NIOSH Skin Notation Profile

Pentachlorophenol (PCP)

SK

- ID^{SK}
- [~~SK~~]
- SYS
- **SYS (FATAL)**
- DIR
- **DIR (IRR)**
- DIR (COR)
- SEN

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Pentachlorophenol (PCP)

Naomi L. Hudson

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 (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 pentachlorophenol (PCP). 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

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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) . . . 4
4 Immune-mediated Responses (SK: SEN) . . . 5
5 Summary . . . 5
References . . . 6
Appendix: Calculation of the SI Ratio for Pentachlorophenol . . . 9
Overview . . . 9
Calculation . . . 10
Appendix References . . . 10

Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
amu	atomic mass unit
CIB	Current Intelligence Bulletin
cm^2	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
DMBA	dimethylbenzanthracene
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
hr	hour
IARC	International Agency for Research on Cancer
ID(SK)	skin notation indicating insufficient data on the health hazards associated with skin exposure
IRR	subnotation of SK: DIR indicating the potential for a chemical to be a skin irritant following exposure to the skin
k_{aq}	coefficient in the watery epidermal layer
k_p	skin permeation coefficient
k_{pol}	coefficient in the protein fraction of the stratum corneum
k_{psc}	permeation coefficient in the lipid fraction of the stratum corneum
LD_{50}	lethal dose resulting in 50% mortality in the exposed population
LD_{Lo}	lowest detected lethal dose
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/kg	milligram(s) per kilogram body weight
mg/m^3	milligram(s) per cubic meter
mL	milliliter(s)
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
PCP	pentachlorophenol
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
TPA	12-O-tetradecanoylphorbol-13-acetate
US EPA	United States Environmental Protection Agency
µg	microgram(s)
µg/cm²	microgram(s) per square centimeter
µg/cm²/hr	microgram(s) per square centimeter per hour
µL	microliter(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 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.

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1 Introduction

1.1 General Substance Information

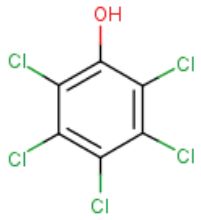
Chemical: Pentachlorophenol (PCP)

CAS No: 87-86-5

Molecular weight (MW): 266.4

Molecular formula: C_6Cl_5OH

Structural formula:



Synonyms: PCP; Penta; 2,3,4,5,6-Pentachlorophenol

Uses: PCP has historically been one of the most widely used biocides in the United States [ATSDR 2001]. Its primary application has been as a wood preservative.

1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with PCP and (2) the rationale behind the hazard-specific skin notation (SK) assignment for PCP. 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 PCP. A literature search was conducted through February 2018 to identify information on PCP, including but not limited to data relating to its dermal absorption, 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 PCP. The criteria for the search strategy, evaluation, and selection of data are described in Appendix E in *Current Intelligence Bulletin 61: A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009].

1.3 Overview of SK Assignment

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

Table 1. Summary of the SK assignment for PCP

Skin notation	Critical effect	Available data
SK: SYS (FATAL)	Metabolic effects (weight loss, profuse sweating); fever; immunotoxicity	Limited human and animal data
SK: DIR (IRR)	Skin irritation; tumor promoter	Sufficient animal data

2 Systemic Toxicity from Skin Exposure (SK: SYS)

Toxicokinetic studies following dermal exposure to PCP were identified. Two epidemiological studies (a cohort study and a case series) were identified [Begley et al. 1977; Jones et al. 1986] that measured the amount of PCP in the plasma and urine in occupationally exposed workers and provided evidence of absorption of PCP. In the cohort study, the blood concentrations of workers exposed to PCP (1.3 micrograms per 100 millilitres [µg/100 mL]) were significantly higher than the mean of the unexposed workers (0.26 µg/100 mL) [Jones et al. 1986]. Begley et al. [1977] reported PCP concentrations in the blood averaging 5.1 parts per million (ppm) in 18 volunteers at a wood treatment plant. However, in both of these studies [Begley et al. 1977; Jones et al. 1986], the contribution of dermal exposure to the total exposure was not quantified. Kehoe et al. [1939] reported that PCP was well absorbed into the tissues of rabbits and caused accelerated respiration, hyperpyrexia, hyperglycemia, and glycosuria following dermal application of PCP to clipped abdominal skin.

In vitro toxicokinetic studies in humans [Hortsman et al. 1989] also demonstrated that PCP is rapidly absorbed following dermal exposure, with 16% (aqueous solution of sodium PCP) and 62% (diesel oil solution of PCP) of the applied dose being absorbed in human cadaver skin. Baynes et al. [2002] evaluated the influence of single and binary solvents, a surfactant, and a rubifacient/vasodilator on the flux, permeability, and diffusivity of PCP following topical doses of 40 micrograms per square centimeter (µg/cm^2) or 4 µg/cm^2 in porcine skin membrane *in vitro*. Absorption of PCP ranged from 1.55 to 15.62% for the high dose and 0.43 to 7.20% for the low dose, depending on the solvent [Baynes et al. 2002]. Flux ranged between 0.18 and 1.54 µg/cm^2 per hour (µg/cm^2/hour) at the high dose and 0.004 and 0.052 µg/cm^2/hour, while permeability values ranged from 0.06 to 0.65 µg/cm (high dose) and 0.04 to 0.19 µg/cm (low dose) [Baynes et al. 2002]. The potential of PCP 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 0.55 was calculated for PCP. An SI ratio of ≥0.1 indicates that skin absorption may significantly contribute to the overall body burden of a substance [NIOSH 2009]; therefore, PCP 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 dermal lethal concentration (LD_{Lo}) for humans has been identified. The reported dermal LD_{50} values (the dose resulting in 50% mortality in the exposed animals) reported for rats were 320 to 330 milligrams per kilogram (mg/kg) [Gaines 1969]. In rabbits the LD_{50} values reported were between 316 mg/kg and 631 mg/kg [Younger Laboratories Incorporated 1974, 1975, 1977]. Deichman [1942] and Kehoe et al. [1939] reported minimal lethal doses of PCP after cutaneous application in rabbits that ranged from 50 mg/kg to 170 mg/kg, depending on the vehicle solution. Kehoe et al. [1939] reported increased respiratory and cardiac rates and anorexia and weight loss when rabbits in other studies were given lethal and sublethal doses. Although the minimum lethal doses for rabbits were less than 200 mg/kg—the critical dermal LD_{50} value that identifies a chemical substance with the potential to be acutely fatal—the reported acute dermal LD_{50} values for rats and rabbits in other studies exceed this value. However, the reported LD_{50} values are lower than the critical dermal LD_{50} value of 2000 mg/kg body weight that identifies chemical substances with the potential for acute dermal toxicity [NIOSH 2009]. Therefore,

on the basis of these data, PCP is considered acutely toxic following dermal exposure.

One epidemiological study and numerous case reports and case series of systemic effects produced by dermal exposure to PCP were identified. The epidemiological study looked at a cohort of workers across six industries, of which 209 workers were exposed to PCP and 101 workers were not exposed [Jones et al. 1986]. The aggregated mean for blood concentrations of PCP was 0.26 µg/100 mL. Jones et al. [1986] reported no effects of PCP on bilirubin, γ-glutamyltransferase, or cholesterol of high-density lipoproteins (HDL). A case report on dermal absorption of PCP, based on urine measurement of the substance from 48 hours to 30 days after exposure, involved an individual exposed to an organic solvent containing PCP while cleaning a paint brush with unprotected hands [Bevenue et al. 1967]. Numerous case reports described severe toxicity and/or death in individuals exposed predominantly by the dermal route to PCP [Blair 1961; Bergner et al. 1965; Robson et al. 1969; Wood et al. 1983]; however, in several of these studies there was also potential for inhalation exposure. Symptoms commonly reported in the case series included weight loss, profuse sweating, and fever. In the fatal cases, extensive dermal exposure occurred. For example, Bergner et al. [1965] presented a case series in which five workers were exposed to PCP while dipping their hands in a mixture containing PCP when they were treating wood; one worker died. Use of gloves or other personal protective equipment (PPE) is not documented; however, the authors did note that the worker who died did not use PPE [Bergner et al. 1965]. Robson et al. [1969] reported the deaths of two infants who had contact with PCP through dermal exposure after bedding linens and diapers had been laundered in PCP. In a fatal case report involving only dermal exposure to PCP, a worker's clothing was reported to have been covered in PCP powder on more than one occasion during the 3 weeks he worked in a chemical plant [Gray et al. 1985]. The autopsy showed that the lungs were congested and edematous, the liver was congested and pale, and there was moderate cerebral edema [Gray et al. 1985].

No subchronic or chronic dermal toxicity studies in animals were identified, and repeat-dose dermal toxicity studies of PCP in animals were limited to one study. In this study, repeated dermal application on the back of rabbits (once or twice a week for periods ranging from 6 to 61 weeks) of 10 to 50 mg/kg of a 4% solution of PCP in Stanolex fuel oil produced no significant changes of the erythrocyte counts, differential counts, and hemoglobin levels, but it resulted in the death of eight of 20 rabbits [Deichmann et al. 1942]. The lowest total dose that resulted in mortality after dermal application was 250 mg/kg [Deichmann et al. 1942]. A Lowest Observed Adverse Effect Level (LOAEL) of 250 mg/kg can be observed from this study since no other health outcomes were reported. Because the LOAEL observed in this study is lower than the critical dose of 1000 mg/kg that identifies chemical substances with the potential for repeated-dose toxicity [NIOSH 2009], this assessment concludes that PCP has the potential to be systemically available and potentially lethal.

No standard toxicity or specialty studies evaluating biological system/function–specific effects (including reproductive and developmental effects and immunotoxicity) following dermal exposure to PCP were identified. However, Daniel et al. [1995] reported alterations in immune functions (severe T lymphocyte dysfunction) in workers exposed to PCP-containing pesticides for more than 6 months. Another case study of immune function alterations was reported following a prolonged exposure in workers who brushed technical-grade PCP onto wood strips [Colosio et al. 1993]. However, the lack of quantitative data regarding the PCP exposure level and duration precludes estimation of the dose at which these effects were elicited.

Two epidemiological studies were identified that reported conflicting findings on the ability of PCP to cause cancer in humans [Gilbert et al. 1990; Hardell et al. 1994]. Hardell et al. [1994] reported that high-grade PCP was statistically significantly associated with non-Hodgkin's lymphoma (odds ratio: 8.8; confidence interval:

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

Organization	Carcinogenic designation
NIOSH [2005]	No designation
NTP [2014]	No designation
US EPA [2014]	Likely to be carcinogenic to humans
European Parliament [2008]	GHS Carcinogenicity Category 2: Suspected of causing cancer
IARC [2012]	Group 2B: Possibly carcinogenic to humans
ACGIH [2014]	Group A3: Confirmed animal carcinogen with 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, because no studies using the dermal route of exposure were available.

3.4–24). A case-control study indicated no increased incidence of mortality resulting from exposure to PCP in wood treaters who worked in the industry for 0.33 to 26.3 years [Gilbert et al. 1990]. No standard rodent cancer bioassays investigating the ability of PCP to cause systemic cancers following dermal exposure were identified. In a skin tumor promotion study, Chang et al. [2003] reported that histological examination revealed lymphomas in the liver, spleen, and kidney in mice treated with 50 µg PCP in 100 microliters (µL) of acetone twice a week for 20 or 25 weeks following treatment with a tumor initiator. Table 2 summarizes carcinogenic designations for PCP by multiple governmental and nongovernmental organizations.

Information from case reports [Begley et al. 1977; Jones et al. 1986] and *in vitro* studies [Hortsman et al. 1989; Baynes et al. 2002] indicate that PCP is absorbed through the skin following dermal exposure. Acute dermal toxicity studies in animals **[Gaines 1969; Younger Laboratories Incorporated 1974, 1975, 1977]**[*], experimental studies in rabbits **[Kehoe et al 1939]**, a repeat dose study **[Deichman et al. 1942]**, and immunotoxicity observed by **Daniel et al. [1995]** demonstrate that the substance is systemically available, is acutely toxic, and can cause hematological effects and immunotoxicity. Several cases of extensive dermal exposure that led to acute toxicity, followed by death, have also been reported **[Blair 1961; Bergner et al. 1965; Robson et al. 1969; Gray et al. 1985]**. Therefore, on the basis of the data for this assessment, PCP is assigned the SK: SYS(FATAL) notation.

3 Direct Effects on Skin (SK: DIR)

No human or animal *in vivo* studies on corrosivity of PCP, *in vitro* tests for corrosivity using human or animal skin models, or in vitro tests of skin integrity using cadaver skin were identified. An epidemiological study looked at a cohort of 310 workers (209 workers exposed to PCP and 101 unexposed workers). Jones et al. [1984] reported no overt cases of chloracne; they did identify some peri-orbital lesions on three workers who used sprayers, but these were difficult to distinguish from common acne. A number of dermal irritation studies in experimental animals were identified. According to Kehoe et al. [1939], the severity of skin irritation of rabbits exposed to PCP depended to a large extent on the vehicle employed, with the most pronounced effects

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

seen with petroleum solvents; however, even the most pronounced effects were reversible. Deichmann et al. [1942] observed local and systemic effects following repeated cutaneous application of PCP in various solvents to the rabbit skin. On the basis of their results, Deichmann et al. [1942] concluded that irritation of the skin and marked reversible local damage are the usual result of cutaneous application of single or repeated doses of PCP in fuel oils. Johnson et al. [1973] reported acne in rabbits after technical-grade PCP was applied to the ear. However, the authors found no such effects after applying chemically pure PCP, an observation that suggests that the contaminant hexachlorodibenzo-p-dioxin rather than PCP may be responsible for the effects. Studies conducted by Younger Laboratories Incorporated [1974, 1975] yielded a primary irritation score of 2.1 for rabbits administered 0.5 mL of undiluted PCP, indicating slight irritation. The authors reported a defatting effect for 10 to 14 days following administration. The structure activity relationship model, Deductive Estimation of Risk from Existing Knowledge *(DEREK™)*, predicted PCP to be negative for skin irritation.

Animal studies were reviewed that investigated the potential for PCP to promote the growth of skin tumors. A skin tumor promotion study involved a single application to the dorsal shaved skin of each of 10 mice, of 100 µg of DMBA in 100 µL of acetone as an initiator; this was followed 1 week later by topical treatment with 0, 2.5, 50, or 1000 µg PCP in 100 µL of acetone twice a week for 20 or 25 weeks from the treatment of DMBA [Chang et al. 2003]. PCP induced a significant increase in squamous cell papillomas, described by Chang et al. [2003] as benign; in mouse skin, however, the effect was less than that seen when using the classical tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA, 2.5 µg per mouse) as a positive control. Epidermal hyperplasia and increased proliferation index were also reported with PCP exposure [Chang et al. 2003]. Chang et al. [2003] concluded that PCP was a tumor promoter in this study.

Although direct skin effect data on humans are unavailable, the animal data indicate PCP is a skin irritant [**Kehoe et al. 1939; Deichmann et al. 1942; Younger Laboratories Incorporated 1974, 1975**] and tumor promoter [**Chang et al. 2003**]. Therefore, on the basis of the data for this assessment, PCP is assigned the SK: DIR (IRR) notation.

4 Immune-mediated Responses (SK: SEN)

There is insufficient information available to suggest that PCP is a skin sensitizer. Although chloracne, chronic urticaria, and pemphigus vulgaris have been reported following exposure to technical grade PCP, possibly with high dioxin levels [Cole et al. 1986; Lambert et al. 1986; Gerhard et al. 1991], these reactions are not delayed-type hypersensitivity reactions. No specific information on skin sensitization due to PCP is available from occupational exposure experience. No standard studies in humans or animals regarding the skin sensitization potential of PCP were identified. *DEREK™* predicted PCP to be negative as a skin sensitizer. The absence of human patch tests or predictive tests in animals precludes adequate evaluation of the potential of PCP to be a skin sensitizer. Therefore, on the basis of the data for this assessment, PCP is not assigned the SK: SEN notation.

5 Summary

Information from case reports [Begley et al. 1977; Jones et al. 1986] and *in vitro* studies [Hortsman et al. 1989; Baynes et al. 2002] indicate that PCP is absorbed through the skin following dermal exposure. Acute dermal toxicity studies in animals [**Gaines 1969; Younger Laboratories Incorporated 1974, 1975, 1977**], experimental studies in rabbits [**Kehoe et al 1939**], a repeat dose study [**Deichmann et al. 1942**], and immunotoxicity observed by **Daniel et al. [1995]** demonstrate that the substance is systemically available, is acutely toxic, and can cause hematological

Table 3. Summary of previous skin hazard designations for PCP

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption
OSHA [2018]*	[skin]: Potential for dermal absorption
ACGIH [2001]	[skin]: PCP caused chloracne in workers and is readily absorbed through the skin, causing systemic toxicity and death

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

effects and immunotoxicity. Several cases of extensive dermal exposure leading to acute toxicity, followed by death, have also been reported **[Blair 1961; Bergner et al. 1965; Robson et al. 1969; Gray et al. 1985]**. Although direct skin effect data on humans are unavailable, the animal data indicate PCP is a likely skin irritant in humans **[Kehoe et al. 1939; Deichmann et al. 1942; et al. 1973]** and a tumor promoter **[Chang et al. 2003]**. Insufficient data are available to determine if PCP is capable of causing systemic or skin cancers following dermal exposures. Because no studies evaluating the skin sensitization potential of PCP were identified, assessment of this endpoint was precluded. Therefore, on the basis of these assessments, PCP is assigned a composite skin notation of **SK: SYS(FATAL)-DIR (IRR)**.

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

References

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

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Appendix: Calculation of the SI Ratio for Pentachlorophenol

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for PCP. 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:

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.

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:

- determining a skin permeation coefficient (k_p) for the substance of interest,
- estimating substance uptake by the skin and respiratory absorption routes, and
- 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 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 squared 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/hour) × S_w (mg/cm^3) × 360 cm^2 × 8 hours

The inhalation dose (in mg) is derived on the basis of the occupational exposure limit (OEL) of the substance—if the OEL is developed to prevent the occurrence of systemic effects rather than sensory/irritant effects or direct effects on the respiratory tract. Assume a continuous exposure of 8 hours, an inhalation volume of 10 cubic meters (m^3) inhaled air in 8 hours, and a factor of 75% for retention of the airborne substance in the lungs during respiration (retention factor, or RF).

Equation 3: Determination of Inhalation Dose

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 PCP. The calculated SI ratio was 0.55. On the basis of these results, PCP is predicted to represent a skin absorption hazard.

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

Variables used in calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path(k_{psc})	cm/hr	0.07596
Permeation coefficient of the protein fraction of the stratum corneum (k_{pol})	cm/hr	9.30659×10^{-5}
Permeation coefficient of the watery epidermal layer (k_{aq})	cm/hr	0.15317
Molecular weight (MW)*	amu	266.4
Base-10 logarithm of its octanol–water partition coefficient (Log K_{ow})*	None	5.12
Calculated skin permeation coefficient (k_p)	cm/hr	5.07832×10^{-2}
Skin dose		
Water solubility (S_w)*	mg/cm^3	0.014
Calculated skin permeation coefficient (k_p)	cm/hr	5.07832×10^{-2}
Estimated skin surface area (palms of hand)§	cm^2	360
Exposure time	hr	8
Calculated skin dose	mg	2.05
Inhalation dose		
Occupational exposure limit (OEL)†	mg/m^3	0.5
Inhalation volume	m^3	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	3.75
Skin dose–to–inhalation dose (SI) ratio	None	0.55

*Variables identified from SRC [ND].
†The OEL used in calculation of the SI ratio for PCP was the NIOSH recommended exposure limit (REL) [NIOSH 2005].
§Hayes WA [2008]. Principles and methods of toxicology. 5th Ed. New York: Informa Healthcare USA.

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