Chemical Information Review Document

for

Trimethylsilyldiazomethane
[CAS No. 18107-18-1]

Supporting Nomination for Toxicological Evaluation by the National Toxicology Program

July 2011

National Toxicology Program
National Institute of Environmental Health Sciences
National Institutes of Health
U.S. Department of Health and Human Services
Research Triangle Park, NC
http://ntp.niehs.nih.gov/

Abstract

TMSD is a derivatizing agent commonly used for the derivatization of carboxylic acid groups to produce methyl esters. It can be prepared by several methods. For example, addition of potassium hydroxide to *N*-nitroso-*N*-(trimethylsilylmethyl)urea yields the desired product. Exposure to TMSD is likely to occur via dermal contact or inhalation in an occupational setting; however, exposure limits have not been established. TMSD is reported to be a skin irritant and in hexane is a suspected human reproductive toxicant. As a solution (in diethyl ether or hexane), it targets the kidney, liver, lungs, gastrointestinal tract, skeletal muscles, testes, and/or the central nervous, respiratory, peripheral, and/or reproductive systems. Two reports have linked TMSD exposure to death. In one case report, a male pharmaceutical chemist used TMSD as part of a chemical analysis. Eight hours after exposure, he developed "cough, pleuritic chest pain, hemoptysis, and progressive shortness of breath." By 15 hours post-exposure, he was in respiratory distress and was hypoxic, hypercarbic, and acidemic. Within 26 hours post-exposure, he required intubation and developed bradycardia, refractory hypotension, and asystole. Acute lung injury was noted on a chest radiograph. The individual died, and a causal relationship between exposure to TMSD and the observed lung effects was proposed. In a second report, a male chemist was synthesizing TMSD. The individual spilled a flask containing the synthesizing solution onto himself. Prior to the end of the day, he reported having shortness of breath. The individual developed progressive respiratory distress and died ~15 hours after the incident. Toxicological studies are very limited. Dermal LD_{50} values of >2000 and >1000 mg/kg have been reported in rats and rabbits, respectively. TMSD was nonmutagenic to *Salmonella* TA100.

Executive Summary

Basis for Nomination

Trimethylsilyldiazomethane (TMSD) was nominated by the Occupational Safety and Health Administration for inhalational toxicological testing based on two fatalities that occurred in 2008 and 2009; both individuals were chemists working with TMSD. Additionally, the available toxicity data available for TMSD is limited, with no inhalation studies conducted.

Nontoxicological Data

TMSD is a derivatizing agent, commonly used for the derivatization of carboxylic acid groups to give methyl esters. Several different methods have been described for the preparation of TMSD. For example, it may be prepared from either ethyl *N*-nitroso-*N*-(trimethylsilylmethyl)urethane or *N*-nitroso-*N*-(trimethylsilylmethyl)urea. Using the urea compound, addition of potassium hydroxide yields the desired product (61%) with hexamethyldisiloxane as a side product (17%). In another method, chloromethyltrimethylsilane is reacted with magnesium to produce trimethylsilylmethylmagnesium chloride. This compound is then reacted with diphenyl phosphorazidate and cold water to yield TMSD. TMSD can then be isolated using gas chromatography or gas-liquid chromatography. It is commercially available from several companies in the United States, such as Kingstom Chemistry, TCI America, Alfa Aesar, and Sigma-Aldrich Corporation, as well as numerous countries globally. Currently, there are no reports of its release into the environment. Exposure to TMSD is likely to occur via dermal contact or inhalation in an occupational setting; however, exposure limits have not been established.

Human Data

TMSD is reported to be a skin irritant. As a solution (in diethyl ether or hexane), it targets the kidney, liver, lungs, gastrointestinal tract, skeletal muscles, testes, and/or the central nervous, respiratory, peripheral, and/or reproductive systems. Additionally, TMSD in hexane is a suspected human reproductive toxicant.

Two reports have linked TMSD exposure to death. In one case report, a male pharmaceutical chemist used TMSD as part of a chemical analysis. Eight hours after exposure, he developed "cough, pleuritic chest pain, hemoptysis, and progressive shortness of breath." By 15 hours post-exposure, he was in respiratory distress and was hypoxic, hypercarbic, and acidemic. Within 26 hours post-exposure, he required intubation and developed bradycardia, refractory hypotension, and asystole. Acute lung injury was noted on a chest radiograph. The individual died, and a causal relationship between exposure to TMSD and the observed lung effects was proposed. In a second report, a male chemist was synthesizing TMSD. The individual spilled a flask containing the synthesizing solution onto himself. Prior to the end of the day, he reported having shortness of breath. The individual developed progressive respiratory distress and died ~15 hours after the incident.

Toxicological Data

No studies regarding chemical disposition, metabolism, and toxicokinetics; short-term/subchronic or chronic exposure, synergist/antagonistic effects; cytotoxicity; reproductive and teratological effects; carcinogenicity; initiation/promotion, cogenotoxicity, or immunotoxicity were located.

Acute Toxicity

Dermal LD_{50} values of >2000 and >1000 mg/kg were reported in rats and rabbits, respectively.

Genotoxicity

TMSD was nonmutagenic to *Salmonella* TA100. [Note: This was a personal communication.]

Other Data

The following hazard notice was in the description of a synthetic method: "TMS-diazomethane should be regarded as having similar toxicity to diazomethane and must be handled with all precautions appropriate for work with highly toxic substances." The risk of personal injury after explosion, spill, or exposure to TMSD in the absence of counter measures (e.g., working in a hood and using goggles) was identified as "Critical. Permanent partial disability." or "Marginal. Lost-time injury or illness." The frequency classification, the probability that a mishap would occur, was identified as occasional to probable. In most cases, application of counter measures reduced the severity or the frequency of the risk of personal injury.

Structure-Activity Relationships

Diazomethane [CAS No. 334-88-3]

Inhalation of diazomethane has been associated with numerous adverse effects including pulmonary and eye irritation, dizziness, headaches, denudation of mucous membranes, asthmatic symptoms, tremors, cyanosis, chest pains, and death. Exposure has also been associated with a flushed skin, pulmonary edema, delayed inflammatory reaction, hepatic enlargement, and hemolysis. While the American Conference of Industrial Hygienists has classified diazomethane as a suspected human carcinogen, the International Agency for Research on Cancer has stated that the agent is not classifiable. Acute exposure studies in rabbits showed that exposure to atmospheres containing 2-12 mg/L diazomethane for ≤20 minutes, one to four times, induced bronchopheumonia followed by death before seven days. Several studies (without controls) have shown that mice and rats exposed to diazomethane developed tumors (e.g., squamous cell carcinoma, spindle cell sarcoma, and pulmonary adenoma). In *Escherichia coli*, it produced lethal and mutagenic effects.

GeneGo

For each GeneGo quantitative structure-activity relationship (QSAR) model, a QSAR value was calculated. For non-binary models, the calculated values ranged between two threshold values to be classified as active in the model. These threshold values corresponded to the negative logarithm of the activity for the most active compound in the training set and the negative logarithm of 50 μM (-1.7). For binary models (e.g., AMES mutagenicity binary model), the definition of an active chemical is model dependent. In addition to the QSAR value, a Tanimoto similarity percentage (TP) was calculated which indicates the percentage of similarity of TMSD to the most similar compound in the training set.

No potential metabolites were predicted using the model. While some protein binding, therapeutic activity, and toxic activity were predicted to be associated with TMSD, these predicted effects were based on comparison to chemicals with low structural similarity (i.e., TP values were ≤25.00 for all models). Due to the limited structural similarity to any of the chemicals in the training sets (TP ≤25.00), no potential targets were identified.

Leadscope

For each Leadscope model suite evaluated, a positive prediction probability (ranging from 0-1) was calculated. Values ≥0.5 were defined as positive. If the test compound was not at least 30% similar to one in the training set and at least one model feature was not in the test compounds, the chemical was defined as "not in the domain" and prediction probability was not determined. TMSD was not in the domain for any of the models evaluated: genetic toxicity, neurotoxicity, reproductive and developmental toxicity, carcinogenicity, and human adverse effects (i.e., cardiological, hepatobiliary, and urinary tract effects).

Table of Contents

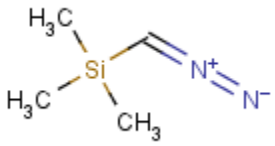
Chemical Information Review Document for Trimethylsilyldiazomethane [CAS No. 18107-18-1]

1.0 Basis for Nomination

Trimethylsilyldiazomethane (TMSD) was nominated by the Occupational Safety and Health Administration (OSHA) for inhalational toxicological testing based on two fatalities that occurred in 2008 and 2009; both individuals were chemists working with TMSD. Additionally, the available toxicity data available for TMSD is limited, with no inhalation studies conducted.

2.0 Introduction

Trimethylsilyldiazomethane
[18107-18-1]



2.1 Chemical Identification and Analysis

Trimethylsilyldiazomethane ($C_4H_{10}N_2Si$; mol. wt. = 114.22) is also called:

Diazo((trimethylsilyl))methane
Diazomethyltrimethyl silane
Silane, (diazomethyl)trimethyl-
TMS-Diazomethane
TMSCHN2

PubChem CID: 167693
InChI: 1S/C4H10N2Si/c1-7(2,3)4-6-5/h4H,1-3H3
Canonical SMILES: C[Si](C)(C)C=[N+]=[N-]

Sources: ChemIDplus (undated); PubChem (undated)

TMSD can be isolated by gas chromatography or gas-liquid chromatography (Seyferth et al., 1972).

2.2 Physical-Chemical Properties

Property	Information	Reference(s)[a]
Physical State	liquid	Sigma-Aldrich (2011a,b)
	yellow liquid	Sigma-Aldrich (2011c)
	greenish-yellow liquid	Seyferth et al. (1972)
Odor	not available	
Boiling Point (°C)	94-95 @ 755 Torr, 96	Registry (2011)
	96 @ 775 Torr	Seyferth et al. (1972)
Melting Point (°C)	not available	
Flash Point (°C)	-35	Sigma-Aldrich (2011a)
[closed cup]	-26	Sigma-Aldrich (2011b)
	-23	Sigma-Aldrich (2011c)
Vapor Pressure (mm Hg)	not available	
Density (g/cm^3)	0.675	Registry (2011)
	0.718 @ 25 °C	Sigma-Aldrich (2011c)
Water Solubility	not available	

Property	Information	Reference(s)[a]
Octanol-Water Partition Coefficient (Log K_{OW})	not available	
Log P	0.17	ChemSpider (undated)[b]
Bioconcentration Factor	1 @ pH 5.5 and 7.4	ChemSpider (undated)[b]

[a]Sigma-Aldrich (2011a): TMSD solution (in diethyl ether), product #527254
Sigma-Aldrich (2011b): TMSD solution (2.0 M in *n*-hexane), product #92738
Sigma-Aldrich (2011c): TMSD solution (in *n*-hexane), product #362832
[b]calculated using ACD/Labs

TMSD is stable in neat or in hydrocarbon solution but is decomposed quickly when in carbon tetrachloride and exposed to light. It is not hydrolyzed by neutral water or by 20% potassium hydroxide solution. It can undergo a number of reactions such as with carboxylic acids, cyclohexene, and activated olefins (Seyferth et al., 1972).

2.3 Commercial Availability

TMSD is commercially available the following U.S. companies: Kingston Chemistry, Gelest, Inc., Pfaltz & Bauer, TCI America, Sigma-Aldrich Corporation, and Alfa Aesar. There are numerous producers/suppliers located in China; examples are Yongyi Chemicals Group Co., Ltd, Shanghai IS Chemical Technology Ltd., Suzhou Rovathin Pharmatech Co., Ltd., Jinan Haohua Industry Co., Ltd., and Simagchem Corporation. Other global suppliers of TMSD include Acros Organics in Belgium, Novasep in France, Chemos GmbH and Chemical Point UG in Germany, Allorachem in Italy, Matrix Marketing GmbH in Switzerland, ATTERCOP-CHEM in the Ukraine, and Ubichem PLC in the United Kingdom (BuyersGuideChem, 2011; ChemBuyersGuide.com, undated; ChemExper, 2011).

3.0 Production Processes

Several methods have been described for the preparation of TMSD. In a method by Seyferth and colleagues (1972), it was shown that TMSD could be prepared from either ethyl *N*-nitroso-*N*-(trimethylsilylmethyl)urethane or *N*-nitroso-*N*-(trimethylsilylmethyl)urea, with the latter giving better product yield. Using the urea compound, addition of potassium hydroxide yields the desired product with hexamethyldisiloxane as a side product; typical preparations reportedly contain 61% and 17% of each, respectively. The reaction can occur at room temperature or below and in various organic solvents (e.g., benzene, decalin, and carbon tetrachloride) or neat. Aoyama and Shiori (1981) described a similar method, but treated chloromethyltrimethylsilane with potassium cyanate followed by ammonia to produce the urea compound. The resulting urea was then treated using the method described above to produce TMSD.

In another method, chloromethyltrimethylsilane is reacted with magnesium to produce trimethylsilylmethylmagnesium chloride. This compound is then reacted with diphenyl phosphorazidate and cold water to yield TMSD (Shiori et al., 1990, 1993).

4.0 Production and Import Volumes

No data were located.

5.0 Uses

TMSD is commonly used for the derivatization of carboxylic acid groups to give methyl esters. For example, an organic acid in dimethyl sulfoxide-methanol mixture was converted to its

methyl ester by treating with trimethylsilyldiazomethane for one hour at room temperature followed by quenching of the reaction by acetic acid. In a similar methylation, the reaction was conducted under nitrogen (Burana-osot et al., 2010; Fukuzumi et al., 2010).

In 1994, TMSD was approved for use as an alternative derivatizing agent for analytical methods previously approved by the U.S. Environmental Protection Agency for several regulated contaminants in drinking water (specifically, Methods 515.1 and 515.2) with one exception. TMSD cannot be used as such for the analysis of dalapon (U.S. EPA, 1994).

6.0 Environmental Occurrence and Persistence

No data were located.

7.0 Human Exposure

Exposure is likely to occur through dermal and inhalation routes. There is potential for occupational exposure to those individuals working in a chemical laboratory setting. Two deaths have been associated with exposure to TMSD (see Section 9.1.1).

8.0 Regulatory Status

Exposure limits have not been established for TMSD. No U.S. regulations were located. Additionally, it is not specified on the Canadian Domestic Substances List or the Non-Domestic Substances List.

9.0 Toxicological Data

9.1 General Toxicology

TMSD is reported to be a skin irritant, harmful via skin absorption as well as ingestion. A solution (in diethyl ether) targets the kidney, liver, lungs, gastrointestinal tract, skeletal muscles, and the central nervous, respiratory, and reproductive systems (Sigma-Aldrich, 2011a). TMSD solution (in hexane) targets the kidney, lungs, testes, and the peripheral, respiratory, and reproductive systems (Sigma-Aldrich, 2011b,c).

9.1.1 Human Data

TMSD in hexane solution is identified as a suspected human reproductive toxicant (Sigma-Aldrich, 2011c).

Two reports have linked TMSD exposure to death. In one case report, a male pharmaceutical chemist used TMSD as part of a chemical analysis. Eight hours after exposure, he developed "cough, pleuritic chest pain, hemoptysis, and progressive shortness of breath." By 15 hours post-exposure, he was in respiratory distress and was hypoxic, hypercarbic, and acidemic. Within 26 hours post-exposure, he required intubation and developed bradycardia, refractory hypotension, and asystole. Acute lung injury [no further detail was provided] was noted on a chest radiograph. The individual died and it was proposed that there was a causal relationship between exposure to TMSD and the observed lung effects. It was proposed that the effects observed could have been due to the presence of diazomethane in the TMSD; direct effect of TMSD, a metabolite, or degradation product; or intracellular formaldehyde formation (Murphy et al., 2009 abstr.).

Another report described a male chemist that was synthesizing TMSD in 2008. The individual spilled a flask containing the synthesizing solution onto himself. He cleaned the spill using gloves and safety glasses. Prior to the end of the day, he reported having shortness of breath. The individual developed progressive respiratory distress and died ~15 hours after spilling TMSD on himself (Yee and De Perio, undated).

9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics
No data were located.

9.1.3 Acute Exposure
The dermal LD_{50} reported in rats is >2000 mg/kg (Sigma-Aldrich, 2011a,c). In rabbits, the dermal acute toxicity value is >1000 mg/kg (Sigma-Aldrich, 2011b).

9.1.4 Short-Term and Subchronic Exposure
No data were located.

9.1.5 Chronic Exposure
No data were located.

9.1.6 Synergistic/Antagonistic Effects
No data were located.

9.1.7 Cytotoxicity
No data were located.

9.2 Reproductive and Teratological Effects
No data were located.

9.3 Carcinogenicity
No data were located.

9.4 Initiation/Promotion Studies
No data were located.

9.5 Genotoxicity
A personal communication cited in Aoyama and Shiori (1981) stated that TMSD was nonmutagenic to *Salmonella* TA100.

9.6 Cogenotoxicity
No data were located.

9.7 Immunotoxicity
No data were located.

9.8 Other Data

The following hazard notice was in the description of a synthetic method: "TMS-diazomethane should be regarded as having similar toxicity to diazomethane and must be handled with all precautions appropriate for work with highly toxic substances" (Shiori et al., 1990, 1993).

A hazard analysis was conducted using methods described by U.S. DOD (2000) and Mohr (2002) which compared the use of counter measures (e.g., working in a hood and using goggles) on hazard risk for TMSD. The risk of personal injury after explosion, spill, or exposure in the absence of counter measures was identified as "Critical. Permanent partial disability." or "Marginal. Lost-time injury or illness." The frequency classification, the probability that a mishap would occur, was identified as occasional to probable. In most cases, application of counter measures reduced the severity or the frequency of the risk of personal injury (van 't Erve et al., 2010).

10.0 Structure-Activity Relationships

10.1 Structurally Similar Chemical

Diazomethane [CAS No. 334-88-3; PubChem CID: 9550]

Diazomethane is highly flammable and gas/air mixtures are explosive (NIOSH, 2009). Inhalation has been associated with numerous adverse effects including pulmonary and eye irritation, dizziness, headaches, denudation of mucous membranes, asthmatic symptoms, tremors, cyanosis, chest pains, and death (HSDB, 2005). Exposure has also been associated with a flushed skin, pulmonary edema, delayed inflammatory reaction, hepatic enlargement, and hemolysis (HSDB, 2005; OSHA, 2006). While the American Conference of Industrial Hygienists has classified diazomethane as a suspected human carcinogen, the International Agency for Research on Cancer has stated that the agent is not classifiable (HSDB, 2005; IARC, 1998). Acute exposure studies in rabbits showed that exposure to atmospheres containing 2-12 mg/L diazomethane for ≤20 minutes, one to four times, induced bronchopheumonia followed by death before 7 days. Several studies have shown that mice and rats exposed to diazomethane developed tumors (e.g., squamous cell carcinoma, spindle cell sarcoma, and pulmonary adenoma); however, no controls were used in these studies. Studies in *Escherichia coli* showed that diazomethane produced lethal and mutagenic effects (HSDB, 2005).

10.2 GeneGo

For each GeneGo quantitative structure-activity relationship (QSAR) model, a QSAR value was calculated. For non-binary models, the calculated values ranged between two threshold values to be classified as active in the model. These threshold values corresponded to the negative logarithm of the activity for the most active compound in the training set and the negative logarithm of 50 µM (-1.7). For binary models (e.g., AMES mutagenicity binary model), the definition of an active chemical is model dependent. In addition to the QSAR value, a Tanimoto similarity percentage (TP) was calculated which indicates the percentage of similarity of TMSD to the most similar compound in the training set. A summary of the results is provided below.

Due to the limited structural similarity to any of the chemicals in the training sets (TP values were ≤25%), no potential targets were identified. While some toxic and therapeutic effects were predicted, the TP values were also ≤25.00.

ADME QSARs for TMSD

No potential metabolites were predicted using the model. One model predicted that TMSD would be metabolized by CYP2B6, however this prediction was based on low structural similarity (TP = 11.54). The remaining CYP model results and additional ADME QSAR models results were also based on low TP values (≤15.00).

Protein Binding QSAR for TMSD

While some protein binding effects were predicted (e.g., androgen receptor ligand), all the models indicated that TMSD had low structural similarity to the chemicals present in the training sets.

Therapeutic Activity QSARs for TMSD

While some therapeutic effects were predicted (e.g., anti-allergy effects), all the models indicated that TMSD had low structural similarity to the chemicals present in the training sets.

Toxic Effects QSARs for TMSD

While several toxic effects were predicted (e.g., cardiotoxicity), all the models indicated that TMSD had low structural similarity to the chemicals present in the training sets.

Possible Targets for TMSD

Due to the lack of structurally similar chemicals in the training sets, no possible targets for TMSD were identified.

10.3 Leadscope

For each Leadscope model suite evaluated, a positive prediction probability (ranging from 0-1) was calculated. Values ≥0.5 were defined as positive. If the test compound was not at least 30% similar to one in the training set and at least one model feature was not in the test compounds, the chemical was defined as "not in the domain" and prediction probability was not determined. TMSD was not in the domain for any of the models evaluated.

Genetic Toxicity

The 29 genetic toxicity models in Leadscope encompass predictions for mutagenicity (13), DNA damage (3), *in vivo* clastogenicity (5), and *in vitro* clastogenicity (8). Sensitivity and specificity of the models range from 6.67% to 96% and 38.7% to 96.8%, respectively. TMSD was defined as not in domain for all of the models.

Neurotoxicity

The neurotoxicity models in Leadscope encompass predictions for newborn rat, rodent, and mouse behavior; sub-models represent optimized active/inactive chemicals. Sensitivity and specificity of the models range from 43.2% to 78.4% and 86.4% to 91.4%, respectively. TMSD was defined as not in domain for all of the models.

Reproductive and Developmental Toxicity

The developmental toxicity models in Leadscope encompass predictions for structural dysmorphogenesis, visceral organ toxicity, fetal survival, and fetal growth. The reproductive toxicity models encompass predictions for toxicity in male and female rats, mice, and rodents. Sub-models in the reproductive and developmental toxicity evaluations represent optimized active/inactive chemical ratios. Sensitivity and specificity of the reproductive models range from 35.4% to 63.8% and 83.9% to 96.5%, respectively. Sensitivity and specificity of the developmental toxicity models range from 22.1% to 57.4% and 84.4% to 95.3%. TMSD was defined as not in domain for all of the models.

Carcinogenicity

TMSD was evaluated in two sets of carcinogenicity endpoint models; seven are rodent models based on the two-year rodent bioassays and four are cell transformation *in vitro* assay models. The sensitivity and specificity of the rodent models range from 32.5% to 44.7% and 90.2% to 95.1%, respectively. The sensitivity and specificity of the *in vitro* models range from 87.8% to 93.9% and 22.5% to 55.8%, respectively. TMSD was defined as not in domain for all of the models.

Human Adverse Effects

Adverse cardiological, hepatobiliary, and urinary tract effects were evaluated in 24 models.

Thirteen models predicted cardiac endpoints, including: conduction disorders, coronary artery disorders, myocardial infarct disorders, palpitations, and rate rhythm disorders. The sensitivity and specificity of the models range from 32.1% to 65.7% and 85.8% to 93.6%, respectively. TMSD was defined as not in domain for all of the models.

Five models predicted hepatobiliary endpoints, including: bile duct, gall bladder, liver jaundice, liver acute damage, and liver enzyme release. The sensitivity and specificity of the models range from 23.9% to 51.7% and 91.4% to 97.9%, respectively. TMSD was defined as not in domain for all of the models.

Six models predicted urinary endpoints, including: bladder, blood in urine, kidney, kidney function tests, nephropathy, and urolithiasis. The sensitivity and specificity of the models range from 34.5% to 55.8% and 89.2% to 96.5%, respectively. TMSD was defined as not in domain for all of the models.

11.0 Online Databases and Secondary References Searched

11.1 Online Databases

National Library of Medicine Databases

PubMed

ChemIDplus – chemical information database that provides links to other databases such as CCRIS, DART, GENE-TOX, HSDB, IRIS, and TRI. A full list of databases and resources searched are available at http://www.nlm.nih.gov/databases/.

STN International Files

AGRICOLA	EMBASE	IPA
BIOSIS	FROSTI	MEDLINE
CABA	FSTA	TOXCENTER

Information on the content, sources, file data, and producer of each of the searched STN International Files is available at http://www.cas.org/support/stngen/dbss/index.html.

Government Printing Office
Code of Federal Regulations (CFR)

11.2 Secondary References

None used.

12.0 References

Aoyama, T., and Shioiri, T. 1981. New methods and reagents in organic synthesis. 17. Trimethylsilyldiazomethane ($TMSCHN_2$) as a stable and safe substitute for hazardous diazomethane. Its application in the Arndt-Eistert synthesis. Chem Pharm Bull, 21(11):3249-3255.

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address: http://monographs.iarc.fr/ENG/Monographs/vol7/volume7.pdf. Last updated on March 19, 1998. Last accessed on July 25, 2011.

Mohr, R. 2002. Preliminary Hazard Analysis, 5th ed. Cited by van 't Erve et al. (2010).

Murphy, N.G., Varney, S.M., Tallon, J.M., Thompson, J.R., and Blanc, P.D. 2009 abstr. Fatal occupational exposure to trimethylsilyldiazomethane. Abstract No. 48. 2009 North American Congress of Clinical Toxicology Annual Meeting, September 21-26, 2009, San Antonio, TX, USA. Clin Toxicol, 47(7):712. Internet address: http://informahealthcare.com/doi/pdf/10.1080/15563650903076924. Last accessed on February 28, 2011.

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OSHA (Occupational Safety and Health Adminsitration). 2006. Diazomethane. Record last revised on December 1, 1998. Internet address: http://www.osha.gov/dts/chemicalsampling/data/CH_231900.html. Page last updated on June 1, 2006. Last accessed on July 25, 2011.

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- Trimethylsilyldiazomethane: http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=167693
- Diazomethane: http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=9550

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None used.

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Appendix A: Units and Abbreviations

ºC = degrees Celsius
CID = chemical identification
g/cm^3 = gram(s) per cubic centimeter
M = molar
mg/kg = milligram(s) per kilogram
mm Hg= millimeter(s) of mercury
OSHA = Occupational Safety and Health Administration
QSAR = quantitative structure-activity relationship
TMSD = trimethylsilyldiazomethane
U.S. DOD = United Dtates Department of Defense
TP = Tanimoto similarity percentage

Appendix B: Description of Search Strategy and Results

February 2011

A February 2011 search of PubMed and Google Scholar for trimethylsilyldiazomethane OR "trimethylsilyl diazomethane" did not find any toxicity studies although a few studies were found that indicated that the compound is "safe and stable" and fewer stated that it had lower toxicity than diazomethane. All of the latter types of studies were examined and the particular references cited were also retrieved and reviewed.

The compound's synonyms were combined with types of toxicity or with the names of common laboratory animals or Salmonella in Google Scholar searches without finding any studies on its physiological activities. The copious results were usually about its use to derivatize the particular toxic substance or its metabolites.

On February 22, 2011, the CASRN for TMSD was linked with the CAPLUS role ADV for adverse effects, but no relevant records were retrieved. A Registry search was also conducted on the same day. Additional fee-based searches were not attempted at this time due to the expected volume of nonpertinent retrievals.

Since Google searches had found reports of two fatalities ascribed to the compound, death was used as a keyword in a Google Scholar search. An abstract describing the clinical signs of the latest fatality preceding his death was found in the results.

July 2011

STN International files MEDLINE, CABA, AGRICOLA, IPA, BIOSIS, TOXCENTER, FSTA, FROSTI, and EMBASE were searched simultaneously on July 22, 2011. The history of the online session is reproduced below.

```
L1          428 S 18107-18-1
L2          607 S TRIMETHYLSILYLDIAZOMETHANE OR (TRIMETHYLSILYL (A)
                DIAZOMETHANE)
L3            2 S DIAZO(A)(TRIMETHYLSILYL)(A)METHANE OR (DIAZOMETHYLTRIMETHYL
                (A) SILANE)
L4           48 S TMSD
L5          754 S L1-L4
                SET DUPORDER FILE
L6          525 DUP REMOVE L5 (229 DUPLICATES REMOVED)
L7           45 S L6 AND (?TOXIC? OR GENOTOXIC? OR NEUOROTOXIC? OR
                CYTOTOXIC?)
L8           10 S L6 AND (SALMONELLA OR MUTAT? OR DNA OR SISTER(W)CHROMATID
                OR CHROMOSOM?)
L9           38 S L6 AND (SENSITI? OR ALLERGEN? OR IRRITAT? OR CHEMOSENSORY
                OR DERMAL OR SKIN)
L10          34 S L6 AND (DERMAL? OR EXPOSURE OR PERSONAL OR TISSUE? OR
                URIN?)
L11           0 S L6 AND INDOOR(W)(AIR OR ENVIRONMENT?)
L12         133 S L6 AND (HUMAN OR MICE OR MOUSE OR RAT? OR HAMSTER? OR
                (GUINEA AND PIG?) OR WORKER? OR CHILDREN OR VOLUNTEER?)
L13          57 S L6 AND (PERMEAT? OR PERMEAB? OR PERCUTANEOUS? OR BLOOD OR
                SERUM OR PLASMA)
L14          54 S L6 AND (TOXICOKINETIC? OR PHARMACOKINETIC? OR HALF(W) LIFE
                OR METAB?)
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L15          37 S L6 AND (BREATH OR EXHAL? OR EXPIR? OR RESPIRATORY OR LUNG
                OR LUNGS OR PULMONARY OR INHAL? OR AIRWAY? OR NASO? OR
                NASAL?)
L16          34 S L6 AND (CELLULAR? OR SYMPTOM? OR ENZYM? OR CYTOCHROME OR
                P450 OR P(W)450)
L17           4 S L6 AND (DEATH OR DIED)
L18         256 S L7-L17
L19         128 S L18 NOT PATENT/DT
L20         267 S L6 NOT PATENT/DT
L21         267 SORT L20 1-267 TI
                SAVE L21 X0810TMSDM/A
```

Eight records were retrieved from answer set L20; the number of records per database were MEDLINE, 1; BIOSIS, 2; TOXCENTER, 2; and EMBASE, 3.

PubMed searches were done using the name and CASRN. An RTECS search was also conducted, but the chemical was not present in the database.