NIOSH Skin Notation Profiles

Trichloroethylene (TCE)

SK

- ID^{SK}
- [~~SK~~]
- **SYS**
- SYS (FATAL)
- DIR
- **DIR (IRR)**
- DIR (COR)
- **SEN**

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

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NIOSH Skin Notation (SK) Profile

Trichloroethylene (TCE)

[CAS No. 79-01-6]

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

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NIOSH [2017]. NIOSH skin notation profile: Tricholoroethylene (TCE). By Hudson NL, Dotson GS. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2017-192.

DHHS (NIOSH) Publication No. 2017-192

August 2017

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 (SKs) that clearly distinguish between the systemic effects, direct (localized) effects, and immune-mediated responses caused by skin contact with chemicals. The key step within assignment of the hazard-specific SK is the determination of the hazard potential of the substance, or its potential for causing adverse health effects as a result of skin exposure. This determination entails a health hazard identification process that involves use of the following:

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

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

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Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
CIB	Current Intelligence Bulletin
cm^2	square centimeter(s)
cm/hour	centimeter(s) per hour
DEREK	Deductive Estimation of Risk from Existing Knowledge
DIR	skin notation indicating the potential for direct effects to the skin following contact with a chemical
GHS	Globally Harmonized System for Classification and Labelling of Chemicals
GPMT	guinea pig maximization test
HPA	2-hydropropyl acrylate
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
k_{aq}	coefficient in the watery epidermal layer
k_p	skin permeation coefficient
k_{pol}	coefficient in the protein fraction of the stratum corneum
k_{psc}	permeation coefficient in the lipid fraction of the stratum corneum
LD_{50}	dose resulting in 50% mortality in the exposed population
LD_{Lo}	dermal lethal dose
LLNA	local lymph node assay
LOAEL	lowest-observed-adverse-effect level
log K_{OW}	base-10 logarithm of a substance's octanol–water partition
M	molarity
m^3	cubic meter(s)
mg	milligram(s)
mg/kg	milligram(s) per kilogram body weight
mg/m^3	milligram(s) per cubic meter
mL	milliliter(s)
MW	molecular weight
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
OEL	occupational exposure limit
OSHA	Occupational Safety and Health Administration
REL	recommended exposure limit
RF	retention factor
SEN	skin notation indicating the potential for immune-mediated reactions following exposure of the skin
SI ratio	ratio of skin dose to inhalation dose

SK	skin notation
S_W	solubility in water
SYS	skin notation indicating the potential for systemic toxicity following exposure of the skin
USEPA	United States Environmental Protection Agency
w/w	weight by weight percentage

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 occur 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.

Permeability coefficient (k_p)–The transdermal penetration rate of a substance and is expressed in cm/hr and represents the overall diffusion of the substance through the stratum corneum and into the blood capillaries of the dermis.

Sensitization—A specific immune-mediated response that develops following exposure to a chemical, which, upon re-exposure, can lead to allergic contact dermatitis (ACD) or other immune-mediated diseases such as asthma, depending on the site and route of re-exposure.

Substance—A chemical.

Systemic effects—Systemic toxicity associated with skin absorption of chemicals after exposure of the skin.

Acknowledgments

This document was developed by the Education and Information Division (Paul Schulte, Ph.D., Director). Naomi Hudson, Dr.P.H., MPH, was the project officer for this document, assisted in great part by G. Scott Dotson, Ph.D., Michael Luster, Ph.D., and Loren Tapp, M.D. The basis for this document was a report (*Toxicology Excellence for Risk Assessment [TERA]*) contracted by NIOSH and prepared by Bernard Gadagbui, Ph.D., and Andrew Maier, Ph.D.

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

Denver Field Office
Eric Esswein, M.Sc.

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

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

Division of Surveillance, Hazard Evaluations, and Field Studies
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Todd Niemeier, M.Sc.
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Education and Information Division
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Richard Niemeier, Ph.D.
Sudha Pandalai, M.D., Ph.D.

Health Effects Laboratory Division
Stacey Anderson, Ph.D.
H. Fredrick Frasch, Ph.D.
Vic Johnson, Ph.D.
Berran Yucesoy, Ph.D.

National Personal Protective Technology Laboratory
Heinz Ahlers, JD, M.Sc.
Gregory Day, Ph.D.
Angie Shepherd

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

Office of Surveillance, Epidemiology and Laboratory Services/Epidemiology and Analysis Program Office

Barbara Landreth, M.A.

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

Karin Pacheco, MD, MSPH, Associate Professor, Division of Environmental and Occupational Health Sciences, National Jewish Medical and Research Center, Denver, CO

Sean Semple, Ph.D., Senior lecturer, Scottish Centre for Indoor Air Division of Applied Health Sciences, University of Aberdeen, Aberdeen, Scotland

Glenn Sipes, Ph.D., Professor Emeritus, Department of Pharmacology, University of Arizona, Tucson, AZ

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

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

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

Jennifer Sahmel, M.Sc., CIH, ChemRisk, Boulder, CO

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

1 Introduction

1.1 General Substance Information:

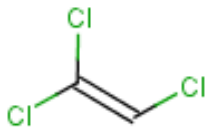
Chemical: Trichloroethylene (TCE)

CAS No: 79-01-6

Molecular weight (*MW*): 131.39

Molecular formula: C_2HCl_3

Structural formula:



Synonyms: Ethylene trichloride; TCE; Trichloroethene; Trilene; TRI

Uses: Trichloroethylene (TCE) is a chlorinated organic compound used primarily as a solvent in metal degreasing operations and as a component of the refrigerant HFC-134a [ATSDR 2014; Bakke et al. 2007; EPA 2014]. TCE is also used as a spotting agent in dry cleaning operations [EPA 2014] and historically has been used as a general anesthetic or analgesic [ATSDR 2014; Bakke et al. 2007; EPA 2014].

1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with TCE and (2) the rationale behind the hazard-specific skin notation (SK) assignment for TCE. 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 TCE. A literature search was conducted through June 2017 to identify information on TCE, 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 TCE. The criteria for the search strategy, evaluation, and selection of data are described in Appendix E in *CIB 61: A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009].

1.3 Overview of SK Assignment

TCE is potentially capable of causing numerous adverse health effects following skin contact. A critical review of available data has resulted in the following SK assignment for TCE: **SK: SYS-DIR (IRR)-SEN**. Table 1 provides an overview of the critical effects and data used to develop the SK assignment for TCE.

2 Systemic Toxicity from Skin Exposure (SK: SYS)

Numerous studies of dermal absorption of TCE in humans have indicated that the substance can be absorbed following skin contact [Stewart and Dodd 1964; Sato and Nakajima 1978; Poet et al. 2000; Kezic et al. 2001]. In a study conducted by Stewart and Dodd [1964], volunteers immersed

Table 1. Summary of the SK assignment for TCE

Skin notation	Critical effect	Available data
SK: SYS	Hepatotoxicity; nephrotoxicity; neurotoxicity	Sufficient human and animal data
SK: DIR (IRR)	Skin irritation	Sufficient human and animal data
SK: SEN	Skin sensitization; liver damage associated with delayed-type hypersensitivity reaction	Limited human and sufficient animal data

their thumbs in TCE for 30 minutes. Concentrations of TCE in exhaled air were determined during exposure and for 5 hours post-exposure; the mean peak breath concentration was reported to be 0.5 parts per million (ppm) [corresponding to 2.7 milligrams per kilogram (mg/kg)] and occurred within 15 minutes post-exposure [Stewart and Dodd 1964]. The rate of dermal uptake of TCE was not determined, although the authors indicated that the amount dermally absorbed would be similar to the amount absorbed by the lung from inhalation at two to five times the peak breath concentration reported in this study [Stewart and Dodd 1964]. The authors noted that factors including integrity as well as thickness of the skin affected dermal penetration [Stewart and Dodd 1964]. Sato and Nakajima [1978] reported dermal absorption in four male volunteers who immersed one hand up to the wrist for 30 minutes in TCE in a covered jar to avoid inhalation exposure. For 10 hours post-exposure, concentrations of TCE in breath and blood, and the concentration of metabolites in urine were measured at regular intervals [Sato and Nakajima 1978]. Sato and Nakajima [1978] indicated that the levels found in the breath and blood from exposure to TCE were similar to those noted after a 4 hour inhalation exposure to TCE (100 ppm; corresponding to 537.4 mg/kg); however, the rate of dermal uptake of TCE was not determined. Poet et al. [2000] estimated that in volunteers, the average dermal permeability coefficient (k_p) values for TCE were 0.019 and 0.015 centimeters per hour (cm/hr) following water-patch and hand-immersion studies, respectively and 0.015 cm/hr of TCE through the skin of volunteers when a fully occluded patch system was used. In another study, volunteers were exposed to neat TCE on the volar forearm over an area of 27 square centimeters (cm^2) for 1 minute [Kezic et al. 2001]. Kezic et al. [2001] noted fast dermal permeation through skin: a flux of 430 nanomoles/cm^2 per minute (nmol/cm^2/min).

Several experimental studies of the dermal absorption of TCE in animals [Tsuruta 1978; Jakobson et al. 1982, Bogen et al. 1992, Nakai et al. 1999; Poet et al. 2000] were identified. Tsuruta [1978] exposed mice to undiluted liquid TCE for 5, 10, or 15 minutes to determine the rate of dermal absorption. The reported results indicated that the amount of TCE absorbed increased linearly, and the rate of dermal absorption through mouse abdominal skin was estimated to be 8 µg/cm^2/min [Tsuruta 1978]. Jakobsen et al. [1982] used guinea pigs to investigate the dermal absorption of undiluted TCE in occluded conditions. Blood samples were collected at intervals of 5 to 20 minutes during the 6-hour exposure period [Jacobsen et al. 1982]. The authors reported that peak blood levels of around 0.79 µg/mL occurred after 30 minutes [Jacobsen et al. 1982]. Bogen et al. [1992], dermally exposed guinea pigs to aqueous diluted solutions (approximately 10 to 100 parts per billion [ppb]; corresponding to 0.05 to 0.54 mg/kg) of TCE, and reported k_p values of 0.21 to 0.23 cm/hr. Poet et al. [2000] measured dermal absorption of TCE using physiologically based pharmacokinetic modeling in a water matrix in rats, and reported a k_p of 0.31 cm/hr [Poet et al. 2000]. *In vitro* studies on dermal absorption

of TCE were identified. Using the aluminum dermal absorption block method reported by Moody et al. [1992], Nakai et al. [1999] reported a k_p of 0.12 cm/hr for human abdomen and breast skin samples.

The potential of TCE 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 with an estimated dose from respiratory absorption associated with a reference occupational exposure limit. On the basis of this algorithm, a ratio of the skin dose to the inhalation dose (SI ratio) of 0.02 was calculated for TCE. An SI ratio of ≥0.1 indicates that skin absorption may significantly contribute to the overall body burden of a substance [NIOSH 2009]; therefore, TCE is not considered to be a skin absorption hazard following dermal exposure. Additional information on the SI ratio and the variables used in its calculation are included in the appendix. Although the mathematical predictive model indicated that TCE is not readily absorbed by the skin, studies in humans and animals indicates that TCE is absorbed by the skin and may be similar to uptake via inhalation [Sato and Nakajima 1978].

Although no estimate of the dermal lethal dose (LD_{Lo}) for humans has been identified, dermal LD_{50} (lethal dose for 50% of exposed population) values of >10,000 milligrams per kilogram (mg/kg) have been reported for the rabbit [Dow Chemical Company 1956; Smyth et al.1969]. Because the reported acute dermal LD_{50} value is greater than the critical dermal LD_{50} value of 2,000 mg/kg that identifies chemical substances with the potential for acute dermal toxicity [NIOSH 2009], TCE is not considered acutely toxic by the dermal route.

No health effects data were identified regarding dermal repeated-dose, subchronic, or chronic toxicity of TCE in humans or animals. However, Yu et al. [2012] evaluated renal impairment in TCE-sensitized guinea pigs. Animals were exposed to three pairs of 0.1 ml injections of 5% TCE solution in olive oil followed by an application of 0.5 ml of 40% TCE solution applied to the skin with non-irritant tape for 24 hours [Yu et al. 2012]. Yu et al. [2012] noted that metabolites of TCE caused the deposition of C3 and MAC renal epithelial cells, and may indicate that this mechanism accounts for TCE induced kidney and liver dysfunction. In a study that assesses liver injury associated with hypersensitive skin reactions in the GPMT, Tang et al. [2008] reported that serum alanine transaminase (ALT) and aspartate aminotransferase (AST), both indicative of liver injury, were significantly increased in guinea pigs exposed to 4,500 mg/kg TCE and 1,500 mg/kg TCE, respectively. Zhang et al. [2015] reported liver and kidney dysfunction after mice received an intradermal injection of 0.1 ml 50% TCE on the first day and 0.1 ml of 50% TCE on the back on days 4, 7 and 10 followed one week later with 0.1 ml of 30% TCE applied on the back. In a later study, Al-Griw et al. [2016] divided Swiss albino mice into four groups: a vehicle control group exposed to corn oil, a sham control group, and 100µg and 400µg TCE in corn oil bi-weekly for three weeks. Hepatocellular apoptosis in the TCE groups, including histophathological changes such as congestion of hepatic blood vessels, perivascular cloudy swelling, and hydropic degeneration. Mice receiving 400µg TCE had significantly different liver weights (1.89g ± 0.21g) than the control group (1.27g ± 0.13g) ($p \leq 0.05$) [Al-Griw et al. 2016]. Moreover, Al-Griw et al. [2016] reported that TCE-treated mice had a statistically significant increase in the number of apoptotic hepatocytes ($p < 0.05$) and MDA levels (a marker for oxidative stress) in the liver ($p \leq 0.05$).

Occupational exposure to an unquantified amount of TCE that involved both dermal and inhalation exposure for up to 20 years has been reported to cause dizziness, headache, insomnia, lethargy, forgetfulness, and loss of feeling in the hands and feet, or enlarged liver [Bauer and Rabens 1974; Kohlmuller and Kochen 1994]. In a case series, Liu [2009] reported the onset of dermatitis and systemic toxicity in workers (six males, one female) who used TCE to clean metal surfaces. Although the report did not precisely describe the exposure conditions, it can

be assumed that skin exposures were a primary pathway since there was onset of dermatitis in all cases, and the degree of liver and renal dysfunction was related to the degree of skin injury [Liu 2009]. Liu [2009] reported that liver or kidney damage in five of the seven workers was attributed to TCE exposures, in addition to effects on the central nervous system (i.e., dizziness) and changes in blood chemistry (i.e., elevated white blood cell count). All five of the workers who had liver dysfunction developed liver steatosis (fatty liver) within 2 months, and one worker had kidney dysfunction with inflammation and swelling [Liu 2009]. Liu [2009] concluded that TCE is capable of causing both systemic and localized adverse health effects. Watanabe et al. [2010] reported a patient that had been exposed to TCE and was hospitalized with severe liver dysfunction. Xu et al. [2009] conducted a study with 21 patients with TCE-induced skin disorders that worked at 3 separate factories from 2003-2005 with an average exposure duration of 38 days. These patients were exposed during cleaning and degreasing operations and did not wear gloves, and were also possibly exposed via inhalation [Xu et al. 2009]. The patients reported neurological symptoms (headache, dizziness), skin effects, and liver dysfunction [Xu, et al. 2009]. Gash et al. [2008] reported 3 workers that were exposed to TCE both through chronic inhalation and dermal contact for 25 years or greater had Parkinson's disease (PD). Of these workers, 2 had no family history of PD. The workers shared the same work hours, including overtime, and cleaned parts directly in a vat of TCE without use of gloves or other protective equipment [Gash et al. 2008]. Other workers in the same factory, more distant from the source of TCE who were exposed via inhalation, reported neurological symptoms, such as significant motor slowing [Gash et al. 2008]. The neurotoxicity of TCE was supported by animal studies conducted by Gash et al. [2008], which demonstrated that oral exposure to TCE was accompanied by complex 1 mitochondrial impairment in the midbrain and loss of dopamine neurons, which is a hallmark of PD.

No epidemiological investigations or experimental animal studies evaluating the potential for TCE to induce cancer following dermal exposure were identified; however, evidence that TCE is carcinogenic to humans has been found in multiple studies but the exposure route (i.e. inhalation, dermal, oral) is unknown [Hansen et al. 2013; Karami et al. 2013]. Hansen et al. [2013] found increased liver cancer 1.93 times more likely (confidence interval [CI] 1.19 to 2.95) and cervical cancer 2.31 times more likely (CI: 1.32 to 3.75) in workers exposed to TCE; however, exposure routes are unknown and were likely a combination of multiple routes (inhalation and dermal). Karami et al. [2013] conducted a meta-analysis of published cohort and case control studies that assessed occupational exposure to TCE and five different cancers: non-Hodgkin's lymphoma, Hodgkin's lymphoma, multiple myeloma, leukemia, and chronic/small lymphocytic leukemia. Routes of exposure were unknown for these studies and cases were likely exposed via multiple routes. These authors reported a significantly raised summary estimate of non-Hodgkin's lymphoma (relative risk=1.93; CI: 1.14 to 1.54) for all cohort and case-control studies [Karami et al. 2013]. Table 2 provides a summary of carcinogenic designations from multiple governmental and nongovernmental organizations for TCE.

Although the toxicokinetic studies indicate that TCE has limited dermal absorption potential, which is supported by the limited available animal data reporting low acute toxicity in rabbits [Dow Chemical Company 1956; Smyth et al.1969], case reports, case series, an occupational exposure study **[Bauer and Rabens 1974; Kohlmuller and Kochen 1994; Liu 2009; Watanabe et al. 2010]**, and animal studies **[Tang et al. 2008; Yu et al. 2012; Zhang et al. 2015; Al-Griw et al. 2016]** provide evidence of TCE-induced liver and kidney dysfunction following subchronic dermal exposures to the substance, and occupational studies **[Gash et al. 2008; Liu 2009; Xu et al. 2009]** reported neurological effects. These human data provide evidence of its ability to cause systemic toxicity following

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

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

Organization	Carcinogenic designation
NIOSH [2005]	Potential occupational carcinogen
NTP [2014]	Reasonably anticipated to be a human carcinogen
USEPA [2014]	Carcinogenic to humans
European Parliament [2008]	GHS Category 1B: May cause cancer
IARC [2014]	Group 1: Carcinogenic to humans
ACGIH [2007]	Group A2: Suspected human carcinogen

ACGIH = American Conference of Governmental Industrial Hygienists; GHS = Globally Harmonized System for Classification and Labelling of Chemicals; IARC = International Agency for Research on Cancer; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; USEPA = United States Environmental Protection Agency.
*The listed cancer designations were based on data from non-dermal (such as oral or inhalation) exposure since studies using the dermal route of exposure were unavailable.

subchronic dermal exposure. Therefore, on the basis of these data, TCE is assigned the SK: SYS notation.

3 Direct Effects on Skin (SK: DIR)

No evidence of skin corrosivity of TCE, no *in vitro* tests for corrosivity in human or animal skin models, and no *in vitro* tests of skin integrity using cadaver skin were identified. Evidence of corrosivity and irritation in humans and animals were identified. Evidence of corrosivity in animals is limited to findings from a single acute toxicity study. In that study, high doses of TCE, ranging from 2,520 to 20,000 mg/kg, were administered to the skin of 16 rabbits under an impervious covering, resulting in burning, scabbing, and scarring [Dow Chemical Company 1956].

In occupational exposures that involved inhalation of the vapor, percutaneous penetration, or both, TCE caused skin irritation and rashes, central nervous system effects, and/or eye effects after repeated exposure [El Ghawabi et al. 1973; Bauer and Rabens 1974; Xu et al. 2009]. Xu et al. [2009] reported skin irritation in 21 patients diagnosed with a TCE-induced skin disorder, and symptoms included skin erythema, rashes, and blistering. Study volunteers have reported burning sensations, erythema, rashes, and dermatitis following exposure to TCE [Stewart and Dodd 1964; Sato and Nakajimi 1978]. Four volunteers who each immersed a single hand up to the wrist for 30 minutes in liquid TCE reported a burning sensation that increased with time and distinct pain toward the end of the exposure, as well as moderate erythema for over an hour post-exposure [Sato and Nakajima 1978]. Similar effects were seen in three volunteers who immersed their thumbs in TCE for 30 minutes [Stewart and Dodd 1964]. Kezic et al. [2001] noted intensive skin irritation, with burning sensation varying from "hardly noticed" to "unbearable pain" in six volunteers. Wahlberg [1984b] reported marked and persistent erythema in a healthy individual following excess application (1.5 mL) of neat TCE to the unoccluded volar forearm (3.1 cm^2) for 5 minutes, and application for 1 or 3 minutes caused transient whitening and then erythema. Wahlberg [1984b] reported stinging and/or burning sensations after exposure to TCE in human volunteers. Liu [2009] investigated seven workers who all experienced erythema and were exposed to TCE when using it to clean metal surfaces. In six of the seven workers, dermatitis occurred within 1 month of exposure to TCE [Liu 2009]. Liu [2009] also reported that the workers experienced a variety of effects,

including erythema with pruritus, rashes on the extremities, and systemic toxic effects attributed to exposures to TCE.

Several studies in rabbits and guinea pigs indicate that TCE caused severe irritation to the skin following occlusive and unocclusive dermal application [Smyth et al. 1969; Wahlberg 1984b]. Anderson et al. [1986] conducted a guinea pig irritant-contact reaction test in which 10 microliters (µL) TCE was applied under occlusion to 1 cm^2 shaved skin on the flank three times daily for 3 days. Macroscopic assessment of erythema and edema as well as microscopic assessments of epidermal thickness and dermal inflammatory cell infiltration (total and differential cell responses) indicated that TCE was irritating to the guinea pig skin [Anderson et al. 1986]. Shen et al. [2008] investigated the effects of TCE on skin irritation and oxidative stress, using hairless mice under acute and cumulative exposure conditions. Mice were administered concentrations of TCE (20%, 40%, 80%, or 100% v/v) dissolved in olive oil [Shen et al. 2008]. In an acute irritation test, TCE administration for 1 day resulted in mild to moderate irritation that was concentration dependent, and erythema and intracellular edema developed [Shen et al. 2008]. Epidermal necrosis occurred in a few mice treated with 100% TCE. In a cumulative irritation test, mice underwent daily topical applications of TCE for 14 days, resulting in epidermal hyperplasia, hyperkeratosis, edema, and inflammation [Shen et al. 2008]. Kronevi et al. [1981] noted degenerative changes in the epidermis, including karyopyknosis, oedema, junctional separation and cellular infiltration in the dermis. The structure-activity relationship model (Deductive Estimation of Risk from Existing Knowledge, or *DEREK*, for Windows) predicted TCE to be negative for skin irritation, indicating that the chemical does not have a structural alert for skin irritation.

An epidemiological study concerning the potential of TCE to cause skin cancer was identified. Axelson et al. [1994] assessed the exposure of workers from a plant in central Sweden that produced TCE. Although the routes of exposure were unknown, the authors noted a doubled incidence of nonmelanocytic skin cancer; however there was no correlation with exposure categories [Axelson et al. 1994]. One dermal carcinogenicity study in animals was identified. Van Duuren et al. [1979] found no tumors in mice at the site of topical application of TCE (1 mg in 0.1 mL acetone per application); in addition, there was no statistically significant difference in the incidence of distant tumors in this group versus no-treatment and vehicle control groups. The investigators also found no skin tumor–initiating activity in a mouse skin initiation promotion experiment [Van Duuren et al. 1970].

Results indicate that undiluted TCE is corrosive to the skin **[Dow Chemical Company 1956; Shen et al. 2008]**. Evidence of skin whitening, erythema, and dermatitis in humans **[Stewart and Dodd 1964; Bauer and Rabens 1974; Sato and Nakajima 1978; Wahlberg 1984 a,b; Kezic et al. 2001; Liu 2009; Xu et al. 2009]** and of erythema, edema, and changes in the epidermis in animals **[Kronevi et al. 1981; Anderson et al.1986; Shen et al. 2008]** indicates that TCE is a skin irritant when TCE is diluted. Therefore, on the basis of the data for this assessment, TCE is assigned the SK: DIR (COR) notation.

4 Immune-mediated Responses (SK: SEN)

Few reports were identified that suggest that TCE may be a skin sensitizer in humans. An occupational study on 19 patients hospitalized for generalized skin disorders and their healthy colleagues by Kamijima et al. [2008], indicated that TCE caused the hypersensitivity disorders. Watanabe et al. [2010] reported a case with generalized rash and liver dysfunction that had been exposed to TCE at work. This patient was patch tested for TCE and its metabolites trichlorethanol and chloral hydrate; the patient had positive reactions to the metabolites but not to TCE [Kamijima et al. 2008]. Similarly, Huang et al. [2015] reported fever, generalized rash, liver dysfunction, and superficial lymphadenopathy in workers exposed to TDI that

exhibited trichloroethylene hypersensitivity disorder. All of these patients developed positive skin reactions to TCE or the metabolites of TCE, including chloral hydrate, trichloroethanol, trichloroacetic acid. Chloral hydrate had the greatest positive response (100%) and 10.5% of patients had positive reactions to TCE [Huang et al. 2015]. Dai et al. [2009] compared 111 workers with hypersensitivity dermatitis and 154 healthy workers, all of whom were exposed to TCE, to determine if there was a gene polymorphism that influenced individual susceptibility to TCE-induced hypersensitivity dermatitis. All of the cases diagnosed with occupational hypersensitivity dermatitis by an occupational disease physician developed skin damage within 3 months of exposure to TCE [Dai et al. 2009]. The authors concluded that a slow metabolic phenotype of N-acetyltransferases (NATs) and combined slow acetylator phenotypes of NAT1 and NAT2, two isoenzymes of NAT that are encoded by separate genes, may be risk factors for TCE-induced hypersensitivity [Dai et al. 2009], In a case report, a worker developed severe dermal effects, including skin lesions and erythroderma with edematous face and eyelids, a combined inhalation and dermal exposure to TCE [Nakayama et al. 1988]. This subject had positive reactions to 10% and 25% TCE in olive oil (and to 0.005%, 0.05%, and 5% trichloroethanol, a metabolite of TCE) [Nakayama et al. 1988]. Nakayama et al. [1988] regarded this result to be due to delayed hypersensitivity to TCE. The findings in that case indicate that the subject was allergic to both TCE and its metabolite, trichloroethanol. In another reported case, a female worker developed erythematous lesions and had a positive reaction when patch tested with TCE (5% in olive oil) [Conde-Salazar et al. 1983]. The worker developed the same lesions when challenged on many occasions, after exposure to TCE. Phoon et al. [1984] reported five cases in which individuals were occupationally exposed to TCE for periods ranging from 2 to 5 weeks and subsequently presented with Stevens-Johnson syndrome (erythema multiforme major). Three of the cases had air exposure only, and the remaining two had air and direct skin contact [Phoon et al. 1984]. One individual exposed to fairly high levels of TCE vapor in the air and by direct skin contact was patch tested with TCE after the episode but tested negative. In spite of the negative reaction, Phoon et al. [1984] did not rule out the possibility of a hypersensitivity response.

Animal studies regarding the potential for TCE to induce immune-mediated responses following skin contact were identified. Yao et al. [2016] investigated the role of transforming growth factor-β activated kinase-1 (TAK1) on contact hypersensitivity in control mice and dendritic cell (DC)-specific TAK1 deletion mice who were exposed to 80% (v/v) TCE using the local lymph node assay (LLNA). Compared to the control mice, the TCE group had an inflammatory response in the ears, increased lymphocyte proliferation, and increased T-cells and interferon (IFN)-γ CD8(+) T cells in the draining lymph nodes [Yao et al. 2016]. Yu et al. [2012] conducted modified guinea pig maximization tests (GPMT), where animals were exposed to three pairs of 0.1 ml injections of 5% TCE solution in olive oil followed by application of 0.5ml of 40% TCE solution was applied to the skin with non-irritant tape for 24 hours [Yu et al. 2012]. The investigators reported a sensitization rate of 63.16% compared to 100% for the positive control [Yu et al. 2012].

In an earlier study, Tang et al. [2002], using a modified GPMT, reported that TCE caused skin sensitization (i.e., edema and erythema) in guinea pigs. The authors reported a sensitization rate of 71.4% (10/14) for TCE and of 58.3% trichloroacetic acid. Histopathological analysis revealed allergenic transformation in guinea pig skin exposed to TCE, and the authors concluded that TCE appeared to be a strong allergen following skin contact [Tang et al. 2002]. In a subsequent investigation, Tang et al. [2008] attempted to characterize the liver injury associated with hypersensitive skin injuries in guinea pigs by using dermal patches containing TCE and performing a GPMT. The results of the study included sensitization rates of TCE-induced dermal allergy of 66%, accompanied by skin edema, and erythema [Tang et al. 2008]. In addition, elevated liver enzymes and the presence of lesions were reported [Tang et al. 2008].

The GPMT revealed histopathologic evidence of fatty degeneration in the liver, hepatic sinusoid dilation, and inflammatory cell infiltration with an acute intradermal dose of 4,500 mg/kg [Tang et al. 2008]. Tang et al. [2008] concluded that TCE may be capable of inducing dermatitis and liver damage, on the basis of delayed-type hypersensitivity in guinea pigs. Wang et al. [2016] evaluated immune-mediated renal injury of TCE on BALB/c mice that received an intradermal injection of 100 µL of 50% TCE on day one, 100 µL of 50% TCE painted on clipped dorsal skin on days four, seven, and ten, and was challenged with 100 µL on clipped dorsal skin on days 17 and 19. The sensitization rate in mice exposed to TCE was 40% (48/120). TDI exposed mice had increased serum urea nitrogen (BUN) and creatinine (Cr) (an indication of how well the kidneys are working) and inflammatory cell infiltration and tubular epithelial cell vacuolar degeneration at 48 and 72 hours after the final challenge with TCE [Wang et al. 2016].

Predictions from structure-activity relationship models provide some information regarding the potential for sensitization. On the basis of its chemical structure, TCE is predicted by *DEREK* to be negative for sensitization, indicating that the chemical does not have a structural alert for skin sensitization.

Although the mathematical model predicted TCE to be negative for sensitization, isolated reports of cases involving humans **[Conde-Salazar et al. 1983; Nakayama et al. 1988]** and an epidemiological study **[Dai et al. 2009]** suggest that TCE may have sensitizing potential. Evidence of immune-mediated responses in workers is often confounded by exposures via both dermal and inhalation routes. Positive results from predictive tests (GPMTs and LLNAs) **[Tang et al. 2002, 2008; Yu et al. 2012; Yao et al. 2016]** demonstrate that TCE is capable of inducing dermatitis and liver damage via delayed-type hypersensitivity in guinea pigs. Therefore, on the basis of the data for this assessment, TCE is assigned the SK: SEN notation.

5 Summary

Although the toxicokinetic studies indicate that TCE has limited dermal absorption potential, which is supported by the limited available animal data reporting low acute toxicity in rabbits [Dow Chemical Company 1956; Smyth et al.1969], case reports, case series, an occupational exposure study **[Bauer and Rabens 1974; Kohlmuller and Kochen 1994; Liu 2009; Watanabe et al. 2010]** and animal studies **[Tang et al. 2008; Yu et al. 2012; Zhang et al. 2015; Al-Griw et al. 2016]** provide evidence of TCE-induced liver and kidney dysfunction following subchronic exposures to the substance, and occupational studies **[Gash et al. 2008; Liu 2009; Xu et al. 2009]** reported neurological effects. These limited human and animal data provide evidence of its ability to cause systemic toxicity following subchronic exposure. Results indicate that undiluted TCE is corrosive to the skin **[Dow Chemical Company 1956; Shen et al. 2008]**. Evidence of skin whitening, erythema, and dermatitis in humans **[Stewart and Dodd 1964; Bauer and Rabens 1974; Sato and Nakajima 1978; Wahlberg 1984 a,b; Kezic et al. 2001; Liu 2009; Xu et al. 2009]** and of erythema, edema, and changes in the epidermis in animals **[Kronevi et al. 1981; Anderson et al.1986; Shen et al. 2008]** indicates that TCE is a skin irritant when diluted. Although the mathematical model predicted TCE to be negative for sensitization, isolated reports of cases involving humans **[Conde-Salazar et al. 1983; Nakayama et al. 1988]** and an epidemiological study **[Dai et al. 2009]** suggest that TCE may have sensitizing potential. Positive results from predictive tests (GPMTs and LLNAs) **[Tang et al. 2002, 2008; Yu et al. 2012; Yao et al. 2016]** demonstrate that TCE is capable of inducing dermatitis and liver damage via delayed-type hypersensitivity in guinea pigs. Therefore, on the basis of these assessments, TCE is assigned a composite skin notation of SK: SYS-DIR (IRR)-SEN.

Table 3 summarizes the skin hazard designations for TCE previously issued by NIOSH and other organizations. The equivalent dermal

Table 3. Summary of previous skin hazard designations for TCE

Organization	Skin hazard designation
NIOSH [2005]	No designation
OSHA [2017]*	No designation
ACGIH [2007]	No designation

ACGIH = American Conference of Governmental Industrial Hygienists; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration.
*Date accessed.

designations for TCE, according to the Globally Harmonized System (GHS) of Classification and Labelling of Chemicals, are Skin Irritation Category 2 (Hazard Statement: Causes skin irritation) and Mutagenicity Category 2 (Hazard Statement: Suspected of causing genetic defects) [European Parliament 2008].

References

ACGIH (American Conference of Governmental Industrial Hygienists) [2007]. Trichloroethylene. In: Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

Al-Griw MA, Alghazeer RO, Al-Azreg SA, Bennour EM [2016]. Cellular and molecular etiology of hepatocyte injury in a murine model of environmentally induced liver abnormality. Open Vet J *6*(3):150–157.

Anderson C, Sundberg K, Groth O [1986]. Animal model for assessment of skin irritancy. Contact Dermatitis *15*(3):143–151.

ATSDR [2014]. Draft toxicological profile for trichloroethylene. U.S. Department of Health and Human Services (HHS), Public Health Service, ATSDR, http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=173&tid=30. Accessed: 06-07-15.

Axelson O, Selden A, Andersson K, Hogstedt C [1994]. Updated and expanded Swedish cohort study on trichloroethylene and cancer risk [1994]. J Occup Med *36*(5):556–562.

Bakke B, Stewart PA, Waters MA [2007]. Uses of and exposure to trichloroethylene in U.S. industry: a systematic literature review. J Occup Environ Hyg *4*(5):375–390.

Bauer M, Rabens SF [1974]. Cutaneous manifestations of trichloroethylene toxicity. Arch Dermatol *110*(6):886–890.

Bauer M, Rabens SF [1977]. Trichloroethylene toxicity. Int J Dermatol *16*:113–116.

Bogen KT, Colston BW Jr, Machicao LK [1992]. Dermal absorption of dilute aqueous chloroform, trichloroethylene, and tetrachloroethylene in hairless guinea pigs. Fund Appl Toxicol *18*(1):30–39.

Conde-Salazar L, Guimarciens D, Romero LV, Yus ES [1983]. Subcorneal pustular eruption and erythema from occupational exposure to trichloroethylene. Contact Dermatitis *19*:235–237.

Dai Y, Leng S, Li L, Niu Y, Huang H, Liu Q, Duan H, Cheng J, Liu Q, Zheng Y [2009]. Effects of genetic polymorphisms of N-Acetyltransferase on trichloroethylene-induced hypersensitivity dermatitis among exposed workers. Ind Health *47*(5):479–486.

Dow Chemical Company [1956]. Results of skin absorption studies on carbon tetrachloride, ethylene dichloride, tetrachlorethylene, trichloroethylene, and chlorothene. Midland, MI: Dow Chemical Company. On file with the U.S. Environmental Protection Agency under TSCA Section 8D. OTS #0515981. Document #86-870002191.

ECB (European Chemical Bureau) [2004]. European Union risk assessment report: trichloroethylene. In: Existing chemicals risk assessment report, http://echa.europa.eu/documents/10162/83f0c99f-f687-4cdf-a64b-514f1e26fdc0. Accessed: 06-07-17.

European Parliament, Council of the European Union [2008]. Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labeling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJEU, Off J Eur Union *L353*:1–1355, http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:353:0001:1355:EN:PDF. Accessed: 06-07-17.

El Ghawabi SM, Mansoor MB, El Gamel MS, El Saharti AA, El Enany FF [1973]. Chronic

trichloroethylene exposure. J Egypt Med Assoc *56*:715–724.

Gash DM, Rutland K, Hudson NL, Sullivan PG, Bing G, Cass WA, Pandya JD, Liu M, Choi D, Hunter RL, Gerhardt GA, Smith CD, Slevin JT, Prince TS [2008]. Trichloroethylene: Parkinsonism and complex 1 mitochondrial neurotoxicity. Ann Neurol *63*:184–192.

Hansen J, Sallmèn M, Seldèn AI, Anttila A, Pukkala E, Andersson K, Bryngelsson IL, Raaschou-Nielsen O, Olsen JH, McLaughlin JK [2013]. Risk of cancer among workers exposed to trichloroethylene: analysis of three Nordic cohort studies. J Natl Cancer Inst *105*(12):869–877.

Huang Y, Xia L, Wu Q, Zeng Z, Huang Z, Zhou S, Jin J, Huang H [2015]. Trichloroethylene hypersensitivity syndrome is potentially mediated through its metabolite chloral hydrate. PLoS One *10*(5): e0127101.

IARC (International Agency for Research on Cancer) [2014]. IARC monographs Trichloroethylene, Tetrachloroethylene, and some other chlorinated agents. Volume 106. In: IARC monographs on the evaluation of carcinogenic risks to humans, http://monographs.iarc.fr/ENG/Monographs/vol106/mono106.pdf. Accessed: 06-07-17.

Jakobson I, Wahlberg JE, Holmberg B , Johanson G [1982]. Uptake via the blood and elimination of 10 organic solvents following epicutaneous exposure of anesthetized guinea pigs. Toxicol Appl Pharmacol *63*(2):18l–l87.

Kamijima M, Wang H, Huang H, Li L, Shibata E, Lin B, Sakai K, Liu H, Tsuchiyama F, Chen J, Okamaura A, Huang X, Hisanaga N, Huang Z, Ito Y, Takeuchi Y, Nakajimi T [2008]. Trichloroethylene causes generalized hypersensitivity skin disorders complicated by hepatitis. J Occup Health *50*: 328–338.

Karami S, Bassig B, Stewart PA, Lee KM, Rothman N, Moore LE, Lan Q [2013]. Occupational trichloroethylene exposure and risk lymphatic and haematopoietic cancers: a meta-analysis. Occup Environ Med *70*(8):591–599.

Kezic S, Monster AC, van de Gevel IA, Kruse J, Opdam JJ, Verberk MM [2001]. Dermal absorption of neat liquid solvents on brief exposures in volunteers. Am Ind Hyg Assoc J *62*:2–18.

Kinkead ER, Wolfe RE [1980]. Single oral toxicity of various organic compounds. J Am Coll Toxicol *11*(6):713.

Kohlmuller D, Kochen W [1994]. Exhalation air analyzed in long-term postexposure investigations of acetonitrile and trichloroethylene exposures in two subjects. Clin Chem *40*:1462–1464.

Kronevi T, Wahlberg JE, Holmberg B [1981]. Skin pathology following epicutaneous exposure to seven organic solvents. Int J Tiss React *111*(1): 21–30.

Liu J [2009]. Clinical analysis of seven cases of trichloroethylene medicamentose-like dermatitis. Indust Health *47*:685–688.

Nakai JS, Stathopulos PB, Campbell GL, Chu I, Li-Muller A, Aucoin R [1999]. Penetration of chloroform, trichloroethylene, and tetrachloroethylene through human skin. J Toxicol Environ Health *58*(3):157–170.

Nakayama H, Kobayashi M, Takahashi M, Ageishi Y, Takano T [1988]. Generalized eruption with severe liver dysfunction associated with occupational exposure to trichloroethylene. Contact Dermatitis 19(1):48–51.

NIOSH (National Institute for Occupational Safety and Health) [1974]. Effects of trichloroethylene on behavioral performance capabilities. Behavioral toxicology: early detection of occupational hazards. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, DHEW (NIOSH) Publication No. 74-126.

NIOSH [2005]. NIOSH pocket guide to chemical hazards. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2005-149, http://www.cdc.gov/niosh/npg/. Accessed: 06-07-17.

NIOSH [2009]. Current intelligence bulletin 61: a strategy for assigning new NIOSH skin notations. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2009-147, http://www.cdc.gov/niosh/docs/2009-147/pdfs/2009-147.pdf. Accessed: 06-07-17.

NTP [2014]. Report on Carcinogens. Thirteenth Edition; U.S. Department of Health and Human Services, Public Health Service. National Toxicology Program, https://ntp.niehs.nih.gov/annualreport/2015/glance/roc/index.html. Accessed: 06-07-17.

OSHA [ND]. Trichloroethylene. In: OSHA Occupational Chemical Database, https://www.osha.gov/chemicaldata/chemResult.html?recNo=684. Accessed: 06-07-17.

Phoon WH, Chan MO, Rajan VS, Tan KJ, Thirumoorthy T, Goh CL [1984]. Stevens- Johnson syndrome

associated with occupational exposure to trichloroethylene. Contact Dermatitis *10*(5):270–276.

Poet TS, Corley RA, Thrall KD, Edwards JA, Tanojo H, Weitz KK, Hui X, Maibach HI, Wester RC [2000]. Assessment of the percutaneous absorption of trichloroethylene in rats and humans using MS/MS real time breath analysis and physiologically based pharmacokinetic modeling. Toxicol Sci *56*(1):61–72.

Sato A, Nakajima T [1978]. Differences following skin or inhalation exposure in the absorption and excretion kinetics of trichloroethylene and toluene. Br J Ind Med *35*(1):43–49.

Shen T, Zhu QZ, Yang S, Wu CH, Zhang HF, Zhou CF, Zhang XJ [2008]. Trichloroethylene induced cutaneous irritation in BALB/c hairless mice: histopathological changes and oxidative damage. Toxicology *248*:113–120.

Smyth HF Jr, Carpenter CP, Weil CS, Pozzani UC, Striegel JA, Nycum JS [1969]. Range-finding toxicity data: list VII. Am Ind Hyg Assoc J *30*(5):470–476.

Stewart RD, Dodd HC [1964]. Absorption of carbon tetrachloride, trichloroethylene, tetrachloroethylene, methylene chloride, and 1,1,1-trichloroethane through the human skin. Am Ind Hyg Assoc J *25*:439–446.

Stewart RD, Dodd HC, Gay HH, Erley DS [1970]. Experimental human exposure to trichloroethylene. Arch Environ Health *20*(1):64–71.

Tang XJ, Li LY, Huang JX, Deng YY [2002]. Guinea pig maximization test for trichloroethylene and its metabolites. Biomed Environ Sci *15*(2):113–118.

Tang XJ, Que B, Song X, Li S, Yang X, Wang H, Huang H, Kamuima M, Nakajima T, Lin Y, Li L [2008]. Characterization of liver injury associated with hypersensitive skin reactions induced by trichloroethylene in the guinea pig maximization test. J Occup Health *50*:114–121.

Tsuruta H [1978]. Percutaneous absorption of trichloroethylene in mice. Ind Health *16*:145–148.

UNECE (United Nations Economic Commission for Europe) [2007]. Part 3: health hazards. In: Globally harmonized system of classification and labelling of chemicals (GHS). 2nd Rev. Ed., http://www.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev02/English/03e_part3.pdf. Accessed: 06-07-17.

USEPA (United States Environmental Protection Agency) [2012]. Integrated Risk Information System (IRIS), http://www.epa.gov/iris/. Accessed: 06-07-17.

USEPA [2014]. TSCA Work plan chemical risk assessment trichloroethylene: Degreasing, spot cleaning and arts and crafts uses. Washington, DC: US Environemntal Protection Agency, EPA Document # 740-R1-4002.

Van Duuren BL, Goldschmidt BM, Loewengart G, Smith AC, Melchionne S, Seldman I, Roth D [1979]. Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice. J Natl Cancer Inst *63*(6):1433–1439.

Wang H, Zhang JX, Ye LP, Li SL, Wang F, Zha WS, Shen T, Wu C, Zhu QX [2016]. Plasma Kallikrein-Kinin system mediates immune-mediated renal injury in trichloroethylene-sensitized mice. J Immunotoxicol *13*(4):567–579.

Wahlberg JE [1984a]. Edema-inducing effects of solvents following topical administration. Derm Beruf Umwelt *32*(3):91–94.

Wahlberg JE [1984b]. Erythema-inducing effects of solvents following epicutaneous administration to man: studied by laser Doppler flowmetry. Scand J Work Environ Health *10*(3):159–162.

Watanabe H, Tohyama M, Kamijima M, Nakajima T, Yoshida T, Hashimoto K, Lijima M [2010]. Occupational tricholoroethylene hypersensitivity syndrome with human herpesvirus-6 and cytomegalovirus reactivation. Dermatology *221*:17–22.

Watanabe H [2011]. Hypersensitivity syndrome due to trichloroethylene exposure: A severe generalized skin reaction resembling drug-induced hypersensitivity syndrome. J Dermatol *38*(3):229–235.

Xu X, Yang R, Wu N, Zhong P, Ke Y, Zhou L, Yuan J, Li G, Huang H, Wu B [2009]. Severe hypersensitivity dermatitis and liver dysfunction induced by occupational exposure to trichloroethylene. Industrial Health *47*:107–112.

Yao P, Honggian C, Qinghe M, Langin S, Jianjun J, Xiaohua Y, Xuetao W, Weidong H [2016]. Lack of TAK1 in dendritic cells inhibits the contact hypersensitivity response induced by trichloroethylene in local lymph node assay. Toxicol Appl Pharmacol. Epub: doi: 10.1016/j.taap.2016.07.019.

Yu J, Leng J, Shen T, Zhou C, Xu H, Jiang T, Xu S, Zhu Q [2012]. Possible role of complement activation in renal impairment in trichloroethylene-sensitized guinea pigs. Toxicology *302*:172–178.

Zhang JX, Zha WS, Ye LP, Wang F, Wang H, Shen T, Wu CH, Zhu QX [2015]. Complement C5a-C5aR interaction enhances MAPK signaling pathway activities to mediate renal injury in trichloroethylene sensitized BALB/c mice. J Appl Toxicol *36*(2):271–284.

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Appendix: Calculation of the SI Ratio for TCE

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for TCE. Although the SI ratio is considered in the determination of a substance's hazard potential following skin contact, it is intended only to serve as supportive data during the assignment of the NIOSH SK. An in-depth discussion on the rationale and calculation of the SI ratio can be found in Appendix B of the *Current Intelligence Bulletin (CIB) 61: A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009].

Overview

The SI ratio is a predictive algorithm for estimating and evaluating the health hazards of skin exposure to substances. The algorithm is designed to evaluate the potential for a substance to penetrate the skin and induce systemic toxicity [NIOSH 2009]. The goals for incorporating this algorithm into the proposed strategy for assigning SYS notation are as follows:

1. Provide an alternative method to evaluate substances for which no clinical reports or animal toxicity studies exist or for which empirical data are insufficient to determine systemic effects.
2. Use the algorithm evaluation results to determine whether a substance poses a skin absorption hazard and should be labeled with the SYS notation.

The algorithm evaluation includes three steps:

1. determining a skin permeation coefficient (k_p) for the substance of interest,
2. estimating substance uptake by the skin and respiratory absorption routes, and
3. evaluating whether the substance poses a skin exposure hazard.

The algorithm is flexible in the data requirement and can operate entirely on the basis of the physicochemical properties of a substance and the relevant exposure parameters. Thus, the algorithm is independent of the need for biologic data. Alternatively, it can function with both the physicochemical properties and the experimentally determined permeation coefficient when such data are available and appropriate for use.

The first step in the evaluation is to determine the 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 outlined in Table A1. Other model-based estimates of k_p may also be used [NIOSH 2009].

Equation 1: Calculation of Skin Permeation Coefficient (k_p)

$$k_p = \frac{1}{\frac{1}{k_{psc} + k_{pol}} + \frac{1}{k_{aq}}}$$

where k_{psc} is the permeation coefficient in the lipid fraction of the stratum corneum, k_{pol} is the coefficient in the protein fraction of the stratum corneum, and k_{aq} is the coefficient in the watery epidermal layer. These components are individually estimated by

$$\log k_{psc} = -1.326 + 0.6097 \times \log K_{ow} - 0.1786 \times MW^{0.5}$$
$$k_{pol} = 0.0001519 \times MW^{-0.5}$$
$$k_{aq} = 2.5 \times MW^{-0.5}$$

The second step is to calculate the biologic mass uptake of the substance from skin absorption (skin dose) and inhalation (inhalation dose) during the same period of exposure. The skin dose is calculated as a mathematical

product of the k_p, the water solubility (S_W) of the substance, the exposed skin surface area, and the duration of exposure. Its units are milligrams (mg). Assume that the skin exposure continues for 8 hours to unprotected skin on the palms of both hands (a surface area of 360 square centimeters [cm^2]).

Equation 2: Determination of Skin Dose

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

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

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

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

Calculation

Table A1 summarizes the data applied in the previously described equations to determinethe SI ratio for TCE. The calculated SI ratio was 0.02. On the basis of these results, TCE is not predicted to represent a skin absorption hazard.

Appendix References

Hayes WA [2008]. Principles and Methods of Toxicology. Fifth Edition. Informa Healthcare USA, Inc. New York, NY.

NIOSH [2005]. NIOSH pocket guide to chemical hazards. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2005–149, http://www.cdc.gov/niosh/npg/. Accessed: 06-07-17.

NIOSH [2009]. Current intelligence bulletin 61: a strategy for assigning new NIOSH skin notations. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2009-147, http://www.cdc.gov/niosh/docs/2009-147/pdfs/2009-147.pdf. Accessed: 06-07-17.

SRC [ND]. Interactive PhysProp database demo, http://esc.syrres.com/fatepointer/webprop.asp?CAS=79016. Accessed: 06-07-17.

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

Variables used in calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path(k_{psc})	cm/hr	0.01266
Permeation coefficient of the protein fraction of the stratum corneum (k_{pol})	cm/hr	1.32519 x 10-5
Permeation coefficient of the watery epidermal layer (k_{aq})	cm/hr	0.21810
Molecular weight (MW)*	amu	131
Base-10 logarithm of its octanol–water partition coefficient (Log Kow)*	None	2.42
Calculated skin permeation coefficient (k_p)	cm/hr	0.01197
Skin dose		
Water solubility (S_w)*	mg/cm^3	1.28
Calculated skin permeation coefficient (k_p)	cm/hr	0.01197
Estimated skin surface area (palms of hand)§	cm^2	360
Exposure time	hr	8
Calculated skin dose	mg	44.14
Inhalation Dose		
Occupational exposure limit (OEL)†	mg/m^3	268
Inhalation volume	m^3	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	2010
Skin dose–to–inhalation dose (SI) ratio	**None**	**0.02**

*Variables identified from SRC [ND].
The OEL used in calculation of the SI ratio was the NIOSH-recommended exposure limit (REL) [NIOSH 2005].
§Hayes WA [2008]. Principles and Methods of Toxicology. Fifth Edition. Informa Healthcare USA, Inc. New York, NY.

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DHHS (NIOSH) Publication No. 2017-192