NIOSH Skin Notation Profile
Formamide

[CAS No. 75-12-7]

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 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]. 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 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 formamide 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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Abbreviations

ACGIH®	American Conference of Governmental Industrial Hygienists
CIB	Current Intelligence Bulletin
cm^2	square centimeter(s)
DIR	skin notation indicating the potential for direct effects to the skin following contact with a chemical
ECHA	European Chemicals Agency
GD	gestation day
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
LD_{50}	median lethal dose
LD_{Lo}	dermal lethal dose
mg	milligram(s)
mg/kg	milligram per kilogram
mg/m^3	milligram per cubic meter
MW	molecular weight
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
NOAEL	no-observed-adverse-effect level
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
µL	microliter(s)

Glossary

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

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

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

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

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

Dermal—Referring to the skin.

Dermal contact—Contact with (touching) the skin.

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

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

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

Substance—A chemical.

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

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1 Introduction

1.1 General Substance Information

Chemical: Formamide

CAS No: 75-12-7

Molecular weight (*MW*): 45.04

Molecular formula: CH_3NO

Structural formula:

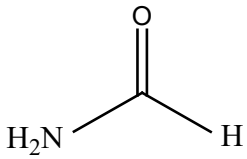

Image Source: Redrawn from PubChem [NLM, no date].

General substance information was obtained from NIOSH [2007].

Synonyms: carbamaldehyde, formic acid, amide, formimidic acid, methanamide, methanoic acid amide

Uses: Formamide is used as a chemical intermediate, a solvent, and a softener for water soluble gums, animal glues, and paper [NLM, no date].

1.2 Purpose

This *Skin Notation Profile* presents (1) a brief summary of technical data associated with skin contact with formamide and (2) the rationale behind the hazard-specific skin notation (SK) assignment for the compound. 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 formamide. A literature search was conducted through February 2023 to identify information on formamide, including but not limited to data relating to its 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 of humans, animals, or appropriate modeling systems that are relevant to assessing the effects of dermal exposure to formamide.

1.3 Overview of SK Assignment for Formamide

Formamide 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 formamide: **SK: SYS-DIR(IRR)**. Table 1 provides an overview of the critical effects and data used to develop the

SK assignment for formamide. The following section provides additional detail about the potential health hazards of skin contact with formamide and the rationale behind the SK assignment.

Table 1. Summary of the SK Assignment for formamide

Skin notation	Critical effect	Available data
SK: SYS	Reproductive toxicity	Limited animal data
SK: DIR(IRR)	Irritation	Limited animal data

2 Systemic Toxicity from Skin Exposure (SK: SYS)

No studies evaluating toxicokinetic properties were identified that quantified dermal absorption after dermal exposure to humans or animals. However, the ability of formamide to be absorbed through the skin may be inferred from the systemic toxicity effects that have resulted from the dermal application of the compound to the skin of experimental animals. There have been considerable improvements and advancements in dermal absorption studies and modeling since the publication of CIB 61 [NIOSH 2017]. 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 dermal lethal dose (LD_{Lo}) has been established for humans. The reported median dermal LD_{50} (the dose resulting in 50% mortality in the exposed population) values for the dermal route of exposure in rats was greater than 17,000 milligrams per kilogram (mg/kg) body weight [Eastman Kodak 1969] This value exceeds the critical dermal LD_{50} of 2,000 mg/kg that identifies chemical substances with the potential for acute dermal toxicity [NIOSH 2009]. Therefore, formamide is not considered acutely toxic following dermal exposure.

While no epidemiological studies were identified that evaluated the potential of formamide to cause systemic effects in humans following dermal exposure, BASF Wyandotte Corporation [1985] addressed the subchronic exposure of Wistar rats via the dermal route. In the 90-day dermal study in Wistar rats [BASF Wyandotte 1985], 0, 30, and 100 mg/kg formamide (10 female and 10 male rats per dosage) was applied to intact skin for 6 hours per day, 5 days per week under a semi-occlusive dressing. Twenty male and female rats were exposed under the same conditions at the high dose of 3,000 mg/kg. No effects were observed in the 30 and 100 mg/kg dosage groups for males or females. Male and female rats receiving 3,000 mg/kg of

formamide exhibited unkempt fur, reduced food intake, and decreased body weight. Decreases in absolute weights of the liver, kidneys, spleen, and testes in male rats were reported [BASF Wyandotte 1985]. The high dose group also exhibited reductions in the leukocyte, lymphocyte, and platelet counts and increases in hemoglobin, erythrocyte count, hematocrit, mean corpuscular hemoglobin and mean corpuscular volume, as well as increases in the reticulocyte count and carboxyhemoglobin content [BASF Wyandotte 1985].

A study evaluated the embryotoxicity of 600 mg/kg formamide when applied to the skin of pregnant Sprague-Dawley rats on gestion day (GD) 9, GDs 10 and 11, GDs 11 and 12, or GDs 12 and 13 [DuPont 1992]. Six control animals were exposed to a blank solution (water only) on GDs 10 and 11 [DuPont 1992]. On GD 13, the rats were necropsied and examined for the number of live and dead fetuses, number of implantation and resorption sites, fetal weight, crown-rump length, and visceral and skeletal abnormalities. The investigators concluded that formamide was a weak embryotoxic agent under the conditions of the experiment and that a higher dose would be needed to produce teratogenic effects. However, there was a slight increased embryolethality in dams, from 2% in controls to 5% in dams exposed to formamide on GDs 11 and 12.

Table 2 summarizes carcinogenic designations of multiple governmental and nongovernmental organizations for formamide.

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

Organization	Carcinogenic designation
ACGIH [2022]	A3: Confirmed animal carcinogen with unknown relevance to humans.
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 data were identified that estimated the degree of absorption of formamide through the skin of humans or animals following dermal exposure. Dermal LD_{50} values in rats of greater than 17,000 mg/kg suggested formamide is not acutely toxic [Eastman Kodak 1969]. However, studies in rats have demonstrated that dermally applied formamide can bring about systemically toxic effects **[BASF Wyandotte 1985]*** and slight increase in teratogenic effects **[DuPont 1992]**. Therefore, on the basis of the data for this assessment, formamide is assigned the **SK: SYS** notation.

3 Direct Effects on Skin (SK: DIR)

No data that evaluated the skin corrosivity of formamide or *in vitro* tests for corrosivity using human or animal skin models or *in vitro* tests of skin integrity using cadaver skin were identified. There is a paucity of information on the capacity of formamide to cause skin irritation in humans or experimental animals. BASF Wyandotte [1985] reported that Wistar rats dermally exposed to 3,000 mg/kg formamide 6 hours/day, 5 days/week for 13 weeks exhibited erythema that

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

disappeared within 1-2 hours, and Eastman Kodak [1969] reported slight irritation when formamide was held in occluded contact with the skin of guinea pigs for 24 hours. No methodological details or experimental results were provided by Eastman Kodak [1969].

Animal studies have shown slight irritation after exposure to formamide [**BASF Wyandotte 1985**] and **[**Eastman Kodak 1969]. Based on the limited evidence, formamide is assigned a SK:DIR (IRR) notation.

4 Immune-mediated Responses (SK: SEN)

No occupational exposure studies or diagnostic patch tests in humans or predictive tests (guinea pig maximization tests, Buehler test, murine local lymph node assays, etc.) that evaluated the potential of formamide to cause skin sensitization were identified.

In a study assessing dermal sensitization, Eastman Kodak [1969] reported that a standard test for skin sensitization in guinea pigs resulted in 0/5 animals being sensitized by formamide; however, study details of the methods were not available. The paucity of data precludes adequate evaluation of the skin sensitization potential of formamide. Therefore, this assessment does not assign a SK: SEN for formamide.

5 Summary

No data that evaluated the skin corrosivity of formamide or *in vitro* tests for corrosivity using human or animal skin models or *in vitro* tests of skin integrity using cadaver skin were identified. Dermal LD_{50} values were reported that suggest formamide is not acutely toxic [Eastman Kodak 1969], however, other experiments have demonstrated that dermally applied formamide can bring about systemically toxic effects **[BASF Wyandotte 1985]** and teratogenic effects in Sprague-Dawley rats [**DuPont 1992]**. Limited data were available that indicated potential for slight irritation [**BASF Wyandotte 1985**]. No occupational exposure studies or diagnostic patch tests in humans or predictive tests (guinea pig maximization tests, Buehler test, murine local lymph node assays, etc.) that evaluated the potential of formamide to cause skin sensitization were identified. Eastman Kodak Corporation [1969] reported that a standard test for skin sensitization in guinea pigs resulted in 0/5 animals being sensitized by formamide. Based on these assessments, formamide is assigned a composite skin notation of **SK: SYS-DIR(IRR)**.

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

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

Organization	Skin hazard designation
ACGIH [2022]	[skin]: Formamide can produce systemic effects following dermal exposure
ECHA [2023]	No designation
NIOSH [2007]	[skin]: Prevent skin contact
OSHA [2020]	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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