NIOSH Skin Notation Profiles

Hydrazine

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

Hydrazine
[CAS No. 302–01–2]

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 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 hydrazine (CAS No. 302–01–2). 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
ATSDR	Agency for Toxic Substances and Disease Registry
CIB	Current Intelligence Bulletin
cm^2	square centimeter(s)
cm/hr	centimeter(s) per hour
cm/s	centimeter(s) per second
(COR)	subnotation of SK: DIR indicating the potential for a chemical to be corrosive following exposure of the skin
DEREK™	Deductive Estimation of Risk from Existing Knowledge
DIR	skin notation indicating the potential for direct effects to the skin following contact with a chemical
EC	European Commission
(FATAL)	subnotation of SK: SYS indicating chemicals are highly or extremely toxic and may be potentially lethal or life-threatening following exposure of the skin
GHS	Globally Harmonized System of Classification and Labeling of Chemicals
GPMT	guinea pig maximization test
H-70	an azeotropic mixture of 70% hydrazine and 30% water
IARC	International Agency for Research on Cancer
kg	kilogram(s)
LD_{50}	dose resulting in 50% mortality in the exposed population
LD_{Lo}	dermal lethal dose
LOAEL	lowest-observed-adverse-effect level
mg	milligram(s)
mg/kg	milligram(s) per kilogram body weight
mL	milliliter(s)
mL/kg	milliliter(s) per kilogram body weight
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
USEPA	United States Environmental Protection Agency

µg/L	microgram per liter
µg/mL	micrograms per milliliter

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: Hydrazine

CAS No: 302–01–2

Synonyms:

Diamide, Diamine, Hydrazine (anhydrous), Hydrazine Base

Molecular weight (MW): 32

Molecular formula: N_2H_4

Structural formula:

$H_2N—NH_2$

Uses:
Hydrazine is used as a chemical intermediate in the production of agricultural chemicals and chemical blowing agents, and as a corrosion inhibitor, water treatment agent, and rocket propellant [ATSDR 1997].

1.2 Purpose

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

1.3 Overview of SK Assignment for Hydrazine

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

2 Systemic Toxicity from Skin Exposure (SK: SYS)

No specific data on the degree of absorption of hydrazine in humans following dermal exposure were found in the literature search. However, there is evidence from kinetic studies in animals that hydrazine is rapidly absorbed through the skin following topical application. Keller et al. [1981] investigated the percutaneous absorption of anhydrous hydrazine (>95%) and an azeotropic mixture of 70% hydrazine and 30% water, referred to as H-70, in rabbits. Test animals received applied doses of 12

Table 1. Summary of the SK assignment for hydrazine

Skin Notation	Critical Effect	Data Available
SK: SYS (FATAL)	Central nervous system and reproductive	Sufficient animal data
SK: DIR (COR)	Skin corrosion	Sufficient animal data
SK: SEN	Skin allergy	Sufficient animal data

milligrams (mg) of the hydrazine solutions per kilogram (kg) body weight (free base) to an 8 square centimeter (cm^2) shaved (occluded) section of the thoraco-abdominal region. Blood samples were taken from the femoral vein of the rabbits to determine serum hydrazine concentrations at various intervals. The authors stated that within 50 to 60 minutes, mean peak serum hydrazine concentrations occurred. The peak values were reported to be 11.1 micrograms per milliliter (µg/mL) for anhydrous hydrazine and 9.3 µg/mL for H-70. In a later study, Keller et al. [1984], using the previously described protocols, reported that 42% of the applied dose of anhydrous hydrazine and 36% of the topically applied dose of H-70 were absorbed through rabbit skin at 6 minutes. Smith and Clark [1972] applied hydrazine to the skin of dogs as single doses ranging from 96 to 480 mg/kg. Hydrazine was detected in the blood within 30 seconds, reached maximum levels of 70 micrograms per liter (µg/L) in the blood after 3 hours, and produced systemic effects, including neurotoxicity and even death. These results indicate that hydrazine solutions are readily absorbed through the skin.

No dermal lethal dose (LD_{Lo}) has been established for humans, but a worker became comatose following dermal exposure that resulted in skin burns [Kirklin et al. 1976]. Smith and Clark [1972] reported the deaths of 10 of 25 dogs following a single topical application of hydrazine to the shaved chest. A dermal LD_{Lo} of 96 mg/kg in dogs has been estimated from the reported results. Values for dermal LD_{50} (the dose resulting in 50% mortality in the exposed population) of 91 to 290 mg/kg have been reported for the free base in rabbits and guinea pigs [Army Chemical Center 1949; Rothberg and Cope 1955; Montgomery and Reeves 1960]. Because the reported LD_{50} values in rabbits and guinea pigs are below the critical LD_{50} value of 200 mg/kg body weight that identifies chemical substances with potential for severe acute dermal toxicity [NIOSH 2009], hydrazine is identified as having the capability of causing extreme systemic toxicity and/or lethality following acute dermal exposure.

The literature search revealed no epidemiological investigations, clinical case histories, occupational worker cases, or animal studies of repeat-dose (21-day or 28-day), subchronic (90-day), or chronic (at least 12-month) dermal toxicity. However, there is suggestive evidence from case studies of humans that hydrazine is immunotoxic, as evidenced by development of systemic lupus erythematosus–like disease following dermal exposure [Reidenberg et al. 1983]. It should be noted that the dose that elicited the response was not quantified. In animals, maternal toxicity (evidenced by decreased body weight at 5 mg/kg or more) and a significant increase in number of resorptions per litter (at 50 mg/kg) were observed in pregnant rats exposed to a single dose of hydrazine (0–50 mg/kg; 95% purity) on gestation day 9 [Keller et al. 1982]. There was no other evidence of fetotoxicity or teratogenicity (no significant changes in

Table 2. Summary of the carcinogenic designations* for hydrazine from numerous governmental and nongovernmental organizations

Organization	Carcinogenic designation
NIOSH [2006]	Potential occupational carcinogen
NTP [2009]	Reasonably anticipated to be a human carcinogen
USEPA [2009]	Group B2: Probable human carcinogen (based on sufficient evidence of carcinogenicity in animals)
IARC [1999]	Group 2B: Possibly carcinogenic to humans
EC [2010]	R45: May cause cancer
ACGIH [2001]	A3: Confirmed animal carcinogen with unknown relevance to humans

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.

fetal body weight or increase in fetal abnormalities) in this single-dose study. Lowest-observed-adverse-effect levels (LOAELs) of 5 mg/kg (for the dams) and 50 mg/kg (for developmental effects) were observed. The single-dose dermal LOAEL of 5 mg/kg (for maternal effects) observed by Keller et al. [1982] suggests that the critical dermal effect level for prolonged exposure is likely to be lower than 1000 mg/kg/day, the level which identifies chemical substances with the potential for repeat-dose, subchronic, or chronic dermal toxicity [NIOSH 2009]. Therefore, hydrazine is considered potentially systemically toxic following dermal exposure.

No epidemiological studies that evaluated the potential of hydrazine to cause cancer following dermal exposure were identified. Helmers et al. [2004] described a case of epithelioid sarcoma in the thumb of a patient after repeated cutaneous exposure to hydrazine fuel; the dose of hydrazine was not reported. Although no standard carcinogenicity bioassay has been established for animals, dermal exposure of mice to 0.1 milliliters (mL) of a 10% solution of hydrazine hydrate for 300 days (for a total of 200 applications and a total dose of 2000 mg/animal) resulted in 50% mortality and lung tumor incidence of 54% (adenomas), 24% (anaplastic adenomas), and 22% (carcinomas) [Milia and Leo 1965]. Among the untreated and vehicle-control animals there were no deaths, but lung adenomas were observed in 16% and 12%, respectively. The dose used in this study was 10 mg/day/animal, corresponding to approximately 430 mg/kg/day, assuming a United States Environmental Protection Agency (USEPA) [1988] default average chronic body weight of 0.023 kg for Balb/c mice used in this study. Table 2 provides a summary of carcinogenic designations from multiple governmental and nongovernmental organizations for hydrazine.

No estimates of hydrazine absorption in humans following dermal exposure were identified. Data from absorption studies in rabbits **[Army Chemical Center 1949; Keller et al. 1981, 1984; Smith and Clark 1972*]**,

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

acute toxicity studies in multiple animals **[Army Chemical Center 1949; Rothberg and Cope 1955]**, and a reproductive toxicity study **[Keller et al. 1982]** following dermal exposure are sufficient to conclude that hydrazine is absorbed through the skin, is systemically available, and is toxic (causing central nervous system effects and a body weight decrease). Therefore, hydrazine is assigned a SK: SYS (FATAL) notation.

3 Direct Effect(s) on Skin (SK: DIR)

Although no evidence of corrosivity in humans has been identified, a number of studies suggest that skin exposure to liquid hydrazine or high concentrations of hydrazine may result in chemical burns and corrosion in animals. Keller et al. [1984] reported severe chemical burns—evidenced by transdermal necrosis, with varying degrees of dermal necrosis—in rabbits topically exposed to anhydrous hydrazine or H-70, but they found no lesions following application of 2% or 15% aqueous solutions of hydrazine. Rothberg and Cope [1955] reported chemical burns in guinea pigs and rabbits following a single topical application of an unspecified hydrazine solution. The authors reported that 15 minutes after exposure the skin was discolored, and at 24 hours post- exposure the discoloration penetrated into the dermis and was accompanied by acute inflammation and edema. In addition, Rothberg and Cope [1955] described erosion at the site of application that extended into the subcutaneous tissue and noted moderate edema 72 hours after application of the hydrazine solution. A single application of liquid, reagent-grade hydrazine to the shaved chests of dogs resulted in burns [Smith and Clark 1972]. The authors noted that within 2 minutes the skin at the site of application became red and progressed to edema, which subsided after 30 minutes. In a study by Miles Inc. [1992], application of 0.5 mL of a 36.1% hydrazine solution, a 56.5% hydrazine hydrate solution, or formulated products containing 35% hydrazine to abraded or intact skin of rabbits under occlusion for 4 hours resulted in skin corrosion. In that study, a formulated product containing 15% hydrazine was corrosive to abraded but not intact rabbit skin. On the basis of its chemical structure, hydrazine is predicted by the structure-activity relationship model (Deductive Estimation of Risk from Existing Knowledge [DEREK™] for Windows) to be a plausible irritant.

Although the literature search produced no evidence of corrosivity of hydrazine to human skin, the chemical is corrosive to the skin of rabbits **[Keller et al. 1984; Miles Inc. 1992]**, guinea pigs **[Rothberg and Cope 1955]**, and dogs **[Smith and Clark 1972]** when applied undiluted or at high concentrations, and more dilute solutions tend to be irritating to the skin. Therefore, on the basis of the data for this assessment, hydrazine is assigned the SK: DIR (COR) notation.

4 Immune-mediated Responses (SK: SEN)

Several diagnostic tests were identified demonstrating that dermal exposure to hydrazine produces allergic contact dermatitis in humans. For example, positive reactions were reported in open epicutaneous or closed patch tests conducted on volunteers or persons presenting with contact dermatitis following occupational exposures to hydrazine and its monochloride, sulfate, and hydrobromide salts [Rothberg and Cope 1955; Evans 1959; Frost and Hjorth 1959; van Ketal 1964; Wheeler et al. 1965; Hovding 1967; Suzuki and Ohkido 1979; Reidenberg et al. 1983; Wrangsjo and Martensson 1986; Goh and Ng 1987].

The studies of Suzuki and Ohkido [1979], Wrangsjo and Martensson [1986], Frost and Hjorth [1959], Hovding [1967], and van Ketel [1964] indicated that in humans, dermal exposure to solutions containing low concentrations of hydrazine (0.00005% to 1%) cause allergic contact dermatitis. No studies of the sensitization potential of hydrazine in animals were identified. Predictions using structure-activity relationship models provide some information regarding this endpoint; on the basis of its chemical structure, hydrazine is predicted by DEREK™ to be a sensitizer.

There is sufficient evidence from diagnostic human patch tests **[Frost and Hjorth 1959; Hovding 1967; Suzuki and Ohkido 1979; Wrangsjo and Martensson 1986]** to demonstrate that exposure to hydrazine causes skin sensitization. Therefore, on the basis of the data for this assessment, hydrazine is assigned the SK: SEN notation.

5 Summary

No specific data were identified that estimated the degree of absorption of hydrazine in humans following dermal exposure. However, sufficient data were identified from absorption studies in rabbits **[Army Chemical Center 1949; Keller et al. 1981, 1984]**, acute toxicity studies in rabbits and guinea pigs **[Army Chemical Center 1949; Rothberg and Cope 1955]**, and a reproductive toxicity study **[Keller et al. 1982]** following dermal exposure to conclude that hydrazine is absorbed through the skin, is systemically available, and is toxic (causing central nervous system effects and a body weight decrease). There is no evidence from studies of humans that hydrazine is corrosive to human skin. However, sufficient information was identified to demonstrate that the chemical is corrosive to the skin of rabbits **[Keller et al. 1984; Miles Inc. 1992]**, guinea pigs **[Rothberg and Cope 1955]**, and dogs **[Smith and Clark 1972]** when applied as undiluted or at high concentrations, whereas more dilute solutions tend to be irritating to the skin. Several human diagnostic patch tests [for example, **Frost and Hjorth 1959; Hovding 1967; Suzuki and Ohkido 1979**; and **Wrangsjo and Martensson 1986**] sufficiently show that exposure to hydrazine causes skin sensitization. Therefore, on the basis of these assessments, hydrazine is assigned a composite skin notation of **SK: SYS (FATAL)-DIR (COR)-SEN**.

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

Table 3. Historical summary of the skin hazard designations for hydrazine

Organization	Skin hazard designation
NIOSH [2006]	No skin notation assigned.
OSHA [2003]	[skin]: Potential for dermal absorption
ACGIH [2001]	[skin]: Based on the reported rapid and significant absorption and significant systemic toxicity following dermal application of hydrazine to test animals
EC [2010]	R24: Toxic in contact with skin R34: Causes severe burns 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.

equivalent Globally Harmonized System (GHS) of Classification and Labeling of Chemicals dermal designation for hydrazine is Acute Toxicity Category 3 (Hazard statement: Toxic in contact with the skin), Skin Corrosion Category 1B (Hazard statement: Causes severe skin burns and eye damage)), and Skin Sensitization Category 1 (Hazard statement: May cause an allergic skin reaction) [European Parliament 2008]. Hydrazine has been identified as a Category 1B Carcinogen (Hazard statement: May cause cancer) [European Parliament 2008].

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

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