Skin Notation (SK) Profile

Allyl glycidyl ether (AGE)

[CAS No. 106-92-3]

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 the hazard potential of the substance, or its potential for causing adverse health effects as a result of skin exposure. This determination entails a health hazard identification process that involves use of the following:

- Scientific data on the physicochemical properties of a chemical
- Data on human exposures and health effects
- Empirical data from in vivo and in vitro laboratory testing
- Computational techniques, including predictive algorithms and mathematical models that describe a selected process (e.g., skin permeation) by means of analytical or numerical methods.

This *Skin Notation Profile* provides the SK assignments and supportive data for allyl glycidyl ether (AGE). In particular, this document evaluates and summarizes the literature describing the hazard potential of the substance and its assessment according to the scientific rationale and framework outlined in CIB 61. In meeting this objective, this *Skin Notation Profile* intends to inform the audience—mostly occupational health practitioners, researchers, policy- and decision-makers, employers, and workers in potentially hazardous workplaces—so that improved risk-management practices may be developed to better protect workers from the risks of skin contact with the chemicals of interest.

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Contents

Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
AGE	allyl glycidyl ether
CIB	Current Intelligence Bulletin
cm^2	square centimeter(s)
cm/hour	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 for Labelling and Classification of Chemicals
GPMT	guinea pig maximization test
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
kaq	coefficient in the watery epidermal layer
k_p	skin permeation coefficient
kpol	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
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
m^3	cubic meter(s)
MEST	mouse ear swelling test
mg	milligram(s)
mg/kg	milligram(s) per kilogram body weight
mg/m^3	milligram(s) per cubic meter
mL	milliliter(s)
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
pmol/g	picomoles per gram
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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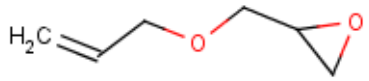
1.0 Introduction

1.1 General Substance Information

Chemical: Allyl glycidyl ether (AGE)
CAS No: 106-92-3
Molecular weight (*MW*): 114.2
Molecular formula: $C_6H_{10}O_2$
Structural formula:



Synonyms: AGE; 1-Allyloxy-2,3-epoxypropane; Glycidyl allyl ether; [(2-Propenyloxy)methyl] oxirane

Uses: AGE is used primarily as a commercial chemical of as a resin intermediate, and is also used as a stabilizer of chlorinated compounds, vinyl resins, and rubber [Waechter et al. 2001].

1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with AGE and (2) the rationale behind the hazard-specific skin notation (SK) assignment for AGE. 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 AGE. A literature search was conducted through September 2012 to identify information on AGE, 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 AGE.

1.3 Overview of SK Assignment

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

Table 1. Summary of the SK Assignment for AGE

Skin Notation	Critical Effect	Available Data
SK: DIR (IRR)	Skin irritation	Limited human and animal data
SK: SEN	Skin allergy	Sufficient human data

2.0 Systemic Toxicity from Skin Exposure (SK: SYS)

There is paucity of data on the toxicokinetic studies of AGE following dermal exposure. A study that provided some evidence for dermal absorption was conducted by Perez and Osterman-Golker [2000] in which application of 4 milligrams (mg) of AGE (99% pure) dissolved in acetone to the skin of mice for 5 or 24 hours resulted in hemoglobin (AGE-Val) adduct levels of about 20 picomoles per gram (pmol/g) globin (median value) compared to undetected levels in control mice (detection limit 2 pmol/g globin). The potential of AGE 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 0.84 was calculated for AGE. An SI ratio of $\geq$0.1 indicates that skin absorption may significantly contribute to the overall body burden of a substance [NIOSH 2009]; therefore, AGE is considered to be absorbed through the skin following dermal exposure. Additional information on the SI ratio and the variables used in its calculation are included in the appendix.

No dermal lethal doses (LD_{Lo}) of AGE for humans have been identified. The reported dermal LD_{50} value (the dose resulting in 50% mortality in the exposed animals) in rabbits was 2550 milligrams per kilogram (mg/kg) bodyweight [Hine et al. 1956]. Although no newer studies have been identified, the available acute dermal LD_{50} value for rabbits is higher than the critical dermal LD_{50} value of 2000 mg/kg body weight that identifies chemical substances with the potential for acute dermal toxicity [NIOSH 2009]. Therefore, AGE is not considered acutely toxic following dermal exposure.

No epidemiological or occupational exposure studies in humans or standard repeat-dose, subchronic, or chronic toxicity studies in animals were identified that evaluated systemic effects following dermal exposure. No studies that evaluated standard biological system or function specific effects (including reproductive and developmental effects and immunotoxicity) in humans or animals following dermal exposure to AGE were identified. No epidemiological studies or animal bioassays were identified that evaluated the carcinogenic potential of AGE following dermal exposure. No other organizations or agencies have classified AGE as a carcinogen by other routes of exposure. Table 2 summarizes carcinogenic designations of multiple governmental and nongovernmental organizations for AGE.

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

Organization	Carcinogenic designation
NIOSH [2005]	No designation
NTP [2011]	No designation
USEPA [2012]	No designation
GHS [European Parliament 2008]	Carcinogenicity Category 2: Suspected of causing cancer
IARC [2011]	No designation
EC [2013]**	No designation
ACGIH [2001]	Group A4: not classifiable as a human carcinogen

ACGIH = American Conference of Governmental Industrial Hygienists; EC = European Commission, Joint Research, Institute for Health and Consumer Protection; GHS = Globally Harmonized System for Labeling and Classification of Chemicals; 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.

*The listed cancer designations were based on data from non-dermal (such as oral or inhalation) exposure rather than dermal exposure.

**Date accessed.

Although the detection of hemoglobin adducts in mice dermally exposed to AGE indicates that the substance was absorbed through the skin, the available acute dermal toxicity study [Hine et al. 1956] indicated that the substance was not acutely toxic following dermal exposure until the applied dose exceeded 2000 mg/kg. Lack of epidemiological studies in exposed workers or repeat-dose, subchronic, or chronic toxicity studies in humans or animals precludes adequate evaluation of the potential of the substance to cause systemic effects following dermal exposure. Therefore, on the basis of the available data for this assessment, AGE is not assigned the SK: SYS notation.

3.0 Direct Effects on Skin (SK: DIR)

No human or animal *in vivo* studies on corrosivity of AGE or *in vitro* tests for corrosivity using human or animal skin models or *in vitro* tests of skin integrity using cadaver skin were identified. Limited occupational exposure data were identified. Dermatitis, consisting of tenderness, itching, swelling, and blister formation, and whitish macules, were observed in 10 of 20 workers dermally exposed to AGE vapor and/or liquid [Hine et al., 1956]. In rabbits, a single application of 0.5 milliliter (mL) of undiluted AGE to the clipped skin for 24 hours, according to the Draize protocol, resulted in moderate skin irritation on intact skin and moderate to severe irritation on abraded skin [Hine et al. 1956; Dow Chemical Company 1957]. The structure activity relationship model, Deductive Estimation of Risk from Existing Knowledge (*DEREK*), predicted AGE to be a skin irritant.

Results from a number of studies, including human experience **[Hine et al. 1956]** [*] and studies conducted using standard methods in animals **[Hine et al. 1956; Dow Chemical Company 1957]**, with supporting information from a structure activity relationship model, demonstrate that AGE is a potential skin irritant. Therefore, on the basis of the data for this assessment, AGE is assigned the SK: DIR (IRR) notation.

4.0 Immune-mediated Responses (SK: SEN)

A limited number of studies were identified that evaluated the potential of AGE to cause skin sensitization in both humans and animals. Hine et al. [1956] provided data that indicated that occupational exposure to AGE resulted in skin sensitization. Occupational exposure to a resin composed of epoxy resin and ortho-cresyl glycidyl ether produced contact dermatitis and airborne contact dermatitis in 10 of 22 workers after 20 days to 2 months of exposure [Angelini et al. 1996]. When these subjects were patch tested, one of the 22 showed allergic reactions to AGE. Dooms-Goossens et al. [1995] also reported a case study in which a worker in the plastics industry who presented with dermatitis on his hands and forearms reacted positively to AGE after patch testing. Fregert and Rorsman [1964] conducted patch tests on people that presented with contact allergies to resins of diglycidyl ethers of bisphenol A. In this study, 2 of 20 subjects were sensitized to AGE. No predictive tests [guinea pig maximization test (GPMT), Buehler test, local lymph node assays (LLNA), mouse ear swelling test (MEST) etc.] were identified. *DEREK* predicted AGE to be a skin sensitizer.

A number of studies from occupational exposures **[Hine et al. 1956; Dooms-Goossens et al. 1995; Angelini et al. 1996]** and patch tests identified **[Fregert and Rorsman 1964]** demonstrate that AGE is a potential skin sensitizer. This conclusion is also supported by a structure activity relationship model. Therefore, on the basis of the data for this assessment, AGE is assigned the SK: SEN notation.

5.0 Summary

No estimates of percent absorption of AGE following dermal exposure were identified. However, a mathematical model predicted that the chemical will be poorly absorbed through the skin. Acute dermal toxicity data demonstrate that AGE has low systemic toxicity. No repeat-dose, subchronic or chronic dermal toxicity studies in animals or epidemiological or occupational exposure studies following dermal exposure that estimated systemic effect levels were identified. Occupational exposure information and standard skin irritation tests **[Hine et al., 1956; Dow Chemical Company 1957]** identified provide sufficient evidence of the potential for AGE to cause skin irritation. Similarly, studies from occupational exposures and positive results from patch testing of individuals occupationally exposed to AGE [**Hine et al. 1956; Fregert and Rorsman 1964; Dooms-Goossens et al. 1995; Angelini et al. 1996**] are sufficient to

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

demonstrate that AGE is a potential skin sensitizer. Therefore, on the basis of these assessments, AGE is assigned a composite skin notation of **SK: DIR (IRR)-SEN**.

Table 3 summarizes the skin hazard designations for AGE previously issued by NIOSH and other organizations. The equivalent dermal designations for AGE, according to the Global Harmonization System (GHS) of Classification and Labeling of Chemicals, are 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]. In addition, AGE has been classified as a Mutagenicity Category 2 (Hazard Statement: Suspected of causing genetic defects) and a Reproductive Toxicity Category 2 (Hazard Statement: Suspected of damaging fertility) [European Parliament 2008].

Table 3. Summary of previous skin hazard designations for AGE

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption; prevent skin contact
OSHA [2012]*	No designation
ACGIH [2001]	No designation
EC [2012]*	R38 - Irritating to skin. R43 - May cause sensitization by skin contact

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.
*Date Accessed.

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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 AGE

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for allyl glycidyl ether. 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 (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 *kp* 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 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 square centimeters [cm^2]).

Equation 2: Determination of Skin Dose

Skin dose = $k_p \times S_w \times$ Exposed skin surface area × Exposure time
= k_p(cm/hour) × S_w (mg/cm^3) × 360 cm^2 × 8 hours

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

Inhalation dose = OEL × Inhalation volume × RF
= OEL (mg/m^3) × 10 m^3 × 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 AGE. The calculated SI ratio was 0.837. On the basis of these results, AGE is predicted to represent a skin absorption hazard.

Table A1. Summary of Data used to Calculate the SI Ratio for AGE

Variables Used in Calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path(k_{psc})	cm/hour	1.099×10^{-3}
Permeation coefficient of the protein fraction of the stratum corneum (k_{pol})	cm/hour	1.4223×10^{-5}
Permeation coefficient of the watery epidermal layer (k_{aq})	cm/hour	0.234089
Molecular weight (MW)[a]	amu	114.06
Base-10 logarithm of its octanol–water partition coefficient (Log K_{ow})[a]	None	0.45
Calculated skin permeation coefficient (k_p)	cm/hour	1.1078×10^{-3}
Skin dose		
Water solubility (S_w)[a]	mg/cm^3	43.3
Calculated skin permeation coefficient (k_p)	cm/hour	1.1078×10^{-3}
Estimated skin surface area (palms of hand)	cm^2	
Exposure time	hour	8
Calculated skin dose	mg	138.15
Inhalation Dose		
Occupational exposure limit (OEL)[b]	mg/m^3	22
Inhalation volume	m^3	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	165
Skin dose–to–inhalation dose (SI) ratio	None	0.837

[a]Variables identified from SRC [2009].
[b]The OEL used in calculation of the SI ratio for allyl glycidyl ether was the NIOSH recommended exposure limit (REL) [NIOSH 2005].

Appendix References

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