

NATIONAL TOXICOLOGY PROGRAM
EXECUTIVE SUMMARY OF SAFETY AND TOXICITY INFORMATION

HEXAMETHYLDISILAZANE

CAS Number 999-97-3

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Submitted to:

NATIONAL TOXICOLOGY PROGRAM

Submitted by:

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I. NOMINATION HISTORY AND REVIEW

Overview¹

Nomination History: *Hexamethyldisilazane (HMDS) was nominated by a private individual for dermal absorption and dermal and inhalation chronic and reproductive studies. The nomination was based on the widespread use of this compound throughout the semiconductor industry, the limited amount of toxicological and industrial exposure data available, and the absence of a threshold limit value. The nomination was supported by the National Cancer Institute and by another private individual.*

Chemical and Physical Properties: *Hexamethyldisilazane is a clear flammable liquid with an ammonia like odor. It has a boiling point of 124.0-127.0°C (255.2-260.6°F). Hexamethyldisilazane is reactive with water, alcohols, and protic solvents, and is incompatible with strong oxidizers and strong acids.*

Production/Uses/Exposure: *Hexamethyldisilazane is widely used as a silylating agent and is referred to as the "work horse" of the photoresist industry. This compound has a number of laboratory applications including the analytical determination of carbohydrates and acids, preparation of tissues for scanning electron microscopy, and derivation of mephentermine, mexiletine, and 2,4-dichlorophenoxy acetic acid. In addition, hexamethyldisilazane is used medicinally as an intermediate in the production of antibodies and anticancer drugs. In 1977, the EPA TSCA Inventory reported a production volume of 120,000-1,201,000 pounds of hexamethyldisilazane by 4 manufacturers. The Silicones Health Council (SHC) reported a production estimate of 300,000 -900,000 pounds of hexamethyldisilazane (by SHC members only) on a current annual basis. There are no data available on consumer exposure to hexamethyldisilazane. Data from the National Occupational Exposure Survey (NOES), which was conducted by NIOSH between 1981 and 1983, estimate that 30,905 workers including 4,222 females were potentially exposed to hexamethyldisilazane. OSHA has not established a permissible exposure limit, ACGIH has not recommended a threshold limit value, and NIOSH has not recommended an exposure limit for hexamethyldisilazane. Petrarch Systems, Incorporated has recommended a TLV for hexamethyldisilazane of 25 ppm (based on ammonia). The Russian maximum permissible exposure limit (MPEL) for hexamethyldisilazane is 25 ppm.*

¹The information contained in this executive summary of safety and toxicity information is based on data from current published literature. The summary represents information provided in selected sources and is not claimed to be exhaustive.

Toxicological Effects:

Human: *No data were found on the toxicological effects of hexamethyldisilazane in humans.*

Animal: *Acute toxicity values for hexamethyldisilazane were reported, including a peroral LD₅₀ of 850 mg/kg and an inhalation LC₅₀ of 8700 mg/m³ in rats. In addition, hexamethyldisilazane was reported to be extremely irritating to the skin and slightly irritating to the eye of an unspecified species. In rats and mice, various routes of administration including peroral, intraperitoneal, and inhalation of hexamethyldisilazane resulted in elevated silicon blood levels. Peak silicon levels occurred within the first few hours following administration and were evenly*

distributed between the blood and fatty tissue. However, silicon gradually accumulated to higher levels in the fat. Silicon was not detected in the urine of test animals. The elimination of hexamethyldisilazane was found to occur primarily via the gastrointestinal tract, and partially through the lungs. Hexamethyl disiloxane was identified as a metabolite of hexamethyldisilazane. Behavioral indications of hexamethyldisilazane toxicity including narcosis, depressed respiration, bradycardia, and areflexia were observed in rats and rabbits following injection into the stomach, abdominal cavity, and upon inhalation. Death occurred in an unspecified number of animals. In rats, inhalation of hexamethyldisilazane at a concentration of 110 mg/m³ (designated as the threshold concentration) caused a decrease in the excitability of the nervous system. Hexamethyldisilazane was not found to be a sensitizer in guinea pigs or rats. Histological changes including cellular desquamation of the bronchial epithelium and vacuolar dystrophic changes in the liver were observed in rats following chronic (4-month study) exposure to hexamethyldisilazane. In addition, slight dystrophic processes in the cerebral cortex, visual tuber, and medulla oblongata were observed in rats after 4 months of exposure to hexamethyldisilazane. Hexamethyldisilazane was found to be inactive in the strain A mouse lung adenoma assay.

Genetic Toxicology: *In an unpublished study, hexamethyldisilazane was reportedly non-mutagenic in the bacterial reverse mutation assay. No other information was provided.*

Structure Activity Considerations: *The authors of a strain A mouse lung adenoma study of 10 silylating agents, including hexamethyldisilazane, suggested that compounds like hexamethyldisilazane, in which the trimethylsilyl group is attached only to an amide or amino group, are inactive in the strain A mouse lung adenoma assay.*

Nomination History and Review

A. Nomination History

1. Source: Private individual [Kiefer, 1987] - the nomination was supported by the NCI [NCI, 1990a], and by another private individual [Stewart, 1990]

2. Date: FY 1988

3. Recommendations:

Dermal absorption studies

Dermal and inhalation chronic and reproductive studies

4. Priority: --

5. Rationale/Remarks:

Widespread use throughout the semiconductor industry

Limited toxicological data available

No established threshold limit value

Limited data available on industrial exposure

B. Chemical Evaluation Committee Review

1. Date of Review: March 13, 1991

2. Recommendations:

Reproductive effects

Carcinogenicity

3. Priority: High

4. NTP Chemical Selection Principles: 3,8

5. Rationale/Remarks:

Widespread use in electronics industry

Potential for high occupational exposure

Important member of organosilicon chemical class

Limited toxicology data available

Chemical will be difficult to test because it is an irritant, and is expected to decompose in moist air

Route of administration should be selected by NTP toxicology design review group

C. Board of Scientific Counselors Review

1. Date of Review:

2. Recommendations:

3. Priority:

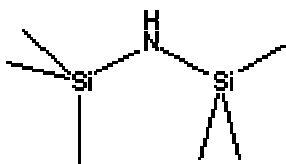
4. Rationale/Remarks:

D. Executive Committee Review

1. Date of Review:

2. Decision:

A. Chemical Identifiers



HEXAMETHYLDISILAZANE

Molecular formula: $C_6H_{19}NSi_2$ Molecular weight: **161.44**

CAS No. 999-97-3

RTECS No. JM9230000

B. Synonyms and Trade Names

Synonyms: silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)- (9CI); disilazane, 1,1,1,3,3,3-hexamethyl-(8CI); bis(trimethyl-silyl)amine; hexamethylsilazane; 1,1,1-trimethyl-N-(trimethylsilyl)silanamine

Trade Names: Hexamethyldisilazane Puranal®

C. Chemical and Physical Properties

Description: Clear colorless liquid [Lenga, 1988] with an ammonia-like odor [Petrarch Systems, Inc., 1981b; Turzhova *et al.*, 1986]

Melting Point: No data were found

Boiling Point: 125.0°C (257.0°F) [Lancaster Synthesis, 1989-1990; Dow Corning Corporation, unspecified date; Aldrich, 1990; Lenga, 1988; Petrarch Systems Inc., 1981b]

124.0-127.0°C (255.2-260.6°F) [Fluka, unspecified date]

126.2°C (259.2°F) [Weast, 1988-1989]

Specific

Gravity: 0.77 @ 25°C (77°F) [Dow Corning Corporation, unspecified date; Petrarch Systems, Inc., 1981b; Weast, 1988-1989]

0.774 @ 20°C [Fluka, unspecified date]

0.765 [Aldrich, 1990; Lenga, 1988]

Refractive Index: 1.405 @ 25°C [Dow Corning Corporation, unspecified date]

1.4070 @ 20°C [Aldrich, 1990]

1.4071 @ 20°C [Lenga, 1988]

1.408 @ 20°C [Petrarch Systems, Inc., unspecified date, a; Fluka, unspecified date]

1.4090 @ 20°C [Weast, 1988-1989]

Solubility in

Water: Insoluble [Dow Corning Corporation, unspecified date; Petrarch Systems, Inc., 1981b; Turzhova *et al.*, 1986]

Solubility in

other Solvents: Soluble in acetone, ethyl ether, benzene, heptane, and slightly soluble in perchloroethylene [Dow Corning Corporation, unspecified date]; soluble in inert organic solvents [Turzhova *et al.*, 1986]

Log Octanol/Water

Partition Coefficient: No data were found

Reactive Chemical

Hazards: Slowly reacts with water [Lancaster Synthesis, 1989-1990; Dow Corning Corporation, unspecified date; Lenga, 1988; Petrarch Systems, Inc., 1981b] and is hydrolyzed to ammonia and siloxanes [SHC, 1990]; methyl alcohol [Dow Corning Corporation, unspecified date], alcohol and protic solvents [Petrarch Systems, Inc., 1981b]. Incompatible with strong oxidizing agents and strong acids [Lenga, 1988; Petrarch Systems, Inc., 1981b]. Decomposition products include nitrogen products [Sax and Lewis, 1989], silicon dioxide, carbon dioxide, and traces of completely burned carbon products [Petrarch Systems, Inc., 1981b]. Corrosive [Aldrich, 1990].

Flammability

Hazards: Flammable liquid [Lancaster Synthesis, 1989-1990; Aldrich, 1990; Lenga, 1988; Petrarch Systems, Inc., unspecified date, a, 1981b]

Flash Point: 27°C (81°F) CC [Petrarch Systems, Inc., 1981b]

25°C (77°F) [Dow Corning Corporation, unspecified date]

8°C (48°F) CC [Aldrich, 1990; Lenga, 1988]

Flammability Limits in Air (% by volume at 121°C): 0.8-16.3% [Petrarch Systems, Inc., 1981b]

Vapor Pressure: 79 mm Hg @ 50°C [Petrarch Systems Inc., 1981b]; 7.84 mm Hg @ 20°C [Turzhova *et al.*, 1986]

III. EXPOSURE INFORMATION

A. Production

1. Manufacturing Process

The following synthetic processes yield hexamethyldisilazane:

(alpha-Chlorobenzyl)trimethylsilane treated with sodium amide in liquid ammonia [Fessenden and Fessenden, 1961]

Trimethylsilyl sulfate treated with ammonia [Fessenden and Fessenden, 1961]

Hexamethylcyclotrisilazane heated in a sealed tube with ammonium chloride [Fessenden and Fessenden, 1961]

2. Producers and Importers	
U.S. Producers:	Reference
Anderson Development Company Adrian, Michigan	Chemical Week Buyer's Guide, 1989
Chemical Dynamics Corporation South Plainfield, New Jersey	Chemical Week Buyer's Guide, 1989; SRI, 1990a
Confederated Specialty Associates, Incorporated Jacksonville, Florida	Chemical Week Buyer's Guide, 1989
Dow Corning Corporation Midland, Michigan	Chemical Week Buyer's Guide, 1989; USEPA, 1990
Dynamic Nobel Chemical Company Rockland, New Jersey	USITC, 1986
Farchan Laboratories, Incorporated Gainesville, Florida	Chemical Week Buyer's Guide, 1989
Far Research, Incorporated Palm Bay, Melbourne, Florida	SRI, 1990a Chemical Week Buyer's Guide, 1989
General Electric Company, Silicone Products Department Waterford, New York	Chemical Week Buyer's Guide, 1989
Glidco Organics Jacksonville, Florida	USITC, 1989

Huls America, Incorporated, Chemical Division Theodore, Alabama	Chemical Week Buyer's Guide, 1989; SRI, 1990a; USITC, 1989
JC Schumacher Company Carlsbad, California	Chemical Week Buyer's Guide, 1989
PCR, Incorporated, Gainesville, Florida	Chemical Week Buyer's Guide, 1989; USEPA, 1990; SRI, 1990a; USITC, 1989
Petrarch Systems, Incorporated, Bristoll, Pennsylvania Cornwells Heights, Pennsylvania	Chemical Week Buyer's Guide, 1989 USEPA, 1990
Pierce Chemical Company Rockford, Illinois	SRI, 1990a
The Proctor & Gamble Company Richardson-Vicks, Incorporated (subsidiary) Shelton, Connecticut J.T. Baker, Incorporated (subsidiary) MOS/Electronic Chemicals Phillipsburg, New Jersey	SRI, 1990a
Union Carbide Corporation Union Carbide Chemicals and Plastics Company, Incorporated (subsidiary) Specialty Chemicals Division Sistersville, West Virginia	SRI, 1990a
<u>European Producers:</u>	<u>Reference</u>
Chemische Fabrik Karl Bucher Waldstetten (Bayern), Germany	SRI, 1990b
Hüls Aktiengesellschaft Rheinfelden (Baden-Württemberg), Germany	SRI, 1990b
Reliance Silicones India Pvt. Ltd. India	American Chemical Society, 1986
<u>Importers:</u>	<u>Reference</u>
J.E. Halma Company, Incorporated Lodi, New Jersey	USEPA, 1990

Mobay Chemical Company Pittsburgh, Pennsylvania	USEPA, 1990
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3. Volume

Hexamethyldisilazane is listed in the United States International Trade Commission's publication Synthetic Organic Chemicals for the years 1985-1988. However, no production information was provided¹[USITC, 1986-1989].

In the public file of the EPA TSCA inventory 5 companies were listed as manufacturers of hexamethyldisilazane. It was reported that 120,000-1,201,000 pounds of hexamethyldisilazane was produced in 1977 by 4 manufacturers. One manufacturer produced an unspecified volume of this compound [USEPA, 1990]. No import data were found in the public file of the EPA TSCA inventory.

The Silicones Health Council (SHC) reported a production estimate of 300,000-900,000 pounds of hexamethyldisilazane (by SHC members only) on a current annual basis [SHC, 1990].

Two companies were listed as importers of hexamethyldisilazane in the EPA TSCA inventory. However, no import data were provided [USEPA, 1990].

4. Technical Product Composition

Hexamethyldisilazane is available in grades of purity ranging from 96% - 99.9% [Lancaster Synthesis, 1989-1990; Aldrich, 1990; Petrarch Systems, Inc., unspecified date, a, 1981b; Lenga, 1988; Dow Corning Corporation, Inc., unspecified date; Fluka, unspecified date].

¹Production statistics for an individual chemical are given only when there are three or more producers, no one or two of which may be predominant. Moreover, even when there are three or more producers, statistics are not given if there is any possibility that their publication would violate the statutory provisions relating to unlawful disclosure of information accepted in confidence by the Commission. Data are reported by producers for only those items where the volume of production or sales or value of sales exceeds certain minimums. Those minimums for all sections are 5,000 pounds of production or sales with the following exceptions: plastics and resin materials-50,000 pounds; pigments, medicinal chemicals, flavor and perfume materials, and rubber processing chemicals-1,000 pounds.

B. Use

Manufacturing Uses:

Coupling agent or adhesion promotor for photoresists [Mittal, 1979; PCR, unspecified date; PSI, unspecified date, Kirk-Othmer, 1982]

Coupling agent for the production of hydrophobic, fumed silica including silicones, coatings, powder, specialty resins, and insulation coatings for moisture sensitive compounds [Adhesives Age, 1990; Kirk-Othmer, 1982]

Coupling agent for semiconductor photolithographic processes as primary agent to enhance photoresist adhesion [Petrarch Systems, Inc., 1981b; Kirk-Othmer, 1982]

Synthesis of methyl isocyanate [Turzhova *et al.*, 1985]

Preparation of ceramic fibers [Engineered Materials, 1990]

Medicinal Uses:

Manufacture of antibodies [Chemical Weekly, 1986]

Synthesis of antineoplastic preparation (fluorofur) [Turzhova *et al.*, 1985]

Synthesis of antisclerotic preparation (parmidine) [Turzhova *et al.*, 1985]

Analytical and Biological Reagent Laboratory Uses:

Analytical determination of carbohydrates [Stabel, 1977]; separation of mannose, galactose, and glucose by gas chromatography [Al-Hazmi *et al.*, 1985]

Gas chromatographic determination of phenolic acids [Blakley, 1966]

Synthesis of liquid chromatography reversed phases of higher efficiency by initial partial deactivation of the silica surface [Marshall *et al.*, 1984]

Desiccant in tissue (retinal) fixation for scanning electron microscopy [Heegaard *et al.*, 1986] and implant specimens [Giammara *et al.*, 1987]

Preparation of soft insect tissues for scanning electron microscopy [Nation, 1983]

Preparation of cultured mammalian cells for scanning electron microscopy of osmium-impregnation and air-drying [Lee and Bell, 1989]

Derivation of mephentermine for identification and analysis of metabolic products [Beckett and Bélanger, 1975]

Derivation of mexiletine for identification and analysis of metabolic products [Beckett and Chidomere, 1977]

Trimethylsilyl derivatization of the metabolites of 2,4-dichloro-phenoxyacetic acid separation by gas chromatographic analysis [Arjmand and Mumma, 1976]

Determination of 4,4'-thiodiphenol in human and rat urine (as an indication of exposure to low levels of the pesticide Abate®) by gas chromatography [Shafik, 1970]

Silicon-selective detection after gas chromatography for the determination of silylated salicylic acid in urine [Osman and Hill, 1982]

Patented Uses:

Preparation of stable, even coatings of silicone lubricant in an atmosphere of a siloxane monomer [United States Patent, 1989]

Preparation of a gas monitoring wafer with a porous, hydrophobic membrane [United States Patent, 1988]

Reagent used in the preparation of hydrophilic siloxane dimers for making contact lenses [United States Patent, 1987]

Reduction of the halogen content of polysilanes and/or polycarbosilanes [Engineered Materials, 1990]

Process for making ceramic fibers containing silicon carbide [Engineered Materials, 1990]

EXPOSURE/REGULATORY STATUS

A. Consumer Exposure

There are no data available on consumer exposure to hexamethyldisilazane.

B. Occupational Exposure

Data from the National Occupational Exposure Survey (NOES) conducted by NIOSH between 1981 and 1983, indicate that 30,905 workers, including 4,222 female employees, were potentially exposed to hexamethyldisilazane in the workplace [NIOSH, 1990].

In an in-depth survey report of Microelectronics Center, Xerox Corporation, monitoring of the photolithographic operations found hexamethyldisilazane levels to be 468.5 $\mu\text{g}/\text{m}^3$ in the wafer track area, and 559.0 $\mu\text{g}/\text{m}^3$, 217.4 $\mu\text{g}/\text{m}^3$, and 74.3 $\mu\text{g}/\text{m}^3$ in 3 different areas of the photoresist application line. All other areas were found to be below the detection limit for hexamethyldisilazane [NIOSH, 1984].

C. Environmental Exposure

No data were found on environmental exposure to hexamethyldisilazane.

D. Regulatory Status

OSHA has not established a permissible exposure limit (PEL) for hexamethyldisilazane.

E. Exposure Recommendations

ACGIH has not recommended a threshold limit value (TLV) for hexamethyldisilazane.

NIOSH has not recommended an exposure limit (REL) for hexamethyldisilazane.

Petrarch Systems, Inc., has recommended a threshold limit value for hexamethyldisilazane of 25 ppm [Petrarch Systems, Inc., 1981b].

Russian scientists have recommended a maximal permissible concentration of 2 mg/m^3 for hexamethyldisilazane [Turzhova *et al.*, 1986].

The Russian maximum permissible exposure limit (MPEL) for hexamethyldisilazane in the industrial workplace is 25 ppm [NCI, 1990].

IV. TOXICOLOGICAL EFFECTS

A. Chemical Disposition

1. Human Data

No data were found on the chemical disposition of hexamethyldisilazane in humans.

2. Animal Data

The information in this section was obtained from English translations of two Russian studies [Turzhova *et al.*, 1985; Turzhova *et al.*, 1986].

peroral, intraperitoneal, inhalator, rats, rabbits In the first study [Turzhova *et al.*, 1985], 240 white rats and 30 rabbits (strain unspecified) were used. Hexamethyldisilazane was administered by three different routes: peroral, intraperitoneal, and inhalation. For both the oral and intraperitoneal studies, HMDS was administered at two doses, 850 mg and 1200 mg/g (LD₅₀ and LD₈₄, respectively). A concentration of 8700 mg/m³ (LC₅₀) was used for the inhalation route. The number and sex of animals employed in each exposure route was not specified.

Table 1 presents silicon levels found in the blood and fatty tissue of rats following administration of equimolar doses of hexamethyldisilazane, and hexamethyl disiloxane, which was identified as a metabolite of HMDS in rabbits (see below). The study of hexamethyl disiloxane was conducted in order to compare the content of the silicon compounds in the biomedica of the rats in both the hexamethyl disiloxane and hexamethyldisilazane studies. The authors did not specify the exact route of exposure. However, on the basis of the dose used for both compounds, the route of administration may be assumed to be either peroral and/or intraperitoneal.

Table 1. The Content of Silicon (in Micrograms Per Milliliter of Blood) in the Blood and in the Fatty Tissue Following Acute Hexamethyldisilazane (850 mg/kg) and Hexamethyl Disiloxane (850 mg/kg) Administration in Rats.

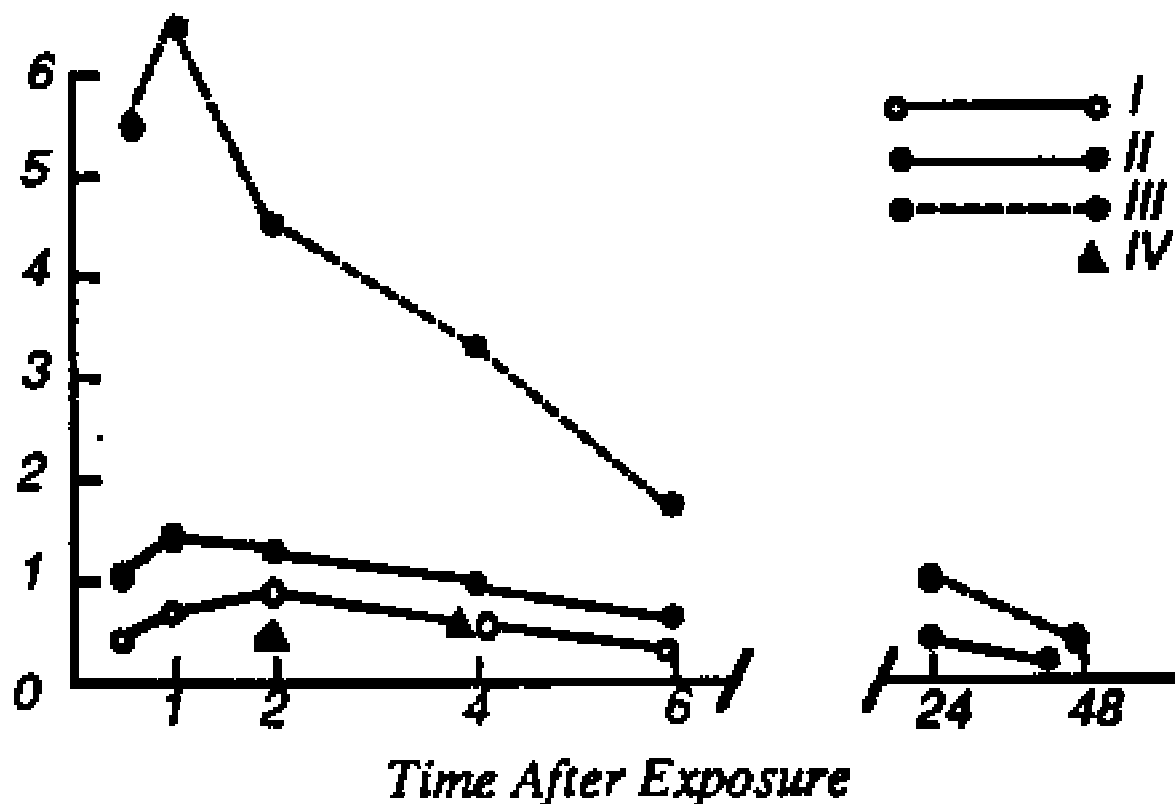
Time After Administration	Hexamethyldisilazane		Hexamethyl Disiloxane	
	Silicon Blood Levels (µg/ml)	Silicon Fatty Tissue Levels (µg/g)	Silicon Blood Levels (µg/ml)	Silicon Fatty Tissue Levels (µg/g)
1 hour	52.0 ± 14.7	195.6 ± 10.5	13.0 ± 1.2	288 ± 25.3
4 hours	47.8 ± 14.8	187 ± 15	16.2 ± 1.8	225 ± 18.5
1 day	35.8 ± 5.6	287 ± 30.5	13.3 ± 1.1	105 ± 10.3
3 days	31.7 ± 3.6	173 ± 16	12.0 ± 1.2	92 ± 9.8
7 days	38.8 ± 3.3	190 ± 18.1	20.5 ± 3.4	85 ± 8.7
11 days	32.4 ± 3.1	152 ± 12.3	16.1 ± 1.5	65 ± 7.3

14 days	18.7 ± 2.8	96 ± 10.6	15.4 ± 1.3	60 ± 5.6
20 days	17.1 ± 1.8	88 ± 8.7	10.2 ± 1.5	32 ± 2.5

In the hexamethyldisilazane study, silicon levels peaked in the blood within the first hour after exposure, and remained constant for 11 days. Initially, there was a uniform distribution of silicon compounds in the organs, and the level of silicon per gram of tissue did not exceed the level of silicon in the blood (microgram/ml of blood). However, the accumulation of silicon in the fatty tissues was eventually several times higher than that in the blood, and this was attributed to the biological affinity of silicon compounds to fats. Comparatively lower silicon levels were detected in the blood and fatty tissues of rats treated with hexamethyl disiloxane.

The levels of ammonia in the blood of rats following exposure to acute doses of hexamethyldisilazane is presented in Figure 1.

Figure 1. Levels of Ammonia (mg%) in the Blood of Rats Following Acute Hexamethyldisilazane Administration.



I. Administration of Hexamethyldisilazane via the intraperitoneal route (850 mg/kg)

II. Administration of Hexamethyldisilazane via the stomach (850 mg/kg)

III. Administration of Hexamethyldisilazane via the stomach (1200 mg/kg)

IV. Administration of Hexamethyldisilazane via inhalation (8700 mg/m³)

An increase in the level of ammonia was detected in the blood of rats in the 850 mg/kg and 1200 mg/kg hexamethyldisilazane groups. Maximum levels in the blood reached 1.7 - 1.9 mg% and 5.0 - 7.0 mg% at dose levels of 850 and 1200 mg/kg hexamethyldisilazane, respectively. The authors suggested that accumulation of ammonia in the blood of the animals in the high dosed group may be due to the profound narcotic state of the animals.

The levels of ammonia in the blood serum of animals exposed to 8700 mg/m³ hexamethyldisilazane by inhalation did not exceed 0.3 - 0.7 mg%. On the basis of these low levels, the authors assumed that hexamethyldisilazane underwent more intensive hydrolysis on the surface of the pulmonary tissue, which resulted in the discharge of ammonia, and the formation of silicon compounds. These silicon compounds lack an amino group, and would be expected to penetrate into the blood.

In rabbits, hexamethyl disiloxane was identified as a metabolite of hexamethyldisilazane by a thin layer chromatography method. Two hours after the peroral administration of 850 mg/kg hexamethyldisilazane, the content of hexamethyl disiloxane in the blood serum of rabbits was at least 50% of the total concentration of silicon compounds in the blood serum. At a combined concentration of silicon compounds and hexamethyldisilazane equal to 30.5 microgram of silicon per ml of blood, the quantity of excreted hexamethyl disiloxane was 12/5 micrograms of silicon per ml of blood.

The authors hypothesized that the elimination of hexamethyldisilazane in rats and rabbits occurs primarily through the gastrointestinal tract and partially via the lungs [Turzhova *et al.*, 1985].

peroral, intraperitoneal, rats, mice, rabbits In the second study [Turzhova *et al.*, 1986], a solution of hexamethyldisilazane in olive oil was administered perorally and intraperitoneally to groups of mice at a dose of 850 mg/kg, rats at 850 mg/kg, and rabbits at 1100 mg/kg. In addition, hexamethyldisilazane was administered by inhalation to mice at a dose of 12,000 mg/kg for 2 hours, and to male rats at a dose of 8,700 mg/kg for 4 hours. There were at least 12 animals in each treated group.

The authors reported that following administration (route of exposure unspecified), hexamethyldisilazane was metabolized to ammonia and silicon-containing metabolites, including hexamethyl disiloxane. The elimination of silicon-containing metabolites occurred via the lungs and partially through the gastrointestinal tract. Silicon metabolites were not detected in the urine. Blood concentrations of silicon-containing metabolites were stable 1 to 11 days after enteral injection of hexamethyldisilazane. Following enteral administration of hexamethyldisilazane, treated animals had 30 micrograms of silicon in 1 ml of blood compared to controls which had 10.5 micrograms of silicon in 1 ml of blood. The selective accumulation of

silicon-containing metabolites which occurred in fatty tissues created a depot from which water insoluble compounds were released into the blood. The authors did not indicate the sex of the animals used in these studies.

A group of at least 12 rats (strain and sex unspecified) were exposed by inhalation to hexamethyldisilazane at a concentration of 1,000 mg/m³ for 4 hours per day for 2 weeks. The silicon blood levels in rats subjected to repeated exposures was approximately twice that observed in rats exposed to a single dose. The silicon level in blood was 19.5 ± 1.5 microgram/ml after a single exposure, and 42.5 ± 3.4 microgram/ml during repeated exposures. Silicon levels in control rats were found to be 10 ± 2.3 microgram/ml [Turzhova *et al.*, 1986].

B. Acute

The SHC reported that hexamethyldisilazane is extremely irritating to the skin and slightly irritating to the eye (no species specified). An unpublished skin corrosiveness study reported that hexamethyldisilazane is corrosive in accordance with U.S. Department of Transportation criteria [SHC, 1990].

1. Human Data

No data were found on the acute toxicity of hexamethyldisilazane in humans.

2. Animal Data

Table 2 presents unpublished acute toxicity data for hexamethyl-disilazane reported in a letter to the National Cancer Institute, Chemical Selection Working Group from the Silicones Health Council as well as data reported by Turzhova *et al.*, 1985; 1986 which are described in greater detail in the text [SHC, 1990].

Table 2. Studies of Acute Toxicity For Hexamethyldisilazane

Route of Administration	Species/Strain	Number of Animals/Sex	Dose (LD ₅₀ or LC ₅₀)	Comments	References
Oral	NR/NR	NR/NR	813 ± 83 mg/kg	NR	SHC, 1990
Peroral	Rats/NR	NR/NR	850 mg/kg (740-930 mg/kg)	see text	Turzhova <i>et al.</i> , 1986
Peroral	Mice/NR	NR/NR	850 mg/kg (750-910 mg/kg)	see text	Turzhova <i>et al.</i> , 1986
Peroral	Rabbits/NR	NR/NR	1,100 mg/kg (850-1,300 mg/kg)	see text	Turzhova <i>et al.</i> , 1986
Inhalation	Rats/NR	NR/NR	8,700 mg/m ³ -4 hr (7,300-10,100 mg/m ³)	see text	Turzhova <i>et al.</i> , 1986

Inhalation	Mice/NR	NR/NR	12,000 mg/m ³ -2 hr (10,000-14,000 mg/m ³)	see text	Turzhova <i>et al.</i> , 1986
Inhalation	NR/NR	NR/NR	10.3 ± 6.3/3/39 mg/L	NR	SHC, 1990
Dermal	NR/NR	NR/NR	1,350 ± 158 mg/kg	NR	SHC, 1990

NR= Not Reported

The following acute toxicity studies were obtained from English translations of 2 Russian studies

stomach, intraperitoneal, inhalation, rats, rabbits Two hundred and forty white rats and 30 rabbits of unspecified strain and sex were exposed to 850 mg/kg (LD₅₀) and 1200 mg/kg (LD₈₄) of hexamethyl-disilazane in olive oil by injection into the stomach and abdominal cavity. In addition, an unspecified number of rats and rabbits were exposed to 8700 mg/m³ (LC₅₀) hexamethyldisilazane by inhalation for an unspecified duration. Behavioral indications of induced toxicity included narcosis, depressed respiration, bradycardia, and areflexia. The symptoms appeared within 5 minutes of administration of 850 mg/kg hexamethyldisilazane into the stomach, and after 20-30 minutes following inhalation exposure to 8700 mg/m³ hexamethyldisilazane. Narcosis lasted from 2-3 hours to 3-4 days, depending on the state of intoxication. Most of the animals died within the first few days following hexamethyldisilazane exposure, although the exact number of deaths was unspecified.

In rats, administration of 850 mg/kg hexamethyl disiloxane into the stomach did not induce narcosis. However, adverse effects which were observed included hypodynamia, flabbiness, and death in an unspecified number of test animals [Turzhova *et al.*, 1985].

peroral, intraperitoneal, inhalation, rats, mice, rabbits Two thousand white rats, 600 white mice, and 45 rabbits were divided into groups (n=12) of unspecified strain and sex and exposed to hexamethyldisilazane perorally or intraperitoneally (dissolved in olive oil), or by inhalation. Mice, rats, and rabbits received injections of 850 mg/kg, 850 mg/kg, and 1,100 mg/kg of hexamethyldisilazane, respectively (doses were equal to the LD₅₀ for hexamethyldisilazane in each species). Mice received 12,000 mg/m³ (LC₅₀) for 2 hours by inhalation and male rats received 8,700 mg/m³ hexamethyldisilazane for 4 hours by inhalation [Turzhova *et al.*, 1986].

inhalation, rats

In rats of unspecified strain and sex (n≥12) inhalation of 110 mg/m³ of hexamethyldisilazane (designated as the threshold concentration) for 4 hours caused a decrease in the excitability of the nervous system immediately following exposure. Significant increases (P< 0.05) in the duration of hexobarbital sleep time (15.0 ± 0.9 minutes) compared to the control value (12.2 ± 0.6 minutes) and in the summation-threshold index (P value not specified) were observed [Turzhova *et al.*, 1986].

dermal, eye, rabbits, guinea pigs Dermal application of an unspecified dose of hexamethyldisilazane to rabbits and guinea pigs of unspecified strain and sex (n≥12) did not cause adverse effects. Injection of hexamethyldisilazane into the conjunctival sac of the rabbit eye was also not found to cause adverse effects [Turzhova *et al.*, 1986].

dermal, mice Dermal absorption of hexamethyldisilazane was demonstrated by the immersion of 2/3 of a mouse tail in hexamethyldisilazane. Narcotic changes were observed in the tail within 1 hour [Turzhova *et al.*, 1986].

C. Prechronic

1. Human Data

No data were found on the prechronic effects of hexamethyldisilazane in humans.

2. Animal Data

The following prechronic animal data were obtained from an English translation of a Russian study .

stomach, rats Repeated doses of 1/5, 1/10, and 1/20 of the LD₅₀ (850 mg/kg) of hexamethyldisilazane injected into the stomach of rats of unspecified strain and sex (n=12) for 4 weeks did not cause death. No other data were provided [Turzhova *et al.*, 1986].

inhalation, rats In rats of unspecified strain and sex (n=12), inhalation of 1,000 mg/m³ hexamethyldisilazane 4 hours per day for 2 weeks did not cause death. No other data were provided [Turzhova *et al.*, 1986].

dermal, rats, guinea pigs Hexamethyldisilazane did not cause sensitization in rats and guinea pigs of unspecified strain and sex (n=12). No other data were provided [Turzhova *et al.*, 1986].

D. Chronic/Carcinogenicity

1. Human Data

No data were found on the chronic/carcinogenic effects of hexamethyl-disilazane in humans.

2. Animal Data

inhalation, rats Rats of unspecified strain and sex (n=80) were exposed to atmospheric concentrations of 2.3 ± 0.2 , 10.5 ± 0.6 , and 98.2 ± 3.3 mg/m³ hexa-methyldisilazane for 4 hours per day, 5 days per week, for 4 months.

The group exposed to 98.2 ± 3.3 mg/m³ hexamethyldisilazane experienced a change in the functional state of the nervous system as indicated by a significant decrease in the summation-threshold index of the nervous system after 2 weeks. Summation-threshold indices were $7.0 \pm 0.3V$ (control value = $8.9 \pm 0.6V$ {P value not reported}), $6.4 \pm 0.3V$ (control value = $8.3 \pm 0.3V$ {P<0.01}); and $6.4 \pm 0.3V$ (control value = $7.8 \pm 0.3V$ {P< 0.05}) after 2 weeks, 2 months, and 3 months, respectively.

The duration of hexobarbital sleep time increased after 2 and 3 months of exposure to hexamethyldisilazane. The duration was 13.2 ± 1.3 minutes (control value = 8.1 ± 0.6 minutes {P value not reported}) and 16.3 ± 0.6 minutes (control value unspecified {P<0.05}) after 2 and 3 months, respectively.

Histological changes observed included cellular desquamation of the epithelium of the bronchi and vacuolar dystrophic changes in the liver. In addition, slight dystrophic processes in the cerebral cortex, visual tuber, and medulla oblongata, and a slight increase in the functional activity of the kidney canals of rats after 4 months exposure were observed.

Hexamethyldisilazane at a concentration of 10.5 mg/m³ caused a significant decrease in the summation-threshold index of the nervous system among test groups. The index was determined to be 7.2 ± 0.4V (control value = 8.9 ± 0.6V {P < 0.05}) after 2 weeks. Compensatory-reparatory processes in the brain and liver were observed by histological analysis.

No notable adverse effects were observed in the 2.3 mg/m³ dosed group. In addition, 1 month after removal from exposure, the observed changes were completely normalized in the other dosed groups. However, a slight decrease in hexobarbital sleep time in the 98.2 mg/m³ hexamethyldisilazane dosed group was observed. The authors concluded that the threshold value for chronic exposure to hexamethyldisilazane vapors in rats was 10.5 mg/m³ [Turzhova *et al.*, 1986].

intraperitoneal, mice Stoner *et al.* conducted a study of ten silylating compounds, including hexamethyl-disilazane, in the strain A mouse lung adenoma assay. Groups of 20 A/He mice were injected intraperitoneally with a maximum tolerated dose (MTD), and a 1:2, and 1:5 dilution of the MTD. Hexamethyldisilazane dissolved in tricapylin was administered twice at 200, 500, or 1000 mg/kg. Three control groups received 2 intraperitoneal injections of tricapylin alone, a single intraperitoneal injection of 10 mg urethan/mouse (a known carcinogen), or no treatment. Twenty four weeks following the first injection, all animals were sacrificed, and the lungs were fixed. After 3-4 days, the milky-white nodules on the lungs were counted, and a few nodules were examined histologically to confirm the appearance of adenomas.

Data for hexamethyldisilazane dosed groups is presented in Table 3. No significant effects were observed. The authors reported that compounds like hexamethyldisilazane in which the trimethylsilyl group is attached only to an amide or amino nitrogen group are inactive in the strain A mouse lung adenoma assay [Stoner *et al.*, 1975].

Table 2 presents unpublished acute toxicity data for hexamethyl-disilazane reported in a letter to the National Cancer Institute, Chemical Selection Working Group from the Silicones Health Council as well as data reported by Turzhova *et al.*, 1985; 1986 which are described in greater detail in the text [SHC, 1990].

Table 3. Pulmonary Tumor Response of A/He Mice to Hexamethyldisilazane

Compound	Total dose/mouse (mg/kg)	# of	animals	Percent of Mice with Lung Tumors	Average No Lung Tumors/Mouse	P value
		Initial	Survivors			
Hexamethyl-disilazane	1000	20	5	60	.60 ± .26	NS

Hexamethyl- disilazane	500	20	17	35	.53 ± .12	NS
Hexamethyl- disilazane	200	20	18	17	.17 ± .03	NS
Tricaprylin	10000	30	29	48	.48 ± .09	---
Urethane	500	15	14	100	8.5 ± 1.2	---
Untreated	---	20	19	37	.37 ± .07	---

NS - Not Significant

E. Reproductive Effects and Teratogenicity

1. Human Data

No data were found on the reproductive effects and teratogenicity of hexamethyldisilazane in humans.

2. Animal Data

No data were found on the reproductive effects and teratogenicity of hexamethyldisilazane in animals.

F. Genetic Toxicology

1. Human Data

No data were found on the genetic toxicology of hexamethyldisilazane in humans.

2. Prokaryotic Data

bacterial reverse mutation assay Hexamethyldisilazane was found to be non-mutagenic in an unpublished bacterial reverse mutation assay. No other data were provided [Silicones Health Council, 1990].

3. Eukaryotic Data

No data were found on the genotoxic effects of hexamethyldisilazane in eukaryotic systems.

G. Other Toxicological Effects

1. Immunotoxicity

intraperitoneal, mice An LD_{Lo} for immunologic effects of 650 mg/kg for hexamethyldisilazane in mice by intraperitoneal injection has been reported. This dose caused a decreased immune (allergic) response [Stoner, 1975].

2. Neurotoxicity

inhalation, rats In rats, inhalation of 110 mg/m³ hexamethyldisilazane for 4 hours caused a decrease of the excitability of the nervous system. Inhalation of hexamethyldisilazane at a concentration of 98.2 mg/m³, 4 hours per day, 5 times per week for 4 months caused a significant decrease in the summation-threshold index of the nervous system, and an increase in the duration of hexobarbital sleep time (see sections V.B.2 and V.D.2 for additional data)[Turzhova *et al.*, 1986].

3. Biochemical Toxicology

inhalation, rats Inhalation of 110 mg/m³ of hexamethyldisilazane for 4 hours in rats of unspecified strain and sex caused a decrease in liver lactate dehydrogenase activity and a decrease in the peroxidase activity in the blood [Turzhova *et al.*, 1986].

inhalation, rats Rats of unspecified strain and sex (n=80) were chronically exposed by inhalation to 2.3 ± 0.2, 10.5 ± 0.6, and 98.2 ± 3.3 mg/m³ hexamethyl-disilazane for 4 hours per day, 5 days per week for 4 months. The highest dose caused a decrease in the activity of succinate dehydrogenase in the lungs and lactate dehydrogenase in the liver. Hexamethyldisilazane at a concentration of 10.5 mg/m³ caused an increase in blood catalysis, and a decrease in blood peroxidase activity [Turzhova *et al.*, 1986].

Structure Activity Relationships

Stoner *et al.* (1975) reported that silylating compounds like hexamethyldisilazane, in which the trimethylsilyl group is attached only to an amide group, were generally inactive in the strain A mouse lung adenoma assay [Stoner *et al.*, 1975].

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APPENDIX I. ON-LINE DATABASES SEARCHED		
-	<u>DATE OF SEARCH</u>	<u>TIME PERIOD</u>
BRS:	-	-
HZBD	October, 1990	-
DIALOG:	-	-
Agricola	October, 1990	1970-1990
Agris International	October, 1990	1974-1990
Aquatic Sciences Abstracts	October, 1990	1974-1990
Biosis Previews	October, 1990	1969-1990
CAB Abstracts	October, 1990	1972-1990
Cancerlit	October, 1990	1963-1990
Chem Bus NewsBase	October, 1990	1984-1990
Chemical Exposure	October, 1990	1974-1990
Compendex Plus	October, 1990	1970-1990
CRIS USDA	October, 1990	-
Embase	October, 1990	1974-1990
Enviroline	October, 1990	1970-1990
Environmental Bibliography	October, 1990	1974-1990
Federal Register	October, 1990	1977-1990
Foods Adlibra	October, 1990	1974-1990
FSTA	October, 1990	1969-1990
Life Sciences Collection	October, 1990	1978-1990
Medline	October, 1990	1966-1990

NTIS	October, 1990	1964-1990
Occupational Safety and Health	October, 1990	1973-1990
PTS Newsletter	October, 1990	1987-1990
PTS Prompt	October, 1990	1972-1990
Pollution Abstracts	October, 1990	1970-1990
Trade and Industry ASAP	October, 1990	1983-1990
MEAD:	-	-
Nexis/Lexis-BNA ENV	October, 1990	-
NLM:	-	-
Chemline	October, 1990	-
HSDB	October, 1990	-
RTECS	October, 1990	-
Toxline 65	October, 1990	1965-1990
Toxline	October, 1990	1981-1990
Toxlit	October, 1990	1981-1990
Toxlit 65	October, 1990	1965-1990
STN:	-	-
CA	October, 1990	1967-1990
Chemlist	October, 1990	-

APPENDIX II. SAFETY INFORMATION

HANDLING AND STORAGE

Hexamethyldisilazane is flammable and reactive with water, alcohol and protic solvents [Lancaster Synthesis, 1989-1990; Petrarch Systems, Inc., 1981b]. Hexamethyldisilazane is incompatible with strong oxidizing agents and strong acids [Lenga, 1988; Petrarch Systems, Inc., 1981b]. Hexamethyldisilazane shall be stored in a cool, well-ventilated area. Outside or detached storage is preferred. If this type of storage is unavailable, then a standard flammable liquids

storage cabinet shall be used. When transferring hexamethyldisilazane between containers, the containers shall be electrically grounded and bonded.

EMERGENCY FIRST AID PROCEDURES

Eye: First check the victim for contact lenses and remove if present. Flush victim's eyes with water or normal saline solution for 20 to 30 minutes while simultaneously calling a hospital or poison control center. Do not put any ointments, oils, or medication in the victim's eyes without specific instructions from a physician. Immediately transport the victim to a hospital even if no symptoms (such as redness or irritation) develop.

Skin: IMMEDIATELY flood affected skin with water while removing and isolating all contaminated clothing. Gently wash affected skin areas thoroughly with soap and water. If symptoms such as inflammation or irritation develop, IMMEDIATELY call a physician or go to a hospital for treatment.

Inhalation: IMMEDIATELY leave the contaminated area and take deep breaths of fresh air. If symptoms (such as wheezing, coughing, shortness of breath, or burning in the mouth, throat, or chest) develop, call a physician and be prepared to transport the victim to a hospital.

Provide proper respiratory protection to rescuers entering an unknown atmosphere. Whenever possible, Self-Contained Breathing Apparatus (SCBA) should be used.

Ingestion: If the victim is conscious and not convulsing, give 1 or 2 glasses of water to dilute the chemical and IMMEDIATELY call a hospital or poison control center. Be prepared to transport the victim to a hospital if advised by a physician.

If the victim is convulsing or unconscious, do not give anything by mouth, ensure that the victim's airway is open and lay the victim on his/her side with the head lower than the body. DO NOT INDUCE VOMITING. IMMEDIATELY TRANSPORT THE VICTIM TO A HOSPITAL.

PROTECTIVE EQUIPMENT

Eye: Safety glasses

Gloves: Two pairs of dissimilar protective gloves shall be worn when handling the neat chemical, otherwise one pair. When contact with this chemical has been known to occur, change gloves immediately.

Clothing: Minimally, a disposable laboratory suit (e.g. Tyvek ®) shall be worn, as specified in the most current NTP Statement of Work or NTP Health and Safety Minimum Requirements.

Respiratory A NIOSH-approved chemical cartridge respirator with an

Protection: organic vapor cartridge.

EXTINGUISHANT

Dry chemical, carbon dioxide or halon extinguisher

MONITORING PROCEDURES

There is no NIOSH analytical method reported in the NIOSH Manual of Analytical Methods for hexamethyldisilazane.

SPILLS AND LEAKAGE

Persons not wearing the appropriate protective equipment and clothing shall be restricted from areas of spills until cleanup has been completed. When exposure to unknown concentrations may occur, air-purifying respirators may not be used. Chemical cartridge respirators with organic vapor cartridges may not be used when airborne concentrations exceed 1000 ppm.

If hexamethyldisilazane is spilled the following steps shall be taken:

1. Remove all heat and ignition sources.
2. If a liquid solution is spilled, use vermiculite, sodium bicarbonate, sand, or paper towels to contain and absorb the spill.
3. Clean the spill area with dilute alcohol (approximately 60-70%) followed by a strong soap and warm water washing.
4. Dispose of all absorbed material as hazardous waste.

DECONTAMINATION OF LABORATORY EQUIPMENT

TDMS Terminal: Whenever feasible, a protective covering (e.g., plastic wrap) shall be placed over the keyboard when in use.

General Equipment: Before removing general laboratory equipment (i.e., lab carts, portable hoods and balances) from animal dosing rooms and/or chemical preparation areas, a decontamination process shall be conducted in addition to routine housekeeping procedures.

WASTE MANAGEMENT AND DISPOSAL PROCEDURES

Waste Management: If an inhalation study is to be conducted, all exhaust air from the inhalation chamber must be cleaned with appropriate air cleaning devices unless the laboratory has informed local and state air pollution regulatory agencies of both the laboratory's operating practices and the potential hazards of the chemicals in use. Compliance with all federal, state and local air pollution laws and regulations is required. A specific air cleaning system design must consider the specific conditions of the laboratory (eg., air flow rates and volumes, mixing of exhaust streams, size of inhalation chamber, etc.) and the dosing regimen selected. Air cleaning systems designs must be described by the laboratory and approved by the NTP Office of Laboratory Health and Safety.

Waste Disposal: Securely package and label, in double bags, all waste material. All potentially contaminated material (i.e., carcasses, bedding, disposable cages, labware) shall be disposed of by incineration in a manner consistent with federal (EPA), state, and local regulations or disposed of in a licensed hazardous waste landfill.

