NIOSH Skin Notation Profiles

Glutaraldehyde

SK

ID^{SK}

[SK]

SYS

SYS (FATAL)

DIR

DIR (IRR)

DIR (COR)

SEN

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

NIOSH Skin Notation (SK) Profiles

Glutaraldehyde
[CAS No. 111–30–8]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

Disclaimer

Mention of any company or product does not constitute endorsement by the National Institute for Occupational Safety and Health (NIOSH). In addition, citations to Web sites external to NIOSH do not constitute NIOSH endorsement of the sponsoring organizations or their programs or products. Furthermore, NIOSH is not responsible for the content of these Web sites.

Ordering Information

To receive documents or other information about occupational safety and health topics, contact NIOSH at

Telephone: **1–800–CDC–INFO** (1–800–232–4636)
TTY: 1–888–232–6348
E-mail: cdcinfo@cdc.gov

or visit the NIOSH Web site at **www.cdc.gov/niosh**.

For a monthly update on news at NIOSH, subscribe to *NIOSH eNews* by visiting **www.cdc.gov/niosh/eNews.**

DHHS (NIOSH) Publication No. 2011–149

April 2011

Safer • Healthier • People™

Foreword

As the largest organ of the body, the skin performs multiple critical functions, such as serving as the primary barrier to the external environment. For this reason, the skin is often exposed to potentially hazardous agents, including chemicals, which may contribute to the onset of a spectrum of adverse health effects ranging from localized damage (e.g., irritant contact dermatitis and corrosion) to induction of immune-mediated responses (e.g., allergic contact dermatitis and pulmonary responses), or systemic toxicity (e.g., neurotoxicity and hepatoxicity). Understanding the hazards related to skin contact with chemicals is a critical component of modern occupational safety and health programs.

In 2009, the National Institute for Occupational Safety and Health (NIOSH) published *Current Intelligence Bulletin (CIB) 61: A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009–147]. This document provides the scientific rationale and framework for the assignment of multiple hazard-specific skin notations (SK) that clearly distinguish between the systemic effects, direct (localized) effects, and immune-mediated responses caused by skin contact with chemicals. The key step within assignment of the hazard-specific SK is the determination of a substance's hazard potential, or its potential for causing adverse health effects as a result of skin exposure. This determination entails a health hazard identification process that involves use of the following:

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

This *Skin Notation Profile* provides the SK assignment and supportive data for glutaraldehyde (CAS No. 111–30–8). 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.

John Howard, M.D.
Director, National Institute for
Occupational Safety and Health
Centers for Disease Control and Prevention

Contents

Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
CIB	Current Intelligence Bulletin
cm^2	square centimeter(s)
cm/hr	centimeter(s) per hour
(COR)	subnotation of SK: DIR indicating the potential for a chemical to be corrosive following exposure of the skin
DEREK™	Deductive Estimation of Risk from Existing Knowledge
DIR	skin notation indicating the potential for direct effects to the skin following contact with a chemical
EC	European Commission
g/mL	gram(s) per milliliter
GHS	Globally Harmonized System of Classification and Labeling of Chemicals
GPMT	guinea pig maximization test
IARC	International Agency for Research on Cancer
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
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/kg/day	milligram(s) per kilogram body weight per day
mg/m^3	milligram(s) per cubic meter
mL/kg	milliliter(s) per kilogram body weight
MW	molecular weight
NIOSH	National Institute for Occupational Safety and Health
$nmol/cm^2/hr$	nanomoles per square centimeter per hour
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
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.

Acknowledgments

This document was developed by the Education and Information Division, Paul Schulte, Ph.D., Director. G. Scott Dotson, Ph.D. was the project officer for this document. Other NIOSH personnel, in particular Charles L. Geraci, Ph.D., Thomas J. Lentz, Ph.D., Richard Niemeier, Ph.D., Todd Niemeier M.Sc., and Aaron Sussell, Ph.D., contributed to its development by providing technical reviews and comments. The basis for this document was a report contracted by NIOSH and prepared by Bernard Gadagbui, Ph.D., and Andrew Maier, Ph.D. (*Toxicology Excellence for Risk Assessment [TERA]*).

For their contribution to the technical content and review of this document, special acknowledgment is given to the following NIOSH personnel:

Denver Field Office
Eric Esswein, M.Sc.

Division of Applied Research and Technology
Clayton B'Hymer, Ph.D.

Division of Respiratory Disease Studies
Gregory A. Day, Ph.D.

Division of Surveillance, Hazard Evaluations, and Field Studies
Loren Tapp, M.D.

Education and Information Division
Ralph Zumwalde, M.Sc.

Health Effects Laboratory Division
Fredrick H. Frasch, Ph.D.
Michael Luster, Ph.D.
Anna Shvedova, Ph.D.
Paul Siegel, Ph.D.

National Personal Protective Technology Laboratory
Heinz Ahlers, J.D.
Angie Shepherd

The authors thank Seleen Collins, Gino Fazio, and Vanessa B. Williams for their editorial support and contributions to the design and layout of this document. Clerical and information resources support in preparing this document was provided by Devin Baker, Daniel Echt, and Barbara Landreth.

In addition, special appreciation is expressed to the following individuals for serving as independent, external reviewers and providing comments that contributed to the development or improvement of this document:

John Cherrie, Ph.D., Institute of Occupational Medicine, Edinburgh, Scotland, United Kingdom

G. Frank Gerberick, Ph.D., The Procter and Gamble Company, Cincinnati, Ohio

Dori Germolec, Ph.D., National Toxicology Program, National Institute for Environmental Health Sciences, Research Triangle, North Carolina

Ben Hayes, M.D., Ph.D., Division of Dermatology, Vanderbilt School of Medicine, Nashville, Tennessee

Howard Maibach, M.D., Department of Dermatology, School of Medicine, University of California, San Francisco, San Francisco, California

Jennifer Sahmel, M.S.c, CIH, ChemRisk, Boulder, Colorado

James Taylor, M.D., Industrial Dermatology, The Cleveland Clinic, Cleveland, Ohio

1 Introduction

1.1 General Substance Information

Chemical: Glutaraldehyde

CAS No: 111–30–8

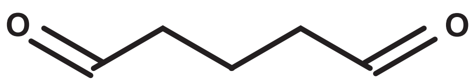
Synonyms:

1,5-Pentanedial; 1,5-Pentanedione; Dioxopentane, Glutaral; Glutaralum; Glutaric Acid Dialdehyde; Glutardialdehyde; Glutaric Aldehyde; Glutaric Dialdehyde; Glutaral; Pentane-1,5-dial; Pentanedial

Molecular weight (MW): 100

Molecular formula: $C_5H_8O_2$

Structural formula:



Uses:
Glutaraldehyde is an organic compound commonly used as a preservative, as a disinfectant in medical applications, and as embalming fluid. In addition, the substance is used within oil exploration as a biocide.

1.2 Purpose

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

1.3 Overview of SK Assignment for Glutaraldehyde

Glutaraldehyde is potentially capable of causing multiple adverse health effects following skin contact. Undiluted glutaraldehyde or solutions containing more than 25% glutaraldehyde are capable of causing skin corrosion, whereas diluted solutions (1 to 25% glutaraldehyde) are irritating to the skin. In addition, available data indicates that glutaraldehyde is a potent sensitizing agent. A critical review of available data has resulted in the following SK assignment for glutaraldehyde: **SK: DIR (COR)-SEN**. Table 1 provides an overview of the critical

Table 1. Summary of the SK assignment for glutaraldehyde

Skin notation	Critical effect	Data available
SK: DIR (COR)	Skin corrosion	Sufficient human and animal data
SK: SEN	Skin sensitization	Sufficient human and animal data

effects and data used to develop the SK assignment for glutaraldehyde.

2 Systemic Toxicity from Skin Exposure (SK: SYS)

No specific human data were identified that reported the degree of absorption of glutaraldehyde following dermal exposure. However, the kinetics of percutaneous absorption have been investigated. For example, Ballantyne and Jordan [2001] reported that 0.3% to 2.1% and 7.5% to 24.9% of the glutaraldehyde administered dose was absorbed percutaneously in the rat and rabbit, respectively. Following a study that evaluated the in vitro penetration of glutaraldehyde in a 10% aqueous solution through isolated human epidermis (chest and abdomen), isolated human epidermis (abdominal), and human thick stratum corneum (blister tops from the sole), Reifenrath et al. [1985] reported that 2.8% to 4.4% and 3.3% to 13.8% of the applied dose penetrated the isolated epidermis and thin stratum corneum, respectively, after 1 hour, but glutaraldehyde did not penetrate the thick stratum corneum. In another in vitro study, Frantz et al. [1993] noted average absorptions of less than 0.5% and less than 0.7%, respectively, of the applied radioactivity following application of 0.75% and 7.5% aqueous solutions of glutaraldehyde to excised skin from rats, mice, guinea pigs, rabbits, and humans (females undergoing reconstructive mammoplasty). These findings indicate that glutaraldehyde did not penetrate human or animal skin *in vitro* to any substantial degree. On the basis of the proportion of the applied dose available for systemic absorption, Ballantyne and Jordan [2001] and Frantz et al. [1993] suggested that only a minimal amount of the chemical may be available for systemic uptake and distribution following dermal exposure and that potential for cumulative toxicity is unlikely because of the rapid biotransformation and elimination of the material from the body. The potential of glutaraldehyde 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 191.55 was calculated for glutaraldehyde. 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.

Although no dermal lethal dose (LD_{Lo}) for humans has been estimated, Ballantyne and Jordan [2001] reported these dermal LD_{50} values (lethal doses in 50% of the exposed population) for rabbits: 1.59 to 2.54 milliliters per kilogram body weight (mL/kg; reported as 434 to 898 milligrams per kilogram body weight [mg/kg]) for a 50% glutaraldehyde solution; 2.00 to 2.71 mL/

kg (reported as 1006 to 1363 mg/kg) for a 45% solution; and 8.80 to 16.00 mL/kg (reported as 2341 to 4256 mg/kg) for a 25% solution. These LD_{50} values are calculated as 1749 to 2970 mg/kg for the 50% solution, based on a density of 1.1 g/mL [International Occupational Safety and Health Information Center 2000]; 2200 to 2981 mg/kg for the 45% solution, based on the density of a 50% solution; and 9346 to 16,992 mg/kg, based on a density of 1.062 g/mL [Sigma-Aldrich 2007]. The animal LD_{50} values were reported to be dependent on the concentration of the aqueous solution used. Because the reported acute dermal LD_{50} values for rabbits are nearly all greater than the critical dermal LD_{50} value of 2000 mg/kg body weight that identifies chemical substances with the potential for acute toxicity [NIOSH 2009], glutaraldehyde is considered to have low acute toxicity following exposure by the dermal route.

Although no epidemiology data were identified concerning systemic effects following human glutaraldehyde exposure, several short-term and subchronic dermal toxicity studies were identified that involved experimental animals. No chronic toxicity studies were identified. In a subchronic study, rats exposed epicutaneously to aqueous glutaraldehyde at concentrations up to 7.5% (reported to be equivalent to doses up to 150 milligrams per kilogram body weight per day [mg/kg/day]) for 6 hours a day for 26 days (for a total of 20 applications) exhibited slight changes in body weight and food consumption, but no treatment-related mortality or biochemical or morphological evidence of systemic target organ or tissue toxicity [Bushy Run Research Center 1994; Werley et al. 1996]. The indicated no-observed-adverse-effect level (NOAEL) was 150 mg/kg/day at the highest dose tested. A 6-week subchronic study in rabbits elicited no evidence of systemic toxicity following topical application of 0.5 milliliter (mL) of a 2% activated glutaraldehyde solution given in a total of 47 applications [Stonehill et al. 1963]. On the basis of a 1.01 g/mL density for a 2% glutaraldehyde solution [Dow Chemical Company 2002] and a default average subchronic body weight of approximately 3 kg for New Zealand rabbits [USEPA, 1988], the dose would be approximately 3 mg/kg. The apparent NOAEL is 47 mg/kg and the apparent lowest-observed-adverse-effect level (LOAEL) is 94 mg/kg for systemic effects in mice, whereas the NOAEL for rats was the highest tested dose of 150 mg/kg. The relative systemic toxicity identified in these studies is consistent with the toxicokinetic differences among species as noted above. Thus, the results of the study involving rats are considered most representative of potential human response and are given greater weight in this assessment than results of the studies involving mice and rabbits. A free-standing NOAEL of 150 mg/kg/day for the most representative species is used for the overall assessment.

No standard toxicity or specialty studies evaluating biological system/function–specific effects (including reproductive and developmental effects and immunotoxicity) following dermal exposure to glutaraldehyde were identified. In addition, no studies evaluating the carcinogenic potential of glutaraldehyde were identified. Table 2 provides a summary of carcinogenic designations from multiple governmental and nongovernmental organizations for glutaraldehyde.

Toxicokinetic studies indicate glutaraldehyde is poorly absorbed, as reflected by the high doses required to elicit acute toxicity. The repeat-dose studies are inadequate to indicate whether an effect level in the most representative species (rats) would occur at doses lower than 1000 mg/kg/

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

Organization	Carcinogenic designation
NIOSH [2005]	None
NTP [2009]	None
USEPA [2009]	None
IARC [2009]	None
EC [2010]	None
ACGIH [2001]	A4: Not classifiable as a human carcinogen

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.

day, because the highest dose tested of 150 mg/kg/day did not cause systemic effects. These data show limited absorption potential and low acute toxicity following exposure by the dermal route, which is consistent with the absence of published reports of systemic effects in exposed workers. Therefore, on the basis of this assessment, glutaraldehyde is not assigned a notation of SK: SYS.

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

Reports of corrosivity and irritancy in humans and animals were identified. Glutaraldehyde solutions may be corrosive or cause mild to severe irritation in the skin of humans and animals, depending on the dose, duration, and site of contact [Takigawa and Endo 2006]. A controlled human study indicated that sustained contact with 1% aqueous glutaraldehyde solution was the threshold for erythema and edema, whereas concentrations of 45% or greater were capable of producing corrosion [Ballantyne and Jordan 2001]. Application of 0.1 mL of a 2% solution to the skin of volunteers for 30 minutes daily for 3 days caused a marked skin irritation [Frosch and Kligman 1976]. A 10% aqueous solution applied to the ankle and heel area of 12 volunteers over an 8-week period produced irritation [Reifenrath et al. 1985]. In patch tests conducted by Union Carbide Corporation [1972; 1980], volunteers showed severe irritation when exposed to 5% glutaraldehyde, symptoms of moderate irritation when exposed to 0.5% to 2% glutaraldehyde solution, but no irritation when exposed to 0.1% to 1% solution. Union Carbide Corporation [1972] indicated that effects of aqueous solutions of 25% and above in animals range from moderate/severe irritation to corrosion, whereas concentrations between 1% and 25% produce slight irritation and 1% solutions produce no effect. The structure activity relationship model, Deductive Estimation of Risk from Existing Knowledge (DEREK™) for Windows, predicted glutaraldehyde to be a skin irritant.

It appears from the available information on humans **[Union Carbide Corporation 1972, 1980; Ballantyne and Jordan**

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

2001*] and animals [Ballantyne and Jordan 2001] that glutaraldehyde is corrosive at concentrations of 25% and above and a skin irritant at concentrations between 1% and 25%. Therefore, on the basis of the data for this assessment, glutaraldehyde is assigned the SK: DIR (COR) notation.

4 Immune-mediated Responses (SK: SEN)

Skin sensitization resulting from dermal exposure to glutaraldehyde has been demonstrated in the reports of cases and controlled volunteer studies. Several exposed workers who developed allergic contact dermatitis, some with no history of atopy or skin disease, tested positive to patch-testing with glutaraldehyde [Nethercott et al. 1988; Fowler 1989; Ballantyne and Jordan 2001]. Sixteen of 109 volunteers had a positive irritant reaction to 0.5% glutaraldehyde, and 2 of 109 had an allergic reaction when a challenge patch was applied thereafter [Ballantyne and Jordan 2001]. The Union Carbide Corporation [1980] reported that weaker solutions, of 0.1% to 0.2%, show no sensitization potential. Repeated topical application of a 10% aqueous solution of glutaraldehyde over an 8-week period produced one case of sensitization in 12 volunteers [Refeinrath et al. 1985]. Union Carbide Corporation [1966] reported no sensitization in subjects exposed to 5% glutaraldehyde.

In a guinea pig maximization test (GPMT), unbuffered glutaraldehyde was reported to produce a higher sensitization incidence index than buffered glutaraldehyde [Union Carbide Corporation 1993]. However, a Magnusson-Kligman sensitization test submitted to the United States Environmental Protection Agency (USEPA) [1991] elicited no positive responses. Investigators have reported a concentration-dependent increase in lymphocyte proliferation when glutaraldehyde in concentrations ranging from 0.1% to 5% [Hilton et al. 1998] or 0.75% to 2.5% [Azadi et al. 2004] were applied to mice in local lymph node assays (LLNA). In a mouse-ear swelling test (MEST), Azadi et al. [2004] reported an immediate contact hypersensitivity response in mice induced and challenged with 2.5% glutaraldehyde, whereas animals induced with 0.1% or 7.5% and challenged with 2.5% exhibited a delayed response. Glutaraldehyde was also reported to induce a contact hypersensitivity-type reaction in a MEST and a concentration-related stimulation of lymph node activity in an LLNA, indicating skin-sensitization potential [Ballantyne and Jordan 2001]. Glutaraldehyde is predicted by DEREK™ to be a skin sensitizer.

The results in several reported cases **[Nethercott et al. 1988; Fowler 1989; Ballantyne and Jordan 2001]**, repeated-insult patch tests in humans **[Union Carbide Corporation 1980]**, and predictive tests in animals (i.e., GPMT, LLNA, MEST) **[Union Carbide Corporation 1993; Hilton et al. 1998; Ballantyne and Jordan 2001; Azadi et al. 2004]** demonstrate that glutaraldehyde is skin sensitizer in both humans and animals. Therefore, on the basis of the data for this assessment, glutaraldehyde is assigned the **SK: SEN** notation.

5 Summary

Toxicokinetic studies of the kinetics of percutaneous absorption of glutaraldehyde indicate that the chemical is poorly absorbed. This finding is also supported by the high doses required to elicit acute toxicity, although a mathematical model predicted the chemical to have the potential for dermal absorption. Findings in the identified repeated-dose studies

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

Organization	Skin hazard designation
NIOSH [2005]	None
OSHA	None
ACGIH [2001]	None
EC [2010]	R34: Causes burns R43: May cause sensitization by skin contact

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; EC = European Commission, Joint Research, Institute for Health and Consumer Protection; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration.

are inadequate to indicate whether an effect level in the most representative species (rats) would occur at doses lower than 1000 mg/kg/day, because the highest dose tested of 150 mg/kg/day did not cause systemic effects. Overall, the data demonstrate limited potential of glutaraldehyde to induce systemic effects following dermal exposure. Several studies involving humans **[Union Carbide Corporation 1972, 1980; Ballantyne and Jordan 2001]** and animals **[Ballantyne and Jordan 2001]** show that glutaraldehyde is corrosive at concentrations of 25% and above and is a skin irritant at concentrations between 1% and 25%. The ability of glutaraldehyde to cause dermal sensitization is well-documented. Allergic reactions observed in several reported cases **[Nethercott et al. 1988; Fowler 1989; Ballantyne and Jordan 2001]**, repeated-insult patch tests in humans **[Union Carbide Corporation 1980]**, and positive sensitization results observed in several predictive tests in animals (GPMT, LLNA, and MEST) **[Union Carbide Corporation 1993; Hilton et al. 1998; Ballantyne and Jordan 2001; Azadi et al. 2004**] demonstrate the sensitization potential of glutaraldehyde. The information available for this assessment, including data on both humans and animals, if sufficient to show that glutaraldehyde is corrosive to the skin and is a skin sensitizer. Therefore, on the basis of these assessments, glutaraldehyde is assigned a composite skin notation of **SK: DIR (COR)-SEN.**

Table 3 summarizes the skin hazard designations for glutaraldehyde previously issued by NIOSH and other organizations. The equivalent dermal designations for glutaraldehyde, according to the Globally Harmonized System (GHS) of Classification and Labeling of Chemicals, are Skin Corrosion Category 1B (Hazard statement: Causes severe skin burns and eye damage), and Skin Sensitization Category 1 (Hazard statement: May cause an allergic skin reaction) [European Parliament 2008].

References

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

*ACGIH (American Conference of Governmental Industrial Hygienists) [2001]. Glutaraldehyde. In: Documentation of threshold limit values and biological exposure indices. 7th Ed., Vol. 2. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

*Azadi S, Klink KJ, Meade BJ [2004]. Divergent immunological responses following glutaraldehyde exposure. Toxicol Appl Pharmacol *197*(1):1–8.

*Ballantyne B, Jordan SL [2001]. Toxicological, medical and industrial hygiene aspects of glutaraldehyde with particular reference to its biocidal use in cold sterilization procedures. J Appl Toxicol *21*(2):131–151.

*Bushy Run Research Centre [1994]. Glutaraldehyde: twenty-eight day repeated cutaneous dose toxicity study in Fischer 344 rats. Unpublished data on file, submitted by Union Carbide, Bound Brook, NJ.

*Dow Chemical Company [2002]. Properties of glutaraldehyde-based formulations. In: Bioshare [http://www.metrex.com/index/cms-filesystem-action?file=Metrex-PDF/glutaraldehydeproperties-dowbiosharedatasheets.pdf]. Accessed 07–07–10.

*EC (European Commission) [2009]. Glutaraldehyde. In: EINICS (European Inventory of Existing Commercial Chemical Substances) [http://ecb.jrc.ec.europa.eu/esis/]. Accessed 07–07–10.

*Fowler JF Jr [1989]. Allergic contact dermatitis from glutaraldehyde exposure. J Occup Med *31*(10):852–853.

*Frantz SW, Beskitt JL, Tallant MJ, Futrell JW, Ballantyne B [1993]. Glutaraldehyde: species comparisons of in vitro skin penetration. J Toxicol Cutan Ocul Toxicol *12*(4):349–361.

*Frosch PJ, Kligman AM [1976]. The chamber-scarification test for assessing irritancy. Contact Dermatitis *2*(6):314–324.

*Hilton J, Dearman RJ, Harvey P, Evans P, Bastetter DA, Kimber I [1998]. Estimation of relative skin sensitizing potency using the local lymph node assay: a comparison of formaldehyde with glutaraldehyde. Am J Contact Dermat *9*(1):29–33.

*HSDB (Hazardous Substance Data Bank) [2010]. Glutaraldehyde [http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB]. Accessed 07–07–10.

*IARC (International Agency for Research on Cancer) [2009]. Agents reviewed by the IARC monographs. In: IARC monographs on the evaluation of carcinogenic risks to humans [http://monographs.iarc.fr/ENG/Classification/Listagentsalphorder.pdf]. Accessed 07–07–10.

*International Occupational Safety and Health Information Center [2000]. Glutaraldehyde 50% solution. ICSC: 3052. International Labor Organization. [http://www.ilo.org/legacy/english/protection/safework/cis/products/icsc/dtasht/_icsc03/icsc0352.htm]. Accessed 07–07–10.

*Nethercott JR, Holness DL, Page E [1988]. Occupational contact dermatitis due to glutaraldehyde in health care workers. Contact Dermatitis *18*(4):193–196.

*NIOSH [2005]. NIOSH pocket guide to chemical hazards. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2005–149 [http://www.cdc.gov/niosh/npg/]. Accessed 07–07–10.

*NIOSH [2009]. Current intelligence bulletin 61: a strategy for assigning new NIOSH skin notations. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2009–147 [http://www.cdc.gov/niosh/docs/2009-147/pdfs/2009-147.pdf]. Accessed 07–07–10.

*NTP (National Toxicology Program) [2009]. Eleventh report on carcinogens [http://ntp.niehs.nih.gov/index.cfm?objectid=32BA9724-F1F6-975E-7FCE50709CB4C932]. Accessed 07–07–10.

*Reifenrath WG, Prystowsky SD, Nonomura JH, Robinson PB [1985]. Topical glutaraldehyde: percutaneous penetration and skin irritation. Arch Dermatol Res *277*(3):242–244.

*Sigma-Aldrich [2007]. Glutaraldehyde solution (25 wt. % in H_2O). In: Sigma-Aldrich catalog [http://www.sigmaaldrich.com/catalog/ProductDetail.do?N4=G4004]. Accessed 12–14–09.

*Stonehill AA, Krop S, Borick PM [1963]. Buffered glutaraldehyde: a new sterilizing chemical solution. Am J Hosp Pharm *20*:458–485.

*Takigawa T, Endo Y [2006]. Effects of glutaraldehyde exposure on human health. J Occup Health *48*(2):75–87.

*UNECE (United Nations Economic Commission for Europe) [2007]. Part 3: health hazards. In: Globally harmonized system of classification and labeling of chemical (GHS). 2nd Rev. Ed. [http://www.unece.org/trans/danger/publi/ghs/ghs_rev02/02files_e.html]. Accessed 07–07–10.

†UNEP (United Nations Environmental Programme), Chemicals Branch [1998]. Screening information datasets (SIDS) for high volume chemicals: glutaraldehyde [http://www.chem.unep.ch/irptc/sids/OECDSIDS/INDEXCHEMIC.htm]. Accessed 07–07–10.

*Union Carbide Corporation [1966]. Repeated insult patch test of glutaraldehyde, 5% solution, with cover letter dated 11/14/95. Danbury, CT: Union Carbide Corporation. On file with the U.S. Environmental Protection Agency under TSCA Section 8D. OTS# 0558276. Document #: 86960000136.

*Union Carbide Corporation [1972]. Dialdehydes, by Dernahl CU. Danbury, CT: Union Carbide Corporation. On file with the U.S. Environmental Protection Agency under TSCA Section 8D.OTS# 0558275. Document #: 86960000135

*Union Carbide Corporation [1980]. Repeated insult patch test of glutaraldehyde (0.1%, 0.2%, 0.5%). New York: Testkit Laboratories Inc. Study #80–39 I and IIf. On file with the U.S. Environmental Protection Agency under TSCA Section 8D. OTS# 0558274. Document # 86960000134

*Union Carbide Corporation [1993]. Letter from Union Carbide Corp. to USEPA regarding acute irritation and sensitization studies of glutaraldehyde. Danbury, CT: Union Carbide Corporation. On file with the U.S. Environmental Protection Agency under TSCA Section 8D. OTS# 0556612. Document # 86940000016.

*USEPA (United States Environmental Protection Agency) [1988]. Recommendations for and documentation of biological values for use in risk assessment. Washington, DC: U.S. Environmental Protection Agency, EPA/600/6-87/008.

*USEPA [1991]. Letter to USEPA regarding the enclosed evaluation summary on the lever modification of the Magnusson-Kligman guinea pig maximization test with glutaraldehyde (sanitized), with attachment [1980]. On file with the U.S. Environmental Protection Agency under TSCA Section 8D. OTS# 0533498. Document # 86-920000277S.

*USEPA [2009]. Integrated Risk Information System (IRIS) [http://www.epa.gov/iris/]. Accessed 07–07–10.

*Werley MS, Ballantyne B, Neptun DA, Losco PE [1996]. Four week repeated skin contact study with glutaraldehyde. J Toxicol Cut Ocul Toxicol *15*:179–193.

Appendix: Calculation of the SI Ratio for Glutaraldehyde

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for glutaraldehyde. 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 the 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 cm/hr, 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

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

Variables used in calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path(K_{psc})	cm/hr	0.00060
Permeation coefficient of the protein fraction of the stratum corneum (K_{pol})	cm/hr	1.51809×10^{-5}
Permeation coefficient of the watery epidermal layer (K_{aq})	cm/hr	0.24985
Molecular weight (MW)*	amu	100
Base-10 logarithm of its octanol–water partition coefficient (log K_{OW})*	None	-0.18
Calculated skin permeation coefficient (K_p)	cm/hr	0.00061
Skin dose		
Water solubility (S_W)*	mg/cm^3	167
Calculated skin permeation coefficient (K_p)	cm/hr	0.00061
Estimated skin surface area (palms of hand)	cm^2	360
Exposure time	hr	8
Calculated skin dose	mg	294.51
Inhalation dose		
Occupational exposure limit (OEL)†	mg/m^3	0.205
Inhalation volume	m^3	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	1.54
Skin dose–to–inhalation dose (SI) ratio	None	191.55

*Variables identified from SRC [2009].
†The OEL used in calculation of the SI ratio was the NIOSH-recommended exposure limit (REL) [NIOSH 2005].

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 cm^2).

Equation 2: Determination of Skin Dose

$$\text{Skin dose} = K_p \times S_W \times \text{Exposed skin surface area} \times \text{Exposure time}$$

$$= K_p(\text{cm/hr}) \times S_W (\text{mg/cm}^3) \times 360 \text{ cm}^2 \times 8 \text{ hours}$$

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

$$\text{Inhalation dose} = \text{OEL} \times \text{Inhalation volume} \times \text{RF}$$

$$= \text{OEL (mg/m}^3) \times 10\ \text{m}^3 \times 0.75$$

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 glutaraldehyde. The calculated SI ratio was 191.55. On the basis of these results, glutaraldehyde is predicted to represent a skin absorption hazard.

Appendix References

NIOSH [2005]. NIOSH pocket guide to chemical hazards. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2005–149 [http://www.cdc.gov/niosh/npg/]. Accessed 07-07-10.

NIOSH [2009]. Current intelligence bulletin 61: a strategy for assigning new NIOSH skin notations. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2009-147 [http://www.cdc.gov/niosh/docs/2009-147/pdfs/2009-147.pdf]. Accessed 07-07-10.

SRC [2009]. Interactive PhysProp database demo [http://www.srcinc.com/what-we-do/databaseforms.aspx?id=386]. Accessed 12-02-09.

Delivering on the Nation's promise: safety and health at work for all people through research and prevention

To receive NIOSH documents or more information about occupational safety and health topics, contact NIOSH at

1–800–CDC–INFO (1–800–232–4636)
TTY: 1–888–232–6348
E-mail: cdcinfo@cdc.gov

or visit the NIOSH Web site at **www.cdc.gov/niosh**.

For a monthly update on news at NIOSH, subscribe to NIOSH *eNews* by visiting **www.cdc.gov/niosh/eNews**.

DHHS (NIOSH) Publication No. 2011–149

SAFER • HEALTHIER • PEOPLE™

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health
4676 Columbia Parkway
Cincinnati, Ohio 45226–1998