NIOSH Skin Notation Profile
Phenothiazine

[CAS No. 92-84-2]

External Review Draft

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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 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]. 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 with an 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 phenothiazine. 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
bw	body weight
CIB	Current Intelligence Bulletin
DIR	skin notation indicating the potential for direct effects to the skin following contact with a chemical
ECHA	European Chemicals Agency
g	gram(s)
g/kg	gram per kilogram
h	hour
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
kg	kilogram(s)
LD_{50}	dose resulting in 50% mortality in the exposed population
LD_{Lo}	dermal lethal dose
mg	milligram(s)
mg/kg	milligram per kilogram
MW	molecular weight
NIOSH	National Institute for Occupational Safety and Health
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
SEN	skin notation indicating the potential for immune-mediated reactions following exposure of the skin
SK	skin notation
SYS	skin notation indicating the potential for systemic toxicity following exposure of the skin
U.S. EPA	United States Environmental Protection Agency

Glossary

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

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

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

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

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

Dermal—Referring to the skin.

Dermal contact—Contact with (touching) the skin.

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

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

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

Substance—A chemical.

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

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1 Introduction

1.1 General Substance Information

Chemical: Phenothiazine

CAS No: 92-84-2

Molecular weight (*MW*): 199.3

Molecular formula: $S(C_6H_4)_2NH$

Structural formula:

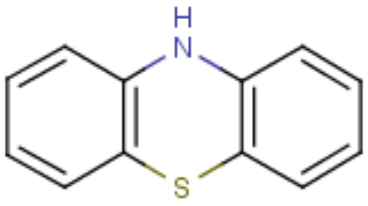

Image source: [NLM 2023b]

General substance information was obtained from NIOSH [2007].

Synonyms: agrazine, afi-tiazin, antiverm, biverm, contaverm, dibenzo-1,4-thiazine, dibenzo-p-thiazine, dibenzoparathiazine, dibenzothiazine, fenothiazine, fenoverm, fentiazine, lethelmin, nemazene, orimon, padophene, souframine, thiodiphenylamine, vermitin

Uses: Phenothiazine is organic substance with multiple applications including as a polymerization inhibitor, insecticide, and antioxidant. Within pharmaceutical manufacturing it is used as the parent compound of antipsychotic drugs [NLM 2023a]. The aggregated product volume for phenothiazine per year from 2016–2019 was 1,000,000 to <20,000,000 pounds [NLM 2023b].

1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with phenothiazine and (2) the rationale behind the hazard-specific skin notation (SK) assignment for phenothiazine. 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 phenothiazine. A literature search was conducted through February 2023 to identify information on phenothiazine toxicokinetic properties, 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 in humans, animals, or appropriate modeling systems that are relevant to assessing the effects of dermal exposure to phenothiazine.

1.3 Overview of SK Assignment

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

Table 1: Summary of the SK assignments for phenothiazine

Skin notation	Critical effects	Available data
SK: DIR(IRR)	Skin irritancy	Limited animal data

2 Systemic Toxicity from Skin Exposure (SK: SYS)

No studies evaluating toxicokinetic properties were identified in humans or animals that estimated the degree of absorption of phenothiazine through the skin following dermal exposure. There have been considerable improvements and advancements in dermal absorption studies and modeling since the publication of CIB 61 [NIOSH 2009]. In response to expert external peer reviewers' comments regarding the limitation of the skin to inhalation dose (SI) ratio information, NIOSH is no longer providing the SI ratio described in CIB 61 in the individual chemical skin notation profile documents.

No estimated human dermal lethal dose (LD_{LO}) was identified for phenothiazine. Dermal LD_{50} (the dose resulting in 50% mortality in the exposed animals) value of greater than 9.4 grams per kilogram body weight (g/kg-bw) or (9,400 milligrams per kilogram body weight, mg/kg-bw) was reported when rabbits were administered 99.8% or 95% phenothiazine solution to the intact or abraded skin [West Agro-Chemical 1977]. Because the LD_{50} value for the rabbits was greater than the cut-off value of 2,000 mg/kg, that identifies chemical substances considered toxic when in contact with the skin, phenothiazine is not considered toxic following acute dermal exposure [NIOSH 2009].

No epidemiological or occupational studies or case reports that investigated the potential for phenothiazine to cause systemic effects following dermal exposure were identified. No repeat-dose, subchronic, or chronic toxicity studies in animals were identified that

investigated the potential for phenothiazine to cause systemic effects following dermal exposure.

No specialty studies were identified that evaluated the biological system/function specific effects (including reproductive and developmental effects and immunotoxicity) of phenothiazine following dermal exposure. No epidemiological studies or animal bioassays were identified that evaluated the potential for phenothiazine to be carcinogenic following dermal exposure. Table 2 summarizes the carcinogenic designations for phenothiazine from governmental and nongovernmental organizations.

Table 2. Summary of the carcinogenic designations for phenothiazine by governmental and nongovernmental organizations

Organization	Carcinogenic designation
ACGIH [2022]	No designation
ECHA [2023]	No designation
IARC [2023]	No designation
NIOSH [2007]	No designation
NTP [2021]	No designation
U.S. EPA [2023]*	No designation

ACGIH = American Conference of Governmental Industrial Hygienists; ECHA = European Chemicals Agency; IARC = International Agency for Research on Cancer; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; U.S. EPA = United States Environmental Protection Agency.

*Year accessed.

No studies evaluating toxicokinetic properties were identified that estimated the degree of absorption of phenothiazine following dermal exposure. No epidemiological or occupational exposure studies or case reports were identified that evaluated the potential of phenothiazine to cause systemic effects following dermal exposure. However, acute toxicity data indicated that phenothiazine is not acutely toxic following dermal exposure [West Agro-Chemical 1977]. Therefore, this assessment does not assign a SK: SYS skin notation for phenothiazine.

3 Direct Effects on Skin (SK: DIR)

No human or animal *in vivo* studies that evaluated the corrosivity of phenothiazine or *in vitro* tests for corrosivity using human or animal skin models or *in vitro* tests of skin integrity using cadaver skin were identified. Application of 0.5 gram (g) phenothiazine (purity: 99.8% and 95%) to the clipped intact or abraded skin of rabbits produced no

signs of erythema or edema at the 24- or 72-hour (h) evaluation interval [West Agro-Chemical 1977]. No skin irritation was observed in an acute dermal toxicity study when 3,900 to 9,400 mg/kg phenothiazine was applied to intact or abraded skin of rabbits for 24 h [West Agro-Chemical 1977].

Haskell Laboratory [1987] reported that solutions of 1% and 10% phenothiazine in acetone were very irritating to the intact skin of guinea pigs, whereas a 0.1% solution was mildly irritating, and a 0.01% solution was non-irritating; however, the volume or amount of the substance applied to the skin was not reported in this study. Varying amounts of solid phenothiazine moistened with water and held against the depilated skin of guinea pigs for 24 h produced slight skin irritation [Eastman Kodak 1960].

Dow Chemical [1937] conducted skin irritation tests involving repeated applications of 1% solutions of phenothiazine in 95% ethanol, with one rabbit tested per solution. The test solutions were repeatedly applied (8 applications over 10 days) as a fresh, but slightly colored solution (decomposition started), as a fresh solution (9 applications over 15 days), or as an old and decomposed, highly colored solution (22 applications over 34 days) to the left ear and abdominal skin of a rabbit. The abdomen was covered by a cloth bandage for the two shorter treatment periods [Dow Chemical 1937]. None of the applications produced irritation on the ear; however, skin reactions on the abdomen were observed. The abdomens of the rabbits exposed to the fresh, but slightly colored solution and the old, highly colored solution began to redden after the second application. By the fourth application, a fine scaliness developed in addition to the redness. Both symptoms continued throughout the treatment periods. Redness of the abdomen and exfoliation were also observed in the rabbit exposed to the fresh solution [Dow Chemical 1937].

In another treatment, a deeply colored decomposed solution of phenothiazine (5 to 6 weeks old) was applied and bandaged on to the abdomen of a rabbit for 24 h. This application caused deep denaturation of the skin [Dow Chemical 1937]. The results from the Dow Chemical [1937] studies indicated that the fresh solutions of phenothiazine were mildly irritating, while the solution in which phenothiazine had decomposed resulted in more severe irritation, suggesting the decomposed products enhanced the severity of the response.

Based on the available data, single doses of phenothiazine were not irritating to rabbit skin [West Agro-Chemical 1977] but were irritating to guinea pig skin, and prolonged and repeated topical applications caused mild irritation to rabbit skin **[Dow Chemical 1937; Eastman Kodak 1960]**[*]. Results also indicated that repeated application of older

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

and more highly colored (decomposed) solutions caused more severe skin irritation in rabbits **[Dow Chemical 1937]**. Therefore, this assessment assigns a skin notation of **SK: DIR(IRR)** for phenothiazine.

4 Immune-mediated Responses (SK: SEN)

No epidemiological or occupational exposure studies or diagnostic (human patch) tests that investigated the potential of phenothiazine to be a skin sensitizer were identified. Haskell Laboratory [1987] reported that three guinea pigs may have been sensitized in a primary irritation and sensitization study. In a pilot photosensitization test, Haskell Laboratory [1987] reported that application of 0 or 5,000 mg/kg of a 30% suspension of phenothiazine in 1% Jaguar to the clipped skin of guinea pigs (one test and one untreated), followed by exposure to direct sunlight, produced no photosensitization. No other predictive tests (for example, guinea pig maximization tests, Buehler tests, murine local lymph node assays, or mouse ear swelling tests) or other tests that evaluated the potential of phenothiazine to cause skin sensitization in animals were identified.

The available evidence is insufficient to adequately evaluate the skin sensitization potential of phenothiazine. Therefore, this assessment does not assign a SK: SEN notation for phenothiazine.

5 Summary

Although no studies evaluating toxicokinetic properties were identified that estimated the degree of absorption of phenothiazine following dermal exposure, acute toxicity data in animals indicated that phenothiazine is not acutely toxic following dermal exposure [West Agro-Chemical 1977]. Available data indicated that phenothiazine was not irritating to rabbit skin [West Agro-Chemical 1977] in single doses, but was irritating to guinea pig skin, and prolonged and repeated topical applications caused mild skin irritation to the skin of rabbits **[Dow Chemical 1937; Eastman Kodak 1987]**. Repeated application of older and more highly decomposed solutions caused more severe skin irritation in rabbits **[Dow Chemical 1937]**.

The lack of predictive tests in animals along with the mixed results from Haskell Laboratory [1987] preclude adequate evaluation of the potential for phenothiazine to be a skin sensitizer. Based on the available data, this assessment assigns a **SK: DIR(IRR)** notation for phenothiazine.

Table 3 summarizes the skin hazard designations for phenothiazine previously issued by NIOSH and other organizations.

Table 3: Summary of the previously issued skin hazard designations for Phenothiazine from NIOSH and other organizations

Organization	Dermal classification
ACGIH [2022]	[skin]: Potential for dermal absorption
ECHA [2023]	No designation
NIOSH [2007]	[skin]: Potential for dermal absorption; Prevent skin contact
OSHA [2021]	No designation

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

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