NIOSH Skin Notation Profiles
Glutaraldehyde
NIOSH Skin Notation (SK) Profiles

Glutaraldehyde
[CAS No. 111–30–8]
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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 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
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACGIH</td>
<td>American Conference of Governmental Industrial Hygienists</td>
</tr>
<tr>
<td>CIB</td>
<td>Current Intelligence Bulletin</td>
</tr>
<tr>
<td>cm²</td>
<td>square centimeter(s)</td>
</tr>
<tr>
<td>cm/hr</td>
<td>centimeter(s) per hour</td>
</tr>
<tr>
<td>(COR)</td>
<td>subnotation of SK: DIR indicating the potential for a chemical to be corrosive following exposure of the skin</td>
</tr>
<tr>
<td>DEREK™</td>
<td>Deductive Estimation of Risk from Existing Knowledge</td>
</tr>
<tr>
<td>DIR</td>
<td>skin notation indicating the potential for direct effects to the skin following contact with a chemical</td>
</tr>
<tr>
<td>EC</td>
<td>European Commission</td>
</tr>
<tr>
<td>g/mL</td>
<td>gram(s) per milliliter</td>
</tr>
<tr>
<td>GHS</td>
<td>Globally Harmonized System of Classification and Labeling of Chemicals</td>
</tr>
<tr>
<td>GPMT</td>
<td>guinea pig maximization test</td>
</tr>
<tr>
<td>IARC</td>
<td>International Agency for Research on Cancer</td>
</tr>
<tr>
<td>Kₐq</td>
<td>coefficient in the watery epidermal layer</td>
</tr>
<tr>
<td>Kₚ</td>
<td>skin permeation coefficient</td>
</tr>
<tr>
<td>Kₚₗ</td>
<td>coefficient in the protein fraction of the stratum corneum</td>
</tr>
<tr>
<td>Kₚₗₑ</td>
<td>permeation coefficient in the lipid fraction of the stratum corneum</td>
</tr>
<tr>
<td>LD₅₀</td>
<td>dose resulting in 50% mortality in the exposed population</td>
</tr>
<tr>
<td>LD₅₀Lo</td>
<td>dermal lethal dose</td>
</tr>
<tr>
<td>LLNA</td>
<td>local lymph node assay</td>
</tr>
<tr>
<td>LOAEL</td>
<td>lowest-observed-adverse-effect level</td>
</tr>
<tr>
<td>log KOW</td>
<td>base-10 logarithm of a substance’s octanol–water partition</td>
</tr>
<tr>
<td>M</td>
<td>molarity</td>
</tr>
<tr>
<td>m³</td>
<td>cubic meter(s)</td>
</tr>
<tr>
<td>MEST</td>
<td>mouse-ear swelling test</td>
</tr>
<tr>
<td>mg</td>
<td>milligram(s)</td>
</tr>
<tr>
<td>mg/kg</td>
<td>milligram(s) per kilogram body weight</td>
</tr>
<tr>
<td>mg/kg/day</td>
<td>milligram(s) per kilogram body weight per day</td>
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<tr>
<td>mg/m³</td>
<td>milligram(s) per cubic meter</td>
</tr>
<tr>
<td>mL/kg</td>
<td>milliliter(s) per kilogram body weight</td>
</tr>
<tr>
<td>MW</td>
<td>molecular weight</td>
</tr>
<tr>
<td>NIOSH</td>
<td>National Institute for Occupational Safety and Health</td>
</tr>
<tr>
<td>nmol/cm²/hr</td>
<td>nanomoles per square centimeter per hour</td>
</tr>
<tr>
<td>NOAEL</td>
<td>no-observed-adverse-effect level</td>
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<tr>
<td>NTP</td>
<td>National Toxicology Program</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>--------------</td>
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<tr>
<td>OEL</td>
<td>occupational exposure limit</td>
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<td>OSHA</td>
<td>Occupational Safety and Health Administration</td>
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<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>REL</td>
<td>recommended exposure limit</td>
</tr>
<tr>
<td>RF</td>
<td>retention factor</td>
</tr>
<tr>
<td>SEN</td>
<td>skin notation indicating the potential for immune-mediated reactions following exposure of the skin</td>
</tr>
<tr>
<td>SI ratio</td>
<td>ratio of skin dose to inhalation dose</td>
</tr>
<tr>
<td>SK</td>
<td>skin notation</td>
</tr>
<tr>
<td>S&lt;sub&gt;W&lt;/sub&gt;</td>
<td>solubility</td>
</tr>
<tr>
<td>SYS</td>
<td>skin notation indicating the potential for systemic toxicity following exposure of the skin</td>
</tr>
<tr>
<td>USEPA</td>
<td>United States Environmental Protection Agency</td>
</tr>
</tbody>
</table>
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: Glutaraldehyde
CAS No: 111–30–8

Synonyms:
1,5-Pentanediol; 1,5-Pentanedi-one; Dioxopentane, Glutaral; Glutaralum; Glutaric Acid Dialdehyde; Glutardialdehyde; Glutaric Aldehyde; Glutaric Dialdehyde; Glutaral; Pentane-1,5-dial; Pentanedial

Molecular weight (MW): 100
Molecular formula: C₅H₈O₂

Structural formula:

O
\[\text{O} \backslash \text{O} \]

Uses:
Glutaraldehyde is an organic compound commonly used as a preservative, as a disinfectant in medical applications, and as an 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 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 (LD₁₀) for humans has been estimated, Ballantyne and Jordan [2001] reported these dermal LD₅₀ 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/
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 2001].

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

<table>
<thead>
<tr>
<th>Organization</th>
<th>Carcinogenic designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIOSH [2005]</td>
<td>None</td>
</tr>
<tr>
<td>NTP [2009]</td>
<td>None</td>
</tr>
<tr>
<td>USEPA [2009]</td>
<td>None</td>
</tr>
<tr>
<td>IARC [2009]</td>
<td>None</td>
</tr>
<tr>
<td>EC [2010]</td>
<td>None</td>
</tr>
<tr>
<td>ACGIH [2001]</td>
<td>A4: Not classifiable as a human carcinogen</td>
</tr>
</tbody>
</table>

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.
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 [Reffinrath 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
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.


*Ballantyne B, Jordan SL [2001]. Toxicological, medical and industrial hygiene aspects of glutaraldehyde with particular reference to its

*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.


*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 III. On file with the U.S. Environmental Protection Agency under TSCA Section 8D. OTS# 0558274. Document #: 86960000134


*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.


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)

\[
K_p = \frac{1}{K_{psc} + K_{pol} + K_{aq}}
\]

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
Skin Notation Profiles | Glutaraldehyde

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

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

*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**

$$\text{Skin dose} = K_P \times S_W \times \text{Exposed skin surface area} \times \text{Exposure time} \times 8 \text{ hours}$$

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

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**

\[
\text{Inhalation dose} = \text{OEL} \times \text{Inhalation volume} \times \text{RF}
\]

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

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**


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