Skin Notation (SK) Profile

Endrin

[CAS No. 72-20-8]

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 endrin. 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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Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
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
g	gram(s)
g/L	gram(s)/liter
GHS	Globally Harmonized System for Labelling and Classification of Chemicals
GPMT	guinea pig maximization test
hr	hour(s)
IARC	International Agency for Research on Cancer
IPCS	International Program for Chemical Safety
(IRR)	subnotation of SK: DIR indicating the potential for a chemical to be a skin irritant following exposure to the skin
kaq	coefficient in the watery epidermal layer
k_p	skin permeation coefficient
kpol	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/kg/day	milligram(s) per kilogram body weight per day
mg/m^3	milligram(s) per cubic meter
mL	milliliter(s)
mL/kg	milliliter(s) per kilogram body weight
MW	molecular weight
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level

NTP	National Toxicology Program
OEL	occupational exposure limit
OSHA	Occupational Safety and Health Administration
ppm	parts per million
REL	recommended exposure limit
RF	retention factor
SEN	skin notation indicating the potential for immune-mediated reactions following exposure of the skin
SI ratio	ratio of skin dose to inhalation dose
SK	skin notation
S_W	solubility
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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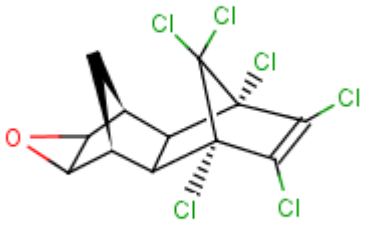
1.0 Introduction

1.1 General Substance Information

Chemical: Endrin
CAS No: 72-20-8
Molecular weight (*MW*): 380.9
Molecular formula: $C_{12}H_8Cl_6O$
Structural formula:



Synonyms: Endrine, hexadrin, mendrin, endricol

Uses: Endrin is a stereoisomer of dieldrin (CAS #60-57-1) and was historically used as a pesticide [ATSDR 1996]. This chlorinated hydrocarbon pesticide is no longer manufactured 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 endrin and (2) the rationale behind the hazard-specific skin notation (SK) assignment for endrin. 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 endrin. A literature search was conducted through October 2012 to identify information on endrin, 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 endrin.

1.3 Overview of SK Assignment

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

Table 1. Summary of the SK Assignment for endrin

Skin Notation	Critical Effect	Available Data
SK: SYS (FATAL)	Acute toxicity; neurotoxicity	Sufficient animal data

2.0 Systemic Toxicity from Skin Exposure (SK: SYS)

No *in vivo* or *in vitro* toxicokinetic data were identified in humans or animals that estimated the degree of absorption of endrin following dermal exposure. The potential of endrin to pose a skin absorption hazard was also evaluated using 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 0.0002 was calculated for endrin. An SI ratio of ≥0.1 indicates that skin absorption may significantly contribute to the overall body burden of a substance [NIOSH 2009]; therefore, endrin is not considered to be absorbed thought he skin following dermal exposure. Additional information on the SI ratio and the variables used in its calculation are included in the appendix.

No estimate of the human dermal lethal dose (LD_{Lo}) was identified for endrin. Treon et al. [1955] reported a minimum lethal dose of 94 milligram per kilogram body weight (mg/kg) in rabbits (1 of 3 died) topically exposed to a crystalline endrin powder for 24 hours. Gaines [1969] reported a dermal LD_{50} value (lethal dose in 50% of exposed animals) for endrin in a xylene solution of 18 mg/kg and 15 mg/kg in male and female rats, respectively. The reported acute dermal LD_{50} values for endrin in rats and is lower than the critical dermal LD_{50} value of 200 mg/kg that identifies chemical substances with the potential to be fatal at low doses following acute dermal exposure [NIOSH 2009]. Although model prediction indicates a low potential for endrin to be absorbed through the skin, the results of the acute dermal toxicity study show that endrin is absorbed through the skin, is systemically available, and can be fatal following dermal exposure.

No case reports or epidemiological studies or chronic toxicity studies were identified that evaluated the potential of endrin to cause systemic effects following dermal exposure. However, a subchronic repeated dose toxicity study in female rabbits was identified. In this study, Treon et al. [1955] administered 27 to 44 milligrams per kilograms per day

(mg/kg-day) of endrin to the abraded skin of 4 female rabbits for 25 to 45 periods of contact, 20 to 42 mg/kg-day of endrin to the intact skin of three female rabbits for 40 to 70 periods of contact, and 67 to 91 mg/kg-day of endrin to the intact skin of 3 female rabbits for 19 to 25 periods of contact; for each group, endrin was topically administered for 2 hours (hr) per day, 5 days a week. Only one of four animals in the 27 to 44 mg/kg-day group and 1 out of 3 animals in the 20 to 42 mg/kg-day group died, while all three animals died in the 67 to 91 mg/kg-day group [Treon et al. 1955]. The chief signs of intoxication observed included convulsions, tremors, and twitching of the facial muscle [Treon et al. 1955]. These effects are consistent with the mode of action of endrin that involves disruption of gamma-aminobutyric acid (GABA) system, which is an inhibitory neurotransmitter system, thus causing hyperexcitability of the central nervous system [Agency of Toxic Substances and Disease Registry (ATSDR) 1996]. Treon et al. [1955] indicated that the data provided no evidence that abrasion of the skin promoted the percutaneous absorption of endrin to any appreciable extent. Although no control group was included in this study, it appears that endrin has the potential to cause nervous system effects and ultimately death with repeated and prolonged dermal exposure. This assessment estimates a Lowest Observed Adverse Effect Level (LOAEL) of 20 mg/kg-day for nervous system effects and mortality, while no No Observed Adverse Effect Level (NOAEL) was established in this study. Because the LOAEL of 20 mg/kg-day in the rabbit is lower than the critical dermal NOAEL value of 1000 mg/kg for repeated-dose toxicity that identifies chemical substances with the potential for dermal toxicity [NIOSH 2009], endrin has the potential to cause adverse nervous system effects and mortality following repeated dermal exposure.

No standard toxicity or specialty studies were identified that evaluated the biological system/function specific effects (including reproductive and developmental effects and immunotoxicity) following dermal exposure to endrin. No epidemiological studies or animal bioassays were identified that evaluated the potential of endrin to be a carcinogen following dermal exposure. Table 2 summarizes carcinogenic designations of multiple governmental and nongovernmental organizations for endrin.

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

Organization	Carcinogenic designation
NIOSH [2005]	No designation
NTP [2011]	No designation
USEPA [2012]	Group D: not classifiable as to carcinogenicity for humans
GHS [European Parliament 2008]	No designation
IARC [2012]	Group 3: not classifiable
EC [2012]*	No designation
ACGIH [2001]	A4: not classifiable as a human carcinogen

ACGIH = American Conference of Governmental Industrial Hygienists; EC = European Commission, Joint Research, Institute for Health and Consumer Protection; GHS = Globally Harmonized System for Labelling and Classification 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.
*Date accessed.

The predictive mathematical model (see Appendix) did not indicate that the chemical can be absorbed through the skin and no toxicokinetic data were identified in humans or animals that estimated the degree of endrin absorption through the skin following dermal exposure; however, the capacity of the compound to penetrate the skin can be inferred from the fact that single dose **[Gaines 1969]**[1] and repeated dose animal studies **[Treon et al. 1955]** demonstrate the potential of endrin to cause systemic effects, including nervous system effects and death at low doses. Therefore, on the basis of the data for this assessment, endrin is assigned the SK: SYS (FATAL) notation.

3.0 Direct Effects on Skin (SK: DIR)

No human or animal *in* vivo studies for corrosivity of endrin or *in vitro* tests for corrosivity using human skin models or *in vitro* tests of skin integrity using cadaver skin were identified. No standard skin irritation tests were identified for humans or animals. However, Treon et al. [1955] found no evidence of irritation or damage to the skin following application of endrin at doses of 60 to 3600 mg/kg on intact and abraded skin of female rabbits under occlusion for 24 hr in an acute dermal toxicity study, nor at doses of 20 to 91 mg/kg-day, 2 hr/day, 5 days/week, for 19 to 70 days. The evidence from animal studies suggests that endrin is not a skin irritant.

Although no human data or standard skin irritation tests were identified, acute and repeated and prolonged dermal exposure to endrin at low to high doses to intact and/or abraded skin of rabbits [Treon et al. 1955] indicate that endrin is not likely to irritate the skin. Therefore, on the basis of the data for this assessment, endrin is not assigned the SK: DIR (IRR) notation.

4.0 Immune-mediated Responses (SK: SEN)

Occupational exposure reports or studies investigating the skin sensitization potential of endrin in humans were limited to a single study that reported no evidence of skin sensitization in workers who were exposed to chlorinated hydrocarbon insecticides (including endrin) in concentrated form for the combined equivalent of more than 1300 person-years [Hoogendam et al. 1965]. No diagnostic (human patch) tests or predictive tests in animals such as guinea pig maximization tests, murine local lymph node assays,

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

mouse ear swelling tests, or any other studies that evaluated the potential of the substance to cause skin sensitization were identified.

No diagnostic tests in humans or predictive tests in animals were identified that evaluated the potential of endrin alone to cause skin sensitization. The data are inadequate to assess the skin sensitization potential of endrin. Therefore, on the basis of the data for this assessment, endrin is not assigned the SK: SEN notation.

5.0 Summary

No studies were identified that estimated the degree of endrin absorption through the skin; however, acute and repeated dose animal studies **[Treon et al. 1955; Gaines 1969]** provide sufficient evidence that endrin has the potential to cause systemic effects, including nervous system effects and death. No human data or standard skin irritation tests were identified that evaluated the potential for skin irritation for endrin; however, acute, repeated, and prolonged dermal exposure to endrin at low to high doses to intact and abraded skin of rabbits indicate that endrin is not likely to be irritating to the skin. No diagnostic tests in humans or predictive tests in animals were identified to adequately evaluate the potential of endrin alone to cause skin sensitization. Therefore, on the basis of these assessments, endrin is assigned a composite skin notation of **SK: SYS (FATAL)**.

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

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption; prevent skin contact
OSHA [1998]	[skin]: Potential for dermal absorption
ACGIH [2001]	[skin]: Endrin is readily absorbed through the skin, producing systemic effects and mortality in animals
EC [2012]*	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.

References

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

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Appendix: Calculation of the SI Ratio for Endrin

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for endrin. 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 *kp* 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 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)

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

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 square 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/hr) × S_w (mg/cm^3) × 360 cm^2 × 8 hr

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 endrin. The calculated SI ratio was 0.0002. On the basis of these results, endrin is predicted to represent a skin absorption hazard.

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

Variables Used in Calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path(k_{psc})	cm/hr	0.0228
Permeation coefficient of the protein fraction of the stratum corneum (k_{pol})	cm/hr	7.823×10^{-6}
Permeation coefficient of the watery epidermal layer (k_{aq})	cm/hr	0.1281
Molecular weight (MW)[a]	amu	380.91
Base-10 logarithm of its octanol–water partition coefficient (Log K_{ow})[a]	None	5.2
Calculated skin permeation coefficient (k_p)	cm/hr	0.0194
Skin dose		
Water solubility (S_w)[a]	mg/cm^3	2.5×10^{-6}
Calculated skin permeation coefficient (k_p)	cm/hr	0.0194
Estimated skin surface area (palms of hand)	cm^2	360
Exposure time	hr	8
Calculated skin dose	mg	0.0001
Inhalation Dose		
Occupational exposure limit (OEL)[b]	mg/m^3	0.1
Inhalation volume	m^3	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	0.75
Skin dose–to–inhalation dose (SI) ratio	None	0.0002

[a]Variables identified from SRC [2009].
[b]The OEL used in calculation of the SI ratio for endrin was the NIOSH recommended exposure limit (REL) [NIOSH 2005].

Appendix References

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