

NIOSH Skin Notation Profiles

Acrylamide

SKK

ID^{SK}

[SK]

SYS

SYS (FATAL)

DIR

DIR (IRR)

DIR (COR)

SEN

NIOSH Skin Notation (SK) Profiles

Acrylamide

[CAS No. 79–06–1]

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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 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 (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 acrylamide (CAS No. 79-06-1). 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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and Health
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Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
ATSDR	Agency for Toxic Substances and Disease Registry
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
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
LOAEL	lowest-observed-adverse-effect level
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/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
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.

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1 Introduction

1.1 General Substance Information

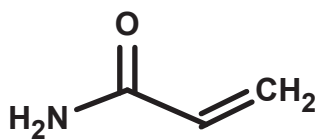
Chemical: Acrylamide

CAS No: 79-06-1

Molecular weight (MW): 71.08

Molecular formula: C₃H₅NO

Structural formula:



Synonyms:

Acrylamide monomer; Acrylic amide; Propenamide; 2-Propenamide; Propenoic acid amide; Vinyl amide

Uses:

The primary use of acrylamide is in the production of polyacrylamide polymers [ATSDR 2009]. Secondary applications include use as a chemical intermediate in the production of dyes and organic substances, such as N-methylol acrylamide and N-butoxyacrylamide, and as a binder and retention aid in pulp and paper production. The Agency for Toxic Substances and Disease Registry (ATSDR) [2009] reported that in 2006 and 2007 the demand for acrylamide in the United States was 245 and 253 million pounds, respectively.

1.2 Purpose

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

Table 1. Summary of the SK assignment for acrylamide

Skin notation	Critical effects	Available data
SK: SYS	Neurotoxicity; reproductive effects	Sufficient human and animal data
SK: DIR (IRR)	Skin irritation; skin tumors (cancer)	Limited human and animal data
SK: SEN	Skin allergy	Limited human data; sufficient animal data

1.3 Overview of SK Assignment for Acrylamide

Acrylamide 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 acrylamide: **SK: SYS-DIR (IRR)-SEN**. Table 1 provides an overview of the critical effects and data used to develop the SK assignment for acrylamide.

2 Systemic Toxicity from Skin Exposure (SK: SYS)

Toxicokinetic studies involving humans and animals following skin exposure to acrylamide were identified. Fennell et al. [2006] applied 3 milligrams per kilogram body weight (mg/kg) of a 50% (weight/volume) radiolabeled acrylamide solution to an occluded 24-square-centimeter (cm²) patch of skin on the forearm of volunteers; it should be noted that the specific vehicle used within this experiment was not disclosed. The authors stated that 0.73 to 0.86 mg/kg per day (mg/kg/day), or 25% to 29%, of the applied dose was absorbed through the skin. In rats, Sumner et al. [2003] reported, 14% to 30% of the applied dose of acrylamide was absorbed,

with a mean of approximately 21%, when these animals were treated with an occluded dermal dose of 162 mg/kg [^{2,3-14}C]-labeled acrylamide in distilled water. The authors reported that acrylamide was distributed throughout the test animals' bodies following the 24-hour dermal exposure period; the locations of highest concentrations of acrylamide (excluding treatment site) were as follows: blood cells > skin at nondosing sites > liver, spleen, testes, and kidneys > lungs, thymus, brain, and epididymis > fat. These findings from in vivo human and rat studies indicate that acrylamide can be readily absorbed through the skin and distributed throughout the body following dermal exposure.

The potential of acrylamide to pose a skin absorption hazard was also evaluated, with 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 2955 was calculated for acrylamide. 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 lethal dermal concentration (LDLo) for humans has been identified for acrylamide. However, following studies of rabbits, dermal LD₅₀ values (doses resulting in 50% mortality in the exposed population) of 252 to 1102 mg/kg were reported [American Cyanamid Company 1973; Dow Chemical USA 1975]. Because the reported acute dermal LD₅₀ values for the rabbit are lower than the critical dermal LD₅₀ value of 2000 mg/kg body weight that identifies substances with the potential for acute dermal toxicity [NIOSH 2009], acrylamide is considered acutely toxic following dermal exposure.

Numerous occupational exposure studies and epidemiological investigations have revealed neurotoxic effects in workers exposed to acrylamide. Despite exposures occurring through the inhalation and dermal routes, the contribution of skin contact with acrylamide to onset of the neurological effects was emphasized. He et al. [1989] investigated the onset of neurotoxicity in 71 workers employed at a plant in China. The authors noted symptoms such as weakness and numbness in extremities, preceded by skin peeling, and reported that the total prevalence of acrylamide poisoning among the workers was 73.2%. Three of the cases involving acrylamide were classified as severe poisonings, six as moderate poisonings, and 43 as mild poisonings. The authors concluded that dermal contact contributed significantly to these cases and that dermal exposure to acrylamide should be prevented. NIOSH [1991] reported neurotoxic effects (peripheral neuropathies)

following a latency period of days to weeks in workers who handled 27% to 30% aqueous solutions of acrylamide for 1 to 18 months. Dermatitis, characterized as peeling of skin at the site of contact (in this case, palms), was observed prior to the development of peripheral neuropathies, indicating that skin exposure had occurred. These workers were likely exposed repeatedly through both inhalation and dermal contact, but it is not clear whether the neuropathies were caused by skin absorption of acrylamide. Bachmann et al. [1992] investigated acrylamide exposures among 82 chemical industry workers. A significantly increased prevalence rate for several neurological symptoms, including numbness, limb pain, and sweating, in addition to skin peeling, was reported for acrylamide-exposed workers in comparison with unexposed controls. The results of this study indicate that dermal contact with acrylamide may have contributed to onset of the reported neurological effects. The International Agency for Research on Cancer (IARC) [1994] also reported that acrylamide causes damage to the central nervous system following occupational dermal and respiratory exposure.

A few repeat-dose dermal toxicity studies in animals were identified. Dow Chemical USA [1975] reported that 10 applications of a 50.7% acrylamide solution (amount or frequency of application not specified) to the intact or abraded skin of rabbits did not produce any signs of systemic toxicity. Eastman Kodak Company [1978] reported that 0.5 mL rubbed on the backs of rats each day for 15 days produced no signs of weakness or ataxia during the following 9-month observation period. Drees et al. [1976] reported peripheral neuropathies at a lowest-observed-adverse-effect level (LOAEL) of 50 mg/kg/

day when acrylamide was applied topically to the skin of newborn rabbits for 5 to 12 weeks. The no-observed-adverse-effect level (NOAEL) in this study was 5 mg/kg/day. A long-term study also identified a NOAEL of 0.5 mg/kg/day when acrylamide was applied to rats' tails (equivalent to 5% body surface area) [Novikova 1979]. This NOAEL was based on pronounced functional neurotoxic effects, characterized by a decrease in motor activity and impaired conditioned reflex response, and a reduction in body weight at 5 mg/kg/day, the LOAEL. On the basis of both the subacute and longer-term animal studies and limited human case reports, it appears that repeated and prolonged dermal exposure to acrylamide may cause systemic effects. Because the NOAELs identified in these studies are potentially lower than the critical dermal NOAEL value of 1000 mg/kg per day for repeat-dose toxicity that identifies substances with the potential for subchronic dermal toxicity [NIOSH 2009], acrylamide is considered to be neurotoxic with repeated dermal exposure.

No standard toxicity or specialty studies were identified that evaluated effects specific to the biological system or biological function (including reproductive and developmental effects and immunotoxicity) following dermal exposure to acrylamide. However, the literature search revealed a genotoxicity study with endpoints (e.g., induction of dominant lethal mutations) that might be considered an indicator of reproductive function. In a mouse dominant lethal study, acrylamide induced a significant increase in the percentage of dead implants per female when male mice were given 5 dermal applications of 25 mg/kg acrylamide 7 to 10 days prior to mating with female mice [Gutierrez-Espeleta et al. 1992]. Adler et al. [2004] also reported

heritable translocations when male mice were dermally exposed to acrylamide 1 day prior to mating with female mice. These findings suggest that acrylamide has the potential to cause reproductive effects via effects on sperm DNA.

Table 2 provides a summary of carcinogenic designations from multiple governmental and nongovernmental organizations for acrylamide. No evidence of a link between dermal exposures to acrylamide and increased risk of systemic cancers in humans or animals has been identified. It should be noted, however, that the reviewed toxicokinetic data indicate that acrylamide is readily absorbed by the skin and contributes to total body burden [Sumner et al. 2003; Fennell et al. 2006]. For this reason, it is assumed that dermal uptake of acrylamide may contribute to the onset of systemic cancers.

Sufficient information was identified from the toxicokinetic data on humans [**Fennell et al. 2006**] and on animals [**Sumner et al. 2003**]; the predictions of the mathematical algorithm; and the data from acute [**American Cyanamid Company 1973; Dow Chemical USA 1975**] and repeat-dose [**Drees et al. 1976; Novikova 1979; Gutierrez-Espeleta et al. 1992; Adler et al. 2004**] dermal toxicity studies in animals to demonstrate that acrylamide is readily absorbed through the skin and can cause systemic effects, including neurotoxicity and reproductive system effects, following dermal exposure. Therefore, on the basis of the data for this assessment, acrylamide is assigned the SK: SYS notation.

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

Table 2. Summary of the carcinogenic designations* for acrylamide by numerous governmental and nongovernmental organization

Organization	Carcinogenic designation
NIOSH [2005]	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 [1994]	Group 2A: Probably carcinogenic to humans
EC [2010]	R45: May cause cancer
ACGIH [2005]	Group 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.

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

Numerous occupational studies reporting adverse effects of the skin following dermal contact were identified. He et al. [1989] assessed acrylamide exposures at a factory in China. The authors reported that workers experienced skin peeling attributed to skin contact with acrylamide. Although acrylamide exposures occurred through the inhalation and dermal routes, the authors specifically emphasized that skin contact was not controlled, indicating its impact on the workers. NIOSH [1991] reported similar findings in workers who handled 27% to 30% aqueous solutions of acrylamide for 1 to 18 months. Bachmann et al. [1992] reported an increased prevalence of skin peeling in acrylamide-exposed chemical industry workers, in comparison with unexposed controls.

A skin irritation test [American Cyanamid Company 1952] in 25 persons at doses of

1% to 25% acrylamide indicated a dose-related increase in the number and degree of irritant responses, which led the author to conclude that acrylamide is a skin irritant. A limited number of dermal irritation studies in experimental animals were identified. Following a skin irritation study in which a 10% solution of acrylamide was applied repeatedly to the ear and shaved intact abdomen of rabbits with a “cuff” technique, McCollister et al. [1964] reported very slight reddening and slight edema, which healed when the application was stopped. Investigators at Dow Chemical USA [1975] also observed no reactions to a single application of a 50.7% solution of acrylamide to intact skin, but they reported that repeated applications of the solution to intact and abraded skin of rabbits produced reddening. In another study, application of 2.0 milliliters per kilogram (mL/kg) of an 80% saline solution of acrylamide to the shaven abdomen of three rabbits provoked slight irritation in one animal for no more than 48 hours

[American Cyanamid Company 1951]. A study conducted by Mukhtar et al. [1981] reported acrylamide-induced depletion of skin glutathione levels in mice topically exposed to the substance. Those authors concluded that such depletion may cause dermal membrane damage with increased loss of cellular enzymes and increased interactions of reactive metabolites with essential macromolecules, resulting in the dermatitis and irritation of skin observed in acrylamide-exposed workers. The structure activity relationship model, Deductive Estimation of Risk from Existing Knowledge (DEREK™) for Windows, predicted acrylamide to be negative for skin irritation.

Bull et al. [1984a] conducted a skin initiation/promotion assay to investigate the potential for acrylamide to be carcinogenic in mouse skin. In that study, an acrylamide solution in ethanol was administered topically in six doses of 12.5, 25, and 50 mg/kg/day, resulting in total doses of 75, 150, and 300 mg/kg, respectively, over a 2-week period. Following the topical applications of acrylamide, a known tumor promoter [12-O-tetradecanoylphorbol-13-acetate (TPA)] in acetone was applied three times a week for 20 weeks to the shaved backs of test animals. Bull et al. [1984a] reported that the incidences of skin tumors were significantly elevated in a dose-response manner. It should be noted that mice that did not receive the TPA applications did not develop tumors. On the basis of these results, the authors theorized that acrylamide may be capable of acting as a skin tumor initiator.

The reports on occupational cases, studies involving volunteers [American Cyanamid Company 1952], and irritation and other studies in animals [American Cyanamid Company 1951; Mukhtar et al. 1981] have provided limited data indicating that

acrylamide is a mild skin irritant. In addition, acrylamide is identified as a potential skin tumor initiator and may increase the risk of skin cancer [Bull et al. 1984a]. Therefore, on the basis of the data for this assessment, acrylamide is assigned the SK: DIR (IRR) notation.

4 Immune-mediated Responses (SK: SEN)

On the basis of occupational exposure experience, the information available is insufficient to conclude that acrylamide is a skin sensitizer. The European Commission (EC) [2002] has reviewed two occupational case reports of allergic skin reactions. In one reported case, a laboratory technician developed “itchy, exudative” lesions on the hands and wrist while preparing substrates for polyacrylamide gel electrophoresis and despite wearing gloves. The reviews indicated that this individual also developed similar lesions 10 years earlier when working with the same material. In the other report, a student developed eczema 4 months after commencing working with a stock solution for polyacrylamide gel electrophoresis in immunological research, despite using latex gloves. This individual was exposed also to a number of “irritants” (unidentified), N,N'-methylenebis-acrylamide, as well as acrylamide and polyacrylamide [ECB 2002]. The individuals described in both of these case reports had no history of allergies; patch tests were positive, and there was improvement following a change of work in each case.

As indicated above, occupationally exposed workers who handled 27% to 30% aqueous acrylamide solution developed—through dermal contact and inhalation—dermatitis characterized by peeling of the skin at

the site of contact (i.e., palms), followed by development of peripheral neuropathies [NIOSH 1991]. However, mixed results were reported following patch testing. For example, the European Union [2002] reported negative results in patch-testing with a standard series, “acrylic and methacrylic allergens,” and a series of undefined acrylic and methacrylic allergens. Its review described positive skin reactions with 1% acrylamide in petrolatum after 48 hours and in an individual patch-tested with 5% acrylamide in petrolatum. A positive result in an open test with a solution containing 30% acrylamide and 0.8% N,N'-methylenebis-acrylamide at 2 and 4 days [ECB 2002]. In animals, acrylamide has been observed to cause skin sensitization. In a guinea pig maximization test, acrylamide elicited a positive skin response (in excess of that seen in controls) in 40% of the test animals [Huntingdon Research Center Ltd. 1995]. Eastman Kodak Company [1978] also reported sensitization in three guinea pigs administered a 10% acrylamide solution. The structure-activity relationship model, DEREK™, predicted acrylamide to be positive for skin sensitization.

Although acrylamide yielded inconsistent results in exposed humans, positive sensitization results from two guinea pig maximization tests [Allan 1995; Eastman Kodak Co. 1978] are sufficient to demonstrate that acrylamide is a skin sensitizer. Therefore, on the basis of the data for this assessment, acrylamide is assigned the SK: SEN notation.

5 Summary

Taken together, data from toxicokinetic studies involving humans [Fennell et al. 2006] and animals [Sumner et al. 2003],

from the predictions of mathematical algorithms, from acute toxicity studies in rabbits [American Cyanamid Company 1973; Dow Chemical USA 1975], and from repeat-dose dermal toxicity studies in animals [Drees et al. 1976; Novikova 1979; Gutierrez-Espeleta et al. 1992; Adler et al. 2004] were sufficient to demonstrate that acrylamide is absorbed through the skin and can cause systemic effects, including neurotoxicity and reproductive system effects, following dermal exposure. On the basis of reports on occupational cases and studies of human volunteers [American Cyanamid Company 1952] and on irritation and other studies in animals [American Cyanamid Company 1951; Mukhtar et al. 1981], there are limited data to indicate that acrylamide is a mild skin irritant. Acrylamide is identified as a potential skin tumor initiator and may increase the risk of skin cancer [Bull et al. 1984]. Although acrylamide yielded inconsistent results in exposed humans, positive sensitization results from two guinea pig maximization tests [Allan 1995; Eastman Kodak Co. 1978] are sufficient to demonstrate that acrylamide is a skin sensitizer. Therefore, on the basis of these assessments, acrylamide is assigned a composite skin notation of **SK: SYS-DIR (IRR)-SEN**.

Table 3 summarizes the skin hazard designations for acrylamide previously issued by NIOSH and other organizations. The equivalent dermal designations for acrylamide, according to the Globally Harmonized System (GHS) of Classification and Labeling of Chemicals, are Acute Toxicity Category 4 (Hazard statement: Harmful in contact with the skin), Skin Irritation Category 2 (Hazard statement: Causes skin irritation), and Skin Sensitization Category 1 (Hazard statement: May cause an allergic skin reaction) [European Parliament 2008].

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

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption; prevent skin contact
OSHA [1990]	[skin]: Based on potential contribution to the overall exposure by the cutaneous route, including the mucous membranes and the eyes, either by airborne route or (more particularly) by direct contact
ACGIH [2005]	[skin]: Based on the limited data demonstrating toxicity following rapid absorption through intact skin of humans and animals
EC [2009]	R21: Harmful if in contact with skin R24: Toxic in contact with skin R38: Irritating to skin R43: May cause sensitization by skin contact

Abbreviation: 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.

Acrylamide has been identified as a Category 1B Mutagen (Hazard statement: May cause genetic defects), a Category 1B Carcinogen (Hazard statement: May cause cancer) and a Category 2 Reproductive toxicant (Hazard statement: Suspected of damaging fertility or the unborn child) [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 Acrylamide

This appendix presents an overview of the ratio of skin dose to inhalation dose (SI ratio) and a summary of the calculation of the SI ratio for acrylamide. Although the SI ratio is included within 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 located 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 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 centimeters per hour (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 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 cm²).

Equation 2: Determination of Skin Dose

$$\begin{aligned} \text{Skin dose} &= K_p \times S_w \times \text{Exposed skin} \\ &\quad \text{surface area} \times \text{Exposure time} \\ &= K_p (\text{cm/hr}) \times S_w (\text{mg/cm}^3) \times \\ &\quad 360 \text{ cm}^2 \times 8 \text{ hours} \end{aligned}$$

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 (m³) 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

$$\begin{aligned} \text{Inhalation dose} &= \text{OEL} \times \text{Inhalation} \\ &\quad \text{volume} \times \text{RF} \\ &= \text{OEL} (\text{mg/m}^3) \times 10 \text{ m}^3 \\ &\quad \times 0.75 \end{aligned}$$

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 acrylamide. The calculated SI ratio was 2,955. On the basis of these results, acrylamide is predicted to represent a skin absorption hazard.

Appendix References

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Table A1. Summary of data used to calculate the SI ratio for acrylamide* variables identified from SRC [2009].

Variables used in calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path (K_{psc})	cm/hr	0.00058
Permeation coefficient of the protein fraction of the stratum corneum (K_{pol})	cm/hr	1.80171×10^{-5}
Permeation coefficient of the watery epidermal layer (K_{aq})	cm/hr	0.29653
Molecular weight (MW)*	amu	71.08
Base-10 logarithm of its octanol–water partition coefficient ($\text{Log } K_{ow}$)*	None	-0.67
Calculated skin permeation coefficient (K_p)	cm/hr	0.00059
Skin dose		
Water solubility (S_w)*	mg/cm ³	390
Calculated skin permeation coefficient (K_p)	cm/hr	0.00059
Estimated skin surface area (palms of hand)	cm ²	360
Exposure time	hr	8
Calculated skin dose	mg	664.86
Inhalation Dose		
Occupational exposure limit (OEL) [†]	mg/m ³	0.03
Inhalation volume	m ³	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	0.2
Skin dose–to–inhalation dose (SI) ratio	None	2954.93

*The OEL used in calculation of the SI ratio was the NIOSH recommended exposure limit (REL) [NIOSH 2005].



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