Skin Notation (SK) Profile

Captafol

[CAS No. 2425-06-1]

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 captafol. 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/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
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.

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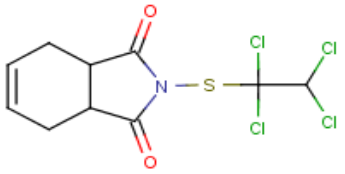
1.0 Introduction

1.1 General Substance Information:

Chemical: Captafol
CAS No: 2425-06-1
Molecular weight (*MW*): 349.1
Molecular formula: $C_{10}H_9Cl_4NO_2S$
Structural formula:



Synonyms: Captofol; N-(1,1,2,2-Tetrachloroethyl)thio)-4-cyclohexene-1,2-dicarboximide; Difolatan

Uses: Captafol has historically been used as a broad spectrum fungicide.

1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with captafol and (2) the rationale behind the hazard-specific skin notation (SK) assignment for captafol. 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 captafol. A literature search was conducted through October 2012 to identify information on captafol, 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 captafol.

1.3 Overview of SK Assignment

Captafol 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 captafol: **SK: DIR (IRR)-SEN**. Table 1 provides an overview of the critical effects and data used to develop the SK assignment for captafol.

Table 1. Summary of the SK Assignment for captafol

Skin Notation	Critical Effect	Available Data
SK: DIR (IRR)	Skin irritation	Sufficient human data
SK: SEN	Skin allergy	Sufficient human and limited animal data

2.0 Systemic Toxicity from Skin Exposure (SK: SYS)

Toxicokinetic studies following dermal exposure to captafol were not identified. The potential of captafol 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 0.024 was calculated for captafol. An SI ratio of ≥0.1 indicates that skin absorption may significantly contribute to the overall body burden of a substance [NIOSH 2009]; therefore, captafol 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 dermal lethal doses (LD_{Lo}s) of captafol for humans or dermal LD_{50} values (the dose resulting in 50% mortality in the exposed animals) in animals have been identified. Lack of these data precludes adequate evaluation of the acute systemic toxicity of dermal exposure to captafol. No case reports or epidemiological studies in humans or repeat-dose, sub-chronic, or chronic studies in animals following dermal exposure were identified. No standard toxicity or specialty studies evaluating biological system/function specific effects (including reproductive and developmental effects and immunotoxicity) following dermal exposure to captafol were identified. Table 2 summarizes carcinogenic designations of multiple governmental and nongovernmental organizations for captafol.

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

Organization	Carcinogenic designation
NIOSH [2005]	Potential occupational carcinogen
NTP [2011]	Reasonably anticipated to be a human carcinogen
USEPA [1987]	No designation
GHS [European Parliament 2008]	Carcinogenicity Category 1B: May cause cancer
IARC [2012]	Group 2A: Probably carcinogenic to humans
EC [2012]*	R45: May cause cancer

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.

Taken together, the limited data are insufficient to demonstrate that captafol has the potential to be absorbed through the skin and to be systemically available and toxic. Therefore, on the basis of the data for this assessment, captafol is not assigned SK: SYS notation.

3.0 Direct Effects on Skin (SK: DIR)

No human or animal *in vivo* studies for corrosivity of captafol or *in vitro* tests for corrosivity using human or animal skin models or *in vitro* tests of skin integrity using cadaver skin were identified. However, evidence of skin irritation is well-documented. Epidemiological studies and case reports showing skin effects in humans exposed to captafol have been identified. Matsushita et al. [1980] conducted an epidemiological study of 216 patients who experienced contact dermatitis following pesticide exposure, of which captafol was responsible for 28.7% of the cases. Lisi et al. [1987] observed irritant contact dermatitis in 3 of 389 agricultural, ex-agricultural, and non-agricultural subjects who were patch-tested with 0.1% captafol. A survey of 14 timber treatment plants conducted by Stoke [1979] found that 23% of 133 workers exposed to captafol experienced occupationally-induced irritant dermatitis. Several case reports were reported by Peoples et al. [1978] from 1974-1976 that demonstrated contact dermatitis upon exposure to captafol.

No studies that evaluated skin irritation potential of captafol were identified in animals. The structure-activity relationship model, Deductive Estimation of Risk from Existing Knowledge (*DEREK*) for Windows, predicted captafol to be negative for skin irritation.

Sufficient data from epidemiological studies **[Matsushita et al. 1980]**[1] and case reports of occupational exposure **[Peoples et al. 1978; Stoke 1979]** following dermal exposure to captafol demonstrate that captafol is a skin irritant in humans. Therefore, on the basis of the data for this assessment, captafol is assigned the SK: DIR (IRR) notation.

4.0 Immune-mediated Responses (SK: SEN)

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

There are sufficient data available to confirm the sensitization potential of captafol. Lisi et al. [1986, 1987] observed allergic contact dermatitis in agricultural and non-agricultural workers. These investigators [Lisi et al. 1987] observed allergic reactions in 5 out of 389 agricultural, ex-agricultural, and non-agricultural subjects) who were patch-tested with 1% captafol and in 3 out of 279 agricultural and non-agricultural subjects who were patch tested with 0.05% captafol concentration. In an earlier study, Lisi et al. [1986] found allergic reactions in 2 out of 50 agricultural, 1 out of 24 ex-agricultural (had worked on land in the past), and 1 out of 126 non-agricultural subjects who were patch-tested with 0.1% captafol. Brown [1984] reported positive results from two persons in the same laboratory who had previously developed irritation and rash following exposure to captofol. One individual was patch tested using technical captafol and a captafol suspension, and the second individual was patch tested using the International Contact Dermatitis Research Group (ICDRG)-recommended Standard Series [Brown 1984]. Mark et al. [1999] reported a positive reaction to captafol in 1 of 12 patients that had positive reactions to patch tests. Rademaker [1998] identified 2 of 46 farmers who experienced dermatitis and had positive patch tests for captafol. Other studies that reported allergic contact dermatitis or skin sensitization following dermal exposure to captafol included Camarasa [1975], Peluso et al. [1991], and Guo et al. [1996]. Cushman and Street [1991] evaluated the ability of captafol to elicit contact hypersensitivity using the mouse ear swelling test (MEST), and demonstrated that captafol induced contact hypersensitivity in the MEST. The structure activity relationship model, *DEREK* for Windows, predicted captafol to be positive for skin sensitization.

The sensitization potential of captafol has been sufficiently demonstrated in human and animals. Human patch tests **[Camarasa 1975; Brown 1984; Lisi et al. 1986, 1987; Peluso et al. 1991; Rademaker 1998; Guo et al. 1996; Mark et al. 1999]** and mouse ear swelling tests **[Cushman and Street 1991]** produced positive skin sensitization responses. Therefore, on the basis of the data for this assessment, captafol is assigned the SK: SEN notation.

5.0 Summary

Taken together, data available are insufficient to demonstrate that captafol has the potential to be absorbed through the skin and to be systemically available and toxic. Although no studies were identified to evaluate the corrosive potential of captafol, Sufficient data from epidemiological studies **[Matsushita et al. 1980]**, and case reports of occupational exposure **[Peoples et al. 1978; Stoke 1979]** demonstrate that captafol is a skin irritant in humans. Based on positive skin sensitization responses, there is sufficient evidence from human patch tests **[Camarasa 1975; Brown 1984; Lisi et al. 1986, 1987; Peluso et al. 1991; Rademaker 1998; Guo et al. 1996; Mark et al. 1999]** and the mouse ear swelling tests **[Cushman and Street 1991]** to conclude that captafol is a potential skin sensitizer. Therefore, on the basis of these assessments, captafol is assigned a composite skin notation of **SK: DIR (IRR)-SEN**.

Table 3 summarizes the skin hazard designations for captafol previously issued by NIOSH and other organizations. The equivalent dermal designation for captafol, according to the Global Harmonization System (GHS) of Classification and Labelling of Chemicals, is Skin Sensitization Category 1 (Hazard statement: May cause an allergic skin reaction) [European Parliament 2008].

Table 3. Summary of previous skin hazard designations for captafol

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption; prevent skin contact
OSHA [2012]*	None assigned
ACGIH [2001]	[skin]: Potential for dermal absorption
EC [2012]*	R43: May cause sensitization by skin contact

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 Captafol

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for captafol. 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 captafol. The calculated SI ratio was 0.024. On the basis of these results, captafol is predicted to represent a skin absorption hazard.

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

Variables Used in Calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path(k_{psc})	cm/hr	0.0045
Permeation coefficient of the protein fraction of the stratum corneum (k_{pol})	cm/hr	8.1303×10^{-6}
Permeation coefficient of the watery epidermal layer (k_{aq})	cm/hr	0.1338
Molecular weight (MW)[a]	amu	349.1
Base-10 logarithm of its octanol–water partition coefficient (Log K_{ow})[a]	None	3.8
Calculated skin permeation coefficient (k_p)	cm/hr	0.0044
Skin dose		
Water solubility (S_w)[a]	mg/cm^3	0.0014
Calculated skin permeation coefficient (k_p)	cm/hr	0.0044
Estimated skin surface area (palms of hand)	cm^2	360
Exposure time	hr	8
Calculated skin dose	mg	0.0176
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	0.0235

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

Appendix References

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