NIOSH Skin Notation Profiles

Aldrin

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

Aldrin
[CAS No. 309-00-2]

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

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Suggested Citation

NIOSH [2015]. NIOSH skin notation profile: Aldrin. By Hudson NL, Dotson GS. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2015-191

DHHS (NIOSH) Publication No. 2015-191

July 2015

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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 aldrin. 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	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 Classification and Labelling 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
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
µg	microgram(s)
µg/cm^2	microgram(s) per square centimeter
µg/cm^2/hr	microgram(s) per square centimeter per hour
µL	microliter(s)
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 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.

Acknowledgments

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

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

Denver Field Office
Eric Esswein, M.Sc.

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

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

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

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

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

National Personal Protection Technology Laboratory
Heinz Ahlers, M.Sc.
Angie Shephard

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

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

Barbara Landreth, M.A.

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

Phil Bigelow, B.Sc., M.H.Sc., Ph.D., University of Waterloo, School of Public Health and Health Systems, Waterloo, ON, Canada

John Herbold, DVM, PhD, MPH., San Antonio, TX

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

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

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

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

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

1 Introduction

1.1 General Substance Information

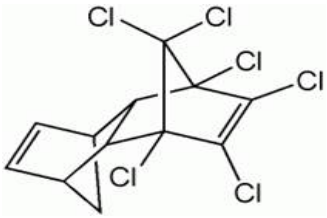
Chemical: Aldrin

CAS No: 309-00-2

Molecular weight (*MW*): 364.9

Molecular formula: $C_{12}H_8C_{16}$

Structural formula:



Synonyms:
1,2,3,4,10,10-Hexachloro-1,4,4a,5,8,8a-hexahydro-endo-1,4-exo-5,8-dimethanonaphthalene; HHDN; Octalene

Uses:
Aldrin is an organochlorine pesticide; approximately 11 million pounds (4.8 million kilograms) of aldrin were used in 1970 [ATSDR 2002]. Due to concerns about carcinogenicity, bioaccumulation, hazards to wildlife and the chronic effects of aldrin, all products containing aldrin were cancelled [US EPA 1990]. Currently there is no use for aldrin in the US.

1.2 Purpose

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

1.3 Overview of SK Assignment

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

Table 1. Summary of the SK assignment for adrin

Skin notation	Critical effect	Available data
SK: SYS (FATAL)	Central nervous system effects; acute toxicity	Limited human and sufficient animal data

2 Systemic Toxicity from Skin Exposure (SK: SYS)

A limited number of toxicokinetic studies were identified in humans and animals following dermal exposure to aldrin. In one study, Feldmann and Maibach [1974] reported dermal absorption of 7.8% of the applied aldrin dose (based on total urinary excretion over a 5-day period) in six human volunteers that received a single dermal application of 0.004 milligrams per square centimeter (mg/cm^2) of aldrin to the unprotected forearm for 24 hours. The potential of aldrin 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 0.0019 was calculated for aldrin. An SI ratio of ≥0.1 indicates that a chemical is capable of producing systemic toxicity from skin exposure [NIOSH 2009]; therefore, aldrin 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.

While no dermal lethal concentration (LD_{Lo}) for humans has been identified, the reported dermal LD_{50} values (the dose resulting in 50% mortality in the exposed animals) have ranged from 98 to 274 milligrams per kilogram of bodyweight (mg/kg) [Gaines 1960] in rats, and 15 to 150 mg/kg in rabbits [Lehman 1952; Johnston and Eden 1953], depending on the vehicle used. Symptoms following exposure to Aldrin in rabbits included loss of appetite, nervousness, and convulsions [Lehman 1952; Johnston and Eden 1953]. Because the majority of reported acute dermal LD_{50} values for all species are lower than the critical dermal LD_{50} value of 200 mg/kg that identifies chemical substances with the potential for acute dermal toxicity [NIOSH 2009], aldrin is considered acutely fatal following dermal exposure.

Although many occupational studies of workers employed in either the manufacture or application of aldrin and dieldrin—a metabolite of aldrin—reported central nervous system effects as the principal toxic effect [Kazantzis et al. 1964; Hoogendam et al. 1965; de Jong 1991], including convuslions and ataxia [Kazantzis et al. 1964]. Exposures involved both inhalation and dermal exposure; however, the contribution from dermal exposure to these effects was not quantified.

Human epidemiological studies [de Jong et al. 1991; Amoateng-Adjepong et al. 1995; de Jong et al. 1997] conducted in two aldrin and dieldrin manufacturing plants determined an observed increase in hepatobiliary cancer incidence was not due to occupational exposure, and that an observed significant increase in mortality from rectal cancer did not demonstrate a dose-response relationship. As is the case with many occupational studies, the dermal contribution to the total exposure was not quantified.

No repeat-dose, subchronic, or chronic dermal toxicity studies in animals were available for evaluation. No standard toxicity or specialty studies that evaluated biological system/function specific effects (including reproductive and developmental effects and immunotoxicity) following dermal exposure to aldrin were identified.

No studies were identified that evaluated the potential of aldrin to be carcinogenic in animals following dermal exposure. Table 2 summarizes carcinogenic designations of multiple governmental and nongovernmental organizations for aldrin.

Although dermal absorption data of aldrin in humans are limited and the predictive mathematical model (see Appendix) did not indicate that the chemical can be absorbed through the skin, acute toxicity studies report

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

Organization	Carcinogenic designation
NIOSH [2005]	Carcinogen
NTP [2014]	No designation
US EPA [2014]	B2: probable human carcinogen
European Parliament [2008]	GHS Carcinogenicity Category 2: suspected of causing cancer
IARC [2012]	Group 3: not classifiable as to carcinogenicity to humans
EC [2014]†	R40: limited evidence of carcinogenic effect
ACGIH [2007]	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 rather than dermal exposure.
†Date accessed.

LD_{50} values generally less than 200 mg/kg [**Lehman 1952; Johnston and Eden 1953; Gaines 1960**].* Potential central nervous system effects from exposure to aldrin were reported in the acute toxicity studies and human epidemiological studies [**de Jong et al. 1991; Amoateng-Adjepong et al. 1995; de Jong et al. 1997**]. However, the epidemiological studies likely involved both inhalation and dermal routes of exposure. Therefore, on the basis of the data for this assessment, aldrin is assigned the SK: SYS (FATAL) notation.

3 Direct Effects on Skin (SK:DIR)

No human or animal *in vivo* studies for corrosivity of aldrin or *in vitro* tests for corrosivity using human or animal skin models or *in vitro* tests of skin integrity using cadaver skin were identified. Occupational studies involving workers employed for four or more years in the manufacture of aldrin reported minor erythema [Jager 1970]. The structure-activity relationship model, Deductive Estimation of Risk from Existing Knowledge (DEREK) for Windows, predicted aldrin to be negative for skin irritation. The limited data describing the direct skin effects of dermal exposure to aldrin precludes adequate evaluation of the corrosivity or irritancy potential of the substance. Therefore, on the basis of the data for this assessment, aldrin is not assigned the SK: DIR (IRR) notation.

4 Immune-mediated Responses (SK: SEN)

A limited number of studies were identified that evaluated the potential of aldrin to cause skin sensitization in both humans and animals. Jager [1970] found no cases of skin sensitization over a period of 20 years in a group of over 1000 workers involved in the manufacture and formulation of aldrin and dieldrin. The structure activity relationship model, *DEREK* for Windows, predicted aldrin to be positive for skin sensitization. However, the positive results of the predictive model are insufficient to demonstrate the skin sensitization potential

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

of aldrin. The lack of data precludes an adequate evaluation of the sensitization potential of the chemical. Therefore, on the basis of the data for this assessment, aldrin is not assigned the SK: SEN notation.

5 Summary

Although dermal absorption data of aldrin in humans are limited and the predictive mathematical model (see Appendix) did not indicate that the chemical can be absorbed through the skin, acute toxicity studies report LD_{50} values generally less than 200 mg/kg **[Lehman 1952; Johnston and Eden 1953; Gaines 1960]**. Potential central nervous system effects from exposure to aldrin were reported in the acute toxicity studies and human epidemiological studies [**de Jong et al. 1991; Amoateng-Adjepong et al. 1995; de Jong et al. 1997**]. However, the epidemiological studies likely involved both inhalation and dermal routes of exposure. Insufficient human data and conflicting animal data preclude adequate assessment of skin irritation or sensitization potential of aldrin. Therefore, on the basis of these assessments, aldrin is assigned a composite skin notation of **SK: SYS (FATAL)**.

Table 3 summarizes the skin hazard designations for aldrin previously issued by NIOSH and other organizations. The equivalent dermal designations for aldrin, according to the Global Harmonization System (GHS) of Classification and Labelling of Chemicals, are Acute Toxicity Category 3 (Hazard statement: Toxic in contact with the skin) [European Parliament 2008].

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Table 3. Summary of previous skin hazard designations for aldrin

Organization	Skin hazard designation
NIOSH [2005]	[skin]: potential for dermal absorption
OSHA [2015]*	[skin]: potential for dermal absorption
ACGIH [2007]	[skin]: based on absorption and deposition of aldrin in subcutaneous fat and toxic effects in the liver and kidneys of animals following topical application
EC [2014]*	R24: toxic in contact with skin
	R48: toxic: danger of serious damage to health by prolonged exposure 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.
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Appendix: Calculation of the SI Ratio

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for aldrin. 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.
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 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 aldrin. The calculated SI ratio was 0.0019. On the basis of these results, aldrin is not predicted to represent a skin absorption hazard.

Appendix References

NIOSH [2005]. NIOSH pocket guide to chemical hazards. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2005–149, http://www.cdc.gov/niosh/npg/. Accessed: 02-10-15.

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

Variables used in calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path(k_{psc})	cm/hr	0.168
Permeation coefficient of the protein fraction of the stratum corneum (k_{pol})	cm/hr	7.952×10^{-6}
Permeation coefficient of the watery epidermal layer (k_{aq})	cm/hr	0.1309
Molecular weight (MW)*	amu	364.9
Base-10 logarithm of its octanol–water partition coefficient (Log K_{ow})*	None	6.5
Calculated skin permeation coefficient (k_p)	cm/hr	0.0736
Skin dose		
Water solubility (S_w)*	mg/cm^3	1.7×10^{-5}
Calculated skin permeation coefficient (k_p)	cm/hr	0.0736
Estimated skin surface area (palms of hand)	cm^2	360
Exposure time	hr	8
Calculated skin dose	mg	0.0036
Inhalation Dose		
Occupational exposure limit (OEL)†	mg/m^3	0.25
Inhalation volume	m^3	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	1.875
Skin dose–to–inhalation dose (SI) ratio	None	0.0019

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

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DHHS (NIOSH) Publication No. 2015–191

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