer. Skin sensitization potential predicted by the model highlights testing for this endpoint as an important data gap. Therefore, on the basis of these assessments, heptachlor is assigned a composite skin notation of **SK: SYS**.

Table 3 summarizes the skin hazard designations for heptachlor previously issued by NIOSH and other organizations. The equivalent dermal designation for heptachlor, according to the Global Harmonization System (GHS) of 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 the previously issued skin hazard designations for heptachlor

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption; prevent skin contact
OSHA [2015]*	[skin]: Potential for dermal absorption
ACGIH [2001]	[skin]: based on systemic toxicity and mortality in animals following dermal application
EC [2013]*	R24 - Toxic in contact with skin

ACGIH = American Conference of Governmental Industrial Hygienists; EC = European Commission, Joint Research, Institute for Health and Consumer Protection; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration.
*Date accessed.

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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 Heptachlor

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

Overview

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

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

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

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

The first step in the evaluation is to determine the k_p for the substance to describe the transdermal penetration rate of the substance [NIOSH 2009]. The k_p, which represents the overall diffusion of the substance through the stratum corneum and into the blood capillaries of the dermis, is estimated from the compound's molecular weight (*MW*) and base-10 logarithm of its octanol–water partition coefficient (log K_{ow}). In this example, k_p is determined for a substance with use of Equation 1. A self-consistent set of units must be used, such as outlined in Table A1. Other model-based estimates of k_p may also be used [NIOSH 2009].

Equation 1: Calculation of Skin Permeation Coefficient (k_p)

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

where k_{psc} is the permeation coefficient in the lipid fraction of the stratum corneum, k_{pol} is the coefficient in the protein fraction of the stratum corneum, and k_{aq} is the coefficient in the watery epidermal layer. These components are individually estimated by

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

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 squared centimeters [cm^2]).

Equation 2: Determination of Skin Dose

Skin dose = $k_p \times S_w \times$ Exposed skin surface area × Exposure time
= k_p(cm/hour) × S_w (mg/cm^3) × 360 cm^2 × 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 × Inhalation volume × RF
= OEL (mg/m^3) × 10 m^3 × 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 heptachlor. The calculated SI ratio was 0.0007. On the basis of these results, heptachlor is not predicted to represent a skin absorption hazard.

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

Variables Used in Calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path(k_{psc})	cm/hour	0.0876
Permeation coefficient of the protein fraction of the stratum corneum (k_{pol})	cm/hour	7.8617×10^{-6}
Permeation coefficient of the watery epidermal layer (k_{aq})	cm/hour	0.1239
Molecular weight (MW)*	amu	373.32
Base-10 logarithm of its octanol–water partition coefficient (Log K_{ow})*	None	6.1
Calculated skin permeation coefficient (k_p)	cm/hour	0.0523
Skin dose		
Water solubility (S_w)*	mg/cm^3	1.8×10^{-3}
Calculated skin permeation coefficient (k_p)	cm/hour	0.0523
Estimated skin surface area (palms of hand)	cm^2	360
Exposure time	hour	8
Calculated skin dose	mg	0.0271
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	375
Skin dose–to–inhalation dose (SI) ratio	None	0.0007

*Variables identified from SRC [ND].

†The OEL used in calculation of the SI ratio for heptachlor was the NIOSH recommended exposure limit (REL) [NIOSH 2005].

Appendix References

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