

# NIOSH Skin Notation Profiles

## Methyl Cellosolve

SKK

ID<sup>SK</sup>

[SK]

**SYS**

SYS (FATAL)

DIR

DIR (IRR)

DIR (COR)

SEN



# NIOSH Skin Notation (SK) Profile

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**Methyl Cellosolve**

**[CAS No. 109–86–4]**

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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 methyl cellosolve (CAS No. 109–86–4). 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
CIB	Current Intelligence Bulletin
cm <sup>2</sup>	square centimeter(s)
cm/hr	centimeter(s) per hour
CNS	central nervous system
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
EEC	European Economic Communities
GHS	Globally Harmonized System of Classification and Labeling of Chemicals
GPMT	guinea pig maximization test
IARC	International Agency for Research on Cancer
K <sub>aq</sub>	coefficient in the watery epidermal layer
K <sub>p</sub>	skin permeation coefficient
K <sub>pol</sub>	coefficient in the protein fraction of the stratum corneum
K <sub>psc</sub>	permeation coefficient in the lipid fraction of the stratum corneum
LD <sub>50</sub>	dose resulting in 50% mortality in the exposed population
LD <sub>Lo</sub>	dermal lethal dose
LOAEL	lowest-observed-adverse-effect level
log K <sub>OW</sub>	base-10 logarithm of a substance's octanol–water partition
m <sup>3</sup>	cubic meter(s)
MCV	mean corpuscular volume
mg	milligram(s)
mg/cm <sup>2</sup> /hr	milligram(s) per square centimeter per hour
mg/kg	milligram(s) per kilogram body weight
mg/kg/day	milligram(s) per kilogram body weight per day
mg/m <sup>3</sup>	milligram(s) per cubic meter
mL	milliliter(s)
mL/kg	milliliter(s) per kilogram body weight
MW	molecular weight
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
OEL	occupational exposure limit
OSHA	Occupational Safety and Health Administration



RBC	red blood cell
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 <sub>w</sub>	solubility
SYS	skin notation indicating the potential for systemic toxicity following exposure of the skin
USEPA	United States Environmental Protection Agency
μL/cm <sup>2</sup>	microliter(s) per square centimeter

## 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:** Methyl Cellosolve

**CAS No:** 109–86–4

**Synonyms:**

EGME; Ethylene Glycol Monomethyl Ether; Glycol Monomethyl ether; 2-Methoxyethanol

**Molecular weight (MW):** 76

**Molecular formula:** C<sub>3</sub>H<sub>8</sub>O<sub>2</sub>

**Structural formula:**



**Uses:**

Methyl cellosolve is used primarily as a jet fuel additive and as an organic solvent [Boatman and Knaak 2001].

## 1.2 Purpose

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

## 1.3 Overview of SK Assignment for Methyl Cellosolve

Methyl cellosolve is potentially capable of causing multiple adverse health effects following skin contact. A critical review of available data has resulted in the following SK assignment for methyl cellosolve: **SK: SYS**. Table 1 provides an overview of the critical effects and data used to develop the SK assignment for methyl cellosolve. The following section provides additional details about the potential health hazards of skin contact with methyl cellosolve and the rationale behind the SK assignment.

## 2 Systemic Toxicity from Skin Exposure (SK: SYS)

A number of studies investigated the percutaneous absorption of methyl cellosolve. Kezic et al. [1997] exposed an area of about 1000 square centimeters (cm<sup>2</sup>) of the forearm and hand of healthy volunteers to vapors of methyl cellosolve (4000 milligrams per cubic meter [mg/m<sup>3</sup>]) for 45 minutes. Those investigators also filled

**Table 1. Summary of the SK assignment for methyl cellosolve**

Skin notation	Critical effect	Data available
SK: SYS	Central nervous system (CNS) effects; Reproductive toxicity; Developmental toxicity; Hematologic effects; Immunotoxicity	Sufficient human and animal data

a gas chamber with an area of 27 cm<sup>2</sup> with liquid methyl cellosolve and placed the chamber on the volar forearm of the volunteers for 15 minutes. On the basis of measurements of the main urinary metabolite, methoxyacetic acid, the investigators concluded that both vapor and liquid methyl cellosolve were readily absorbed through the skin, with an average absorption rate of 2.9 milligrams per square centimeter per hour (mg/cm<sup>2</sup>/hr) for liquid and a penetration rate of 36 centimeter per hour (cm/hr) for vapor. Kezic et al. [1997] estimated uptake through the skin to be 55% of the total uptake of methyl cellosolve in a combined inhalation and dermal exposure when the whole body surface was exposed to the vapor. During the inhalation experiments, airborne concentrations of methyl cellosolve vapor were estimated at 16 mg/m<sup>3</sup>. Kezic et al. [1997] reported that during contact of both hands and forearms (10% of the total body surface area) with liquid methyl cellosolve for 60 minutes, dermal absorption was more than 100 times the inhalation absorption during an 8-hour exposure to 16 mg/m<sup>3</sup> methyl cellosolve vapor.

Sabourin et al. [1992] noted a linear relationship between the absorption and the applied dermal dose; dermal absorption ranged from 19.4% to 26.9% following nonoccluded application of 34.2 to 304 milligrams per kilogram body weight (mg/kg) on the clipped backs of rats. The potential of methyl cellosolve 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 588.5 was calculated for methyl cellosolve. An SI ratio of  $\geq 0.1$  indicates that a chemical is capable of producing systemic toxicity from skin exposure [NIOSH 2009]. Additional information on the SI ratio and the variables used in its calculation are included in the appendix.

No dermal lethal dose (LD<sub>L0</sub>) for humans has been identified. However, the reported values for dermal LD<sub>50</sub> (the dose resulting in 50% mortality in the exposed population) in rabbits range from 0.891 milliliter per kilogram body weight (mL/kg), which corresponds to 860 mg/kg [Union Carbide Corporation 1984] to 1.34 mL/kg (corresponding to 1,290 mg/kg) [Carpenter et al. 1956]. The range of LD<sub>50</sub> values in rabbits is lower than the critical dermal LD<sub>50</sub> value of 2000 mg/kg body weight that identifies chemical substances with the potential for acute dermal toxicity [NIOSH 2009]. Therefore, methyl cellosolve is considered acutely toxic following dermal exposure.

Several case studies were identified that reported neurological effects following occupational exposures to methyl cellosolve. Within these reports, the contribution of exposure via the inhalation route cannot be excluded, but the authors indicate that dermal exposure to methyl cellosolve was the primary exposure pathway within each case.

Ohi and Wegman [1978], Donley [1936], and Parsons and Parsons [1938] reported adverse central nervous system (CNS) effects (i.e., encephalopathy) and hematotoxic effects (i.e., bone marrow depression, anemia, and leukopenia) in workers exposed dermally to methyl cellosolve. Immunological effects have been reported to occur in workers following prolonged dermal and inhalation exposure, for 8 to 35 years [Denkhaus et al. 1986]. Welch and Cullen [1988] and Shih et al. [2003] reported various hematological effects (anemia, granulocytopenia, and low polymorphonuclear leukocyte count) among workers exposed to methyl cellosolve in a cross-sectional study and a follow-up study. In a reported case, macrocytic anemia and reversible subjective CNS effects occurred in a worker with inhalation and dermal exposures to methyl cellosolve during microfilm manufacturing [Cohen 1984].

Epidemiologic studies that concerned the reproductive and developmental effects of methyl cellosolve in exposed workers were identified. Several studies have revealed increased frequency of spontaneous abortions, disturbed menstrual cycles, and subfertility in female workers [Pastides et al. 1988; Eskenazi et al. 1995; Gold et al. 1995; Schenker 1995; Pinney and Lemasters 1996] and increased frequency of reduced sperm counts and a decrease in testicular size in males [Cook et al. 1982; Welch et al. 1988]. However, no exposure data are available to evaluate the dose response for these effects. As a result of extensive, prolonged dermal

and inhalation exposure to unspecified amounts of methyl cellosolve and ethylene glycol in a factory, the children of workers developed dysmorphic features as well as persistent cytogenetic damage, including polyploidy, endoreduplication, and mental retardation [Saavedra and Tena 1997; El-Zein et al. 2002].

The hematological changes seen in humans have been observed in animals as well. Hobson et al. [1986] reported significant changes in hematological parameters (decreased red blood cell [RBC] counts and increased mean corpuscular volume [MCV]); increased urinary calcium values; statistically significantly reduced body, testicular, and splenic weights; and testicular lesions (moderate to severe segmental degeneration of the seminiferous tubules) in guinea pigs tested at 1000 mg/kg/day (the only dose tested). The neat chemical was applied to the shaved backs of the animals under gauze patches 6 hours per day, 5 days per week, for 13 weeks. Fairhurst et al. [1989] exposed clipped skin of rats to 99% pure methyl cellosolve at concentrations of 10 or 1000 milligrams per kilogram per day (mg/kg/day) under occlusive or nonocclusive conditions on 5 consecutive days per week for 28 days. In comparison with that in control animals, body weight gain was reduced in the occluded animals at applications of 10 mg/kg/day and above and also in the nonoccluded animals, but only at applications of 1000 mg/kg/day. The statistical significance of the change was not reported. Additionally, methyl cellosolve caused hematological effects (a decrease in the number of reticulocytes and increases in RBC count, white blood cell count, hemoglobin, MCV, and packed cell volume) and histopathological changes in the testis (described in more detail below) and bone marrow (generalized hypocellularity) in occluded animals treated at 1000 mg/kg/day. Results in the studies of Fairhurst et al. [1989] and Hobson et al.

**Table 2. Summary of the carcinogenic designations\* for methyl cellosolve 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]	None

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.

[1986] show a lowest-observed-adverse-effect level (LOAEL) of 1000 mg/kg/day, with some indication of effects at doses as low as 10 mg/kg/day.

Dermal studies in animals showed that methyl cellosolve is a reproductive and developmental toxicant. Methyl cellosolve topically applied to guinea pigs for 13 weeks at a dosage of 1000 mg/kg/day caused statistically significant reductions in testicular weight as well as testicular lesions [Hobson et al. 1986]. The same dose applied for 28 days also caused histopathological changes in the testes of rats, described as depletion of pachytene spermatocytes, almost complete absence of spermatids, and reduction in the germinal epithelium of the tubules [Fairhurst et al. 1989]. Feuston et al. [1989] reported that repeated dermal exposure to methyl cellosolve in rats for 7 consecutive days induced effects on the testes (including declines in epididymal sperm count and testicular spermatid count and reductions in weight of the testes and epididymides), on sperm parameters (increases in the number of sperm with abnormal morphology), and on fertility (reductions in fertility) at 625 mg/kg/day (the lowest dose tested)

and above following occlusive application. With nonocclusive conditions, these effects were observed at 1250 mg/kg/day (the lowest dose tested) and above.

The developmental toxicity of dermally applied methyl cellosolve has also been explored. Feuston et al. [1990] reported a LOAEL of 500 mg/kg in rats dosed on gestation day 12 for maternal toxicity (for decrease in mean body weight gain) and for developmental toxicity (for increases in external, visceral, and skeletal malformations). The no-observed-adverse-effect level (NOAEL) in this study for both maternal and developmental toxicity was 250 mg/kg/day. Wickramaratne [1986] exposed the shaved skin of pregnant rats to a solution of methyl cellosolve in saline for 6 hours a day on gestation days 6 to 17. Application of 10 mL/kg of a 10% solution of methyl cellosolve in physiological saline was fetotoxic, causing a decrease in fetal survival and a reduction in litter size, whereas application of the same volume of a 3% solution did not cause any adverse effects. On the basis of this study, the NOAEL was 3% (corresponding to approximately 300 mg/kg/day) and the LOAEL was 10% (approximately 1000 mg/kg/day).



The developmental toxicity studies yielded evidence of fetotoxicity but did not show teratogenic effects as described in the epidemiologic study by Saavedra and Tena [1997] and El-Zein et al. [2002].

Dermal exposure of rats to methyl cellosolve under occlusion for 4 consecutive days also induced immunotoxicity, as evidenced by a decreased ability to produce primary antibodies to the antigen at 300 mg/kg/day and above, decreased thymus weight following exposure to 600 mg/kg/day and above, and reduced spleen weight at 900 mg/kg/day and above [Williams et al. 1995]. These results are generally consistent with the findings of Hobson et al. [1986] and Fairhurst et al. [1989], who reported the ability of methyl cellosolve to impact hematological parameters and bone marrow, although the array of specific effects in these studies were not entirely consistent with impaired immune function.

Overall, these studies of repeated dermal dosing provide a LOAEL of 625 mg/kg/day or more for induced reproductive toxicity (testicular toxicity and sperm effects) [Feuston et al. 1989], and doses in the range of 500 mg/kg/day induced developmental toxicity (including malformations) in guinea pigs and/or rats [Feuston et al. 1990]. The NOAEL for maternal and developmental effects is in the range of 250 mg/kg/day. The substance may also be immunotoxic at doses as low as 300 mg/kg/day [Williams et al. 1995].

No data were identified regarding the carcinogenic potential of methyl cellosolve following dermal exposure. Table 2 provides a summary of carcinogenic designations from multiple governmental and nongovernmental organizations for methyl cellosolve.

Data from the toxicokinetic studies in humans [Sabourin et al. 1992; Kezic et

al. 1997\*], acute dermal toxicity studies [Carpenter et al. 1956; Union Carbide Corporation 1984], and repeat-dose toxicity studies in rats [Hobson et al. 1986; Wickramaratne 1986; Fairhurst et al. 1989; Feuston et al. 1989; Williams et al. 1995] demonstrate that methyl cellosolve is absorbed through the skin and can cause systemic effects within the CNS, in addition to the reproductive, developmental, hematological, and immune systems. Therefore, on the basis of the data for this assessment, methyl cellosolve is assigned the SK: SYS notation.

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

No human or animal data were identified that assessed the corrosive potential of methyl cellosolve. Additionally, no in vitro tests for corrosivity in human or animal skin models were found. No information on occupational exposure has suggested that methyl cellosolve is a skin irritant. Jacobs et al. [1989] performed a series of tests in volunteers that evaluated the skin irritation potential of methyl cellosolve by measuring cutaneous blood flow values with laser Doppler flowmetry following occluded application of patches to intact forearm. The patches contained approximately 18 microliters per square centimeter ( $\mu\text{L}/\text{cm}^2$ ) of undiluted substance, applied for 48 hours, or 10% solution of the substance in water, applied for 3 hours. Neither diluted nor undiluted methyl cellosolve was irritating to human skin in that study. In the same study, methyl cellosolve was not irritating to rabbit skin, according to the Draize score for erythema, following application of a patch soaked with 0.5

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

**Table 3. Summary of the previously issued skin hazard designations for methyl cellosolve**

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption
OSHA [2009]	[skin]: Potential for dermal absorption
ACGIH [2001]	[skin]: Based on the ready absorption through the skin in amounts sufficient to elicit systemic toxicity
EC [2010]	R21: Harmful if in contact with skin 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.

milliliter (mL) of undiluted substance to 6 cm<sup>2</sup> of rabbit skin under occlusion for 4 hours. In an earlier study conducted according to the European Economic Communities (EEC) method, methyl cellosolve was not irritating after the substance was applied to the shaved skin of rabbits for 4 hours, and erythema and edema were scored on the Draize scale for up to 72 hours after removal of the patch [Jacobs et al. 1987]. Bushy Run Research Center [1984] observed no irritation when rabbits were administered 0.5 mL methyl cellosolve for 4 hours under occlusion. However, Zissu [1995] found methyl cellosolve to be slightly irritating to rabbit skin according to the Draize method but nonirritating according to the EEC method. Dugard et al. [1984] utilized human abdominal whole skin to evaluate the skin damage caused by topical applications of methyl cellosolve. During the *in vitro* study, the authors applied a “damage ratio,” which compared the final tritiated water permeability constant to the initial permeability constant as an indication of irreversible alterations in epidermal diffusion barrier function occurring during the experiment. Dugard et al. [1984] reported a damage ratio of 3.51 for methyl cellosolve. For comparison purposes, it should be noted that the control damage ratio

values for distilled water contact alone were between 1.0 and 2.0. The structure-activity relationship model (Deductive Estimation of Risk from Existing Knowledge, or DEREK™, for Windows) predicted methyl cellosolve to be negative for skin irritation.

The weight of evidence from the standard skin irritation studies indicates that methyl cellosolve is not a primary skin irritant. Therefore, on the basis of the data for this assessment, methyl cellosolve is not assigned the SK: DIR notation.

## 4 Immune-mediated Responses (SK: SEN)

There is limited information available to evaluate the sensitization potential of methyl cellosolve. No specific information on skin sensitization due to methyl cellosolve is available from occupational exposure experience, in spite of extensive reports of exposure. Zissu [1995] investigated the potential of methyl cellosolve to be a skin sensitizer in the guinea pig maximization test and found the substance to be nonsensitizing. DEREK™ predicted ME to be negative for skin sensitization. Therefore, on the basis of the data for this

assessment, methyl cellosolve is not assigned the SK: SEN notation.

## 5 Summary

Sufficient data were identified from toxicokinetic studies in humans [Dugard et al. 1984; Sabourin et al. 1992; Kezic et al. 1997], acute dermal toxicity studies [Carpenter et al. 1956; Union Carbide Corporation 1984], and repeat-dose toxicity studies in rats [Hobson et al. 1986; Wickramaratne 1986; Fairhurst et al. 1989; Feuston et al. 1989; Williams et al. 1995] to demonstrate that methyl cellosolve is absorbed through the skin, is systemically available, can cause systemic effects within the CNS, in addition to the reproductive, developmental, hematological, and immune systems. Standard skin irritation studies in rabbits show that methyl cellosolve is not a primary skin irritant. A guinea pig maximization test demonstrated that methyl cellosolve was not a skin sensitizer. Therefore, for this assessment, a **SK: SYS** notation is assigned to methyl cellosolve.

Table 3 summarizes the skin hazard designations for methyl cellosolve previously issued by NIOSH and other organizations. The equivalent dermal designations for methyl cellosolve, according to the Global Harmonization System (GHS) of Classification and Labelling of Chemicals, are Acute Toxicity Category 4 (Hazard statement: Harmful in contact with the skin) and Skin Irritation Category 2 (Hazard statement: Causes skin irritation) [European Parliament 2008]. Methyl cellosolve has been identified as a Category 1B Reproductive toxicant (Hazard statements: May damage fertility; May damage the unborn child) [European Parliament 2008].

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

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## Appendix: Calculation of the SI Ratio for Methyl Cellosolve

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for methyl cellosolve. 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, 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 methyl cellosolve**

Variables used in calculation	Units	Value
<b>Skin permeation coefficient</b>		
Permeation coefficient of stratum corneum lipid path ( $K_{psc}$ )	cm/hr	0.00044
Permeation coefficient of the protein fraction of the stratum corneum ( $K_{pol}$ )	cm/hr	$1.74127 \times 10^{-5}$
Permeation coefficient of the watery epidermal layer ( $K_{aq}$ )	cm/hr	0.28658
Molecular weight (MW)*	amu	76
Base-10 logarithm of its octanol–water partition coefficient ( $\log K_{OW}$ )*	None	-0.77
Calculated skin permeation coefficient ( $K_p$ )	cm/hr	0.00046
<b>Skin dose</b>		
Water solubility ( $S_w$ )*	mg/cm <sup>3</sup>	1000
Calculated skin permeation coefficient ( $K_p$ )	cm/hr	0.00046
Estimated skin surface area (palms of hand)	cm <sup>2</sup>	360
Exposure time	hr	8
Calculated skin dose	mg	1324.17
<b>Inhalation dose</b>		
Occupational exposure limit (OEL)†	mg/m <sup>3</sup>	0.3
Inhalation volume	m <sup>3</sup>	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	2.25
<b>Skin dose–to–inhalation dose (SI) ratio</b>	None	588.52

\*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<sup>2</sup>).

#### Equation 2: Determination of Skin Dose

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

The inhalation dose (in mg) is derived on the basis of the occupational exposure limit (OEL) of the substance—if the OEL is developed to prevent the occurrence of



systemic effects rather than sensory/irritant effects or direct effects on the respiratory tract. Assume a continuous exposure of 8 hours, an inhalation volume of 10 cubic meters (m<sup>3</sup>) inhaled air in 8 hours, and a factor of 75% for retention of the airborne substance in the lungs during respiration (retention factor, or RF).

### Equation 3: Determination of Inhalation Dose

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

The final step is to compare the calculated skin and inhalation doses and to present the result as a ratio of skin dose to inhalation dose (the SI ratio). This ratio quantitatively indicates (1) the significance of dermal absorption as a route of occupational exposure to the substance and (2) the contribution of dermal uptake to systemic toxicity. If a substance has an SI ratio greater than or equal to 0.1, it is considered a skin absorption hazard.

## Calculation

Table A1 summarizes the data applied in the previously described equations to determine the SI ratio for methyl cellosolve. The calculated SI ratio was 588.52. On the basis of these results, methyl cellosolve is predicted to represent a skin absorption hazard.

## Appendix References

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