# Skin Notation (SK) Profile

# Pentachlorophenol (PCP)

# [CAS No. 87-86-5]

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

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# Foreword

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

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

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

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

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# Contents

# Abbreviations

| | |
|---|---|
| ACGIH | American Conference of Governmental Industrial Hygienists |
| CIB | Current Intelligence Bulletin |
| $cm^2$ | squared centimeter(s) |
| cm/hour | centimeter(s) per hour |
| *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 |
| GHS | Globally Harmonized System for Classification and Labelling of Chemicals |
| IARC | International Agency for Research on Cancer |
| (IRR) | subnotation of SK: DIR indicating the potential for a chemical to be a skin irritant following exposure to the skin |
| $k_{aq}$ | coefficient in the watery epidermal layer |
| $k_p$ | skin permeation coefficient |
| $k_{pol}$ | coefficient in the protein fraction of the stratum corneum |
| $k_{psc}$ | permeation coefficient in the lipid fraction of the stratum corneum |
| $LD_{50}$ | dose resulting in 50% mortality in the exposed population |
| $LD_{Lo}$ | dermal lethal dose |
| 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 |
| REL | recommended exposure limit |
| RF | retention factor |
| SEN | skin notation indicating the potential for immune-mediated reactions following exposure of the skin |
| SI ratio | ratio of skin dose to inhalation dose |
| SK | skin notation |

| | |
|---|---|
| $S_W$ | solubility in water |
| SYS | skin notation indicating the potential for systemic toxicity following exposure of the skin |
| TPA | 12-O-tetradecanoylphorbol-13-acetate |
| USEPA | United States Environmental Protection Agency |
| µg | microgram(s) |
| µg/cm$^2$ | microgram(s) per square centimeter |
| µg/cm$^2$/hour | 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 occurs when cells in the body become abnormal and grow or multiply out of control.

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

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

**Dermal—**Referring to the skin.

**Dermal contact—**Contact with (touching) the skin.

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

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

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

**Substance—**A chemical.

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

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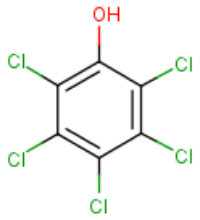
# 1.0 Introduction

## *1.1 General Substance Information:*

**Chemical:** 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 (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 PCP. A literature search was conducted through February 2013 to identify information on PCP, 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 PCP.

## *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) | Immunotoxicity; CNS effects (weight loss, profuse sweating); fever | Limited human and animal data |
| SK: DIR (IRR) | Skin irritation; tumor promoter | Sufficient animal data |

# 2.0 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/100mL]) were significantly higher than the mean of the unexposed workers (0.26 µg/100mL) [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 to the exposed rabbits.

*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 microgram 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 microgram per square centimeter 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 0.77 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 absorbed through the skin following dermal exposure. Additional information on the SI ratio and the variables used in its calculation are included in the appendix.

No dermal lethal 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. [1039] reported minimal lethal doses of PCP after cutaneous application that ranged from 50 mg/kg to 170 mk/kg, depending on the vehicle solution. Kehoe et al. [1939] reported increased respiratory and cardiac rates and anorexia and weight loss when rabbits were given lethal and sub lethal doses. While 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 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 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 6 industries, of which 209 workers were exposed to PCP and 101 workers were not exposed [Jones et al. 1986]. A case report from dermal absorption of PCP, based on urine measurement of the substance from 48 hours to 30 days after exposure, was reported in an individual exposed to an organic solvent containing PCP when cleaning a paint brush using unprotected hands during the process [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, there was extensive dermal exposure that occurred. For example, Bergner et al. [1965] presented a case series where five workers were exposed to PCP when dipping their hands in a mixture containing PCP when they were treating wood, one of which was a fatality. Use of gloves or other personal protective equipment (PPE) is not documented; however the authors did note that the fatality did not use PPE [Bergner et al. 1965]. Robson et al. [1969] reported 2 deaths in infants that had dermal contact to 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, the worker's clothing was reported to have been covered in PCP powder on more than one occasion during the 3 weeks he worked in the chemical plant [Gray et al. 1985]. After death, 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 cutaneous 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 resulted in the death of eight of 20 rabbits [Deichmann et al. 1942]. The lowest dose that resulted in mortality after dermal application was 250 mg/kg [Beichmann 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 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, lack of quantitative data regarding the PCP exposure level and duration precludes estimation of the dose at which these effects were elicited.

Several epidemiological studies were identified that reported conflicting findings on the ability of PCP to cause cancer in humans [Gilbert et al. 1990; Johnson et al. 1990; Hardell et al. 1994]. In a study that reported a positive correlation between skin contact to PCP and systemic cancers, the investigators described potential confounding factors including the possibility that the effects observed may also be due to other components/impurities of commercial grade of PCP used [Hardell et al. 1994]. 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 micrograms (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 of multiple governmental and nongovernmental organizations for PCP.

**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 |
| USEPA [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 |
| EC [2013]† | R40: Limited evidence of a carcinogenic effect |
| ACGIH [2014] | Group A3: Confirmed animal carcinogen with unknown relevance to humans |

ACGIH = American Conference of Governmental Industrial Hygienists; EC = European Commission, Joint Research, Institute for Health and Consumer Protection; GHS = Globally Harmonized System for Labelling and Classification of Chemicals; IARC = International Agency for Research on Cancer; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; USEPA = United States Environmental Protection Agency.

* 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.

†Date accessed.

Information from case reports **[Begley et al. 1977; Jones et al. 1986]** [1], 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;** Gasiewicz 1991**]**, experimental studies in rabbits **[Kehoe et al 1939]**, a repeat dose study **[Beichmann et al. 1942],** and immunotoxicity observed by **Daniel et al. [1995]** demonstrate that the substance is systemically available, acutely toxic and can cause hematological effects and immunotoxicity. Several cases of acute toxicity followed by death has also been reported **[Blair 1961; Bergner et al. 1965; Robson et al. 1969; Gray et al. 1985]** following dermal exposure. Therefore, on the basis of the data for this assessment, PCP is assigned the SK: SYS(FATAL) notation.

# 3.0 Direct Effects on Skin (SK: DIR)

No human or animal *in vivo* studies on corrosivity of PCP or *in vitro* tests for corrosivity using human or animal skin models or *in vitro* tests of skin integrity using cadaver skin were identified. 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 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. Based on their results, Deichmann et al. [1942] concluded that irritation of the skin and marked reversible local damage is 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 contaminants rather than PCP may be responsible for the effects. Studies conducted by Younger Laboratories Incorporated [1974, 1975] observed a primary irritation score of 2.1 in rabbits administered 0.5 milliliters (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, followed one 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 what was 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.

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

Although direct skin effect data in humans is unavailable, the animal data indicate PCP is a skin irritant **[Kehoe et al. 1939; Deichmann et al. 1942; Johnson et al. 1973]** 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.

# 4.0 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 were identified regarding skin sensitization potential of PCP. *DEREK* predicted PCP to be negative as a skin sensitizer. Absence of human patch tests or predictive tests in animals preclude 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.

# 5.0 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;** Gasiewicz 1991**]**, experimental studies in rabbits **[Kehoe et al 1939]**, a repeat dose study **[Beichmann et al. 1942],** and immunotoxicity observed by **Daniel et al. [1995]** demonstrate that the substance is systemically available, acutely toxic and can cause hematological effects and immunotoxicity. Several cases of acute toxicity followed by death has also been reported **[Blair 1961; Bergner et al. 1965; Robson et al. 1969; Gray et al. 1985]** following extensive dermal exposure. Although direct skin effect data in humans are unavailable, the animal data indicate PCP is a likely skin irritant in humans **[Kehoe et al. 1939; Deichmann et al. 1942; Johnson et al. 1973]** and 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. Studies that evaluated the skin sensitization potential of PCP were not identified, precluding assessment of this endpoint. 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) of 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].

**Table 3. Summary of previous skin hazard designations for PCP**

| Organization | Skin hazard designation |
|---|---|
| NIOSH [2005] | [skin]: Potential for dermal absorption |
| OSHA [2015]* | [skin]: Potential for dermal absorption |
| ACGIH [2001] | [skin]: PCP caused chloracne in workers and is readily abosrped through the skin cauing systemic toxicity and death |
| EC [2013]* | R24: Toxic in contact with skin<br>R38: Irritating to skin |

ACGIH = American Conference of Governmental Industrial Hygienists; EC = European Commission, Joint Research, Institute for Health and Consumer Protection; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration.
*Date accessed.

# References

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

*ACGIH (American Conference of Governmental Industrial Hygienists) [2014]. Pentachlorophenol. In: 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 Industrial Hygienists.

*ATSDR [2001]. Toxicological profile for pentachlorophenol. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, ATSDR, http://www.atsdr.cdc.gov/toxprofiles/tp51.pdf. Accessed: 01-27-15.

*Baynes RE, Brooks JD, Mumtaz M, Riviere JE [2002]. Effect of Chemical Interactions in PCP Mixtures on Skin and Membrane Transport. Tox Sci *69*:295-305.

*Begley J, Reichert EL, Rashad MN, Klemmer HW [1977]. Association between renal function tests and pentachlorophenol exposure. Clin Toxicol *11*(1): 97-106.

*Bergner H, Constantinidis P, Martin JH [1965]. Industrial pentachlorophenol poisoning in Winnipeg. Can Med Assoc J *92*: 448-451.

*Bevenue A, Haley TJ, Klemmer HW [1967]. A note on the effects of a temporary exposure of an individual to pentachlorophenol. Bull Environ Contam Toxicol *2*: 293-296.

*Blair DM [1961]. Dangers in using and handling sodium pentachlorophenate as a molluscicide. Bull World Health Organ *25*: 597-601.

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

*Chang WC, Jeng JH, Shieh CC, Tsai YC, Ho YS, Guo HR, Liu HI, Lee CC, Ho SY, Wang YJ [2003]. Skin tumor-promoting potential and systemic effects of pentachlorophenol and its major metabolite tetrachlorohydroquinone in CD-1 Mice. Mol Carcinog *36*(4): 161-170.

*Cole GW, Stone O, Gates D, Culver D [1986]. Chloracne from PCP-preserved wood. Contact Dermatitis *15*: 164-168.

*Colosio C, Maroni M, Barcellini W, Maroni P, Alcini D, Colombi A, Cavallo D, Foa V [1993]. Toxicological and immune findings in workers exposed to PCP (PCP). Arch Environ Health *48*:81-88.

*Daniel V, Huber W, Bauer K, Opelz G [1995]. Impaired in-vitro lymphocyte responses in patients with elevated PCP (PCP) blood levels. Arch Environ Health *50*:287-292.

*Deichmann W, Machle W, Kitzmiller KV, Thomas G [1942]. Acute and chronic effects of PCP and sodium pentachlorophenate upon experimental animals. J Pharmacol Exp Ther *76*:104-117.

*EC (European Commission) [ND]. Pentachlorophenol. In: EINICS (European Inventory of Existing Commercial Chemical Substances), http://esis.jrc.ec.europa.eu/. Accessed: 04-04-13.

*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://eurex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:353:0001:1355:EN:PDF. Accessed: 01-27-15.

*Gasiewicz TA [1991]. Nitro Compounds and Related Phenolic Pesticides – PCP. In: Handbook of Pesticide Toxicology, Vol. 3, Classes of Pesticides, pp 1206-1253, Hayes, WJ and Lews Jr., Eds. Adademic Press, Inc. New York.

*Gerhard I, Derner M, and Runnebaum B [1991]. Prolonged Exposure to Wood Preservatives Induces Endocrine and Immunologic Disorders in Women. J. Obstet. Gynecol. *165*: 487-488.

*Gilbert FI Jr, Minn CE, Duncan RC, Wilkinsin J [1990]. Effects of PCP and other chemical preservatives on the health of wood-treating workers in Hawaii. Arch Environ Contam Toxicol *19*:603-609.

*Gray RE, Gilliland RD, Smith EE, Lockard VG, Hume AS [1985]. PCP intoxication: Report of a fatal case, with comments on the clinical course and pathologic anatomy. Arch Environ Health *40*:161-164.

*Hardell L, Eriksson M, Degerman A [1994]. Exposure to Phenoxyacetic Acids, Chlorophenols, or Organic Solvents in Relation to Histopathology, Stage, and Anatomical Localization of Non-Hodgkin's Lymphoma. Cancer Res *54*: 2386-2389.

†Hardell L, Erikksson M, Degereman A [1995]. Meta-analysis of four Swedish case-control studies on exposure to pesticides as risk-factor for soft-tissue sarcoma including the relation to tumour localization and histopathological type. Int J Oncol *6*:847-851.

†Hertzman C, Teschke K, Ostry A, Hershler R, Dimich-Ward H, Kelley S, Spinelli JJ, Gallagher RP, McBride M, Marion SA [1997]. Mortality and cancer incidence among sawmill workers exposed to chlorophenate wood preservatives. Am J Public Health *87*:71-79.

*Horstman SW, Rossner A., Kalman DA, Morgan MS [1989]. Penetration of PCP and tetrachlorophenol through human skin. Journal of Environmental Science and Health - Part A Environmental Science and Engineering *24*: 229-242.

†Hoppin JA, Tolbert PE, Herrick RF, Freedman DS, Ragsdale BD, Horvat KR, Brann EA [1998]. Occupational chlorophenol exposure and soft tissue sarcoma risk among men aged 30-60 years. Am J Epidemiol *148*:693-703.

*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. Accessed: 01-27-15.

†Jäppinen P, Pukkala E, Tola S [1989]. Cancer incidence of workers in a Finnish sawmill. Scand J Work Environ Health *15*:18-23.

*Johnson RL, Gehring PJ, Kociba RJ, Schwetz BA [1973]. Chlorinated dibenzodioxins and PCP. Environ Health Perpect. *5*: 171-175.

*Johnson CC, Feingold M, Tilley B [1990]. A meta-analysis of exposure to phenoxy acid herbicides and chlorophenols in relation to risk of soft tissue sarcoma. Int Arch Occup Environ Health *62*:513-520.

*Jones RD, Winter DP, Cooper AJ [1986]. Absorption study of PCP in persons working with wood preservatives. Human Toxicol *5*:189-194.

†Jorens PG, Schepens JC [1993]. Human PCP poisoning. Human and Exp Toxicol 12:479-495.

*Kehoe, RAW [1939]. Toxic effects upon rabbits of PCP and sodium pentachlorophenate. J. Ind. Hyg. Toxicol. *21*: 160.

*Lambert J, Schepens P, Janssens J, Dockx P [1986]. Skin lesions as a sign of subacute PCP intoxication. Acta Derm Venreol *66*:170-172.

*Lampi P, Hakilinen T, Luostarinen T, Pukkala E, Teppo L [1992]. Cancer incidence following chlorophenol exposure in a community in South Finland. Arch Environ Health *47*(39): 167-175

*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: 01-27-15.

*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: 01-27-15.

*NTP [2014]. Report on Carcinogens. Thirteenth Edition; U.S. Department of Health and Human Services, Public Health Service. National Toxicology Program, http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html. Accessed: 01-27-15.

*OSHA [ND]. Pentachlorophenol. In: OSHA occupational and chemical database, https://www.osha.gov/chemicaldata/chemResult.html?recNo=726. Accessed: 01-27-15.

†Qiao GL, Brooks JD, Riviere JE [1997]. PCP dermal absorption and disposition from soil in swine: Effects of occlusion and skin microorganism inhibition. Toxicol Appl Pharmacol *147*:234-246.

*Robson AM, Kissane JM, Elvick HN, Pundavcla L [1969]. PCP poisoning in a nursery for newborn infants: I. Clinical features and treatment. J Pediatr *75*:309-316.

*USEPA [2014]. Integrated Risk Information System: pentachlorophenol. In: Integrated Risk Information System, http://www.epa.gov/iris/subst/0086.htm. Accessed: 01-27-15.

†Wester RC, Maibach HI, Sedik L, Melendres J, Wade M, DiZio S [1993]. Percutaneous absorption of PCP from soil. Fundam Appl Toxicol *20*:68-71.

*Wood S, Rom WN, White GL, Logan DC [1983]. PCP poisoning. J Occup Med *25*:527-530.

*Younger Laboratories Incorporated [1974]. Toxicologic investigation of AD 73/penta blend. Younger Laboratories Incorporated, Project #Y-74-121 for Monsanto Company. On file with the U.S. Environmental Protection Agency under TSCA Section 8D. OTS #0546023. Document #88-920007878.

*Younger Laboratories Incorporated [1975]. Toxicologic investigation of penta (prilled). Younger Laboratories Incorporated, Project #Y-74-261 for Monsanto Company. On file with the U.S. Environmental Protection Agency under TSCA Section 8D. OTS #0570564. Document #88-920007950.

*Younger Laboratories Incorporated [1977]. Toxicity studies on penta oil E101-6001. Younger Laboratories Incorporated, Project #Y-77-255 for Monsanto Company. On file with the U.S. Environmental Protection Agency under TSCA Section 8D. OTS #0545854. Document #88-920007660.

# Appendix: Calculation of the SI Ratio for PCP

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 (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 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 0.77. On the basis of these results, PCP is predicted to represent a skin absorption hazard.

**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/hour | 0.1284 |
| Permeation coefficient of the protein fraction of the stratum corneum ($k_{pol}$) | cm/hour | $1.0097 \times 10^{-5}$ |
| Permeation coefficient of the watery epidermal layer ($k_{aq}$) | cm/hour | 0.1662 |
| Molecular weight ($MW$)* | amu | 226.34 |
| Base-10 logarithm of its octanol–water partition coefficient (Log $K_{ow}$)* | None | 5.12 |
| Calculated skin permeation coefficient ($k_p$) | cm/hour | $7.2448 \times 10^{-2}$ |
| **Skin dose** | | |
| Water solubility ($S_w$)* | mg/cm$^3$ | 0.014 |
| Calculated skin permeation coefficient ($k_p$) | cm/hour | $7.2448 \times 10^{-2}$ |
| Estimated skin surface area (palms of hand) | cm$^2$ | 360 |
| Exposure time | hour | 8 |
| Calculated skin dose | mg | 2.92 |
| **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 | 0.77 |

*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].

## *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: 01-27-15.

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: 01-27-15.

SRC [ND]. Interactive PhysProp database demo, http://esc.syrres.com/fatepointer/webprop.asp?CAS=87865. Accessed: 01-27-15.