

NIOSH Skin Notation Profiles

Formaldehyde/Formalin

SKK

ID^{SK}

[SK]

SYS

SYS (FATAL)

DIR

DIR (IRR)

DIR (COR)

SEN

NIOSH Skin Notation (SK) Profile

Formaldehyde/Formalin

[CAS No. 50–00–0]

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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 formaldehyde/formalin (CAS No. 50–00–0). In particular, this document evaluates and summarizes the literature describing the substance's hazard potential and its assessment according to the scientific rationale and framework outlined in CIB 61. In meeting this objective, this *Skin Notation Profile* intends to inform the audience—mostly occupational health practitioners, researchers, policy- and decision-makers, employers, and workers in potentially hazardous workplaces—so that improved risk-management practices may be developed to better protect workers from the risks of skin contact with the chemical of interest.

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Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
ATSDR	Agency for Toxic Substances and Disease Registry
CIB	Current Intelligence Bulletin
cm ²	square centimeter(s)
cm/hr	centimeter(s) per hour
cm/s	centimeter(s) per second
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
DMBA	dimethylbenz(a)anthracene
EC	European Commission
GHS	Globally Harmonized System of Classification and Labeling 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
kg	kilogram(s)
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
mg	milligram(s)
mg/cm ²	milligram(s) per square centimeter
mg/cm ² /hr	milligram(s) per square centimeter per hour
mg/kg	milligram(s) per kilogram
mg/kg/day	milligram(s) per kilogram body weight per day
mL	milliliter(s)
MW	molecular weight
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
ppm	parts per million
SEN	skin notation indicating the potential for immune-mediated reactions following exposure of the skin
SK	skin notation

SYS	skin notation indicating the potential for systemic toxicity following exposure of the skin
USEPA	United States Environmental Protection Agency
µg	microgram(s)
µg/cm ² /hr	microgram(s) per square centimeter per hour
µL	microliter(s)

Glossary

Absorption—The transport of a chemical from the outer surface of the skin into both the skin and systemic circulation (including penetration, permeation, and resorption).

Acute exposure—Contact with a chemical that occurs once or for only a short period of time.

Cancer—Any one of a group of diseases that 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: Formaldehyde/Formalin*

CAS No: 50–00–0

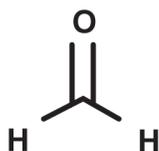
Synonyms:

Methanal; Methyl aldehydes; Methylene oxide; Formol; Formic aldehydes; Oxymethylene; Formalith; Morbicide; Paraform

Molecular weight (MW): 30.03

Molecular formula: CH₂O

Structural formula:



Uses:

Formaldehyde is used as a chemical intermediate during the production of organic compounds, especially urea-formaldehyde resins [ATSDR 1999]. Additional applications of formaldehyde include as a disinfectant and sterilizing agent, biocide (e.g., germicides, bactericides and fungicides), embalming fluid, and preservative in some food products. In 1995, the demand for formaldehyde in North America was estimated at 11.6 billion pounds (5.3 billion kilograms [kg]). Formaldehyde is ranked within the top 50 produced chemicals.

1.2 Purpose

This *Skin Notation Profile* presents (1) a brief summary of technical data associated with skin contact with formaldehyde and (2) the rationale behind the hazard-specific skin notation (SK) assignment for formaldehyde. 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 formaldehyde. A literature

search was conducted through July 2010 to identify information on formaldehyde, 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 formaldehyde.

1.3 Overview of SK Assignment for Formaldehyde

Formaldehyde is potentially capable of causing multiple adverse health effects following skin contact. A critical review of available

*The exposure guidelines and SK assignment stated in this document apply to formaldehyde and formalin. Unless otherwise specified, the term formaldehyde refers to all evaluated substances.

Table 1. Summary of the SK assignment for formaldehyde

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

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

2 Systemic Toxicity from Skin Exposure (SK: SYS)

The literature search revealed no in vivo toxicokinetic studies of humans that estimated the percent absorption of formaldehyde following dermal exposure. Several animal studies were identified. Bartnik et al. [1985] applied 200 milligrams (mg) of cream containing 0.1% ^{14}C -formaldehyde to the clipped skin of male and female rats for 48 hours without occlusion, and to two male rats with occlusion. At the end of the study period, total absorption over 48 hours ranged from 6.1% (in males) to 9.2% (in females) of the applied radioactivity. Absorption through occluded skin was 3.4%, whereas that through nonoccluded skin was 6.1%. The amount of ^{14}C remaining at the site of application was similar in occluded and nonoccluded animals (69.9% versus 70.2%). Unexpectedly, absorption following occlusive application was less than after nonocclusive application, a difference that the authors attributed to inhalation of the volatile formaldehyde following the nonocclusive application. To offset the contribution of inhaled formaldehyde, Bartnik et al. [1985] conducted a substudy during which measurements of $^{14}\text{CO}_2$ and volatile formaldehyde were omitted and

it was assumed that approximately 1% of the percutaneously absorbed formaldehyde would be eliminated as $^{14}\text{CO}_2$. The reported results of the substudy indicate that approximately 4.4% and 5.1% of the percutaneously applied dose of formaldehyde for male and female rats, respectively, was absorbed in 48 hours. Although studies revealed that less than 10% of the applied amount of formaldehyde is absorbed, the low values may reflect that excess amounts of the compound were applied to skin in these experiments. Using excised human skin, Loden [1986] reported that the skin absorption of formaldehyde from a concentrated solution of formalin (37% formaldehyde) and formaldehyde in phosphate buffer (10%) was 319 and 16.7 micrograms per square centimeter per hour ($\mu\text{g}/\text{cm}^2/\text{hr}$), respectively, indicating the dependency of flux on the concentration of formaldehyde and vehicle.

No human dermal lethal dose (LD_{Lo}) estimate or animal dermal LD_{50} value (the dose resulting in 50% mortality in the exposed population) has been identified. The lack of such data precludes adequate evaluation of the acute dermal toxicity of formaldehyde.

No epidemiological studies were identified that evaluated the potential of formaldehyde to cause systemic effects following dermal exposure. However, a case was identified in which a solution of phenol-formaldehyde resin accidentally came into contact with a large area of human skin [Cohen et al. 1989]. The skin contact became necrotic, and exposure resulted in

life-threatening systemic effects involving multiple organs several days after the massive skin exposure to the resin. The systemic effects, consisting of fever, adult respiratory distress syndrome, hypertension, proteinuria, and renal functional impairment, were noted several days after the exposure. According to the authors, the free forms of phenol and formaldehyde were 3.0% and 0.5%, respectively; the free forms were present in relatively low concentrations. Consequently, phenol involvement was ruled out as the cause of the renal impairment. Cohen et al. [1989] also ruled out inhalation of the low concentration (0.5%) of free formaldehyde as the cause of the lung effects observed. The authors therefore proposed that the multi-system involvement was secondary to the necrotic skin lesions as well as the continued facilitated absorption of the resin and/or its components via the skin lesions.

Two skin-painting carcinogenicity studies in animals have been conducted. In these studies, application of 200 microliters (μL) of 1%, 4%, or 10% formaldehyde in water to the shaved back skin of mice twice a week for 58 weeks (4% solution) or 60 weeks (1% and 10% solutions) did not affect survival of these animals [Iversen 1986, 1988], the only noncancer endpoint reported. The investigator did not provide average body weights for the hairless mice of the Oslo strain and SENCAR mice used in the study. Therefore, assuming a default average chronic body weight of 0.03 kg [USEPA 1988] (representing average body weights for male and female BAF1 and B6C3F1 mice), the doses used corresponded to 19, 76, and 189 milligrams per kilogram body weight per day ($\text{mg}/\text{kg}/\text{day}$), respectively, indicating that doses up to 189 $\text{mg}/\text{kg}/\text{day}$, the highest dose tested, did not affect survival of the animals under the conditions of the study.

No standard toxicity or specialty studies evaluating biological systemic/function (including reproductive toxicity or immunotoxicity) were identified. Overman [1985] evaluated the embryotoxic effects of topical exposure to formaldehyde in pregnant hamsters. Pregnant hamsters received 0.5 milliliter (mL) formaldehyde solution (37%) (corresponding to 1850 milligrams per kilogram [mg/kg] formaldehyde, according to information provided by the investigator) on gestation days 8, 9, 10, or 11 for 2 hours. Fetuses were evaluated at gestation day 15. Exposure did not significantly affect maternal weight gain, fetal length, or fetal weight. An increase in the incidence of resorptions was observed (3% to 8% of sites resorbed, versus none in controls), but the author attributed the increase to the stress of treatment during pregnancy rather than to a direct effect of formaldehyde. Although this is not a standard developmental toxicity study, the results suggest that dermal exposure to formaldehyde on any of these days is not likely to exert any developmental or embryotoxic effect or cause significant systemic maternal effects.

The literature search revealed no epidemiological studies or cases involving humans in which the potential of formaldehyde to contribute to the onset of systemic cancers following dermal exposure was evaluated. Several organizations have evaluated the carcinogenicity of formaldehyde on the basis of data from other routes of exposure. Table 2 provides a summary of carcinogenic designations from multiple governmental and nongovernmental organizations for formaldehyde.

No estimates of percent absorption of formaldehyde in humans following dermal exposure in vivo were identified. In vivo toxicokinetic data from animals suggest a limited potential for formaldehyde to be

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

Organization	Carcinogenic designation
NIOSH [2005]	Potential occupational carcinogen
NTP [2009]	Reasonably anticipated to be a human carcinogen
USEPA [2009]	Group B1: Probable human carcinogen
IARC [2009]	Group 1: Human carcinogen
EC [2010]	R40: Limited evidence of carcinogenic effect
ACGIH [2001]	Group A2: Suspected 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.

absorbed through the skin. Only limited data on toxicity following dermal exposure are available. Although a chronic study in mice and a nonstandard developmental dermal toxicity study [Overman 1985] did not identify any adverse systemic or developmental effects at the doses tested, exposure of a large area of skin to resins containing low concentrations of formaldehyde and phenol may lead to severe skin lesions that can potentially cause renal, cardiovascular, and lung effects [Cohen et al. 1989] directly or increase the absorption of toxicants. However, the causative agent(s) in the formaldehyde-phenol resin have not been identified. Carcinogenicity studies following dermal exposure indicate that formaldehyde is probably not a complete carcinogen or an initiator of carcinogenicity, but data regarding the promotion potential were inconclusive. Because of limited toxicokinetic findings and the absence of standard toxicity tests, the data are insufficient for reaching a conclusion regarding the systemic toxic effects associated with skin contact with formaldehyde. Therefore, on the basis of this assessment, formaldehyde is not assigned a SK: SYS notation.

3 Direct Effects on Skin (SK: DIR)

Evidence of the corrosive potential of formaldehyde is limited to a case report of skin necrosis resulting from dermal exposure. Cohen et al. [1989] reported the case of a man who developed severe skin necrosis after a large, acute dermal exposure to free formaldehyde (0.5%) as part of phenol-formaldehyde resin. Although the authors stated that phenol and formaldehyde concentrations were low, they did not indicate what agent was responsible for the necrosis resulting from the exposure to the resin; however, phenol, being corrosive to the skin, is a confounding factor and may have been responsible for the reported skin necrosis.

The direct skin effects of formaldehyde have been evaluated in human skin-patch tests. Fischer et al. [1995] conducted standard patch tests in nonsensitized individuals and observed that application of formaldehyde to skin in amounts ranging from 0.57 to 1.12 mg per square centimeter (mg/cm²) tends to produce skin irritation. Trattner et al. [1998] also indicated that a 2% concentration of formaldehyde produced significantly more irritant reactions than a

1% concentration. Numerous skin irritancy studies have involved animals. Celanese Chemical Company Inc. [1972] observed a 37% formaldehyde solution to be non-corrosive but irritating to rabbit skin in a standard irritation test, with a mean primary irritation score of 2.0 on an 8.0 scale. In another skin irritation test in rats, mice, and guinea pigs, Sekizawa et al. [1994] reported that formaldehyde solutions of various concentrations (7% to 9%, 15% to 18%, and 37%) are moderately irritating to the skin of rats and mice. However, for guinea pigs, solutions of 15% to 18% (the highest concentration tested) are moderately irritating to the skin, whereas those of 7% to 9% are not irritating. In a 9-day repeated-dose study in guinea pigs, daily treatment with 0.1 mL of formalin dilutions (1%, 3%, and 10%, corresponding to 0.4%, 1.2%, and 4% formaldehyde) to the nonoccluded skin produced a statistically significant increase in skinfold thickness on day 3 of high-dose application [Wahlberg 1993]. Erythema appeared on day 2 (4% formaldehyde), day 5 (1.2% formaldehyde), and day 6 (0.4% formaldehyde). Increased skinfold thickness was statistically significant on days 3 (4% formaldehyde), 7 (1.2% formaldehyde), and 9 (0.04% formaldehyde). Although manufacturers and distributors list formaldehyde as corrosive to the skin, they provide no primary sources for adequate evaluation. Results from the identified studies suggest that solutions of formaldehyde at concentrations up to 37% can be regarded as mild to moderate skin irritants. It is possible that higher concentrations may be corrosive to the skin, indicating that skin corrosivity or irritancy is dependent on the formaldehyde concentration. On the basis of the chemical structure of formaldehyde, the structure-activity relationship model (Deductive Estimation of Risk from Existing Knowledge [DEREK™] for Windows) predicted the chemical to be negative for skin irritation.

However, Iversen [1986, 1988] evaluated the carcinogenic potential of formaldehyde in a pair of skin-painting experiments in animals. No carcinogenicity was observed when hairless mice were topically exposed to 200 μ L of 1% or 10% formaldehyde in distilled water twice a week (corresponding to 19 or 189 mg/kg/day; see above) for 60 weeks [Iversen 1986]. The author also evaluated the promotion potential of formaldehyde by initially painting mice with 51.2 micrograms (μ g) dimethylbenz(a)anthracene (DMBA; a known tumor initiator) in 0.1 mL acetone, followed by semiweekly treatment with 10% formaldehyde in water. In this treatment, formaldehyde shortened the latency of DMBA-induced tumors [Iversen 1986]. In a follow-up study, Iversen [1988] repeated the skin-painting study in SENCAR mice bred for maximum sensitivity to chemical tumorigenesis. Topical application of 4% formaldehyde in water, 200 μ L twice weekly (corresponding to 76 mg/kg/day) produced a total of two benign tumors among 32 mice. Initial application of 51.2 μ g DMBA followed by semiweekly applications of 1% or 4% formaldehyde solutions produced no statistically significant difference in tumor incidence in comparison with DMBA alone. Iversen [1988] concluded that formaldehyde had no skin tumorigenic or carcinogenic potency of its own. In a promotion/initiation study, Spangler and Ward [1982] applied single doses of 3.7% to 4.0% formaldehyde in acetone to the skin of 30 female SENCAR mice. Results indicated formaldehyde is probably not a complete carcinogen or an initiator of carcinogenicity, whereas the data regarding its promotion potential were inconclusive.

One case report described skin corrosivity resulting from a massive skin exposure to formaldehyde-containing resin [Cohen et al. 1989]. However, the authors did not

provide any evidence that the low concentration of either formaldehyde or phenol in the resin was responsible for the effect observed. Several skin irritation tests identified in animals [**Celanese Chemical Company Inc. 1972; Wahlberg 1993; Sekizawa et al. 1994; Fischer et al. 1995; Trattner et al. 1998[†]**] indicate that solutions of formaldehyde at concentrations up to 37% are likely to cause mild to moderate skin irritation. Solutions at concentrations that exceed 37% may be capable of causing severe skin irritation resulting in corrosion. Therefore, on the basis of the data for this assessment, formaldehyde is assigned the SK: DIR (IRR) notation.

4 Immune-mediated Responses (SK: SEN)

Skin sensitization following dermal exposure to formaldehyde in humans and animals has been well documented. Human skin sensitivity to formaldehyde has been associated with many dermal exposure situations, including exposure to formalin (a saturated solution of formaldehyde, water, and typically another agent, most commonly methanol), formaldehyde-containing resins, formaldehyde-treated fabrics, and formaldehyde-containing household products and facial tissues [Fisher 1981; Lembo et al. 1982; Lee et al. 1984; DeGroot et al. 1988; Massone et al. 1988; Meding and Swanbeck 1990; Flyvholm 1991; Menne et al. 1991; Flyvholm and Menne 1992; Sanchez et al. 1997]. Formaldehyde has been widely reported to cause dermal allergic reactions in occupationally exposed nurses, doctors, and dentists [Agathos 1982; Rudzki et al. 1989], cosmetic workers [Ancona-Alayon et al. 1976], textile workers [Andersen and

Maibach 1984; Donovan and Skotnicki-Grant 2006], and construction workers [Bell and King 2002; Ezughah et al. 2001; Finch et al. 1999]. Kiec-Swierczynska [1996] observed allergic responses in 18.1% of 330 occupationally exposed subjects patch-tested between 1990 and 1994. Several studies have reported allergic contact dermatitis in patch tests of patients with nonoccupational or occupational formaldehyde contact dermatitis resulting from contact with clothes pretreated with formaldehyde [Berrens et al. 1964; O'Quinn and Kennedy 1965; Fowler et al. 1992; García Bracamonte et al. 1995; Donovan and Skotnicki-Grant 2006].

Historical rates of formaldehyde-induced sensitization have been measured with patch testing. Patients diagnosed with hand eczema from occupational and non-occupational exposures within 1 year were patch-tested with a standard series of 25 substances, including formaldehyde [Meding and Swanbeck 1990]. The authors observed positive responses in 1.6% of 1,081 patients patch-tested with 2% formaldehyde. In a study conducted between 1988 and 1989 involving patch-testing of 4,713 patients who presented with eczematous dermatitis, Menné et al. [1991] reported that 2.6% of the patients exhibited allergic reactions to 1% formaldehyde solution. Marks et al. [1998] reported results of patch tests conducted on patients between 1992 and 1994. The authors found that 7.8% of 3,239 patients had allergic reactions to formaldehyde (1% aqueous), and the rate of allergenicity was higher (9.2% of 3,111 patients). Trattner et al. [1998] reported a positive patch-test response in 121 of 3,734 patients who presented with dermatitis or atopic dermatitis and were tested with 1% and/or 2% formaldehyde in water. Those authors recommended a patch-test concentration of 1% formaldehyde, based on findings that the 2% concentration produced significantly more irritant reactions

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

than the 1% concentration. Cronin [1991] reported a formaldehyde sensitivity prevalence rate of 98 (2.2%) per 4,552 men (total patch-tested, 4,553) and 235 (3.7%) per 6,479 women who were patch-tested with a standard series of allergens containing 1% formaldehyde in water at a hospital from 1984 to 1989. Some of these patients were exposed to formaldehyde occupationally or domestically (in cosmetics and household cleaning products). In a more recent study, Beliauskiene et al. [2010] examined the prevalence of contact allergy in the 816 patients with suspected allergic contact dermatitis in Lithuania via patch testing following the guidelines of the International Contact Dermatitis Research Group. A 1% solution of formaldehyde was applied for 48 hours in water using Finn Chambers on Scanpor; readings were performed on day 2 and day 3. The authors reported that 24 patients or 3.1% (95% CI 1.8–4.4) of the study population exhibited positive reactions towards formaldehyde.

Other studies have investigated the threshold concentration of formaldehyde below which formaldehyde-sensitive patients can be protected. Jordan et al. [1979] conducted a double-blind, controlled study on formaldehyde threshold responses in allergic patients by repeated applications of patch tests at the same site for 1 week. In another test, the authors used a threshold level obtained by long-term, closed patch tests to more closely assess the effect of chronic use on a skin site known for its susceptibility to irritants and allergens. Jordan et al. [1979] determined that aqueous concentrations of formaldehyde below 30 parts per million (ppm) should be tolerated by sensitive subjects if repeatedly applied to normal skin. Those authors also suggested that popular formaldehyde-releasing preservatives can be above or below this threshold-eliciting response. Scheman et al. [1998] reported that resins yielding fabrics with less than

75 ppm free formaldehyde may cause occasional reactions but are more likely to be tolerated. Flyvholm et al. [1997] investigated the eliciting threshold concentration of formaldehyde in formaldehyde-sensitive individuals in occluded and nonoccluded patch tests. In addition, the authors evaluated the relationship to repeated open-application tests using a product containing formaldehyde releaser. The study involved occluded and nonoccluded patch tests with formaldehyde solutions from 25 to 10,000 ppm applied to 20 formaldehyde-sensitive patients and a control group of 20 healthy volunteers. The repeated open-application test was conducted by applying, for 1 week, a leave-on cosmetic product containing on average 300 ppm formaldehyde. The frequency of resulting sensitization was concentration-dependent. Under occlusion, sensitization was observed in 10 of 20 patients administered 10,000 ppm; 9 of 20 administered 5,000 ppm; 3 of 20 administered 1,000 ppm; 2 of 20 administered 500 ppm; and 1 of 20 administered 250 ppm. The authors observed no definite positive reactions in the nonoccluded patch test, in the repeated open-application test, or in the control group. On the basis of their results, Flyvholm et al. [1997] concluded that the threshold concentration for occluded patch-testing of formaldehyde-sensitive patients was 250 ppm. This threshold is greater than the 30 ppm and 75 ppm reported by Jordan et al. [1979] and Scheman et al. [1998], respectively.

The sensitizing potential of formaldehyde has been evaluated in experimental animals in predictive tests. In a guinea pig maximization test (GPMT), Magnusson et al. [1969] reported a sensitization rate of 16/20 (80%) following induction with a 5% concentration (an intradermal concentration of 5% in adjuvant and a topical concentration of 5% in petrolatum) and a challenge concentration of 10% in

petrolatum. In another GPMT, pretreatment with a series of intradermal injections of 0.25% formalin (37% formaldehyde) solutions, followed by occluded patch-testing with 10% formaldehyde, produced sensitization in 100% of the treated animals [Hilton et al. 1996]. Andersen et al. [1985] conducted GPMTs using two different guinea pig strains. Induction was done with 6 intradermal injections (0.01% to 3% formaldehyde) or 6 topical (0.5% to 20%) formaldehyde concentrations, followed by challenge doses of 0.1% or 1% formaldehyde. Allergic response rates varied more with the intradermal dose than with the topical dose. The authors reported values for the animals challenged with the 1% solution EC_{50} (the concentration at which 50% of the animals were sensitized) values of 0.061% and 0.024% in the two different strains after the 72-hour scoring. Goodwin et al. [1981] reported that formaldehyde was a strong sensitizer in a GPMT and moderate sensitizer in a single-injection adjuvant test and a modified Draize procedure. Buehler [1965] reported that formaldehyde is a contact allergen in the guinea pig, as evidenced by the Buehler test. In another Buehler test, a series of 6-hour occluded patch applications of 5% formaldehyde solutions caused sensitization to subsequent exposures to 1% formaldehyde in 70% of treated guinea pigs [Hilton et al. 1996]. Guillot et al. [1983] conducted seven independent sensitization tests (GPMT, split adjuvant, guinea-pig optimization test, Guillot/Barulos test, Freund's complete adjuvant test, Dossou and Sicard method, and open epicutaneous test) and assessed the sensitization potential of formaldehyde macroscopically and histologically. The response rates ranged from 0 to 100% and 0 to 70% in the macroscopic and histological assessments, respectively. Results indicate that formaldehyde is a skin sensitizer in

guinea pigs. Marzulli and Maguire [1982] tested the allergenicity of formaldehyde in five guinea pig bioassays (GPMT, Draize method, Buehler test, split adjuvant technique, and cyclophosphamide/complete Freund's adjuvant bioassay). In that study, formaldehyde was a sensitizer in all the assays except the Buehler test.

Hilton et al. [1996] reported that formaldehyde elicited strong positive responses in the GPMT, the occluded patch test of Buehler, and the murine local lymph node assay (LLNA). The response rates were reported to be 100% and 70% for the GPMT and Buehler test, respectively. In the LLNA, Hilton et al. [1996] reported that formaldehyde induced vigorous lymph node cell proliferative responses at the 10%, 25%, and 50% concentrations tested, with the respective stimulation indices reported as 8.58, 9.72, and 9.04. The response rate was lower in guinea pigs (1/20) with use of the Lansteiner-Draize test [Magnusson et al. 1969]. Several other investigators have reported the potential of formaldehyde to be a skin sensitizer in animals [e.g., Guillot et al. 1983; Hilton et al. 1996]. DEREK™ predicted formaldehyde to be a skin sensitizer.

Several reports on cases of occupational exposure [Cronin 1991; Bell and King 2002; Donovan and Skotnicki-Grant 2006], historical patch-testing in humans [Meding and Swanbeck 1990; Fischer et al. 1995; Kiec-Swierczynska 1996; Marks et al. 1998; Beliauskiene et al. 2010], repeated-application testing in humans [Jordan et al. 1979; Flyvholm et al. 1997; Scheman et al. 1998], and positive responses in predictive tests in animals (such as GPMTs, Buehler tests, and LLNAs) [Buehler 1965; Magnusson et al. 1969; Goodwin et al. 1981; Guillot et al. 1983; Andersen et al. 1985; Hilton et al. 1996] indicate that formaldehyde or formaldehyde-releasing

chemicals in resins, fabrics, facial tissues, cosmetics, and cleaning agents have the potential to cause skin sensitization. Therefore, on the basis of the data for this assessment, formaldehyde is assigned the SK: SEN notation.

5 Summary

No in vivo human studies were identified that estimated the percent absorption of formaldehyde following dermal exposure. However, data on in vivo toxicokinetics in animals suggest that formaldehyde has limited potential to be absorbed through the skin (i.e., percent absorption of less than 10%). Although a nonstandard chronic study and a nonstandard developmental dermal toxicity study suggest that the substance is not likely to be a systemic or developmental toxicant at the doses tested, formaldehyde exposure to a large area of the skin has resulted in severe skin lesions with multisystem effects, including renal, cardiovascular, and lung impairments [Cohen et al. 1989]. The lack of toxicokinetic data needed to determine the extent of absorption and lack of standard animal studies of toxicity after dermal administration preclude evaluation of the systemic toxicity potential of formaldehyde by the dermal route. A case report provides some evidence of the potential of formaldehyde to be corrosive to the skin. However, data from several skin irritation studies in animals [Celanese Chemical Company Inc. 1972; Wahlberg 1993; Sekizawa et al. 1994; Fischer et al. 1995; Trattner et al. 1998] indicate that solutions of formaldehyde at concentrations up to 37% are likely to cause mild to moderate skin irritation. Concentrations above 37% may cause severe irritation or corrosion. Numerous reports of cases of occupational exposure [Cronin 1991; Bell and King 2002; Skotnicki-Grant

2006], historical patch-testing in humans [Meding and Swanbeck 1990; Fischer et al. 1995; Kiec-Swierczynska 1996; Marks et al. 1998; Beliauskiene et al. 2010], repeated-application testing in humans [Jordan et al. 1979; Flyvholm et al. 1997; Scheman et al. 1998], and positive responses in predictive tests in animals (including GPMTs, Buehler tests, and LLNAs) [Buehler 1965; Magnusson et al. 1969; Goodwin et al. 1981; Guillot et al. 1983; Andersen et al. 1985; Hilton et al. 1996] provide sufficient information on the potential of formaldehyde or formaldehyde-releasing chemicals in resins, fabrics, facial tissues, cosmetics, and cleaning agents to cause skin sensitization. Therefore, on the basis of the data for this assessment, formaldehyde is assigned the notation **SK: DIR (IRR)-SEN**.

Table 3 summarizes the skin hazard designations for formaldehyde previously issued by NIOSH and other organizations. The equivalent dermal designations for formaldehyde, according to the Global Harmonized System (GHS) of Classification and Labeling of Chemicals, are Acute Toxicity Category 3 (Hazard statement: Toxic in contact with the skin), Skin Corrosion Category 1B for solution that contains >25% formaldehyde (Hazard statement: Causes skin irritation), Skin Irritant Category 2 for solutions that contains between 5 to 25% formaldehyde (Hazard statement: Causes skin irritation), and Skin Sensitization Category 1 (Hazard statement: May cause an allergic skin reaction) [European Parliament 2008]. Formaldehyde has been identified as a Category 2 Carcinogen (Hazard statement: Suspected of causing cancer) [European Parliament 2008].

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

Organization	Skin hazard designation
NIOSH [2005]	None
OSHA [2009]	None
ACGIH [2001]	SEN: Based on the reports of allergic reactions/sensitization following occupational and nonoccupational exposures to formaldehyde
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.

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

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