

NIOSH Skin Notation Profile

Catechol

SKK

ID^{SK}

[SK]

SYS

SYS (FATAL)

DIR

DIR (IRR)

DIR (COR)

SEN



Centers for Disease Control
and Prevention
National Institute for Occupational
Safety and Health

This page intentionally left blank.

NIOSH Skin Notation Profile

Catechol

Naomi L. Hudson

This document is in the public domain and may be freely copied or reprinted.

Disclaimer

Mention of any company or product does not constitute endorsement by the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention (CDC). In addition, citations of websites external to NIOSH do not constitute NIOSH endorsement of the sponsoring organizations or their programs or products. Furthermore, NIOSH is not responsible for the content of these websites.

Get More Information

Find NIOSH products and get answers to workplace safety and health questions:

1-800-CDC-INFO (1-800-232-4636) | TTY: 1-888-232-6348

CDC/NIOSH INFO: cdc.gov/info | cdc.gov/niosh

Monthly *NIOSH eNews*: cdc.gov/niosh/eNews

Suggested Citation

NIOSH [2019]. NIOSH skin notation profile: catechol. By Hudson NL. 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. 2019-118, <https://doi.org/10.26616/NIOSH PUB2019118>.

DHHS (NIOSH) Publication No. 2019-118

DOI: <https://doi.org/10.26616/NIOSH PUB2019118>

January 2019

Foreword

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

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

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

This *Skin Notation Profile* provides the SK assignments and supportive data for catechol. 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.

John Howard, M.D.
Director
National Institute for Occupational Safety and Health
Centers for Disease Control and Prevention

This page intentionally left blank.

Contents

Foreword.	iii
Abbreviations.	vi
Glossary	viii
Acknowledgments.	ix
1 Introduction	1
1.1 General Substance Information	1
1.2 Purpose	1
1.3 Overview of SK Assignment.	1
2 Systemic Toxicity from Skin Exposure (SK: SYS)	2
3 Direct Effects on Skin (SK: DIR)	3
4 Immune-mediated Responses (SK: SEN)	4
5 Summary	4
References.	5
Appendix: Calculation of the SI Ratio for Catechol	7
Overview	7
Calculation	8
Appendix References	8

Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
amu	atomic mass unit
ATSDR	Agency for Toxic Substances and Disease Registry
BaP	benzo[a]pyrene
BaP-7,8-diol	7,8-dihydroxy-7,8-dihydrobenzo[a]pyrene
CIB	Current Intelligence Bulletin
cm²	square centimeter(s)
cm/hr	centimeter(s) per hour
cm/s	centimeter(s) per second
COR	subnotation of SK: COR indicating the potential for a chemical to be a skin corrosive following exposure to the skin
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
FATAL	subnotation of SK: SYS indicating the potential for the chemical to be fatal following dermal absorption
GHS	Globally Harmonized System for Classification and Labelling of Chemicals
GPMT	guinea pig maximization test
hr	hour(s)
ID^{SK}	skin notation indicating insufficient data on the health hazards associated with skin exposure
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
LD₅₀	lethal dose resulting in 50% mortality in the exposed population
LD_{Lo}	lowest detected 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
m³	cubic meter(s)
mg	milligram(s)
mg/cm²	milligram(s) per square centimeter
mg/kg	milligram(s) per kilogram body weight

mg/m³	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
SK	skin notation indicating that the reviewed data did not identify a health risk associated with skin exposure
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/cm²/hr	microgram(s) per square centimeter per hour

Glossary

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

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

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

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

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

Dermal—Referring to the skin.

Dermal contact—Contact with (touching) the skin.

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

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

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

Substance—A chemical.

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

Acknowledgments

This document was developed by the Education and Information Division (Paul Schulte, Ph.D., Director). Naomi Hudson, Dr.P.H., was the project officer for this document, assisted in great part by G. Scott Dotson, Ph.D., Stacey Anderson, Ph.D., and Loren Tapp, M.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, the following NIOSH personnel are specially acknowledged:

Western States Division

Eric Esswein, M.Sc.

Division of Applied Research and Technology

Clayton B'Hymer, Ph.D.

John Snawder, Ph.D.

Respiratory Health Division

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 W. Niemeier, Ph.D.

Ralph Zumwalde, M.Sc.

Health Effects Laboratory Division

H. Fredrick Frasch, Ph.D.

Michael Luster, Ph.D.

Anna Shvedova, Ph.D.

Paul Siegel, Ph.D.

Berran Yucesoy, Ph.D.

National Personal Protective Technology Laboratory

Heinz Ahlers, J.D., M.Sc.

Angie Shepherd

For their contribution to the technical content and review of this document, the following CDC personnel are specially acknowledged:

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

Barbara Landreth, M.A.

Special appreciation is expressed to the following individuals for serving as independent, external peer reviewers:

William E. Luttrell, Ph.D., Fellow, American Industrial Hygiene Association; Diplomat, American Academy of Industrial Hygiene, Associate Professor and Chair, Department of Chemistry and Physics, Eastern Virginia Medical School and Old Dominion University, Norfolk, VA

Carrie Redlich, MD, Ph.D., Director, Occupational and Environmental Medicine Program, School of Public Health, Yale University, New Haven, CT

Sean Semple, Ph.D., Senior Lecturer, Scottish Centre for Indoor Air, Division of Applied Health Sciences, University of Aberdeen, Aberdeen, Scotland

The following individuals contributed to the development or improvement of the skin notation profiles:

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

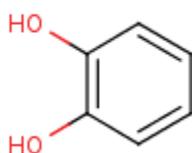
Chemical: Catechol

CAS No: 120-80-9

Molecular weight (MW): 110.1

Molecular formula: C₆H₄(OH)₂

Structural formula:



Synonyms: 1,2-Benzenediol; o-Benzenediol; 1,2-Dihydroxybenzene; Pyrocatechol; Pyrocatechin; o-Dihydroxybenzene; 2-Hydroxyphenol

Uses: Catechol is used primarily as an antioxidant in rubber, dye fat, and oil industries and is used in pesticides, pharmaceutical ingredients, and aroma chemicals [ACGIH 2001].

1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with catechol and (2) the rationale behind the hazard-specific skin notation (SK) assignment for catechol. The SK assignment is based on the scientific rationale and logic outlined in the *Current Intelligence Bulletin 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 catechol and the potential for direct skin injuries from catechol. A literature search was conducted through February 2018 to identify catechol 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 catechol. The criteria for the search strategy, evaluation, and selection of data are described in Appendix E in the *Current Intelligence Bulletin 61: A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009].

1.3 Overview of SK Assignment

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

Table 1. Summary of the SK assignment for catechol

Skin notation	Critical effect	Available data
SK: SYS	Acute toxicity	Limited animal data
SK: DIR(IRR)	Skin irritancy; skin depigmentation	Sufficient animal data
SK: SEN	Skin allergy	Limited human data

2 Systemic Toxicity from Skin Exposure (SK: SYS)

No *in vivo* toxicokinetic studies of humans or animals that evaluated the degree of skin absorption of catechol from dermal exposure were identified. Rhodia Incorporated [2005] investigated the *in vitro* percutaneous penetration of [¹⁴C]-labeled catechol through human skin membranes. When an aqueous solution was applied at a concentration of 1 milligram per cubic centimeter (mg/cm³), corresponding to an area concentration of 0.1 mg/cm³, the author reported that 0.04% and 0.22% of the applied dose penetrated through the skin membrane within 10 and 60 minutes, respectively [Rhodia Incorporated 2005]. Within 24 hours, 26.65% of the applied dose penetrated through the membrane [Rhodia Incorporated 2005]. Rhodia Incorporated [2005] also reported a penetration rate of 1.425 micrograms per square centimeter per hour (µg/cm²/hr) after a lag time of 6 hours. In that study, the permeability constant, k_p , was reported as 1.430×10^{-3} cm/hr [Rhodia Incorporated 2005]. This k_p is greater than the value of 0.001 cm/hr that identifies a chemical as readily absorbed by the skin [NIOSH 2009]; therefore, catechol is considered to be absorbed through the skin via dermal exposure. The potential of catechol 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 242.20 was calculated for catechol. An SI ratio of ≥ 0.1 indicates that skin absorption may significantly contribute to the overall body burden of a substance [NIOSH 2009]; therefore, catechol is considered to be a skin absorption hazard 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}) of catechol has been reported in the literature. A dermal LD₅₀ (the dose resulting in 50% mortality in the exposed population) value of 800 milligrams per kilogram body weight (mg/kg) in rabbits was reported [Flickinger 1976]. Because the reported acute dermal LD₅₀ value is lower than the critical dermal LD₅₀ value of 2,000 mg/kg that identifies chemicals with the potential for acute dermal toxicity [NIOSH 2009], catechol is considered acutely toxic following dermal exposure.

No epidemiological or occupational exposure studies of humans and no repeated-dose, subchronic, or chronic exposure studies in animals have evaluated the potential of catechol to cause systemic effects following dermal exposure. In addition, no standard toxicity or specialty studies evaluating biological system/function-specific effects (including reproductive and developmental effects and immunotoxicity) following dermal exposure to catechol were identified in the literature.

No epidemiological studies or standard animal bioassays have evaluated the carcinogenic potential of catechol. In two-stage carcinogenicity studies in mice, topically applied catechol did not exhibit tumor-promoting activity with benzo[a]pyrene (BaP) as an initiator [Van Duuren and Goldschmidt 1976], but co-application of the substance with the racemic mixture or either of the enantiomers of 7,8-dihydroxy-7,8-dihydrobenzo[a]pyrene (BaP-7,8-diol) increased the tumor-initiating activity of racemic BaP-7,8-diol [Melikian et al. 1989]. However, it had no statistically significant effect on the tumor-initiating activity of the (+)- or (-)-enantiomers in mouse skin [Melikian et al. 1989]. Catechol was a potent co-carcinogen when tested for co-carcinogenic activity by dermal application at doses of 0.01 to 2 mg to mouse skin three times per week with a low dose of BaP (3 µg) for 48 to 59 weeks [Van Duuren and Goldschmidt 1976; Hecht et al. 1982; Melikian et al. 1989] or with racemic and enantiomeric BaP-7,8-diols for

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

Organization	Carcinogenic designation
NIOSH [2005]	No designation
NTP [2014]	No designation
US EPA [2015]	No designation
European Parliament [2008]	No GHS designation
IARC [2012]	Group 2B: Possibly carcinogenic to humans
ACGIH [2001]	Group A3: Confirmed animal carcinogen of unknown relevance to humans

ACGIH = American Conference of Governmental Industrial Hygienists; 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; US EPA = 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.

48 weeks [Melikian et al. 1989]. Co-carcinogenesis is a process in which a co-carcinogen, applied repeatedly (in this case, on mouse skin) with low doses of a known carcinogen such as benzo[a]pyrene (BaP), enhances considerably the carcinogenic activity of the carcinogen [Van Duuren and Goldschmidt 1976]. Although these studies indicate a co-carcinogenic effect of catechol, the lack of data precludes adequate evaluation of the underlying mode of action or of whether catechol itself has carcinogenic potential following skin contact. Table 2 summarizes carcinogenic designations for catechol by multiple governmental and nongovernmental organizations.

Although no *in vivo* toxicokinetic data have been reported reflecting the degree of skin absorption following dermal exposure, an *in vitro* study [Rhodia Incorporated 2005], supported by a model prediction and acute toxicity data from rabbits [**Flickinger 1976**]*, indicate that catechol has the potential to be absorbed through the skin and can cause acute toxicity following dermal exposure. No epidemiological or case studies of humans and no repeated-dose, subchronic, or chronic exposure studies or specialty studies of animals have investigated the potential of catechol to

cause systemic effects following dermal exposure. Therefore, on the basis of this assessment, catechol is assigned the SK:SYS notation.

3 Direct Effects on Skin (SK: DIR)

No data from human or animal *in vivo* testing of the skin corrosivity of catechol, from *in vitro* tests for corrosivity in human or animal skin models, or from *in vitro* tests for skin integrity in cadaver skin were found in the literature. O'Malley et al. [1988] reported the finding of vitiligo (an acquired skin disease characterized by patches of unpigmented skin, often surrounded by a heavily pigmented border) in five of 200 workers who handled catecholic substances on a regular basis; however, the authors did not find any evidence of para-substituted phenolic or catecholic derivatives in the rubber formulations and adhesive sprays, indicating that another substance caused the occupational cases of vitiligo. Gellin et al. [1979] noted moderate depigmentation following application of 5% and 10% catechol to the clipped dorsal skin of guinea pigs. These authors also noted primary skin irritation following application of catechol [Gellin et al. 1979]. Bleehen et al. [1968]

*References in **bold** text indicate studies that served as the basis of the SK assignment.

applied 1% to 10% catechol in creams once daily, five times a week, to wax-epilated skin of the back and the unepilated skin of the ear of black guinea pigs for up to 1 month. Catechol did not depigment or irritate rabbit skin at a concentration of 1.0%, but at 3.0% it induced depigmentation, and very strong depigmentation was induced at 7% to 10%. Flickinger [1976] reported moderate erythema and slight edema on intact skin and necrosis on abraded skin of rabbits after exposure to 500 mg/kg of catechol on the abdomen.

Sufficient data in animals [Bleehen et al. 1968; Flickinger 1976; Gellin et al. 1979] are available to indicate that repeated application of catechol is irritating to the skin and generates skin depigmentation. Therefore, the notation SK: DIR(IRR) is assigned to catechol.

4 Immune-mediated Responses (SK: SEN)

A limited number of diagnostic patch tests have investigated the skin sensitization potential of catechol in humans. Morelli et al. [1989] described a patient occupationally exposed to catechol as a radiographer, who presented with contact dermatitis of the hands. Patch tests showed strong positive reactions to 0.1%, 0.5%, and 2% catechol [Morelli et al. 1989]. In a nonoccupational exposure case, a patient presented with acute contact dermatitis around the eyes from treatment of the eyelashes and eyebrows with a permanent dye cream and had positive reactions when patch-tested with 0.1% to 2% catechol [Andersen and Carlsen 1988]. Keil [1962] reported that persons sensitive to resorcinol have mild cross-reactions to catechol. No predictive tests in animals (for example, guinea pig maximization tests, murine local lymph node assays, or mouse ear swelling tests) or any other studies have evaluated the potential of the substance to cause skin sensitization.

A limited number of patch tests [Keil 1962; Andersen and Carlsen 1988; Morelli et al. 1989] have indicated the potential of

catechol to cause skin sensitization in humans. Although no predictive tests in animals have been reported, the notation SK: SEN is assigned to catechol on the basis of the limited number of human cases identified.

5 Summary

No *in vivo* toxicokinetic data have been reported on the degree of skin absorption of catechol via dermal exposure. However, the findings of an *in vitro* study [Rhodia Incorporated 2005], supported by a model prediction and acute toxicity data in rabbits [Flickinger 1976], indicate catechol has the potential to be absorbed through the skin and can cause acute toxicity following dermal exposure. No epidemiological or case studies of humans or repeated-dose, subchronic, or chronic exposure studies or specialty studies of animals have investigated the potential of catechol to cause systemic effects via dermal exposure. Sufficient data are available in animals [Bleehen et al. 1968; Flickinger 1976; Gellin et al. 1979] to indicate that catechol has the potential to irritate and depigment the skin following repeated contact. No predictive tests have investigated the potential of catechol to cause skin sensitization in animals, but a limited number of case reports [Keil 1962; Andersen and Carlsen 1988; Morelli et al. 1989] have indicated that catechol has the potential to cause skin sensitization. On the basis of the available information, a composite skin notation of SK: SYS-DIR(IRR)-SEN is assigned to catechol.

Table 3 summarizes the skin hazard designations for catechol previously issued by NIOSH and other organizations. The equivalent dermal designations for catechol, according to the Globally Harmonized System (GHS) of Classification and Labelling of Chemicals, are Acute Toxicity Category 4 (Hazard statement: Harmful in contact with the skin), and Skin Irritation Category 2 (Hazard statement: Causes skin irritation) [European Parliament 2008].

Table 3. Summary of the previously issued skin hazard designations for catechol

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption; prevent skin contact
OSHA [2018]*	None
ACGIH [2001]	[skin]: Based on dermal studies of mice and data on dermally exposed workers with symptoms of illness resembling those associated with phenol as well as central nervous system effects

ACGIH = American Conference of Governmental Industrial Hygienists; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration.

*Year accessed

References

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

- *ACGIH (American Conference of Governmental Industrial Hygienists) [2001]. TLVs and BEIs based on the documentation of threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental and Industrial Hygienists.
- *Andersen KE, Carlsen L [1988]. Pyrocatechol contact allergy from a permanent cream dye for eyelashes and eyebrows. *Contact Dermatitis* 18(5):306–307.
- †Baer H, Dawson CR, Byck JS, Kurtz AP [1970]. The immunochemistry of immune tolerance: II. The relationship of chemical structure to the induction of immune tolerance to catechols. *J Immunol* 104(1):178–184.
- *Bleehen SS, Pathak MA, Hori Y, Fitzpatrick TB [1968]. Depigmentation of skin with 4-isopropylcatechol mercaptoamines, and other compounds. *J Invest Dermatol* 50(2):103–117.
- †Elder R [1986]. Final report on the safety assessment of hydroquinone and pyrocatechol. *J Am Coll Toxicol* 15:123–165.
- *ECHA (European Chemicals Agency) [ND]. EC (European Commission) Inventory. <https://echa.europa.eu/information-on-chemicals/ec-inventory>. Accessed: 09-03-13.
- *European Parliament, Council of the European Union [2008]. Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labeling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJEU, Off J Eur Union L353:1–1355, <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:353:0001:1355:EN:PDF>.
- *Flickinger CW [1976]. The benzenediols: catechol, resorcinol and hydroquinone. A review of the industrial toxicology and current industrial exposure limits. *Am Ind Hyg Assoc J* 37:596–607.
- †Forsyth WGC, Quesnel VA [1957]. Intermediated in the enzymic oxidation of catechol. *Biochem Biophys Acta* 25:155–160.
- *Gellin GA, Maibach HI, Misiaszek MH, Ring M [1979]. Detection of environmental depigmenting substances. *Contact Dermatitis* 5(4):201–213.
- †Gellin GA, Maibach HI [1983]. Detection of environmental depigmenting chemicals. In: Marzulli FN, Maibach HI, eds. *Dermatotoxicology*. 2nd ed. New York, NY: Hemisphere Publishing, pp. 443–459.
- *Hecht SS, Carmella S, Furuya K, LaVoie EJ [1982]. Polynuclear aromatic hydrocarbons and catechol derivatives as potential factors in digestive tract carcinogenesis. In: *Environmental mutagens and carcinogens. Proceedings of the 3rd International Conference on Environmental Mutagens*. Tokyo: Mishima and Kyoto, pp. 545–556.
- †Hirosawa I, Asaeda G, Arizono H, et al. [1976]. Effects of catechol on human subjects: a field study. *Int Arch Occup Environ Health* 37:107–114.
- *IARC (International Agency for Research on Cancer) [2012]. Agents reviewed by the IARC monographs. In: *IARC monographs on the evaluation of carcinogenic risks to humans*, <http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php>.
- †Kavlock RJ [1990]. Structure-activity relationships in the developmental toxicity of substituted phenols: in vivo effects. *Teratology* 41(1):43–59.
- *Keil H [1962]. Group reactions in contact dermatitis due to resorcinol. *Arch Dermatol* 86:212–234.

- †Melikian AA, Leszczynska JM, Hecht SS, Hoffman D [1986]. Effects of the co-carcinogen catechol on benzo[a]pyrene metabolism and DNA adduct formation in mouse skin. *Carcinogenesis* 7(1):9–15.
- *Melikian AA, Jordan, KG, Braley J, Rigotty J, Meschter CL, Hecht SS, Hoffman D [1989]. Effects of catechol on the induction of tumors in mouse skin by 7,8-dihydroxy-7,8-dihydrobenzo[a]pyrenes. *Carcinogenesis* 10(10):1897–1900.
- †Melikian AA, Bagheri K, Goldin BF, Hoffman D [1989]. Catechol-induced alterations in metabolic activation and binding of enantiometric and racemic 7,8-dihydroxy-7,8-dihydrobenzo[a]pyrenes to DNA in mouse skin. *Carcinogenesis* 10(10):1863–1870.
- †Melikian AA, Bagheri K, Hoffman D [1990]. Oxidation and DNA binding of (+)-7,8-dihydroxy-7,8-dihydrobenzo(a)pyrene in mouse epidermis in vivo and effects of coadministration of catechol. *Cancer Res* 50:1795–1799.
- *Morelli R, Piancastelli E, Lanzarini M, Restani S [1989]. Occupational contact dermatitis from pyrocatechol. *Contact Dermatitis* 21:201–202.
- †Nakamura S [1981]. The effects of oral administration of catechol in mice. *Osaka-furitsu Koshu Eisei Kenkyusho Kenkyu Hokoku Rodo Eisei-Hen (Proceedings of the Osaka Prefectural Institute of Public Health, Edition of Industrial Health)* 19:33–37.
- *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/npgd0211.html>.
- *NIOSH [2009]. Current intelligence bulletin 61: a strategy for assigning new NIOSH skin notations. 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. 2009-147, <http://www.cdc.gov/niosh/docs/2009-147/pdfs/2009-147.pdf>.
- *NTP [2014]. Report on carcinogens. 13th ed. Research Triangle Park, NC: U.S. Department of Health and Human Services, National Institute for Environmental Health Sciences, National Toxicology Program, <https://ntp.niehs.nih.gov/pubhealth/roc/index.html>.
- *O'Malley MA, Mathias CGT, Priddy M, Molina D, Grote AA, Halperin WE [1988]. Occupational vitiligo due to unsuspected presence of phenolic antioxidant byproducts in commercial bulk rubber. *J Occup Med* 30(6):512–516.
- *Occupational Safety and Health Administration (OSHA) [2018]. Catechol. In: OSHA occupational chemical database, Washington, DC: U.S. Department of Labor, Occupational Safety and Health Administration. <https://www.osha.gov/chemicaldata/chemResult.html?recNo=160>.
- *US EPA (United States Environmental Protection Agency) [2015]. Integrated risk information system, <http://www.epa.gov/iris/>. Washington, DC: United States Environmental Protection Agency.
- *Rhodia Incorporated [2005]. [14C]Catechol: percutaneous penetration of [14C]catechol through human split-thickness skin membranes in vitro. Cranbury, NJ: Rhodia, Inc.
- *Van Duuren BL, Goldschmidt BM [1976]. Cocarcinogenic and tumor-promoting agents in tobacco carcinogenesis. *J Natl Cancer Inst* 56(6):1237–1242.
- †Van Duuren BL [1980]. Carcinogenicity of hair dye components. *J Environ Pathol Toxicol* 3:237–251.
- †Yonemoto K, Gellin GA, Epstein WL, Fukuyama K [1983]. Glutathione reductase activity in skin exposed to 4-tertiary butyl catechol. *Int Arch Occup Environ Health* 51:341–345.

Appendix: Calculation of the SI Ratio for Catechol

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for catechol. 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 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 [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

$$\begin{aligned} \log k_{psc} &= -1.326 + (0.6097 \times \log K_{OW}) - \\ &\quad (0.1786 \times MW^{0.5}) \\ k_{pol} &= 0.0001519 \times MW^{-0.5} \\ k_{aq} &= 2.5 \times MW^{-0.5} \end{aligned}$$

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

$$\begin{aligned} \text{Skin dose} &= k_p \times S_w \times \text{Exposed skin surface} \\ &\quad \text{area} \times \text{Exposure time} \\ &= k_p(\text{cm/hr}) \times S_w(\text{mg/cm}^3) \times 360 \\ &\quad \text{cm}^2 \times 8 \text{ hr} \end{aligned}$$

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

$$\begin{aligned} \text{Inhalation dose} &= \text{OEL} \times \text{Inhalation} \\ &\quad \text{volume} \times \text{RF} \\ &= \text{OEL}(\text{mg/m}^3) \times 10 \text{ m}^3 \times 0.75 \end{aligned}$$

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 catechol. The calculated SI ratio was 242.20. On the basis of these results, catechol is 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/>.
- NIOSH [2009]. Current intelligence bulletin 61: a strategy for assigning new NIOSH skin notations. 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. 2009-147, <http://www.cdc.gov/niosh/docs/2009-147/pdfs/2009-147.pdf>.
- SRC [2009]. Interactive PhysProp database demo, <http://esc.syrres.com/fatepointer/webprop.asp?CAS=120809>.

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

Variables used in calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path (k_{psc})	cm/hr	0.0309
Permeation coefficient of the protein fraction of the stratum corneum (k_{pol})	cm/hr	1.4477×10^{-5}
Permeation coefficient of the watery epidermal layer (k_{aq})	cm/hr	0.23826
Molecular weight (MW)*	amu	110.1
Base-10 logarithm of its octanol–water partition coefficient ($\text{Log } K_{ow}$)*	None	0.88
Calculated skin permeation coefficient (k_p)	cm/hr	0.027364
Skin dose		
Water solubility (S_w)*	mg/cm ³	461
Calculated skin permeation coefficient (k_p)	cm/hr	0.027364
Estimated skin surface area (palms of hand) [§]	cm ²	360
Exposure time	hr	8
Calculated skin dose	mg	36330
Inhalation Dose		
Occupational exposure limit (OEL) [†]	mg/m ³	20
Inhalation volume	m ³	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	150
Skin dose–to–inhalation dose (SI) ratio	None	242.20

*Variables identified from SRC [ND].

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

[§]Hayes WA [2008]. Principles and methods of toxicology. 5th ed. New York: Informa Healthcare USA.



Promoting productive workplaces through safety and health research

DHHS (NIOSH) Publication No. 2019-118

DOI: <https://doi.org/10.26616/NIOSH PUB2019118>