NIOSH Skin Notation Profiles

Phenol

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

NIOSH Skin Notation (SK) Profiles

Phenol

[CAS No: 108–95–2]

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 a substance's hazard potential, 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 assignment and supportive data for phenol (CAS No. 108–95–2). In particular, this document evaluates and summarizes the literature describing the substance's hazard potential 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 chemical 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
(COR)	subnotation of SK: DIR indicating the potential for a chemical to be corrosive following exposure of 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 chemicals are highly or extremel toxic and may be potentially lethal or life-threatening following exposure of the skin
g	gram(s)
g/L	gram(s)/liter
GHS	Globally Harmonized System of Classification and Labeling of Chemicals
IARC	International Agency for Research on Cancer
IPCS	International Program for Chemical Safety
K_{aq}	coefficient in the watery epidermal layer
K_p	skin permeation coefficient
K_{pol}	coefficient in the protein fraction of the stratum corneum
K_{psc}	permeation coefficient in the lipid fraction of the stratum corneum
LD_{50}	dose resulting in 50% mortality in the exposed population
LD_{Lo}	dermal lethal dose
LOAEL	lowest observed adverse effect level
log K_{OW}	base-10 logarithm of a substance's octanol–water partition coefficient
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 per kilogram body weight

MW	molecular weight
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no observed adverse effect level
NTP	National Toxicology Program
OEL	occupational exposure limit
OSHA	Occupational Safety and Health Administration
REL	recommended exposure limit
RF	retention factor
S_W	solubility
SYS	skin notation indicating the potential for systemic toxicity following exposure of the skin
USEPA	United States Environmental Protection Agency

Glossary

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

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

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

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

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

Dermal—Referring to the skin.

Dermal contact—Contact with (touching) the skin.

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

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

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

Substance—A chemical.

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

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1 Introduction

1.1 General Substance Information

Chemical: Phenol

CAS No.: 108–95–2

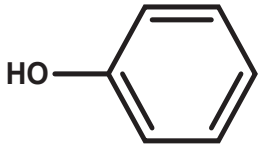
Synonyms:

Benzenol, Benzophenol, Carbolic acid, Hydroxybenzene, Monohydroxybenzene, Monophenol, Phenic acid, Phenylic acid, Phenylic alcohol, Phenyl hydroxide, Phenyl hydrate, Oxybenzene

Molecular weight (MW): 94.11

Molecular formula: C_6H_6O

Structural formula:



Use:

The Agency for Toxic Substances and Disease Registry (ATSDR) [2008] reported that the total annual production capacity of phenol in 2004 was 6.6 billion pounds (~3 billion kilograms). The substance is used primarily in the manufacturing of bisphenol-A (48%) and phenolic resins; secondary uses include medicinal applications.

1.2 Purpose

This *Skin Notation Profile* presents (1) a brief summary of technical data associated with skin contact with Phenol and (2) the rationale behind the hazard-specific skin notation (SK) assignment for Phenol. 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 Phenol. A literature search was conducted through July 2010 to identify information on Phenol, 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 Phenol.

1.3 Overview of SK Assignment for Phenol

Phenol is potentially capable of causing both systemic toxicity and direct adverse effects on the skin following dermal exposure. A critical review of available data indicates that contact of a significant area of skin with subjectively low concentrations of phenol (5–6%) may be extremely hazardous and life-threatening [ATSDR 2008]. Undiluted phenol or solutions containing more than 3% phenol are capable of causing skin corrosion, whereas diluted solutions (1 to 3% phenol) are irritating to the skin [European Parliament 2008]. NIOSH has designated phenol with the following SK assignment: **SK: SYS (FATAL)-DIR (COR)**. Table 1

Table 1. Summary of the SK assignment for phenol

Skin notation	Critical effect(s)	Available data
SK: SYS (FATAL)	Central nervous system (CNS) effects; respiratory depression; cardiovascular effects; severe (life-threatening) acute toxicity	Sufficient human data; sufficient animal data
SK: DIR (COR)	Skin corrosivity	Sufficient human data; sufficient animal data

provide an overview of the critical effects and data considered in the development of this SK assignment. The following section provides additional detail about the potential health hazards of skin contact with phenol and the rationale behind the SK assignment.

2 Systemic Toxicity from Skin Exposure (SK: SYS)

No toxicokinetic studies of phenol have been identified. Dermal absorption of phenol in human subjects has been reported to range from 4% to 23% of the applied dose; the extent of the absorption depends on the period of exposure and the concentration of phenol [Feldman and Maibach 1970; Piotrowski 1971; Roberts et al. 1977; Baranowska-Dutkiewicz 1981]. In male volunteers, the rate of absorption of an aqueous phenol solution (2.5, 5.0, or 10.0 grams per liter [g/L]) from a 2-milliliter (mL) reservoir applied directly to the forearm (15.6 square centimeters [cm^2]) was found to be concentration-dependent, with the rate ranging from 0.079 milligrams per square centimeter per hour ($mg/cm^2/hr$) at the low concentration to 0.301 $mg/cm^2/hr$ at the high concentration [Baranowska-Dutkiewicz 1981]. In that study, the total amount of phenol absorbed—but not the rate of absorption—at the low concentration increased with time; 12.6% and 22.7% of the applied dose were absorbed in 30 and 60 minutes, respectively. Feldman and Maibach [1970] reported the degree of dermal absorption of phenol to be 4.4% of a single topical application of 4 micrograms (µg)/cm^2 on 13 cm^2 of the unprotected ventral forearm of human adults. Phenol vapors are also reported to readily penetrate the skin, with an absorption efficiency equal to that of inhalation, thus contributing to the total dermal exposure [Piotrowski 1971]. Following a whole-body skin exposure study in which lightly clothed and unclothed volunteers were exposed to phenol vapors at concentrations from 1.3 to 6.5 parts per million (ppm) for 6 hours but were breathing clean air by mask, Piotrowski [1971] reported that absorption increased proportionately with air concentration. These studies generally demonstrated that phenol can be absorbed through the human skin.

The potential of phenol to be absorbed through the skin has also been evaluated in laboratory animals. Hughes and Hall [1997] reported a 120-hour cumulative dermal absorption of 66% to 80% in young (29-day-old female) rats. Following an earlier study, Hughes and Hall [1995] reported that approximately 85% of a dermal dose of phenol was absorbed in 72 hours in 90-day-old female rats. In vitro studies of laboratory animal tissues also indicate that phenol is absorbed through the skin. For example, in an in vitro system using

dermatomed rat skin, Hughes et al. [1993] reported a 72-hour dermal absorption of phenol of 95% of the applied dose. In a recent study that evaluated dermal absorption of phenol in acetone and water in nonoccluded and occluded applications to isolated perfused porcine skin, Brooks and Riviere [1996] found absorption, penetration into tissues, and total recoveries of phenol to be greater under occluded than nonoccluded conditions. They also noted that for each solvent, the absorption percentage was greater with the low dose (4 μg/cm^2) than with the high dose (40 μg/cm^2) of phenol, suggesting saturation of absorption or other nonlinear kinetics under some conditions of exposure. The investigators reported that, depending on the solvent and dose, dermal absorption ranged from 9.24% to 14.62% under occluded conditions at the low dose and from 2.90% to 5.45% under nonoccluded conditions. In vitro permeability coefficients for phenol were found to increase with increasing concentration of aqueous phenol applied to mouse skin [Behl et al. 1983], with a 12-fold increase in mean coefficient (0.007–0.085 cm/hour) resulting from doubling the concentration from 20 g/L to 40 g/L; a value of 0.169 centimeter per hour (cm/hr) was noted when 60 g/L was applied [Behl et al. 1983]. The authors concluded that phenol concentrations exceeding 20 g/L may destroy a diffusion barrier normally provided by the intact stratum corneum, permitting increased percutaneous absorption.

In vivo studies of animals and in vitro studies of animal skin also demonstrated that phenol is absorbed through the skin of animals. The potential of phenol to pose a skin absorption hazard was also evaluated with 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, the ratio of the skin dose to the inhalation dose (SI ratio) was calculated to be 10.97 for phenol. An SI ratio of ≥0.1 indicates that a chemical is capable of producing systemic toxicity from skin exposure [NIOSH 2009]. Additional information on the SI ratio and the variables used in its calculation are included in the appendix.

Numerous cases of severe acute toxicity in humans exposed to phenol via skin contact have been reported [Turtle and Dolan 1922; Griffiths 1973; Soares and Tift 1982; Lewin and Cleary 1982; Foxhall et al. 1989]. In these reports, accidental exposure of intact skin or intentional (therapeutic) topical application of phenol to the skin resulted in fatalities or severe acute toxicity associated with respiratory depression and cardiac arrest. However, because the doses were uncertain, the lethal dermal dose for humans could not be estimated. Griffiths [1973] reported that in one case, death occurred within 10 minutes after ~25% of the patient's body surface was exposed to liquid phenol. Foxhall et al. [1989] described a case in which a man was immersed in a shallow vat containing 40% phenol in dichloromethane. The man sustained chemical burns over 50% of his body, and percutaneous absorption of phenol contributed to acute renal failure. Investigators at ATSDR [2008] have critically reviewed the literature associated with phenol and concluded that exposures of the skin to subjectively low concentrations of phenol (5–6%) over a

sufficient surface area of the body may cause death. In animals, the dermal LD_{50} values (the doses resulting in 50% mortality in the exposed population) range from 0.5 milliliter per kilogram body weight (mL/kg) to 0.68 mL/kg (corresponding to 669–1500 milligrams per kilogram body weight [mg/kg]) [Conning and Hayes 1970; Brown et al. 1975] in rats under both occlusive and nonocclusive conditions and 1400 mg/kg in rabbits [Vernot et al. 1977]. Corning and Hayes [1970] reported severe muscular tremors, twitching, generalized convulsions with loss of consciousness, and prostration within 10 minutes, and severe hemoglobinuria occurred at between 45 and 90 minutes after dermal exposure to phenol in water. Brown et al. [1975] reported hematuria and convulsions as clinical signs of phenol toxicity. Because the reported acute dermal LD_{50} values for the rat and rabbit are both lower than the critical dermal LD_{50} value of 2000 mg/kg body weight that identifies substances with the potential for acute dermal toxicity [NIOSH 2009], phenol is considered systemically toxic by the acute dermal route.

Quantitative information is lacking on doses of phenol that cause systemic effects during repeated occupational exposures. However, chronic doses (unspecified) to humans may result in neurological damage [Merliss 1972]. A number of repeated-dose studies have evaluated systemic effects in animals following dermal exposure to phenol. For example, Deichmann et al. [1950] exposed the tail of rabbits to aqueous phenol solutions of 1.18% to 7.12% in water (reported as 64–380 mg/kg by the International Program for Chemical Safety [IPCS] 1994) for 5 hours/day, 5 days/week, for a total of 18 days. Dose-related systemic effects, including tremors and death, were observed at 130 mg/kg and above. A no-observed-adverse-effect level (NOAEL) of 64 mg/kg/day and a lowest-observed-adverse-effect level (LOAEL) of 130 mg/kg/day to protect against occasional mild tremors and skin irritation were identified in this study. Boutwell and Bosch [1959] conducted a study in mice involving painting an application of 25 microliters (μL) of a phenol solution (5% [1.2 mg] or 10% [2.5 mg] in benzene) on the skin twice weekly for 52 weeks. The high dose caused decreased body weight (average body weight at week 20 was 35.0 g, compared with 38.9 g with the 5% level of phenol) and decreased survival (24/30 mice survived, compared with 30/30 at the 5% level of phenol, at week 20). The resulting doses were reported as 41.7 and 83.3 mg/kg/treatment [ATSDR 2008]. Although the potential dermal and systemic effects of the benzene solvent were not investigated in this study, the effect levels of 18 mg/kg/day in the Boutwell and Bosch study [1959] and 130 mg/kg/day in the shorter-duration study by Deichmann et al. [1950] together indicate the potential for effects at doses significantly lower than the critical dermal NOAEL value of 1000 mg/kg for repeat-dose toxicity that identifies substances with the potential for subchronic dermal toxicity [NIOSH 2009]. Therefore, phenol is considered to be systemically toxic following repeated dermal exposure.

No standard toxicity or specialty studies have been conducted to evaluate biological system/function–specific effects (including reproductive and developmental effects and immunotoxicity) in humans or animals following dermal exposure to phenol.

No epidemiological studies that evaluated the potential of phenol to be carcinogenic were identified. A few studies

involving repeated application of phenol in benzene [Boutwell and Bosch 1959] or in acetone [Salaman and Glendenning 1957; Wynder and Hoffman 1961] in two-stage carcinogenicity protocols in mice indicated that phenol has promoting activity. Studies conducted by Boutwell and Bosch [1959] in several strains of mice also suggested that phenol in benzene or dioxane is a tumor promoter and possibly a complete carcinogen (i.e., having both promoting and initiating activity). In the latter study, phenol elicited skin tumors in mice even in the absence of a tumor-initiating agent, 9,10-dimethyl-1,2-benzanthracene. These studies are inadequate for evaluating the carcinogenicity potential of phenol, for three reasons: short duration (32 weeks [Salaman and Glendenning 1957] and 12 months, or 52 weeks [Salaman and Glendenning 1957; Boutwell and Bosch 1959]); lack of appropriate controls [Salaman and Glendenning 1957, for example]; and use of vehicles (dioxane, benzene) that are skin irritants and defatting agents. Table 2 provides a summary of carcinogenic designations from multiple governmental and nongovernmental organizations for phenol.

Data from identified studies of humans **[Feldman and Maibach 1970; Piotrowski 1971; Baranowska-Dutkiewicz 1981]*** and animals **[Behl et al. 1983; Hughes and Hall 1995; Brooks and Riviere 1996]** and from studies of toxicokinetics, acute dermal toxicity **[Conning and Hayes 1970; Brown et al. 1975; Vernot et al. 1977]**, and repeat dosing **[Deichmann et al. 1950; Boutwell and Bosch 1959]** are sufficient to demonstrate the potential for phenol to be dermally absorbed and systemically toxic. Systemic toxicity includes cardiovascular effects, pulmonary depression, and central nervous system (CNS) effects. On the basis of these findings, coupled with the reports of multiple fatalities of humans **[Turtle and Dolan 1922; Griffiths 1973; Soares and Tift 1982; Lewin and Cleary 1982; Foxhall et al. 1989]** and the critical assessment by ATSDR [2008], phenol is assigned the SK: SYS (FATAL) notation.

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

Table 2. Summary of the carcinogenic designations* for phenol from numerous governmental and nongovernmental organizations

Organization	Carcinogenic designation
NIOSH [2006]	No designation
NTP [2005]	No designation
USEPA [2007]	Data inadequate for an assessment of human carcinogenic potential
IARC [2007]	Group 3: Not classifiable as to its carcinogenicity to humans
EC [2010]	No designation
ACGIH [2001]	A4: Not classifiable as a human carcinogen

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; Joint Research, Institute for Health and Consumer Protection; 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.

*Note: The listed cancer designations were based on data from nondermal (such as oral or inhalation) exposure rather than dermal exposure.

3 Direct Effects on Skin (SK: DIR)

The available information indicates that phenol may be either irritating or corrosive to the skin, depending on the concentration of the phenol solution. For example, dermal exposure to liquid phenol or concentrated phenol vapor causes corrosive effects, including tissue death (necrosis), in humans [Schmidt and Maibach 1981; Foxhall et al. 1989; Horch et al. 1994], rats [Conning and Hayes 1970], mice [Patrick et al. 1985], and pigs [Pullin et al. 1978; Hunter et al. 1992]. Other effects, such as erythema, inflammation, discoloration, eczema, redness, and severe edema have been reported to occur after skin contact with solid or liquid phenol [Brown et al. 1975; Conning and Hayes 1970]. The effects of phenol on the skin have been attributed to its ability to impair the barrier function of the stratum corneum and produce coagulation necrosis by denaturing and precipitating proteins. Hayashi et al. [1999] developed a quantitative structure-activity relationship (QSAR) model that incorporated the results of an experimental animal study to estimate the skin irritancy potential of 24 phenolic compounds, including phenol. The authors reported positive skin irritation results for phenol, which exhibited the highest experimental skin irritation score of the 24 substances investigated within the study. Hayashi et al. [1999] theorized that the skin irritation induced by phenol is caused by reactions of the substance with macromolecules found within the epidermal and dermal levels of the skin. The structure activity relationship model, Deductive Estimation of Risk from Existing Knowledge (DEREK) for Windows, did not predict phenol as a skin irritant.

Several studies involving humans and animals have shown that phenol is corrosive to the skin or is a skin irritant, depending on its concentration. Reports of necrosis and chemical burns in humans **[Schmidt and Maibach 1981; Foxhall et al. 1989; Horch et al. 1994]** and animals **[Conning and Hayes 1970; Pullin et al. 1978; Patrick et al. 1985; Hunter et al. 1992]** following direct contact with undiluted phenol or concentrated solutions are sufficient to demonstrate the corrosivity of phenol. More-diluted solutions are more likely to be irritating to the skin. On the basis of the data for this assessment, phenol is assigned the SK: DIR (COR) notation.

4 Immune-mediated Responses (SK: SEN)

A limited number of studies have been identified that evaluated the potential of phenol to cause skin sensitization in both humans and animals. In one study of 24 volunteers, phenol produced negative results in skin sensitization tests [Kligman 1966]. Phenol yielded negative results in the Magnussen and Kligman skin sensitization test in guinea pigs [Itoh 1982]. Predictions based on structure-activity relationship models provide some information regarding this endpoint. On the basis of its chemical structure, phenol is predicted by DEREK™ to be negative for sensitization. This prediction of negative sensitization potential is consistent with the limited empirical evidence and lack of published reports of sensitization in workers handling phenol. The limited information available indicates that phenol is not likely to be a skin sensitizer. Therefore, NIOSH does not assign an SK: SEN notation for phenol.

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

Organization	Dermal classification
NIOSH [2006]	[skin]: Potential for skin and eye irritation and dermal absorption
OSHA [2007]	[skin]: Indicates that the cutaneous route of exposure (including mucous membranes and eyes) contributes to overall exposure
ACGIH [2001]	[skin]: As a vapor, liquid, or solid, can penetrate the intact skin, causing systemic effects
EC [2010]	Group 3: Not classifiable as to its carcinogenicity to humans
	R21: Harmful; danger of serious damage to health by prolonged contact with skin
	R24: Toxic in contact with skin
	R34: Corrosive; causes burns
	C: Corrosive

Abbreviations: 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.

5 Summary

There is sufficient information from studies of toxicokinetics **[Feldman and Maibach 1970; Piotrowski 1971; Baranowska-Dutkiewicz 1981]**, acute dermal toxicity **[Conning and Hayes 1970; Brown et al. 1975; Vernot et al. 1977]**, and repeat-dose dermal toxicity **[Deichmann et al. 1950; Boutwell and Bosch 1959]** to indicate that phenol is absorbed through the skin, is acutely toxic, and induces pulmonary depression and systemic, cardiovascular, and central nervous system (CNS) effects. Exposure of a significant portion of the body surface to subjectively low concentrations of phenol may result in severe acute toxicity and, in some cases, death **[Turtle and Dolan 1922; Griffiths 1973; Soares and Tift 1982; Lewin and Cleary 1982; Foxhall et al. 1989; ATSDR 2008]**. Information from human experience **[Merliss 1972; Schmidt and Maibach 1981; Horch et al. 1994]** and animal studies **[Conning et al. 1970; Pullin et al. 1978; Patrick et al. 1985; Hunter et al. 1992]** is sufficient to demonstrate that phenol is corrosive, whereas more-dilute solutions are irritating to the skin. The limited information available indicates that phenol is not a skin sensitizer. Therefore, on the basis of the data for this assessment, the composite skin notation of **SK: SYS (FATAL)-DIR (COR)** is assigned to phenol.

Table 3 summarizes the skin hazard designations for phenol previously issued by NIOSH and other organizations. The equivalent Globally Harmonized System of Classification and Labeling of Chemicals dermal designation for phenol is Acute Toxicity Category 3 (Hazard statement: Toxic in contact with the skin), Skin Corrosion Category 1B (Hazard statement: Causes severe skin burns and eye damage) for solutions containing greater than 3% phenol, and Skin Irritation Category 2 (Hazard statement: Causes skin irritation) for solutions containing 1 to 3% phenol [European Parliament 2008]. Phenol has been identified as a Category 2 Mutagen (Hazard statement: Suspected of causing genetic defects) [European Parliament 2008].

References

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

*ACGIH (American Conference of Governmental Industrial Hygienists) [2005]. Phenol. In: Documentation of threshold limit values and biological exposure indices. 7th ed., Vol. 1. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

*ATSDR (Agency for Toxic Substances and Disease Registry) [2008]. Toxicological profile for phenol. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, ATSDR. [http://www.atsdr.cdc.gov/toxprofiles/tp115.pdf]. Accessed 07–07–10.

*Baranowska-Dutkiewicz B [1981]. Skin absorption of phenol from aqueous solutions in men. Int Arch Occup Environ Health *49*:99–104.

*Behl CR, Linn EE, Flynn GL, Pierson CL, Higuchi WI, Ho NF [1983]. Permeation of skin and eschar by antiseptics. I: Baseline studies with phenol. J Pharm Sci *72*:391–397.

*Boutwell RK, Bosch DK [1959]. The tumor-promoting action of phenol and related compounds for mouse skin. Cancer Res *19*:413–424.

*Brooks JD, Riviere JE [1996]. Quantitative percutaneous absorption and cutaneous distribution of binary mixtures of phenol and para-nitrophenol in isolated perfused porcine skin. Fund Appl Toxicol *32*:233–243.

*Brown VKH, Box VL, Simpson BJ [1975]. Decontamination procedures for skin exposed to phenolic substances. Arch Environ Health *30*:1–6.

*Conning DM, Hayes MJ [1970]. The dermal toxicity of phenol: an investigation of the most effective first-aid measures. Br J Ind Med *27*:155–159.

†Deichmann WB [1949]. Local and systemic effects following skin contact with phenol: a review of the literature. J Ind Hyg Toxicol *31*:146–154.

*Deichmann WB, Miller T, Roberts JB [1950]. Local and systemic effects following application of dilute solutions of phenol in water and in camphor-liquid petrolatum on the skin of animals. Arch Ind Hyg Occup Med *2*:454–461.

*EC (European Commission) [2010]. Phenol. In: EINICS (European Inventory of Existing Commercial Chemical Substances) [http://ecb.jrc.ec.europa.eu/esis/]. Accessed 07–07–10.

*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, labelling 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]. Accessed 07–07–10.

*Feldman RJ, Maibach HI [1970]. Absorption of some organic compounds through the skin in man. J Invest Dermatol *54*(5):399–404.

*Foxhall PJD, Bending MR, Gartland KPR, Nicholson JK [1989]. Acute renal failure following accidental cutaneous absorption of phenol: application of NMR urinalysis to monitor the disease process. Human Toxicol *9*:491–496.

*Griffiths GJ [1973]. Fatal acute poisoning by intradermal absorption of phenol. Med Sci Law *13*:46–48.

*Hayashi M, Nakamura Y, Higashi K, Kato H, Kishida F, Kaneko H [1999]. A quantitative structure-activity relationship study of the skin irritation potential for phenols. Toxicology in Vitro *13*:915–922.

*Horch R, Spilker G, Stark GB [1994]. Phenol burns and intoxication. Burns *20*:45–50.

*Hughes MF, Hall LL [1995]. Disposition of phenol in rat after oral, dermal, intravenous, and intratracheal administration. Xenobiotica *25*:873–883.

*Hughes MF, Hall LL [1997]. In vivo disposition of p-substituted phenols in the young rat after intraperitoneal and dermal administration. Food Chem Toxicol *35*:697–704.

*Hughes MF, Shrivastava SP, Fisher HL, Hall LL [1993]. Comparative in vitro percutaneous absorption of p-substituted phenol through rat skin using static and flow-through diffusion systems. Toxicology in Vitro *7*:221–227.

*Hunter DM, Timerding BL, Leonard RB, McCalmoat TH, Schwartz E [1992]. Effects of isopropyl alcohol, ethanol, and polyethylene glycol/industrial methylated spirits in the treatment of acute phenol burns. Ann Emerg Med *21*:1303–1307.

*IARC (International Agency for Research on Cancer) [2007]. IARC monographs on the evaluation of carcinogenic risks to humans: list of all agents evaluated to date. Overall evaluations of carcinogenicity to humans. Vol. 1–96, 1972 to present. Lyon, France: World Health Organization, IARC [http://monographs.iarc.

fr/ENG/Classification/Listagentsalphorder.pdf]. Accessed 07–07–10.

*IPCS (International Programme on Chemical Safety) [1994]. Environmental health criteria: 161. Phenol. Geneva: World Health Organisation, International Programme on Chemical Safety [http://www.inchem.org/documents/ehc/ehc/ehc161.htm]. Accessed 07–07–10.

*Itoh M [1982]. Sensitisation potency of some phenolic compounds. J Dermatol *9*(3):223–283.

*Kligman AM [1966]. The identification of contact allergens by human assays. III. The maximum test: a procedure for screening and rating contact sensitizers. J Invest Dermatol *47*(5):393–409.

*Lewin JF, Cleary WT [1982]. An accidental death caused by the absorption of phenol through skin: a case report. Forensic Sci Int *19*:177–179.

*Merliss RR [1972]. Case report: phenol marasmus. J Occup Med *14*:55–56.

*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 07–07–10.

*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]. Accessed 07–07–10.

*NTP (National Toxicology Program) [2005]. 11th Report on Carcinogens. [http://ntp.niehs.nih.gov/index.cfm?objectid=32BA9724-F1F6-975E-7FCE50709CB4C932]. Accessed 12–02–09.

*OSHA (Occupational Safety and Health Administration) [2009]. Occupational safety and health guideline for phenol. In: NIOSH/OSHA/DOE health guideline [http://www.osha.gov/SLTC/healthguidelines/phenol/recognition.html]. Accessed 07–07–10.

*Patrick E, Maibach HI, Burkhalter A [1985]. Mechanisms of chemically induced skin irritation. Toxicol Appl Pharmacol *81*:476–490.

*Piotrowski JK [1971]. Evaluation of exposure to phenol: absorption of phenol vapor in the lungs through the skin and excretion of phenol in urine. Br J Ind Med *28*:172–178.

*Pullin TG, Pinkerton MN, Johnston RV, Kilian DJ [1978]. Decontamination of the skin of swine following phenol exposure: a comparison of the relative efficiency of water versus polyethylene glycol/industrial methylated spirits. Toxicol Appl Pharmacol *43*:199–206.

*Roberts MS, Anderson RA, Swarlrich J [1977]. Permeability of human epidermis to phenolic compounds. J Pharm Pharmacol *29*:677–683.

*Salaman MH, Glendenning OM [1957]. Tumor promotion in mouse skin by sclerosing agents. Br J Cancer *11*(3):434–444.

*Schmidt R, Maibach H [1981]. Immediate and delayed onset "skip area" dermatitis presumed secondary to topical phenol exposure. Contact Dermatitis *7*(4):199–202.

*Soares ER, Tift JP [1982]. Phenol poisoning: three fatal cases. J Forensic Sci *27*(3):729–731.

*Turtle WRM, Dolan T [1922]. A case of rapid and fatal absorption of carbolic acid through the skin. Lancet *2*:1273–1274.

*UNECE (United Nations Economic Commission for Europe) [2007]. Part 3: health hazards. In: Globally harmonized system of classification and labelling of chemicals (GHS). 2nd Rev. Ed. [http://www.unece.org/trans/danger/publi/ghs/ghs_rev02/02files_e.html]. Accessed 07–07–10.

*USEPA (United States Environmental Protection Agency) [2007]. Phenol. Washington, DC: USEPA, Integrated Risk Information System (IRIS), National Center for Environmental Assessment, Office of Research and Development [http://www.epa.gov/iris/subst/0088.htm]. Accessed 07–07–10.

*Vernot EH, MacEwen JD, Haun CC, Kinkead ER [1977]. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxicol Appl Pharmacol *42*(2):417–424.

*Wynder E, Hoffman D [1961]. A study of tobacco carcinogenesis. VIII. The role of acidic fractions as promoters. Cancer *14*:1306–1315.

Appendix: Calculation of the SI Ratio for Phenol

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

Overview

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

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

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

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

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

Equation 1: Calculation of Skin Permeation Coefficient (K_p)

$$K_p + \frac{1}{\frac{1}{K_{psc} + K_{pol}} + \frac{1}{K_{aq}}}$$

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

Variables used in calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path(K_{psc})	cm/hr	0.00679
Permeation coefficient of the protein fraction of the stratum corneum (K_{pol})	cm/hr	1.56581×10^{-5}
Permeation coefficient of the watery epidermal layer (K_{aq})	cm/hr	0.25771
Molecular weight (MW)*	amu	94.11
Base-10 logarithm of its octanol–water partition coefficient (Log K_{OW})*	None	1.46
Calculated skin permeation coefficient (K_p)	cm/hr	0.00633
Skin dose		
Water solubility (S_W)*	mg/cm^3	82.8
Calculated skin permeation coefficient (K_p)	cm/hr	0.00663
Estimated skin surface area (palms of hand)	cm^2	360
Exposure time	hr	8
Calculated skin dose	mg	1580.04
Inhalation dose		
Occupational exposure limit (OEL)†	mg/m^3	19.2
Inhalation volume	m^3	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	144
Skin dose–to–inhalation dose (SI) ratio	None	10.97

*Variables identified from SRC [2009].

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

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

$$\log K_{psc} = -1.326 + 0.6097 \times \log K_{OW} - 0.1786 \times MW^{0.5}$$

$$K_{pol} = 0.0001519 \times MW^{-0.5}$$

$$K_{aq} = 2.5 \times MW^{-0.5}$$

The second step is to calculate the biologic mass uptake of the substance from skin absorption (skin dose) and inhalation (inhalation dose) during the same period of exposure. The skin dose is calculated as a mathematical product of the K_p, the water solubility (S_W) of the substance, the exposed skin surface area, and the duration of exposure. Its units are milligrams (mg). Assume that the skin exposure continues for 8 hours to unprotected skin on the palms of both hands (a surface area of 360 squared centimeters [cm^2]).

Equation 2: Determination of Skin Dose

$$\text{Skin dose} = K_p \times S_W \times \text{Exposed skin surface area} \times \text{Exposure time}$$

$$= K_p(cm/hr) \times S_W\ (mg/cm^3) \times 360\ cm^2 \times 8\ hr$$

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

$$\text{Inhalation dose} = \text{OEL} \times \text{Inhalation volume} \times \text{RF}$$

$$= \text{OEL } (mg/m^3) \times 10\ m^3 \times 0.75$$

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 summaries the data applied in the previously described equations to determine the SI ratio for phenol. The calculated SI ratio was 10.97. On the basis of these results, phenol 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/]. Accessed 07–07–10.

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]. Accessed 07–07–10.

SRC [2009]. Interactive PhysProp database demo [http://www.srcinc.com/what-we-do/databaseforms.aspx?id=386]. Accessed 12–02–09.

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