NIOSH Skin Notation Profiles

p-Phenylene Diamine (PPD)

SK

ID^{SK}

[~~SK~~]

SYS

SYS (FATAL

DIR

DIR (IRR)

DIR (COR)

SEN

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

NIOSH Skin Notation (SK) Profile

p-Phenylene Diamine
[CAS No. 106–50–3]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

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DHHS (NIOSH) Publication No. 2011–154

April 2011

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Foreword

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

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

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

This *Skin Notation Profile* provides the SK assignment and supportive data for *p*-phenylene diamine (PPD; CAS No. 106–50–3). In particular, this document evaluates and summarizes the literature describing the substance's hazard potential and its assessment according to the scientific rationale and framework outlined in CIB 61. In meeting this objective, this *Skin Notation Profile* intends to inform the audience—mostly occupational health practitioners, researchers, policy- and decision-makers, employers, and workers in potentially hazardous workplaces—so that improved risk-management practices may be developed to better protect workers from the risks of skin contact with the chemical of interest.

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Contents

Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
CIB	Current Intelligence Bulletin
cm^2	squared centimeter(s)
cm/hr	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
EC	European Commission
GHS	Globally Harmonized System of Classification and Labeling of Chemicals
GPMT	guinea pig maximization test
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
log K_{OW}	base-10 logarithm of a substance's octanol–water partition
m^3	cubic meter(s)
mg	milligram(s)
mg/kg	milligram(s) per kilogram body weight
mg/kg/day	milligram(s) per kilogram body weight per day
mg/m^3	milligram(s) per cubic meter
mL	milliliter(s)
mL/kg	milliliter(s) per kilogram body weight
MW	molecular weight
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
OEL	occupational exposure limit
OSHA	Occupational Safety and Health Administration
PPD	*p*-phenylene diamine
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
SYS	skin notation indicating the potential for systemic toxicity following exposure of the skin
USEPA	United States Environmental Protection Agency

Glossary

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

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

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

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

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

Dermal—Referring to the skin.

Dermal contact—Contact with (touching) the skin.

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

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

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

Substance—A chemical.

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

Acknowledgments

This document was developed by the Education and Information Division, Paul Schulte, Ph.D., Director. G. Scott Dotson, Ph.D. was the project officer for this document. Other NIOSH personnel, in particular Heinz Ahlers, JD, Fredrick H. Frasch, Ph.D., Charles L. Geraci, Ph.D., Thomas J. Lentz, Ph.D., Richard Niemeier, Ph.D., and Angie Shepherd, contributed to its development by providing technical reviews and comments. The basis for this document was a report contracted by NIOSH and prepared by Bernard Gadagbui, Ph.D., and Andrew Maier, Ph.D. (*Toxicology Excellence for Risk Assessment [TERA]*).

For their contribution to the technical content and review of this document, special acknowledgment is given to the following NIOSH personnel:

Denver Field Office
Eric Esswein, M.Sc.

Division of Applied Research and Technology
Clayton B'Hymer, Ph.D.

Division of Respiratory Disease Studies
Gregory A. Day, Ph.D.

Division of Surveillance, Hazard Evaluations, and Field Studies
Todd Niemeier, M.Sc.
Aaron Sussell, Ph.D.
Loren Tapp, M.D.

Education and Information Division
Ralph Zumwalde, M.Sc.

Health Effects Laboratory Division
Michael Luster, Ph.D.
Anna Shvedova, Ph.D.
Paul Siegel, Ph.D.

The authors thank Seleen Collins, Gino Fazio, and Vanessa B. Williams for their editorial support and contributions to the design and layout of this document. Clerical and information resources support in preparing this document was provided by Devin Baker, Daniel Echt, and Barbara Landreth.

In addition, special appreciation is expressed to the following individuals for serving as independent, external reviewers and providing comments that contributed to the development or improvement of this document:

G. Frank Gerberick, Ph.D., The Procter and Gamble Company, Cincinnati, Ohio

Dori Germolec, Ph.D., National Toxicology Program, National Institute for Environmental Health Sciences, Research Triangle, North Carolina

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1 Introduction

1.1 General Substance Information

Chemical: *p*-Phenylene Diamine (PPD)

CAS No: 106–50–3

Synonyms:

PPD; 1,4-Diaminobenzene; p-Diaminobenzene; 4-Aminoaniline; 1,4-Benzenediamine

Molecular weight (MW): 108

Molecular formula: $C_6H_8N_2$

Structural formula:

Uses:
p-Phenylene Diamine (PPD) is used primarily as a fur and hair dye and as a chemical intermediate in the production of numerous substances, including dyes and polymers [HSDB 2010].

1.2 Purpose

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

1.3 Overview of SK Assignment for PPD

PPD is potentially capable of causing multiple toxic effects following skin contact. A critical review of available data has resulted in the following SK assignment for PPD: **SK: DIR (IRR)-SEN**. Table 1 provides an overview of the critical effects and data used to develop the SK assignment for PPD.

2 Systemic Toxicity from Skin Exposure (SK: SYS)

Few studies were identified that investigated the dermal absorption potential of PPD in humans and animals. The dermal absorption or the percutaneous penetration rate of PPD in cosmetic hair dyes has been investigated under exposure conditions that mimicked the intended-use conditions for such hair dyes. Under the intended-use conditions, dermal

Table 1. Summary of the SK assignment for PPD

Skin notation	Critical effect	Data available
SK: DIR (IRR)	Skin irritation	Sufficient human and animal data
SK: SEN	Skin allergy	Sufficient human and animal data

absorption of 0.54% to 2.7% in volunteers [Wolfram and Maibach 1985; Goetz et al. 1988; Steiling et al. 2001; Hueber-Becker et al. 2004] and 2.7% in monkeys [Maibach and Wolfram 1981; Wolfram and Maibach 1985; Steiling et al. 2001] has been reported. Dermal absorption of 2.7% has been noted in human cadaver skin [Dressler 1990]. The degree of dermal absorption was reported as 0.93% [Steiling et al. 2001] in excised pig skin. Hueber-Becker et al. [2004] reported similar dermal absorption values, of 2.44% and 3.39% in vitro, in human and pig skin, respectively. These results indicate that the chemical is absorbed to a lesser extent from hair-dye formulations than from the neat chemical, presumably because lower amounts of PPD are applied under typical use conditions.

The potential of PPD 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 chemical 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 63.1 was calculated for PPD. An SI ratio of ≥0.1 indicates that a chemical is capable of producing systemic toxicity from skin exposure [NIOSH 2009]. Additional information on the SI ratio and the variables used in its calculation are included in the appendix.

No quantitative estimate of the lethal dermal dose (LD_{Lo}) for humans has been identified for PPD. A value for dermal LD_{50} (the dose resulting in 50% mortality in the exposed population) of greater than 7,940 milligrams per kilogram body weight (mg/kg) was identified in a study of rabbits [Younger Laboratories 1978], whereas an LD_{Lo} (the lowest reported lethal dose) of 5,000 mg/kg was reported in another study of rabbits [Burnett et al. 1977]. Because the lowest lethal dose of 5,000 mg/kg for rabbits is greater than the critical dermal LD_{50} value of 2000 mg/kg body weight that identifies chemical substances with the potential for significant acute dermal toxicity [NIOSH 2009], PPD is not considered acutely toxic following dermal exposure. However, because no standard dermal acute toxicity studies have been conducted, this conclusion cannot be considered certain.

No epidemiological studies have been identified for PPD. However, repeated-dose (subchronic and chronic) studies with PPD alone or with hair formulations containing varying amounts of PPD mixed with hydrogen peroxide have been conducted. In a well-conducted chronic study [Stenback et al. 1977], percutaneous application of 5% or 10% PPD in acetone applied in a volume of 0.02 milliliter (mL), which was administered twice per week for a lifetime to mice or for 85 weeks to rabbits, did not result in any treatment-related systemic toxicity or local toxicity at the site. On the basis of the default average chronic body weight of 0.0332 kg for Swiss mice of both sexes [United States

Environmental Protection Agency (USEPA) 1988] used in the study, the applied doses were 8.6 milligrams per kilogram per day (mg/kg/day) (mg/kg/day) and 17.2 mg/kg/day, respectively. The no-observed-adverse-effect level (NOAEL) in that study was estimated to be 17.2 mg/kg/day, the highest dose tested.

Toxicity studies with hair formulations containing PPD did not result in treatment-related systemic effects in Swiss mice or New Zealand white rabbits. For example, topical application of 0.05 mL (5 mg) of three different oxidative hair-dye formulations containing 1.5% PPD, mixed 1:1 with 6% hydrogen peroxide, to mouse shaved skin once weekly or once every other week for 18 months elicited no systemic toxicity or skin irritation [Burnett et al. 1975]. In that study, the NOAEL was 3.2 mg/kg/day, with the assumption (1) of a default body weight value as above, (2) that the formulation was diluted with an equal volume of hydrogen peroxide prior to topical application, and (3) that the chemical was applied once weekly. In another chronic study involving four hair-dye-composite formulations containing 1%, 2%, 3%, or 4% PPD mixed 1:1 with hydrogen peroxide, topically applied once a week for 21 to 23 months (0.025 mL/mouse) [Burnett et al. 1980], the highest NOAEL of 4.3 mg/kg/day could be calculated. A dermal, 13-week, subchronic study was also identified for hair-dye formulations containing 1% to 4% PPD [Burnett et al. 1976]. No evidence of systemic toxicity was observed. The available findings from animal studies using product formulations do not indicate the potential for systemic effects; however, doses of PPD in these studies were well below the 1000 mg/kg/day criterion established for assessing systemic toxicity from dermal application [NIOSH 2009]. No subchronic or chronic toxicity studies using neat PPD at doses higher than 4.3 mg/kg/day were identified, precluding estimation of the threshold for systemic effect following prolonged or high-dose dermal exposures.

No epidemiology studies were identified that investigated the carcinogenic potential of PPD alone following dermal exposure. Several dermal carcinogenicity studies [Boutwell and Bosch 1959; Burnett et al. 1975, 1977, 1980; Stenback et al. 1977] in mice and rabbits, involving the use of PPD alone or hair-dye formulations containing PPD mixed with the oxidant hydrogen peroxide, revealed no increase in the incidence of tumor formation in any of the species that were attributable to such applications. One carcinogenicity study in rats revealed mammary gland tumors in females but no tumors of statistical significance in males, following application of a 1:1 mixture of 5% PPD (in 2% ammonium hydroxide) and 6% hydrogen peroxide once per week for 18 months [Rojanapo et al. 1986]. This finding has not been demonstrated in other species. Table 2 provides a summary of carcinogenic designations from multiple governmental and nongovernmental organizations for PPD.

No standard toxicity or specialty studies evaluating biological system/function–specific effects (including reproductive and developmental effects and immunotoxicity) following dermal exposures were identified for PPD. However, Burnett et al. [1976] reported no reproductive or developmental effects of biological significance when hair-dye formulations containing 1% to 4% PPD, mixed with an equal volume of 6% hydrogen peroxide just before application, were applied topically at doses of 2 milliliter per kilogram body weight (mL/kg), equivalent to 2 mg/kg, to groups of pregnant rats with seven intermittent applications over 19 days of gestation.

The available information on kinetics following dermal absorption in humans and

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

Organization	Carcinogenic designation
NIOSH [2005]	None
NTP [2009]	None
USEPA [2009]	None
IARC [1999]	Group 3: Not classifiable as to carcinogenicity to humans
EC [2010]	None
ACGIH [2001]	Group A4: Not classifiable as a human carcinogen

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

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

animals indicates that PPD has limited absorption potential in humans but somewhat greater absorption in guinea pigs. Furthermore, the limited acute dermal toxicity studies provide no evidence that PPD is acutely toxic. Data are inadequate to assess the threshold for effects following subchronic and chronic exposure. Available data indicates that PPD does not cause cancer in animals. Therefore, on the basis of the data for this assessment, PPD is not assigned the SK: SYS notation.

3 Direct Effects on Skin (SK: DIR)

No evidence of skin corrosivity of PPD was identified. E.I. DuPont De Nemours and Company [1981a] reported no skin corrosion in rabbits administered 500 mg of PPD. The direct skin effects of PPD and hair-dye formulations containing PPD have been evaluated both in humans and in several experimental animals. In humans, baboons, dogs, pigs, guinea pigs, and mice, the chemical was mildly irritating [Davies et al. 1972], and in rabbits it was mildly to moderately irritating [Hanzlik 1932; E.I. DuPont De Nemours and Company 1970a, 1970b, 1970c; Morikawa 1976; Herve-Bazin et al. 1977; Loyd et al. 1977]. In three separate studies conducted in guinea pigs, E.I. DuPont De Nemours and Company reported mild to moderate irritation following administration of 40 mg to 90 mg PPD to the intact or abraded skin [DuPont 1970a] and reported mild to strong erythema following application of 0.05 mL, equivalent to 0.05 mg PPD, of a 1% PPD solution [E.I. DuPont De Nemours and Company 1970b] or a 25% PPD solution [E.I. DuPont De Nemours and Company 1981]. No irritation was reported when guinea pigs received 0.05 mL of a 25% or 10% PPD solution (weight/volume basis) [E.I. DuPont De Nemours and Company 1973b], a 2.5% PPD solution [E.I. DuPont De Nemours and Company 1981b], or a 3% or 30% PPD solution [E.I. DuPont De Nemours and Company 1982]. In rabbits, E.I. DuPont De Nemours and Company [1970a] observed that doses above 450 mg/kg produced erythema and edema in rabbits, whereas Younger Laboratories [1978] reported no signs of irritation following a 500-mg/kg dose. Predictions made with structure-activity relationship models provide some information regarding this endpoint. On the basis of the chemical

structure of PPD, it is predicted by Deductive Estimation of Risk from Existing Knowledge (DEREK™) for Windows to be negative for irritation.

The available data indicate skin irritation following dermal exposure to PPD in a variety of species **[Davies et al. 1972; E.I. DuPont De Nemours and Company 1970a, 1970b, 1970c, 1973a, 1973b, 1981a, 1981b, 1982*]**. Therefore, on the basis of the data for this assessment, PPD is assigned the SK: DIR (IRR) notation.

4 Immune-mediated Responses (SK: SEN)

Data from studies of both humans and animals are sufficient to demonstrate that PPD has potent skin-sensitizing properties. Beliauskiene et al. [2010] examined the prevalence of contact allergy in the 816 patients with suspected allergic contact dermatitis in Lithuania via patch testing using standard criteria. A 1% solution of PPD was applied for 48 hours in petrolatum using Finn Chambers on Scanpor; readings were performed on day 2 and day 3. Forty-seven patients exhibited positive reactions towards PPD. Beliauskiene et al. [2010] concluded that PPD was one of the most prevalent contact allergens and affects 6.0% (95% CI 4.3–7.8) of the study population.

Several cases of contact dermatitis have been reported following occupational exposure to dyes containing the chemical. Birnie and English [2007] described a case of immediate hypersensitivity in a trainee hairdresser following application of numerous hair dyes on her right arm. The arm became red and extremely pruritic. The hairdresser revealed that she had a history of mild asthma that had worsened noticeably in the 5 months since her training commenced. Although no standard patch testing was conducted, Birnie and English [2007] reported that scratch testing with PPD-containing hair dyes used by the patient resulted in a strong urticarial reaction within 10 minutes and thus a diagnosis of immediate hypersensitivity (type 1 allergy) to PPD causing contact urticaria. Balato et al. [2008] reported a case of erythema multiforme–like lesions attributed to dermal contact with PPD. The patient was admitted to the hospital with acute dermatitis involving the scalp, ears, and limbs, following application of hair dyes believed to contain PPD. Balato et al. [2008] stated that patch testing with the standard Società Italiana di Dermatologia Allergologica, Professionale e Ambientale series yielded positive reactions to PPD and nickel sulfate. In another study, Dickel et al. [2002] conducted standard patch testing on over 4,000 workers who had been identified as having previously had occupational skin disease. The authors identified PPD (free base) as one of the most common sensitizers to which these workers were exposed. Adams and Maibach [1985] and Eiermann et al. [1982] have also identified the chemical as the third most common ingredient, after fragrances and preservatives, that can cause contact dermatitis from cosmetics (mainly skin-care products, hair preparations and colorants, and facial makeup products). Several other studies have also reported positive patch tests with the chemical in hairdressers or their clients who presented with dermatological problems due to hair cosmetics.

PPD is also a potent sensitizer in the guinea pig maximization test (GPMT) [Xie et al. 2000; Basketter et al. 2005] and a strong sensitizer in the Buehler test [Basketter et al. 2005]. In guinea pigs, positive sensitization reactions to challenge were noted [American Cyanamid Company 1956; E.I. DuPont De Nemours and Company

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

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

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption
OSHA [2009]	[skin]: Potential for dermal absorption
ACGIH [2001]	None
EC [2010]	R24: Toxic in contact with skin R43: May cause sensitization by skin contact

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

1970b, 1970c, 1973b, 1981b, 1982]. Basketter et al. [2005] have listed the substance as sensitizing to mice skin also [Kalish and Wood 1995]. On the basis of its chemical structure, PPD is predicted to be a probable skin sensitizer by DEREK™.

There is sufficient information available from human studies **[Eiermann et al. 1982; Adams and Maibach 1985; Dickel et al. 2002; Beliauskiene et al. 2010]** as well as positive results of predictive tests in animals (GPMTs and Buehler tests) **[Kalish and Wood 1995; Xie et al. 2000; Basketter et al. 2005]** to demonstrate that PPD is a skin sensitizer. Therefore, on the basis of the data for this assessment, PPD is assigned the SK: SEN notation.

5 Summary

The available information on kinetics following dermal absorption in humans and animals indicates that PPD has limited absorption potential in humans. Dermal toxicity studies indicate low acute toxicity. The available human experience and animal data indicate that PPD is a skin irritant in a variety of species **[Davies et al. 1972; E.I. DuPont De Nemours and Company 1970a, 1970b, 1970c, 1973b, 1981b, 1982]**. There is sufficient information available from human studies **[Eiermann et al. 1982; Adams and Maibach 1985; Dickel et al. 2002; Beliauskiene et al. 2010]** as well as positive results of predictive tests in animals (GPMTs and Buehler tests) **[Kalish and Wood 1995; Xie et al. 2000; Basketter et al. 2005]** to demonstrate that PPD is a skin sensitizer. Therefore, on the basis of these assessments, PPD is assigned a composite skin notation of **SK: DIR (IRR)-SEN**.

Table 3 summarizes the skin hazard designations for PPD previously issued by NIOSH and other organizations. The equivalent dermal designations for PPD, according to the Global Harmonization System (GHS) of Classification and Labelling of Chemicals, are Acute Toxicity Category 3 (Hazard statement: Toxic in contact with the skin) and Skin Sensitization Category 1 (Hazard statement: May cause an allergic skin reaction) [European Parliament 2008].

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

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Appendix: Calculation of the SI Ratio for PPD

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for PPD. 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 the SYS notation are as follows:

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

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

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

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

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

Variables used in calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path(K_{psc})	cm/hr	0.00043
Permeation coefficient of the protein fraction of the stratum corneum (K_{pol})	cm/hr	1.46071×10^{-5}
Permeation coefficient of the watery epidermal layer (K_{aq})	cm/hr	0.24041
Molecular weight (MW)*	amu	108
Base-10 logarithm of its octanol–water partition coefficient (log K_{OW})*	None	-0.3
Calculated skin permeation coefficient (K_p)	cm/hr	0.00044
Skin dose		
Water solubility (S_W)*	mg/cm^3	37
Calculated skin permeation coefficient (K_p)	cm/hr	0.00044
Estimated skin surface area (palms of hand)	cm^2	360
Exposure time	hr	8
Calculated skin dose	mg	47.33
Inhalation dose		
Occupational exposure limit (OEL)†	mg/m^3	0.1
Inhalation volume	m^3	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	0.75
Skin dose–to–inhalation dose (SI) ratio	None	63.1

*Variables identified from SRC [2009].
†The OEL used in calculation of the SI ratio was the NIOSH-recommended exposure limit (REL) [NIOSH 2005].

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 cm^2).

Equation 2: Determination of Skin Dose

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

$$= K_p(cm/hr) \times S_w\ (mg/cm^3) \times 360\ cm^2 \times 8\ \text{hours}$$

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

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

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

The final step is to compare the calculated skin and inhalation doses and to present the result as a ratio of skin dose to inhalation dose (the SI ratio). This ratio quantitatively indicates (1) the significance of dermal absorption as a route of occupational exposure to the substance and (2) the contribution of dermal uptake to systemic toxicity. If a substance has an SI ratio greater than or equal to 0.1, it is considered a skin absorption hazard.

Calculation

Table A1 summarizes the data applied in the previously described equations to determine the SI ratio for PPD. The calculated SI ratio was 63.1. On the basis of these results, PPD is predicted to represent a skin absorption hazard.

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DHHS (NIOSH) Publication No. 2011–154

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