NIOSH Skin Notation Profile

2,4-Toluene diisocyanate (2,4-TDI)
2,6-Toluene diisocyanate (2,6-TDI)
2,4- and 2,6-Toluene diisocyanate mixture

SK

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

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2,4- and 2,6-Toluene diisocyanate mixture
[CAS No. 584-84-9; 91-08-7; 26471-62-5]

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Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

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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 (such as irritant contact dermatitis and corrosion) to induction of immune-mediated responses (such as allergic contact dermatitis and pulmonary responses), or systemic toxicity (such as 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]. 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 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 (such as skin permeation) by means of analytical or numerical methods.

This *Skin Notation Profile* provides the SK assignments and supportive data for 2,4-toluene diisocyanate (2,4-TDI), 2,6-toluene diisocyanate (2,6-TDI), and the mixture of 2,4- and 2,6-toluene diisocyanates. 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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Contents

Abbreviations

ACGIH®	American Conference of Governmental Industrial Hygienists
AHR	airway hyperresponsiveness
CIB	Current Intelligence Bulletin
COR	subnotation of SK: DIR indicating the potential for a chemical to be corrosive to the skin following exposure
2,4-TDI	2,4-toluene diisocyanate
2,6-TDI	2,6-toluene diisocyanate
DIR	skin notation indicating the potential for direct effects to the skin following contact with a chemical
DSEN	Dermal (skin) sensitization
EC	European Commission
FATAL	subnotation of SK: SYS, indicating the potential for the chemical to be fatal during dermal absorption
GHS	Globally Harmonized System for Classification and Labelling of Chemicals
IARC	International Agency for Research on Cancer
ID^{SK}	skin notation indicating that a chemical has been evaluated, but insufficient data exist to accurately assess the hazards of skin exposure
IgE	immunoglobulin E
IgG	immunoglobulin G
IRR	subnotation of SK: DIR indicating the potential for a chemical to be a skin irritant following exposure to the skin
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
M	molarity
m^3	cubic meter(s)
mg	milligram(s)
mg/kg	milligram(s) per kilogram
mg/m^3	milligram(s) per cubic meter
miRNA	micro ribonucleic acid
µL	microliter(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
RNA	ribonucleic acid

SEN	skin notation indicating the potential for immune-mediated reactions following exposure of the skin
SK	skin notation
~~**SK**~~	skin notation indicating that the reviewed data did not identify a health risk associated with skin exposure
SYS	skin notation indicating the potential for systemic toxicity following exposure of the skin
U.S. EPA	United States Environmental Protection Agency

Glossary

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

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

Cancer—Any one of a group of diseases that occurs when cells in the body become abnormal and grow or multiply out of control.

Contaminant—A chemical that is (1) unintentionally present within a neat substance or mixture at a concentration less than 1.0% or (2) recognized as a potential carcinogen and present within a neat substance or mixture at a concentration less than 0.1%.

Cutaneous (or percutaneous)—Referring to the skin (or through the skin).

Dermal—Referring to the skin.

Dermal contact—Contact with (touching) the skin.

Direct effects—Localized, non-immune-mediated adverse health effects on the skin, including corrosion, primary irritation, changes in skin pigmentation, and reduction/disruption of the skin barrier integrity, occurring at or near the point of contact with chemicals.

Immune-mediated responses—Responses mediated by the immune system, including allergic responses.

Sensitization—A specific immune-mediated response that develops following ex¬posure 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

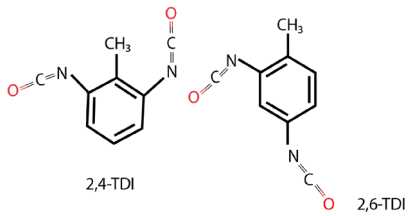
Chemical: 2,4-Toluene diisocyanate (2,4-TDI) and 2,6-Toluene diisocyanate (2,6-TDI)

CAS No: 584-84-9; 91-08-7; 26471-62-5 (as a mixture)

Molecular weight *(MW)*: 174.16

Molecular formula: $C_9H_6N_2O_2$

Structural formula:



The general substance information was obtained from NIOSH [2007] and the image was obtained from ChemIDplus [NLM, no date].

Synonyms: 2,4-diisocyanato-1-methyl-benzene, tolylene diisocyanate, methyl phenylene diisocyanate, 1,3-diisocyanatomethyl benzene; isocyanic acid, methyl-m-phenylene ester

Uses: 2,4-Toluene diisocyanate is used as a chemical intermediate in the production of polyurethane products such as foams, coatings, elastomers, adhesives, and sealants.

1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with 2,4-toluene diisocyanate (2,4-TDI), 2,6-toluene diisocyanate (2,6-TDI), and their mixture, as well as (2) the rationale behind the hazard-specific skin notation (SK) assignment for these compounds. 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 2,4-TDI and 2,6-TDI. A literature search was conducted through March 2021 to identify information on 2,4-TDI and 2,6-TDI, 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 these compounds. The criteria for the search strategy, evaluation, and selection of data are described in Appendix E in the aforementioned *CIB 61* [NIOSH 2009].

1.3 Overview of SK Assignment for 2,4-TDI and 2,6-TDI, and the Mixture of 2,4- and 2,6-TDI

2,4-TDI and 2,6-TDI are 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 2,4-TDI and 2,6-TDI: SK: DIR(IRR)-SEN. Table 1 provides an overview of the critical effects and the rationale behind the SK assignment for 2,4-TDI and 2,6-TDI.

Table 1. Summary of the SK assignment for 2,4-TDI and 2,6-TDI

Skin notations	Critical effect	Available data
2,4-TDI Skin notation		
SK: DIR(IRR)	Skin irritation	Limited human and animal data
SK: SEN	Skin sensitization	Sufficient human and animal data
2,6-TDI Skin notation		
SK: DIR(IRR)	Skin irritation	Limited animal data
SK: SEN	Skin sensitization	Sufficient animal data
2,4- and 2,6-TDI mixture skin notation		
SK: DIR(IRR)	Skin irritation	Limited animal data
SK: SEN	Skin sensitization	Sufficient human and animal data

2 Systemic Toxicity From Skin Exposure (SK:SYS)

No quantitative estimates of absorption of 2,4-TDI or 2,6-TDI were identified following dermal exposure in humans. Hoffman et al. [2010] evaluated dermal uptake of 2,4-TDI in male Wistar rats. Three groups of four rats were dermally exposed to 350 milligrams per kilogram of body weight (mg/kg) of ^{14}C-2,4-TDI. The investigators estimated that 0.031 mg/kg (less than 1%) was dermally absorbed. A separate group of Wistar rats was dermally exposed to 360.90 mg/kg of unlabeled 2,4-TDI and 2,6-TDI to assess their systemic availability [Hoffman et al. 2010]. Both isomers were detected on rat skin in animals being dosed with an 80:20 mixture of 2,4-TDI and 2,6-TDI using high performance liquid chromatography analysis. An increase in exposure time from 1 to 8 hours (h) resulted in the decreased concentration of 2,4-TDI from 59 to 14–18 mg/sample and 2-6-TDI decreased from 12 to 2–3 mg/sample [Hoffman et al. 2010]. In another study, dermal absorption of 2,4-TDI was compared to 2,6-TDI in rats [Yeh et al. 2008]. Rats were exposed to 0.2%, 1%, or 5% solutions of 80:20 mixture of 2,4-TDI and 2,6-TDI in olive oil. The TDI mixture was applied to the clipped skin on the back for 5 h under occlusive conditions. Urine samples were collected and 2,4- and 2,6-toluene diamine (2,4-TDA, 2,6-TDA) were used as biomarkers of exposure for 2,4-TDI and 2,6-TDI, respectively. Yeh et al. [2008] noted that the peak urinary excretion of an 80:20 mixture of 2,4- and 2,6-TDI happened in the first 12-hour collection interval for the three doses (0.2%, 1%, and 5%), and that the peak urinary excretion for 2,4-TDI and 2,6-TDI were dose dependent. The overall ratios for total urinary TDA (i.e., 2,4-TDA and 2,6-TDA) were 1.1, 0.9, and 1.6, for the 0.2%, 1%, and 5% solution, respectively, rather than the 4:1 ratio that would be expected from the mixture. Nayak et al. [2014] reported that TDI-haptenated proteins (TDI-hp) may persist for up to 15 days in the stratum corneum and up to 9 days in hair follicles following exposure to 0.1% and 4% 2,4-TDI. These authors concluded that the hair follicles and associated sebaceous glands may act as route of re-entry and a reservoir for TDI-hp and appear to be essential in uptake of TDI-hp antigens [Nayak et al. 2014].

Austin [2007] evaluated 26 workers at a polyurethane block plant, of which 13 were dermally exposed to an 80:20 mixture of 2,4-TDI, the remaining 2,6-TDI; the remaining 13 did not have direct contact with polyurethane foam. Personal air samples were collected in the breathing zone of each worker and urine samples were collected at the beginning and at the end of the work shift. All workers had a potential for inhalation exposure to the 80:20 mixture of 2,4-TDI and 2,6-TDI since they worked in the same environment. There was no statistical

difference in personal breathing-zone levels of TDI between the two worker groups. Ten of the 13 workers who had dermal exposure to TDI had detectable levels of TDA in urine at the end of the shift compared to 2 of 13 workers with no dermal contact with TDI, indicating that TDI was dermally absorbed. Świerczyńska-Machura et al. [2015] evaluated 30 workers in a plant manufacturing TDI-based flexible polyurethane foam in continuous foam blocks. Thirty-nine percent (7 of 18) of workers had TDI metabolite concentrations post-shift that exceeded the British Biological Monitoring Guidance Value of 1 µmol TDA/mol creatinine. The highest levels of metabolites in the urine samples were in maintenance workers and cutting machine operators [Świerczyńska-Machura et al. 2015].

A dermal lethal dose (LD_{Lo}) for humans has not been identified. The reported dermal median lethal dose (LD_{50}; the dose resulting in 50% mortality in the exposed animals) was reported to be greater than 16,000 mg/kg when undiluted 2,4-TDI was dermally applied to rabbits [Zapp 1957]. Because the reported acute dermal LD_{50} value for rabbits is higher than the critical dermal LD_{50} value of 2,000 mg/kg, which identifies a concentration of a substance that is considered acutely toxic [NIOSH 2009], 2,4-TDI is not considered to be acutely toxic following dermal exposure.

No epidemiological studies were identified that evaluated the potential of 2,4-TDI or 2,6-TDI to cause systemic effects following dermal exposure. Additionally, no information was identified about the potential systemic effects in animals following repeat-dose (21-day or 28-day), sub-chronic (90-day), or chronic (at least 12-month) dermal exposure to either 2,4-TDI or 2,6-TDI. No standard toxicity or specialty studies of biological system or function-specific effects (including reproductive and developmental effects and immunotoxicity) following dermal exposure to 2,4-TDI or 2,6-TDI were identified. In addition, no studies were located regarding cancer in humans after dermal exposure to 2,4-TDI or 2,6-TDI. Table 2 summarizes carcinogenic designations of multiple governmental and nongovernmental organizations for 2,4-TDI, 2,6-TDI or a mixture of 2,4- and 2,6-TDI.

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

Organization	Carcinogenic designation
NIOSH [2007]†	Potential occupational carcinogen
NTP [2016]§	Reasonably anticipated to be a human carcinogen
U.S. EPA [2021]§	No designation
ECHA [2020]**	Suspected to be carcinogenic
IARC [2012]§	Group 2B: Possibly carcinogenic to humans
ACGIH® [2018]**	A3: Confirmed animal carcinogen with unknown relevance to humans

ACGIH® = American Conference of Governmental Industrial Hygienists; ECHA = European Chemicals Agency; IARC = International Agency for Research on Cancer; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; U.S. EPA = United States Environmental Protection Agency.

*The listed cancer designations were based on data from nondermal (such as oral or inhalation) exposure rather than dermal exposure.

†2,4-TDI; CAS No. 584-84-9

§Toluene diisocyanates (mixture); CAS No. 26471-62-5

**The carcinogenic designation is for all forms of TDI, 2,4-TDI (CAS No. 584-84-9); 2,6-TDI (CAS No. 91-08-7); and the mixture of 2,4- and 2,6-TDI (CAS No. 26471-62-5).

Toxicokinetic studies in rats [Hoffman et al. 2010; Yeh et al. 2008] and epidemiological studies in humans assessing urinary metabolite concentrations [Austin 2007; Świerczyńska-Machura et al. 2015] indicate the potential for dermal absorption for 2,4-TDI and 2,6-TDI. However, an acute toxicity study in rabbits indicates that 2,4-TDI and 2,6-TDI are not acutely toxic following dermal exposure [Zapp 1957]. No epidemiological studies, repeat dose, sub-chronic, or chronic toxicity studies on systemic toxicity following dermal exposure to 2,4-TDI or 2,6-TDI were identified. Therefore, based on the available data, 2,4-TDI, 2,6- TDI, and the mixture of 2,4- and 2,6-TDI are not assigned a SK: SYS notation.

3 Direct Effects on Skin (SK: DIR)

No human or animal *in vivo* studies on corrosivity of 2,4-TDI or 2,6-TDI or *in vitro* tests for corrosivity using human skin models or *in vitro* tests of skin integrity using cadaver skin were identified. Daftarian et al. [2002] examined the incidence of skin problems in workers who were exposed to 2,4-TDI in a cross-sectional study conducted at a flexible foam manufacturing plant. While all workers were invited to participate in the study, only 114 of 290 workers participated, and included 88 production workers and 26 nonproduction workers. The production workers were more than twice as likely to report skin problems compared with those in nonproduction areas (prevalence rate ratios [PRR] = 2.66; 95% confidence interval [CI] 1.14–16.32; $p<0.02$). A subset of the participants that reported dermal symptoms (n = 38) provided blood samples, three of whom (8%) had immunoglobulin E (IgE) levels above the upper limit of normal. No specific IgE antibodies against TDI were found. However, a single positive immunoglobulin G (IgG) reaction to TDI was detected in a worker that reported dermal symptoms. Twenty-six of 40 eligible workers underwent skin-patch testing to a diisocyanate panel including TDI (isomer not specified) (2.0% in petrolatum); diphenylmethane-4,4-diisocyanate (MDI) (2% petrolatum; diaminodiphenylmethane (0.5% petrolatum); isophorone diisocyanate (IPDI) (1% petrolatum); and isophorone diamine (IPD) (0.1% in petrolatum), but no positive reactions were observed [Daftarian et al. 2002]. The authors suggested that the skin symptoms were more likely to be due to irritation rather than to an immunological reaction to TDI. Świerczyńska-Machura et al. [2015] reported that skin symptoms were the second most common symptom, reported in 5 of 30 workers. Specific IgE antibodies were not detected in the serum of these workers.

Mild to moderate skin irritation and erythema with edema were reported after 1% 2,4-TDI was dermally applied in guinea pigs [E.I. Du Pont de Nemours 1970a,b]. Hoffman et al. [2010] exposed 12 rats to 350 mg/kg of undiluted 2,4-TDI or 2,6-TDI on the clipped skin in semi-occluded conditions. Edema, slight hydropic degeneration of the basal cell layer, was observed after 8 h, and full-thickness necrosis with sub- and intra-epidermal and follicular and perifollicular micro-abscesses, and erosion was observed at 48 h post-exposure for both 2,4- and 2,6-TDI. On the contrary, Yeh et al. [2008] reported no skin irritation at low concentrations (0.2–5%) of 2,4-TDI and/or 2,6-TDI under occluded conditions on rats.

Nayak et al. [2014] applied 20 µL per ear of 0.1% or 4% 2,4-TDI on mice. Mice receiving 4% 2,4-TDI exhibited inflammation characterized by increased cellular infiltration, tissue damage, and interstitial edema; mice receiving 0.1% 2,4-TDI displayed no immunoreactivity but had increasing intensity over time in the epidermis and hair follicles [Nayak et al. 2014]. Epidermal thickening was mostly noted in animals that received 4% 2,4-TDI; however, the thickening resolved in all animals by day 15 post-exposure [Nayak et al. 2014]. Long et al. [2016] applied 25 µL of 0.5–4% TDI in acetone to the dorsal surface of each ear of mice. Mice were assayed for dermal irritancy potential using ear swelling measurements and ear inflammatory cytokine mRNA production. Inflammatory cytokine (IL-1β, IL-6, and TNF-α) mRNA levels were increased within four days following exposure to 4% TDI.

Severity of skin irritation is related to concentration of 2,4-TDI and 2,6-TDI. Reports of skin irritation in workers exposed to 2,4-TDI [Daftarian et al. 2002; Świerczyńska-Machura et al. 2015], and studies in animals provide evidence that 2,4-TDI is irritating to the skin at concentrations as low as 1% [E.I. Du Pont de Nemours 1970a,b; Long et al. 2016; Nayak et al. 2014] and 2,4-TDI and 2,6-TDI may cause necrosis and skin erosion when undiluted when dermally applied for up to 48 h [Hoffman et al. 2010]. However, it is unlikely that workers would be continuously exposed to undiluted TDI for extended periods (up to 48 h). Based on these data, 2,4-TDI, 2,6-TDI, and the mixture of 2,4- and 2,6-TDI are assigned a SK: DIR(IRR) notation.

4 Immune-mediated Responses (SK: SEN)

Skin sensitization induced by dermal exposure to TDI has been well-documented in humans. Over a period of 13 years, 345 people who were examined for suspected occupational skin diseases, such as allergic contact dermatitis, were tested for sensitization to isocyanate monomers, and 6 of them had a positive reaction to 2,4-TDI [Aalto-Korte et al. 2012]. However, direct exposure to TDI (isomer not specified) could be traced to only one of these workers, suggesting cross-reactions between TDI and other isocyanates accounted for the remaining 5 positive skin reactions. A study conducted in a paint workshop of a furniture manufacturing factory in China consisted of 15 painters who were exposed to TDI (isomer not specified) from applying polyurethane varnish to furniture, with a mean duration of 7.5 years, and 18 controls [Huang et al. 1991a]. The workers were interviewed using a standardized questionnaire, and two occupational physicians established diagnoses based on the questionnaire results. The workers were also patch tested with 0.1% (isomer not specified) TDI in petroleum on the inner sides of the forearms, and 0.05% potassium dichromate, 0.05% Daconil, and 5% formaldehyde were used as negative control substances. One third (5/15) of the painters had a positive reaction to 0.1% TDI, and among these, three of the painters reported contact dermatitis. All controls had negative reactions to 0.1% TDI. In another study conducted by Huang et al. [1991b] in three furniture manufacturing factories, workers at two of the factories were exposed to high levels of TDI (0.79 mg/m^3 and 0.31 mg/m^3, corresponding to 0.11 parts per million and 0.44 parts per million) and 20% and 10% of these workers ($p<0.01$), respectively, reported contact dermatitis. Huang et al. [1991b] concluded that the workers experienced both pulmonary hypersensitivity and contact sensitization.

In addition to Nayak et al. [2014] reporting general irritation in mice following exposure to 20 µL per ear of 0.1% or 4% 2,4-TDI, the authors reported that the hair follicles and sebaceous glands may provide a reservoir for TDI-hp and antigen uptake by immune cells. This is noted by the increase in CD103 cells (these cells have been implicated in contact hypersensitivity to chemical allergens) in the hair follicle for up to 9 days following exposure to 0.1% and 4% 2,4-TDI. The sensitizing potential of 2,4-TDI and 2,6-TDI has also been well documented in animals. Dermal sensitization [Koschier et al. 1983; Sugawara et al. 1993; Yasuda et al. 1980] and hypersensitivity in the airways following sensitization in guinea pigs and mice have been reported following exposure to 2,4-TDI and an 80:20 mixture of 2,4-TDI and 2,6-TDI [De Vooght et al. 2013; Karol 1981; Li et al. 2015; Liang et al. 2015; Scheerens et al. 1999; Selgrade et al. 2006; Tarkowski et al. 2007; Yao et al. 2015]. Of these, several studies examined options to reduce airway hyperresponsiveness (AHR), including treatment with phosphatidylinositol 3-kinase (P13K) inhibitor [Liang et al. 2015; Yao et al. 2015] and 1,25-dihydroxyvitamin D3 to prevent airway epithelial barrier disruption [Li et al. 2015]. Li et al. [2015] reported AHR, increased levels of serum IgE, IL-4, and IFN-γ in BALB/c mice following dermal sensitization. Animals were sensitized following 20 µL/ear of 0.3% 2,4-TDI in acetone-olive oil on days 1 and 8, oropharyngeal aspiration of 20 µL 0.01% TDI on days 15, 18, and 21 (one day prior to challenge of TDI for 8 consecutive days). Pollaris

et al. [2016] evaluated cross-reactivity of TDI and MDI after 8 days of dermal application of 20 µL of 2% TDI, 3% MDI, or acetone-olive oil followed by an oropharyngeal instillation of 20 µL of 0.01% TDI, 0.04% MDI, or the vehicle. Twenty-four hours after the challenge, airway hyperreactivity to methacholine was measured, blood samples and lymph nodes were collected. Pollaris et al. [2016] reported that mice exposed to TDI or MDI had significant increases in AHR, lymph nodes (both T and B lymphocytes), and increases in total numbers of neutrophils and eosinophils in the bronchoalveolar lavage. There were no statistically significant increases in cross-reactivity groups in AHR response and only limited inflammation was present in the bronchoalveolar lavage [Pollaris et al. 2016].

The murine local lymph node assay (LLNA) was used in several studies to assess sensitization potential of 2,4-TDI. These studies compared the TH1 response (dermal allergen) to the TH2 response (respiratory allergen) [Dearman et al. 2003; Manetz and Meade 1999; Potter and Wederbrand 1995; van Och et al. 2000; Vandebriel et al. 2000], or respiratory response following dermal sensitization to 2,4-TDI or an 80:20 mixture of 2,4-TDI and 2,6-TDI [Satoh et al. 1995; Vanoirbeek et al. 2004; Vanoirbeek et al. 2008]. Potter and Wederbrand [1995] treated mice with 50 µL of an 80:20 mixture of 2,4-TDI and 2,6-TDI, respectively, in acetone-olive oil on the shaved flank and dorsum of ears on alternate ears five times per week for three weeks. These mice had statistically significantly ($p<0.01$) higher concentrations of serum IgE antibodies than control mice. Additionally, Potter and Wederbrand [1995] noted that the TDI threshold for IgE antibody production significantly increased with the number of TDI applications. Dearman et al. [2003] reported a 15-fold increase in proliferation compared to controls following topical application of 2% TDI. Manetz and Meade [1999] noted that ear swelling, using the Mouse Ear Swelling Test (MEST), without increases to B220 +, IgE+B220+ cell populations, indicates that a chemical is an irritant. Manetz and Meade [1999] reported that exposure to 2,4-TDI (41%) statistically and significantly ($p<0.01$) elevated IgE+B220+ population, suggesting a TH2 response. Vandebriel et al. [2000] applied 25 µL of 0.75% 2,4-TDI to both ears of BALB/c mice and noted that exposure to TDI resulted in 1.8 fold higher lymphocyte proliferation than 1% 2,4-dinitrochlorobenzene (DNCB), a potent contact allergen. Van Och et al. [2000] reported that the threshold dose (EC3; 3 times background lymph node cell proliferation) for 2,4-TDI is 0.101%. Under the European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC) LLNA potency ranking scheme, TDI would be considered a strong sensitizer (≥0.1–<1.0%) [ECETOC 2003]. Satoh et al. [1995] applied 200 µL 0.5% of an 80:20 2,4- and 2,6-TDI mixture or DNCB in acetone-olive oil epicutaneously to the shaved abdomen of mice, that were challenged on day 8 with an intranasal application of 50 µL if a 0.6% solution of the sulfonic acid analog of TDI in a 0.02 M phosphate buffered saline. Mice exposed to TDI had increased hapten-specific IgG, but hapten-specific IgG was not detected for DNCB. Vanoirbeek et al. [2004] applied 20 µL 2,4-TDI to each ear either on three consecutive days (days 1, 2, and 3; 0.3 or 3% TDI) or only on one day (1% TDI on day one), and each group received a dermal application of 20 µL of the same concentration of TDI on day 7 and 10 µL of 0.1% TDI intranasally on day 10. Vanoirbeek et al. [2004] reported that mice that had received prior applications of TDI before the intranasal challenge exhibited ventilator responses, bronchoconstriction, enhanced methacholine responsiveness 24 h later, and pulmonary inflammation.

Several studies induced dermal sensitization using 2,4-TDI or an 80:20 mixture of 2,4-TDI and 2,6-TDI to induce contact dermatitis in order to find treatments for inflammation or allergen-induced itching and comparing different methods to assess inflammatory responses [Bäumer et al. 2002; Fukuyama et al. 2015; Rossbach et al. 2009; Wijsbek et al. 1991]. Fuchibe et al. [2003] sensitized mice by dermally exposing the animals to 20 microliters (µL) of 1% 2,4-TDI once every 2 days for 4 days. Fourteen days after the mice were sensitized, the animals were exposed to 0.1 or 1% of 2,4-TDI epicutaneously every 10 days until the 10th challenge dose was

received. Non-sensitized mice also received repeated exposures of 0.1% and 1% 2,4-TDI as a comparison. Repeated application of 2,4-TDI caused scratching and edema in mice sensitized to 2,4-TDI, whereas there was no increased scratching in mice that were not sensitized to 2,4-TDI. Fukuyama et al. [2015] reported that topical treatment of janus-kinase inhibitors reduced itch and inflammatory response, whereas oral treatment only reduced itch in mice sensitized to 2,4-TDI. Long et al. [2016] applied 25 µL of 0.5–4% TDI in acetone to the dorsal surface of each ear of mice. The ears were measured at 4 days post-exposure and euthanized 1 to 11 days post-exposure. Total serum IgE statistically significantly increased over 4, 7, and 9 days in mice that received 4% TDI.

Ebino et al. [2001] used the Buehler test (closed patch test) to compare skin and airway (intranasal, intratrachael, and inhalation) sensitization reactions between guinea pigs exposed to an 80:20 mixture of 2,4-TDI and 2,6-TDI. Nine of 10 guinea pigs exposed to TDI through the Buehler test exhibited skin sensitization; however, 4 of 5 guinea pigs exposed through intratrachael instillation, 11 of 12 guinea pigs exposed by intranasal instillation and 8 of 8 guinea pigs exposed to TDI by inhalation had exhibited skin sensitization. These results indicate that airway exposure alone may cause skin sensitization [Ebino et al. 2001]. Pauluhn [2014] reported that repeated priming exposure to TDI caused an amplification in response. Pauluhn [2014] applied 100 µL of an 80:20 mixture of 2,4- and 2,6-TDI on days 0 and 7 to dermally sensitize rats, followed by one or three inhalation challenges of 85 mg/m^3 of TDI for 10, 30, or 60 minutes. Following one 30-minute challenge, the rats displayed a concentration-dependent decrease in respiratory frequency but the changes returned to baseline 15 minutes post-exposure; however, sensitized rats exhibited labored breathing patterns from the second challenge onward. Increased lung weights and BAL protein were reported following the 60-minute challenge in rats receiving primary inhalation challenges at 10 minutes, 30 minutes, or 60 minutes [Pauluhn 2014]. Haag et al. [2002] sensitized mice to 80:20 mixture of 2,4-TDI and 2,6-TDI. A significant increase in CYP1A1 protein was detected in sensitized mice by western blotting. Anderson et al. [2013] sensitized BALB/c mice by dermal exposure to 1% 2,4-TDI for 4 consecutive days to ensure sensitization, followed by a single dose of a 0.1–15% solution of 2,4-TDI to evaluate microRNA (miRNA). The miRNA was isolated from the parotid lymph node between 1 h and 15 days post-exposure and was analyzed using polymerase chain reaction (PCR). Anderson et al. [2013] confirmed sensitization by the expression of allergic cytokines (IL-4, IL-5, IL-13, and IFNγ), and were able to identify 11 miRNA that were potentially involved in sensitization. Manetz et al. [2001] also reported elevated IL-4, IL-10, 9, IL-13, IL-15 cytokines, and IFN-γ after mice were dermally exposed to 2,4-TDI.

An abundance of literature in humans [**Aalto-Korte et al. 2021; Huang et al. 1991a,b**][*] and animals [**Anderson et al. 2013; Bäumer et al. 2002; Dearman et al. 1996; Ebino et al. 2001; Fuchibe et al. 2003; Fukuyama et al. 2015; Haag et al. 2002; Karol 1981; Koschier et al. 1983; Li et al. 2014; Liang et al. 2015; Long et al. 2016; Manetz and Meade 1999; Manetz et al. 2001; Pauluhn 2014; Pollaris et al. 2016; Potter and Wederbrand 1995; Robach et al. 2009; Satoh et al. 1995; Scheerens et al. 1999; Selgrade et al. 2006; Sugawara et al. 1993; Tarkowski et al. 2007; Wijsbek et al. 1991; van Och et al. 2000; Vandebriel et al. 2000; Yao et al. 2015; Yasuda et al. 1980**] indicates that 2,4-TDI and 2,6-TDI and the mixture of 2,4- and 2,6-TDI induce skin sensitization. Therefore, based on the available data, 2,4-TDI, 2,6-TDI, and the mixture of 2,4- and 2,6-TDI are assigned a **SK: SEN** notation.

5 Summary

Toxicokinetic studies in rats indicate that 2,4-TDI and 2,6-TDI can be dermally absorbed [Hoffman et al. 2010; Yeh et al. 2008]. However, an acute toxicity study in rabbits [Zapp 1957] indicates that 2,4-TDI and 2,6-TDI are

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

not acutely toxic following dermal exposure. No epidemiological studies, repeat dose, subchronic, or chronic toxicity studies that reported systemic toxicity following dermal exposure to 2,4-TDI or 2,6-TDI were identified. Severity of skin irritation is related to concentration of 2,4-TDI and 2,6-TDI. Reports of skin irritation in workers exposed to 2,4-TDI [**Daftarian et al. 2002; Świerczyńska-Machura et al. 2015**],* and studies in animals provide evidence that 2,4-TDI is irritating to the skin at concentrations as low as 1% [**E.I. Du Pont de Nemours 1970a,b; Long et al. 2016; Nayak et al. 2014**] and undiluted 2,4-TDI and 2,6-TDI may cause necrosis and skin erosion when dermally applied for up to 48 h [Hoffman et al. 2010]. However, it is unlikely that workers would be continuously exposed to undiluted TDI for extended periods (up to 48 h). An abundance of literature in humans [**Aalto-Korte et al. 2012; Huang et al. 1991a,b**] and animals [**Anderson et al. 2013; Bäumer et al. 2002; Dearman et al. 1996; Ebino et al. 2001; Fuchibe et al. 2003; Haag et al. 2002; Karol 1981; Koschier et al. 1983; Long et al. 2016; Manetz et al. 2001; Manetz and Meade 1999; Pollaris et al. 2016; Potter and Wederbrand 1995; Robach et al. 2009; Satoh et al. 1995; Scheerens et al. 1999; Selgrade et al. 2006; Sugawara et al. 1993; Tarkowski et al. 2007; Wijsbek et al. 1991; van Och et al. 2000; Vandebriel et al. 2000; Yasuda et al. 1980**] indicates that 2,4-TDI and 2,6-TDI induce skin sensitization. Therefore, based on the available data, 2,4-TDI, 2,6-TDI, and the mixture of 2,4- and 2,6-TDI are assigned a composite skin notation of **SK: DIR(IRR)-SEN**.

Table 3 summarizes the skin hazard designations for 2,4-TDI previously issued by NIOSH and other organizations.

Table 3. Summary of previous skin hazard designations for TDI from NIOSH and other organizations

Organization	Skin hazard designation
NIOSH [2007]*	No designation
OSHA [2018]†§	No designation
ECHA [2020]	No designation
ACGIH® [2018]**	DSEN††

ACGIH® = American Conference of Governmental Industrial Hygienists; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration.
*2,4-TDI
†Year accessed.
§OSHA did not have a skin hazard designation for either 2,4-TDI or 2,6-TDI.
**The skin hazard designation is for all forms of TDI, 2,4-TDI (CAS No. 584-84-9); 2,6-TDI (CAS No. 91-08-7); and the mixture of 2,4- and 2,6-TDI (CAS No. 26471-62-5).
††Dermal (skin) sensitization

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

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