NIOSH Skin Notation Profile

Chlorodiphenyl (42% Chlorine)

SK

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

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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 chlorodiphenyl (42% chlorine). 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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Abbreviations

ACGIH®	American Conference of Governmental Industrial Hygienists
ATSDR	Agency for Toxic Substances and Disease Registry
CIB	Current Intelligence Bulletin
ChE	cholinesterase
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 to the skin following exposure
DIR	skin notation indicating the potential for direct effects to the skin following contact with a chemical
DMBA	7,12-dimethylbenz(a)antracene
ECHA	European Chemicals Agency
GHS	Globally Harmonized System for Classification and Labelling of Chemicals
GPMT	guinea pig maximization test
hr	hour(s)
IARC	International Agency for Research on Cancer
ID(SK)	skin notation indicating that a chemical has been evaluated, but insufficient data exist to accurately assess the hazards of 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}	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/cm^3	milligram(s) per cubic centimeter
mg/kg	milligram(s) per kilogram body weight
mg/min	milligram(s) per minute
MW	molecular weight
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
ODC	ornithine decarboxylase
OEL	occupational exposure limit

OSHA	Occupational Safety and Health Administration
PCB	polychlorinated biphenyl
ppb	parts per billion
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)
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 carcino¬gen 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, oc¬curring at or near the point of contact with chemicals.

Immune-mediated responses—Responses mediated by the immune system, in¬cluding allergic responses.

Sensitization—A specific immune-mediated response that develops following ex¬posure to a chemical, which, upon re-exposure, can lead to allergic contact derma¬titis 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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- G. Frank Gerberick, Ph.D., The Procter and Gamble Company, Cincinnati, OH
- Dori Germolec, Ph.D., National Toxicology Program, National Institute for Environmental Health Sciences, Research Triangle, NC
- Ben Hayes, M.D., Ph.D., Division of Dermatology, Vanderbilt School of Medicine, Nashville, TN
- Jennifer Sahmel, M.Sc., CIH, ChemRisk, Boulder, CO
- James Taylor, M.D., Industrial Dermatology, The Cleveland Clinic, Cleveland, OH

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1 Introduction

1.1 General Substance Information

Chemical: Chlorodiphenyl (42% chlorine)

CAS No: 53469-21-9

Molecular weight (*MW*)**:** 258 (approximate)

Molecular formula: $C_6H_4ClC_6H_3Cl_2$

Structural formula:

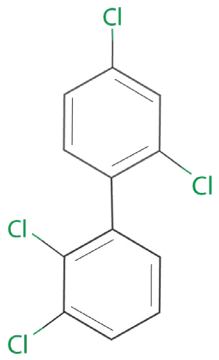

Image by National Center for Biotechnology Information [2020]

Synonyms: Aroclor® 1242, PCB, Polychlorinated biphenyl

Uses: Chlorodiphenyl (42% chlorine) has historically been used as a dielectric fluid, hydraulic fluid, and rubber plasticizer. Since 1977, the substance has not been produced or used in the United States [National Center for Biotechnology Information 2020]. It should be noted that chlorodiphenyl (42% chlorine) may still be present in transformers and capacitors now in use.

1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with chlorodiphenyl (42% chlorine) — a commercial mixture of polychlorinated biphenyl (PCB) compounds—and (2) the rationale behind the hazard-specific skin notation (SK) assignment for chlorodiphenyl (42% chlorine). 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 chlorodiphenyl (42% chlorine). A search of all available relevant literature was conducted through January 2020 to identify information on chlorodiphenyl (42% chlorine) 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 chlorodiphenyl (42% chlorine). The criteria for the search strategy, evaluation, and selection of data are described in Appendix E in the aforementioned *CIB 61* [NIOSH 2009].

1.3 Overview of SK Assignment

Chlorodiphenyl (42% chlorine) is potentially capable of causing adverse health effects following skin contact. A critical review of available data has resulted in the following SK assignment for chlorodiphenyl (42% chlorine): **SK: SYS-DIR (IRR)**. Table 1 provides an overview of the critical effects and data used to develop the SK assignment for chlorodiphenyl (42% chlorine).

Table 1. Summary of the SK assignments and supporting data for chlorodiphenyl (42% chlorine)

Skin notation	Critical effect	Available data
SK: SYS	Hepatotoxicity; central nervous system effects	Limited human and animal data
SK: DIR(IRR)	Skin irritancy, chloracne, and pigmentation of nails and skin	Limited human and animal data

2 Systemic Toxicity from Skin Exposure (SK: SYS)

No *in vivo* human studies were identified that estimated the degree of absorption of chlorodiphenyl (42% chlorine) following dermal exposure. However, in vivo dermal absorption studies in monkeys and guinea pigs and *in vitro* dermal absorption studies in human skin were identified [Wester et al. 1983, 1990, 1993]. In a previous study, Wester and Maibach [1975] reported that percutaneous absorption in the Rhesus monkey showed the same absorption in humans for selected compounds, hydrocortisone, testosterone, and benzoic acid. Wester et al. [1983] applied 50 microliters (µL) of a chlorodiphenyl (42% chlorine) in 1:1 benzene/hexane solution to a 13-square-centimeter (cm^2) area of abdominal skin of Rhesus monkeys [corresponding to either 4.1 micrograms (µg) of chlorodiphenyl (42% chlorine) per square centimeter (µg/cm^2) or 19.3 µg/cm^2], which was washed from the skin surface with soap and water after 24 hours. The authors reported the average total absorption into the skin of two animals that received 4.1 µg of applied chlorodiphenyl (42% chlorine) was 25.6% and the average for the two animals that received 19.3 µg/cm^2 of applied chlorodiphenyl (42% chlorine) was 17.3%. The average mass of applied chlorodiphenyl (42% chlorine) absorbed was 1.0 and 3.3 µg/cm^2, respectively. The average absorption into the skin of three guinea pigs was 33.2% after exposure to 4.6 µg/cm^2 of chlorodiphenyl (42% chlorine) applied in 50 µL of acetone to 11.4 cm^2 of skin on the back of the ears, which were washed with acetone and water after 24 hours [Wester et al. 1983]. However, less than 1% of the applied dose was recovered in the skin wash used by Wester et al. [1983] to clean chlorodiphenyl (42% chlorine) from the guinea pig skin.

Wester et al. [1990] applied 10 µL of a chlorodiphenyl (42% chlorine) solution to a 10 cm^2 area of abdominal skin of four Rhesus monkeys [corresponding to 4.1 µg/cm^2 of chlorodiphenyl (42% chlorine)] delivered in mineral oil or 4.0 µg/cm^2 delivered in trichlorobenzene. The authors reported absorption into the skin over 24 hours of 20.4% in the mineral oil solution and 18.0% in the trichlorobenzene solution [Wester et al. 1990], which corresponds to 0.84 µg/cm^2 and 0.72 µg/cm^2, respectively. In an in vitro study, 1–2 µg/cm^2 of chlorodiphenyl (42% chlorine) in a mineral oil or trichlorobenzene solution was applied to human cadaver skin for 17 hours, and the reported absorption out of the skin was less than 1% [Wester et al. 1990]; the amount in the skin at the end of the skin exposure was not reported. Wester et al. [1993] also reported *in vitro* absorption of chlorodiphenyl (42% chlorine) after 24 hours on human cadaver skin from 4 µL/cm^2 of mineral oil and water at unspecified concentrations. The total amount of chlorodiphenyl (42% chlorine) that absorbed into the skin over 24 hours was reported to be 10.1% from mineral oil [10.0 ± 16.5% (mean ± standard deviation) and 0.12 ± 0.07% were in the skin and receptor solution, respectively] and 44.4% from water [42.9 ± 24.1% and 1.5 ± 1.3%

were in the skin and receptor solution, respectively]. Some of the differences between vehicles probably is related to differences in evaporation of the solvent. Results from the *in vivo* dermal absorption studies show that chlorodiphenyl (42% chlorine) in the skin at the end of the exposure does absorb systemically. Given this, both the *in vitro* and *in vivo* results indicate that chlorodiphenyl (42% chlorine) is absorbed (more than 10% of the applied dose) through the skin following dermal exposure.

The potential for chlorodiphenyl (42% chlorine) to pose a skin absorption hazard was also evaluated with the NIOSH [2009] predictive algorithm for estimating and evaluating the health hazards of dermal exposure to chemical substances. The evaluation method compares an estimated chemical dose accumulated in the body from skin absorption to an estimated dose from respiratory absorption associated with a reference occupational exposure limit. Based on this algorithm, a ratio of skin dose to inhalation dose (the SI ratio) of 12.43 was estimated. An SI ratio of ≥0.1 indicates that skin absorption may significantly contribute to the overall body burden of a substance [NIOSH 2009]; therefore, chlorodiphenyl (42% chlorine) is considered to be a skin absorption hazard following dermal exposure. Additional information on the SI ratio and the variables used in its calculation are included in the appendix.

No estimate of the human dermal lethal dose (LD_{Lo}) was identified for chlorodiphenyl (42% chlorine). In animals, dermal LD_{50} (lethal dose in 50% of exposed animals) values ranged from 794 to 1269 milligrams per kilogram (mg/kg) for the undiluted chlorodiphenyl (42% chlorine) for rabbits [Fishbein 1974]. Because the reported dermal LD_{50} values for rabbits are lower than the critical dermal LD_{50} value of 2000 mg/kg that identifies chemical substances with the potential to be acutely toxic following dermal exposure [NIOSH 2009], chlorodiphenyl (42% chlorine) is considered systemically available and acutely toxic following dermal exposure.

Several epidemiological studies and clinical surveys of PCB-exposed workers have revealed hepatic effects including increased serum levels of liver related enzymes [Agency for Toxic Substances and Disease Registry (ATSDR) 2000]. Several occupational studies were also identified that examined workers who had occupational exposure to chlorodiphenyl (42% chlorine), where sequential or concurrent exposure to other chlorodiphenyl mixtures nearly always occurred [ATSDR 2000]. For example, Ouw et al. [1976] reported that 34 workers exposed to 0.32 to 2.22 milligrams per cubic meter (mg/m^3) of chlorodiphenyl (42% chlorine), had a mean blood chlorodiphenyl (42% chlorine) level of 394 parts per billion (ppb); no chlorodiphenyl (42% chlorine) was detected in the blood of 30 individuals that served as a control group. A subgroup of the exposed workers, consisting of workers in the handling process, had excessive skin absorption due to the exposure to hot chlorodiphenyl (42% chlorine); however, while 4 of 7 of these workers had abnormal hepatic function in tests (there was no history of drug or alcohol use or hepatitis in these workers), the mean value for the whole group was within normal limits [Ouw et al. 1976]. Maroni et al. [1981] evaluated the health of 80 workers with long occupational exposure (an average of 12 years) to PCB mixtures, with 42% mean chlorine content, in electric capacitor manufacturing and testing plants. Absorption of PCBs in these workers had occurred mainly through the skin, but the relative contribution of the dermal route to the total exposure in the workers was unknown. The workers had blood PCB concentrations ranging from 41 to 1319 micrograms per kilogram body weight (µg/kg). The authors reported that 16 of the 80 workers had signs of pronounced hepatic involvement, consisting most often of hepatomegaly (abnormal enlargement of the liver) with an increase in several serum enzymes including gamma-glutamyl transferase, aspartate transaminase, alanine transaminase, and ornithine carbamyl transferase. Fischbein et al. [1979] also reported central nervous system effects as one of the most prevalent symptoms among 326 capacitor workers employed at two capacitor manufacturing facilities where dielectric fluids containing various mixtures of PCBs (i.e., Aroclor 1254, 1242, and others) had been extensively used for approximately 30 years. About

Table 2. Summary of the carcinogenic designations for chlorodiphenyl (42% chlorine) by governmental and nongovernmental organizations

Organization	Carcinogenic designation
NIOSH [2005]	Potential occupational carcinogen
NTP [2011]	Reasonably anticipated to be a human carcinogen
US EPA [2020]	No designation
ECHA [2020]	No GHS designation
IARC [2016]	1: Carcinogenic to humans
ACGIH® [2001]	No designation

ACGIH® = American Conference of Governmental Industrial Hygienists; ECHA = European Chemicals Agency; 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.

40% of the workers were employed for 20 years or longer, and the prevalence of abnormal liver findings in these workers was low [Fischbein et al. 1979]. These epidemiological and occupational exposure studies involved inhalation and dermal routes, but the relative contribution by each route was unknown. However, PCBs are known to be absorbed by humans through ingestion, inhalation, and dermal routes, after which they are transported similarly through the systemic circulation [ATSDR 2000]. Similarity in the mode of transport indicates that different routes of exposure to chlorodiphenyl (42% chlorine) and other PCB mixtures can produce similar systemic effects.

No repeat-dose, subchronic, or chronic toxicity studies involving animals were identified that specifically investigated the potential for chlorodiphenyl (42% chlorine) alone to cause systemic effects following dermal exposure. No standard toxicity or specialty studies were identified that evaluated the biological system/function–specific effects (including reproductive and developmental effects and immunotoxicity) following dermal exposure to chlorodiphenyl (42% chlorine).

No epidemiological studies or animal bioassays were identified that evaluated the potential for chlorodiphenyl (42% chlorine) to be carcinogenic in humans or animals. Table 2 summarizes the carcinogenic designations for chlorodiphenyl (42% chlorine) from governmental and nongovernmental agencies.

Although no *in vivo* studies were identified for humans that estimated the degree of absorption for chlorodiphenyl (42% chlorine) following dermal exposure, *in vivo* dermal absorption studies in monkeys and guinea pigs [Wester et al. 1983, 1990] and in vitro dermal absorption studies in human skin [Wester et al. 1993], supported by results of a mathematical model prediction, indicate that chlorodiphenyl (42% chlorine) is readily absorbed through the skin. An acute dermal toxicity study [Fishbein 1974] and several epidemiological and occupational exposure studies that involved both inhalation and dermal exposures to PCB mixtures or chlorodiphenyl (42% chlorine) with sequential or concurrent exposure to other chlorodiphenyl compounds [**Ouw et al. 1976; Fischbein et al. 1979; Maroni et al. 1981**] indicate that PCBs have the potential to be acutely toxic and may cause systemic toxicity including liver and central nervous system effects. On the basis of available data, chlorodiphenyl (42% chlorine) is assigned the SK: SYS notation.

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

3 Direct Effects on Skin (SK: DIR)

No human or animal *in vivo* studies on corrosivity of chlorodiphenyl (42% chlorine) or *in vitro* tests for corrosivity using human skin models or *in vitro* tests of skin integrity using cadaver skin were identified. There is limited information on humans that indicates that chlorodiphenyl (42% chlorine) is irritating to the skin. Ouw et al. [1976] reported that 34 employees exposed to air concentrations of 0.32–2.22 mg/m^3 of chlorodiphenyl (42% chlorine) for 5–23 years experienced sensations of burning skin. Of these workers, one developed chloracne (an acne-like skin eruption of blackheads, cysts, and pustules associated with over-exposure to certain halogenated aromatic compounds, including PCBs and dioxins) but did not exhibit systemic symptoms such as anorexia, nausea, edema of the face and hands, or abdominal pain [Ouw et al. 1976]. Fischbein et al. [1979] examined the dermatological effects among 326 capacitor-manufacturing workers handling various mixtures of PCBs [including chlorodiphenyl (42% chlorine)] at two facilities. The overall prevalence of dermatological symptoms was high, with 76 (45%) of the male workers and 87 (55%) of the female workers reporting a history of dermatologic symptoms. Skin rash, the most prevalent symptom, was reported by 128 workers (39%), acne by 35 workers (11%), thickening of the skin by 12 workers (3%), and pigmentation disturbances (darkening) and discoloration of the nails by 8 workers each (3%). Although a mixture of chlorodiphenyls was used in these facilities, it is not specified whether these effects were caused by direct dermal contact with chlorodiphenyl (42% chlorine) or if they were a systemic effect resulting from dermal contact and inhalation of chlorodiphenyl (42% chlorine). Smith et al. [1982] investigated direct skin effects in cross-sectional surveys of 228 workers occupationally exposed to PCBs in an electrical equipment plant. The greatest exposure to chlorodiphenyl (42% chlorine) was presumed to occur during the manufacture of electrical power capacitors. Skin wipes of selected workers indicated work-related skin contamination by PCBs. Although none of the participants was found to have acneform lesions suggestive of chloracne, rash or dermatitis was reported by some workers [Smith et al. 1982]. Direct skin effects including skin irritation, chloracne, and pigmentation of nails and skin have also been observed in humans following occupational exposure to PCBs [ATSDR 2000].

A study in mice has shown that chlorodiphenyl (42% chlorine) may be a tumor co-promoter in the skin. Dwivedi and Sitzman [1998] applied a mixture of 600 µg chlorodiphenyl (42% chlorine) alone or in combination with 2.5 nanomoles (nmol) of 12-*O*-tetradecanoylphorbol-13-acetate (TPA) in acetone to the shaved skin of mice for 5 hours. Epidermal ornithine decarboxylase (ODC) activity—a prominent feature among the various biochemical changes observed during tumor promotion—was slightly but significantly increased in the skin following exposure to chlorodiphenyl (42% chlorine) alone [Dwivedi and Sitzman 1998]. When applied with TPA, chlorodiphenyl (42% chlorine) caused a synergistic effect on the induction of ODC activity in the skin, indicating the potential for the test substance to act as a tumor co-promoter with TPA [Dwivedi and Sitzman 1998]. To test the tumor promotion qualities of chlorodiphenyl (42% chlorine), the authors applied 200 nmol of the tumor initiator, 7,12-dimethylbenz(a) antracene (DMBA), to the shaved backs of mice [Dwivedi and Sitzman 1998]. One week after DMBA treatment, either TPA (2.5 or 5 nmoles) in acetone, 600 µg of chlorodiphenyl (42% chlorine) in acetone, or a combination of chlorodiphenyl (42% chlorine) and TPA (2.5 nmols) was applied to the shaved backs of the mice twice a week for 24 weeks. Chlorodiphenyl (42% chlorine) alone did not significantly increase skin papilloma development in any of the mice; however, a combination of chlorodiphenyl (42% chlorine) and TPA caused a significant decrease in the incidence (number of papillomas per mouse) or multiplicity (mean number) of papillomas per mouse when compared with TPA alone [Dwivedi and Sitzman 1998].

Limited data were identified from occupational exposure studies that likely involved both dermal and inhalation routes **[Ouw 1976; Fischbein et al. 1979, 1982; Smith et al. 1982]** that indicate that chlorodiphenyl (42% chlorine) has the potential to cause direct skin effects including irritation, chloracne, and pigmentation of nails and skin. In mice, chlorodiphenyl (42% chlorine) alone slightly increased mouse epidermal ODC activity, but in combination with TPA there was a synergistic effect on ODC activity **[Dwivedi and Sitzman 1998]**. Because PCBs are mixtures of chlorodiphenyls and chloracne has been observed to be associated with PCBs, it is concluded that chlorodiphenyl (42% chlorine) has the potential to cause direct skin effects including skin irritation, chloracne, and pigmentation of nails and skin following dermal exposure. Therefore, chlorodiphenyl (42% chlorine) is assigned an SK: DIR(IRR) notation.

4 Immune-mediated Responses (SK: SEN)

No occupational exposure studies, diagnostic (human patch) tests or predictive tests in animals (for example, guinea pig maximization tests, Buehler tests, murine local lymph node assays, or mouse ear swelling tests), or any other studies were identified that evaluated the potential of chlorodiphenyl (42% chlorine) to cause skin sensitization. In the absence of relevant data, chlorodiphenyl (42% chlorine) is not assigned a SK: SEN notation.

5 Summary

No *in vivo* toxicokinetic studies were identified for humans that estimated the degree of absorption for chlorodiphenyl (42% chlorine) following dermal exposure in humans. *In vivo* toxicokinetic studies in monkeys [Wester et al. 1990], supported by results of a mathematical model prediction, indicate that chlorodiphenyl (42% chlorine) is readily absorbed through the skin. An acute animal study [Fishbein 1974] indicates that following dermal exposure, chlorodiphenyl (42% chlorine) has the potential to be absorbed through the skin, become systemically available, and cause acute toxicity. No epidemiological or occupational exposure studies and no repeat-dose, subchronic or chronic toxicity studies in animals were identified that specifically evaluated the potential for chlorodiphenyl (42% chlorine) alone to cause systemic effects following dermal exposure. Several studies in humans that involved both inhalation and dermal exposures to PCB mixtures or chlorodiphenyl (42% chlorine) with sequential or concurrent exposure to other chlorodiphenyls **[Ouw et al. 1976; Fischbein et al. 1979; Maroni et al. 1981]** indicate that PCBs can cause systemic toxicity including hepatotoxicity. Although no standard irritation tests were identified in animals, limited data from occupational exposure studies **[Ouw 1976; Fischbein et al. 1979; Maroni et al. 1981; Smith et al. 1982]** indicate that chlorodiphenyl (42% chlorine) has the potential to cause direct skin effects including irritation, chloracne, and pigmentation of nails and skin. Chlorodiphenyl (42% chlorine) alone induced ODC activity in mouse epidermis or, in combination with TPA, produced a synergistic effect on this activity **[Dwivedi and Sitzman 1998]**. No diagnostic (human patch) tests or predictive tests in animals were identified that evaluated the potential of the substance to cause skin sensitization. On the basis of the available data, chlorodiphenyl (42% chlorine) is assigned a composite **SK: SYS-DIR(IRR)** notation.

Table 3 summarizes the skin hazard designations for chlorodiphenyl (42% chlorine) previously issued by NIOSH and other organizations. There were no equivalent dermal designations for chlorodiphenyl (42% chlorine) according to the Globally Harmonized System (GHS) for Classification and Labelling of Chemicals [ECHA 2020].

References

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

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Table 3. Summary of previous skin hazard designations for chlorodiphenyl (42% chlorine) from NIOSH and other organizations

Organization	Skin hazard designation
NIOSH [2005]	No designation
OSHA [2019]	[skin]: Potential for dermal absorption
ACGIH® [2001]	[skin]: Potential for dermal absorption

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

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Appendix: Calculation of the SI Ratio for Chlorodiphenyl (42% Chlorine)

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for chlorodiphenyl (42% chlorine). Although the SI ratio is considered in the determination of a substance's hazard potential following skin contact, it is intended to serve only 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 its 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_{aq})

$$k_p = \frac{1}{\frac{1}{k_{psc} + k_{pol}} + \frac{1}{k_{aq}}}$$

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

$$\log k_{psc} = -1.326 + (0.6097 \times \log K_{ow}) - (0.1786 \times MW^{0.5})$$

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

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

The second step is to calculate the biologic mass uptake of the substance from skin absorption (skin dose) and inhalation (inhalation dose) during the same period of exposure.

The skin dose is calculated as a mathematical product of the k_p, the water solubility (S_W) of the substance, the exposed skin surface area, and the duration of exposure. Its units are milligrams (mg). Assume that the skin exposure continues for 8 hours to unprotected skin on the palms of both hands (a surface area of 360 square centimeters [cm^2]).

Equation 2: Determination of Skin Dose

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

Equation 3: Determination of Inhalation Dose

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

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 summarizes the data applied in the previously described equations to determine the SI ratio for chlorodiphenyl (42% chlorine). The calculated SI ratio was 12.43. On the basis of these results, chlorodiphenyl (42% chlorine) is predicted to represent a skin absorption hazard.

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Table A1. Summary of data used to calculate the SI ratio for chlorodiphenyl (42% chlorine)

Variables Used in Calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path *(k_{psc})*	cm/hr	-0.32924
Permeation coefficient of the protein fraction of the stratum corneum *(k_{pol})*	cm/hr	9.4569×10^{-6}
Permeation coefficient of the watery epidermal layer *(k_{aq})*	cm/hr	0.15564
Molecular weight *(MW)*†	amu	258
Base-10 logarithm of its octanol–water partition coefficient *(Log K_{ow})**	None	6.34
Calculated skin permeation coefficient *(k_p)*	cm/hr	0.11683409
Skin dose		
Water solubility *(S_w)**	mg/cm^3	2.77×10^{-4}
Calculated skin permeation coefficient *(k_p)*	cm/hr	0.11683409
Estimated skin surface area (palms of hand)§	cm^2	360
Exposure time	hr	8
Calculated skin dose	mg	0.93205561
Inhalation Dose		
Occupational exposure limit (OEL)†	mg/m^3	0.001
Inhalation volume	m^3	10
Retention Factor (RF)	None	0.75
Inhalation dose	mg	0.0075
Skin dose–to–inhalation dose (SI) ratio	**None**	**12.4275**

*Variables identified from NLM [ND].
†The OEL used in calculation of the SI ratio for chlorodiphenyl (42% chlorine) 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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