NIOSH Skin Notation Profile

Sodium Fluoroacetate

SK

ID^{SK}

[~~SK~~]

SYS

SYS (FATAL)

DIR

DIR (IRR)

DIR (COR)

SEN

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NIOSH Skin Notation Profile

Sodium Fluoroacetate

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 sodium fluoroacetate. 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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Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
amu	atomic mass unit
ATSDR	Agency for Toxic Substances and Disease Registry
CIB	Current Intelligence Bulletin
cm²	square centimeter(s)
cm/hr	centimeter(s) per hour
cm/s	centimeter(s) per second
COR	subnotation of SK: COR indicating the potential for a chemical to be a skin corrosive following exposure to 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 the potential for the chemical to be fatal following dermal absorption
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
IRR	subnotation of SK: DIR indicating the potential for a chemical to be a skin irritant following exposure to the skin
ID$^{(SK)}$	skin notation indicating insufficient data on the health hazards associated with skin exposure
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$_{50}$	lethal dose resulting in 50% mortality in the exposed population
LD$_{Lo}$	lowest detected lethal dose
LLNA	local lymph node assay
LOAEL	lowest-observed-adverse-effect level
log K_{OW}	base-10 logarithm of a substance's octanol–water partition
M	molarity
m³	cubic meter(s)
mg	milligram(s)
mg/cm²/hr	milligram(s) per square centimeter per hour
mg/kg	milligram(s) per kilogram body weight
mg/m³	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
ppm	parts per million
REL	recommended exposure limit
RF	retention factor
SEN	skin notation indicating the potential for immune-mediated reactions following exposure of the skin
SFA	sodium fluoroacetate
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
US EPA	United States Environmental Protection Agency
µg	microgram(s)
µg/cm²	microgram(s) per square centimeter
µg/cm²/hr	microgram(s) per square centimeter per hour
µL	microliter(s)
µmol	micromole(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 occur 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

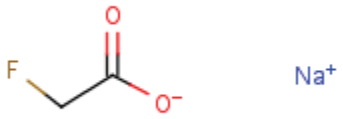
Chemical: Sodium fluoroacetate (SFA)

CAS No: 62-74-8

Molecular weight (*MW*): 100.3

Molecular formula: FCH_2COONa

Structural formula:



Synonyms: SFA; sodium monofluoroacetate

Uses: SFA is an organofluorine compound used primarily as a predacide against coyotes that prey on farm animals [USEPA 1995]. No estimate of the annual volume produced or used in the United States was identified during this assessment.

1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with SFA and (2) the rationale behind the hazard-specific skin notation (SK) assignment for SFA. The SK assignment is based on the scientific rationale and logic outlined in the *Current Intelligence Bulletin 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 SFA. A literature search was conducted through February 2018 to identify information on SFA, including but not limited to data relating to its 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 SFA. The criteria for the search strategy, evaluation, and selection of data are described in Appendix E in *Current Intelligence Bulletin 61: A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009]

1.3 Overview of SK Assignment

SFA may potentially be capable of causing adverse health effects following skin contact. A critical review of available data has resulted in the following SK assignment for SFA: **ID**$^{(SK)}$, indicating that SFA has been evaluated, but insufficient data exists to accurately assess the hazards of skin exposure. Table 1 provides an overview of the critical effects and data used to develop the SK assignment for SFA.

Table 1. Summary of the SK assignment for SFA

Skin notation	Critical effect	Available data
ID$^{(SK)}$	—	—

2 Systemic Toxicity from Skin Exposure (SK: SYS)

No *in vivo* or *in vitro* toxicokinetic studies were identified that estimated the degree of absorption of SFA through the skin of humans or animals following dermal exposure. The potential of SFA 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 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 3.24 was calculated for SFA. An SI ratio of ≥0.1 indicates that skin absorption may significantly contribute to the overall body burden of a substance [NIOSH 2009]; therefore, SFA has the potential to be absorbed through the skin and to become available systemically following dermal exposure. Additional information on the SI ratio and the variables used in its calculation are included in the SI ratio appendix.

No estimate of the human dermal lethal dose (LD_{Lo}) was identified for SFA, and no dermal LD_{50} (the dose resulting in 50% mortality in the exposed animals) values were identified for SFA.

No epidemiological, occupational exposure studies, or case reports and no repeat-dose, subchronic or chronic toxicity studies in animals were identified that evaluated the potential for SFA to cause systemic toxicity following dermal exposure. Burns and Connolly [1995] reported that lambs wearing punctured livestock protection collars for seven days, exposing them to SFA, did not exhibit dermal erythema or edema but died after ingesting the product.

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

Although the mathematical model predicted SFA to be dermally absorbed through the skin following dermal exposure, no toxicokinetic studies or acute toxicity studies were identified that estimated the degree of absorption of SFA or toxicity following dermal exposure. Therefore, on the basis of the data for this assessment, SFA is not assigned the SK: SYS notation.

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

Organization	Carcinogenic designation
NIOSH [2005]	No designation
NTP [2014]	No designation
US EPA [2015]	No designation
European Parliament [2008]	No GHS designation
IARC [2012]	No designation
ACGIH [2001]	No designation

ACGIH = American Conference of Governmental Industrial Hygienists; 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.

3 Direct Effects on Skin (SK: DIR)

No human or animal *in vivo* studies that evaluated the skin corrosivity of SFA, *in vitro* tests for corrosivity using human or animal skin models, or *in vitro* tests of skin integrity using cadaver skin were identified. Additionally, no case reports or standard skin irritation tests were identified that evaluated the potential of SFA to be corrosive or irritating to the skin of humans or animals. Therefore, on the basis of the data for this assessment, SFA is not assigned the SK: DIR notation.

4 Immune-mediated Responses (SK: SEN)

No 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 that evaluated the potential for SFA to cause skin sensitization were identified. However, the US EPA [1995] waived the requirement for dermal sensitization study for SFA because of the severe acute oral toxicity, reported oral LD_{50} values of 0.22 mg/kg in rats, 0.055 mg/kg for dogs, and 0.34 mg/kg for rabbits, and in the restriction of its use in livestock protection collars. Therefore, on the basis of the data for this assessment, SFA is not assigned the SK: SEN notation.

5 Summary

Although the mathematical model predicted sodium fluoroacetate to be dermally absorbed through the skin following dermal exposure, no toxicokinetic studies or acute toxicity studies were identified that estimated the degree of absorption of SFA or toxicity following dermal exposure. No epidemiological or occupational exposure studies or case reports and no repeat-dose, subchronic or chronic toxicity studies were identified that evaluated the potential for SFA to be systemically toxic. No studies were identified that evaluated the skin corrosivity or potential for skin irritation after dermal exposure to SFA. Although no diagnostic (human patch) tests or predictive tests in animals were identified that evaluated the potential of the compound to be a skin sensitizer, the US EPA [1995] waived the requirement for dermal sensitization study for SFA because of severe acute toxicity of the compound and the restriction of its use in a livestock protection collar. However, these data could not be included in this assessment since the acute toxicity studies were based on oral LD_{50} values. Therefore, on the bases of these assessments, SFA is assigned a skin notation of **ID**$^{(SK)}$.

Table 3 summarizes the skin hazard designations for SFA previously issued by NIOSH and other organizations. The equivalent dermal designation for SFA, according to the Globally Harmonized System (GHS) of Classification and Labelling of Chemicals, is Acute Toxicity Category 1 (Hazard statement: Fatal in contact with the skin) [European Parliament 2008].

Table 3. Summary of previous skin hazard designations for SFA

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption
OSHA [2018]*	[skin]: Potential for dermal absorption
ACGIH [2001]	[skin]: Based on rapid absorption through intact and abraded or cut skin

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

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Appendix: Calculation of the SI Ratio for Sodium Fluoroacetate

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for SFA. 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 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 the 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 (kp)

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

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 squared centimeters [cm^2]).

Equation 2: Determination of Skin Dose

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

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

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

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 SFA. The calculated SI ratio was 3.24. On the basis of these results, SFA is predicted to represent a skin absorption hazard.

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Table A1. Summary of data used to calculate the SI ratio for sodium fluoroacetate

Variables used in calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path(k_{psc})	cm/hr	3.8312×10^{-6}
Permeation coefficient of the protein fraction of the stratum corneum (k_{poi})	cm/hr	1.519×10^{-5}
Permeation coefficient of the watery epidermal layer (k_{aq})	cm/hr	0.25
Molecular weight (MW)†	amu	100
Base-10 logarithm of its octanol–water partition coefficient (Log K_{OW})*	None	-3.78
Calculated skin permeation coefficient (k_p)	cm/hr	1.9012×10^{-5}
Skin dose		
Water solubility (S_W)*	mg/cm^3	1110
Calculated skin permeation coefficient (k_p)	cm/hr	1.9012×10^{-5}
Estimated skin surface area (palms of hand)§	cm^2	360
Exposure time	Hr	8
Calculated skin dose	Mg	60.80
Inhalation Dose		
Occupational exposure limit (OEL)‡	mg/m^3	2.5
Inhalation volume	m^3	10
Retention factor (RF)	None	0.75
Inhalation dose	Mg	18.75
Skin dose–to–inhalation dose (SI) ratio	None	3.24

*Variables identified from SRC [2009].
†NIOSH Pocket Guide to Chemical Hazards [2005]
‡The OEL used in calculation of the SI ratio for sodium fluoroacetate 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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