Danish Ministry of the Environment
Environmental Protection Agency

Siloxanes (D3, D4, D5, D6, HMDS)

Evaluation of health hazards and proposal of a health-based quality criterion for ambient air

Environmental Project No. 1531, 2014

Title:

Siloxanes (D3, D4, D5, D6, HMDS)

Editing:

Krestine Greve, Elsa Nielsen, Ole Ladefoged.
Division of Toxicology and Risk Assessment.
National Food Institute, Technical University of Denmark

Published by:

The Danish Environmental Protection Agency
Strandgade 29
1401 Copenhagen K
Denmark
www.mst.dk/english

Year:

Authored 2010.
Published 2014.

ISBN no.

978-87-93026-85-8

Content

1 General description

Siloxanes form a group of chemicals with molecular weights from a few hundreds to several hundred thousands. Siloxanes consist of silicon atoms linked via oxygen atoms, forming a cyclic or linear backbone structure. Each silicon atom bears one or several side chains, which may form cross-links and influence the properties of the polymer (e.g. phenyl side groups provide oxidative stability, aminopropyl side groups provide water solubility, and trifluoropropyl side groups provide high resistance to solvents). In the simplest form the side-chains consist of methyl groups (dimethylsiloxanes).

In this evaluation, only one linear polydimethylsiloxane (HMDS) and four cyclic polydimethylsiloxane (D3, D4, D5 and D6), of low molecular weight, are considered in relation to an estimation of a health based quality criterion in air. For D3, D4, D5, D6 and HMDS, on the contrary to other siloxanes, data on toxicity have been located and they are all chemically defined. The identity and physico-chemical properties of D3, D4, D5, D6 and HMDS are summarised in Table 1 and 2, respectively. Other commonly used siloxanes are listed in Table 3 (Section 1.2).

This document is primarily based on reviews and evaluations published by MST (2005), TemaNord (2005) and SCCP (2005).

Although “silicone” is the most used term when referring to products, the term “siloxanes” will be used throughout this evaluation.

1.1 Identity and physico-chemical properties

The identity and physico-chemical properties of the selected siloxanes are presented in Table 1 and Table 2, respectively.

1.2 Production and use

Siloxanes are produced by acid hydrolysis of silanes (e.g. dimethyldichlorosilane, chlorotrimethylsilane) and purification by distillation (HSDB 2005).

About 200 siloxanes and siloxane derivatives are listed in the inventory of ingredients used in cosmetic products compiled by the European Commission INCI (2000 – quoted from MST 2005).

Globally the total consumption of siloxanes is approximately 850,000 tonnes, with Western Europe accounting for about 296,000 tonnes (Will et al 2003 – quoted from MST 2005).

According to the Danish Product Register, the total amount of siloxanes in imported products and products produced in Denmark are 1269-1483 tonnes and 162-1143 tonnes, respectively (quoted from MST 2005). See also Table 3.

Table 1. Identity (ChemFinder, ChemIDplus Advanced, HSDB 2005, MST 2005).

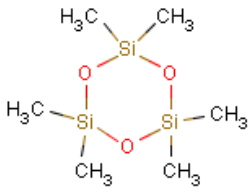
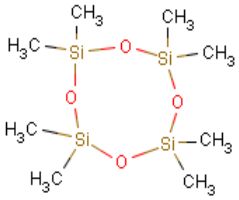
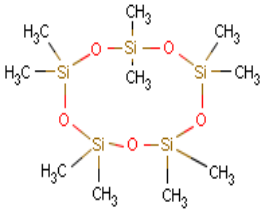
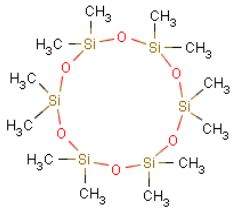
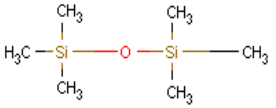
Name	**Hexamethylcyclo-trisiloxane (D3)**	**Octamethylcyclo-tetrasiloxane (D4)**	**Decamethylcyclo-pentasiloxane (D5)**	**Dodecamethylcyclo-hexasiloxane (D6)**	**Hexamethyldisiloxane (HMDS)**
Molecular formula	C_6-H_{18}-O_3-Si_3	C_8-H_{24}-O_4-Si_4	C_{10}-H_{30}-O_5-Si_5	C_{12}-H_{36}-O_6-Si_6	C_6-H_{18}-O-Si_2
Structural formula					
Molecular weight	222.46	296.64	370.80	444.93	162.42
CAS-no	541-05-9	556-67-2	541-02-6	540-97-6	107-46-0
Synonyms (among others)	Dimethylsiloxane cyclic trimer	Cyclic dimethylsiloxane tetramer, KF994 Part of Cyclomethicone	Cyclic dimethylsiloxane pentamer, KF995 Dow corning 245 fluid. Part of Cyclomethicone	Cyclohexasiloxane	Oxybis(trimethylsilane), Bis(trimethylsilyl)ether

Table 2. Physico/chemical properties (ChemFinder, ChemIDplus Advanced, HSDB 2005, TemaNord 2005).

Name	**Hexamethylcyclo-trisiloxane (D3)**	**Octamethylcyclo-tetrasiloxane (D4)**	**Decamethylcyclo-pentasiloxane (D5)**	**Dodecamethylcyclo-hexasiloxane (D6)**	**Hexamethyldisiloxane (HMDS)**
Description		Oily liquid	Oily liquid		Liquid
Melting point °C	64.5	17.5	-38	-3.0	-68
Boiling point °C	134	175	210	245	99.5
Density g/ml		0.9 at 25°C	0.9593 at 20°C /4°C		0.7638 at 20°C
Solubility	Water solubility: 1.570 mg/l at 25°C	Water solubility: 0.9 mg/l at 25°C	Water solubility: 0.24 mg/l at 25°C	Water solubility: 0.0051 mg/l at 25°C	Water solubility: 2 mg/l at 25°C
Odour threshold		Odourless			
Vapour pressure	3.53 mm Hg at 25°C (470.6 Pa)	1 mm Hg at 21.7°C (133.3 Pa)	0.2 mm Hg at 25°C (26.7 Pa)	0.0225 mm Hg at 25°C (3.0 Pa)	42 mm Hg at 25°C (5600 Pa)
Concentra-tion of saturated vapours (20 °C, 760 mmHg)	42,900 mg/m^3	16,200 mg/m^3	4,050 mg/m^3	550 mg/m^3	370.000 mg/m^3
Conversion factor (20 °C, 760 mmHg)	1 ppm = 9.25 mg/m^3 1 mg/m^3 = 0.108 ppm	1 ppm = 12.3 mg/m^3 1 mg/m^3 = 0.081 ppm	1 ppm = 15.4 mg/m^3 1 mg/m^3 = 0.065 ppm	1 ppm = 18.5 mg/m^3 1 mg/m^3 = 0.0541 ppm	1 ppm = 6.75 mg/m^3 1 mg/m^3 = 0.148 ppm
Henry's constant	0.064 atm-cu m^3/mol at 25°C	0.42 atm-cu m^3/mol at 20°C	0.4 atm-cu m^3/mol at 25°C	0.105 atm-cu m^3/mol at 23°C	4.5 atm-cu m^3/mol at 25°C
$logP_{octanol/water}$	4.470	5.1	5.2	6.330	4.2
BCF (L/kg)	1353	12400 (experimental)	5300	39874	900

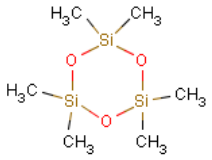
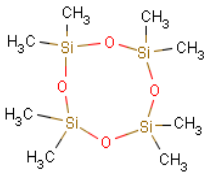
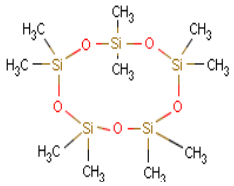
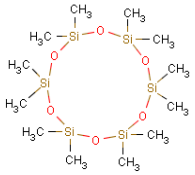
Siloxanes are used in processing aids, textile applications, cosmetics, toiletries, medical/pharmaceutical preparations, paper coatings, defoamers, paints, coatings, waxes, mechanical fluids, sealants and rubber (Will et al 2003 – quoted from MST 2005).

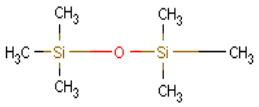
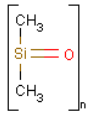
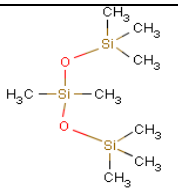
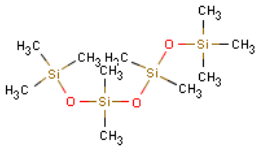
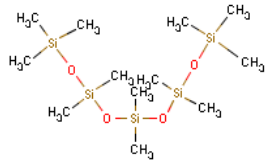
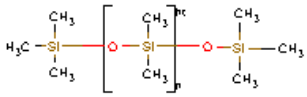
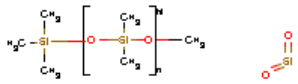
D5 is used in dry cleaning and in industrial cleaning as an alternative to tetrachloroethylene (US-EPA 2005a).

Cyclic siloxanes are used as precursors in the production of polymers (polydimethylsiloxane). The polymers contain some residual monomers and are used in industrial and consumer applications, in topical pharmaceutical formulations and in breast implants. (Dow Corning Technical Report 1999 – quoted from SCCP 2005).

In Denmark the main application areas for siloxanes are sealants for construction (29%), processing aids (15%) and textile applications (12%). About 175 different siloxane products are registered in the Danish Product Register and include 53 registered as used in sealants and 98 registered as used in paints and lacquers. (MST 2005). See also Table 3.

Table 3. Production/import of selected siloxanes in Denmark according to DPR and use according to INCI and DPR (INCI database, Danish Product Register (DPR) – quoted from MST 2005; ChemFinder, ChemIDplus Advanced).

Name/ CAS-no	**Use** **Import (average tonnes)** **Production (average tonnes)** **Number of products**	**Structural formula**
Hexamethylcyclotrisiloxane (D3)/ 541-05-9	Hair conditioning, emollient, solvent (INCI). 0 0 9	
Octamethylcyclotetrasiloxane (D4)/ 556-67-2	Poliching agent, antistatic, emollient, humectant, hair conditioning, solvent (DPR, INCI). 35 (max) 0 160	
Decamethylcyclopenta-siloxane (D5)/ 541-02-6	Car wax, hair conditioning, emollient, solvent (DPR, INCI). 37 (max) 0.028 70	
Dodecamethylcyclohexa-siloxane (D6)/ 540-97-6	Hair conditioning, emollient, solvent (INCI). 0.03 (max) 0.003 (max) 17	

Name/ CAS-no	Use Import (average tonnes) Production (average tonnes) Number of products	Structural formula
Hexamethyldisiloxane (HMDS)/ 107-46-0	Antifoaming, emollient, antistatic (INCI). 0.083 (max) 0.033 (max) 37	
Polydimethylsiloxane (PDMS)/ 9016-00-6	Sealants, anti-setoff agents, paint, lacquers, varnishes, ant-foaming agents (DPR). 3.5 (max) 0.25 (max) 123	
Octamethyltrisiloxane (MDM)/ 107-51-7	Skin conditioning (INCI). 0.242 (max) 0.6 (max) 14	
Decamethyltetrasiloxane/ 141-62-8	- 0.001 (max) 0 10	
Dodecamethylpentasiloxane/ 141-63-9	- - - -	
Dimethicone/ 9006-65-9	Paint, lacquers and varnishes, resins for 1- and 2- component hardening adhesives, anti-setoff agents, antifoaming, emollient (DPR, INCI). 21 (max) 195 (max) 458	
Simethicone/ 8050-81-5	Emollient, hair conditioning, antifoam (INCI). 0.003 (max) 0 5	

1.3 Environmental occurrence and fate

No data have been located regarding a natural occurrence of siloxanes. Siloxanes are anthropogenic compounds (HSDB 2005).

Siloxanes enter the environment by a variety of human activities. In general volatile siloxanes are released into the atmosphere. Non-volatile siloxane fluids will end up in wastewater and then be directed to wastewater treatment plants. By the treatment process the siloxanes mainly follow the sludge and are either spread on agricultural fields, incinerated or disposed of for landfills. Siloxanes in solids will after use most often be disposed of for incineration and are nearly 100% mineralised by this process. Incineration plants are not considered significant sources of siloxane releases to the atmosphere. (MST 2005).

Siloxanes are resistant to chemical reactions such as oxidation, reduction and photodegradation. As varying information exists, it is not clear whether it is possible for siloxanes to undergo hydrolysis under environmental conditions. (TemaNord 2005).

1.3.1 Air

The main source of emissions of siloxanes into the air is volatile siloxanes used in cosmetics, wax and polishes. Volatile cyclosiloxanes used in cosmetic products, are meant to evaporate during use. Based on American experience, 92% of the volatile siloxanes will be emitted to the air. (Allan et al. 1997 – quoted from MST 2005).

No quantitatively information is available, but for the US it is roughly estimated that between 50 and 200 tonnes volatile siloxanes, used for cosmetics, is released to the air each year (MST 2005).

Once released into the atmosphere the volatile siloxanes may react with hydroxyl radicals. Half-lives for reaction with hydroxyl radicals in air for D4, D5, and HMDS are 16, 10 and 12 days, respectively. (TemaNord 2005).

In Denmark, air concentrations measurements of siloxanes have been taken at four locations of which three were taken outdoors and one was taken inside a sewage treatment plant. The air concentrations of D4, D5 and D6 were in the range 0.26-2.4 $\mu g/m^3$, 0.19-1.3 $\mu g/m^3$ and 0.07-0.44 $\mu g/m^3$, respectively. The measured air concentrations of HMDS were <0.004 $\mu g/m^3$ (below detection limit). (TemaNord 2005).

Emission of D4 to indoor air has been associated with new carpets (HSDB 2005).

1.3.2 Water

The non-volatile siloxanes used in cosmetics, toiletries, textile applications, cleaning agents and maintenance will mainly be discharged with wastewater. A few per cent of the siloxanes in waterborne paints may also end up in the sewage system by washing of brushes and paint pots. In Denmark, the total release of non-volatile siloxane fluids to wastewater is estimated at 200-700 tonnes/year. (MST 2005).

During the treatment processes in treatment plants, approximately 97% of polydimethylsiloxanes will be bound to the sludge. The remaining will be discharged to surface water. (MST 2005).

In Denmark, concentrations of siloxanes in surface water have been measured at three locations. The concentrations of D4, D5, D6 and HMDS were <0.04 μg/L, <0.02 μg/L, <0.02 μg/L and <0.0005 μg/L, respectively (TemaNord 2005).

In Denmark, concentrations of siloxanes in sludge have been measured at two locations. The concentrations of D4, D5, D6 and HMDS were in the range 470-740 ng/g dry weight (dw), 27000-50000 ng/g dw, 1100-2800 ng/g dw and <1-<3 ng/g dw, respectively. (TemaNord 2005).

In Denmark, concentrations of siloxanes in sediment have been measured at three locations. The concentrations of D4, D5, D6 and HMDS were in the range <3-84 ng/g dw, <2-2000 ng/g dw, <1-170 ng/g dw and <0.03-<0.3 ng/g dw, respectively. (TemaNord 2005).

1.3.3 Soil

No data have been located.

1.3.4 Foodstuffs

Certain food products are processed using antifoam containing D4 (SCCP 2005).

1.3.5 Bioaccumulation

D3, D4, D5 and D6 have octanol-water partition coefficients of 4.47, 5.1, 5.2 and 6.33 (log value), respectively, which indicate a high potential for bioaccumulation. HMDS has an octanol-water partition coefficient of 4.2 (log value), which indicate a moderate potential for bioaccumulation.

For D4 an experimental bioconcentration factor of 12400 was obtained in fathead minnows. This indicates a potential for D4 to bioconcentrate in fish and aquatic organisms, although some reports indicate that this is unlikely in the environment due to its rapid rate of volatilization to the atmosphere. (HSDB 2005).

In Denmark, concentrations of siloxanes in marine fish and mammals have been measured at four locations. For marine fish the concentrations of D4, D5 and D6 were in the range <5-13 ng/g wet weight (ww), <5-52 ng/g ww and <5-8.7 ng/g ww, respectively, and for HMDS the concentrations were <0.4 ng/g ww. For seals the concentrations of D4, D5 and D6 were in the range <5-12 ng/g ww, 17-24 ng/g ww and <5-7.9 ng/g ww, respectively, and for HMDS the concentrations were <0.4 ng/g ww. (TemaNord 2005).

TemaNord (2005) concluded that siloxanes are present as common pollutants in the Nordic environment and in many different matrices. They seem to be emitted through diffuse pathways and they enter the aquatic food chain. At present, the observed concentrations are not alarmingly high, and background sites seem to be non-contaminated. However, the use of siloxanes is extensive and it is possible that continued use will lead to increased environmental levels, eventually reaching effect concentrations. (TemaNord 2005).

1.4 Human exposure

In Sweden, 39 human breast milk samples have been analysed for three cyclic siloxanes, D4, D5 and D6 and for four linear siloxanes, including HMDS. Eleven of the 39 samples contained one or more of the cyclic siloxanes. The maximum concentrations of D4, D5 and D6 were 10 μg/L, 4.5 μg/L and 4.8 μg/L, respectively. Trace amounts of linear siloxanes were found in 6 samples in concentrations <0.04 μg/L. (IVL 2005).

In 1982, the U.S. National Survey of human adipose tissue analysed composite samples and qualitatively found D4 in 21 and D5 in 28 of 46 analysed samples (Onstot et al. 1987 – quoted from US-EPA 1992).

Because of lack of meaningful information/data on actual consumer exposure to D4, the Scientific Committee on Consumer Products (SCCP) was unable to assess the risk of D4 to consumers when used in cosmetic products. Adequate data by manufactures are requested by October 2006. (SCCP 2005).

2 Toxicokinetics

2.1 Absorption, distribution and elimination

2.1.1 Inhalation

No data have been located for D3, D6 and HMDS.

2.1.1.1 D4

Six male volunteers were exposed to 10 ppm (123 mg/m^3) ^{14}C-D4 for one hour. Plasma measurements immediately post exposure revealed a mean peak value of 115 ± 50 ng/g D4 (161 ± 53 in ^{14}C activity equivalents). Metabolites were far more persistent in blood and plasma than parent D4 and were still present at 24 hours post-exposure. Approximately 25-30 % of absorbed D4 was found in urine when the ^{14}C activity of the metabolites was expressed in D4 equivalents. (Dow Corning Corporation, University of Rochester Medical Center 2000 – quoted from SCCP 2005).

In rats, exposed to 700 ppm (8610 mg/m^3) ^{14}C-D4 (vapour) for 6 hours, 5.6 % was absorbed. Radioactivity was readily taken up in tissues with the highest concentration in fat. The elimination half-life was 13 hours in blood, 59 hours in plasma and ranged from 34 to 158 hours in tissues. 31% of the radioactivity was recovered as expired volatiles, 47% by renal excretion and 12% by faecal excretion. Radioactivity in urine and faeces was mainly due to polar metabolites. Approximately 11% of the body burden was recovered in the carcasses at 168 hours. The overall recovery as expired $^{14}CO_2$ was low (1.8%) indicating that its formation was not a major route of elimination. (Dow Corning Corporation, Bio-Research Laboratories Ltd. 1996 – quoted from SCCP 2005).

Rats were exposed nose-only for 4 or 6 hours to 7, 70 or 700 ppm (86.1, 861 or 8610 mg/m^3) ^{14}C-D4 (vapour). The radioactivity was readily taken up by the tissues, especially by fat. Maximum concentrations were observed at end of exposure to 3 hours post-exposure, except in fat where radioactivity was sustained up to 48 hours post-exposure. Except for the testes, the mean radioactivity half-time ranged from 68 hours in plasma to 154 hours in skin. The mean radioactivity half-time in testes were 273 hours. The excretion of radioactivity was mainly via the pulmonary (expired volatiles: 23-35%; expired CO_2: 0.4-5.4%) and renal routes (32-43%), and to a lesser extent via faeces (9.5-15%). Elimination of radioactivity was most rapid during the first 0 to 12 hours interval and more prolonged up to 7 days (168 hours) post-exposure. (Dow Corning Corporation, Bio-Research Laboratories Ltd. 1996 – quoted from SCCP 2005).

Rats were exposed nose-only to concentrations of 7 and 700 ppm (86.1 and 8610 mg/m^3) unlabeled D4 (vapour) for 14 days, 6 hours/day. On day 15 the rats were exposed to ^{14}C-D4 (7 or 700 ppm) for 6 hours. The fraction of the radioactivity retained ranged from 4.4-6.1%. In blood, plasma and all tissues, maximum concentrations of radioactivity were observed between the end of exposure to 3 hours post-exposure. Radioactivity was readily taken up by the tissues, especially by fat and was eliminated at rates similar to or somewhat lower than from plasma

(half-life 56 ± 10 hours). With the exception of fat, the elimination profile in blood, plasma and tissues was characterised by an initial, relatively rapid decline up to 24 hours post exposure followed by a long apparent terminal elimination phase (mean radioactivity half-time ranged from 56 to 253 hours). The tissues containing the highest amount of radioactivity were the liver and fat. Recovery of radioactivity in both sexes for both concentrations were 37-40% in urine, 13-19% in faeces, 26-35% in expired volatiles, 2.1-4.5% in expired $^{14}CO_2$ and 1.3-2 % in cage wash. The fraction of radioactivity remaining in the carcasses at 168 hours post-exposure ranged from 6.5 to 8.5%. Small amount of radioactivity were recorded in all analysed tissues at 168 hours; the total (sum of the mean values) ranged between 0.19 and 0.47% of the body burden. (Dow Corning Corporation, ClinTrials Bioresearch 1997 – quoted from SCCP 2005).

Rats were exposed nose-only to 700 ppm (8610 mg/m^3) ^{14}C-D4 as a vapour for 6 hours. Maximum concentrations in blood, plasma and tissues were observed at the end of the exposure period. The total body burden of radioactivity retained by the animals during exposure was 6.5%. Elimination of radioactivity from tissues was approximately at the same rate as from plasma (except for peri-renal fat and lung). Recovery of radioactivity was 35.8 ± 1.1% in urine, 29.7 ± 2.8% in faeces, 33.7 ± 14.7 in expired volatiles, 1.72 ± 0.1% in expired CO_2 and 0.24 ± 1.97% in cage washes. One hour post-exposure, 12.4 ± 3.4% of the body burden was exhaled. Twenty-four hours post-exposure, approximately 85% of the expired volatiles were recovered. Forty-eight hours post-exposure, 86% of the radioactivity in the urine was recovered. (Dow Corning Corporation 1996 – quoted from SCCP 2005).

Female Fisher 344 rats (F344) and Sprague-Dawley rats (SD) were exposed nose-only to 700 ppm (8610 mg/m^3) ^{14}C-D4 mixed with unlabeled D4 (vapour) for 6 hours. F344 rats retained a significantly higher amount ($p<0.05$) of radioactivity (8.3 ± 0.22%) than SD rats (5.9 ± 0.13%) at the end of the 6-hour exposure period. Excretion of retained radioactivity was similar in both strains. The concentration of radioactivity over time in blood and lung was also similar over the 168-hour post exposure period while differences were seen in fat, liver, faeces and urine. F344 rats generally showed a lower percentage of the total radioactivity present as parent D4, suggesting that the F344 rats may more readily metabolise D4 as compared to SD rats. Recovery of parent D4 in faeces was 2% and 2.3% for the female F344 and SD rats respectively. No parent D4 was found in the urine samples from either strain suggesting that the radioactivity present in the urine was as metabolites. Two major metabolites comprising 70-100% of the urinary radioactivity for both strains were identified as dimethylsilanediol [$(CH_3)_2Si(OH)_2$] and methylsilanetriol [$CH_3Si(OH)3$]. No significant differences in urinary metabolism were found between the F344 and SD rats. Following sacrifice at 168 hours post exposure, the total percent of body burden remaining in the tissues (combined) was 0.4% for both F344 and SD rats. Radioactivity remaining in the carcasses was 9.17% and 15.95% of the body burden for female F344 and SD rats, respectively. (Dow Corning Corporation 2000 – quoted from SCCP 2005).

2.1.1.2 D5

Rats were exposed nose-only to 7 or 160 ppm (107.8 or 2464 mg/m^3) ^{14}C-D5 vapour for 6 hours. Approximately 2% of the inhaled ^{14}C-D5 was retained in both sex and both exposure group. Mean percent recovery of body burden dose for the 7-ppm exposure group was approximately 83% and 72% for males and females, respectively, and for the 160-ppm group approximately 110% and 80%, respectively. Distribution of radioactivity among tissues and over time was approximately the same for both sexes. However, the percentage of radioactivity

cleared as expired volatiles was significantly greater in males than females for both exposure concentrations ($p \leq 0.01$). Radioactivity was excreted in approximately equal amounts in the urine and the faeces for all groups except for the 2464 mg/m^3 males, where faecal excretion was greater than urinary excretion. A metabolite profile analysis using HPLC showed that the major ^{14}C-peak in the faeces was parent D5 and that the major peak in the urine did not correspond to ^{14}C-D5. Maximum concentrations occurred at the end of the exposure period for most tissues. Exceptions were for the thyroid gland in the 2464 mg/m^3 group where maximum concentration occurred at 120 hours post exposure, and for the peri-renal fat where maximum concentration varied from 3-168 hours post-exposure. (US-EPA 2002a).

2.1.2 Oral intake

No data have been located for D3 and D5.

2.1.2.1 D4

In rats, given a single oral dose of 300 mg/kg bw ^{14}C-D4 in corn oil, dimethicone fluid or undiluted, the absorption was 52 ± 5%, 12 ± 1.2% and 28 ± 5.8%, respectively. Absorption was expressed as the percentage of total recovered radioactivity from urine, carcass, expired volatiles and expired CO_2. (Dow Corning Corporation 1998 – quoted from SCCP 2005).

2.1.2.2 D6

Rats were given a single oral dose of 1000 mg/kg bw of ^{14}C-D6 in corn oil. The absorption of D6 in males and females was 11.9% and 11.8% (urine: 0.38 and 0.32%; expired volatiles: 11.20 and 11.21%; expired CO_2: 0.13 and 0.09%; tissues: 0.03 and 0.04%; carcass: 0.14 and 0.17%), respectively. The majority of D6 was excreted in the faeces. The entire radioactivity in expired volatiles was attributed to parent D6. Metabolic profile evaluations of urine and faeces showed that the entire radioactivity in the urine consisted of polar metabolites, whereas in the faeces the majority was parent D6 with a trace of a non-polar metabolite. Whole-body autoradiography showed that the majority of administered D6 was retained in the gastro-intestinal tract and was excreted in faeces within 448 hours. Low levels of radioactivity were detected in organs and tissues such as the liver, fat and bone marrow. (US-EPA 2004).

2.1.2.3 HMDS

Rats were administered ^{14}C-HMDS orally and intravenously and major metabolites of HMDS were identified in urine. $(CH_3)_2Si(OH)_2$, $HO(CH_3)_2SiCH_2OH$, $HOCH_2(CH_3)_2SiOSi(CH_3)_2CH_2OH$ (predominant), $HOCH_2(CH_3)_2SiOSi(CH_3)_3$, $HO(CH_3)_2SiOSi(CH_3)_3$ and $(CH_3)_3SiOH$ were among the major metabolites identified. No parent HMDS was found in the urine. (US-EPA 2001a).

2.1.3 Dermal contact

No data have been located for D3 and HMDS.

2.1.3.1 D4

Percutaneous absorption levels of 0.57 – 1.09% were observed in humans following 1 to 24 hour topical application of D4 (US-EPA 1998, 2000 – quoted from MST 2005).

2.1.3.2 D5

Three male and three female volunteers had 1.4 g or 1.0 g, respectively, of ^{13}C-D5 applied in a divided dose to each axilla. Blood samples were obtained prior to exposure and at ½, 1, 2, 4 and 6 hours after application. Exhaled air samples were obtained prior to exposure and up to 24 hours after application. D5 levels were significantly elevated in blood, plasma and in exhaled air at all time points after application. The highest average level in plasma was 1.2 ng D5/g plasma at 60 minutes. The highest average level in exhaled air was 0.64 ng D5/mL air at 30 minutes. D5 levels did not differ significantly between male and female volunteers. (US-EPA 2002b).

2.1.3.3 D6

In order to evaluate the percutaneous absorption of D6, ^{14}C-D6 was applied to human skin in an *in vitro* assay, under semi-occluded conditions using a flow-through diffusion cell system. Twenty-four hours after application 3.08% of the applied dose was found in the skin, 46.4% on the skin surface and 40.1% was volatilised from the application site and collected in the charcoal traps. After a wash at 24 hours after application, the portion of D6 that appeared in the skin did not penetrate through the skin but continued to evaporate. (US-EPA 2003).

2.2 Mode of action

Rats, following oral or inhalation exposure to D4 or D5, showed reversible hepatomegaly as a result of hepatic hyperplasia and hepatic hypertrophy. Several studies have shown an induction of rat hepatic cytochrome P450 enzymes, after exposure to D4 or D5, which is similar to that observed following exposure to phenobarbital. Therefore, D4 and D5 may be considered as enzyme inducers in the rat liver. See also section 4.4.1. (Dow Corning Corporation 1996, 1999, 1991 – quoted from SCCP 2005).

Rats exposed to D4 show an impaired female fertility that is related to a reduction of the number of mean corpora lutea and implantation sites and increased post-implantation losses. A direct mode of action could be that D4 acts as a weak oestrogen or anti-oestrogen. Data indicate that D4 has a weak anti-oestrogenic activity in rats. At the 50% of maximal response D4 was approximately 1.2 to 25 million times less potent than ethinyl oestradiol or diethylstilbestrol diproprionate in Sprague-Dawley rats and Fischer 344 rats, respectively. Data from studies in mice orally exposed to D4 indicate that D4 has a weak estrogenic activity that is mediated through the oestrogen receptor (ER), probably by direct binding via ERa. The data indicate that the stimulatory effect of D4 on the mouse uterus is not related to oestradiol activity. (Dow Corning Corporation, MPI Research 1999 and Bin et al. 2003 – quoted from SCCP 2005).

An indirect mode of action appears to be the most relevant explanation for the female fertility effects observed. Data from studies in rats indicate that D4 can

cause a delay or blockage of the luteinising hormone (LH) surge necessary for optimal timing of ovulation. In a study on SD rats, exposed to 700 or 900 ppm (8610 or 11070 mg/m^3) D4 by inhalation, only 42% and 31%, respectively, ovulated compared to 79% in controls. On the morning of oestrus, higher levels of oestradiol were found in rats at 700 or 900 ppm relative to controls, indicating failure of mature follicles to ovulate. (Dow Corning Corporation 2001, 2002 – quoted from SCCP 2005).

Supporting evidence for an indirect mode of action may be results showing that barbiturates given during a critical time period, which is about seven to eight hours before the LH release on the day of pro-oestrus, can block or delay the LH surge and delay ovulation for 24 hours. The extent of the decrease in ovulation is time- and dose-dependent. Repeated administration of barbiturates during this critical period on subsequent days continues to suppress the LH surge and consequently ovulation. (Everett and Sawyer 1950, Tyler and Gorski 1980, Toyoda and Chang 1969 – all quoted from SCCP 2005).

Endometrial adenomas have been observed in female rats exposed to 8610 mg/m^3 D4 and 2464 mg/m^3 D5. The neoplastic effects observed after D4 exposure has been attributed to a hormonal dysregulation resulting from interaction of D4 with the dopamine D2-receptor. Pre-treatment of F344 rats with sulpiride (a dopamine receptor antagonist) blocked the effect of D4 to reduce the serum prolactin levels, suggesting that D4 act on the pituitary as a dopamine D2-receptor agonist *in vivo*. A reduction of prolactin in the rat causes luteolysis and new ovarian follicle stimulation resulting in oestrogen dominance, which leads to persistent endometrial stimulation leading to uterine tumours. Prolactin is luteotropic in rodents but not in primates and humans. (Jean et al. 2005 – quoted from SCCP 2005).

2.3 Species differences

D4-induced hepatomegaly and phenobarbital-like induction of hepatic cytochrome P450s has been demonstrated in rats after exposure to D4. A study was conducted in order to confirm the previously reported inability of D4 to induce hepatomegaly in guinea pigs and to measure liver content of D4 in both guinea pigs and rats. Repeated doses of D4 (301 mg/kg bw/day for 14 days) administrated to female guinea pigs by gavage did not cause hepatomegaly or significant induction of liver microsomal CYP2B, CYP1a and epoxide hydrolase. This lack of hepatic effect in the guinea pig was not attributable to poor absorption and distribution to the liver as mean liver D4 content was determined to be 9-fold greater in guinea pigs than in rats. (US-EPA 2002c).

A multi-species 35-day inhalation study (rat, rabbit, hamster, mouse) was conducted in order to characterize species differences of liver response by studying urinary metabolites, induction of liver enzymes and cell replication. Animals were exposed by inhalation to concentrations of D4 of 0, 10 or 700 ppm (0, 120 or 8400 mg/m^3) 6 hours/day, 5 days/week, followed by a 14-day recovery period. A statistically significant increase in liver weights was observed in male and female hamster, mice and rats exposed to D4, but there was no change in guinea pigs and rabbits. To investigate possible enzyme induction, glutathione-S-transferase, epoxide hydrolase, and ethoxycumarin deethylase were measured (not further specified) in rats and guinea pigs. Enzyme induction and increased hepatocyte proliferation were observed in rats but not guinea pigs. Urine sampled on day 3 and day 25 was analysed for $(CH_3)_2SiO$ (D) and $CH_3SiO_{3/2}$ (T) moieties. Demethylated D4 (T) ranged from 1 to 9 µg/l in the low dose group and from 40 to 400 µg/l in the high dose group. The amount of T in the different species roughly followed the

order: Hamster and mice > rat > rabbit > guinea pig. The D/T ratio was similar in all species. There was a correlation between the amount of T produced and liver weight increase. Metabolism showed no gender differences. (Dow Corning Corporation, Siddiqui 2001 – both quoted from SCCP 2005).

3 Human toxicity

3.1 Single dose toxicity

Twelve healthy volunteers were exposed to 10 ppm (122 mg/m^3) D4 or air (control) for one hour (two exposures separated by one week). Three months later the exposure was repeated. After the one-hour exposure the mean D4 concentration in the blood plasma was 56 ng/g of plasma. No significant change in forced vital capacity (FVC), and FVC in 1 sec (FVC1) was observed immediately after exposure or 24 hours post-exposure for either the air or D4 group compared with the baseline measurements immediately prior to exposures. In the same study immunological assays, including enumeration of peripheral lymphocyte subsets and functional assays using peripheral blood mononuclear cells, were used to screen for immunotoxicity or a systemic inflammatory response. Pro-inflammatory cytokines and acute-phase reactants in peripheral blood (markers for a systemic inflammatory response) were analysed as surrogate markers for adjuvancy. Blood was collected prior to exposure, immediately after exposure, and 6 and 24 hours post-exposure. No immunotoxic or pro-inflammatory/adjuvant effect was found. (Dow Corning Corporation 1997 and Looney et al 1998 – both quoted from SCCP 2005).

3.2 Irritation

3.2.1 Skin irritation

HMDS is reported to be a skin irritant (Sax 1984 – quoted from HSDB).

3.2.2 Eye irritation

HMDS is reported to be an eye irritant. It irritates conjunctiva but does not attack the cornea (Lefaux 1968 – quoted from HSDB).

3.3 Sensitisation

3.3.1 Skin sensitisation

3.3.1.1 D4

Human repeated insult patch test with 50 subjects did not result in skin sensitisation (IUCLID 2000).

3.3.1.2 HMDS

Repeated insult patch tests were conducted with 100 volunteers to determine the ability of HMDS to sensitise the skin. Results of the study, which extended over a six-week period, showed no evidence of sensitisation. (IUCLID 2000).

3.4 Repeated dose toxicity

Human volunteers were orally exposed to 12 mg/day of D4 in corn oil for 2 weeks. Immunological assays, including enumeration of peripheral lymphocyte subsets and functional assays using peripheral blood mononuclear cells were used to screen for an immunotoxic or adjuvant effect. Pro-inflammatory cytokines and acute-phase reactants in peripheral blood were analysed as surrogate markers for adjuvancy. Blood was collected prior to exposure and after 7 and 14 days. No immunotoxic or pro-inflammatory/adjuvant effect was found. (US-EPA 1998a).

3.5 Toxicity to reproduction

No data have been located.

3.6 Endocrine disruption

In an *in vitro* oestrogen responsive reporter gene study, using the MCF-7 human cell line, indicated that D4 could elicit an oestrogenic effect that is dose-dependent with no significant anti-oestrogenic activity. (US-EPA 2000a).

3.7 Mutagenic and genotoxic effects

No data have been located.

3.8 Carcinogenic effects

No data have been located.

4 Animal toxicity

4.1 Single dose toxicity

4.1.1 Inhalation

4.1.1.1 D4

For F344 rats, exposed nose-only to D4 (vapour and aerosol) for four hours, an LC_{50}-value at 36000 mg/m^3 was calculated. The study was indicated to have followed OECD TG 403, but there was no control group. (Dow Corning Corporation 1994 – quoted from SCCP 2005).

The LC_{50}-value in rats exposed to D4 was >12170 mg/m^3 when exposed for four hours (aerosol) and >17600 mg/m^3 when exposed for one hour (IUCLID 2000).

4.1.1.2 D5

In rats, exposed to the maximum attainable concentration (2700 mg/m^3) of D5 for four hours, no visible adverse effects were observed (US-EPA – quoted from TSCATS).

4.1.1.3 HMDS

The LC_{50}-value in rats exposed to HMDS was >48000 mg/m^3 (no toxic effects) when exposed for one hour. In dogs an LC_{100}-value for HMDS at approximately 3300 mg/m^3 was reported. (IUCLID 2000).

The LC_{50}-value in male and female F344 rats exposed to HMDS by inhalation for four hours was calculated to be 107700 mg/m^3 (US-EPA 1996a).

4.1.2 Oral intake

4.1.2.1 D4

Oral LD_{50}-values in rats were reported to be in the range >2000 - >4800 mg/kg bw. Initial weight loss, slight diarrhoea, slight diuresis and liver and kidney injury were observed after oral exposure to 2000 mg/kg bw D4 in corn oil to rats (IUCLID – quoted from SCCP 2005).

4.1.2.2 D5

An oral LD_{50}-value >24134 mg/kg bw has been reported in rats (ChemIDplus Advanced, US-EPA 1993 – quoted from TSCATS).

4.1.2.3 D6

The LC_{50}-value in rats exposed to D6 was >50000 mg/kg bw. Behavioural and pulmonary effects were reported. (ChemIDplus Advanced).

4.1.2.4 HMDS

An oral LD_{50}-value >5000 mg/kg bw has been reported in rats. In guinea pigs, an oral LD_{L0} for HMDS at approximately 50000 mg/kg bw was reported. (IUCLID 2000).

4.1.3 Dermal contact

4.1.3.1 D4

LD_{50} in rats after dermal exposure to D4 was >2400 mg/kg bw (no mortalities). In rabbits, an LD_{50} for D4 at >4640 mg/kg bw (no mortalities) was reported. (IUCLID 2000).

4.1.3.2 D5

In rabbits, an LD_{50} for D5 at >15400 mg/kg D5 was reported (ChemIDplus Advanced).

4.1.3.3 HMDS

An LD_{50}-value in rabbits following dermal application of HMDS was >2000 mg/kg bw (no mortalities). In rabbits, mortality was observed at 10000 mg/kg bw after dermal exposure to HMDS. Toxic effects at 10000 mg/kg included gross pathological findings (lung, kidney, bladder, heart), while clinical findings (altered activity, ataxia, gasping and eschar formation) occurred in small numbers of rabbits. In contrast to rabbits, no mortality or signs of toxicity were observed in rats at the dose tested. (IUCLID 2000).

4.2 Irritation

4.2.1 Skin irritation

4.2.1.1 D4

D4 was not irritating on rabbit ear after application of 0.5 ml/animal. In another study, D4 was reported to be slightly irritating without further data. (IUCLID 2000).

4.2.1.2 HMDS

In one study, HMDS was reported to be slightly irritating to the skin of rabbits. In three other studies, HMDS was tested on rabbit skin without signs of irritation. (IUCLID 2000).

4.2.2 Eye irritation

4.2.2.1 D4

D4 was tested on rabbit eyes without signs of irritation (IUCLID 2000).

4.2.2.2 HMDS

HMDS was tested on rabbit eyes without signs of irritation (IUCLID 2000).

4.2.3 Respiratory irritation

D4 was an irritant to the respiratory tract when inhaled. See section 4.4.1.

4.3 Sensitisation

4.3.1 Skin sensitisation

4.3.1.1 D4

D4 was not sensitising in a guinea pig maximisation test (IUCLID 2000).

4.3.1.2 HMDS

HMDS was not sensitising in a guinea pig maximisation test (IUCLID 2000).

4.4 Repeated dose toxicity

The information on repeated dose toxicity of relevance for the estimation of a health-based quality criterion in ambient air for the five selected siloxanes is summarised below. The NOAELs and LOAELs presented in this section are those stated in the reviews and criteria documents.

4.4.1 Inhalation

Repeated dose toxicity studies with inhalation are available for D3, D4, D5 and HMDS whereas no information has been located for D6.

4.4.1.1 D3

One repeated dose toxicity study with inhalation of D3 has been located. The information is summarised in Table 4 and supplementary information is presented in the text.

Rat, 28 or 29 days (US-EPA 2002d)
Combined repeated dose toxicity study with reproductive/developmental toxicity screening test according to OECD TG 422 / US-EPA OPPTS 870.3650. The exposure levels were 0, 100, 500 and 2500 ppm (0, 925, 4625 and 23125 mg/m^3),

Table 4. Animal repeated dose toxicity studies on D3, inhalation

Species/strain/sex **Guideline**	**Duration/** **Dose levels (mg/m^3)/** **Chemical form**	**Effects** **(mg/m^3)**	**NOAEC** [1)] **(mg/m^3)**	**LOAEC** [1)] **(mg/m^3)**	**Reference**
Rat SD 10/sex/group Combined Repeated Dose Toxicity Study with Reproductive/ Developmental Toxicity screening Test OECD TG 422 US-EPA OPPTS 870.3650	28 (♂) 29 (♀) days 0, 925, 4625, 23125 6 hours/day D3 vapour whole body	No histomorphologic evidence of neurotoxicity. 23125: Lack of significant clinical signs of toxicity and minimal effects on clinical pathology parameters. Minimal effects on body weight and food consumption. Slight atrophy of the seminal vesicles (4/10 ♂). Protein droplet nephropathy in kidneys (♂). ↑ Liver weight (♀♂) (not further specified) ↑ Centrilobular hepatocellular hypertrophy (♀♂). ↓ Motor activity (♂♀). ↓ Reaction to handling (♀). ↓ Absolute weight of epididymides(10%) (♂). ↓ Absolute weight of seminal vesicles (30%) (♂). 4625: Protein droplet nephropathy (♂). 925: Very slight protein droplet nephropathy in one male.	925 (protein droplet nephropathy (♂)) 4625 (decreased seminal vesicle weight (♂))		US-EPA (2002d)

♂ = male
♀ = female
SD = Sprague Dawley

1) The NOAECs presented are those stated in the reference.

whole-body vapour inhalation. Male and female rats exposed to concentrations up to 23125 mg/m^3 had no significant clinical signs of toxicity and only minimal effects on clinical pathology parameters. Slight atrophy of the seminal vesicles was identified microscopically in four of the 10 males at 23125 mg/m^3. The change was characterised by decreased fluid in the gland lumen and decreased cell height and epithelial folding of the luminal epithelium. The epididymides, testes and prostate were histologically normal. It was noted by the authors that protein droplet nephropathy observed in kidneys of males at 23125 mg/m^3 was consistent in incidence and histomorphology with that caused by excessive accumulation of $\alpha_{2\mu}$-globulin in renal cortical tubules.

4.4.1.2 D4

Repeated dose toxicity studies with inhalation of D4 are summarised in Table 5 and supplementary information on selected studies is presented in the text.

Rat, 5 days (Dow Corning Corporation 1999 – quoted from SCCP 2005: reference number 60)
The concentrations used were 0, 1, 7, 30, 70, 150, 300, 500, 700 and 900 ppm (0, 12.3, 86, 369, 861, 1845, 3690, 6150, 8610 and 11070 mg/m^3). The study was conducted in order to investigate the effects of D4 on hepatic microsomal enzyme induction. Positive controls were given phenobarbital in drinking water (500 ppm) and negative controls received filtered air. Within each group, three subgroups were used for liver biochemical analyses and two subgroups were used for determining D4 in blood, fat and liver. A dose-related increase in liver weight was observed. The liver/plasma D4 ratio remained constant over the dose range. D4 content in fat, liver and plasma increased proportionately with increasing exposure concentrations. A dose-dependent increase occurred in pentoxyresorufin O-dealkylase (PROD) activity and in CYP2B1/2 proteins with a maximum response at 500 ppm D4.

Rat, 14 days (Dow Corning Corporation 1988 – quoted from SCCP 2005: reference number 8)
The concentrations used were 0, 100, 200 and 400 ppm (0, 1230, 2460 and 4920 mg/m^3). A slightly lower food intake was noted in females at 400 ppm in week 1. This reduction was less in the second week of the study. No clinical pathology or necropsy was performed.

Rat, 14 days (Dow Corning Corporation 1988 – quoted from SCCP 2005: reference number 9)
The concentrations used were 0 and 950 ppm (0 and 11685 mg/m^3). One-week recovery followed after 14 days of exposure. The average daily concentration was 854 ppm D4. The animals were checked daily for clinical signs. Body weights and food consumption were recorded every fourth day. Adult females showed a significant weight loss compared with the controls over the 2-week treatment period. In contrast, the adult males and young males and females gained approximately 40% and 30% less body weight than controls, respectively, over the treatment period. Both adult and young rats showed improved weight gain during the one-week recovery period. Appetite returned during the recovery period. No clinical pathology or necropsy was performed.

Table 5. Animal repeated dose toxicity (RDT) studies on D4, inhalation

Species/strain/sex **Guideline**	**Duration/** **Dose levels (mg/m^3)/** **Chemical form**	**Effects** **(mg/m^3)**	**NOAEC[1)]** **(mg/m^3)**	**LOAEC[1)]** **(mg/m^3)**	**Reference**
Rat F344 ♀	5 days 6 hours/day 0, 12.3, 86, 369, 861, 1845, 3690, 6150, 8610, 11070 D4 whole body	No effects on bw. ↑ PROD activity and CYPB1/2 proteins with maximum response at 3690 mg/m^3. 1845: Significant induction of hepatomegaly.	861 (enzyme induction ♀)		Dow Corning Corporation (1999 – reference number 60 in SCCP 2005)
Rat CD 5/sex/group	14 days 6 hours/day 0, 1230, 2460, 4920 D4 whole body vapour	No deaths or treatment-related clinical signs. No effects on bw gain.			Dow Corning Corporation (1988 - reference number 8 in SCCP 2005)
Rat DS 5/sex/group Young/adult	14 days 6 hour/day 0 and 11685 One week recovery D4 whole body	No deaths or treatment-related clinical signs. ↓ Bw (adult ♀). ↓ Bw gain (adult males and young males and ♀) ↓ Food intake, slightly (not after recovery).			Dow Corning Corporation (1988 – reference number 9 in SCCP 2005)
Rat F344 10/sex/group OECD TG 412	28 days 6 hour/day, 5 days/week 0, 2780, 5130, 8620, 14210 D4 nose only	14210: ↓ Bw, bw gain. ↓ Food intake ↑ Adrenal weights (absolute and relative) (♂). ↓ Thymus weights (absolute and relative) (♂). Histopathological changes (minimal to slight goblet cell proliferation in the nasal cavity). 8620: ↑ Mortality ↑Adrenal weights (absolute and relative) (♀). ↓ Thymus weights (absolute and relative) (♀). Hepatocellular hypertrophy. ↑ Smooth endoplasmic reticulum. 5130: ↑ Clinical signs (e.g. hunched posture, stiff or abnormal gait, head tilt and ruffled fur), dose related. 2780: ↑ Liver weights (absolute and relative). ↑ Vaginal mucification (♀). ↓ Relative mitochondria volume. Histopathological changes (minimal to slight alveolar inflammation). Ultrastructural changes in hepatocyte, dose-dependent	<2800		Dow Corning Corporation, RCC Group (1995 – reference number 10 in SCCP 2005)

Species/strain/sex Guideline	Duration/ Dose levels (mg/m^3)/ Chemical form	Effects (mg/m^3)	NOAEC[1)] (mg/m^3)	LOAEC[1)] (mg/m^3)	Reference
Rat F344 24/sex/group	28 days 6 hours/day 5 days/week 861 and 8610 D4 whole body	No effects on mortality and bw. 8610: ↑ Liver weight (17%) (not further specified), significant. ↑ mEH mRNA protein (♂). 861: Induction of hepatic cytochrome P450 enzymes. Induction of hepatic phase-II conjugation enzymes. Trend to increased liver weight. ↑ mEH mRNA protein (♀). ↓ Lung PROD activity.			Dow Corning Corporation (1996 – reference numbers 57 and 58 in SCCP 2005)
Rat Fisher ♀♂	28 days 6 hours/day, 5 days/week 86, 246, 738, 2214 14 days recovery D4 vapour whole body	No alterations in immune system function. No effects on bw, food consumption or urinalysis parameters. No histopathological alterations at any site. 2214: ↑ Liver weight (♂), significant (not after recovery) (not further specified). 246: ↑ Liver weight (♀), (relative and absolute), significant (not after recovery).			US-EPA (1997a)
Rat SD 10/sex/group	35 days 6 hours/day, 5 days/week 0, 123, 8610 14 days recovery D4 whole body	8610: No mortality or overt signs of toxicity. ↑ Liver weights, statistically significant (not further specified). Induced hepatic cell proliferation (♀) (♂: BrdU only). Induction of glutathione-S-transferase, epoxide hydrolase, and ethoxycumarin deethylase (♂). Induction of epoxide hydrolase and ethoxycumarin deethylase (♀).			Dow Corning Corporation, Siddiqui (2001 – reference number 12 in SCCP 2005)
Rat F344 20-30/sex/group OECD TG 413	13 weeks 6 hours/day, 5 days/week 0, 430, 1500, 6000, 11050 4 week recovery in control and high dose group. D4 nose only	11050: Vaginal mucification, reversible. ↑ Mortality (♀). ↓ Food intake and bw gains (not after recovery). ↑ Lung weight, reversible (not further specified). ↓ Ovary weights, reversible (♀) (not further specified). ↓ Mean corpuscular haemoglobin ↑ Incidence and severity of goblet cell proliferation in the nasal cavity, reversible.	430 (liver weight)	430 (lung lesion)	Dow Corning Corporation, RCC Group (1995 – reference number 15 in SCCP 2005)

Species/strain/sex Guideline	Duration/ Dose levels (mg/m^3)/ Chemical form	Effects (mg/m^3)	NOAEC[1)] (mg/m^3)	LOAEC[1)] (mg/m^3)	Reference
		↑ Incidence of ovarian atrophy. 6000: ↓ Erythrocytes, significant (♂). ↑ MCV ↑ Liver weights (♂) (not further specified). ↑ Adrenal weights, reversible (♀) (not further specified). ↓ Thymus weights, reversible (♀) (not further specified). 1500: Significant alteration in blood biochemistry. ↑ Liver weights (♀)(not further specified). 430: Chronic interstitial inflammation of the lungs, reversible. ↑ Alveolar macrophage foci in the lungs, reversible.			
Rat SD ♀♂	13 weeks 6 hours/day, 5 days/week 0, 62, 123, 3690 14 days recovery D4 whole body	3690: No exposure-related abnormalities in clinical signs, food consumption, bw, haematology, serum biochemistry, urinalysis, ophthalmology, or macroscopic or microscopic tissue evaluations. No exposure related histopathological findings. No pathological evidence of hepatomegaly. ↑ Liver weight (~28%) (♀) (not further specified).	123		Global Silicon Producer Association (1991 – reference number 13 in SCCP 2005)
Rat SD 10-20/sex/group	13 weeks 6 hours/day, 7 days/week 0, 615, 3690, 8610 4-week recovery in control and high dose group. D4 whole body	8610: No mortality or overt signs of toxicity No exposure-related abnormalities in haematology, serum biochemistry, urinalysis, ophthalmology (♂) ↓ Bw gain, slight and reversible (♀). 3690: ↑ Liver weight, irreversible (♀) (not further specified). 615: ↑ Liver weight, reversible (♂)(not further specified).	615 (♀),(liver weight) <615 (♂) (liver weight)		Dow Corning Corporation (1989 – reference number 14 in SCCP 2005)
Rat SD F0 and F1: 30/sex/group Two-generation (reproduction	70 days prior to mating, during mating until GD 20 and during LD 5 to termination. 6 hr/day. 0, 861, 3690, 6150, 8610 D4	Lung interstitial inflammation and alveolar histiocytosis (see notes in section 4.5.1.2). 8610: ↓ Mean bw gain (F1). ↑ Liver weight (♂ F0) (not further specified). ↑ Kidney weights (♀ F1) (not further specified).			Dow Corning Corporation (2001 – reference number 34 in SCCP 2005)

Species/strain/sex Guideline	Duration/ Dose levels (mg/m^3)/ Chemical form	Effects (mg/m^3)	NOAEC[1)] (mg/m^3)	LOAEC[1)] (mg/m^3)	Reference
toxicity and developmental neurotoxicity) (US-EPA OPPTS test guideline)		↑ Pituitary gland weights ♀ F1) (not further specified). ↑ Incidence of renal tubular mineralisation (F0+F1) Thyroid follicular cell hypertrophy (F1). 6150: ↓ Mean bw gain (F0). ↑ Kidney weights (♀♂ F1) (not further specified). ↑ Incidence of renal tubular mineralisation, not statistical significant (F0+F1). ↑ Incidence of hepatocyte hypertrophy (F0+F1). Bile duct hyperplasia (F1). 3690: ↑ Kidney weights (♂ F0) (not further specified). ↑ Liver weight (♀ F0, ♂♀ F1) (not further specified). ↑ Incidence of hepatocyte hypertrophy, not statistical significant (F1). Hepatic pigment (F1). 861: ↑ Incidence of hepatocyte hypertrophy, not statistical significant (F1).			
Rat F344 10-20/sex/group	12 month (6 month) 6 hours/day, 5 days/week 0, 123, 369, 1845, 8610 12 month recovery D4 whole body	8610: No changes in mortality No exposure-related clinical signs. No clearly exposure-related eye lesions. No effects on erythrocyte and urinalysis parameters. Leukocytosis resulting from increased lymphocytes. ↑ Absolute liver weight (centrilobular hypertrophy) (♀). ↑ Kidney weight (relative and absolute). 369: ↑ Absolute liver weight (♂).	123 (liver weight, 6 month) (♂) 1845 (liver weights and centrilobular hypertrophy of hepatocytes, 12 month) (♂)		Plotzke et al. (2005 – reference number AR4 in SCCP 2005)
Rat F344 60/sex/group	Two years 6 hours/day, 5 days/week 0, 123, 369, 1845, 8610 D4 whole body	No histopathological effects in liver. 8610: ↑ Mortality. ↓ Bw and bw gain (♂), significant. ↑ Kidney weights, absolute and relative, significant (♀♂). ↑ Liver weights (♂),absolute and relative, significant. ↑ Uterine weight (51% increase), absolute and relative. ↑ Incidence of cystic endometrial hyperplasia.	1845 (MNCL, endometrial adenomas)		Plotzke et al. (2005 – reference number AR in SCCP 2005)

Species/strain/sex Guideline	Duration/ Dose levels (mg/m^3)/ Chemical form	Effects (mg/m^3)	NOAEC[1)] (mg/m^3)	LOAEC[1)] (mg/m^3)	Reference
		↑ Incidence of uterine endometrial adenomas ↑ MNCL (♂). 1845: ↑ Liver weights (♀),absolute and relative, significant.			
Mouse CD-1 10/sex/group	28 days 6 hours/day 0 and 8610 D4 whole body	8610: No deaths or treatment-related clinical signs. No significant effect on bw or food intakes. Increased relative liver weights of mice appeared to be treatment-related although no histopathological changes were noted.			Dow Corning Corporation (1989 – reference number 11 in SCCP 2005)
Mouse CD-1 10/sex/group	35 days 6 hours/day, 5 days/week 0, 123, 8610 14 days recovery D4 whole body	8610: No mortality or overt signs of toxicity ↑ Liver weights, statistically significant (not further specified).			Dow Corning Corporation, Siddiqui (2001 – reference number 12 in SCCP 2005)
Rabbit New Zealand White 5/sex/group	28 days 6 hours/day 0 and 8610 D4 whole body	8610: No deaths or treatment-related clinical signs. No significant effect on bw or food intakes.			Dow Corning Corporation (1989 – reference number 11 in SCCP 2005)
Rabbit New Zealand White 5/sex/group	35 days 6 hours/day, 5 days/week 0, 123, 8610 14 days recovery D4 whole body	8610: No mortality or overt signs of toxicity			Dow Corning Corporation, Siddiqui (2001 – reference number 12 in SCCP 2005)
Guinea pig Hartley 10/sex/group	28 days 6 hours/day 0 and 8610 D4 whole body	8610: No deaths or treatment-related clinical signs. No effects.			Dow Corning Corporation (1989 – reference number 11 in SCCP 2005)
Guinea pig 10/sex/group	35 days 6 hours/day, 5 days/week 0, 123, 8610 14 days recovery D4 whole body	8610 : No mortality or overt signs of toxicity No induction of enzymes assayed.			Dow Corning Corporation, Siddiqui (2001 – reference number 12 in SCCP 2005)
Hamster Golden Syrian 10/sex/group	28 days 6 hours/day 0 and 8610 D4 whole body	8610: No deaths or treatment-related clinical signs. No significant effect on body weight or food intakes Increased relative liver weights of ♀ hamsters appeared to be treatment-related although no histopathological changes were noted.			Dow Corning Corporation (1989 – reference number 11 in SCCP 2005)

Species/strain/sex **Guideline**	**Duration/** **Dose levels (mg/m^3)/** **Chemical form**	**Effects** **(mg/m^3)**	**NOAEC[1)]** **(mg/m^3)**	**LOAEC[1)]** **(mg/m^3)**	**Reference**
Hamster Golden Syrian 10/sex/group	35 days 6 hours/day, 5 days/week 0, 123, 8610 14 days recovery D4 whole body	8610: No mortality or overt signs of toxicity ↑ Liver weight, statistically significant (not further specified).			Dow Corning Corporation, Siddiqui (2001 – reference number 12 in SCCP 2005)

♂ = male
♀ = female
Bw = body weight
CD = Charles River
SD = Sprague Dawley
PROD = pentoxyresorufin O-dealkylase
mEH = Microsomal epoxide hydrolase
BrdU = Bromodeoxyuridine (a synthetic thymidine analogue)
MCV = Mean corpuscular volume
MNCL = mononuclear cell leukaemia
GD = gestation days
LD = lactation day
F0 = parent generation
F1 = first generation

1) The NOAECs and LOAECs presented are those stated in the references.

Rat, 28 days (Dow Corning Corporation, RCC Group 1995 – quoted from SCCP 2005: reference number 10)
The concentrations used were 0, 2780, 5130, 8620 and 14210 mg/m^3. Only the 3 lower concentrations were as vapour. At the highest exposure level, 20% of the test atmosphere was expected to be a liquid aerosol. The droplet size was not measured. According to the author, biochemical changes noted suggest metabolic adaptation or stress that was treatment related; however, the results were equivocal as there was great variation within groups. The authors proposed that adrenocortical functional activity may have had an influence on some of the biochemical changes, especially those associated with carbohydrate, protein and fat metabolism. There was a reduction in rough endoplasmic reticulum at higher doses. Vacuolation of the zona fasciculata of the adrenal cortex was evident in most of the animals. Thymic atrophy was seen in all animals but was most pronounced at the highest concentration.

Rat, 28 days (Dow Corning Corporation 1996 – quoted from SCCP 2005: references number 57 and 58)
The concentrations used were 70 and 700 ppm (861 and 8610 mg/m^3). Two identically designed studies. Liver size decreased to within control values during the 14-day post-exposure (recovery) period. The induction of hepatic cytochrome P450 enzymes and the decrease in lung PROD activity was dose-dependent. According to SCCP, the magnitude of the enzyme induction was nearly identical to that observed in the phenobarbital treated positive control animals.

Rat, 13 weeks (Global Silicon Producer Association, International Research and Development Corporation 1991 – quoted from SCCP 2005: reference number 13)
The concentrations used were 0, 5, 10 and 300 ppm (0, 62, 123, 3690 mg/m^3). Ophthalmological examination, haematology, biochemistry and urine were tested at 3 months and at end of recovery period. At post mortem, all organ weights were recorded and histopathology of a complete set of tissues from high dose group and controls, and with nasal cavity, trachea, larynx, lungs and liver from low- and mid-exposure groups. High-dose females had increased liver weight (~28%) at the end of the 13-week exposure period, but it was comparable to controls after the 4 week recovery period.

Rat, 13 weeks (Dow Corning Corporation, RCC Group 1995 – quoted from SCCP 2005: reference number 15)
The concentrations used were 0, 35, 122, 488 and 898 ppm (0, 430, 1500, 6000 and 11050 mg/m^3). Haematology, biochemistry and urine were tested at 3 months and at the end of the recovery period. Ophthalmological examination of control and high exposure animals was at the end of treatment and recovery. At post mortem, all organ weights were recorded and histopathology of a complete set of tissues from the high dose group and controls and with lungs, adrenals, heart, kidney, liver, lymph nodes, spleen and thymus and all affected tissues from lower exposure level groups. Significant alteration in blood biochemistry (increases in gamma-glutamyl-transferase and alanine aminotransferase in male and female, in total cholesterol, slight decreases in triglyceride in both male and female, phospholipids in males, and total bilirubin in females) occurred in the low-mid exposure group and above. During the recovery period, these returned to levels comparable with the control.

Rat, 13 weeks (Dow Corning Corporation 1989 – quoted from SCCP 2005: reference number 14)
The concentrations used were 0, 50, 300 and 700 ppm (0, 615, 3690 and 8610 mg/m^3). Ophthalmological examination, haematology, biochemistry and urine were tested at 3 months and at the end of the recovery period. At post mortem, all organ

weights were recorded and histopathology of a complete set of tissues from the high dose group and controls and with nasal cavity, trachea, larynx, lungs and liver from low- and mid-exposure groups. A decreased ovary weight at the high exposure level was noted in the recovery group only. No other exposure related histopathological findings were found at 13 weeks or after the 4-week recovery period.

Rat, 2 generation study (Dow Corning Corporation 2001 – quoted from SCCP 2005: reference number 34)
The concentrations used were 0, 70, 300, 500 and 700 ppm (0, 861, 3690, 6150 and 8610 mg/m^3). Lung interstitial inflammation and alveolar histiocytosis: The F_0 incidence (control, 861, 3690, 6150 and 8610 mg/m^3, respectively) in males: 1/20, 0/30, 4/30, 1/29, 5/28 and in females: 0/30, 7/30, 5/30, 7/30, 8/26. The F_1 incidence of alveolar histiocytosis in males was: 10/30 (control) versus 22/29 (8610 mg/m^3); in females: 3/30 (control) versus 8/30, 9/30, 7/29, 13/29. Interstitial inflammation was increased at 8610 mg/m^3 only, males: 3/30 (control) versus 10/29, females: 4/30 (control) versus 9/29.

Rat, 12 month, 6 month (Plotzke 2005 – quoted from SCCP 2005: reference number AR4)
The concentrations used were 0, 10, 30, 150 and 700 ppm (0, 123, 369, 1845 and 8610 mg/m^3). There was an exposure related decrease in aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine kinase (CK), and lactate dehydrogenase (LDH) activities at 3, 6, 9, and 12 months of exposure. These decreases were frequently present in a dose-related manner, in particular at the 6- and 9-month time-points.
After 6 months exposure, the absolute liver weight tended to increase with increasing D4 exposure concentration and the difference was statistical significant at 700 ppm for females and at 30 ppm for males, respectively, relative to the concurrent controls. At 12 months, the absolute liver weights were significantly increased at 150 and 700 ppm compared to controls for both sexes and the relative liver weights (either to body or brain weight) generally increased with increasing exposure concentrations. The absolute and/or relative kidney weights increased in some exposed males and females at 12 months, but the differences were statistically significant at 700 ppm when compared with the controls.

Rat, 24 month, (Plotzke et al 2005 – quoted from SCCP 2005: reference number AR4)
The concentrations used were 10, 30, 150 and 700 ppm (0, 123, 370, 1850 and 8600 mg/m^3). Survival at 8600 mg/m^3 was 38% in treated males compared to 58% for controls and 58% in treated females compared to 72% for controls. It was stated by the authors that mortality was likely due to early onset and increased incidence of mononuclear cell leukaemia (MNCL) that occurred at 8600 mg/m^3. No increase in MNCL was found among the exposed female rats, see section 4.7.1.1. It was stated by the authors that the increases in kidney weights may reflect the observed increases in severity of chronic nephropathy.

Multi-species (rabbit, hamster, mouse, guinea pig), 28 days (Dow Corning Corporation 1989 – quoted from SCCP 2005: reference number 11)
The concentrations used were 0 and 700 ppm (0 and 8600 mg/m^3). Males showed non-significant slightly lower average body weight gains over the study period. Food intakes were similar for males and females throughout the study period.

Multi-species (rat, guinea pig, rabbit, hamster, mouse), 35 days (Dow Corning Corporation, Siddiqui 2001 – quoted from SCCP 2005: reference number 12)

The concentrations used were 0, 10 and 700 ppm (0, 123 and 8600 mg/m^3). The study was conducted in order to characterise species differences of the liver response by studying urinary metabolites, induction of liver enzymes and cell replication. A statistically significant increase in liver weights was observed in male and female hamsters, mice, and rats exposed to D4, but there was no change in guinea pigs and rabbits. To investigate possible enzyme induction, glutathione-S-transferase, epoxide hydrolase, and ethoxycumarin deethylase were measured in rats and guinea pigs. Enzyme induction and increased hepatocyte proliferation were observed in rats but not guinea pigs.

4.4.1.3 D5

Repeated dose toxicity studies with inhalation of D5 are summarised in Table 6 and supplementary information on selected studies is presented in the text.

Rat, 28 days, (US-EPA 1996b)
The concentrations used were 0, 10, 25, 75, and 160 ppm (0, 154, 385, 1155, and 2464 mg/m^3). Toxic effects, immunotoxicity response and assessment of liver and lung cytochrome P450, following exposure to D5, were investigated in three phases (toxicity phase, immunotoxicity phase and enzyme induction phase). A statistically significant decrease (approximately 5%) in red blood cell count, haematocrit and haemoglobin were present in females at 2464 mg/m^3 (not after recovery); however, the values were within the normal range of biological variation. There was a very slight increase in the severity of goblet cell proliferation of the nasal cavity in the 160-ppm group males, and a greater increase in severity in the 160-ppm group females. After recovery, minimal goblet cell proliferation of nasal cavity was only noted for one male in the 10-ppm group, one male and one female in the 75 ppm group and three females in the 160-ppm group. According to the authors, there was morphologic evidence that the histopathological changes observed at necropsy, were reversible following the 14 days recovery.

Rat, 28 days (US-EPA 1997b)
The concentration used was 160 ppm (2464 mg/m^3). The primary objectives of the present study were to determine the extent of liver enlargement and to study the effects on various hepatic enzymes. The induction pattern of hepatic phase I and II metabolising enzymes was nearly identical to that observed following exposure to 861 or 8610 mg/m^3 D4 and to 80 mg/kg bw phenobarbital (see above). However the magnitude of induction following exposure to 2464 mg/m^3 D5 for 28 days was much lower than that observed following exposure to 861 mg/m^3 D4 for 28 days. The liver enlargement following exposure to 2464 mg/m^3 D5 for 28 days was only slightly less than after exposure to 8610 mg/m^3 D4 for 28 days and considerably greater than observed following exposure to 861 mg/m^3 D4 for 28 days.

Rat, three month, (US-EPA 1995b)
The concentrations used were 0, 440, 750, 1330 and 3530 mg/m^3. The multifocal alveolitis was sub-pleural, sub-acute to chronic and associated with alveolar macrophage aggregation and pleural fibrosis. Tubular atrophy of the testes was noted in all treated groups but the incidence and severity of this finding were similar in treated and control rats. Interstitial gland hyperplasia in the ovaries and mucification and atrophy of the vaginal mucosa were noted in all treated groups. The incidence was increased at 3530 mg/m^3, however, the severity of these findings was not different from that in the controls. At the end of recovery, interstitial gland hyperplasia in the ovaries and vaginal mucosal mucification were noted in some rats at 3530 mg/m^3. Minimal to moderate vaginal mucification was

recorded in all treated groups with a higher incidence at 3530 mg/m^3 which was accompanied by an increase in slight to moderate degrees of mucosal atrophy at 1330 and 3530 mg/m^3.

4.4.1.4 HMDS

Repeated dose toxicity studies with inhalation of HMDS are summarised in Table 7 and supplementary information on selected studies is presented in the text.

Rat, one month (US-EPA 2001 – quoted from MST 2005)
The concentrations used were 0, 900, 3400, 12700, 59200 mg/m^3. The minimal hepatocellular hypertrophy was evident in males from 12700 mg/m^3 and in one female at 59200 mg/m^3.

Rat, 13 weeks (US-EPA 1998b)
The concentrations used were 0, 330, 1300, 4000, 10000 and 33300 mg/m^3. According to the authors, the pattern of histological lesions observed in the kidneys of the male rats is considered to be mediated by α2μ-globlin.

Rat, three month, (US-EPA 1996c)
The concentrations used were 0, 140, 730, 3420 and 13640 mg/m^3. A higher incidence of occult blood was observed in the males at 3420 and 13640 mg/m^3 after one month and in males at 13640 mg/m^3 at the end of the treatment period; these differences were not apparent at the end of the recovery period. The testes of two rats at 0 mg/m^3, five rats at 140 mg/m^3, seven rats at 730 mg/m^3, six rats at 3420 mg/m^3 and 11 rats at 13640 mg/m^3 were found to be reduced in size and/or flaccid. Similar findings were only recorded after recovery in four rats at 0 mg/m^3. Multifocal, sub-pleural, sub-acute to chronic interstitial inflammation, associated with alveolar macrophage aggregation, was noted in the lungs of rats of all groups. The incidence was slightly increased in males at 13640 mg/m^3 and females at 140 to 13640 mg/m^3. After recovery, an increase of these findings was still seen in males and females at 13640 mg/m^3. According to the authors, these increases were not excluded as test article related. The incidence and severity of the tubular atrophy of testes were minimally increased at 13640 mg/m^3. Mucification of the vaginal mucosa was noted in rats of all groups; however, the severity of these findings did not distinguish exposed rats from the controls. According to the authors, changes observed in the testes and vagina were regarded to be associated with the daily restrainment of the rats; however, the slightly increased incidence and severity of testicular tubular atrophy at 13640 mg/m^3 was not excluded as possibly test article related. The incidence of proteinaceous casts and severity of tubular regeneration were minimally increased in males at 13640 mg/m^3, and were not, according to the authors, excluded as possibly test article related effects. Goblet cell distension was noted in nasal cavity of some females at 13640 mg/m^3. According to the authors, this finding was considered to be a post-mortem/fixation artefact.

Table 6. Animal repeated dose toxicity studies on D5, inhalation

Species/strain/sex Guideline	**Duration/ Dose levels (mg/m^3)/ Chemical form**	**Effects (mg/m^3)**	**NOAEC[1)] (mg/m^3)**	**LOAEC[1)] (mg/m^3)**	**Reference**
Albino rat F344 4 groups 10/sex/group	20 days (♂) 21 days (♀) 6 hours/day, 5 days/week 0, 440, 650, 1500, 2270(day 1-6)/3060(day 7-20) D5 vapour except at 3060 (liquid aerosol)	No treatment related ophthalmological findings. 2270/3060: ↑ Absolute liver weight ↑ Incidence and severity of goblet cell proliferation in nasal cavity Slight degree of hepatocellular hypertrophy in six animals (♀). Minimal to light interstitial inflammation in lungs. 1500: Minor haematological changes. 440: Slightly higher blood concentration of glucose and phosphorus (♂).			US-EPA (1995a)
Rat F344 15/sex/group (tox phase). 10/sex/group (immun phase). 20♀ (enzyme induc phase).	28 days 6 hours/day 7 days/week 0, 154, 385, 1155, 2464 (tox, immune phase). 2464 (enzyme induc phase). 14 days recovery (tox phase, enzyme induc phase). D5 whole body	No effects on survival, clinical condition, bw, bw gain, food consumption and serum chemistry or urinalysis parameters. No ophthalmological findings. No gross findings at necropsies after 4 weeks exposure or after 14 days recovery. No effects on IgM antibody response. ↑ Relative and absolute lung weight, not after recovery (no further details). 2464: ↑ Relative and absolute liver weight, not after recovery (♀♂). Alveolar macrophage accumulation (♂) (♀-slight). Low incidence of interstitial inflammation in lungs. Minimal submucosal inflammation (level I) of nasal cavity (♀). 1155: Minimal submucosal inflammation (level I) of nasal cavity (♂). 154: Increased incidence of goblet cell proliferation (level I) of the nasal cavity.	1155 (systemic toxicity – liver weight increases) 2464 (immuno-suppression)	154 (histopathological changes of nasal cavity)	US-EPA (1996b)

Species/strain/sex Guideline	Duration/ Dose levels (mg/m^3)/ Chemical form	Effects (mg/m^3)	NOAEC[1)] (mg/m^3)	LOAEC[1)] (mg/m^3)	Reference
Rat F344 ♀	28 days 6 hours/day; 7 days/week 0, 2464 14 days recovery D5 vapour whole body	No measurable change in total hepatic P450. 2464: ↑ Bw (not after recovery). ↑ Liver weight (15.9%) (3.8% after recovery) (not further specified) ↑ Oxidoreductase activity (1.4-fold). ↑ Induction of hepatic phase I and phase II enzymes.			US-EPA (1997b)
Albino rat Fisher 344 4 groups 20/sex/group 30 in the high dose group	Three months 6 hours/day; 5 days/week 0, 440, 750, 1330, 3530 4 weeks recovery in high dose group. D5 vapour	No histopathological findings. No clinical signs. No ophthalmoscopic alterations. No effect on urinalysis parameters. 3530: ↓ Mean bw gain (not after recovery). ↑ MCV, slightly (♀). ↓ MCH, slightly. ↓ Reticulocyte count, slightly. ↑ Gamma-glutamyltransferase activity (♂). ↑ Relative lung weight, slight, significant (not ♂ after recovery). ↑ Relative liver weight, slight, significant (♂). ↓ Relative thymus weight, slight after recovery (♂). ↓ Relative testes weight, marginally (♂). ↑ Multifocal alveolitis. Interstitial gland hyperplasia (in some rats). Vaginal mucosal mucification (in some rats). 1330: ↓ Calcium concentration, slightly (♀). ↓ Relative testes weight, marginally (♂) (not after recovery). ↑ Multifocal alveolitis, minimal. Goblet cell hyperplasia in the nasal cavity (not after recovery). 750: ↑ Gamma-glutamyltransferase activity (♀). ↑ Relative liver weight, slight, significant (♀).			US-EPA (1995b)

Species/strain/sex **Guideline**	**Duration/** **Dose levels (mg/m^3)/** **Chemical form**	**Effects** **(mg/m^3)**	**NOAEC[1)]** **(mg/m^3)**	**LOAEC[1)]** **(mg/m^3)**	**Reference**
Rat F344 10-30/sex/greoup	Three months 6 hours/day 5 days/week 400.4, 708.4, 1324, 3449 D5 nose only	No histopathological finding in the liver (not further specified and no further details)			Burns et al. (1997 – in MST 2005)

♂ = male
♀ = female
Bw = body weight
MCV = Mean corpuscular volume
MCH = Mean corpuscular haemoglobin

1) The NOAECs and the LOAEC presented are those stated in the reference.

Table 7. Animal repeated dose toxicity studies on HMDS, inhalation

Species/strain/sex **Guideline**	**Duration/** **Dose levels (mg/m^3)/** **Chemical form**	**Effects** **(mg/m^3)**	**NOAEC[1)]** **(mg/m^3)**	**LOAEC[1)]** **(mg/m^3)**	**Reference**
Albino rat F344 5 groups 10/sex/group	One month 6 hours/day, 5 days/week 0, 900, 3400, 12700, 59200 HMDS nose only	59200: ↑ Focal inflammatory lesions in the lungs (♀♂). ↑ Pigment accumulation in bile ducts (♂), slight. Minimal hepatocellular hypertrophy (♂). Hyaline droplet accumulation, protein casts and granular casts in kidneys (♂). 12700: ↑ Renal tubule regeneration (♂). Minimal hepatocellular hypertrophy (♂).			US-EPA (2001 - in MST 2005)
Rat F344 6 groups 20/sex/group	13 weeks 6 hours/day, 5 days/week 0, 330, 1300, 4000, 10000, 33300 HMDS vapour whole body	No mortalities or clinical signs No abnormal findings at ophthalmoscopic or macroscopic examination. No significant effects on food consumption and bw. No test article related effects on the weight of adrenal glands, brain, heart, kidney, liver, lungs, ovaries, spleen, testes and thymus. 33300: ↑ Incidence and severity of tubular granular casts and papillary mineralisation (♂). 10000: ↑ Incidence and severity of tubular regeneration with interstitial fibrosis and tubular hyaline casts (♂). 4000: ↑ Incidence and severity of tubular regeneration (♂).	1300 (♂) 33300 (♀)		US-EPA (1998b)
Rat F344 6 groups 20/sex/ group	13 weeks 6 hours/day, 5 days/week 338, 1350, 4050, 10125, 33750 (nominal) HMDS Whole body	No effect on mortality, bw gain or food consumption, ophthalmoscopic changes, gross macroscopic necropsy findings, or organ weight changes. 4050: Histological lesions in the kidney (apparently consistent with male rat-specific $\alpha_{2\mu}$-globulin nephropathy). ↑ Plasma urea and creatinine concentrations, slight.			Cassidy et al. (2001 – in MST 2005)
Albino rat F344 5 groups 30 or 20/sex/group	Three months 6 hours/day, 5 days/week 0, 140, 730, 3420, 4900, 13640	No effect on bw, food consumption, or haematology or clinical biochemistry parameters. Multifocal, sub-pleural, subacute to subchronic interstitial			US-EPA (1997 - in MST 2005)

Species/strain/sex Guideline	Duration/ Dose levels (mg/m^3)/ Chemical form	Effects (mg/m^3)	NOAEC[1)] (mg/m^3)	LOAEC[1)] (mg/m^3)	Reference
	HMDS Nose only	inflammation in lungs of all groups. After the recovery period an increase of these finding were still seen at 13640 mg/m3. 13640: ↑ Testicular tubular atrophy (♂). ↑ Incidence of proteinaceous casts and severity of tubular regeneration in the kidneys (♂), slight.			
Albino rat F344 5 groups 30 or 20/sex/group OECD TG 413	Three months 6 hours/day, 5 days/week 0, 140, 730, 3420, 13640 HMDS One month recovery Nose only	No treatment-related mortality or clinical signs. No effects on ophthalmical parameters. No effects on bw, body weight gain and food intake. No effects on haematological and clinical chemistry parameters. Tubular atrophy of testes. Proteinaceous casts and severity of tubular regeneration in the kidneys (including controls). 13640: ↑ Testicular tubular atrophy (♂). ↓ Testes weight (♂) (not after recovery) (no further details). ↑ Multifocal, subpleural, subacute to chronic interstitial inflammation, associated with alveolar macrophage aggregation (♂). ↑ Lung weight (not after recovery) (♂) (no further details). ↑ Adrenal gland weights (not after recovery) (♂) (no further details). 3420: Occult blood in urine (♂). 140: ↑ Multifocal, subpleural, subacute to chronic interstitial inflammation, associated with alveolar macrophage aggregation (♀).			US-EPA (1996c)

♂ = male
♀ = female
Bw = body weight

1) The NOAECs presented are those stated in the reference.

4.4.2 Oral intake

Repeated dose toxicity studies with oral administration are available for D3 and D4 whereas no information has been located for D5, D6 and HMDS.
The study of D3 is summarised in Table 8 and the studies of D4 in Table 9. Supplementary information on selected studies of D4 is presented in the text.

Rat, 28 days (Dow Corning Corporation 1988 – quoted from SCCP 2005: reference number 5)
The test dose level was 2.1% D4 in basal diet. No dietary analyses were performed. Therefore, actual intake of D4 was not determined. The estimated intakes of D4 for young and old male and female rats were approx. 200-300 mg/kg/day. No histopathology was performed.

Rat, 28 days (Dow Corning Corporation, Medical College of Virginia 1997 – quoted from SCCP 2005: reference number 54)
Test dose levels were 10, 30, 100 or 300 mg/kg bw. Immunotoxicity was assessed by splenocyte phenotyping, peripheral blood phenotyping, spleen IgM antibody response to the T-dependent antigen sRBC, serum IgM antibody titres, mixed leukocyte response to Long Evans and Brown Norway rat spleen cells, mixed leukocyte response, clearance of sRBC by the reticulo-endothelial system and natural killer cell activity.

Rabbit, 14 days (Dow Corning Corporation 1992 – quoted from SCCP 2005: reference number 6)
The test dose levels were 0, 500 and 1000 mg/kg bw/day. There were no mortalities due to the test substance but one low-dose female died due to a gavage error. Changes in the liver in some animals at 1000 mg/kg bw included accentuated lobular pattern, pale areas and increased fragility. These changes were attributed to marked reductions in food intake and body weights.

4.4.3 Dermal contact

One repeated dose toxicity study with dermal contact is available for D4 whereas no information has been located for D3, D5, D6 and HMDS. The study is summarised in Table 10.

Table 8. Animal repeated dose toxicity studies on D3, oral administration

Species/strain/sex	**Duration/ Dose levels/ Chemical form**	**Effects (mg/kg bw/day)**	**NOAEL**	**LOAEL**	**Reference**
Rat SD 6/sex	28 days 1500 mg/kg bw/day 5 days/week D3 by gavage	1500: No signs of toxicity or behavioural changes. ↑ Bw and food consumption (♂). ↑ Liver weight (absolute and relative)			US-EPA (1990 in TSCATS)

♂ = male
♀ = female
Bw = body weight

Table 9. Animal repeated dose toxicity studies on D4, oral administration

Species/strain/sex	Duration/ Dose levels/ Chemical form	Effects (mg/kg bw/day)	NOAEL	LOAEL	Reference
Rat Immature SD and F344 12/group Draft OECD TG	3 days 0, 50, 100, 250, 500, 1000 mg/kg bw/day D4 by gavage in uterotrophic assay	500: Inhibition of uterotrophic response of ethinylestradiol (EE) (weak anti-oestrogenic activity) (SD, F344). 250: ↓ Bw (SD, F344). ↑ Liver weights (SD) (not further specified). ↑ Uterus weights (SD, F344) (not further specified). 100: ↑ Liver weights (F344) (not further specified).			Dow Corning Corporation MPI Research (1999 - reference number 69 in SCCP 2005)
Rat F344 ♀	14 days 301 mg/kg bw/day D4 by gavage	301: Hepatomegaly ↑ Liver weights (59%) (not further specified). Induced hepatomegaly and hepatic cytochrome P450s.			US-EPA (2002c)
Rat SD 8/sex/group	14 days 5 days/week 0, 25, 100, 400, 1600 mg/kg bw/day D4 by gavage	1600: No overt signs of toxicity were observed. ↓ Bw, significant. 400: ↑ Liver weights, significantly in both sexes (not further specified). 100: ↑ Liver weights (not further specified). 25: Liver weight increase was slight, but in males the relative liver weight increase was significant (not further specified).			Dow Corning Corporation (1990 - reference number 4 in SCCP 2005)
Rat SD, young/adult 5/sex/group	28 days 2.1% D4 in basal diet D4 microencapsulated in diet	No deaths were recorded. Signs of stress (rough fur and emaciation). The faecal contents were watery. ↓Food consumption ↓ Body weight gains (depleted body fat reserves).			Dow Corning Corporation (1988 reference number 5 in SCCP)
Rat F344	28 days 10, 30, 100 or 300 mg/kg bw D4 by gavage	No immune suppression observed			Dow Corning Corporation, Medical College of Virginia (1997 - reference number 54 in SCCP 2005)

Species/strain/sex	Duration/ Dose levels/ Chemical form	Effects (mg/kg bw/day)	NOAEL	LOAEL	Reference
Rabbit New Zealand White 6 ♀/group	14 days Dosed daily 0, 500, 1000 mg/kg bw/day D4 by gavage	No overt signs of toxicity were observed. 500: ↓ Body weight, significant. ↓ Thymus size, in most animals. ↓ Spleen size, in some animals ↓ Mesenteric lymph nodes size, in some animals ↓ Food intakes			Dow Corning Corporation (1992 - reference number 6 in SCCP 2005)
Guinea pig Hartley ♀	14 days 301 mg/kg bw/day D4 by gavage	No hepatomegaly was observed. Minor effect on microsomal CYP2B, CYP1A and epoxide hydrolase.			US-EPA (2002c)

♂ = male
♀ = female
Bw = body weight
SD = Sprague Dawley

Table 10. Animal repeated dose toxicity studies on D4, dermal

Species/strain	**Duration/ Dose levels/ Chemical form**	**Effects**	**NOAEL[1)]**	**LOAEL**	**Reference**
Rabbit New Zealand White 5/sex/dose	28 days 5 days/week 96, 190, 960 mg/kg bw D4	No clinical signs of toxicity. No effects on survival, bw gain, food consumption, haematology, clinical chemistry, urinalysis, macro and micro pathology.	960 mg/kg bw		Bayer (1988 - reference number 7 in SCCP 2005)

Bw = body weight

1) The NOAEL presented is this stated in the reference.

4.5 Toxicity on reproduction

The information on toxicity on reproduction of relevance for the estimation of a health-based quality criterion in ambient air for the five selected siloxanes is summarised below. The NOAELs and LOAELs presented in this section are those stated in the reviews and criteria documents.

4.5.1 Inhalation

Studies of toxicity on reproduction with inhalation are available for D3, D4, D5 and HMDS whereas no information has been located for D6.

4.5.1.1 D3

One study on reproductive toxicity with inhalation of D3 has been located. The information is summarised in Table 11 and supplementary information is presented in the text.

Rat, 28 or 29 days (US-EPA 2002d)
Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test according to OECD TG 422 and US-EPA OPPTS 870.3650. The concentrations used were 0, 100, 500 and 2500 ppm (0, 925, 4625 and 23125 mg/m^3). Slight atrophy of the seminal vesicles was identified microscopically in four of the 10 males at 23125 mg/m^3. The change was characterised by decreased fluid in the gland lumen and decreased cell height and epithelial folding of the luminal epithelium. The epididymides, testes and prostate were histologically normal.

4.5.1.2 D4

Studies on reproductive toxicity with inhalation of D4 are summarised in Table 12 and supplementary information on selected studies is presented in the text.

One-generation range finding study, rat (Dow Corning Corporation, WIL Research Laboratories, Inc 1996 – quoted from SCCP 2005: reference number 27)
The concentrations used were 0, 70 and 700 ppm (0, 861 and 8610 mg/m^3). Exposure did not have any treatment-related effects on pup viability as measured by the number of pups born dead or the pup viability indices on postnatal days (PND) 1 and 4.

One-generation range finding study, rat (Dow Corning Corporation, WIL Research Laboratories, Inc 1996 – quoted from SCCP 2005: reference number 28)
The concentrations used were 0 and 700 ppm (0 and 8610 mg/m^3). The gestation length was statistically significantly increased compared to concurrent controls (21.8 days in control and 22.3 days in the treatment group); however, the gestation length in the treated group was within the historical control range for the laboratory (21.5-22.8 days). Exposure did not have any treatment-related effects on pup viability as measured by the number of pups born dead or the pup viability indices on postnatal days 1 and 4.

Table 11. Animal reproductive toxicity studies on D3, inhalation

Species/strain/sex **Study type**	**Duration/** **Dose levels (mg/m^3)/** **Chemical form**	**Effects** **(mg/m^3)**	**NOAEC[1)]** **(mg/m^3)**	**LOAEC** **(mg/m^3)**	**Reference**
Rat SD 10/sex/group Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Screening Test OECD TG 422 US-EPA OPPTS 870.3650	♀: 14 days prior to mating to GD 19 ♂: 28 days 6 hours/day 0, 925, 4625, 23125 D3 vapour whole-body.	No effects on gestation length, pup sex ratio, pup weight and viability, and corpora lutea counts. 23125: Slight atrophy of the seminal vesicles (4/10 ♂). ↓ Absolute weight of epididymides(10%) (♂). ↓ Absolute weight of seminal vesicles (30%) (♂). ↓ Relative weight of seminal vesicles (27%) (♂). ↓ Litter size (33%) and number of implantation sites.	4625 (decreased litter size and number of implantation sites)		US-EPA (2002d)

♂ = male
♀ = female
GD = gestation days
SD = Sprague Dawley

1) The NOAEC presented is this stated in the reference.

Table 12 Animal reproductive toxicity studies on D4, inhalation

Species/strain/sex **Study type**	**Duration/** **Dose levels (mg/m^3)/** **Chemical form**	**Effects** **(mg/m^3)**	**NOAEC[1)]** **(mg/m^3)**	**LOAEC** **(mg/m^3)**	**Reference**
Rat SD 6 ♀/group Dose range-finding	GD 6-15, 6 hours/day 0, 123, 1230, 3690, 8610 D4 Whole body	No teratogenicity <u>Maternal toxicity:</u> No mortality 8610: ↓ Food consumption and bw			Global silicone producers association, International Research and Development Corporation (1993 - reference number 22 in SCCP 2005)
Rat SD 30 ♀/group Embryo-foetal toxicity	GD 6-15, 6 hours/day 0, 1230, 3690, 8610 D4 Whole body	No teratogenicity <u>Maternal toxicity:</u> No mortality or overt signs of toxicity. 8610: ↓ Food consumption and bw	3690 (Maternal toxicity)		Global silicone producers association, International Research and Development Corporation (1993 - reference number 25 in SCCP 2005)
Rat SD 2 groups F0: 20/sex/ group One generation range- finding	28 days prior to mating to GD 21, then LD 4 to termination. Termination: F0 on LD 21, F1 on PND 28. 6 hours/day 0, 861 and 8610 D4 Whole body	No postnatal toxicity <u>Maternal toxicity:</u> 8610: ↓ Uterine implantation sites and mean live litter size.			Dow Corning Corporation, WIL Research Laboratories, Inc (1996 - reference number 27 in SCCP 2005)
Rat SD 2 groups F0: 22/sex/ group One generation range- finding	28 days prior to mating to GD 20. Termination: F0 on LD 4, F1 on PND4. 6 hours/day 0, 8610 D4 Whole body	No postnatal toxicity 8610: Parental toxicity ↓ Corpora lutea, uterine implantation sites and mean live litter size			Dow Corning Corporation, WIL Research Laboratories, Inc (1996 - reference number 28 in SCCP 2005)
Rat SD 4 groups 40/sex/group Reproductive toxicity dose range-finding (♀ exposed to filtered air only)	70 days prior to mating to GD 13. Termination: F0 (♀) and F1 on PND 21, F0 (♂) 5 weeks later. 6 hours/day 0, 6150, 8610 (♂ only) 5 weeks recovery D4 Whole body vapour	No adverse effects on F1. No effect on the number of implantation sites or litter size No effect on sperm, reproductive or accessory sex organs (♂). No effects on organ weights (absolute, not further specified) (♂). 8610: F0 (♂) toxicity ↓ Mean bw gain and food consumption during the first week.	6150 (F0 toxicity) 8610 (F1)		US-EPA (1997 - in MST) Dow Corning Corporation, WIL Research Laboratories, Inc (1997 - reference number 29 in SCCP 2005) US-EPA (1997c)

Species/strain/sex Study type	Duration/ Dose levels (mg/m^3)/ Chemical form	Effects (mg/m^3)	NOAEC[1)] (mg/m^3)	LOAEC (mg/m^3)	Reference
		6150: ↑ Incidence of ejaculatory plug formation (decreased during the recovery period).			
Rat SD. F022/sex/group One generation range-finding (♀ exposed to filtered air only)	70 days prior to mating and throughout mating. Termination: F0 (♂) after mating, F0 (♀) and F1 on PND 4. 6 hours/day 0, 861, 3690, 6150, 8610 (♂ only) D4 Whole body	8610: No effect on the number of implantation sites or litter size No effect on sperm, reproductive or accessory sex organs (♂). ↑ Liver and thyroid weights (absolute, reversible). ↓ Pup survival (% per litter) on PND 0 and during PND 0-4 interval (statistically insignificant). ↓ Mean pup bw on PND 1 and PND 4. 3690: No parental and neonatal toxicity. 861: ↑ Incidence of ejaculatory plug formation.			US-EPA (1997 in MST) Dow Corning Corporation, WIL Research Laboratories, Inc (1997 - reference number 30 in SCCP 2005) US-EPA (2001b)
Rat SD F0: 22/sex/group One generation range- finding (♂ exposed to filtered air only)	At least 70 days prior to mating to GD 21 and from LD 3 to 21. Termination: F0 (♂) after mating, F0 (♀) on LD 21, F1 on PND 28. 6 hours/day 0, 861, 3690, 6150, 8610 (♀ only) D4 Whole body	8610: Postnatal toxicity. ↓ Mean live litter size and implantation site (statistically significant). 3690: Maternal toxicity in F0 ♀.			US-EPA (1997 in MST) Dow Corning Corporation, WIL Research Laboratories, Inc (1997 - reference number 31 in SCCP 2005)
Rat SD 24 ♀/group One-generation “phased-female” Overall phase (♂ unexposed)	28 days prior to mating to GD 19. 6 hours/day 0, 861, 3690, 6150, 8610 Termination: GD 20 D4 whole body vapour	8610: ↑ Post-implantation loss. 6150: ↓ Foetal survival ↓ Number of uterine implantation sites and foetuses ↑ Pre-implantation loss. 3690: ↓ Number of corpora lutea. ↓ Maternal bw and food intake			Dow Corning Corporation, WIL Research Laboratories, Inc (1998 - reference number 32 in SCCP 2005)
Rat SD 60 ♀/group	31 days prior to mating until 3 days before mating. 6 hours/day 0, 8610	8610: ↓ Food and bw. No effect on corpora lutea and foetal survival.			Dow Corning Corporation, WIL Research Laboratories, Inc (1998 - reference number 32 in

Species/strain/sex Study type	Duration/ Dose levels (mg/m^3)/ Chemical form	Effects (mg/m^3)	NOAEC[1)] (mg/m^3)	LOAEC (mg/m^3)	Reference
One-generation "phased-female" Ovarian phase (♂ unexposed)	Termination: GD 20 D4 whole body vapour				SCCP 2005)
Rat SD 60 ♀/group One-generation "phased-female" Fertilisation phase (♂ unexposed)	3 days prior to mating to GD 3. 6 hours/day 0, 8610 Termination: GD 20 D4 whole body vapour	8610: ↓ Food and bw. ↓ Number of corpora lutea, implantation sites and intrauterine survival. ↑ Mean pre-implantation sites and post-implantation losses.			Dow Corning Corporation, WIL Research Laboratories, Inc (1998 reference number 32 in SCCP)
Rat SD 24 ♀/group One-generation "phased-female" Implantation phase (♂ unexposed)	From GD 2 to GD 5. 6 hours/day 0, 8610 Termination: GD 20 D4 whole body vapour	8610: ↓ Food and bw during GD 2-6. No effect on number of corpora lutea and foetal survival.			Dow Corning Corporation, WIL Research Laboratories, Inc (1998 - reference number 32 in SCCP 2005)
Rat SD 25-70 ♀/group One-generation "phased-female" Pre-mating phase (♂ unexposed)	Group 2-5 on 1, 2, 3 or 4 days prior to mating. Group 6 from 3 days prior to mating until 1 day before mating. Group 7 from 3 days prior to mating to GD 3. 6 hr/day. Termination: GD 8 0, 8610 D4 Whole body	8610: Effects on mean bw gain. ↓ Pregnancy rate. ↓ Reduced food consumption. ↓ Number of corpora lutea and implantation sites. ↑ Number of small implantation sites. ↓ Uterine weight (not further specified).			Dow Corning Corporation, WIL Research Laboratories, Inc (1999 - reference number 33 in SCCP 2005)
Rat SD 25 ♀/group One-generation "phased-female" Post-mating phase (♂ unexposed)	Group 2 on GD 0. Group 3 on GD 1. Group 4 on GD 2. Group 5 from GD 0 to GD 2 6 hr/day. Termination: GD 8 0, 8610 D4 whole body	8610: ↓ Maternal food consumption and mean bw gain in group 5. No reproductive toxicity.			Dow Corning Corporation, WIL Research Laboratories, Inc (1999 - reference number 33 in SCCP 2005)

Species/strain/sex Study type	Duration/ Dose levels (mg/m^3)/ Chemical form	Effects (mg/m^3)	NOAEC[1)] (mg/m^3)	LOAEC (mg/m^3)	Reference
Rat SD F0 and F1: 30/sex/group Two-generation (reproduction toxicity and developmental neurotoxicity) (US-EPA OPPTS test guideline)	70 days prior to mating, during mating until GD 20 and during LD 5 to termination. 6 hr/day. 0, 861, 3690, 6150, 8610 D4	<u>Reproduction:</u> No effect on spermatogenic endpoints and male reproductive tissue (♂). 8610: ↓ Mating and fertility indices (F1). ↑ Oestrous cycle length (F1). 6150: ↓ Mating and fertility indices (second F1 mating). ↓ Mean litter size and mean number of pups born (F0+F1). Extended parturition and/or dystocia (F0). 3690: Extended parturition and/or dystocia (F1).			Dow Corning Corporation (2001 - reference number 34 in SCCP 2005) US-EPA (2001c)
Rabbit New Zealand White 6 ♀/group Dose range-finding	GD 6-18, 6 hours/day 0, 123, 1230, 3690, 8610 D4 Whole body	No teratogenicity <u>Maternal toxicity</u>: No mortality 8610: ↓ Food consumption and bw 3690: ↓ Defecation Soft stool and/or ano-genital staining.			Global silicone producers association, International Research and Development Corporation (1993 - reference number 22 in SCCP 2005)
Rabbit New Zealand White 20 ♀/group Embryofoetal toxicity study	GD 6-18, 6 hours/day 0, 1230, 3690, 6150 D4 Whole body	No teratogenicity <u>Maternal toxicity</u>: No mortality or overt signs of toxicity. 6150: ↓ Food consumption.	3690 (Maternal toxicity)		Global silicone producers association, International Research and Development Corporation (1993 - reference number 26 in SCCP 2005)

♂ = male
♀ = female
GD = gestation days
LD = lactation day
PND = postnatal day
F0 = parent generation
F1 = first generation
SD = Sprague Dawley

1) The NOAECs presented are those stated in the references.

One-generation studies, rat (Dow Corning Corporation, WIL Research Laboratories, Inc 1998 – quoted from SCCP 2005: reference number 32)
The concentrations used were 0, 70, 300, 500 and 700 ppm (0, 861, 3690, 6150 and 8610 mg/m^3). Four groups of female rats were exposed to D4 during selected phases of the reproductive cycle and were mated with unexposed males.

One-generation studies, rat (Dow Corning Corporation, WIL Research Laboratories, Inc 1999 – quoted from SCCP 2005: reference number 33)
The concentrations used were 0 and 700 ppm (0 and 8610 mg/m^3). Female rats were exposed to D4 during selected phases of the reproductive cycle and were mated with unexposed males. Apart from the reduced pregnancy rate in the group exposed one day before mating (day-1 group), no impairment in pregnancy rates was observed. According to the authors, the temporal nature of this effect in the day-1 group was demonstrated by the lack of effect on pregnancy rates of animals exposed two, three or four days before mating. Maternal toxicity was expressed in the post-mating phase by reduced mean body weight gain and food consumption in the GD 0 - GD 2 group. There was no evidence of reproductive toxicity on GD 8.

Two-generation study, rat (Dow Corning Corporation 2001 – quoted from SCCP 2005: reference number 34)
The concentrations used were 0, 70, 300, 500 and 700 ppm (0, 861, 3690, 6150 and 8610 mg/m^3). Reduced mating and fertility indices in the second F_1 mating were observed in all treated groups, but the difference from controls only attained statistical significance at exposure concentrations ≥ 500 ppm.
Reductions in mean live litter size and mean number of pups born were recorded at 500 and 700 ppm (F_0, F_1) and similar changes (not statistically significant) were noted sporadically at 70 and 300 ppm (F_0, F_1) without a clear dose-response relationship.
Extended parturition and/or dystocia were observed in F_0 females (2/30 at 500 ppm and in 3/30 at 700 ppm) and in F_1 females (1/30 at 300, 500 and 700 ppm).
No changes in ovary, uterus, vagina, mammary gland and pituitary gland in F_0 animals were reported. In F_1 animals, oestrus cycle irregularities, reductions in corpora lutea were reported. According to the authors, the subtle change reported in the ovaries (anovulatory), and mammary glands (ductal/acinar proliferation and evidence of secretion) were considered to be part of the oestrous cycle perturbation. It was also noted by the authors that the effects seen in the F_1 generation were possibly a combination of D4's effect on the LH surge as well as a slight acceleration of the spontaneous process of reproductive senescence in the F_1 females.
The differences in general toxicity responses to inhalation of D4 between the F_0 and F_1 generations were minimal. Overall the responses were slightly more severe in F_1 than in F_0 animals except for respiratory tract reactions, see section 4.4.1.2. The general lack of reproduction toxicity in the F_0 generation compared to the F_1 generation may, according to the authors, be associated with the small difference in age at start of treatment (F_0 – 44 days old, F_1 – 22 days old).
No adverse effects were observed on ano-genital distance, vaginal patency and preputial separation. No adverse effects were observed on male functional reproductive parameters, on male spermatogenic endpoints, on microscopic evaluation of male reproductive tissue, or when exposed F1 males were mated with unexposed females. (US-EPA 2001c).

4.5.1.3 D5

Studies on reproductive toxicity with inhalation of D5 are summarised in Table 13.

Table 13. Animal reproductive toxicity studies on D5, inhalation

Species/strain/sex **Study type**	**Duration/** **Dose levels (mg/m^3)/** **Chemical form**	**Effects** **(mg/m^3)**	**NOAEC** **(mg/m^3)**	**LOAEC** **(mg/m^3)**	**Reference**
Rat SD 2 groups of F0 22/sex/group Range-finding reproductive toxicity study	F0: 28 days prior to mating to termination (♀ not from GD 21 to LD 4). 6 hours/day 400, 2033 D5 Whole body	No effects on reproductive parameters. No effects on mean live litter size or on the number of uterine implantations. 2033: Total litter loss in 2 dams, significance uncertain.			US-EPA (1996d)
Rat SD 30/sex/group Two-generation (reproduction toxicity and developmental neurotoxicity)	F0+F1: 70 days prior to mating to termination (♀ not from GD 20 to LD 5). 6 hours/day 462, 1078, 2464 D5 whole body	No parental toxicity in F0 + F1. No effects on reproductive performance in F0 + F1. No neonatal toxicity in F1 + F2. No developmental neurotoxicity in F2. No exposure-related differences in absolute mean organ weight data in F0 + F1. No effect on mean ovarian primordial follicle counts. No effect on spermatogenic endpoints.			US-EPA (1999)

♂ = male
♀ = female
Bw = body weight
GD = gestation days
LD = lactation day
F0 = parent generation
PND = postnatal day
F1 = first generation
F2 = second generation
SD = Sprague Dawley

4.5.1.4 HMDS

One study on reproductive toxicity with inhalation of HMDS has been located. The information is summarised in Table 14 and supplementary information is presented in the text.

One-generation study, rat (US-EPA 2000b)
The concentrations used were 0, 100, 1000 and 5000 ppm (0, 675, 6750 and 33750 mg/m^3). F1 pups were exposed to HMDS from postnatal day (PND) 22 to PND 27. Mean lung and liver weights were increased (F0) at 33750 mg/m^3 but no macroscopic lung or liver findings were observed. Mean F_1 live litter size, number of pups born, percentage of males per litter at birth and ano-genital distances were unaffected in all dose groups. F_1 pup survival was slightly decreased at 33750 mg/m^3 but was limited to three litters and was not statistically significant. One dam at 675, one dam at 6953 mg/m^3 and two dams at 33750 had total litter loss on PND 1 or 5. At all exposure levels there were no effects on body weight and general physical condition of the F_1 pups and no gross internal findings of differences in mean organ weight data attributed to parental exposure.

4.5.2 Oral intake

One study on reproductive toxicity with oral administration of D4 has been located. The information is summarised in Table 15 and supplementary information is presented in the text.

4.5.2.1 D4

Dose-range finding study, rabbit (Global silicone producers association, International Research and Development Corporation 1993 – quoted from SCCP 2005: reference number 24)
The test dose levels were 0, 50, 100, 500 and 1000 mg/kg bw/day. The treatment-related abortions observed at 500 and 1000 mg/kg bw/day and the markedly increased post implantation losses at 1000 mg/kg bw/day correlated with reductions in the number of live foetuses and gravid uterine weights at 1000 mg/kg bw/day. By gestation day 13 most rabbits at 500 or 1000 mg/kg bw/day were consuming less than 20 g/day or not eating at all. According to the authors, it is considered likely that the increase in abortions and post implantation losses are the consequence of reduced food consumption and not a direct effect of D4.

Some studies have indicated that D4 may have a weak oestrogenic and anti-oestrogenic activity in the rat Uterotrophic Assay in both immature Sprague Dawley and Fisher 344 rats. D4 was 77,000 to 25 million times less potent than ethinyloestradiol or diethylstilbestrol in Sprague Dawley or Fischer 344 rats. In a series of studies in mice, in which D4 was administered orally, D4 significantly reduced serum oestradiol levels. On the other hand, uterine peroxidase activity, a marker for oestrogenic activity, and uterine weights were significantly increased. The uterotrophic effects of D4 were not seen after pre-treatment with ICI 182,780, an oestrogenic receptor (ER) antagonist, and ovariectomised ERα (oestrogen receptor alpha) knock-out mice showed no increases in uterine weights when treated with D4. (Dow Corning Corporation, MPI Research 1999, Bin et al. 2003 – quoted from SCCP: reference numbers 69 and 70).

Table 14. Animal reproductive toxicity studies on HMDS, inhalation

Species/strain/sex **Study type**	**Duration/** **Dose levels (mg/m^3)/** **Chemical form**	**Effects** **(mg/m^3)**	**NOAEC** **(mg/m^3)**	**LOAEC** **(mg/m^3)**	**Reference**
Rat SD 4 groups F0: 24/sex/group F1: 60/sex/group Range-finding study	F0: 28 consecutive days prior to mating to termination (♀ not from GD 20 to LD 5). 6 hrs/day 0, 675, 6750, 33750 HMDS	All F0 animals survived. No effects on reproductive parameters in F0. No histopathological findings in F0. No effect on litter size, number of pups and ano-genital distances in F1 33750: Transient effect on bw gain and food consumption in F0. ↑ Mean lung and liver weight in F0 (not further specified). Slight but not statistically significant effect on postnatal pup survival.			US-EPA (2000b)

♂ = male
♀ = female
Bw = body weight
GD = gestation days
LD = lactation day
F0 = parent generation
PND = postnatal day
F1 = first generation
F2 = second generation
SD = Sprague Dawley

Table 15. Animal reproductive toxicity studies on D4, oral administration

Species/strain/sex **Study type**	**Duration/** **Dose levels/** **Chemical form**	**Effects**	**NOAEL**	**LOAEL**	**Reference**
Rabbit New Zealand White 6 ♀/group Dose range finding	GD 7-19 0, 50, 100, 500 and 1000 mg/kg bw/day D4 by gavage	No teratogenicity. 1000: ↑ Post implantation losses. ↓ Food consumption and bw Anogenital staining and hair loss 500: Treatment-related abortions. Mucoid stool. Tissue and/or red fluid on cage tray (often associated with abortion).			Global silicone producers association, International Research and Development Corporation (1993 - reference number 24 in SCCP 2005)

♀ = female
bw = body weight
GD = gestation days

4.6 Mutagenic and genotoxic effects

In vitro and *in vivo* studies on mutagenicity and genotoxicity of D3, D4 and HMDS are summarised in Tables 16 to 18. No data on D5 and D6 were located.

4.7 Carcinogenic effects

4.7.1 Inhalation

4.7.1.1 D4

In a carcinogenicity study, F344 rats (60 rats/sex/group, 7-8 weeks old) were exposed to D4 (vapour) at concentrations of 0, 120, 360, 1820 or 8490 mg/m^3 (6 hours/day, 5 days/week) by whole-body inhalation for 24 months. Survival at 8490 mg/m^3 was 38% in treated males compared to 58% for controls and 58% in treated females compared to 72% for controls. It was stated by the authors that this effect on mortality was likely due to an early onset and increased incidence of mononuclear cell leukaemia (MNCL) that occurred at 8490 mg/m^3. The terminal mean body weight and weight gain of male rats were significantly lower than the controls (8490 mg/m^3). A 51% increase in absolute and relative uterine weight was seen in female rats (8490 mg/m^3). At 8490 mg/m^3 the total incidence of cystic endometrial hyperplasia (histopathologically) was 78% compared to 19% in the control group and four of the 35 (11%; $p<0.04$) female animals in this dose group that survived two years were diagnosed with endometrial adenomas. No uterine adenomas were diagnosed in the intercurrent mortality animals or in any of the other groups. The frequency of MNCL in male rats was: 73% in the controls (43/59; historical controls 474/1059 [45%]; $p<0.0001$); 10-ppm group 45% (27/60); 30-ppm group 43% (26/60); 150-ppm group 48% (29/60); and 700-ppm group 69% (41/59). The frequency of MNCL in surviving male rats at 8490 mg/m^3 was similar to the control; however, the frequency in the control group was significantly higher than in the historical controls. The frequency of MNCL was increased in early death and moribund sacrificed male rats exposed to 8490 mg/m^3 compared to male controls. This increase was statistically significant ($p < 0.05$) using the Peto analysis. The frequencies of MNCL in the 120 and 360 mg/m^3 groups were similar to the historical controls. If the MNCL in the 8490 mg/m^3 group is compared to the 120 mg/m^3 group, the increase in the 8490 mg/m^3 group is significant ($p<0.0094$). No increase in MNCL was found among the exposed female rats. (Plotzke et al. 2005 – quoted from SCCP 2005: reference number AR4). Non-neoplastic findings are addressed in section 4.4.1.

4.7.1.2 D5

A two-year chronic toxicity and carcinogenicity study in rats exposed to vapour concentrations of 0, 154, 616 or 2464 mg/m^3 of D5 for 6 hours per day, 5 days per week for 24 months, showed that female rats exposed to the highest dose exhibited a statistically significant increase of uterine tumours. No significant increases in tumours were observed at lower concentrations. An additional study was conducted to determine the specific mode of action for the D5-induced uterine tumours in rats. US-EPA is in the process of evaluating these studies and anticipates that the mode of action analyses will be complete by the end of 2006. (US-EPA 2005b).

In a letter to US-EPA, the Dow Corning Corporation comments on the preliminary results of the two-year chronic toxicity and carcinogenicity study in rats: "*While*

several of the statistical methods applied showed a statistically significant trend for uterine endometrial adenocarcinomas, statistical significance was reduced or eliminated when the adenomas and adenomatous polyps were combined with the adenocarcinomas. It is generally expected that cellular hyperplasia precedes the formation of an adenoma, which precedes the formation of an adenocarcinoma. There are no observations in this bioassay that support the normal progression of these tumors. There is neither an increase in the incidence or severity of hyperplasia and there is no dose-related or statistically significant increase in adenomas. There is also no indication of hormonal alteration or cycle disruption in this study or any previous studies that would provide an potential mode of action for this lesion. In other words, there does not appear to be a biologically plausible explanation for these tumors". (Communication between US-EPA and Dow Corning Corporation 2003).

4.7.1.3 HMDS

In a two-year chronic toxicity and carcinogenicity study (study has been completed but the final report is not yet available – quoted from OSPAR Commission 2004), F344 rats were exposed by inhalation to 0, 675, 2700, 10800 or 33750 mg/m^3 of HMDS, 6 hours/day, 5 day/week for up to two years.
An apparent dose related increase in Leydig cell tumours in the testes of male rats was observed after one year of exposure and an increase in testicular weights in a dose related manner in all exposure groups was observed following two years of exposure. There was nearly a 100% incidence of Leydig cell tumours in the male rats in all dose groups including controls at two years. It was noted by the authors that this is an expected observation in this strain of male rats at this time point. An increase in kidney tumours in male rats exposed to 10800 or 33750 mg/m^3 HMDS was also observed following two years of exposure. Recently completed mechanistic work confirms that the kidney tumours are mediated through $\alpha_{2\mu}$-globulin that is male rat-specific and not relevant to humans (OSPAR Commission 2004).

Table 16. Mutagenicity and genotoxicity studies of D3

Test system Guideline	**Test object**	**Dose levels/concentration/**	**Results**	**Conclusion**	**Reference**
In vitro mammalian cell culture assay	L5178Y mouse lymphoma cell line	0.067, 0.130, 0.270, 0.530 and 1.06 mg/ml (point mutations) 0.976, 0.1953, 0.3906, 0.7812, 1.5625 and 3.1250 mg/ml (sister chromatid exchanges and primary DNA damage). D3 with and without metabolic activation.	No evidence of point mutations or primary DNA damage was reported. Slight elevations in sister chromatid exchange were observed at concentrations near 1 mg/ml, with no associated increase in chromosomal aberrations. This elevation could be explained by significant cytotoxicity at this concentration (authors). These results were not sufficient to classify the test chemical as a clastogen, since cytotoxicity was present.	Equivocal	US-EPA (1978 in TSCATS)
In vitro Bacterial gene mutation assay	*S. typhimurium* (TA 1535, TA1537, TA1538, TA98, and TA100). *S. cerevisiae* (D4). *E. coli* (polA+ and polA-).	0.1, 1, 10, 100 and 500 μg/plate D3 with and without metabolic activation.	No evidence of mutagenicity except a slight increase in revertants observed in the TA1538 strain without activation. The test was rerun and no evidence of mutagenicity was observed. These results were not sufficient to classify the test chemical as a clastogen, since cytotoxicity was present.	Equivocal	US-EPA (1978 in TSCATS)
In vivo Chromosome aberration test	Rat bone marrow cells	125, 225, 300, 400, 515 mg/kg bw D3 injected intraperitoneally	Some lethality at doses higher than 515 mg/kg bw.	Negative	US-EPA (1982 in TSCATS)

Bw = body weight

Table 17. Mutagenicity and genotoxicity studies of D4

Test system Guideline	Test object	Dose levels/concentration/	Results	Conclusion	Reference
In vitro Bacterial gene mutation assay (Ames test)	*S. typhimurium* (TA98, TA100, TA1535, TA1537, TA1538)	100 – 5,000 µg/plate D4 with and without metabolic activation	No mutagenic activity was observed in any of the five strains tested, either by evidence of a dose-response relationship or a doubling of the mean number of colonies over the mean control level, either in the absence or presence of S9 activation. These results were observed in two independent experiments. All five bacterial strains exhibited mutagenic response to the appropriate positive control substance. Negative (solvent) controls were also tested with each strain and the mean numbers of spontaneous revertants were considered acceptable.	Negative	Global silicone producers association, International Research and Development Corporation (1993 - reference number 49 in SCCP 2005)
In vitro Chromosome aberration test	Chinese hamster ovary cells (CHO-K1-BH4) (subclone D1)	0.3 – 10 µg/ml without metabolic activation. 3 – 30 µg/ml with metabolic activation. D4	No unusual types or distribution of aberration were observed. Endo-reduplication was observed in both replicates at 30 µg/ml in the presence of metabolic activation, but was not evaluated quantitatively. The positive controls produced significant numbers and types of chromosome damage, demonstrating the responsiveness of the test system. Under the conditions of the assay described, D4 did not induce an increase in structural chromosome aberrations in CHO cells in the presence and absence of metabolic activation system.	Negative	Global silicone producers association, International Research and Development Corporation (1993 - reference number 50 in SCCP 2005)
In vitro Sister chromatid exchange (SCE)	Chinese hamster ovary cells (CHO-K1-BH4) (subclone D1)	0.03 – 3 µg/ml without metabolic activation. 3 – 30 µg/ml with metabolic activation. D4	The SCE frequencies for the culture medium controls were in the acceptable range. The positive controls produced significant numbers of SCE demonstrating the responsiveness of the test system. Under the conditions of the assay described, D4 did not induce an increase in SCE in CHO cells in the absence of metabolic activation system. D4 produced statistically significant increases in the incidence of SCE in the presence of S9 metabolic activation. These increases were not considered dose-related and were of a small magnitude and were considered not to be of biological relevance (authors).	Negative	Global silicone producers association, International Research and Development Corporation (1994 - reference number 51 in SCCP 2005)
In vitro Ames test	*S. typhimurium* (TA98, TA100, TA1535, TA1537, TA1538)	5 mg/plate. D4 with and without metabolic activation	No mutagenicity was detected.	Negative	Vergnes et al. (in MST 2005)
In vitro SCE assay	Chinese hamster ovary cells	≤0.003 mg/ml D4 with and without metabolic activation	No significant dose-related increases in chromosomal aberration frequencies.	Negative	Vergnes et al. (in MST 2005)
In vivo Chromosome aberration test	Rat SD ♂/♀	5 days 6 hours/day 8610 mg/m^3 D4 by whole body inhalation	No significant treatment-related increases in chromosomal aberration frequencies.	Negative	Vergnes et al. (in MST 2005)

Test system Guideline	Test object	Dose levels/concentration/	Results	Conclusion	Reference
In vivo Chromosome aberration test	Rats SD ♂/♀ 8 weeks old	5 days 6 hours/day 8610 mg/m^3 D4 by inhalation	No statistically significant or exposure-related increases in the incidence of chromosomal aberrations were observed in rats of either sex at the 6 h or 24 h sampling intervals. Positive control produced significant numbers and types of damage with both ♂ and ♀.	Negative	Global silicone producers association, International Research and Development Corporation (1994 - reference number 52 in SCCP 2005
In vivo Dominant lethal assay (OECD 426)	Rats SD 15/sex/group 10-12 weeks old (♂)	8 weeks prior to mating 5 days/week 100, 500 and 1000 mg/kg bw/day D4 by gavage	Uterine dissection of the pregnant females 14 days after confirmation of mating revealed no evidence of a treatment-related effect on corpora lutea or implant counts or on litter size. The positive control group utilising triethylenemelamine (TEM) produced a significant reduction in fertility, an increase in dead implants and a decrease in litter size, thus validating the test system. It is concluded by the authors, that the test gave no evidence of D4 inducing chromosomal damage in germinal tissue.	Negative	Dow Corning Corporation 1982 - reference number 53 in SCCP 2005

♂ = male
♀ = female
Bw = body weight

Table 18. Mutagenicity and genotoxicity studies of HMDS

Test system Guideline	Test object	Dose levels/concentration/	Results	Conclusion	Reference
In vitro Bacterial gene mutation assay (Ames test)	*S. typhimurium* TA98, TA100, TA1535, TA1537 and TA1538.	Up to 5.0 µl/plate HMDS with and without metabolic activation		Negative	IUCLID (2000)
In vitro Bacterial gene mutation assay (Ames test)	*S. typhimurium* TA1535 ,TA1537, TA1538, TA98, TA100	0.001 to 5 µl/plate HMDS with and without metabolic activation	The results of the tests conducted in the absence of a metabolic activation system were all negative. The test with TA98 was repeated because of slightly increased revertants observed in the initial test. The repeat test was negative. The results of the tests conducted in the presence of a metabolic activation (rat liver) system were all negative. The test with TA98 was repeated because of increased revertants observed with this strain in the initial test. The repeat test was negative. The test substance was not considered mutagenic.	Negative	IUCLID (2000)
In vitro Bacterial gene mutation assay (Ames test)	*S. typhimurium* TA1535, TA100, TA1537, TA98	12500 µg/plate HMDS with and without metabolic activation		Negative	IUCLID (2000)
In vitro Bacterial gene mutation assay (Ames test)	*S. typhimurium* TA1535, TA1537, TA1538, TA98, TA100	312.5 to 5000 µg/plate HMDS with and without metabolic activation		Negative	IUCLID (2000)
In vitro Bacterial gene mutation assay (Ames test)	*S. typhimurium* TA1535, TA1537, TA1538, TA98, TA100	0.5 to 500 µg/plate HMDS with and without metabolic activation		Negative	IUCLID (2000)
In vitro DNA damage and repair assay	*E. coli* W3110/polA+, P3478/polA	0.001 µl/plate to 5 µl/plate HMDS with and without metabolic activation		Negative	IUCLID (2000)
In vitro Mouse lymphoma assay	L5178Y	0.0125 to 0.2 microl/ml HMDS with and without metabolic activation	The test substance was evaluated for genetic activity in the L5178Y mouse lymphoma cell line. Observations were made for chromosome aberrations, sister chromatid exchanges, forward mutation at the TK locus and primary DNA damage. Positive reference mutagens were used to test responsiveness of the cells with and without metabolic activation. Point mutation assay: negative Chromosomal events: The result from SCE analysis and cytogenetic analysis showed scattered points of elevated chromosome alterations, but the pattern of responses was not consistent with clastogenic activity, except in one case. Primary DNA damage assay: negative. The test substance did not	Negative	IUCLID (2000)

Test system Guideline	Test object	Dose levels/concentration/	Results	Conclusion	Reference
			produce response which indicated consistent genetic activity. According to the authors, some data showed evidence of a weak clastogenic activity.		
In vivo Cytogenetic assay	Rat ♂ SD	6, 24 and 48 hours. 255, 515 and 1030 mg/kg bw HMDS i.p.	Doses higher than 1030 mg/kg were not tested since some lethality was observed at 1825 mg/kg. Animals were sacrificed at 6, 24 or 48 hours after injection. There was no evidence that the test substance induced chromosomal damage in rats following ip injection. No complex rearrangements were detected in animals injected with the test substance. A comparison of the frequencies of breaks for 1030, 515 and 255 mg/kg at the three time points showed no significant differences. There was no evidence in this study that the test substance caused chromosomal damage.	Negative	IUCLID (2000)
In vivo Cytogenetic assay	Rat ♂ SD	6, 24 and 48 hours 0, 255, 575 and 1030 mg/kg bw HMDS i.p.	The test substance did not produce significant increase in chromosome aberrations in the assay. The test substance is not considered genotoxic in the in vivo clastogencity test employed in this study.	Negative	IUCLID (2000)

♂ = male
Bw = body weight

5 Regulations

5.1 Ambient air

-

5.2 Drinking water

-

5.3 Soil

-

5.4 Occupational Exposure Limits

-

5.5 Classification

5.5.1.1 D4

D4 is classified Repr. Cat. 3 R62 (possible risk of impaired fertility), and R53 (may cause long-term adverse effects in the aquatic environment) (MM 2002).

5.6 IARC

-

5.7 US-EPA

-

6 Summary and evaluation

6.1 Description

Siloxanes form a group of chemicals with molecular weights from a few hundreds to several hundred thousands. Siloxanes consist of silicon atoms linked via oxygen atoms, forming a cyclic or linear backbone structure. Each silicon atom bears one or several side chains, which may form cross-links and influence the properties of the polymer (e.g. phenyl side groups provide oxidative stability, aminopropyl side groups provide water solubility, and trifluoropropyl side groups provide high resistance to solvents). In the simplest form, the side-chains consist of methyl groups (dimethylsiloxanes), e.g., D3, D4, D5, D6 and HMDS.

6.2 Environment

Siloxanes are anthropogenic compounds and enter the environment by a variety of human activities. The main source of emissions into the air is volatile siloxanes used in cosmetics, wax and polishes. Once released into the atmosphere the volatile siloxanes may react with hydroxyl radicals. Half-lives for reaction with hydroxyl radicals in air for D4, D5, and HMDS of 16, 10 and 12 days, respectively, have been reported. In Denmark, measurements of air concentrations of siloxanes have been taken at four locations of which three were taken outdoors and one was taken inside a sewage treatment plant. The air concentrations of D4, D5 and D6 were in the range 0.26-2.4 μg/m^3, 0.19-1.3 μg/m^3 and 0.07-0.44 μg/m^3, respectively. The measured air concentrations of HMDS were <0.004 μg/m^3 (below detection limit).

The non-volatile siloxanes used in cosmetics, toiletries, textile applications, cleaning agents and maintenance will mainly be discharged with wastewater. During the waste water treatment processes in treatment plants, approximately 97% of polydimethylsiloxanes will be bound to the sludge and spread on agricultural fields, incinerated or disposed of for landfills. The remaining, approximately 3%, will be discharged to surface water.

Siloxanes in solids will after use most often be disposed of for incineration and are nearly 100% mineralised by this process. Incineration plants are not considered significant sources of siloxane releases to the atmosphere.

In Denmark, concentrations of D4, D5, D6 and HMDS in surface water, measured at three locations, were <0.04 μg/L, <0.02 μg/L, <0.02 μg/L and <0.0005 μg/L, respectively. Concentrations of D4, D5, D6 and HMDS in sludge, measured at two locations, were in the range 470-740 ng/g dry weight (dw), 27000-50000 ng/g dw, 1100-2800 ng/g dw and <1-<3 ng/g dw, respectively. Concentrations of D4, D5, D6 and HMDS in sediment, measured at three locations, were in the range <3-84 ng/g dw, <2-2000 ng/g dw, <1-170 ng/g dw and <0.03-<0.3 ng/g dw, respectively. No data for concentrations of siloxanes in soil have been located.

Concentrations of siloxanes in marine fish and mammals have been measured in Denmark at four locations. For marine fish the concentrations of D4, D5, D6 and HNDS were in the range <0.4-52 ng/g wet weight (ww). For seals the concentrations of D4, D5, D6 and HMDS were in the range <0.4-24 ng/g ww.

Siloxanes are resistant to chemical reactions such as oxidation, reduction and photodegradation. As the available data provide equivocal information, it is not clear whether siloxanes undergo hydrolysis under environmental conditions.

6.3 Human exposure

In Sweden, human breast milk samples were analysed for three cyclic siloxanes, D4, D5 and D6 and for four linear siloxanes, including HMDS. Eleven of 39 samples contained one or more of the cyclic siloxanes. The maximum concentrations of D4, D5 and D6 were 10 μg/L, 4.5 μg/L and 4.8 μg/L, respectively. Trace amounts of linear siloxanes were found in 6 samples in concentrations <0.04 μg/L.

6.4 Toxicokinetics

Human data indicate that D4 is absorbed after inhalation. Metabolites were found to be more persistent in plasma than parent D4 and were still present at 24 hours post-exposure.
Low percutaneous absorption was observed in humans following topical application of D4 and D5. D6 tested in a human skin *in vitro* assay showed no penetration through the skin.

In rats, 4.4-8.3% of inhaled ^{14}C-D4 and 2% of inhaled ^{14}C-D5 was retained. The radioactivity elimination half-life, after exposure to 86.1 to 8610 mg/m^3 ^{14}C-D4, was 13 hours in blood, 59 hours in plasma and ranged from 34 to 158 hours in tissues. Following inhalation of D4, 23-35% of the radioactivity was recovered as expired volatiles, 0.4-5.4% as expired CO_2, 32-47% by renal excretion and 9.5-30% by faecal excretion. The radioactivity measured in the urine after inhalation exposure of ^{14}C-D4 or ^{14}C-D5 was only or mainly due to metabolites.

In rats, 12-52% of orally administrated D4 and approximately 12% of oral administrated D6 was absorbed. After oral administration of HMDS, the predominant metabolite in the urine was $HOCH_2(CH_3)_2SiOSi(CH_3)_2CH_2OH$ whereas no parent HMDS was detected.

6.5 Mode of action

Studies in rats indicate that D4 and D5 induce hepatic cytochrome P450 enzymes similarly to that observed following exposure to phenobarbital.

Rats exposed to D4 showed an impaired female fertility related to a reduction of the number of mean corpora lutea and implantation sites and increased post-implantation losses. An indirect mode of action appears to be the most relevant explanation for those effects at high doses. Data from studies in rats indicate that D4 can cause a delay or blockage of the luteinising hormone (LH) surge necessary for optimal timing of ovulation.

Endometrial adenomas have been observed in female rats exposed to D4 or D5. The neoplastic effects observed after D4 exposure has been attributed to a hormonal dysregulation resulting from interaction of D4 with the dopamine D2-receptor. Data suggest that D4 can act as a dopamine D2-receptor agonist *in vivo* causing a reduction in prolactin. A reduction of prolactin in the rat causes luteolysis

and new ovarian follicle stimulation resulting in oestrogen dominance, which leads to persistent endometrial stimulation leading to uterine tumours. Prolactin is not luteotropic in non-human primates and humans.

6.6 Human toxicity

6.6.1 Single dose toxicity

No significant change in forced vital capacity and no immunotoxic or proinflammatory/adjuvant effect was observed immediately after exposure or 24 hours post-exposure in 12 healthy volunteers exposed by inhalation to 122 mg/m^3 D4 for one hour, separated by one week.

6.6.2 Irritation and sensitisation

HMDS is reported to be a skin and an eye irritant.

Repeated insult patch tests, with D4 or HMDS, did not result in skin sensitisation.

6.6.3 Repeated dose toxicity

No human data regarding repeated dose toxicity following inhalation exposure to D3, D4, D5, D6 or HMDS have been located.

6.6.4 Toxicity to reproduction

No human data regarding reproductive effects following exposure to D3, D4, D5, D6 or HMDS have been located.

In an *in vitro* oestrogen responsive reporter gene study, using the MCF-7 human cell line, it was suggested that D4 could elicit an oestrogenic effect that is dose-dependent with no significant anti-estrogenic activity.

6.6.5 Mutagenic and genotoxic effects

No human data regarding mutagenic or genotoxic effects following exposure to D3, D4, D5, D6 or HMDS have been located.

6.6.6 Carcinogenic effects

No human data regarding carcinogenic effects following exposure to D3, D4, D5, D6 or HMDS have been located.

6.7 Animal toxicity

6.7.1 Single dose toxicity

LC_{50}-values in rats were reported to be 36000, >2700 and 107700 mg/m^3 for D4, D5 and HMDS, respectively. An LC_{50}-value of 3300 mg/m^3 was reported for dogs exposed to HMDS.

Oral LD_{50}-values in rats were reported to be >4800, >24100, >50000 and >5000 mg/kg bw for D4, D5, D6 and HMDS, respectively. In rats, effects observed after oral exposure to 2000 mg/kg bw D4 (in corn oil), included initial weight loss, slight diarrhoea, slight diuresis, and liver and kidney injury.

6.7.2 Irritation

Both positive results (slight irritating) and negative result (not irritating) are reported for skin irritation after dermal application of D4 or HMDS to rabbits. D4 and HMDS were tested on rabbit eyes without signs of irritation.

6.7.3 Sensitisation

D4 and HMDS were not sensitising in a guinea pig maximisation test.

6.7.4 Repeated dose toxicity

6.7.4.1 D3

Following inhalation of D3, liver toxicity has been observed in rats at 23125 mg/m^3 for 28 days (increased weight, hepatocellular hypertrophy). Other effects observed included decreased motor activity and reaction to handling, decreased absolute weight of epididymides and decreased relative weight of seminal vesicles. Protein droplet nephropathy was reported in males exposed to 4625 mg/m^3 D3 for 28 days.

6.7.4.2 D4

Following inhalation of D4, liver toxicity has been observed in rats at exposure levels at 1845 mg/m^3 for 5 days (hepatocellular hypertrophy), from 246 mg/m^3 for 28 days (increased absolute and relative weight), from 861 mg/m^3 for 28 days (induction of hepatic enzymes), from 861 mg/m^3 in the two-generation study (hepatocellular hypertrophy), and from 369 mg/m^3 for one year (increased absolute weight in males). In mouse and hamster, increased liver weight was observed at 8610 mg/m^3 (only dose level in the study) for 28 or 35 days. In rabbits and guinea pigs exposed to 8610 mg/m^3 (only dose level in the study) for 35 or 28 days, no liver effects were reported. Other effects observed in rats included interstitial inflammation and alveolar macrophage foci in the lungs (430 mg/m^3 for 13 weeks – lowest concentration in the study), increase in lung pentoxyresorufin O-dealkylase (PROD) (861 mg/m^3 for 28 days), alteration in blood biochemistry (1500 mg/m^{3}for 13 weeks), vaginal mucification and decreased mitochondria volume (2780 mg/m^3 for 28 days – lowest concentration in the study), increased adrenal and decreased thymus weights (6000 mg/m^3 for 13 weeks), increased kidney weight (8610 mg/m^3 for two years).

6.7.4.3 D5

Following inhalation of D5, liver toxicity has been observed in rats at dose levels from 750 mg/m^3 for three months (increased relative weight) and 2464 mg/m^3 (only concentration in the study) for 28 days (induction of hepatic enzymes). Other effects observed in rats included increased gamma-glutamyltransferase activity

(750 mg/m^3 for three months), decreased testes weight, increased multifocal alveolitis and goblet cell hyperplasia (1330 mg/m^3 for three months), vaginal mucosal mucification, interstitial gland hyperplasia, decreased relative thymus weight, increased relative lung weight and changes in blood biochemistry (3530 mg/m^3 for three months).

6.7.4.4 D6

No data on repeated dose toxicity of D6 have been located.

6.7.4.5 HMDS

Following inhalation of HMDS, minimal liver effects were observed in rats at 12700 mg/m^3 for one month (hepatocellular hypertrophy). Effects in kidneys were observed at concentrations from 4000 mg/m^3 for 13 weeks (histological lesions, tubular regeneration). Other effects included slight increased plasma urea and creatinine concentrations (4050 mg/m^3 for 13 weeks), testicular tubular atrophy (13640 mg/m^3 for 3 months), and interstitial inflammation in lungs (from 140 mg/m^3 for three months but after recovery only at 13640 mg/m^3 for three months).

6.7.5 Toxicity to reproduction

6.7.5.1 D3

In rats exposed to D3 by inhalation at 925, 4625 or 23125 mg/m^3 (from 14 days prior to mating to GD 19) in a combined toxicity study that included a reproductive and developmental toxicity screening, there was a decrease in litter size (33%) and in the number of implantation sites at the highest exposure level whereas gestation length, pup sex ratio, pup weight and viability, and corpora lutea counts were unaffected.

6.7.5.2 D4

No developmental toxicity was observed after inhalation of concentrations up to 8610 mg/m^3 in neither rats (exposed on GD 6-15) nor rabbits (exposed on GD 6-18).

Effects on reproduction and fertility, and developmental toxicity have been investigated in rats in one-generation inhalation studies (range finding, crossover and phased female studies) and in a two-generation inhalation study.
In one-generation inhalation studies, exposure of female rats to D4 (3-28 days prior to mating to GD 3-21) resulted in decreased number of corpora lutea (3690 mg/m^3) and uterine implantation sites (8610 mg/m^3), and decreased total number of pups born (6150 mg/m^3) and mean live litter size (6150 mg/m^3). No effects on the number of implantation sites or litter size were observed in studies where males exposed to 8610 mg/m^3 D4 (70 days prior to mating and throughout mating) were mated to unexposed females. Also no effects were observed on sperm or male reproductive or accessory sex organs. In phased female studies, no effects on corpora lutea and foetal survival were observed when female rats were exposed from day 31 before mating to day 3 before mating or when exposed from GD 2 to GD 5. However, when female rats were exposed from day 3 before mating to GD 3 (8610 mg/m^3), reduced number of corpora lutea, implantation sites and intrauterine

survival were reported together with increased mean pre-implantation sites and post-implantation losses.
In a two-generation inhalation study in rats, effects observed included extended parturition and/or dystocia (3690 mg/m^3), decreases in mating, fertility indices, mean litter size and mean number of pups born (6150 mg/m^3), and increased oestrous cycle length (8610 mg/m^3).

Some studies have indicated that D4 may have a very weak oestrogenic and anti-oestrogenic activity in the rat uterotrophic assay in both immature Sprague-Dawley and Fisher 344 rats.

6.7.5.3 D5

In rats, exposed by inhalation at concentrations up to 2033 mg/m^3 D5 (from 28 days prior to mating), no effects on reproductive parameters, mean live litter size or number of uterine implantations were observed. In a two-generation inhalation study in rats exposed up to 2464 mg/m^3, neither parental toxicity nor effects on reproductive performance, total litter losses, neonatal toxicity and developmental neurotoxicity (F_2) were observed.

6.7.5.4 D6

No studies have been located regarding reproductive or developmental effects in animals following exposure to D6.

6.7.5.5 HMDS

In rats exposed by inhalation at concentrations up to 33750 mg/m^3 HMDS (from 28 days prior to mating), no effects on reproductive parameters, litter size, number of pups, or ano-genital distance were observed.

6.7.6 Mutagenic and genotoxic effects

D3, D4 and HMDS have been tested in a number of *in vitro* and *in vivo* systems. Two *in vitro* tests with D3 were concluded to be equivocal whereas an *in vivo* test was clearly negative. For D4 and HMDS, all the available tests showed a negative result.

No data regarding mutagenic and genotoxic effects of D5 and D6 have been located.

6.7.7 Carcinogenic effects

No studies have been located regarding carcinogenic effects in animals following exposure to D3 or D6.

6.7.7.1 D4

In a 2-year inhalation study in rats, an increased incidence of cystic endometrial hyperplasia (78% compared to 19% in the control group) was observed in females

exposed at the highest concentration (8610 mg/m^3). Eleven percent of the females in this group that survived two years were diagnosed with endometrial adenomas. No uterine adenomas were diagnosed in the intercurrent mortality animals or in any of the other groups. An early onset and increased incidence of mononuclear cell leukaemia (MNCL) was observed in male rats but not in female rats at 8610 mg/m^3.

6.7.7.2 D5

In a 2-year inhalation study in rats, a statistically significant increase of uterine endometrial adenocarcinomas was observed in females exposed at the highest concentration (2464 mg/m^3). No significant increase in tumours was observed at lower concentrations.

6.7.7.3 HMDS

In a 2-year inhalation study in rats, an apparent dose related increase in Leydig cell tumours (nearly a 100% incidence in all groups including controls after two years) was observed in the testes of male rats. After two years of exposure, kidney tumours were observed in male rats exposed to 10800 or 33750 mg/m^3 HMDS.

6.8 Evaluation

Human data indicate that D4 is absorbed following inhalation. In rats, 4.4-8.3% of inhaled ^{14}C-D4 and 2% of inhaled ^{14}C-D5 was retained. The radioactivity elimination half-life, after exposure to 86.1 to 8610 mg/m^3 ^{14}C-D4, was 13 hours in blood, 59 hours in plasma and ranged from 34 to 158 hours in tissues. Following inhalation of D4, 23-35% of the radioactivity was recovered as expired volatiles, 0.4-5.4% as expired CO_2, 32-47% by renal excretion, and 9.5-30% by faecal excretion. After inhalation exposure to ^{14}C-D4 or ^{14}C-D5, the radioactivity measured in the urine was only or mainly due to metabolites.

Studies in rats indicate that D4 and D5 induce hepatic cytochrome P450 enzymes similarly to that observed following exposure to phenobarbital. Species differences regarding hepatic effects have been observed. In a study where D4 induced hepatomegaly and hepatic cytochrome P450s in rats, repeated doses of D4 in female guinea pigs did not cause hepatomegaly or significant induction of liver microsomal CYP2B, CYP1a and epoxide hydrolase. This lack of hepatic effect in the guinea pig was not attributable to poor absorption and distribution to the liver as mean liver D4 content was determined to be 9-fold greater in guinea pigs than in rats. In another study, a statistically significant increase in liver weights was observed in male and female hamsters, mice, and rats exposed to D4, but not in guinea pigs and rabbits.

Humans exposed by inhalation of D4 at 122 mg/m^3 D4 for one hour showed no significant change in forced vital capacity immediately and no immunotoxic or proinflammatory/adjuvant effects immediately after exposure or 24 hours post-exposure.
The acute toxicity following inhalation of D4, D5 and HMDS is low in a number of animal species with reported LC_{50}-values of 36000, >2700 and 3300-107700 mg/m^3, respectively.

HMDS is reported to be a skin and an eye irritant in humans. Both positive results and negative result have been reported for skin irritation after dermal application of D4 or HMDS to rabbits. No signs of eye irritation have been noted for D4 and HMDS when tested in rabbits.

In humans, repeated insult patch tests with D4 or HMDS did not result in skin sensitisation. D4 and HMDS were not sensitising in the guinea pig maximisation test.

No human data regarding repeated dose toxicity following exposure to D3, D4, D5, D6 or HMDS have been found.

The repeated dose toxicity of D3, D4, D5 and HMDS has been studied in rats using the inhalation route. For D4, inhalation studies are also available for mouse, rabbit, guinea pig and hamster. No data regarding repeated dose toxicity following inhalation exposure to D6 have been located.

In the most valid study of D3 performed according to OECD TG 422 (US-EPA 2002d), effects observed in rats exposed at 23125 mg/m^3 for 28 days included increased liver weight, hepatocellular hypertrophy, decreased motor activity and reaction to handling, and decreased absolute weight of epididymides and seminal vesicles. Protein droplet nephropathy was reported in males exposed at 4625 mg/m^3 for 28 days; however, this finding was reported to be consistent with that caused by excessive accumulation of $\alpha_{2\mu}$-globulin in renal tubules, a mechanism which is specific to the male rat and therefore not considered as being relevant to humans. Based on this inhalation study, a NOAEC of 4625 mg/m^3 is considered for repeated dose toxicity of D3 in the rat.

The repeated dose toxicity inhalation studies of D4 have identified the liver and the lung as the predominant target organs. Effects observed in the liver include increased liver weight, hepatocellular hypertrophy and induction of hepatic enzymes. In the lungs, interstitial inflammation was noted. The effects in the liver and the lungs were reversible in several studies. Other effects observed include alteration in blood biochemistry, vaginal mucification, decreased mitochondria volume, increased adrenal and decreased thymus weights, increase in kidney weight, increased uterus weight, decreased body weight and reduction in thymus, spleen and mesenteric lymph node size. In the most valid studies, liver effects were observed at exposure levels from 861 mg/m^3 in rats and at 8610 mg/m^3 in mice and hamsters (only exposure level in the studies). In contrast, no liver effects were reported in rabbits and guinea pigs exposed at 8610 mg/m^3. Interstitial inflammation in the lung of rats has been observed at 430 mg/m^3 in a 13-week study performed according to OECD TG 413 (the lowest exposure level in the study); in this study, liver effects (increased weight in females) were observed from 1500 mg/m^3. Based on the 13-week OECD TG 413 inhalation study (Dow Corning Corporation, RCC Group 1995 – quoted from SCCP: reference number 15), a LOAEC of 430 mg/m^3 is considered for repeated dose toxicity of D4 in the rat, the lowest exposure level in the study.

The repeated dose toxicity inhalation studies of D5 in the rat have identified the liver and the lung as the predominant target organs. Effects observed in the liver include increased liver weight and induction of hepatic enzymes, and effects observed in the lungs include increased multifocal alveolitis and increased relative lung weight. Other effects observed include increased gamma-glutamyltransferase activity, decreased testes weight, increased goblet cell hyperplasia, vaginal mucosal mucification, interstitial gland hyperplasia, decreased relative thymus weight, and changes in blood chemistry. In the 13-week study (US-EPA 1995b), liver effects

were observed at exposure levels from 750 mg/m^3 and effects in the lung were observed from 1330 mg/m^3. Based on this study, a NOAEC of 440 mg/m^3 is considered for repeated dose toxicity of D5 in the rat.

The repeated dose toxicity inhalation studies of HMDS in the rat have identified the liver, the kidneys and the lungs as the predominant target organs. Effects observed in the liver include hepatocellular hypertrophy, in the kidneys hyaline droplets, protein casts, granular casts, and in the lungs interstitial inflammation. Other effects observed include slight increased plasma urea and creatinine concentrations, and testicular tubular atrophy. The effects observed in the kidneys seem to be consistent with the male rat-specific $\alpha_{2\mu}$-globulin nephropathy, which is not considered as being relevant to humans. In the 13-week study performed according to OECD TG 413 (US-EPA 1996c), lung effects were observed from 140 mg/m^3. Based on this study, a LOAEC of 140 mg/m^3 is considered for repeated dose toxicity of HMDS in the rat, the lowest exposure level in the study.

The reproductive and developmental toxicity of D3, D4, D5 and HMDS has been studied in rats using the inhalation route. For D4, inhalation studies are also available for the rabbit. No data regarding reproductive and developmental toxicity following inhalation exposure to D6 have been located.

In a combined toxicity study of D3 that included a reproductive and developmental toxicity screening and performed according to OECD TG 422 (EPA 2002d), a decrease in litter size (33%) and in the number of implantation sites, and a decrease in the weight of seminal vesicles (30%) were observed the highest concentration (23125 mg/m^3). Gestation length, pup sex ratio, pup weight and viability, and corpora lutea counts were unaffected. Based on this study, a NOAEC of 4625 mg/m^3 is considered for reproductive effects of D3 in the rat.

A number of reproductive toxicity inhalation studies of D4 in rats have shown impaired female fertility identified as an decrease in number of corpora lutea, number of uterine implantation sites, total number of pups born, and mean live litter size. Phased-female studies demonstrated that this effect occurs at ovulation, apparently with reduced number of eggs ovulated. In a two-generation study (Dow Corning Corporation 2001 – quoted from SCCP 2005: reference number 34), similar reproductive effects were observed together with increased oestrous cycle length. In the two-generation study, extended parturition and/or dystocia was also observed (F_0 from 6150 mg/m^3; F_1 from 3690 mg/m^3). Based on the two-generation study, a NOAEC of 3690 mg/m^3 is considered for reproductive effects of D4 in the rat; however, it should be noted that this exposure level is a LOAEC for the extended parturition and/or dystocia observed in one F_1 dam.

In a two-generation inhalation study of D5 in rats (US-EPA 1999), no parental toxicity, neonatal toxicity or developmental neurotoxicity were observed following exposure at up to 2464 mg/m^3 from day 70 prior to mating to termination. Based on this study, a NOAEC of 2464 mg/m^3 is considered for reproductive effects of D5 in the rat. It should be noted, however, that reproductive toxicity of D3 and D4 was observed at higher concentrations (NOAEC of 4625 and 3690 mg/m^3, respectively, than the highest concentration of 2464 mg/m^3 used in the D5 studies. Therefore, it cannot be evaluated whether D5 may result in reproductive toxicity at higher exposure levels than those tested.

In a one-generation study of HMDS in rats (US-EPA 2000b), a slight but not statistically significant effect on postnatal pup survival was observed following exposure at 33750 mg/m^3 from day 28 prior to mating to termination. Based on this

study, a NOAEC of 33750 mg/m^3 is considered for reproductive effects of HMDS in the rat.

D3, D4 and HMDS have been tested mutagenicity and genotoxicity in a number of *in vitro* and *in vivo* systems. Two *in vitro* tests with D3 were concluded to be equivocal whereas an *in vivo* test was clearly negative. For D4 and HMDS, all the available tests showed a negative result. No data have been located for D5 and D6. Overall, the selected siloxanes are not considered to possess a mutagenic or genotoxic potential.

D4, D5 and HMDS have been tested for carcinogenic effects in two-year combined chronic toxicity and carcinogenicity inhalation study in rats. No data have been located for D3 and D6.

For D4, effects were observed at the highest exposure concentration (8610 mg/m^3) and included increases in kidney weights associated with chronic nephropathy, increases in mean uterine weight and uterus-to-body weight ratios, an increase in cystic endometrial hyperplasia, an increased incidence of uterine endometrial adenomas, and an earlier onset and increased incidence of mononuclear cell leukemia (MNCL) in male rats. The available data indicate that D4 is not a mutagenic or genotoxic compound and therefore, an epigenetic mode-of-action is considered to be responsible for its neoplastic effect. Some studies support the conclusion that a secondary effect of D4 on the uterus exists, see section 2.2. Based on this 2-year study (Plotzke et al. 2005 –quoted from SCCP 2002: reference number AR4), a NOAEC of 1845 mg/m^3 is considered for the carcinogenic effects of D4 in the rat.

For D5, female rats exhibited a statistically significant increase of uterine tumours at the highest concentration (2464 mg/m^3). No significant increase in tumours was observed at lower concentrations. No mechanism of tumour induction has been established and D5 has not been tested for mutagenicity or genotoxicity. Although D5 is not considered to possess a mutagenic or genotoxic potential, no firm conclusion can be drawn regarding the mode-of-action underlying the carcinogenic potential of D5. However, the tumours induced by D5 are similar to those induced by D4; therefore, in concordance with D4, an epigenetic mode-of-action is considered to be responsible for the neoplastic effect of D5. Based on this 2-year study (US-EPA 2005b), a NOAEC of 616 mg/m^3 is considered for the carcinogenic effects of D5 in the rat.

For HMDS, a dose-related increase in Leydig cell tumours in the testes after one year and nearly a 100% incidence in all groups including controls after two years were observed in males together with kidney tumours after two years of exposure (10800 mg/m^3). The available data indicate that HMDS is not a mutagenic or genotoxic compound. Mechanistic studies confirm that the kidney tumours are mediated through $\alpha_{2\mu}$-globulin nephropathy, which is not considered as being relevant to humans. Leydig cell tumours are an expected observation in this strain of male rats at this time point. Thus, the carcinogenic effects reported in this study are not considered relevant to humans.

6.8.1 Critical effect and NOAEL

6.8.1.1 D3

No data have been located regarding acute toxicity, irritation, sensitisation or carcinogenicity. Data on mutagenicity and genotoxicity indicate that D3 is not a

mutagenic or genotoxic compound. In repeated-dose studies, no clinical signs of toxicity and minimal effects on clinical pathology parameters were observed. Hepatocellular hypertrophy and decreased weight of seminal vesicles were observed at high concentrations of D3. Reproductive toxicity, expressed as reduced litter size and implantation sites, was observed also at high concentrations of D3.

Overall, a NOAEC of 4625 mg/m^3 is considered for repeated dose toxicity (liver effects) and reproductive effects for rats following exposure to D3 by inhalation (US-EPA 2002d).

6.8.1.2 D4

D4 has a very low order of acute inhalation toxicity and is not an eye irritant or skin sensitiser. Repeated dose toxicity inhalation studies have identified the liver and the lung as the predominant target organs. Reproductive effects (reductions in corpora lutea, implantation sites and number of pups born) have been observed in rats; however, there is evidence for an indirect mode of action that may not be of concern for human health. Extended parturition and/or dystocia was also noted in the two-generation study at high exposure levels (F_0 from 6150 mg/m^3; F_1 from 3690 mg/m^3). D4 at a high exposure concentration (8610 mg/m^3) resulted in an increase in cystic endometrial hyperplasia, an increased incidence of uterine endometrial adenomas, and an earlier onset and increased incidence of mononuclear cell leukaemia (MNCL) in male rats. The available data indicate that D4 is not a mutagenic or genotoxic compound and therefore, an epigenetic mode-of-action is considered to be responsible for its neoplastic effects.

Overall, a LOAEC of 430 mg/m^3 is considered for repeated dose toxicity for rats exposed to D4 by inhalation, based on the interstitial inflammation in the lung observed in the OECD TG 413 13-week study (Dow Corning Corporation, RCC Group 1995 – quoted from SCCP: reference number 15).

6.8.1.3 D5

D5 has a low order of acute inhalation toxicity. No data have been located regarding irritation, sensitisation or mutagenicity and genotoxicity. Repeated dose toxicity inhalation studies have identified the liver and the lung as the predominant target organs. No parental toxicity, neonatal toxicity or developmental neurotoxicity were observed in the two-generation study at the highest exposure level tested (2464 mg/m^3). Female rats exhibited a statistically significant increase of uterine tumours after exposure to D5 (2464 mg/m^3 - highest exposure level in the study). No mechanism of tumour induction has been established and D5 has not been tested for mutagenicity or genotoxicity. Although D5 is not considered to possess a mutagenic or genotoxic potential, no firm conclusion can be drawn regarding the mode-of-action underlying the carcinogenic potential of D5. However, the tumours induced by D5 are similar to those induced by D4; therefore, in concordance with D4, an epigenetic mode-of-action is considered to be responsible for the neoplastic effect of D5.

Overall, a NOAEC of 440 mg/m^3 is considered for repeated dose toxicity for rats exposed to D5 by inhalation, based on the liver effects observed in the 13-week study (US-EPA 1995b).

6.8.1.4 D6

D6 has a low order of acute oral toxicity. No data have been located regarding acute inhalation toxicity, irritation, sensitisation, repeated dose toxicity, toxicity to reproduction, mutagenicity, genotoxicity or carcinogenicity. Therefore no conclusion can be drawn regarding the toxicity of D6.

6.8.1.5 HMDS

HMDS has a very low order of acute inhalation toxicity and has been reported to be a skin and an eye irritant in humans. Animal data from repeated dose toxicity studies indicate that the kidney, liver and lung are the target organs. However, the effects observed in the kidney are presumably due to the male rat specific $\alpha_{2\mu}$-globulin nephropathy, which is not considered as being relevant to humans. No reproductive effects in the rat were observed at the highest concentration tested (33750 mg/m^3). HMDS is not mutagenic or genotoxic. Leydig cell tumours in the testes and kidney tumours were observed in male rats. However, data indicate that the observed effects are male rat-specific and not relevant to humans.

Overall, a LOAEC of 140 mg/m^3 is considered for repeated dose toxicity for rats exposed to HMDS by inhalation, based on the lung effects observed in the OECD TG 413 study (US-EPA 1996c).

6.8.2 Read-across

The critical effects following exposure to the siloxanes covered in this evaluation, i.e., D3, D4, D5, D6 and HMDS, are considered to be the effects observed in the liver (D3, D4, D5 and HMDS) and the lung (D4, D5 and HMDS) of rats as well as reproductive toxicity (D3 and D4).

Based on the available toxicological data, no firm conclusions can be drawn with respect to possible differences in the toxicity of D3, D4, D5, D6 and HMDS as a result of different chain length and structure, i.e. cyclic (D3, D4, D5 and D6) or linear (HMDS).

For the critical target organs (liver, lung), data indicate a similarity, at least in qualitative terms, in the toxicological profile of the tested siloxanes, i.e., D3, D4, D5 and HMDS. In the liver, effects observed include increased liver weight (D3, D4, D5), hepatocellular hypertrophy (D3, D4, HMDS), and induction of hepatic enzymes (D4, D5). In the lung, effects observed include interstitial inflammation (D4, D5, HMDS), increased lung weight (D4, D5, HMDS), alveolar macrophage accumulation or aggregation (D4, D5, HMDS), multifocal alveolitis (D5), and alveolar histiocytosis (D4).
Regarding reproductive toxicity, effects observed include decreased weight of the seminal vesicles and epididymides (D3), a decrease in the number of implantation sites (D3, D4), a decrease in litter size (D3, D4), and decreased pup survival (D4); however, no reproductive toxicity were observed in the available studies on D5 and HMDS. It should be noted that D5 has only been tested at lower concentrations (up to 2464 mg/m^3 in a two-generation study) than the other cyclic siloxanes, D3 (NOAEC 4625 mg/m^3 and LOAEC 23125 mg/m^3 in an OECD TG screening test) and D4 (NOAEC 3690 mg/m^3 and LOAEC 6150 mg/m^3 in a two-generation study), whereas HMDS has been tested up to a very high concentration (NOAEC 33750 mg/m^3 in a range-finding one-generation study).

In quantitative terms, some differences are indicated as a result of structure, i.e. cyclic (D3, D4, D5 and D6) or linear (HMDS). The linear siloxane HMDS seems much less potent in terms of liver toxicity than the cyclic siloxanes as the NOAECs for liver effects are 4625 mg/m^3 for D3 (28-day study), 123 mg/m^3 for D4 (12-month study), and 440 mg/m^3 for D5 (13-week study) are much lower than that of 12,700 mg/m^3 for HMDS (4-week study). On the other hand, the linear siloxane HMDS seems more potent in terms of lung effects than the cyclic siloxanes as the LOAEC for lung effects for HMDS is 140 mg/m^3 (13-week OECD TG 413 study) lower than the LOAEC for D4 of 430 mg/m^3 (13-week OECD TG 413 study) and the NOAEC for D5 of 1330 mg/m^3 (13-week study).
Regarding chain length, in quantitative terms, some data indicate a trend of decreased toxicity with increasing chain length as illustrated for lung toxicity by a LOAEC for D4 of 430 mg/m^3 (13-week OECD TG 413 study) compared with a NOAEC for D5 of 1330 mg/m^3 (13-week study), and for liver toxicity by a NOAEC for D4 of 123 mg/m^3 (12-month study) and a NOAEC for D5 of 440 mg/m^3 (13-week study).

Overall, it seems reasonable to consider that a 'read-across' of toxicological data between D3, D4, D5, D6 and HMDS is valid for the purpose of setting a health based quality criterion in air for these siloxanes.

The lung toxicity is considered as being the critical effect following inhalation of the siloxanes covered in this evaluation as the lung is a critical target following inhalation in general and because the effects on the lung for D4 and HMDS have been observed at lower concentrations than the effects on the liver as well as reproductive toxicity. Lung effects were observed from 430 mg/m^3 for D4 and from 140 mg/m^3 for HMDS (the lowest concentrations in the respective OECD TG 413 studies), thus precluding the setting of a NOAEC for lung toxicity. For the purpose of setting a health based quality criterion in air for the siloxanes covered in this evaluation, i.e., D3, D4, D5, D6 and HMDS, an overall LOAEC of 140 mg/m^3 is considered for lung toxicity. This LOAEC is considered to take into account the liver effects observed for D3, D4, D5 and HMDS and the reproductive toxicity observed for D3 and D4. Adjustment of the LOAEC of 140 mg/m^3 to a LOAEC for continuous exposure is relevant as the inflammatory effects in the lung are considered to be related to the total dose of the siloxanes rather than to the concentration of siloxanes in the air. The adjusted LOAEC is estimated to 25 mg/m^3 (140 mg/m^3 x 6/24 x 5/7).

No toxicity data have been located for other siloxanes than those covered in this evaluation. Consequently, no conclusion can be drawn with respect to possible differences in the toxicity of the selected siloxanes and other siloxanes thus precluding a 'read-across' for the purpose of setting a health-based quality criterion in air for other siloxanes than those covered in this evaluation.

7 Quality criterion in ambient air

7.1 Critical effects and NOAEC/LOAEC

The critical effects following exposure to the siloxanes covered in this evaluation, i.e. D3, D4, D5, D6 and HMDS, are considered to be the effects observed in the liver (D3, D4, D5 and HMDS) and the lung (D4, D5 and HMDS) of rats as well as reproductive toxicity (D3, D4).

For D4 and HMDS, the effects on the lung have been observed at lower concentrations than the effects on the liver as well as reproductive effects with a LOAEC for interstitial inflammation in the lung of 430 mg/m^3 for D4 and a LOAEC of 140 mg/m^3 for HMDS (lowest concentrations in the respective OECD TG 413 studies). For the purpose of setting a health-based quality criterion in air for D3, D4, D5, D6 and HMDS, an overall LOAEC of 140 mg/m^3 is considered for effects in the lung. This LOAEC is adjusted to a LOAEC of 25 mg/m^3 (140 mg/m^3 x 6/24 x 5/7) for continuous exposure.

7.2 Tolerable concentration

The tolerable concentration (TC) is estimated based on an overall LOAEC of 25 mg/m^3 for effects in the lung:

$$TC = \frac{LOAEC}{UF_I * UF_{II} * UF_{III}} = \frac{25\ mg/m^3}{2.5 * 10 * 10} = 0.1\ mg/m^3$$

The uncertainty factor UF_I accounting for interspecies variability in toxico-dynamics is set to 2.5 assuming that humans are more sensitive than animals.
The UF_{II} accounting for intraspecies variability is set to 10 reflecting the range in biological sensitivity within the human population.
The UF_{III} is set to 10 as a LOAEC is used as a starting point for the estimation of the TC and because of the less than chronic duration of exposure (13-week study). Furthermore, a concern remains for the reproductive toxicity observed for D3 and D4 because the mode of action underlying the observed effects as well as the relevance of these effects to humans have not been clearly elucidated for the time being. In addition, some studies have indicated that D4 may have a very weak oestrogenic and anti-oestrogenic activity in the rat uterotrophic assay.

7.3 Allocation

The general population is predominantly exposed to siloxanes from the use of consumer products. No data on industrial releases of siloxanes into air have been located. Very low levels of siloxanes have been detected in ambient air, water and fish; no measured concentrations have been located in soil or in food stuffs. Because of the extensive use of siloxanes in consumer products and because the volatile siloxanes used in cosmetic products are meant to evaporate during use,

only 10% of the tolerable concentration (TC) is allocated to exposure from ambient air.

7.4 Quality criterion in ambient air

The quality criterion in air QC_{air} is calculated based on the TC of 0.1 mg/m^3, assuming 100% absorption following inhalation in experimental animals as well as in humans:

$$QC_{air} = TC * f = 0.1 \text{ mg/m}^3 * 0.1 = 0.01 \text{ mg/m}^3$$

A quality criterion of 0.01 mg/m^3 has been calculated. A C-value of 0.01 mg/m^3 and placing in Main Group 2 is proposed.

7.5 C-value

0.01 mg/m^3, Main Group 2.

8 References

ChemFinder: http://chemfinder.cambridgesoft.com/.

ChemIDplus Advanced: http://chem.sis.nlm.nih.gov/chemidplus/.

HSDB (2005). Hazardous Substances Data Bank. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB.

IUCLID (2000). International Uniform Chemical Information Database. European Commission, ECB, JRC, Ispra.

IVL (2005). Results from the Swedish national screening programme 2004. Subreport 4: Siloxanes. Swedish Environmental Research Institute. Ocotber 2005.

MM (2002). The Statutory Order from the Ministry of the Environment no. 439 of June 3, 2002, on the List of Chemical Substances.

MST (2005). Siloxanes – Consumption, toxicity and alternatives. Lassen C, Hansen CL, Mikkelsen SH & Maag J, COWI A/S. Environmental Project No. 1031 2005, Miljøstyrelsen, Miljøministeriet.

OSPAR Commission (2004). OSPAR background document on hexamethyldisiloxane (HMDS). Hazardous Substances Series. ISBN 1-904426-41-7.

SCCP (2005). Opinion of octamethylcyclotetrasiloxane (D4). Scientific Committee on Consumer Products (SCCP). Adopted by the SCCP during the 6th plenary meeting of 13 December 2005. European Commission, Health & Consumer Protection Directorate-General.

TemaNord (2005). Siloxanes in the Nordic environment. TemaNord 2005:593. Nordic Council of Ministers, Copenhagen 2005. IBSN 92-893-1268-8.

TSCATS. The Toxic Substance Control Act Test Submission database. http://www.syrres.com/esc/tscats.htm.

US-EPA (1992). Federal Register vol. 57, no. 132, 1992. Thirtieth report of the interagency testing committee to the administrator, receipt of report and request for moments regarding priority testing list of chemicals.

US-EPA (1995a). One-Month Repeated Dose Inhalation Toxicity Study with Decamethylcyclopentasiloxane (D5) in Rats. DCN 86950000174 abstract.

US-EPA (1995b). Three-month repeated dose inhalation toxicity study with D5 in rats. DCN 86950000154 abstract.

US-EPA (1996a). An acute whole body inhalation study of HMDS in albino rats. DCN 86970000724 abstract.

US-EPA (1996b). A 28-Day Inhalation Toxicity and Splenic Antibody Formation Study of Decamethylcyclopentasiloxane (D5) in Rats. DCN 86970000385 abstract.

US-EPA (1996c). A Three-Month Repeated Dose Nose-Only Inhalation Toxicity Study with Hexamethyldisiloxane in Rats with a One-Month Recovery Period. DCN 86980000048 abstract.

US-EPA (1996d). An Inhalation Range-Finding Reproductive Toxicity Study of Decamethylcyclopentasiloxane (D5) in Rats. DCN 86970000006 abstract.

US-EPA (1997a). Toxicology and Humoral Immunity Assessment of Octamethylcyclotetrasiloxane (D4) Following a 28-day Whole Body Vapour Inhalation Exposure in Fischer 344 Rats. DCN 86980000040 abstract.

US-EPA (1997b). Effects of Decamethylcyclopentasiloxane (D5) on Hepatic Cytochrome P450 UDP-Glucuronosyltransferase and Epoxide Hydrolase in the Female Fischer 344 Rat. DCN 86980000020 abstract.

US-EPA (1997c). An Inhalation Range-Finding Reproductive Toxicity Study of Octamethylcyclotetrasiloxane (D4) in Male Rats. DCN 86980000061 abstract.

US-EPA (1998a). Non-Regulated Study: Immune Effects of Oral Exposure of Human Volunteers to Octamethylcyclotetrasiloxane (D4). DCN 86990000015 abstract.

US-EPA (1998b). A 13-Week Whole Body Inhalation Study of HMDS in Fischer-344 Rats. DCN 86980000182 abstract.

US-EPA (1999). A Two-Generation Inhalation Reproductive Toxicity and Developmental Neurotoxicity Study of Decamethylcyclopentasiloxane (D5) in Rats. DCN 86990000032 abstract.

US-EPA (2000a). In vitro evaluation of estrogenicity of D4 using human MCF-7 cell line. DCN 86010000004 abstract.

US-EPA (2000b). An inhalation range-finding reproductive toxicity study of hexamethyldisiloxane (HMDS) in Sprague Dawley rats. DCN 86000000019 abstract.

US-EPA (2001a). Non-regulated study: Identification of metabolites of HMDS. DCN 86020000001 abstract.

US-EPA (2001b). An Inhalation Range-Finding Reproductive Toxicity Study of Octamethylcyclotetrasiloxane (D4) in Male Rats. DCN 86980000049 abstract.

US-EPA (2001c). A Two-Generation Inhalation Reproductive Toxicity and Developmental Neurotoxicity Study of Octamethylcyclotetrasiloxane (D4) in Rats. DCN 88020000003 abstract.

US-EPA (2002a). Single exposure pharmacokinetics and metabolism of 14C-D5 via nose-only vapour inhalation. DCN 84030000027 abstract.

US-EPA (2002b). Absorption, distribution and elimination of D143-D5 in humans after dermal administration. DCN 84030000008 abstract.

US-EPA (2002c). Effects of D4 on liver size and hepatic phase I and phase II xenobiotic metabolizing enzymes in rats and guinea pigs following 14 day oral gavage: A study of species-specific response. DCN 84030000007 abstract.

US-EPA (2002d). Combined repeated dose toxicity study with the reproductive/developmental toxicity screening test for D3 in SD rats. DCN 89030000196 abstract.

US-EPA (2003). Absorption of D6 using the flow-through diffusion cell system for in vitro absorption in human skin. DCN 84030000026 abstract.

US-EPA (2004). Pharmacokinetics of 14C-D6 in the rt following single oral exposure. DCCN 84040000016 abstract.

US-EPA (2005a). Evaluation of new and emerging technologies for textile cleaning. Prepared for California Air Resources Board and the California EPA under Agreement Number 02-408 and the US EPA.

US-EPA (2005b). Siloxane D5 in dry cleaning applications. Office of Pollution Prevention and Toxics (7404). 744-F-03-004. December 2005.

Siloxanes (D3, D4, D5, D6, HMDS)

The Danish Environmental Protection Agency has requested an evaluation of health hazards by exposure to siloxanes (D3, D4, D5, D6 and HMDS). This resulted in 2010 in the present report which includes a health-based quality criterion for the substances in ambient air.

Danish Ministry of the Environment
Environmental Protection Agency

Strandgade 29
1401 Copenhagen K, Denmark
Tel.: (+45) 72 54 40 00

www.mst.dk