Linear Polydimethylsiloxanes
CAS No. 63148-62-9
(Second Edition)

JACC No. 55

EUROPEAN CENTRE FOR ECOTOXICOLOGY AND TOXICOLOGY OF CHEMICALS

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CONTENTS

EXECUTIVE SUMMARY

This report presents a critical evaluation of the toxicity, physico-chemical properties, and environmental fate and effects of linear polydimethylsiloxanes (PDMSs), a type of non-volatile (odourless), fluid (viscous) "silicones" that are virtually insoluble in water. PDMSs are widely used in industrial, consumer, food and medicinal or pharmaceutical applications. The report has been produced as part of the ECETOC Joint Assessment of Commodity Chemicals (JACC) programme and updates an earlier ECETOC review [a].

Almost all PDMS discarded 'down-the-drain' is expected to be removed during sewage treatment. Any PDMS released into the environment will strongly sorb to particulate matter in water and soil. PDMSs are immobile in soil and sediment, but will break down slowly (abiotic) to dimethylsilanediol, which is soluble in water and can biodegrade to carbon dioxide, water and inorganic silicate, as demonstrated in the laboratory. Due to its molecular size, bioconcentration of PDMS is very unlikely. PDMSs are not detected in surface waters, except at low concentrations downstream from wastewater treatment plants.

PDMS has no effects when tested on aquatic organisms (fish, daphnia, algae), sediment-dwelling organisms (e.g. midge larva) and little or no effect on soil organisms (e.g. earthworm). PDMS is lethal to insects when applied directly, probably due to a physical rather than toxicological action.

Humans may be exposed to PDMS via oral ingestion and dermal contact. In laboratory animals, PDMS had a low potential for absorption via these routes. Swallowed PDMS is rapidly excreted unchanged in the faeces. Aerosolised PDMS may give rise to inhalation exposure, but there is no indication of any adverse effects. PDMS is not a skin irritant or a skin sensitiser and it is only mildly to non-irritating to the eyes.

Acute and repeated dose toxicity studies conducted in laboratory animals on PDMS of different viscosities do not show any significant adverse effects. Long-term chronic/carcinogenicity and reproductive toxicity studies were also without adverse effects. PDMS is not mutagenic *in vitro*.

In humans, PDMS has no effect on the immune system. PDMS is used in urology, ophthalmology and dermatology (skin correction). Autoimmune disorders (e.g. scleroderma) cannot be linked to PDMS. Several human diseases (connective tissue, atypical connective tissue, rheumatic and autoimmune diseases, and breast cancer) have been reported after injection of PDMS (for cosmetic purposes) or placement of breast implants (made of high viscosity PDMS). These diseases are, however, not associated with PDMS.

Overall, PDMS does not present a risk to the environment or to human health.

[a] ECETOC. 1994. Joint Assessment of Commodity Chemicals No. 26

THE ECETOC SCHEME FOR THE JOINT ASSESSMENT OF COMMODITY CHEMICALS

This report has been produced as part of the ECETOC programme for preparing critical reviews of the toxicology and ecotoxicology of selected existing industrial chemicals. In the programme, commodity chemicals (i.e. those produced in large tonnage by several companies and having widespread and multiple uses) are jointly reviewed by experts from a number of companies with knowledge of the chemical. It should be noted that in a JACC review only the chemical itself is considered; products in which it appears as a component or an impurity are not normally taken into account.

This report presents a critical evaluation of the available data on the toxicity, physico-chemical properties, and environmental fate and effects of linear polydimethylsiloxane (PDMS) (CAS No. 63148-62-9). It updates an earlier ECETOC review [a].

A list of symbols, units and abbreviations is given in Appendix A.

Where relevant, the Task Force has graded the studies by means of a 'code of reliability' (CoR) to reflect the degree of confidence that can be placed on the reported results. The codes and criteria used to assess reliability are included in Appendix B.

It should be noted that not all of the references reviewed by the Task Force were quoted in the report. A number of earlier studies (e.g. by IBT) quoted by ECETOC (1994) were subsequently found to be unreliable because the documentation was insufficient for assessment or there were methodological deficiencies. Many of those studies have been superseded by more recent work as explained in the text of the report. Furthermore, a number of other studies consulted by the Task Force were also excluded. A full list of references is given in the bibliography (Section 11).

[a] ECETOC. 1994. Joint Assessment of Commodity Chemicals No. 26

1. SUMMARY AND CONCLUSIONS

Linear polydimethylsiloxanes (PDMSs) are polymeric organosilicon substances commonly referred to as "silicones". This report covers PDMS fluids of viscosities ranging from 10 to > 100,000 centistoke (cSt). At normal (ambient) temperature and pressure, PDMSs are clear, colourless, odourless and viscous fluids and have no detectable vapour pressure. They exhibit remarkable stability to chemical and oxidative degradation and radiation and are essentially insoluble in water. PDMSs strongly sorb to particulate matter in water and soil and are essentially immobile in the soil and sediment compartments of the environment. The reliability of PDMS analysis methods varies as a function of extraction efficiency, method of detection and types of media.

No special protective measures are required for storage and handling of PDMS and they are not classified as 'dangerous' under European or other chemical laws or international transport regulations. Special packaging and labelling are not required.

PDMSs have a wide range of industrial, consumer, food and medicinal or pharmaceutical applications, either in pure form or as an ingredient in a formulated product (e.g. emulsions).

The total worldwide use of PDMS was estimated to be 238 kilotonnes (kt) in 2007, including 77 kt in the EU-27, 68 kt in the USA, 7 kt in Japan and 86 kt in the rest of the world.

PDMSs of > 10 cSt viscosity are essentially non-volatile. They have an extremely low water solubility (< 1 ng/l) and high affinity for organic matter and, therefore, more than 97% of the PDMS discarded 'down-the-drain' to water is expected to be removed from the aqueous phase during sewage treatment by adsorption to particulate matter (sludge). PDMS in contact with soil will undergo abiotic degradation over time to smaller, more water soluble species. The principal degradation product is dimethylsilanediol (DMSD), which is very soluble. Laboratory experiments have demonstrated that dimethylsilanediol can undergo biodegradation to carbon dioxide, water and inorganic silicate, the ultimate degradation products of PDMS. Bioconcentration studies with short-chain PDMS suggest that, due to molecular size, passage of PDMS of > 10 cSt viscosity across biological membranes is very unlikely.

Environmental monitoring shows that PDMSs are not detected in surface waters, except possibly downstream from wastewater treatment plants, where concentrations are at or below the level of detection (µg/l) have been measured.

Evaluation of PDMS effects on a range of aquatic and terrestrial organisms shows no effect on aquatic organisms, which is probably due to its extremely low water solubility and no effects on sediment-dwelling organisms. Little or no effect of PDMS has been observed in soil organisms.

PDMS does show toxicity to insects when applied directly to the insect. This activity is believed to be a physical action rather than a toxicological effect even though this has yet to be substantiated.

PDMS has been shown to have a low potential for either oral or dermal absorption. Following oral ingestion, PDMS is rapidly excreted unchanged in the faeces.

Oral ingestion and dermal contact are the primary routes of exposure for non-occupational exposure resulting from their use in PDMS applications. Little or no exposure to PDMS occurs in the occupational setting and no occupational exposure limit (OEL) has been set for this material. Inhalation exposure normally does not occur due to the extremely low vapour pressure. Applications where PDMS may be aerosolised may give rise to inhalation exposure. The available inhalation data do not indicate any adverse effects.

Acute, short-term repeated dose and subchronic studies on PDMS of different viscosities in laboratory animals do not show any significant adverse effects in a variety of mammalian species following oral, dermal, intraperitoneal, intradermal or subcutaneous administration. In chronic/carcinogenicity studies, no significant adverse effects were seen in mice or rats. PDMS is not a skin irritant and is only mildly to non-irritating to the eyes. It is non-sensitising to human skin. *In vitro* genotoxicity studies show no indication that PDMS has mutagenic activity. PDMS studies with rabbits do not show any teratogenic effects and studies with rats and rabbits do not show any adverse effects of PDMS on fertility, gestation, peri- or post-natal development.

In humans, no adverse immunological activity has been seen with PDMS. PDMS is reportedly used for the treatment of urological and ophthalmological problems (e.g. retinal detachment and endotamponade) as well as soft tissue augmentation to correct specific cutaneous and subcutaneous atrophies. Attempts to link PDMS to autoimmune disorders (e.g. scleroderma) have not been proven and have been shown to be flawed methodologically.

A number of human case control studies have been reported on PDMS. The case reports have primarily resulted from PDMS injections for a variety of purposes including cosmetics. Epidemiological studies of breast implants of which the main component is high viscosity PDMS have evaluated connective tissue, atypical connective tissue, rheumatic and autoimmune diseases, and breast cancer. The results of these studies relative to these endpoints have failed to show an association between human disease and PDMS.

Overall, the data indicate that PDMS does not represent a risk to the environment or to human health. The safety of PDMS has been recognised by its widespread use in a wide range of applications that have resulted in environmental and human exposure for nearly 50 years.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

PDMSs are polymeric organosilicon substances with the structural formula shown below. The linear polymer is composed of dimethylsiloxy units with trimethylsilyl end groups. Polysiloxanes based on other units, with side groups other than methyl or with cyclic structures, are not considered here. This report is limited to liquid PDMS with a (kinematic [a]) viscosity of 10 to > 100,000 cSt [b], corresponding to a number average molecular weight of approximately 1,125 to 74,000.

Commercially available PDMSs are also referred to as:

- 'Siloxanes'; general name for oligomeric or polymeric substances which are characterised by Si-O-Si bonds, methyl groups are usually bound to Si-atoms, but some siloxanes contain vinyl, hydroxyl or other groups in addition;

- 'Silicone fluids' or 'silicone oils', often abbreviated to 'silicones'; these terms cover all types of linear and branched siloxanes, and the preparations and products made from them;

- 'Dimethicone'; which is commonly used for PDMS in medical, pharmaceutical and cosmetic applications;

- 'E 900', which is used for PDMS with a viscosity of 350 to 1,050 cSt approved for specific applications as a food additive.

2.1 Identity

Name:	Polydimethylsiloxane (PDMS)
IUPAC [c] name:	Poly[oxy(dimethylsilylene)]
Synonyms:	Dimethicone, Dimeticone (INN), Dimethylsiloxane, Dimethylsilicone, Silicone oil, Dimethylpolysiloxane, Dimethylpoly-siloxane hydrolyzate, E 900, Permethylsiloxane, Polydimethylsiloxane, Polydimethyl-siloxane, methyl end-blocked, Polyoxy(dimethylsilylene), Siloxane, dimethyl-, α-(Trimethylsilyl)-ω-hydroxy

[a] Kinematic viscosity (m^2/s) is the dynamic (or absolute) viscosity (Pa·s = kg/m/s) divided by the density (kg/m^3)
[b] 1 St = 1 cm^2/s, 1 cSt = 1 mm^2/s
[c] International Union of Pure and Applied Chemistry

Trade names: 612S,AK fluid, B 8919, BX 16-152B, BY 11-042, BY 222-067R, Byk 336, C 800, DA 6523, DC 2-3150, DC 200-60M, DC 65, DMS 1000, Dehesive 940A, Dehesive 942, Dicsilicone softener 120, Dicsilicone softener 300, Dow Corning 200 Fluid, ECC 4865, F 370, FM 58, FZ 4157, FZ 4174, FZ 4185, Finish C 800, GP 197, Gensil 2000, GlassClad PSA, H 1-10000, K 901, KET 3001, KF 9008, KF 96A2CS, KF 96L5CS, KS 772, KS 778, L 6910, LDC 2577D, LS 5257, LTC 1051L, LTC 1100L, Levaslip 407, MED 4905, MED 6340, Magnasoft HWS, Matsumoto silicone softener 302, Matsumoto silicone softener 318, NUC silicone L 9000, NuSil CV 2946, Nusil LS 6946, PLY 7511, PMS 150, PMS 200A, PS 038, PS 221, Polydimethylsiloxanes, Protect 5000, Q 2-7735, RES 422, RTV 3838A, Reactosil RWS, Rhodorsil 340, Rhodorsil 47V60000, Rossil fluid, S 5100A, SFD 1, SH 200-1000CS, SI-UGE, SLJ 1320, Sani-Pure, Silquat AT 5-49, Silquat AT 5-52, Silquest PA 1, Silres BS 10421581, Sitren 595, Sofeksil 9056-20Kh, TC 1, TPR 6600, TSF 451-5A, TSF 458-100, Tegostab B 8919, Tex 100, UAX 1600, UV 9440E, V 12100, Versilic, Xiameter 200 fluid, X 21-3043, X 21-5613, X 21-5842, X 24-4044, X 62-7629, X 62-7655, X 62-7658, Y 12147, ZBH 201

CAS [a] name: Siloxanes and silicones, di-Me

CAS Registry number: 63148-62-9

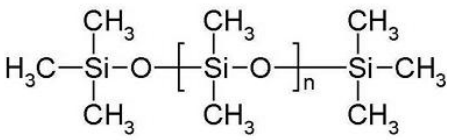
EC (EINECS) number: None (polymer)

Formula: MD_nM

where M = $-Si(CH_3)_3-O_{1/2}$, D = $-Si(CH_3)_2-O-$ and n = number

Molecular mass: $162 + (74 \times n)$ (where $n \geq 13$)

Chemical structure:



The general formula is MD_nM, where D_n represents the number of dimethylsiloxy units and M the trimethylsilyl end groups (Colas and Curtis, 2004) following General Electric's original siloxane notation (Hurd, 1946 cited by Varaprath, 2006). Thus, for example, MM, MDM,

[a] Chemical Abstracts Service

MD_2M, MD_3M represent hexa-, octa-, deca- and dodeca-trimethylsiloxane, respectively. The molecular weight, which determines the viscosity of PDMS, is governed by the number of D-units in the molecule. As with other polymeric substances, commercial PDMSs contain a mixture of polymeric molecules exhibiting Gaussian molecular weight distribution. Table 1 shows the relationship between the viscosity, degree of polymerisation and molecular weight.

Table 1: Relationship between viscosity, degree of polymerisation and molecular weight
(Wacker, 2002)

Viscosity (cSt) at 25 °C	Average number of D-units	Number-average molecular weight
10	15	1,125
50	40	3,000
100	70	5,000
1,000	200	15,000
10,000	500	37,000
100,000	1,000	74,000

2.2 EU classification and labelling

PDMS is not hazardous and has not been classified by the European Commission under the Dangerous Substances Directive (67/548/EEC) and its subsequent amendments. It remains unclassified under the Classification, Labelling and Packaging (CLP) Regulation (EC 1272/2008).

Classification:	None
Labelling:	None
Pictogram(s) and/or signal word(s):	None
Hazard statement(s):	None
Precautionary statement(s):	None

PDMS is not considered persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) as defined in Annex XIII of the EU Regulation (EC 1907/2006) concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (EU, 2007).

2.3 Physico-chemical properties

At normal (ambient) temperature and pressure, PDMSs are clear, colourless and viscous liquids with an extremely low vapour pressure. PDMS may be odourless (Wacker, 2009). The physical properties vary only slightly with viscosity (degree of polymerisation) (Table 1).

Some physical properties are listed in Table 2.

Table 2: Physico-chemical properties

Parameter	Value, unit	Reference
Freezing (melting) point, 350 cSt	–50 - –35 °C	Wacker, 2009
Boiling point at 1,013 hPa, 350 cSt 10,000 cSt 100,000 cSt	No data [a] > 65 °C > 65 °C	Wacker, 2009 Dow Corning, 2007 Dow Corning, 2009
Viscosity (cSt)	10 - > 100,000	Wacker, 2002
Relative density of liquid at 25°C (density of water at 4ºC is 1,000 kg/m^3), D_4^{25}	930 - 970	Wacker, 2002
Surface tension at 25°C (mN/m)	20.2 - 21.5	Wacker, 2002
Specific heat at 20°C (J/g·C)	1.45 - 1.55	Wacker, 2002
Refractive index (n_D^{25})	1.399 - 1.404	Wacker, 2002
Vapour pressure at 20°C (Pa)	Not measurable	
Vapour density at 20°C (air = 1)	Not measurable	
Threshold odour concentration	Not relevant for a non-volatile substance	
Solubility in water at 23°C	< 1 ng/l	Varaprath *et al*, 1996 (Section 2.3.1)
Partition coefficient, log K_{ow} (octanol-water) at 22°C	>> 8.21 [b]	Kozerski and Mosey, 2009 (Section 2.3.2)
Partition coefficient, log K_{oc} (organic carbon-water) at 26°C	>> 5.16 [b]	Durham and Kozerski, 2010 (Section 2.3.3)
Henry's Law constant at 20°C and 1 atm (1,013 hPa) partial pressure of PDMS (10^3 Pa·m^3/mol)	Not determined [c]	
Solubility in organic solvents, e.g. hexane, toluene, chloroform, diethylether	Miscible in all proportions	
Flash point, closed cup, 10 - 100,000 cSt	> 100 °C	Wacker, 2002, 2009; Dow Corning, 2007, 2009; Bluestar Silicones, 2010
Explosion/flammability limits in air at room temperature and 1,013 hPa (% by volume)	Not applicable	
Auto-flammability, ignition temperature, 350 cSt 2,500 mPa·s [2,525 cSt]	450 °C > 400°C	Wacker, 2009 Bluestar Silicones, 2010

[a] Decomposes at > 250 °C

[b] Value for decamethyltetrasiloxane (MD_2M)

[c] As PDMS is non-volatile

Typically, commercial PDMS has a purity of ≥ 99.5% by weight. Common low molecular weight impurities are dimethylcyclosiloxanes (< 0.5% by weight), specifically octamethylcyclotetrasiloxane (< 0.1% by weight) and decamethylcyclopentasiloxane (< 0.1% by weight), depending on the conditions of the production process (Section 3.1).

PDMSs are chemically stable substances with a remarkable resistance to thermal and oxidative degradation and radiation. Dry heat of 150°C has little effect, but traces of formaldehyde can be detected (Bienert, 1984; Wacker, 2009), resulting from reaction of oxygen with the methyl groups. Wet heat (steam) at 120°C or higher causes depolymerisation of PDMS. Strong acids and alkalis attack the Si-O-Si bonds, forming siloxane structures of varying molecular size (rearrangement); eventually a thermodynamic equilibrium of polymer species is established (Smith, 1991). Traces of catalyst residue from the manufacturing process may also cause rearrangement. Clay containing soils promote rearrangement and hydrolysis to form oligomers and water soluble fractions (Section 4.3.1).

PDMSs do not absorb radiation energy over the spectral range of tropospheric light. High energy irradiation causes crosslinking reactions demonstrated by an increase in viscosity and resulting in a gel (Wacker, 2002).

2.3.1 Solubility in water

Unlike the water solubility of a pure compound, the solubility of a polymeric material such as PDMS is not a rigorous thermodynamic quantity. For this reason, the measured "solubility" will always be sensitive to the composition of the polymer or the presence of low molecular weight impurities. Extreme care is also always needed when conducting the measurements as PDMS fluids are extremely hydrophobic and there is a high risk of inconsistent results due to contamination or the formation of micelles. This is illustrated by the wide variation in water solubility that was observed in some of the older studies (see below). In addition, many of the older studies did not detail or characterise the PDMS under investigation, so the possibility that hydroxyl-terminated PDMS was investigated or that there was a higher concentration of more soluble low molecular weight impurities cannot be excluded. Furthermore some of the studies were not performed specifically as water solubility studies. For example, Eales and Taylor (1983) using atomic absorption spectroscopy (AAS), measured the water solubility of PDMS (50 cSt) in seawater to be 36 µg/l as part of a sediment fate study and the Watanabe *et al* (1984a) investigation was in conjunction with a bioconcentration study. Watanabe *et al* (1984a) who measured water solubility using inductively coupled plasma (ICP) emission spectroscopy, eluted PDMS from coated glass beads with a water (flow rate 3.5 ml/min). For various PDMS viscosities, the water solubility was as follows (Table 3).

Table 3: Water solubility of PDMS (Watanabe *et al*, 1984a)

Number-average molecular weight	Viscosity (cSt)	Solubility (µg/l)
1,200	10	1,600
6,000	100	560
25,000	1,000	170
56,000	10,000	76

These results were broadly in line with Parker and Tapscott (1993; CoR3b) who reported the water solubility of PDMS 350 and 1,000 cSt to be 201 and 90 µg/l, respectively, using the column elution method (EEC guideline 92/69, method A6, OECD guideline No 105). The study does not adhere to several recommendations in the guidelines. Regardless, the analytical method used to determine aqueous concentrations lacked the specificity to distinguish between oligomeric PDMSs and more polar impurities, presumably silanols. In addition, the guideline (and endpoint) applies to "essentially pure substances" which polymers, by their very nature, are not. Therefore, the study would be more appropriately termed a study of the extraction behaviour of PDMS in water.

It is now known that any method which generates turbulent flow may create micelles, which will result in an 'apparent' higher water solubility. Only by using the slow, non-turbulent stirring method of Varaprath *et al* (1996) can the true water solubility be measured. Varaprath *et al* measured the water solubility of pure individual linear siloxane oligomers and found that it decreased with increasing chain length. Octamethyltrisiloxane (MDM) had a solubility of 34 ppb (34 µg/l), while the water solubility of dodecamethylpentasiloxane (MD_3M) was only 70 ppt (0.07µg/l). It was not possible to measure the water solubility of higher molecular weight polymers. Using linear regression of the semi-log plots of the measured solubility values against molecular weight, Varaprath *et al* predicted that the water solubility of commercially available PDMS polymers would be < 1 ppt (1 ng/l). He also confirmed the higher water solubility of hydroxyl terminated PDMS. For this reason, Varaprath *et al* (1996) should be taken as the 'key' study for evaluating water solubility of PDMS and earlier work should only be considered from the perspective of understanding how some of the ecotoxicological effects testing or environmental monitoring may appear inconsistent.

2.3.2 Partition coefficient octanol-water

Measurements of the octanol-water partition coefficient (K_{ow}) (following OECD guideline 107, shake flask method) were reported by Watanabe *et al* (1984a) (Table 4).

Table 4: Measured log K_{ow} values (Watanabe et al, 1984a)

Number-average molecular weight	log K_{ow} [a]
1,200	2.86
6,000	3.26
25,000	3.83
56,000	4.25

[a] Reported as log P_{ow}

As indicated in the previous section, these findings are questionable as commercial products were used, which may contain low molecular siloxane impurities and/or possibly be hydroxy terminated siloxanes which will increase the partitioning into water. As a consequence, the log K_{ow} will be erroneously low if concentrations are determined by a non-specific analytical method such ICP or AAS for total Si.

Using reverse phase high performance liquid chromatography (HPLC), Bruggeman *et al* (1984) estimated the log K_{ow} of PDMS with up to 14 repeating siloxy ($Si[CH_3]_2O$) units and reported a log K_{ow} of 12.5. It is now recognised that the HPLC method and the US EPA EPI Suite model version 4.10 (US EPA, 2011), which predicts a log K_{ow} of 25.6 for a PDMS polymer of 14 repeating units, have not been validated with silicon based materials. In recent studies, using a slow stirring method combined with analysis by gas chromatography (GC) and detection by mass spectrometry (MS, octanol phase) or flame ionisation (FID, water phase), the log K_{ow} values of octamethyltrisiloxane (MDM) and decamethyltetrasiloxane (MD_2M) (containing 3 or 4 siloxane units, respectively, in a linear polymer) were determined to be 6.60 and 8.21, respectively (Miller and Kozerski, 2008; Kozerski and Mosey, 2009). This confirms that the measurements of Watanabe *et al* (1984a) were a significant underestimation and support the work of Bruggeman *et al* (1984) that the log K_{ow} of PDMS increases with increasing number of siloxy units and that the log K_{ow} of high molecular weight PDMS is expected to be at least above 8.21 and probably significantly greater than 12.5.

2.3.3 Sorption to solid-phase organic matter

The affinity of a substance to associate with soil and sediment in aquatic systems is described by the solid-water distribution coefficient K_d = [s]/[c], where [s] is the concentration of chemical on the solid and [c] is the concentration in water. The K_d per fraction of organic carbon in soil or sediment is the partition coefficient organic carbon-water (K_{oc}). High K_d and K_{oc} values indicate strong sorption.

The K_{oc} values of substances with discrete structures are well-defined, but because PDMS is composed of molecules with similar structures but varying molecular weights, K_{oc} measurements are difficult to interpret and depend on the experimental design. Watanabe *et al* (1985a) found a log K_{oc} of 3.69 for PDMS 10,000 cSt. A commercial grade PDMS was used containing, most probably, small amounts of soluble siloxanols (hydroxyl terminated siloxanes); the K_{oc} therefore probably reflects the solubility of these siloxanols and is associated with the use of a non-specific analytical determination (i.e. ICP emission spectrometry) and has little bearing on the sorption of the hydrophobic PDMS. The presence of small quantities of siloxanol/siloxane impurities would not be an issue if the analytical technique were able to distinguish between the siloxanes and the siloxanols.

Measuring the sorption and desorption on sediments depends on the analytical methods, especially the methods to analyse PDMS sorbed to sediment. Watanabe reported PDMS present in water and sediment that was extracted with petroleum ether and analysed using ICP emission spectrophotometry. In the above study the recovery efficiency was not mentioned while in an earlier study Watanabe *et al* (1984b) reported a recovery efficiency of PDMS on sediment of 58%. This could suggest a similarly poor recovery in the Watanabe *et al* (1985a) study, resulting in an artificially low K_{oc} value (though the presence of polar impurities or emulsified PDMS would introduce a greater error). This conclusion is supported by the work of Lehmann *et al* (1995). Using ^{14}C-PDMS 350 cSt, Lehmann used desorption data for seven US soils to calculate an average K_d of 5,000 giving a log K_{oc} of 5.78. Also using ^{14}C-PDMS, Fendinger and Whittington (1994 cited by Fendinger *et al*, 1997a) reported a solids/water partition coefficient K_d for sewage sludge of 25,000 (log K_d 4.4). Further work on obtaining a reliable estimate of log K_{oc} for organosilicon based materials has been conducted by Miller and Kozerski (2007) and Durham *et al* (2007). They found that the log K_{oc} values for two cylic siloxanes, octamethylcyclotetrasiloxane (D_4) and decamethylcyclopentasiloxane (D_5), were 4.22 and 5.17, respectively. This work has now been extended to two short chain linear siloxanes, octamethyltrisiloxane (MDM) and decamethyltetrasiloxane (MD_2M), where the log K_{oc} values were 4.34 and 5.16, respectively (Durham and Kozerski, 2010). The log K_{oc} value of PDMS > 10 cSt is therefore likely to be >> 5.16.

Further understanding of the sorption of PDMS can be gained from a comparison of measured K_{oc} values for D_4 and D_5 with the estimated values derived from the octanol/water partition coefficients using an empirical single-parameter linear relationship. The study also included measured values and predictions for a large number of other non-ionic organic compounds. The lower than predicted K_{oc} values based on the traditional model for hydrophobic organic compounds, were ascribed to two factors. Firstly, relative to wet *n*-octanol, wet organic carbon is a more cohesive matrix, stronger H-bonding donor and more effective at inducing dipoles in polarisable molecules. Secondly, relative to the data set of non-organosilicon compounds for which the correlation between K_{oc} and K_{ow} was derived, cyclic siloxanes have larger size, greater

H-bonding basicity and lower polarisability (Xu and Kozerski, 2010). Together, these factors give rise to a difference in the K_{oc}-K_{ow} relationship for PDMS compared to traditional hydrophobic organic chemicals. The work of Xu and Kozerski (2010) supports the general idea that K_{oc} values will increase with increasing molecular weight of the oligomeric PDMS, but some caution should be exercised in extrapolating this to 10,000 cSt PDMS as the sorption mechanisms may not be exactly the same, i.e. adsorption versus absorption.

The conclusion is that earlier measurements of the organic carbon normalised sorption of PDMS, reported by a number of authors may significantly underestimate this property. The implication of this is that PMDS will be virtually immobile in the terrestrial environment.

2.4 Conversion factors

While for experiments conducted on single substances, it is common to consider the exposure concentrations in either molarity, parts per million (ppm) or milligrams per cubic meter (mg/m^3), PDMS is polymeric and has a molecular weight range. Exposure concentrations, therefore, can only be represented in mg/m^3 or mg/kg (for sediment studies for example).

2.5 Analytical methods

2.5.1 General considerations

Widespread use of a variety of silicone materials in personal care products and also in the laboratory (for example silicone gaskets and greases) can lead to contamination of samples. Extreme care must be taken when analysing environmental samples or body fluids for silicones, in order to avoid contamination. Frye (1987) recognised the risk of contamination and suggested that some published papers reporting PDMS in environmental samples could be artefacts resulting from contamination. The challenges of trace analysis and the potential artefacts that may arise are summarised by Varaprath *et al* (2006).

A number of environmental studies have been published in which the authors refer to “siloxanes”, “silicones” or “organosilicon compounds”, assuming that the organic solvent extractable silicon compounds were PDMS without analytical confirmation. Until twenty years ago, monitoring of siloxanes in the environment was conducted with non-specific analytical methods such as AAS or gel permeation chromatography (GPC) coupled to an ICP atomic emission spectrometer (AES). These methods suffer from the disadvantage that there may be interference from inorganic silicates. The more recently developed GPC interfaced with ICP (GPC/ICP) cannot distinguish between natural and synthetic organosilicon compounds. Nuclear magnetic resonance (NMR) has been used and can distinguish between organosilicon compounds and silicates. The ‘natural’

organosilicon compounds are thought to be a complex between the 1,2-dihydroxyaryl functionality of humic substances, such as humic and fulvic acids or tannic acid and silicic acid [$Si(OH)_4$] (Powell, 2004). Only the NMR technique can clearly distinguish if a material is actually PDMS. The recovery efficiencies for extracting PDMS from soil, sediment and sludge, were lower in studies conducted pre-1993, so the findings can only be regarded as an approximate indication of the concentration of PDMS in the environment.

The reliability of PDMS analysis methods that appear in the literature varies as a function of extraction efficiency, method of detection and the type of media. Early reviews of the methodology were prepared by Kreshkov (1962), Crompton (1989) and Smith (1991). A more recent review on the extraction and detection of PDMS, in environmental samples was completed by Carpenter and Gerhards (1997). Included in this review is a detailed analytical cross-validation of the methods used by the North American Silicone Industry Association (Silicone Environmental, Health and Safety Council – SEHSC) and the European Silicone Industry Association (Centre Européen des Silicones – CES). SEHSC conducted studies to compare the recovery efficiency from PDMS-spiked media. They found 100% recovery from sewage sludge but < 50% from water. This reflects the much lower concentrations present in aqueous media (Carpenter and Gerhards, 1997). In general, studies conducted post 1990 have a greater reliability, although some of the earlier work (for example Siebert, 1988) paid great attention to evaluating extraction efficiency and reliability.

A review of methods for low and high molecular weight silicones including soluble species, together with discussion about possible artefacts has been published by Varaprath *et al* (2006).

2.5.2 Extraction procedures

The first step in the analytical process is the extraction of PDMS into an organic solvent. Methods reported in the literature used extraction solvents such as diethylether (Pellenbarg, 1979a; Harzdorf, 1993), toluene (Tsuchitani *et al*, 1978), petroleum ether (Watanabe *et al*, 1984b) or hexane (Batley and Hayes, 1991). Lehmann (1993) used tetrahydrofuran to extract ^{14}C-PDMS 200 cSt from soil, applying a shaking method. Depending on the solvent and matrix being extracted, the usual procedure used was to dry the extract using anhydrous sodium sulphate and then concentrate it. The residue was dissolved in an appropriate solvent for the subsequent analysis. Recovery efficiencies for these methods were > 90%; similar values were obtained for sludge and sediment after an initial methanol extraction was performed to remove water.

Analysis

Many of the early analytical studies relied on AAS (e.g. Siebert, 1988; Pellenbarg, 1979b) or ICP-AES (Watanabe *et al*, 1984b; Batley and Hayes, 1991). These techniques were used

because they were specific for the element of silicon; they are unable to distinguish different chemical forms of silicon (inorganic versus organic). Due to concerns about interference with inorganic silica, Pellenbarg (1979a) and Siebert (1988) investigated the potential that clays, minerals and silicates may be extracted with the same non-polar solvents used to extract PDMS. Results from this work indicated that inorganic silica containing materials did not interfere with PDMS analyses at the concentrations under investigation.

Subsequently, ICP has been linked with GPC to give a technique known as GPC-ICP. GPC, also known as size exclusion chromatography (SEC), is able to separate on the basis of molecular size. It has therefore been useful in the demonstration of the degradation in soil of PDMS polymers (Lehmann *et al*, 2000). Although ICP does not differentiate between inorganic and organic forms of silicon, GPC analysis is performed on an organic extract of the medium (which will not extract inorganic silicates) and hence interference from silicates is minimised. This technique has been valuable in providing both quantifiable information on the amount of PDMS present in an environmental sample and molecular weight distribution information.

HPLC has been linked to ICP to successfully analyse PDMS in a range of environmental media, but this technique has been used more commonly for silanols than for PDMS (Dorn and Skelly-Frame, 1994),

Bellama *et al* (1991) were one of the first groups of researchers to use stable silicon isotope (^{29}Si) NMR to analyse environmental samples for PDMS. However, the detection limit was not sufficiently low to make it a viable method for trace level analysis. The advantage of NMR is that there is no interference from inorganic silicates in the soil. Much improved detection limits for PDMS in environmental samples have been developed by using proton (^{1}H) NMR (Carpenter and Gerhards, 1997). This technique has a detection limit for PDMS in soil of 0.05 ppm (based on a 100 g soil sample).

In addition to the nonspecific methods of PDMS detection, Weschler (1981, 1988) developed a specific pyrolysis GC-MS method for the analysis of PDMS. This method was developed to analyse PDMS associated with airborne particulates.

2.5.3 Conversion of analytical results to PDMS

Scientists who use analytical techniques such as AAS or ICP, which rely on the detection of elemental silicon must subsequently convert the Si result into silicone using the formula $[SiO(CH_3)_2]_n$ by assuming that 37.9% of the siloxane moiety is comprised of silicon. The true concentration of the siloxane could be underestimated if substituents having greater formula weights than methyl, e.g. amino- or phenyl-polymers, are present. At the time of Siebert (1988) or Watanabe *et al* (1984a,b,c, 1988), this was probably not an unrealistic assumption as

functional fluids were used to a much more limited extent than now (2011). When ^{1}H NMR is used it detects the hydrogen nuclei on the methyl groups. The assumption used is that PDMS is comprised only of dimethyl alkyl groups. Thus silicones with substituents other than dimethyl (e.g. amino-functional or vinyl) will not be included when specifically monitoring the chemical shift of silicon methyl groups. If this were the case then the concentration of the siloxane will again be underestimated just like in the case of the ICP method.

2.6 Summary and evaluation

The PDMSs reviewed in this report are linear polymers with a viscosity of 10 to > 100,000 cSt, composed of 15 to 1,000 dimethylsiloxy units with trimethylsilyl end groups, abbreviated as $MD_{13}M$ to $MD_{1,000}M$. PDMS of this type are clear, colourless and viscous liquids with an extremely low vapour pressure. PDMSs are chemically inactive and highly stable to thermal and oxidative degradation and radiation. Common impurities found in commercial PDMSs are octamethylcyclotetrasiloxane and decamethylcyclopentasiloxane (Section 2.3).

Based on measured data for pure MDM and MD_3M, the true water solubility of commercial PDMS has been predicted to be < 1 ppt (1 ng/l). The 'apparent' solubility values reported earlier are higher due to interference with the formation of micro-emulsions and presence of hydroxyl-terminated PDMS (i.e. siloxanols) or (more soluble) PDMS.

Measurements with short-chain PDMS up to $MD_{14}D$ showed that the log K_{ow} increases with increasing number of siloxy units and that the log K_{ow} of long-chain PDMS ($\geq MD_{15}M$) is expected to be at least above 8.21 (measured for MD_2M) and probably significantly greater than 12.5 (measured for $MD_{14}M$). Earlier measurements are questionable because of assumptions made in the application of the methodologies used for those studies).

The log K_{oc} of PDMS ($\geq MD_{15}M$) is likely to be >> 5.16 (measured for MD_2M). Previously reported lower values are significant underestimates. The K_{oc} will increase with increasing molecular chain length.

The reliability of PDMS analytical methods that appear in the literature varies as a function of extraction efficiency, method of detection and the type of media. Extraction of PDMS into a suitable organic solvent is usually followed by drying and concentrating the extract. The residue is dissolved in an appropriate solvent for the subsequent analysis, previously by means of non-specific techniques (interference from inorganic silicates) such as AAS or ICP and more recently by means of GPC-NMR, a technique that can clearly distinguish if a material is actually PDMS. The detection limit for PDMS in soil using ^{1}H NMR is 0.05 ppm (based on a 100 g soil sample).

3. PRODUCTION, STORAGE AND HANDLING, TRANSPORT AND USE

3.1 Production

Industrial silicone production has its commercial basis in the direct synthesis of methylchlorosilane via a process called the Müller-Rochow synthesis invented in 1942. In this process, methylchlorosilanes (a silane mixture from which the most important organochlorosilanes are derived) are synthesised by a reaction of elemental silicon with methyl chloride (CH_3Cl) using a copper catalyst. Methyl chloride is generated by reacting methanol (CH_3OH) with hydrogen chloride (HCl). The methylchlorosilanes are distilled to purify and separate the main reaction components, the most important of which is dimethyldichlorosilane (EIPPCB, 2007).

The production facilities for PDMS in Europe are located in France (Roussillon), Germany (Burghausen, Leverkusen and Nünchritz) and UK (Barry) (EIPPCB, 2007).

Based on sales figures, the amount of PDMS produced worldwide was 237,752 tonnes in 2007, divided between Japan 7,000, USA 68,113, EU 77,066 and rest of the world 85,573 tonnes (CES, 2010).

3.2 Storage and handling

No special protective measures are required for storage and handling of PDMS.

PDMS fluids are stored during production in tanks under a nitrogen atmosphere. General guidance given on suppliers' Material Safety Data Sheets is to avoid eye contact and maintain general ventilation. PDMS should not come in contact with strongly oxidising agents (Dow Corning, 2007, 2009; Bluestar Silicones, 2010) or alkalis and hot concentrated caustic products (Bluestar Silicones, 2010).

There are no special conditions for PDMS storage rooms and vessels; they may be stored in any typical storage container (drums, intermediate bulk containers, *etc.*). Containers should be kept tightly closed to avoid contamination. PDMSs are stored in a dry and cool place (below 50°C) (Wacker, 2009).

Like all liquid silicone based materials, PDMSs have lubricating properties that can substantially reduce or eliminate traction and may pose a slip hazard. In case of an accidental spill (Section 3.3), sand or another inert granular material is applied to improve traction (Wacker, 2009).

Combustion of PDMS yields carbon oxides (CO + CO_2) and amorphous silica (Bluestar Silicones, 2010). General precautions apply for prevention of fire and explosion. Suitable (normal) extinguishing media include water mist, extinguishing powder, alcohol-resistant foam, carbon dioxide or sand (excluding water spray and water jet because of the slip hazard) (Wacker, 2009). Fires can be quenched by dry chemical, foam or water spray (fog) and carbon dioxide (CO_2). Water can be used to cool fire exposed containers (Dow Corning, 2007, 2009; Bluestar Silicones, 2010). Thermal decomposition of PDMS may yield silica, carbon oxides and traces of incompletely burned carbon compounds, e.g. formaldehyde (Dow Corning, 2007, 2009). Bluestar Silicones (2010) recommends foam, powders or carbon dioxide. A strong water jet is not suitable.

Large spills should be contained by bunding procedures. Excess PDMS can be mopped, wiped or soaked up with absorbent material and placed in a container with a lid. The spilled product produces an extremely slippery surface (e.g. floor) (Dow Corning, 2007, 2009; Bluestar Silicones, 2010).

3.3 Transport

PDMS is transported in closed containers (Wacker, 2009) made of coated steels or plastic material (Bluestar Silicones, 2010). They are also transported in epoxy lined drums, plastic totes [tote bags], stainless steel tanker trucks or railcars.

PDMS is not classified as “dangerous” under European and other chemical laws or under international transport regulations. Special packaging and labelling is not required (Section 2.2). The maximum temperature for (storage and) transport is 50°C (Wacker, 2009). There are no international regulations for the transport of PDMS by rail, road, sea or air (ADR/RID, IMDG, IATA).

In Germany, PDMS is classified as “slightly water polluting” (Wassergefährdungsklasse [WGK] 1). In consequence, it is necessary to comply with the regulations for the protection of ground water and surface water. This classification is determined by the fact that PDMS fluids are non-biodegradable and is not related to specific ecotoxicological or toxicological effects.

Accidental releases of PDMS should be bunded and prevented from entering surface waters, drains or sewers and soil. Spilled PDMS can be taken up mechanically; small quantities are absorbed using suitable material such as diatomaceous earth. Any slippery coating that remains is removed using a detergent / soap solution or another biodegradable cleaner (Dow Corning, 2007, 2009; Bluestar Silicones, 2010).

3.4 Use

The viscosities of PDMS fluids mainly used are 350 and 1,000 cSt, although other viscosities are used for specialised purposes. PDMS has a wide range of industrial and consumer uses, either in the pure form or as an ingredient of a formulated product (e.g. emulsions). The broad categories for use of PDMS are listed in Table 5.

Table 5: Applications of PDMS (after Wacker, 2002)

Industrial
Adhesives
Antifoam in wastewater treatment plant
Damping fluid
Electrical
Heat transfer fluid
Hydraulic fluid
Industrial antifoam (e.g. mineral oil)
Liquid dielectric (transformer cooling fluid)
Lubricant (grease)
Mould release agent
Reprography
Sealants
Softener in silicon rubber product (e.g. silicone sealant)
Textile softening
Water repellent
Consumer
Antifoam in detergent
Anti-gas agent
Cosmetic (lipstick, make-up, foundation)
Domestic rinse agent
Head lice treatment
Personal care product (hair care, skin care, soap, cream, lotion, insect repellent)
Polish (e.g. furniture, car, shoes)
Sunscreens
Food
Antifoam in food processing, e.g. beer, jam, etc.
Antifoam in frying fat and vegetable oil
Medicinal/Pharmaceutical
Anti-gas/anti-flatulent
Head Lice

PDMS is not sold directly to the detergent industry, but is first mixed with silica and then marketed as an antifoam (Andriot *et al*, 2007). Based on a consumption/production survey conducted by the Association Internationale de la Savonnerie, de la Détergence et des Produits d'Entretien (AISE) formulators sub-team and the European Silicone Industry, 7,200 tonnes of siloxanes were used in detergent applications in the EU in 2000 (HERA, 2007a).

Information on the worldwide use of PDMS , including a percentage breakdown in the EU-27 is given in Chapter 10.

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, TRANSFORMATION AND IMPACT

4.1 Emissions

4.1.1 Natural sources

There are no known natural sources of PDMS polymers.

Powell (1999) and Powell *et al* (1999) suggested that natural silicon materials may be extracted (by tetrahydrofuran) from sediments that cannot be analytically resolved from PDMS polymers by size-exclusion chromatography. In the environment, silicic acids and silicates are known to exist in stable complexes with humic, fulvic and tannic acids (Goldberg Federico and Vandoni, 1969; Weiss and Herzog 1978; Panov *et al*, 1987; Schulthess and Huang, 1991; Hahn *et al*, 1995). Although a discrete structure could not be identified, Powell *et al* (2004) demonstrated that these natural organosilicon compounds were due to the formation of stable octahedral complexes between the 1,2-dihydroxyaryl functionality of humic substances and silicic acid. The presence of these naturally occurring organosilicon complexes in soils may explain why some monitoring studies that used non-specific extraction and analytical methods reported wide-spread distribution of PDMS polymers even in remote areas (e.g. Siebert, 1988; Fendinger *et al*, 1997a,b; Powell *et al*, 1999).

4.1.2 Emissions during production and use

As a hydrolysis step is involved in the conversion of chlorosilanes to polymeric PDMS materials, PDMS may be released into the aqueous waste stream during production. Typically, wastewater treatment includes at least one precipitation-flocculation step that is followed by sedimentation to remove solids, heavy metals and oils. PDMS polymers in wastewater that enter a treatment facility are largely removed by sorption to sludge solids. Approximately 97% or more of the PDMS polymers will be bound to sludge and removed by the flocculation and sedimentation process (Fendinger *et al*, 1997a). As PDMS polymers are non-volatile, no emissions to the atmosphere are expected (EIPPCB, 2007).

PDMS polymers are found in a wide range of industrial and consumer products. The environmental fate of PDMS polymers depends to a large extent on the nature of the application, the physical form of the material and the method of disposal. High molecular weight PDMS polymers have many diverse applications. In some cases, they become incorporated into a matrix and therefore become solid, for example silicone rubbers or sealants. At the end of their life-cycle, such materials become part of solid municipal or industrial waste.

PDMS fluids are used in down-the-drain applications such as shampoo, hair conditioner, silicone antifoaming agent in detergents or textile softener that will become part of municipal wastewater and ultimately released to the environment (i.e. point source emission). Unlike other down-the-drain chemicals in consumer products, there is also a significant mass released from non-point sources. For example, PDMS fluids used in applications such as automobile polish, deck coatings or exterior paints may be released to environment as dispersed or non-point source emissions. Such emissions will end up in various compartments such as wastewater, rivers or soil. The mass of PDMS fluids released to the environment from point source or non-point source emissions are about the same (Allen *et al*, 1997).

4.2 Environmental distribution

'Solid' PDMS polymers enter the environment as a component of domestic or industrial waste and will either go to landfill or be incinerated. In the latter case, they are converted back to inorganic ingredients, amorphous silica, carbon dioxide and water vapour. 'Liquid' PDMS polymers, both high and low molecular weight, are used in rinse-off applications (such as shampoo, hair conditioner or silicone antifoaming agent in detergents) that become part of municipal wastewater.

In the EU, the average connectivity to a municipal wastewater treatment plant (WWTP) was defined for risk assessment purposes in the Technical Guidance Document in 2003 (EC, 2003) as 80%. The connectivity has increased significantly since the full implementation of the Urban Wastewater Treatment Directive (91/271/EEC) in 2005. Eurostat (2010) has published data up to 2007 showing that at least 80%of households in half of the EU member states were connected to municipal wastewater treatment. ECHA (2010) in their guidance on environmental exposure estimation proposed that this should rise to 90 to 95% connectivity following full implementation of the Urban Wastewater Treatment Directive.

On entering the wastewater treatment plant, PDMS will partition to organic matter that ultimately forms sewage sludge. This is because of the extremely low water solubility of PDMS (< 1 ng/l; Table 1), coupled with the high K_{oc} value of 10,000 to 600,000 (Watanabe *et al*, 1985a; Lehmann *et al*, 1995), although the exact K_{oc} value may vary depending on the viscosity and the presence of lower molecular weight siloxanes. Analysis of sewage sludge from a number of wastewater treatment facilities reveals that PDMS concentrations in sludge are between 122 and 5,155 mg/kg (on a dry weight basis), with the highest concentrations being associated with inputs from industrial sources (Fendinger *et al*, 1997a,b). A bench scale model of a wastewater treatment process using ^{14}C-PDMS showed that > 99.9% was removed from the aqueous phase (Watts *et al*, 1995). Extensive studies of wastewater treatment plants show that more than 95% of PDMS is

removed from effluents by sorption and that the concentration in discharged effluents borders the level of detection (5 µg/l) (Fendinger *et al*, 1997a).

Depending on where the sewage sludge is generated in the European Union, the primary routes for disposal are either landfill, incineration or use as a soil amendment (Hall and Dalimier, 1994). If incinerated, silicones form carbon dioxide and amorphous silica. The other principal outlet for sludge is as a soil conditioner or amendment. PDMS may, therefore, enter the terrestrial environment as a component of sewage sludge. The quantity of sewage sludge disposed to agricultural land varies throughout the EU from < 1% in the Netherlands (year 2003) and Greece (2006) to 70% in France (2007) and 68% in the UK (2006) (Milieu *et al*, 2009). Sludge may also be disposed in municipal landfill sites. Previously significant quantities of sewage sludge were disposed at sea, particularly in the coastal waters of the UK. This is no longer permitted by law and the practice ceased in 1996.

Pellenbarg (1979a) reported that PDMS associated with WWTP sludge and sludge disposed at sea does not migrate from the sediment. Movement of PDMS is expected only when sediment layers are moved, e.g. by tides and currents. With time, additional layers of sediments will be deposited, such that PDMS-bound sludge will become buried.

4.2.1 EQC modelling

Environmental partitioning is typically assessed by means of the fugacity-based equilibrium criteria (EQC) model (Mackay *et al*, 1996). Required input parameters are: Molar mass, vapour pressure, water solubility, K_{ow}, melting point and degradation half-lives in air, water, soil and sediment.

The EQC model was never intended to be applied to polymeric materials, such as PDMS, which falls outside the domain of applicability for the model. Furthermore there are additional issues concerning the input parameters: Molar mass will vary with the viscosity and size of the polymer, vapour pressure cannot be measured, water solubility cannot be measured and only extrapolated from data on lower molecular weight siloxane polymers and K_{ow} of polymeric materials cannot be reliably measured or estimated. The model is known to overestimate K_{oc} from K_{ow} for siloxane materials. Melting point is represented by a melting range rather than a specific value. The rate of degradation of PDMS depends on moisture content of the medium, thus an exact value cannot be determined.

For these reasons, the environmental distribution of PDMS has not been estimated by modelling. The emphasis is therefore on actual measurements which are documented in Chapter 5.

4.3 Environmental fate and biotransformation

4.3.1 Atmospheric fate

As PDMS polymers > 10 cSt ($n \geq 15$ in MD_nM) are essentially non-volatile, PDMS vapours will not be found in the atmosphere, although low molecular weight cyclic and linear impurities will volatilise from PDMS fluids over time. PDMS fluids of intermediate viscosity (< 1,500 cSt approximately) may become airborne if aerosolised in a product intended for spray applications, for example some personal care or textile products. PDMS is less dense than water and will partition to the surface microlayer, the boundary layer at the air-water interface of a receiving water (Section 5.1.1), though in systems with suspended solids or dissolved organic carbon present, adsorption would possibly dominate (Section 4.3.2). Any PDMS in the microlayer would be susceptible to aerosolisation by wind and wave activity. Theoretically PDMS bound to soil could also become airborne as a component of dust.

There have been no studies published on atmospheric lifetime [a] or degradation in the atmosphere of high molecular weight PDMS. A limited analysis of oligomeric PDMS polymers was reported by Markgraf and Wells (1997) who studied the hydroxyl radical reaction rate constants and atmospheric reaction products of three short chain linear siloxanes; hexamethyldisiloxane (MM), octamethyltrisiloxane (MDM) and decamethyltetrasiloxane (MD_2M). While these substances are outside the scope of this report, the study showed that the hydroxyl radical rate constant increased with increasing length of the siloxane backbone from $1.32 \pm 0.05 \times 10^{-12}$ cm^3/molecule·s for MM, $1.83 \pm 0.09 \times 10^{-12}$ cm^3/molecule·s for MDM to $2.66 \pm 0.13 \times 10^{-12}$ cm^3/molecule·s for MD_2M. Assuming the concentration of OH radicals in the atmosphere to be 1×10^6 molecules/cm^3, Markgraf and Wells (1997) calculated the atmospheric lifetimes of MM, MDM and MD_2M to be 8.8, 6.3 and 4.3 days (half-life 6.1, 4.3, 2.8 d), respectively. This degradation mechanism is only relevant for gas-phase siloxanes. It is highly unlikely that high molecular weight PDMS will degrade via this route as such molecules are effectively non-volatile. No data is available on the degradation of PDMS in aerosol particles.

The limited analyses of the atmospheric compartment are discussed in Section 5.1.1.

4.3.2 Aquatic fate

As PDMS fluids are used in a broad range of industrial, medical and consumer applications that are eventually discarded 'down-the-drain' to wastewater − for example shampoos, hair conditioners, antifoams, antiflatulants, lubricants, detergents and textile coatings (Allen *et al*, 1997; Fendinger *et al*, 1997a), small amounts of PDMS may be detected in untreated wastewater. Extensive monitoring in the US, Japan and Australia show that even near WWTP outlets,

[a] Lifetime is the time necessary for 63% degradation; it is equal to 'half-life' divided by ln 2 (= 0.69)

concentrations were at or below the level of detection (≈ 5 µg/l) (Fendinger *et al*, 1997a; Watanabe *et al*, 1988; Batley and Hayes, 1991). The low concentrations in the water phase are due to the very low water solubility of PDMS (< 1 ng/l; Table 1), coupled with the very high adsorption coefficient for organic matter (Fendinger *et al*, 1997a), such that PDMS is removed from the aqueous phase during sewage treatment by adsorption to particulate matter. This has been demonstrated in laboratory (Watts *et al*, 1995) and field studies (Fendinger *et al*, 1997b).

In the event of an accidental spill of PDMS fluid to surface water, the PDMS will spread rapidly on the surface to form a very fine film, as a result of its very low surface tension (≈ 20 dynes/cm) and a density less than water. Depending on the environmental conditions, this film is likely to break up to form tiny droplets which adsorb to suspended particles, eventually settling out of the water column and becoming part of the sediment compartment.

Palmer (1992) performed two sets of experiments to determine whether biological degradation of PDMS occurred in aerobic or anaerobic sludge. The experiments used radiolabelled ^{14}C-PDMS 200 cSt and unlabelled PDMS 35 and 1,000 cSt. There was no significant degradation reported in either test system.

PDMS fluids depositing in the sediment compartment slowly hydrolyse to DMSD. After an incubation period of 1 year, 5 to 10% of ^{14}C-PDMS had been hydrolysed to DMSD and approximately 0.25% of the total ^{14}C oxidised to carbon dioxide (Carpenter, 1996).

4.3.3 Terrestrial fate

Initial studies on PDMS degradation in soils (Buch and Ingebrigtson, 1979) showed that PDMS fluids of various viscosities could undergo hydrolysis and rearrangement. Samples were heated at 80 degrees for 7 days. The rate at which this abiotic degradation occurred was highly dependent on soil moisture content. The reactions were fastest at very low moisture contents (0.13%) and decreased rapidly as the moisture content increased above 3.56%. The primary degradation products detected were D_4 and hexamethyldisiloxane (MM). The presence of primarily volatile siloxanes as opposed to the water soluble silanol species found in later experiments, was later (Lehmann *et al*, 1995) attributed to the high loading rates (0.6 g PDMS/100 g soil) used by Buch and Ingebrigtson (1979) together with the fact that the soils were finely ground and dried in an oven at 80°C for 7 days. Clay minerals were the most active, with little or no activity observed in humus or sand.

Subsequent studies, focused on more environmentally realistic experiments (Lehmann *et al*, 1994a). In the former study, ^{14}C-PDMS 200 cSt was added (100 mg/kg) to a moist sandy clay loam soil, which was then allowed to air-dry at 25°C for 0, 1, 2, 3, 4, 7, 10 or 14 days. The soil dried rapidly and after 4 days reached about 2 to 3% moisture. PDMS degradation was

monitored by first performing a series of soil extractions with tetrahydrofuran, aqueous methanol, water and dilute hydrogen chloride. The extracts were analysed by HPLC-GPC which monitored for changes in the molecular weight of the PDMS polymer and the presence of low molecular weight water soluble species by GC. As PDMS is virtually insoluble in water, any increase in extractability of ^{14}C material into the aqueous phase implied that a breakdown to smaller water soluble species must have been occurring. No changes in extractability were observed for the first 3 days when moisture content of the soils was > 3.5%. After day 4, moisture content of the soils was < 3.0% and increasing concentrations of water-extractable ^{14}C material were observed, a trend that increased with time. GC-MS analysis confirmed that > 98% of the water-extractable ^{14}C material was DMSD (Formula 1) (Lehmann *et al*, 1994a).

$(CH_3)_2\ Si(OH)_2$ …… (Formula 1)

Little ^{14}C material ($\leq$ 0.11% of material applied) was detected in traps used to collect volatile materials, such as the cyclosiloxanes and CO_2. At the same time, HPLC-GPC revealed that the molecular weight of the non-aqueous extractible ^{14}C material decreased from around 7,000 to about 160, with only low concentrations of ^{14}C material having intermediate molecular weights. The observed decrease in molecular weight was attributed to scission of the Si-O-Si bonds of the siloxane backbone, rather than to loss of methyl groups (Lehmann *et al*, 1994a). This was confirmed by the authors who showed that demethylation of PDMS did not occur during the 2-week incubation with dry soil.

Although this abiotic degradation occurred most rapidly in air-dry soil, extraction of moist soil after 25 weeks also showed the formation of low concentrations of low molecular weight species. A study to monitor degradation of PDMS bound to sewage sludge under field conditions was also conducted by Traina *et al* (2002). The soil moisture was > 10% for most of the duration of the 4-year study. Under these conditions of moisture, the half-life of PDMS in soil was 2.4 to 3.9 years. When samples of the soil were taken into the laboratory to simulate arid conditions, > 80% of the PMDS had degraded to low molecular weight species within 20 days. The study also confirmed that there was no difference in the degradation pattern between PDMS applied directly to the soil or applied bound to sewage sludge.

It was subsequently confirmed that DMSD was the major PDMS degradation product (Lehmann *et al*, 1994b, 1995). This apparent contradiction with earlier work (Buch and Ingebrigtson, 1979) is attributed to the fact that Buch and Ingebrigtson used high loadings (0.6%) of PDMS where subsequent degradation of the PDMS polymer resulted in high concentrations of DMSD, which self-condensed leading to formation of octamethylcyclotetrasiloxane.

Lehmann *et al* (1995) found that the degradation products were the same with either PDMS 200 or 350 cSt fluids, suggesting that the size of the polymer had no influence on the mechanism of degradation. This viscosity-independent mechanism was also confirmed by Carpenter *et al*

(1995), who applied PDMS 350 cSt dissolved in hexane to soil and then allowed the solvent to evaporate. The soil was allowed to age for one week. Analysis of tetrahydrofuran extracts of the soil by liquid chromatography-mass spectrometry (LC-MS) revealed a series of silanol-terminated oligomers HD_nH (where n = 8 or less).

No volatile cyclosiloxanes were detected. This therefore confirms that linear silanols, rather than cyclic siloxanes are the principal products of degradation when PDMS is tested at lower concentrations and more typical of those found in the environment (Section 5.1.5).

This degradation pattern does not appear to change with time. Analysis by high-performance liquid chromatography-ICP emission spectroscopy (HPLC-ICP) demonstrated that DMSD was the major component in an aqueous extract of a soil 1 year after it had been spiked with PDMS.

Carpenter *et al* (1995) also confirmed by GC-MS the presence of low concentrations of trimethylsilanol (Formula 2).

$(CH_3)_3SiOH$ …… (Formula 2)

Trimethylsilanol was believed to be generated from scission of the terminal trimethyl groups of the polymer chains and therefore was present at much lower concentrations than the degradation products (e.g. DMSD).

DMSD was also the primary degradation product detected in the work of Spivack and Dorn (1994). They studied the equilibrium between DMSD and its dimer and trimer diols by ^1H NMR and GC analysis of derivatised extracts. The equilibrium constants they determined indicated that DMSD would be the predominant species that existed in aqueous solutions at environmentally relevant concentrations.

4.3.4 Degradation of dimethylsilanediol

The solubility of DMSD is 245 g/100 g of water (≈ 2,450 g/l) and thus DMSD is very water soluble (Hyde, 1953). Therefore the primary degradation product of PDMS is now in a form which is biologically available to microorganisms. With the advent of ^{14}C-PDMS, it became possible to demonstrate that a biological mechanism was also involved with the degradation of PDMS.

Lehmann *et al* (1994b) using ^{14}C labelled PDMS showed that, if soil was allowed to dry out over a 2-week period to 2% moisture (during which time no $^{14}CO_2$ was generated) and then rewetted to 14% moisture, the optimum content for biological activity, $^{14}CO_2$ was evolved. The biodegradation of ^{14}C-DMSD also was demonstrated in four different soil types (Carpenter 1996;

Lehmann *et al*, 1997), confirming that the biodegradation was possible. Initial rates in the four soils varied from 0.4 to1.6% per week. These results confirmed that, the methyl groups of DMSD had been oxidised as a result of biological activity. It was postulated that the ultimate degradation product would therefore be silicic acid ($Si[OH]_4$). Due to the large excess of siliceous material present in soils, it was not possible to demonstrate an increase in silicic acid concentration in a soil environment; only in liquid culture does this become possible. Two microorganisms, a fungus, *Fusarium oxysporum* Schlectendahl and a bacterium, *Arthrobacter* species, isolated from soils, were shown to metabolise DMSD in pure culture (Sabourin *et al* 1996). The fastest rate was observed with the *Arthrobacter* species, which achieved a conversion of ^{14}C-DMSD to $^{14}CO_2$ at a rate of about 3.5% per month. This rate could be enhanced further by the addition of dimethylsulphone, a structural analogue of DMSD.

In a subsequent experiment, both methylsilanetriol and inorganic silicate were identified as degradation products, supporting the hypothesis that biodegradation is a possible step in the ultimate degradation of PDMS in the environment (Sabourin *et al,* 1999).

In common with many environmental pathways, biodegradation of DMSD is not the only fate path involved. DMSD is relatively volatile and depending on the soil type, appreciable quantities are volatilised from the soil into the atmosphere (Lehmann and Miller, 1996). Whereas $^{14}CO_2$ from ^{14}C-DMSD varied from 0.4 to 1.6% per week in four soils from pasture, deciduous woodland, cropland and pine woodland (Lehmann *et al*, 1997), volatilisation varied from 1.4 to 7.7% per week, with the highest rate being observed in sandy soils (Lehmann and Miller, 1996). A comparison of biodegradation and volatilisation rates for specific soils suggests that volatilisation will dominate in dry, sandy soils and biodegradation in damp, heavy soils (Lehmann *et al*, 1997; Lehmann and Miller, 1996). Lehman *et al* (2002) also showed that DMSD was readily taken up by plants growing in the soil.

After DMSD has volatilised, it is predicted to undergo reaction with OH radicals that are generated in the presence of sunlight. This is based on experiments that have been conducted on trimethylsilanol (Sommerlade *et al*, 1993), where the rate constant for the reaction with OH radicals to form DMSD was measured as $3.95 \pm 0.95 \times 10^{-12}$ cm^3/molecule·s. This compares favourably with other organic molecules such as toluene, which has a rate constant for the same reaction of $6.82 \pm 1.6 \times 10^{-12}$ cm^3/molecule·s. The atmospheric lifetime for trimethylsilanol was estimated to be between 2 and 9 days (half-life 1.4 - 6.2 d). It is predicted that the atmospheric lifetime for DMSD would be similar. The degradation products, i.e. for methylsilanetriol and silicic acid would be washed out by rainfall as would DMSD.

The potential for oxidative demethylation of DMSD by hydroxyl radicals has also been demonstrated in water containing nitrate or nitrite (Buch *et al*, 1984). Irradiation of aqueous solutions of DMSD with UV light (peak wavelength of 365 nm) resulted in decreased

concentrations of DMSD and a concomitant increase in concentrations of $Si(OH)_4$. The authors proposed that oxidative demethylation of DMSD occurred by hydroxyl radicals that were formed during intense irradiation of nitrate and nitrite ions in the following manner (Equation 1 and 2).

$$NO_3^- + H_2O \xrightarrow{hv} NO_2^{\cdot} + {}^{\cdot}OH + OH^- \quad \text{(Eq. 1)}$$

$$NO_2^- + H_2O \xrightarrow{hv} NO^{\cdot} + {}^{\cdot}OH + OH^- \quad \text{(Eq. 2)}$$

where *hv* denotes a photon (light), $^-$ an anion and $^{\cdot}$ a radical.

Since nitrate and nitrite ions possess absorption maxima in the range of the sunlight radiation (wavelengths above 295 nm), the formation of hydroxyl radicals was predicted to occur under natural environmental conditions.

The reaction was also demonstrated for natural waters, demonstrating that there were sufficient levels of nitrates and nitrites in inland lakes and waterways to catalyse the photolytic oxidative demethylation of DMSD. Other anions such as sulphate or phosphate did not catalyse the reaction.

Similar results were reported demonstrating that silicate ion was produced when using a mixture of short chain dimethylsiloxanes with OH functional groups and dimethylcyclosiloxanes (Anderson *et al*, 1987). The average half-life of the oligomeric dimethylsiloxanes was found to be between 4 and 9 days in the presence of 50 mg/l nitrate. Irradiation of a high molecular weight polydimethylsiloxane for 5 weeks failed to result in any significant increase in silicate levels.

4.3.5 Bioaccumulation

The European Chemicals Agency (ECHA, 2008a) outlines three indicators for limited bioaccumulation as follows:

- Octanol-water partition coefficient: log K_{ow} > 10.
- Molecular size: A maximum cross-sectional diameter > 1.7 nm (equivalent to > 17 Å) which limits the ability of a molecule to pass across a biological membrane or a molecular weight > 700 is indicative that a substance will not fulfil the ‘B’ or ‘vB’ criteria (i.e. not be bioaccumulative or very bioaccumulative) and that the bioconcentration factor is therefore <

2,000. The US EPA also exempts chemicals with a molecular weight > 1,100 in the PBT assessment conducted under the Toxic Substances Control Act (US EPA, 1999).

- Results from an animal study (mammalian or fish) confirming no or low bioaccumulation.

When PDMS is compared against these given criteria the following can be concluded.

Octanol-water partition coefficient

As discussed in Section 2.3.2, PDMS fluids with viscosities > 10 cSt are expected to have log K_{ow} values that are > 10. There are few measured log K_{ow} values of > 10, as it is recognised that measurements in this region are difficult due to the extremely low water solubility (< 1 ng/l; Table 1). Bruggeman *et al* (1984), using reverse phase HPLC, estimated the log K_{ow} of PDMS with up to 14 repeating siloxy ($Si[CH_3]_2O$) units. The log K_{ow} increased as expected with molecular weight and PDMS with a molecular weight of 1,198 (14 repeating siloxy units) had a log K_{ow} of 12.5. Confidence in the validity of this value is also demonstrated by running the EPI Suite model version 4.10 (US EPA, 2011), which for a PDMS polymer of 14 repeating units has a predicted log K_{ow} of 25.6. Since the number of repeating units in the PDMS of > 10 cSt viscosity is greater than 14, the expected log K_{ow} is clearly in excess of that likely to bioaccumulate.

Molecular size

Opperhuizen *et al* (1987) proposed that a substance with an effective molecular length of > 43 Å would not pass biological membranes, neither the gills nor the gastro-intestinal tract, on the basis of a series of bioaccumulation and bioconcentration studies with linear and cyclic PDMS (silicones) varying in chain length. Opperhuizen *et al* (1987) hypothesised that passage across a biological membrane was very unlikely because such large molecules would disturb the entire interior structure of the lipid membrane. Woodburn *et al* (2007) who studied *in vivo* fish bioconcentration data from 15 chemicals, including two short chain linear PDMS, found that a maximum mean diameter of 15Å (based on modelling using the Oasis Forecast model [Oasis, 2010]) was associated with reduced bioconcentration. The maximum mean diameter of cyclic and linear siloxanes was found to increase with an increasing number of siloxy units such that PDMS with 4 repeating siloxy units (MD_2M) had a maximum mean diameter of 14.4 Å. The threshold value of 1.5nm (15Å), above which passage across a biological membrane was very unlikely, was originally proposed by Dimitrov *et al* (2002). It is therefore expected that the maximum mean diameter of high molecular weight PDMS fluids addressed in this document, will, due to folding of the linear molecules, be higher, thereby further reducing the potential for bioconcentration.

Results from bioaccumulation studies in animals

Aquatic phase: Annelin and Frye (1989) studied the uptake by *Oncorhynchus mykiss* (rainbow trout) of a series of individual linear PDMS from 2 to 7 repeating siloxy groups. The latter showed no detectable uptake (detection limit 0.3 mg/kg in fish) after 56 days exposure in water containing a 24 µg/l colloidal dispersion. Opperhuizen *et al* (1987) evaluated dietary exposure of *Carassius auratus* (goldfish) for 67 days and aqueous exposure of *Poecilia reticulata* (guppy) for 20 days to a PDMS fluid with a viscosity of 5 cSt, which had an average of 12 siloxy units MD_nM (where n = 3 - 15). Lower molecular weight PDMS was detected in some fish tissue samples but no PDMS molecules with more than 12 siloxy units (corresponding to a molecular weight of 1,050) were found in the fish. Thus linear siloxanes with a molecular weight ≥ 1,050 showed no bioconcentration or bioaccumulation in fish.

Bioaccumulation in the marine environment was studied in a mesocosm food chain that included phytoplankton, molluscs, annelids and fish. There was no evidence of bioaccumulation in these tests (Aubert *et al*, 1985; Guillemaut *et al*, 1987).

Sediment: The potential for bioaccumulation of PDMS from sediment was evaluated for two benthic macro-invertebrates, the midge larva of *Chironomus tentans* (Putt, 1994a) and the sediment worm, *Lumbriculus variegatus* (Kukkonen and Landrum, 1995). The study on *C. tentans* was a combined toxicity and bioaccumulation study that was conducted in three sediments containing high (4.3%), medium (1.5%) and low (0.1%) organic matter content (Putt, 1994a). The mean measured concentrations of PDMS 350 cSt in these three sediments were 560, 450 or 350 mg PDMS/kg dry weight, respectively. Biota-sediment accumulation factors were calculated by comparing measured residue concentrations of radiolabelled ^{14}C-PDMS in the exposed organisms and the sediment, following 14 days exposure. The values of the biota-sediment accumulation factors were 1.5, 0.50 and 0.59 for the midge larvae exposed to PDMS in low, medium and high organic sediment, respectively, indicating limited bioaccumulation potential of PDMS in midge tissue from PDMS-dosed sediment. In the study on *L. variegatus*, Kukkonen and Landrum (1995) used PDMS as a tracer of ingestion and elimination of sediment particles. The authors observed that increased concentrations of PDMS appeared to decrease uptake of benzo(a)pyrene. The worms were exposed to Lake Michigan sediments amended with radiolabelled ^{14}C-PDMS 200 cSt at 50 and 150 mg/kg and benzo(a)pyrene at levels of 190 µg/kg. Worms were also exposed to benzo(a)pyrene alone. The only ^{14}C-PDMS found associated with the worms was in the gut contents; this was excreted within 10 hours following exposure. Therefore there was no evidence of bioaccumulation of PDMS from sediment by *L. variegatus*. In addition, the presence of PDMS in sediment was found to have reduced the bioavailability of benzo(a)pyrene.

Soil: The absence of bioaccumulation also has been observed in soil organisms. A PDMS uptake-depuration study was conducted in earthworms (*Eisenia foetida*) at nominal soil concentrations of 100 or 1,000 mg/kg (90.5 and 925 mg/kg measured) radiolabelled ^{14}C-PDMS 350 cSt was used. The study consisted of a 28-day exposure phase followed by 14 days depuration. The calculated bioaccumulation factors were 0.057 and 0.049 for the 100- and 1,000-mg/kg nominal treatment concentrations, respectively. The small amount of PDMS residues that accumulated during the exposure phase (average 5 and 45.5 mg/kg for the low and high PDMS concentrations, respectively) due to ingested food in the gut, were almost completely eliminated during the initial 2 days of the 14-day depuration period (Garvey *et al*, 1998). These results further support the conclusion that PDMS in soil does not bioaccumulate in soil-feeding organisms.

A microcosm study was conducted where sludge containing^{14}C-PDMS was added to two types of soil (silty clay and sandy loam) and used to grow wheat and soybeans over a 7-month period (Lehmann *et al*, 1996). Up to 50% of the applied^{14}C was unaccounted for at the end of the study. The majority of the ^{14}C recovered was found in the topsoil (43% of that applied). Only small amounts were detected in the plants, ranging from 0.0% in wheat grain to 2.25% in soybean shoots.

Terrestrial vertebrate organisms: Absorption studies were conducted in rats using ^{14}C-PDMS 10 and 350 cSt administered via oral gavage at a dose of 1,000 mg/kg body weight (bw). Excreta were collected for 96 hours, the animals were then killed and whole body autoradiography was performed. Radioactivity was almost totally associated with either the gastrointestinal tract or the faeces. No significant radioactivity was detected outside the gastrointestinal tract with the exception of exterior contamination, 99.6 to 99.8% of the recovered dose (> 93.6%) was found in the faeces. No detectable degradation products were present in the faeces and there was no evidence of absorption of high molecular weight PDMS via the gastrointestinal tract (Jovanovic *et al*, 2002).

4.3.6 Summary and evaluation

There are no data on atmospheric lifetime or degradation of linear PDMS with a viscosity of > 10 cSt ($n \geq 15$ in MD_nM). These PDMSs are essentially non-volatile and no PDMS vapours have been reported in the atmosphere although PDMS in aerosol particles have been detected (Section 5.1.1.).

PDMSs have an extremely low water solubility and a high affinity for organic matter. The vast majority (> 97%) of PDMS fluid discarded 'down-the-drain' to wastewater is expected to be removed from the aqueous phase during sewage treatment by adsorption to particulate matter (sludge). This has been demonstrated in laboratory and field studies. Accidentally spilled PDMS

will spread on the water surface to form a very fine film, and then is likely to adsorb to suspended particles and eventually settle out as sediment.

In the laboratory, PDMS in contact with air-dry soil, mimicking arid conditions, will start to undergo abiotic degradation, involving breakdown to smaller water soluble species (water extractable s), after 3 to 4 days. Under field conditions, when PDMS was applied onto moist soil, the half-life of PDMS was 2.4 to 3.9 years. In freshwater sediments, 5 to 10% PDMS was hydrolysed after 1 year. The principal degradation product (> 98%) is DMSD formed by breaking up the Si-O-Si bonds. DMSD is very soluble and possibly subject to biodegradation into CO_2, water and organic silicate, the ultimate degradation products of PDMS, as demonstrated in laboratory experiments. A rate of DMSD conversion of 3.5% per month was achieved in pure culture under optimal conditions. Minor PDMS degradation products may include short-chain silanol terminated oligomers and trimethylsilanol (from the terminal trimethyl groups). Little or no cyclosiloxanes are expected to form except under conditions of high PDMS loading rates. DMSD and trimethylsilanol are also expected to volatilise into the atmosphere and react with hydroxyl radicals to form CO_2 and silicic acid.

No reliable value of K_{oc} has been measured for PDMS of > 10 cSt viscosity. Evidence from studies with short-chain PDMS < 10 cSt supports the conclusion that log K_{ow} increases with molecular weight and that the log K_{ow} is > 10. Bioconcentration studies with short-chain PDMS (n up to 12) also suggest that, due to their molecular size (effective length and maximum mean diameter) being > 15 Å), the potential for PDMS fluids > 10 cSt to cross biological membranes (gills or the gastro-intestinal tract) is very unlikely. Relevant studies on PDMS 200 and 350 cSt showed limited evidence of bioaccumulation potential in the sediment-dwelling midge larva of *Chironomus tentans* and the sediment worm, *Lumbriculus variegatus*, and there was no biomagnification in the earthworm (*Eisenia foetida)*. No absorption took place during studies on PDMS 10 and 350 cSt in rats. Based on this information, there is no evidence of PDMS bioaccumulating in aquatic or terrestrial organisms.

5. ENVIRONMENTAL CONCENTRATIONS AND HUMAN EXPOSURE

5.1 Environmental concentrations

5.1.1 Air

Weschler (1981) identified PDMS at levels of approximately 8 ng PDMS/m^3 of air extracted from aerosol particles collected at Barrow, Alaska, USA using a pyrolysis-GC-MS procedure. No PDMS was detected in field blanks. Weschler suggested that the PDMS-containing particles/aerosols may have been generated in distant countries and transported to the sampling point by air currents. Xu (2011) checked the validity of the results by Weschler by taking an estimated typical aerosol concentration in Alaska of ~10 µg/m^3 and the levels measured by Weschler of 8 ng PDMS/m^3 of air. Xu calculated that this was equivalent to 160 to 800 mg/kg PDMS on aerosols, which is equivalent to levels found on sewage sludge (Section 5.1.4). It is concluded that, since sewage sludge is known to have the highest PDMS concentrations detected in the environment, Weschler's results are in doubt.

Airborne particles from outdoor air samples from four US cities were found to contain organosilicon compounds (but not specifically PDMS) in the order of 1 ng/m^3 with a maximum of 2 ng/m^3 in samples taken from the Newark, New Jersey area. The sensitivity of the method was only approximately 1 ng/m^3 (Weschler, 1988).

5.1.2 Water

Pellenbarg (1979b) monitored the surface microlayer (air-water interface) at Chesapeake Bay and Delaware Bay and noted elevated concentrations of MIBK-extractable silicon (22.8 - 41.1 ppb [µg/kg]), which were attributed to PDMS.

Concentrations of PDMS in treated wastewater effluents were generally found to be below the analytical detection limits of 1 to 5 µg/l. Measured concentrations did not exceed 13 µg/l (AATS, 1985; Fendinger *et al*, 1997b; Pellenbarg, 1979b; Watanabe *et al*, 1984b).

Silicones have been detected in the aquatic surface microlayer of the Chesapeake and Delaware Bays Pellenbarg (1979b). The maximum concentration was 44 µg/l, analysed by AAS. Batley and Hayes (1991) also detected silicones in SML at 1.7 µg of Si/l (equivalent to 4.5 µg Si/l), analysed by ICP. The presence of silicones in surface microlayers is not unexpected as their density is less than water and they are highly hydrophobic (Section 4.3.1, 5.1.1). Surface microlayers are known to contain elevated concentrations of other insoluble organic compounds, which may be enriched by up to 500 times relative to concentrations in the underlying bulk water column (Wurl and Obbard, 2004).

5.1.3 Sediment

PDMS fluids in wastewater will partition onto suspended solids and dissolved organic content (DOC) and are removed as a component of sludge during sewage treatment (Watts *et al*, 1995; Fendinger *et al*, 1997a) or partition onto suspended solids in effluent or receiving waters. Sediments therefore logically represent the ultimate sink for PDMS fluids in the aquatic environment. Monitoring studies have therefore focused on "worst-case" situations such as river catchment areas receiving large quantities of municipal and industrial treated wastewater and sewage sludge disposal areas often at sea.

Freshwater sediments

Siebert (1988) was the first to complete a comprehensive analysis of extractable organosilicon compounds in river, lake and marine sediments. In 1985, using AAS, Siebert analysed a total of 105 samples from rivers in Germany. The highest level detected in sediment was 83 mg/kg dry weight and was from the heavily contaminated River Rhine. The average level detected was 2 to 5 mg/kg dry weight. A more recent monitoring study by Gerhards (1999) using NMR analysis, detected a maximum concentration of PDMS in the River Rhine of <15 mg/kg dry weight. Gerhards (1999) also analysed sediments from the River Loire in France and River Po in Italy and found comparable concentrations. The 90^{th} percentile of all samples analysed was 10.8 mg/kg dry weight. The higher values recorded were associated with high total organic carbon (TOC) content of the sediment, which supports the theory that wastewater treatment effluent was the primary contributing factor to the high PDMS content in sediment.

This conclusion also is supported by Powell *et al* (1999). In a comprehensive monitoring programme using GPC/ICP-AES and focusing on worst-case situations, Powell *et al* demonstrated that retention of solids during wastewater treatment was key to controlling the level of PDMS discharged and deposited to sediments in areas heavily impacted by municipal and industrial wastewater. In those areas where wastewater treatment standards were very poor, concentrations exceeded 300 mg/kg dry weight. These results are atypical, as evidenced by Siebert (1988). Fendinger *et al* (1997a) analysed for PDMS in sediment from 6 North American rivers using a tetrahydrofuran extraction technique followed by GPC-ICP analysis. Samples were collected both upstream and downstream from WWTP outfalls. A maximum concentration of 6 mg/kg dry weight was recorded. At all but one site, the concentrations in sediment were higher downstream from the WWTP outfall.

In areas where there are no anthropogenic inputs, concentrations of PDMS in sediments are very low. Technically, there should be no PDMS in these areas. Detection is probably the combined result of non-specific analytical methods, contamination and the existence of natural silicon complexes with dissolved organic carbon (DOC) that are extracted into the solvent phase. Powell *et al* (1999) estimated that concentrations in 25% of the samples from "worst-case" monitoring

may have been natural silicon rather than PDMS. The concentrations measured in these samples were < 0.6 µg/g dry weight. Siebert (1988) analysed sediments from Lake Constance in western Europe and detected low concentrations (≤ 0.84 mg/kg) of organosilicon materials in 3 of the 25 samples collected. The presence of silicones was attributed to poorly treated effluents from domestic sources. Gerhards (1999) found that concentrations of organosilicones in an unpolluted river in eastern Germany to be < 0.1 mg/kg.

Marine sediments

Offshore disposal of sewage sludge was common practice in Europe until 1996, particularly in the UK and Ireland, where 30% and 35% (respectively) of sludge was discarded via this route (Hall and Dalimier, 1994). In the UK alone, this represented 334,000 tonnes of dry solids per year. The disposal of sewage sludge at sea was likely to lead to the deposition of PDMS in marine sediments. Environmental monitoring studies have therefore typically focused on sludge disposal areas as locations where the highest (i.e. worst-case) concentrations of PDMS in marine sediments were likely to occur.

Gerhards (1999) reported results from sediment samples from UK sludge disposal areas in Liverpool Bay and Plymouth Sound. Sediments also were collected from the Minches, off the west coast of Scotland, an area which receives very little wastewater and where sludge had not previously been disposed. Measured dry weight concentrations of PDMS in the sediments ranged from below the detection limit (0.03 mg/kg) to 2.3 mg/kg (Table 7).

Table 6: Concentration of PDMS in marine surface sediments from areas used for disposal of sewage sludge

Sample location	Number of samples	Concentration (mg/kg dry weight)		Reference
		Mean	Maximum	
Minches [a], UK	5	0.03	0.04	Gerhards, 1999
Plymouth Sound, UK	20	0.06	0.41	Gerhards, 1999
Liverpool Bay, UK	20	0.33	2.30	Gerhards, 1999
Boston Harbor, USA	12	16.60	34.20	Powell *et al*, 1999
New York Bight, USA	24	20.50	126.00	Pellenbarg, 1979b

[a] Uncontaminated area

Low-level concentrations of PDMS were measured in Plymouth Sound, where only sludge from municipal sources had been dumped. The greatest concentrations of PDMS were found in sediments from Liverpool Bay, where sludge from both industrial and municipal sources had

been disposed. In addition, the river Mersey, which drains into Liverpool Bay, receives large volumes of industrial wastewaters, which could have been a significant source of PDMS.

Other monitoring studies (Table 6) measured "worst-case scenario" concentrations of PDMS in sediments from former sludge disposal areas in the USA. The greatest concentrations were observed in New York Bight, where approximately 17×10^6 tonnes of sewage sludge and other wastes were dumped up to 1975 (Pellenbarg, 1979a). Dry weight concentrations of PDMS in sediments from New York Bight ranged from < 1.05 to 126 mg/kg (mean < 20.5 mg/kg) and decreased with distance from the primary disposal site (Pellenbarg, 1979b). Powell *et al* (1999) analysed sediments from Puget Sound, Boston Harbor, Hillborough Bay and San Franscisco Bay. The highest concentrations were found in sediment from Boston Harbor where dry weight concentrations of PDMS ranged from 1.10 to 34.2 mg/kg (mean 15.8 mg/kg). Mean concentrations at the other sites were < 1.8 mg/kg. In all areas, dry weight concentrations of PDMS were strongly correlated with organic carbon content of the sediments, strongly suggesting that PDMS concentrations detected in sediment are influenced by the amount of sewage sludge that has been deposited in the area.

5.1.4 Sewage sludge

Analysis of sewage sludge from a number of wastewater treatment facilities found PDMS concentrations in sludge of between 300 to 5,000 mg/kg (dry weight), with the highest concentrations associated with inputs from industrial sources (AATS, 1985; Batley and Hayes, 1991; Fendinger *et al*, 1997a; Pellenbarg, 1979a; Siebert, 1988; Watanabe *et al*, 1984b).

5.1.5 Soil

Siebert (1988) analysed a range of forest and agricultural soils in Germany. Soil cores from forest regions contained organosilicon compounds in the range of 0.24 to 1.38 mg/kg dry weight down to a depth of 5 centimetres. This was attributed at the time to the atmospheric deposition of volatile cyclic siloxanes, which is now understood not to occur (Xu, 2007). Siebert (1988) also analysed ten soil samples representing meadows and gardens and only detected organosilicon compounds in 3 of them (maximum 0.92 mg/kg dry weight). Concentrations of organosilicones were very low (0.33 - 0.63 mg/kg dry weight), even in agricultural soils which had received varying amounts of sewage sludge amendments.

A more comprehensive analysis of sewage sludge amended soils was conducted by Fendinger *et al* (1997a). Concentrations of PDMS in agricultural sludge-amended soil ranged from < 0.41 to 10.4 mg/kg, while soils amended with sludge at higher rates for land reclamation purposes contained between 2.63 and 100 mg PDMS/kg.

In a parallel study of five experimental sites in the USA that had received high quantities of sewage sludge up to 2,880 t/ha/y, PDMS concentrations in the soil ranged from < 0.37 to 93.8 mg/kg and averaged 18.0 mg/kg. Concentrations were highest at the sites receiving the highest rainfall, rather than highest quantity of sludge. PDMS concentration was also dependent on depth with lower concentrations detected in the surface 0 to 10 cm. There was little or no evidence for migration of PDMS in the soil below the ploughing depth. It was concluded that all sites showed a loss of PDMS in the ploughing zone, i.e. upper 10 cm soil horizon, when compared to 10 to 20 cm depth. Significant loss of PDMS occurred at sites with low soil moisture conditions (e.g. Moreno, California) (McAvoy *et al*, 1996).

Gerhards (1999) analysed PDMS concentrations in soils receiving up to 100 t/ha/y of sewage sludge (the typical permitted amount in the EU is < 2 t/ha/y). The sites were selected in order to study the effect of soil type on PDMS concentration and to evaluate the theory that PDMS degrades in soil under dry conditions. The typical concentration of PDMS in the applied sludge was 1g/kg dry weight though exact records were not maintained. Up to 100 mg/kg dry weight was detected in soils receiving high levels of sludge, but at sites where no sludge had been applied for 10 years, concentrations were much lower (2 - 8 mg/kg dry weight), supporting the view that PDMS slowly degrades in soil.

5.1.6 Biota

Samples of fish from various locations throughout Japan were analysed for organosilicon using AAS or ICP (detection limit 1 mg/kg) and found to contain 1 to 16 mg/kg (EAJ, 1981a,b; the latter cited by ECETOC, 1994). This result could not be confirmed in a later study in which fish from the same locations were analysed and found to contain ≤ 0.7 mg/kg (SIA, 1982).

Watanabe *et al* (1984b) detected organosilicon compounds in muscle of carp, barbel and dace from the Nagara River, Japan in the range of 0.36 to 0.89 mg/kg (recovery efficiency 49%). The inconsistencies of the results may be related to organosilicon compounds other than PDMS or to analytical artefacts as later proposed by Frye (1988) and Pellenbarg and Tevault (1988).

5.2 Human exposure concentrations and hygiene standards

5.2.1 Non-occupational exposure

Polydimethylsiloxane fluids are found in a wide variety of industrial, consumer and medicinal or pharmaceutical applications (Section 3, Table 5). These applications can lead to direct human contact either by oral ingestion or dermal contact.

Oral

Ingestion results from addition of antifoaming agents containing PDMS to foods like frying oil, jams and marmalade, dry tea and coffee extracts and fruit juice concentrates. Dietary limits are specified by food category in the Codex Standard 192-1995, a joint effort by the United Nations Food and Agriculture Organization and the World Health Organization (Codex Alimentarius Commission, 2010). The permitted levels of PDMS range from 10 mg/kg in vegetables – and many other types of food and foodstuffs like oils and fats – to 100 mg/kg in chewing gum and 110 mg/kg in fruit-based desserts.

PDMS is approved as an antifoaming food additive 'E 900' in the EU, at a maximum level of 10 mg/kg in solid foodstuffs and 10 mg/l in liquids (EU, 1995, 1998, 2003). The acceptable daily intake (ADI) is 1.5 mg/kgbw (CHPC, 2009). PDMS of viscosity 300 to 1,050 cSt is allowed by the US Food and Drug Administration (FDA) as a defoaming agent for use (generally) up to 10 ppm (10 mg/l) in food with the exception of milk (US FDA, 2010a). PDMS is also accepted for use as a defoaming agent in the manufacture of paper and paperboard for packaging, transporting and holding of food products (US FDA, 2010b).

PDMS has been evaluated by the joint FDA/WHO Expert Commission on Food Additives. A review of the toxicological data was conducted and concluded that PDMS, with and without silica (max 5%), presented no significant toxicity. Metabolic studies conducted on PDMS (Chapter 7) indicated that orally administered PDMS is not absorbed and that most, if not all, is excreted unchanged in the faeces.

PDMS is also used as a food processing aid but is only present in trace quantities in the final product. PDMS is added either as a pure substance or as an aqueous 10 to 20% water emulsion to control for the formation of foam (e.g. washing of fruits and vegetables and in beverage manufacturing).

In the manufacturing of food packaging such as paper, paperboard and plastics, PDMS is used as an antifoam or release agent. Extensive residue analysis and migration studies have been carried out to assess the potential human exposure resulting from these applications. In most cases, no residue was detected in the final product and the migration level into food was far below that allowed by national or EEC regulations.

PDMS containing silica (known as simethicone) is commonly used as an ingredient in anti-gas and anti-flatulent products. It is regulated in the US by FDA (2011a). Anti-gas products are sold both to adults and children as well as infants who may suffer from colic. The product dose is the amount (mg) in each dose recommended by the manufacturer. There are both regular, extra-strength and children's formulations. The concentrations of simethicone (PDMS) in each

formulation are 20 mg/5 ml dose, 40 mg/5 ml dose and 20 mg/0.3 ml dose, respectively. Most anti-gas and anti-flatulent products are labelled for both typical and maximum use rates. Frequency of use ranges from once per day up to a frequency of use not to exceed 12 uses per day.

Dermal

PDMS is used in a number of consumer products (Section 3.4, Table 5) and medicinal/pharmaceutical products that can lead to dermal exposure. These include, but are not limited to, personal care products, cosmetics, antifoams in detergents, domestic rinse products, sunscreens and head lice treatment. In the US, the Cosmetic Ingredient Review (CIR) committee reviewed the toxicological data on a number of PDMS related products used for skin and hair care products and sunscreens and concluded PDMS and related products are safe for use (CIR, 2003). In general, PDMS is used in these applications at a level up to 15%, which are applied liberally to the whole body.

Concentrations of PDMS contained in household cleaning products are detailed in Table 7.

Table 7: Concentration of PDMS in cleaners per product type (AISE, 2002 cited by HERA, 2007a,b)

Cleaner	Concentration (% w/w)		
	Minimum	Maximum	Typical
Laundry regular			
Powder	0.004	2	0.006 - 0.12
Liquid	0.0015	0.23	0.1 - 0.12
Laundry compact			
Powder	0.004	0.6	0.01 - 0.4
Liquid/gel	0.003	0.45	0.13 - 0.2
Tablet	0.005	4.5	0.005 - 3.5
Fabric conditioner			
Liquid regular	0.002	1.7	0.002 - 1.7
Liquid concentrate	0.002	5	0.002 - 5
Laundry additive			
Powder bleach	0.01	0.15	0.1
Liquid bleach	0.05	0.1	0.1
Machine dish washing			
Powder	0.4	4.5	2
Tablet	0.3	4	2
Surface			
Liquid	0.006	0.05	0.006 - 0.05
Powder	0	0	0
Gel	0	1.5	0.02
Spray	0.0075	0.0075	0.0075
Toilet			
Liquid	0.005	0.005	0.005

HERA (2007b) documents a risk assessment of PDMS used in detergent applications. Exposure of consumers to household cleaners can occur in four main areas: Laundry, dishwashing, surface cleaning and toilet cleaning. Additionally, exposure via residues of the cleaner on washed clothing and utensils is also a possibility. HERA (2007b) calculates exposure for a range of different scenarios, compares the results with any known health effects and concludes that the use of PDMS in household laundry and cleaning detergents is safe and that consumer exposures from these uses are not of concern.

Dimethicone (PDMS) is identified as an active ingredient for skin protection and can be used from 1 to 30 per cent in an over-the-counter drug product. A skin protectant is defined as drug

that temporarily protects and may provide relief to injured or exposed skin or mucous membrane surfaces from harmful or annoying stimuli (US FDA, 2003).

5.2.2 Occupational exposure

PDMS fluids are non-volatile with a molecular weight > 1,200. The primary route of exposure in the occupational setting is dermal contact. Pharmacokinetic studies show little or no potential for absorption following dermal contact and therefore, little risk to human health.

5.2.3 Hygiene standards

No occupational exposure limit (OEL) has been set for PDMS.

5.3 Summary and evaluation

Extensive environmental monitoring shows that because of the extremely low water solubility, PDMS is not detected in surface water, except for down-stream from wastewater treatment plants, where concentrations are at or below the level of detection.

Due to the high partition coefficient for organic carbon, PDMS will partition from wastewater onto sludge during sewage treatment. Concentrations in sewage sludge vary from 300 to 5,000 mg/kg (dry weight) with the highest concentrations being associated with inputs from industrial sources. Concentrations in river, estuarine or marine sediments vary according to the location, but are closely linked with either proximity to wastewater treatments plants) or to areas where sewage sludge was historically deposited in off-shore coastal waters. PDMS is also is detected in agricultural soils where sewage sludge is used as a soil amendment. The concentrations in amended soils vary according to soil type and the time from the last application of sewage sludge. Concentrations of up to 100 mg/kg dry weight may be detected initially but gradually decline as the PDMS is degraded in the soil by clay catalysis.

The few available data on the level of PDMS in biota are of questionable reliability.

Oral ingestion and dermal contact are the primary routes of exposure for non-occupational exposure resulting from their use in PDMS applications such as shampoos, hair care products, silicone antifoams in detergents, textile softeners as well as anti-gas and anti-flatulent applications.

No OEL has been set for this material.

6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

6.1 Micro-organisms

PDMS is used in 'down-the-drain' applications as well as in antifoams used for foam suppression in WWTPs. The effect of PDMS on inhibition of bacterial respiration has been therefore studied. PDMS 200 cSt was found to have no effect on the activity of aerobic or anaerobic sludge in pilot-scale (60 l) digesters at concentrations up to 10,000 mg PDMS/kg of mixed liquor suspended solids (Watts *et al*, 1995; CoR 1d).

The effects of hydroxy-terminated PDMS 55 cSt on a natural water and sediment microcosm has been studied over a 6-month period. The water and sediment contained ostracods and daphnids (both crustacea), blue-green algae and bacteria. Radiolabeled ^{14}C-PDMS at 9 mg/l was added to either water or sediment in the systems, which after equilibration gave up to 260 µg^{14}C-PDMS/l in water. Filtering with a 0.2 micron filter reduced the aqueous concentration to 40 to 50 µg/l. This concentration was maintained throughout the 6-month study. The authors concluded that there were no adverse effects of PDMS on any of the organisms. This conclusion was based on periodic measurements of nitrite, nitrate and ammonia (which are all part of the nitrogen cycle) and oxygen, carbon dioxide and pH (which are indicators for the carbon cycle). In addition, anaerobic activity in the sediment was evaluated based on methane monitoring of the head-space gases and visual observations of gas bubbles from the sediment. The changes in gas concentrations mirrored the visual changes in the biological populations, for example during the cycle of algal die-off and organic deposition, there was an increase in oxygen and methane and a decrease in nitrogen concentration. The subsequent decomposition of the new organic layer in the sediment (due to the algal die-off) caused a population increase of bacteria. This led to a flourishing protozoa population and a new algal bloom. DMSD (the principal degradation product of PDMS in soil) was also studied in a parallel microcosm at a concentration of 60 to 65 mg/l. No adverse effects were seen (Gettings and Lane, 1982; CoR 2e).

Earlier studies reviewed by ECETOC (1994; CoR 4b) indicate no toxicity to bacteria, sewage sludge and fungi but it has not been possible to ascertain whether these were conducted according to recognised international protocols.

6.2 Aquatic organisms

6.2.1 Fish

Early studies were conducted at PDMS concentrations far in excess of the low water solubility of < 1 ng/l (Table 1). While such results are therefore not relevant for risk assessment purposes, they do demonstrate that PDMS has a very low acute toxicity to fish. ECETOC (1994; CoR 4b) and Fendinger *et al (*1997a; CoR 2g) summarised the available information. Most studies only reported nominal rather than measured concentrations of PDMS and the median lethal concentration (LC_{50}) values determined from acute fish toxicity testing were generally > 1,000 mg PDMS/l.

A fish early life-stage test was conducted with sheepshead minnow (*Cyprinodon variegatus*), using a PDMS 50 cSt emulsion. Embryos and larvae were exposed for 33 days. Adverse effects were observed on hatchability at 606 mg emulsion/l (measured, equivalent to 212 mg PDMS/l). The emulsion control without PDMS caused significant mortality and reduction in larval weight and length compared with the blank. The authors concluded that the adverse effects were partially due to the emulsion components (Hill *et al*, 1984; CoR 3b). In a fish feeding study, 10 rainbow trout (*Oncorhynchus mykiss*) received food containing 350 cSt PDMS for 28 days at a rate estimated to be 10 mg of PDMS per day, corresponding to 10,000 mg/kgbw. After 28 days exposure, the fish received untreated food for a further 14 days. No mortality or change in behaviour or growth of the exposed fish relative to the control fish was observed. Histopathological examination of skin, muscle, liver, bile, adrenal, stomach and gut revealed no abnormalities (Mann *et al*, 1977; CoR 2e). This is not a standard procedure for toxicity testing, but fish-feeding studies are used for the purposes of studying bioaccumulation, albeit at lower doses. Uptake from food is the only logical route of exposure of aquatic organisms because of the extremely low water solubility of PDMS (< 1 ng/l; Table 1). The study by Mann *et al* (1977) demonstrated that chronic exposure through food resulted in no adverse effects.

While these studies demonstrate the absence of toxicity even at very high loading rates, no meaningful no observed effect concentration (NOEC) can be derived.

6.2.2 Invertebrates

PDMS fluids have been tested in *Daphnia* sp., but at concentrations above the water solubility, PDMS will form a surface film and physical entrapment of *Daphnia* may be observed. Early studies with daphnids, as reviewed by ECETOC (1994; CoR 4b) and Fendinger *et al (*1997a; CoR 2g), have therefore not been considered to be relevant for the assessment of aquatic toxicity of PDMS.

Daphnia were tested with PDMS 50, 350 and 1,000 cSt using the water soluble fraction and water accommodated fraction techniques at concentrations of 50 to 100 ng/l. No mortalities were observed after 48 hours (Annelin and Chandra, 1997; CoR 2). Since most of the water extractable silicon was lost (probably due to evaporation) from the test system, water accommodated fractions and water soluble fractions, these tests cannot be used to determine an accurate LC_{50} or NOEC value.

Most PDMS that enters the surface water is sorbed to particulate matter. As a result, aquatic organisms have the highest potential for exposure to PDMS through sediment. In order to simulate this type of exposure, *Daphnia magna* was tested in a 21-day life-cycle study in aquaria that contained PDMS-amended sediment. Sediments with a medium (2 - 4%) organic carbon content were treated with 572 ± 23 mg/kg (measured) radiolabelled 350 cSt PDMS. These sediments were added to each of 4 treatment replicates. Sixty control and sixty treatment daphnids (15 per replicate) were exposed in flow-through test chambers for 21 days. The number of immobilised parental daphnids, cumulative number of offspring produced per adult female, and growth of offspring (length and weight) were assessed. At the end of the test, no adverse effects on organism survival, reproduction or growth (length and dry weight) were observed among daphnids exposed to sediments treated with PDMS. No PDMS, as indicated by the presence of ^{14}C, was measured in the overlying water during the study, which is consistent with the limited water solubility of the compound (Putt, 1994b).

The swimming behaviour of the marine copepod *Acartia tonsa* was not influenced when exposed to water-accommodated fractions (prepared by low-energy mixing for 20 h) of PDMS 10 cSt for 48 hours. The LC_{50} for immobilisation was reported to be > 88,865 mg/l (Aunaas and Altin, 1996a; CoR 2), but the concentration value refers to the PDMS-water mix from which the water accommodated fraction was derived rather than the final solution. This test is required for the registration in Europe of chemicals for use in offshore oil and gas exploration/production (OSPAR, 2006).

6.2.3 Algae

PDMS 10 cSt was evaluated for effects on growth rate and biomass increase of the diatom alga *Skeletonema costatum*, as measured by fluorometry in an acute test (72 hours) at nominal concentrations up to 100,000 mg/l prepared from the water soluble fractions. The EC_{50} for biomass and growth was > 100,000 mg/l. A slight effect on biomass was observed at 33,900 mg PDMS/l. The EC_{10} value calculated to be at that value with a confidence interval from 33 to 9,771 mg/l (Aunaas and Brakstad, 1996a; CoR 2). The alga is stipulated by OSPAR (2006; ISO, 2006) for evaluating chemicals used in offshore applications, since this species is found in the open sea as well as in coastal waters.

Early studies reviewed by ECETOC (1994) suffered from deficiencies such as using PDMS concentrations far above the water solubility or interference by an emulsifier.

6.2.4 Conclusions on aquatic phase

Adverse effects were not observed at concentrations up to and exceeding the aqueous solubility of PDMS. Therefore, no environmentally realistic NOEC can be derived for free swimming aquatic organisms.

6.3 Sediment organisms

The results of short-term testing PDMS on sediment-dwelling organisms are summarised in Table 8.

Table 8: Acute studies on PDMS in sediment-dwelling marine and estuarine organisms

Species	**Viscosity of PDMS (cSt)**	**Test condition**	**Duration (h)**	**LC_{50} (mg/l, unless mg/kg dry weight)**	**Reference**	**CoR**
Mytilus edulis[a] (mussel)	50	Emulsion	96	>1,020	Hill, 1980a	2e
Mytilus edulis	50	20% emulsion	96	1,980	Hill, 1980b	2e
Nereis diversicolor (polychaete worm)	50	10,000 mg/kg in sediment	96	> 10,000 mg/kg [b]	Craig and C0aunter, 1990	2e
			(d)	**EC_{50} (mg/l, unless mg/kg dry weight)**		
Corophium volutator (amphipod)	10		10	> 30,715 mg/kg [c]	Aunaas and Altin, 1996b	1c
Ampelisca abdita (amphipod)	10		10	> 2,300	Putt and Mihaich, 1996	4a
Corophium volutator (amphipod)	350		10	> 1,523 mg/kg	Andersen, 2010	1a

[a] Colonises hard surfaces, not strictly sediment-dwelling
[b] Slight effect on burrowing
[c] Some signs of narcosis

Hill *et al* (1980a,b) studied the effect on blue mussel (*Mytilus edulis*) to exposure of PDMS emulsions via the water column. The studies are difficult to interpret because of the presence of

the emulsifier. It is noted that *Mytilus edulis* is not strictly speaking a sediment-dwelling organism but colonises hard surface substrates in high energy marine environments.

More realistic studies on PDMS fluid alone, avoiding any adverse effects due to a surfactant or other components, have been conducted in *Nereis diversicolor* using sediment amended with PDMS 50 cSt at 10,000 and 1,000 mg/kg, for 96 hours and 28 days, respectively (Craig and Caunter, 1990). There was no evidence of acute toxicity or body weight gain in either test but a slight reduction in burrowing activity was observed. The concentrations used in these studies exceed the solubility in the test system and were 1,000- to 10,000-fold higher than typical measured concentrations from estuarine areas [Table 6].

The testing of the marine sediment-dwelling amphipod *Corophium volutator* is required for the registration in Europe of chemicals for use in offshore oil and gas exploration/production (OSPAR, 2006). Results from this test have been reported by Aunaas and Altin (1996b) and Andersen (2010). Testing of another infaunal amphipod, *Ampelisca abdita,* is preferred in USA. Results from this test have been reported by Putt and Mihaich (1996). Except for one *Corophium* test (Aunaas and Altin, 1996b), where there were some signs of narcosis at 30,715 mg/kg (the highest test concentration tested and in excess of the water solubility), no adverse effects of PDMS fluid were observed on sediment-dwelling organisms.

A summary of sub-chronic and chronic toxicity testing on sediment-dwelling organisms is shown in Table 9. All studies have been conducted by spiking the sediment with PDMS. The effect of organic carbon content on potential toxicity and bioaccumulation has also been investigated.

Table 9: Sub-chronic and chronic studies on PDMS in sediment-dwelling organisms

Species	Test method	Duration (d)	NOEC (mg/kg dry weight)	Reference	CoR
Chironomus tentans (midge larva)	EPA/600/R-99/064 [a]	20	> 2,590	Henry *et al*, 2001	1
Chironomus tentans		14	> 560[b]	Putt, 1994a	1
Hyallela azteca (freshwater amphipod)	Compliant with US EPA guidelines [a]	28	> 2,200	Putt and Mihaich, 1998	1
Hyallela azteca		42	> 994	Henry *et al*, 2001	1
Nereis diversicolor (marine polychaete, ragworm)		28	> 1,000	Craig and Caunter, 1990	2

[a] EPA, 1994
[b] Maximum concentration tested. No effects observed at any tested concentration.

Putt (1994a) reported the results of a sub-chronic test on midge larvae (*Chironomus tentans*) in three sediments of high, medium and low organic content using 350 cSt PDMS fluid. No adverse effects were observed at the nominal test concentration of 700 mg/kg (measured maximum concentration 560 mg PDMS/kg).

Two chronic tests were conducted on the freshwater amphipod *Hyallela azteca.* Putt and Mihaich (1998) studied the effect of natural sediments containing 1 to 2% organic carbon and measured ^{14}C-PDMS 350 cSt concentrations of 140, 280, 580, 1,100 or 2,200 mg/kg. No effects on survival or growth were noted for the duration of the 28-day study. Henry *et al* (2001) also conducted a 42-day full life-cycle study with *Hyallela azteca,* at concentrations up to 994 mg PDMS/kg. No adverse effects were observed on growth or reproduction of the adult organisms or on the viability of the offspring.

In studies with other benthic invertebrates, a 28-day study with polychaete ragworms (*Nereis diversicolor*) exposed to sediment-borne PDMS 50 cSt at 1,000 mg/kg showed no adverse effects on survivability or weight gain. A slight reduction in burrowing activity was noted (Craig and Caunter, 1990). Henry *et al* (2001), evaluated the potential chronic toxicity of PDMS-amended sediments on *Chironomus tentans* at concentrations up to 2,590 mg/kg. No effects on survival, growth, emergence or reproduction were observed at any concentration over a 20-day period.

6.3.1 Conclusions on sediment phase

The available data support the conclusion that PDMS has no effect on sediment living organisms.

6.4 Terrestrial organisms

6.4.1 Soil organisms

A number of chronic studies have investigated the effect of PDMS on soil organisms. PDMS was either added directly to the soil or, in order to simulate the real world, was incorporated into the soil as a component of treated sewage sludge. A summary of the results from these studies is presented in Table 10.

Table 10: Chronic studies on PDMS in soil-dwelling organisms

Species	Test method	Parameter	Test duration (d)	NOEC (mg/kg dry weight)	Reference	CoR
Eisenia foetida (earthworm)		Number and weight of offspring	21	>1,100	Garvey, 1997	1
Folsomia candida (springtail)	OECD Draft protocol	Emergence of offspring	28	230	Collins, 1998	1
Soil microflora	BBA [a] guideline VI1-1	Respiration, C/N mineralisation	28, 58 [b]	>1,000	Forster, 1997	2
Soil microcosm (wheat, soybean)		Seed germination, plant growth, number of *Rhizobium* nodules, number of bacteria, actinomycetes, fungi	214 [c]	≥ 9.5 [d]	Tolle *et al*, 1995	2

[a] Biologische Bundesanstalt für Land und Forstwirtschaft (Braunschweig, Germany)
[b] Mineralisation only
[c] Reported as 7 months
[d] Maximum feasible concentration that could be tested due to physical separation of PDMS from sewage sludge (prior to incorporation into the soil). This value is therefore not suitable for risk assessment purposes.

An earthworm (*Eisenia foetida)* reproductive assay was conducted using a soil rich in organic matter with PDMS 350 cSt at a nominal soil concentration of 1,000 mg/kg (1,100 mg/kg measured concentration) for 21 days. No adverse effect on the reproduction of the earthworm was observed (Garvey, 1997).

A reproduction study was conducted in the springtail (*Folsomia candida*) using an artificial soil matrix dosed with 350 cSt PDMS-saturated sludge over 28 days. PDMS concentrations in the artificial soil were measured at 230, 660, 980, 1,800 and 3,800 mg/kg dry weight. The number of offspring was found to be reduced at concentrations ≥ 660 mg/kg and the NOEC was therefore determined to be 230 mg/kg. After 28 days, 58% survival was observed in adult springtails at the top dose (3,800 mg/kg). The LC_{50} value was therefore above 3,800 mg/kg (Collins, 1998).

The observation of effects in this study can be considered as surprising, due to the high molecular weight of the substance. It is not possible to ascertain the cause of the effects (possibly artefacts, e.g. some physical effect) and that the data are, therefore, not suitable for extrapolation to a PNEC.

The possible effects of PDMS 346 cSt on soil microflora activity, i.e. respiration and carbon/nitrogen mineralisation, were evaluated on day 0, 14 and 28 in two soils (loam or sandy loam) and on day 58 for mineralisation in sandy loam only. No effects were observed at PDMS

concentrations in soil equivalent to 500 or 1,000 mg/kg dry weight, based on the criterion in the BBA guideline VI1-1 which states that < 15% deviation from the control is not considered relevant (Forster, 1997).

An assessment of the effect of PDMS (a 35, 200 and 1,000 cSt mix) on seed germination, plant growth and soil micro-organisms was made using soil-core microcosms from two soil types (silty clay and sandy loam). The soils were amended with sludge containing 0, 290, 1,000 or 3,500 mg PDMS/kg, at a rate of 1.57 tons sludge/acre. This resulted in a maximum PDMS concentration of 9.5 mg/kg soil. Microcosms were sequentially cropped with spring wheat (*Triticum aestivum*), followed by soybeans (*Glycine max*). After 214 days, no effect on germination or total dry weight of spring wheat or soybeans was observed. In addition, PDMS had no effect on the number of *Rhizobium* nodules, the bacteria responsible for nitrogen fixation in soybeans. The total number of bacteria, actinomycetes and fungi were also similar for the control and high-PDMS treatments (Tolle *et al*, 1995).

6.4.2 Insects

The insecticide activity of PDMS 5 to 1,000 cSt was evaluated by direct application of 5 µl pure substance to the ventral thorax of adult crickets *Acheta domesticus* (LeVier, 1988). The median lethal dose (LD_{50}) value for 10 cSt PDMS was 0.87 µl/insect. The time of loss of righting reflex increased with the viscosity of the PDMS and the mortality at 48 hours decreased 2-fold when the viscosity of PDMS increased 200 fold demonstrating that greater toxicity was observed at lower viscosities. A similar effect of PDMS 10 cSt was observed by Nielsen *et al* (1975).

Rottink (1976; CoR 3) studied the lethality of PDMS in *Tribolium castaneum* (red flour beetle) using a 50% emulsion of 10 cSt PDMS and reported a LD_{50} value of 0.04 to 0.06 µg/2.2 mgbw. It is noted that these early results are something of an anomaly when compared to later studies. Unfortunately, the study details are not available in the reference to aid in the interpretation of results. In another study on PDMS in *Tribolium castaneum*, 100% mortality occurred at 285 µg/mgbw. This study too is poorly reported (Schmolesky JE, 1978; CoR 3).

Insect toxicity is only seen when PDMS is applied directly to the insect and, thus, it is believed that the mechanism of action is a physical action rather than a toxicological effect though there has been little evidence available to substantiate this theory until recently.

The insecticidal activity of PDMS is now being commercially exploited in the form of head lice treatments such as Hedrin lotion (Thornton and Ross, Huddersfield, UK) and Nyda pump spray (G. Pohl-Boskamp, Hohenlockstedt, Germany). The lice are generally knocked out to the status of “no major vital signs” within less than a minute, followed by death. Burgess (2009) investigated the mechanism using scanning electron microscopy coupled with X-ray

microanalysis to detect silicon which showed PDMS lotion was deposited in the spiracles and distal region of the tracheae. Burgess postulated that the cause of death is a lethal disturbance in their water balance. Richling and Böckeler (2008) postulate, using an approach combining scanning electron microscopical studies on the effects on the surface of the insects with *in vivo* observations, that the mechanism is suffocation caused by PDMS filling the tracheal system.

6.5 Calculation of PNEC

6.5.1 Aquatic phase

Since no NOEC could be derived for pelagic aquatic organisms, no PNEC can be determined.

6.5.2 Sediment phase

Since PDMS will partition more readily to the sediment phase rather than the aquatic phase, then it is more appropriate to calculate the $PNEC_{Sediment}$. None of the studies performed to date have shown any adverse effects so it is therefore not possible to derive a NOEC value other than to estimate that it would be > 1,000 mg/kg. Since results on three trophic levels are available the $PNEC_{Sediment}$ value can be estimated as being > 100 mg/kg.

6.5.3 Terrestrial phase

Based on the NOECs from three trophic levels (soil micro-organisms, earthworms and arthropods), a safety factor of 10 is applied to the lowest NOEC of 230 mg/kg dry weight for *Folsomia* to give a PNEC of 23 mg/kg dry weight.

7. KINETICS AND METABOLISM

7.1 Animal studies

The absorption, tissue distribution and excretion of radiolabelled ^{14}C-PDMS of 100 cSt viscosity was determined in male Sprague-Dawley rats that were given a single oral dose of about 830 mg/kgbw. This study showed that 96% of the administered dose was recovered in faeces collected over 6 days. Only 0.05% of the administered dose was detected in liver, kidneys and lung; no radioactivity was observed in any of the other organ systems evaluated. No ^{14}C was detected in plasma, expired air or urine samples collected at various time intervals. This study showed that little, if any, of the PDMS 100 cSt was absorbed from the gastro-intestinal tract and that the majority of the administered oral dose was eliminated unchanged in the faeces (Siddiqui *et al*, 1984; CoR 1).

Single and repeated oral dose studies were carried out to determine the pharmacokinetics of PDMS. A single dose of ^{14}C-PDMS 35 or 1,000 cSt was administered to male Sprague-Dawley rats at 250 or 2,500 mg/kgbw (0.5% or 5.0%) in the food. In the repeated dose study, unlabelled 35 cSt or 1,000 cSt PDMS was administered in the diet at 250 or 2,500 mg/kgbw/d for 13 days followed by a single oral dose of radiolabelled PDMS on day 14. Selected animals in the single dose groups were killed at 4, 8, 24 or 48 hours after oral administration. All animals receiving repeated doses were killed 48 hours after receiving the radiolabelled PDMS. In all groups of the 35 cSt and 1,000 cSt PDMS (both single and repeated dose), the bulk of the test material was found in the gastro-intestinal tract or faeces. Virtually no radioactivity was found in any of the tissues examined at any time point. The absence of detectable levels of PDMS fluid in tissues indicated that, if absorbed at all, PDMS fluid is rapidly eliminated. Analysis of the faecal sample were analysed by chromatography and compared to the original solutions. The results indicated that there was no shift in molecular weight and no metabolites. The results of this study indicated that little, if any, of the 35 cSt and 1,000 cSt PDMS was absorbed from the gastro-intestinal tract and that the majority of the administered oral dose was eliminated unchanged in faeces (Annelin *et al*, 1989; CoR 2).

The absorption and distribution of PDMS 10 or 350 cSt were evaluated in male and female Fischer 344 rats that were given 1,000 mg ^{14}C-PDMS/kgbw by oral gavage and excreta were collected over 96 hours. At the end of the study, animals were killed and blood and several organs were taken and processed for the determination of radioactivity. Other groups of animals were treated similarly and were killed at 12, 24, 48 or 97 hours. Whole-body autoradiography was performed at several levels on the animals. No significant radioactivity was detected outside of the gastrointestinal tract. Approximately 93.6% of the administered dose was recovered and virtually all (99.6 - 99.8%) of the recovered dose was found in the faeces. No detectable degradation products or potential metabolites were found in the faeces. Overall, the data suggest

that the majority of ^{14}C-PDMS was rapidly excreted in the faeces unchanged following oral administration with little, if any, absorption (Jovanovic, 2000, 2001; both CoR 1).

In vitro percutaneous absorption experiments were performed with PDMS of 10 and 350 cSt viscosity. Infinite doses (10 mg/cm^2) were applied for 96 hours to the donor side of split-thickness human abdominal skin sections (reference standard) and full-thickness human vaginal tissue mounted in Franz *in vitro* diffusion cells. In order to facilitate the measurement of percutaneous absorption, doses were spiked with the respective ^{14}C-PDMS prior to the study. The dermal flux rate of 350 cSt PDMS was 0.3 and 2 ng/cm^2/h for abdominal skin and vaginal tissue, respectively. For the 10 cSt PDMS, flux rates were 0.2 and 6 ng/cm^2/h for abdominal skin and vaginal tissue, respectively. Thus, as measured by flux through the skin barrier, dermal absorption of 10 cSt and 350 cSt PDMS is approximately an order of magnitude greater in vaginal tissue than in abdominal tissue. Even if residual radioactivity at the dosing site is assumed to be absorbed test material, overall $\leq$ 0.5% (detection limit?) of the applied dose was shown to be bioavailable regardless of the tissue or the viscosity of the PDMS (Plotzke *et al*, 2000; CoR 1a).

An *in vivo* percutaneous absorption study was conducted on ^{14}C-PDMS of 350 cSt viscosity. The ^{14}C-PDMS was maintained in occlusive contact with the dorsal surface of male CD rats for 24 hours. At the termination of the 24-hour exposure period, the animals were removed from the metabolism cages and the exposure site was washed. Animals were re-wrapped with a fresh non-occlusive bandage and returned to the metabolism caging for continued collection of urine, faeces and expired air. The animals were removed from the metabolism caging 72 hours post-initial exposure, killed, and the exposure site was carefully excised. Disposition of radioactivity at 72 hours post-initial exposure showed that approximately 70% of the administered dose was found on the surface (dosing bandages, gauze, swab, tape and filter) and 11.4% was present in the skin at the site of application. Low but detectable levels were found in the faeces (0.01%) and CO_2 traps (0.001%). Total recovery was 85.3%. No radioactivity was detected in the blood at any of the time points sampled and the disposition of radioactivity in the blood groups was similar to the excreta group. This study demonstrated little dermal absorption of 350 cSt ^{14}C-PDMS fluid under the conditions of this study (Plotzke, 1994).

7.2 Human studies

No human data are available.

8. EFFECTS ON EXPERIMENTAL ANIMALS AND *IN VITRO* TEST SYSTEMS

8.1 Single exposure

8.1.1 Oral

The acute oral toxicity of 1,000 cSt PDMS was investigated in Wistar rats (5/sex) at a dosage level of 5 ml/kgbw (≈ 4.8 g/kgbw). The animals were starved 16 hours prior to dosing. Mortality and signs of reaction to treatment were recorded during a subsequent 14-day observation period. The animals were killed after this period and subjected to necropsy. There were no deaths and no signs of reaction to treatment. All animals achieved anticipated bodyweight gains. Necropsy revealed no substance-related macroscopic lesions. The LD_{50} was found to be > 4.8 g/kgbw (Bomhard, 1983; CoR 2c).

In a similar test with 100 cSt PDMS, no signs of toxicity were observed in Wistar rats (5/sex) after single application (gavage) of 5 ml/kgbw (≈ 4.8 g/kgbw) (Löser, 1981; CoR 2c).

These results are in accordance with other studies conducted in rats with various viscosities of PDMS. The LD_{50} was found to be > 5 g/kgbw in every case. No mortality and virtually no signs of toxicity were observed in any of these studies. Symptoms reported were diarrhoea, weakness and pilo-erection (Rondot, 1985a,b,c,d; all CoR 2b).

PDMS 60,000 cSt was administered in corn oil at a dose of 2 g/kgbw by oral gavage to a group of 5 male and 5 female Sprague-Dawley rats. The rats were observed for 14 days after test substance administration. No overt signs of systemic toxicity were observed in any rat during the study. All of the rats gained weight during the study and no gross necropsy lesions were observed in any rat. None of the animals died during the study. Therefore, under the specific conditions of testing, the acute oral median lethal dose (LD_{50}) of 60,000 cSt PDMS in male and female rats was > 2 g/kgbw (Findlay, 1998a; CoR 1a).

PDMS 140 cSt was administered to rats (2/group) at doses of 10, 15 and 20 ml/kgbw (≈ 9.6, 14.3, 19 g/kgbw). No signs of toxicity have been observed. Therefore the LD_{50} was > 19 g/kgbw in every case. Application of 10 ml/kgbw (≈ 9.6 g/kgbw) to one dog, cat or rabbit induced no signs of toxicity (LD_{50} > 9.6 g/kgbw) (Gloxhuber and Hecht, 1955, 1956; CoR 2e,g).

8.1.2 Dermal

The reported dermal LD_{50} was > 2 g/kgbw (Monnot, 1982; CoR 2; Rondot 1985b,c,d; all CoR 2b). In an *in vitro* study, it was demonstrated that ^{14}C-PDMS 350 cSt does not penetrate the skin (Plotzke *et al*, 2000; CoR 1d).

PDMS 60,000 cSt, was applied undiluted to the shaved backs of 5 male and 5 female adult New Zealand White rabbits at a dose of 2 g/kgbw. The test sites were wrapped and the test substance left in contact with the skin for 24 hours. Residual test material was removed with the aid of 350 cSt PDMS-moistened gauze. All rabbits were observed frequently on the day of treatment and at least once daily during the subsequent 14-day observation period. No overt signs of systemic toxicity were observed in any rabbit during study. Signs of dermal irritation consisting of erythema at the application site were observed in all ten rabbits. All animals appeared normal by day 7 and remained so for the rest of the observation period. All 10 rabbits gained weight during the study and gross necropsy findings were within normal limits. No rabbits died during the study. Therefore, under the specific conditions of testing, the acute dermal LD_{50} of 60,000 cSt PDMS in adult male and female rabbits was > 2 g/kgbw (Findlay, 1998b; CoR 1a).

In a limit test, PDMS 350 cSt (as supplied) was applied once only to Sprague-Dawley rats (5/sex) by the cutaneous route at a dose level of 2,008 mg/kgbw, in accordance with OECD Test Guideline 402. The substance was spread over a skin area equal to approximately 10% of the total body surface. The test article was held in contact with the skin with a bandage for 24 hours. At the end of the application period, remaining PDMS was wiped away by rinsing with lukewarm water. Mortality and clinical signs were noted 15 minutes after application, then at 1, 2 or 4 hours and finally daily for the 14 day study period. All animals were weighed immediately before administration of the test substance (day 1) and on day 8 and 15. A necropsy was performed on all animals after the 14 day observation period. No mortality and no behavioural abnormality were noted during the test. The cutaneous tolerance of the PDMS was good. No erythema or oedema was observed. The body weight was not affected by the test substance. No noticeable macroscopic abnormality was noted during necropsy. The LD_0 in this test was $\geq$ 2,008 mg/kgbw (Lheritier*et al*, 1988; CoR 1a).

8.1.3 Inhalation

Two inhalation studies with respirable aerosols have been conducted on PDMS.

An acute aerosol inhalation toxicity study on PDMS 100,000 cSt has been conducted similar to OECD Test Guideline 403. Wistar rats (5/sex/group) were exposed (nose only) for a single period of 4 hours to solutions of 25% PDMS dissolved in petroleum ether. In parallel two solvent control groups (5/sex/group) were used. The measured mean concentrations during exposure

were 4,315 mg PDMS/m^3 (Group 1) or 11,582 mg PDMS/m^3 (Group 2), respectively (the latter was the highest technically achievable concentration). The mass median particle size of the test atmosphere during exposure was 1.55 µm (Group 1), 1.52 µm (Group 2) and 0.846 µm (control). After exposure the animals were kept for a 14-day observation period. Clinical symptoms and mortality were comparable between test substance groups and controls. Therefore all observed effects were related to the solvent. During the observation period no clinical effects were noted. At necropsy, there were no substance related organ changes. The LC_{50} was > 11,582 mg/m^3 (Pauluhn, 1985; CoR 2b).

In a second study, 10,000 cSt PDMS dissolved in dichloromethane was used to perform an acute aerosol inhalation toxicity test in Wistar rats (5/sex/group), in accordance with OECD Test Guideline 403. Four measured concentrations of the substance (153.3, 322.0, 445.6 or 694.8 mg/m^3) were tested. The top dose was the highest technically achievable concentration. In parallel, groups of animals (5/sex) were exposed to corresponding concentrations of the solvent as control. The mass median particle size of the test atmosphere during exposure was in the range of 1.3 to 1.8 µm (standard deviation 1.8 – 2.0). The particle mass ≤ 3 µm was between 81% and 91%. After exposure the animals were kept for a 14-day observation period. No clinical signs, no changes in reflexes and no mortality were observed in all test groups. At necropsy, no specific organ changes were identified. The body weight was not affected by the test substance. Therefore the LC_{50} was > 695 mg/m^3, the highest concentration tested, without any effects (Pauluhn, 1990; CoR 1b).

8.1.4 Intraperitoneal

Intraperitoneal (*i.p.*) injection of 350 cSt PDMS at 50 ml/kgbw (≈ 47.5 g/kgbw) in male Charles River CD-1 mice (5/group) did not show any significant reactions. The LD_{50} was shown to be > 50 ml/kgbw (≈ 47.5 g/kgbw) (Henrich and McMahon, 1990; CoR 2a).

PDMS 350 cSt dissolved in cotton seed oil was given by single *i.p.* injection (5 ml/kgbw [≈ 4.8 g/kgbw]) to two groups of Wistar rats (3/sex) at doses of 200 or 2,000 mg/kgbw, respectively. The test was performed in accordance with OECD Test Guideline 423 (acute toxic class method) under GLP conditions. After exposure the animals were killed following a 14-day observation period. No mortality and no clinical signs of toxicity were observed in either dose group throughout the observation period. No significant gross pathological changes were found. All animals showed normal weight gain. Therefore the LD_{50} was > 2,000 mg/kgbw, the highest concentration tested, without any effects (Haist and Lutterbach, 2000; CoR 1a).

Gloxhuber and Hecht (1955, 1956; CoR 2e,g) administered by single *i.p.* injection PDMS 60 cSt to 5 rats and PDMS 140 cSt to 10 rats, both at a dose level of 1,000 mg/kgbw. Not-killed animals died more than 1 year after injection. There was no evidence of tumours in any of these animals.

The PDMS did not remain in the free abdominal cavity but it was dispersed into fine droplets and deposited in the peritoneal tissues where it produced mild granulomatous reactions. This can be regarded as a response to a foreign substance.

8.1.5 Subcutaneous

Carshalton bred mice (45/sex/group) received a single subcutaneous (*s.c.*) injection of 0.2 ml of PDMS (94% mixed with 6% silicon dioxide) at weaning; a control group was given a single *s.c.* injection of 0.2 ml liquid paraffin (control). All surviving mice were killed when 80 weeks old. Fifteen percent of the males displayed an increased incidence of cysts at the site of injection throughout the lifespan. In addition, this group showed a significant reduction in the percentage of animals which displayed a proteinaceous plug in the urinary bladder. No PDMS was detectable in the liver, kidneys, spleen or perirenal fat of mice given the injection. The authors concluded that there was no increase in the incidence of malignant or benign tumours in the groups of mice receiving the antifoam agent either in the diet or by *s.c.* injection. No toxic effects were observed that could be ascribed to the administration of the substance (Cutler *et al,* 1974; CoR 2e). There was no indication of relevant resorption after oral exposure or distribution of the substance in the animals after *s.c.* injection.

8.1.6 Intradermal

No erythema or oedema was seen in 2 male New Zealand White rabbits following intradermal injection (5 × 0.2 ml) of PDMS 350 cSt (Henrich and McMahon, 1990; CoR 2e).

8.2 Skin, respiratory tract and eye irritation, sensitisation

Over the past six decades, numerous publications and study reports dealing with the irritating and sensitising potential of PDMS fluids of varying viscosities were issued. The most relevant ones are summarised in Tables 11 and 12.

8.2.1 Skin irritation

PDMS of various viscosities was evaluated for skin irritation (Table 11).

Table 11: Summary of skin irritation tests on PDMS under semi-occlusive dressing

Viscosity (cSt)	Number of rabbits	Aliquot	Time (h)	Result	Reference	CoR
20	6	0.5 ml	4	Not irritant [a]	Gonnet and Guillot, 1985	1b
100	2	500 mg	24	Not irritant [a]	Thyssen, 1980	3a
100	6	500 mg	4	Not irritant [a]	Julou *et al*, 1973a	2a
350	6	500 mg	4	Not irritant [a]	Julou *et al*, 1973b	2a
350	6	0.5 ml	4	Not irritant [a]	Mercier and Guillot, 1989	1d
1,000	3	0.5 ml	4	Not irritant [a]	Suberg, 1984a	1b
5,000	6	500 mg	4	Not irritant [a]	Julou *et al*, 1973c	2a
30,000	6	500 mg	4	Not irritant [a]	Julou *et al*, 1974a	2a
60,000	3	500 mg	4	Not irritant [a]	Findlay, 1998c	1a
100,000	6	500 mg	4	Not irritant [a]	Julou *et al*, 1974b	2a

[a] All scores = 0

In an acute dermal toxicity limit test in the rabbit, hydroxy-terminated PDMS 60,000 cSt caused erythema at the site of application when applied for 24 hours under occlusive dressing. The irritation was fully reversible (Findlay, 1998b; CoR 1a). In 28-day dermal studies in the rabbit, PDMS 10 and 350 cSt were non-irritant when applied daily during 6 hours under semi-occlusion (Blee, 1999a,b; CoR 1a).

Repeated treatment of the ear of a rabbit with 140 cSt PDMS (applied dose not specified) over 60 working days produced no signs of toxicity (Gloxhuber and Hecht 1955, 1956; CoR 2e,g).

Some additional papers confirm the non-irritant character of PDMS with varying viscosities (Stanton, 1984; Guillot *et al*, 1979; Clark *et al*, 1979; all CoR 3a; Kumar *et al*, 1985, CoR 2e). PDMSs are even used as a non-irritating reference compounds in the validation process of *in vitro* skin irritation assays (Cotovio *et al*, 2005; CoR 3a).

The CIR paper on PDMS also reported skin irritation after 24 hours of contact with rabbit skin under occlusive dressing. On the other hand, a 24-hour occlusive patch in the forearm did not to produce any irritation in 54 male volunteers. Multiple sources mentioned in the CIR report point towards the non-irritation character of PDMS fluids when tested in the classic Draize irritation test setting. Therefore, the CIR expert panel concludes that PDMS is classified as a minimal

irritant (CIR, 2003; CoR 4b). This conclusion is supported by the results of a human skin irritation assay (Section 9.1).

Taking into account the above and the results of the assays summarised in Table 12, it can be concluded that PDMS fluids mainly cause irritation effects when applied under extreme conditions (i.e. 24 hours under occlusion). The effects noted in those cases are fully reversible. As such, it can be concluded that PDMS silicones can be generally considered non-irritant to human skin under normal conditions of use.

8.2.2 Eye irritation

In vivo

PDMS of various viscosities was evaluated for *in vivo* eye irritation (Table 12).

Table 12: Summary of acute eye irritation tests on PDMS

Viscosity (cSt)	Protocol	Number of rabbits	Aliquot (ml)	Time (h)	Result	Reference	CoR
20	Draize	6	0.1		Not irritant, mean scores <S>$_{cornea}$= 0.0 <S>$_{iris}$= 0.17 <S>$_{conjunctiva\ redness}$= 0.5 <S>$_{conjunctiva\ chemosis}$ = 0.33	Gonnet and Guillot, 1985	1b
100	Draize	6	0.1		Not irritant [a]	Julou *et al*, 1973a	2a
100	Draize	2	0.1		Not irritant [a]	Thyssen, 1980	3a
350	Draize	6	0.1		Not irritant [a]	Julou *et al*, 1973b	2a
350	Draize	6			Not irritant, mean scores <S>$_{cornea}$= 0.0 <S>$_{iris}$= 0.78 <S>$_{conjunctiva\ redness}$= 1.1 <S>$_{conjunctiva\ chemosis}$ = 0.38	Mercier and Guillot, 1989	1d
500 1,000 12,500	*In vivo*	3	0.7 - 1.0	3 - 6	Mild epithelial oedema, most intense for PDMS of lowest viscosities.	Refojo *et al*, 1985	4b
1,000	Draize	3	0.1		Not irritant, individual scores <S>$_{cornea}$= 0.0, 0.0, 0.0 <S>$_{iris}$= 0.0, 0.0, 0.0 <S>$_{conjunctiva\ redness}$= 0.0, 0.7, 0.7 <S>$_{conjunctiva\ chemosis}$ = 0.0, 0.0, 0.3	Suberg, 1984b	1b

Table 12: Summary of acute eye irritation tests on PDMS (cont'd)

Viscosity (cSt)	Protocol	Number of rabbits	Aliquot (ml)	Time (h)	Result	Reference	CoR
5,000	Draize	6	0.1		Not irritant [a]	Julou *et al*, 1973c	2a
5,000	Rabbit eyes filled with PDMS after vitrectomy			Long term	Severe loss of myelinated optic nerve fibres	Papp *et al*, 2007	4b
30,000	Draize	6	0.1		Not irritant [a]	Julou *et al*, 1974a	2a
60,000	Draize	3	0.1		Not irritant, individual scores $<S>_{cornea}$= 0.0, 0.0, 0.0 $<S>_{iris}$= 0.0, 0.0, 0.0 $<S>_{conjunctiva\ redness}$= 1.0, 1.0, 1.3 $<S>_{conjunctiva\ chemosis}$ =1.0, 1.0, 1.3	Findlay, 1998d,e	1a
100,000	Draize	6	0.1		Not irritant [a]	Julou *et al*, 1974b	2a

[a] All scores = 0

In an additional, poorly documented assay, PDMS (no viscosity stated) is described to cause slight and transient redness of the conjunctiva 1 hour after instillation of 0.1 ml. This redness would persist for a longer time as viscosity increases (Rasmussen and Siddiqui, 1992; CoR 4e).

Some other studies describe PDMSs of varying viscosities to be mildly and transiently irritating to the eyes (Clark *et al*, 1979; CoR 3a). Five PDMS 100 cSt samples with diverging acidities were tested for their eye irritation potential in mice, guinea pigs and rabbits. When a drop of test substance was instilled once daily for 10 days into the conjunctival sac of the animals, only the two samples with high acidity values, were able to cause eye irritation (Kumar *et al*, 1985; CoR 2e). PDMSs are also used as non-irritating reference compounds in the validation process of *in vitro* eye irritation assays (Cassidy and Stanton, 1997; CoR 3a).

The CIR review paper on PDMS summarises that most rabbit eye irritation studies classify the substance as a mild to minimal irritant, with a conjunctival reaction as the most frequently observed adverse effect (CIR, 2003; CoR 4b).

Considering the above and the results of the assays displayed in Table 13, PDMS fluids of a wide range of viscosities generally can be considered mildly irritating to non-irritating to the human eye. Contact with low viscosity liquid may cause transitory conjunctival redness, but this is probably due to the physical effect of the silicone causing disruption of the tear film and hence producing a ‘dry eye’ effect.

Atypical contact over a prolonged period may cause more marked irritation (see also Section 5.2 on human exposure).

In vitro

Confirmation of the generally accepted non-irritating character of PDMS can be found in the fact that a PDMS with viscosity 10 cSt was used as a non-irritating reference compounds in the validation process of three promising alternative methods for eye irritation testing (Cassidy and Stanton, 1997; CoR 3a). More specifically, two commercially available *in vitro* assays (tissue construct models: Epi-ocular tissue model OCL-100 and skin ZK-1200 model) and the bovine corneal opacity and permeability assay (BCOP) were assessed with regard to their ability to predict the eye irritation potential of several organosilicon compounds. All *in vitro* assays correctly confirmed the non-irritant nature of PDMS.

8.2.3 Vaginal irritation

PDMS is used as a condom lubricant. Kumar *et al* (1985; CoR 2e) tested five PDMS 100 cSt samples with diverging acidities for their irritation potential on the vaginal mucosa in rats. They observed that the PDMS samples of comparable purity to commercially available PDMS were non-irritant to the vagina (as measured by the absence of inflammatory leucocytes in vaginal smears). Two samples of PDMS with high acidity values, indicative of unusual impurities, caused irritation.

When a drop of test substance was instilled once daily for 10 days into the conjunctival sac of the animals, only the two samples with high acidity values, were able to cause eye irritation (Kumar *et al*, 1985; CoR 2e).

After introduction of 500 mg of a muco-adhesive paste (53% PDMS) into the vaginal cavity of 6 rabbits, only slight erythema, but no oedema or signs of toxicity were observed (CIR, 2003; CoR 4b).

8.2.4 Skin sensitisation

The potential for PDMS to sensitise the skin was evaluated using PDMSs of various viscosities (Table 13).

Table 13: Summary of maximisation tests for skin sensitisation of PDMS in guinea pigs following Magnusson and Kligmann

Viscosity (cSt)	Induction (intradermal injection)	Topical application	Challenge (topical application)	Result	Reference	CoR
10	7.5% v/v	Undiluted	75% v/v	Non-sensitising	Coleman, 1998a	1a
350	Undiluted	Undiluted	75% v/v	Non-sensitising	Coleman, 1998b	1a
350	Undiluted	Undiluted	Undiluted	Non-sensitising	Mercier and Guyot, 1989	1d
60,000	5% v/v	Undiluted	Undiluted	Non-sensitising	Findlay, 1998f	1a

On the basis of the outcome of the studies summarised in Table 13, it can be concluded that PDMSs of various viscosities do not display any evidence of cutaneous allergenic potential. The CIR on PDMS describes the outcome of sensitisation studies using mice and guinea pigs, as well as the results of a clinical HRIPT with 83 panellists. All assays point towards the non-sensitising character of PDMS (CIR, 2003; CoR 4b).

Therefore, PDMS fluids are expected to be non-sensitising to human skin.

8.3 Repeated exposure

8.3.1 Subacute toxicity

Oral

In a 28-day oral study in rats, 10 cSt and 350 cSt PDMS was administered to CDF-(F344)-CrlBr rats (10/sex/group) in the diet at concentrations of 10,000 to 100,000 ppm (1 - 10%). The animals were observed for clinical signs and effects on body weight, food consumption and clinical pathology parameters. Ophthalmoscopy and necropsies were performed on all animals. Selected organs were weighed and tissues were examined microscopically from all groups. None of the animals died before schedule. Test article related clinical signs consisted of a dose-related increase of matting of the fur of male and female rats at 50,000 and 100,000 ppm (10 cSt) or 100,000 ppm only (350 cSt). Increased incidences of corneal opacities and inflammation (microscopically confirmed) were observed in males and females of all treated groups. The area

involved in the ocular changes was dose-dependently increased. Both findings are regarded as consequences of direct contact of fur and eyes with the test material contained in the food at high concentrations (1 - 10%). No effect was observed on body weight, although a treatment-related compensatory increase in food intake was recorded at 5 and 10% (10 cSt) or 5 to 10% (350 CSt). Haematology and urinalysis parameters were unaffected. Mean triglycerides and low and very low density lipoprotein levels were significantly decreased in the 2.5 and 5% group males and in males and females at the 10% dietary level. This was not regarded as an adverse effect. Necropsy did not reveal additional alterations and organ weights were normal. The no observed adverse effect level (NOAEL) of systemic toxicity was above 100,000 ppm (10%) in the diet (Tompkins, 1995a,b; CoR 1).

Dermal

PDMS, 350 cSt, was administered by dermal application to three groups of 10 male and female New Zealand White rabbits for 4 weeks at dosages of 0, 100, 300 or 1,000 mg/kg/d. The test material was removed after 6 hours of exposure on each day of treatment. Before administration of each dose, the dermal site was examined for signs of irritation. Animals were observed daily for signs of toxicity. Body weights were determined twice each week and food consumption was measured weekly. Blood samples were taken for haematology and blood chemistry evaluations on day 29 for males and day 30 for females. Animals were subjected to a full macroscopic evaluation at the end of the treatment period. Selected organs were weighed and processed for microscopic examination. There were no deaths and no adverse signs related to treatment. Body weight, body weight changes and food consumption were unaffected by treatment. There were no haematology or blood chemistry changes that were considered of toxicological significance. There were no treatment related macroscopic or histopathological findings that were considered related to treatment. Therefore, dermal application of 350 cSt to rabbits at dosages of 100, 300 or 1,000 mg/kg/d for at least 28 days was considered non-toxic and the NOAEL for this study was considered to be 1,000 mg/kg/d (Blee, 1999b; CoR 1).

Inhalation

No data are available.

8.3.2 Subchronic toxicity

A 90-day feeding study was conducted in Sprague-Dawley rats (10/sex/group) using 35 cSt, 350 cSt or 1,000 cSt PDMS at dose levels of 1, 5 or 10% in the diet. Animals were observed daily. Body weights and food consumption were recorded. At the end of the treatment animals were necropsied and organs examined for gross and microscopic alterations. No signs of systemic toxicity were seen during the study or during the post-study pathologic examinations. Anal

leakage of the test substance was detected predominantly in the high dose groups and the more viscous material. Food consumption was increased at the mid and high dose levels with all three viscosities of PDMS. This was considered by the authors as compensation for the reduced nutritional value of the diet in these groups. No significant changes were noticed in clinical pathology. Treatment-related changes, for example slight chronic corneal inflammation (opacities) and neovascularisation, were present in the eyes of the animals. These effects were non-dose-related and regarded as local effects after direct ocular contact with PDMS in the food (Hoffman *et al* 1989; CoR 1a).

A subchronic oral toxicity study in male rats was conducted using 35 cSt, 350 cSt or 1,000 cSt PDMS. One hundred male animals per group were treated with diets containing 10% of the PDMS fluids for 90 days. The parameters examined included clinical signs, mortality, body weight, food consumption, haematology, gross necropsy and histopathology of major organs (liver, brain, kidneys, heart, lungs, thymus, sternum/bone, femur, lymph nodes and spleen). No treatment-related alterations of behaviour were detected in any group. Body weights were different when compared to one of the two control groups but not the other. This was interpreted as sign of incidental occurrence. The increases of food consumption seen in all treated groups were considered as a compensation for the high volume of non-nutritive material in these diets. No biologically relevant differences were found in the haematology parameters. Treatment related findings could not be noted either at necropsy or at the histopathological examination. The NOEL was 10% in the diet for all three PDMS fluids (Manston *et al*, 1989; CoR 1a).

PDMS 10 cSt was administered orally to Fischer 344 rats (15/sex/group) in the diet at concentrations of 10,000 to 50,000 ppm (1 - 5%) for 13 weeks. The animals were observed for clinical signs and effects on body weight, food consumption and clinical pathology parameters. Ophthalmoscopy and necropsies were performed on all animals. Selected organs were weighed and selected tissues were examined microscopically from all groups. None of the animals died before schedule. Test-article related clinical changes consisted of a dose-related increase of matting of the fur in the 25,000 and 50,000 ppm group male and female rats. An increased incidence of corneal opacity (crystals) and inflammation with vascularisation (microscopically confirmed) were observed in males and females of the 25,000 and 50,000 ppm groups. Both findings are regarded as consequences of direct contact of fur and eyes with the test material contained in the food at high concentrations (2.5 - 5%). No effect was observed on body weight, although a treatment-related, presumably compensatory, increase in food uptake was recorded at 1, 2.5 and 5%. Haematology and urinalysis parameters were unaffected. Cholesterol and high-density lipoprotein levels and phospholipids were decreased in all treated males. This was not regarded as an adverse effect. Necropsy did not reveal additional alterations and organ weights were normal. The NOAEL of systemic toxicity was above 50,000 ppm (5%) in the diet (Tompkins, 1995d; CoR 1).

PDMS 350 cSt was administered orally to Fischer 344 rats (15/sex/group) in the diet at concentrations of 5,000 to 50,000 ppm (0.5 - 5%) in an analogous 13-week study. Two additional groups received doses of 500 or 2,500 mg/kg/d via gavage to determine the potential of the test substance to induce corneal opacity after dietary and gavage administration. A gavage control group received tap water. The animals were observed for clinical signs and effects on body weight, food consumption and clinical pathology parameters. Ophthalmoscopy and necropsies were performed on all animals. Selected organs were weighed and selected tissues were examined microscopically from all dose groups. One male and 2 females of the 2,500 mg/kg/d gavage group died during week one. Test-article related clinical signs consisted of yellow matting at the base of the tail in the 2,500 mg/kg/d group rats during the second half of the study. Corneal opacities and inflammation (microscopically confirmed) were observed in all animals of all groups (including control) after 3 weeks of treatment. A dose-dependent increase of the intensity of this finding was recorded. No effect was observed on body weight, although a treatment-related, presumably compensatory, increase in food uptake was recorded at 5% PDMS in the diet. Haematology and urinalysis and clinical chemistry parameters were unaffected. Necropsy and microscopic examination did not reveal additional alterations and organ weights were normal. The NOAEL of systemic toxicity was above 50,000 ppm in the diet (Tompkins, 1995c; CoR 1).

PDMS 35cSt was given orally to CD-1 mice (15/sex/group) for 90 days *via* the diet at concentrations of 0, 5 or 10%. Animals were observed for signs of toxicity daily. Mortality, body weights and food consumption were determined. After 90 days of treatment, the animals were killed and major organs inspected, weighed and examined histopathologically (liver, spleen, kidney, lung, oesophagus, gastrointestinal tract, eyes and lymph nodes). No clinical pathology parameters were determined. None of the clinical parameters showed signs of toxicity. Food consumption of the treated animals was increased. This was interpreted as a compensation for the high amount of non-nutritive material in these diets. Neither mortality nor histopathological changes were noticed (King and Siddiqui, 1989; CoR 2).

8.3.3 Chronic

See Section 8.5.

8.4 Genotoxicity and cell transformation

8.4.1 *In vitro*

PDMS, 60,000 cSt, was tested in the bacterial reverse mutation assay using *S. typhimurium* tester strains TA98, TA100, TA1535, TA1537 and *E. coli* strains WP2 uvrA and WP2 uvrA (pKM 101) in the presence and absence of metabolic activation using centrifuged (9,000 × g) supernatant of Aroclor-induced rat liver homogenate (S9). The assay was performed in two phases, using the pre-incubation method. The first phase, the preliminary toxicity assay, was used to establish the dose range for the mutagenicity phase. The second phase, the mutagenicity phase (initial and independent repeat assays), was used to evaluate the mutagenic potential of the test article. In the preliminary toxicity phase, the maximum dose tested was 5,000 µg per plate. Precipitate was observed at ≥ 333 or at ≥ 667 µg per plate, but no appreciable toxicity was observed. Based on these findings of the toxicity assay, the maximum dose plated in the mutagenicity assay was 5,000 µg per plate. No positive response was observed in the mutagenicity assay. Precipitate was observed at ≥ 500 or at ≥ 1500 µg per plate but no appreciable toxicity was observed. Under the conditions of the study, 60,000 cSt PDMS was considered non-mutagenic in the Bacterial Reverse Mutation Assay (Wagner, 1998; CoR 1a).

PDMS 350 cSt was tested in 5 strains of *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537, TA1538) in a plate incorporation assay with and without metabolic activation. The test substance was applied as an emulsion in water using Tween 80 at 10%. A range of sub-toxic concentrations were determined in a preliminary test on the strain TA98 without metabolic activation. A concentration 100 µl/plate was shown not to be toxic in this strain. The five concentrations chosen (1, 5, 10, 50, 100 µl/plate) were tested 3 times on the 5 strains. Negative and positive controls were included. The results were confirmed in a second independent study. PDMS did not show mutagenic activity in all tested strains with or without metabolic activation (Weill *et al*, 1988; CoR 1a).

No mutagenic activity was seen when PDMS 50 cSt was assayed in 5 strains of *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537, TA1538), following incorporation of 0.5, 5, 100 or 500 µl/plate with or without S9 metabolic activation. Dilutions were prepared using deionised water, absolute alcohol or dimethylsulphoxide (DMSO). Positive and solvent controls were included. There was no toxicity at the highest concentration tested (Isquith and Whaley, 1979; CoR 1a).

PDMS of 0.65, 100 and 1,000 cSt viscosity was tested for mutagenic activity *in vitro* employing *Salmonella* tester strains TA-1535, TA-1537, TA-1538, TA-98 and TA-100, with and without liver microsomal activation. All three PDMSs gave negative results, both with and without metabolic activation. Each PDMS was considered non-mutagenic (Isquith and Whaley, 1978; CoR 2e)

8.4.2 *In vivo*

No data are available

8.5 Chronic toxicity and carcinogenicity

In a combined chronic toxicity and oncogenicity study, 10 cSt PDMS was administered orally to Fischer 344 rats (90/sex/group) in the diet at dose levels of 0 (control), 100, 300 or 1,000 mg/kgbw/d for 24 months. Thirty animals/sex/group were assigned to the chronic portion of the study. Ten animals/sex/group were necropsied following 12 months of test article administration. Twenty animals/sex/group were treated for 12 months followed by a 12-month recovery period. The animals were observed for clinical signs and effects on body weight, food consumption and clinical pathology changes. Ophthalmoscopy and necropsies were performed on all animals. Selected organs were weighed and tissues were examined microscopically from all animals. Survival was unaffected by test article administration. Palpable mass data were unaffected. There were no toxicologically significant test article related effects on body weights, food consumption or clinical pathology parameters. There were no test article related ophthalmic findings. Organ weights were unaffected. There were no test article related macroscopic or microscopic findings. No test article related proliferative changes were observed in the chronic recovery animals. Test article clinical findings consisted of slightly increased incidences of ocular opacities in the 300 mg/ kgbw/d group females and the 1,000 mg/kgbw/d group males and females; the findings were most probably the result of local irritation. Possible test article related macroscopic findings were limited to increased incidences of eye opacity for the chronic recovery group (incidence slightly increased in all test article treated male groups without dose correlation). Eye opacity correlated with the microscopic finding of keratitis and for the incidental microscopic finding of corneal dystrophy. The NOEL for systemic toxicity of 10 cSt PDMS fluid in this test was 1,000 mg/kgbw/d, the highest tested dose (Mertens, 2003; CoR 1). This result is supported by an earlier dietary study in Carshalton bred mice of both sexes dosed up to 3,750 mg PDMS/kgbw for 76 weeks. The authors concluded that there was no increase in the incidence of malignant or benign tumours in the groups of mice receiving the antifoam agent either in the diet or by *s.c.* injection. No toxic effects were observed that could be ascribed to the administration of the substance (Cutler *et al*, 1974; CoR 2e).

In a combined chronic toxicity and oncogenicity study in rats 10 cSt PDMS was administered to Fischer 344 rats (90/sex/group) in the diet at dose levels of 0 (control), 100, 300 or 1,000 mg/kgbw/d for 24 months (Mertens, 2003; CoR 1 [see chronic study above]). Sixty animals/sex/group were assigned to the oncogenicity portion of the study. These animals were treated for 24 months and were assessed for oncogenic effects. No test article related neoplastic

or pre-neoplastic changes were observed. The NOEL for oncogenicity of 10 cSt PDMS fluid was 1,000 mg/kgbw/d, the highest tested dose. There was no indication of carcinogenicity of PDMS.

KS66, a mixture which is composed of 92% PDMS and 8% silica, has been tested for carcinogenic potential. Groups of 50 female and 50 male Fischer 344 rats were given a diet containing 0% (control), 1.25% or 5% KS66 for 104 weeks. The highest dose was determined based on a subchronic study. The average KS66 intake in the 1.25% groups was 444.9 (female) and 530.1 mg/kgbw/d (male) and 1,893.9 (female) and 2,233.9 mg/kgbw/d (male) in the 5% groups. All rats were examined for general health and signs of toxicity, body weight and food intake. After 104 weeks, all surviving animals were killed. Haematological determinations including red blood cell/white blood cell counts, haemoglobin concentration, haematocrit values and platelet counts were performed. Blood smears were used to check for leukaemia. A gross pathology was performed and the brain, liver, kidneys, spleen, heart, adrenals and testes/ovaries were weighed. A full histopathology was performed on the control and 5% groups. Some rats in the 1.25% group died or were killed when they became moribund during the test. In surviving animals of the 1.25% group, the spleen, lung, liver, kidneys and gross lesions were examined. Statistical analysis was performed concerning body weight, haematology, organ weight (intergroup differences) and macroscopic and histopathological lesions (difference between control and dose groups).

The physical appearance and behaviour of the rats were not affected. At study termination the survival rates for female rats were 84% (control), 80% (1.25% KS66) and 88% (5.0% KS66) and those of male rats were 82% (control), 88% (1.25% KS66) and 80% (5.0% KS66). Body weight elevation was observed in females (1.25% and 5% groups) and males (1.25% group). No treatment related changes regarding food consumption and haematology data were observed. Relative liver weights were significantly decreased in the male 5% group. Significant increase in the incidence of thyroid C-cell adenomas was found in females of the 5% group, but the authors regarded this incidence as spontaneous based on historical data. In the male 5% group, the incidence of carcinomas of the prostate was significantly decreased in comparison to the control. The incidence of other lesions (neoplastic and non-neoplastic) was similar to those in the control and all were considered as spontaneous in nature. The authors concluded that KS66 which contains 92% PDMS is not carcinogenic in Fischer 344 rats of either sex (Kawabe *et al*, 2005; CoR 1a).

8.6 Embryo toxicity, teratology and reproductive performance

8.6.1 Reproductive

Male Sprague-Dawley rats (10/group) received (5 d/wk) orally either one ml of 350 cSt PDMS/kgbw (≈ 1,000 mg/kgbw) or tap water for 4 weeks. Body weights and food consumption

were measured weekly and clinical observations were made daily following dosing. At the end of the study the animals were killed and a gross necropsy performed. The weights of the testes, epididymides and prostate were measured. No clinical signs of toxicity were noted during the study and no effects on body weight or body weight gain were determined. No effects were measured on the weights of the male sex organs examined. Therefore, administration of 350 cSt PDMS had no effect on male reproductive organs compared to controls (Campbell and Sewell, 1969; CoR 1a). The NOAEL was considered to be > 1,000 mg/kgbw.

In a follow-up study, 5 male albino rabbits were used to assess the effect of 350 cSt PDMS on the sex organs following dermal application. The test material (3 ml/kgbw [≈ 3 g/kgbw]) was applied (1 ×/d, 5 d/wk) to the shaved backs of the rabbits for 4 weeks. Each animal was immobilised in a restrainer for 6 to 7 hours following application of the test material. At the end of the immobilisation period, the test material was gently swabbed from the animals backs. The control animals received distilled water or 'White's A&D ointment' without hexachlorophene. Body weights were obtained weekly and semen samples were collected from each rabbit weekly and evaluated. At the end of the study, semen samples were obtained and the testes and epididymides were removed, carefully separated, cleaned of fat and extraneous tissue, weighed and examined microscopically. Semen samples were evaluated for volume, viscosity and colour, sperm number, motility and morphology. There was no effect of 350 cSt PDMS on any of the parameters evaluated including the reproductive system following dermal application (Campbell and Sewell, 1969; CoR 1a). The NOAEL was considered to be > 3 g/kgbw.

Charles River CD rats (30/sex/group) were implanted with a cross-linked silicone gel. Males and females were treated 61 days and 47 days, respectively, before mating. The dose levels (3, 10 or 30 ml/kgbw; 2.8, 9.5 or 28.5 g/kgbw) were selected on a projected final body weight of a 300 gram rat. Control rats were injected with carboxymethylcellulose or saline. Parameters recorded were body weights, gross necropsy (day 20 of gestation or day 21, after delivery), histopathology of implantation sites, number of implantations / resorptions and corpora lutea, external malformations, weight, sex of pups at birth, duration of gestation, litter size, still births, nursing, survival and growth of pups and nursing behaviour. Parental males were not further evaluated; females were subjected to gross necropsy. No treatment-related mortality occurred. No differences in behaviour and general condition, body weight gain or reproductive behaviour and success were recorded in the parental generation. None of the parameters determined in the pups showed significant difference compared to control animals. The NOAEL was 30 ml/kgbw (28.5 g/kgbw) in dams and offspring (Siddiqui 1994a,b; CoR 1).

8.6.2 Teratogenicity

Siddiqui *et al* (1994a,b; CoR 1) determined the possible teratogenic effects of PDMS gel in pregnant New Zealand White rabbits. Implantation was performed 6 weeks prior to insemination.

Dose levels were 3, 10 or 30 ml/kgbw/d (2.85, 9.5 or 28.5 g/kgbw) for the gel. Four 2.5 cm diameter discs of the elastomer were used. Animals were observed for appearance, behaviour and signs of toxicity. Body weight gain was recorded. On day 29 of gestation, all surviving animals were killed and a gross necropsy was performed. Standard reproductive and developmental endpoints (e.g. Implantations, corpora lutea, resorptions, abortions, number of live/ dead, male/ female foetuses, external/ visceral/ skeletal malformations) were determined. No behavioural changes were observed in dams treated with the gel. One of the mid-dose gel-treated animals died of an unknown cause one day after delivering on day 28 of gestation. No significant differences of any kind between the groups were detected before or during pregnancy. The reproductive parameters were not affected by the treatment. There were no adverse effects on the numbers and development of foetuses of gel-treated does. No alterations regarding type and incidence of malformations/ variations were noted in these animals. The maternal and developmental NOAEL was 30 ml/kgbw (28.5 g/kgbw).

Three groups each of 23 pregnant New Zealand White rabbits were treated with PDMS 10 or 350 cSt at dose levels of 33, 300 or 1,000 mg/kgbw/d by gavage from days 6 to 19 after mating. None of the reproductive parameters was significantly affected. Type and incidence of abnormalities in both treated and control offspring were not significantly different. The NOAEL was 1,000 mg/kgbw (Blee, 1999c,d; CoR 1).

8.7 Immunotoxicity

In a 10-day immunotoxicity study of PDMS, Bradley *et al* (1994a; CoR 2e) determined the subchronic immunotoxic potential of the principal constituents of breast implants: Silicone fluid, silicone gel and silicone elastomer. Silicone fluid and gel were injected *s.c.* into female $B6C3F_1$ mice (1 ml (0.95 g)/mouse) and 6 cm disks of silicone elastomer were implanted *s.c.* There were no treatment-related deaths or overt signs of toxicity. The tested silicones did not alter the distribution of β-cells and T-cells in the spleen. Natural killer cell activity and serum complement were not altered.

Subcutaneous injection of female $B6C3F_1$ mice with PDMS fluid, gel or elastomer for 180 days elicited no overt toxicity and elicited few alterations in the toxicology and immunology panel of tests used particularly a modest depression of natural killer cell activity (Bradley *et al*, 1994b; CoR 2e).

Naim *et al* (2000; CoR 1) investigated the effects of PDMS on autoantibody and immunoglobulin production and macrophage activation in female A.SW mice. The mice (15/group) received a 0.5-ml *i.p.* injection of either phosphate-buffered saline, pristane, silicone gel or PDMS. Test bleeds were taken periodically for 6 months. The study suggests that the *i.p.* administration of

PDMS or silicones gels in mice induce some of the abnormalities typical of the pristane-induced lupus in mice, which is predominately hyper-γ-globulinaemia. In contrast to pristane-induced lupus, there is a quantitative difference in the stimulation of IgG2a production, a difference presumably related to lower levels of IFN-γ. This may be responsible for the relatively poor efficacy of silicone gels and oils in stimulating autoantibody production. Nevertheless, the high levels of anti-chromatin auto antibodies produced by some of the mice suggest that in some cases chronic immune stimulation by silicones gels and oils may lead to the production of a subset of antibodies, although not the full spectrum seen in pristane-treated lupus. The authors concluded that these observations may be relevant to understanding the vague and often poorly defined autoimmune-like phenomena occurring in certain individuals with silicone implants.

Frondoza *et al* (1996; CoR 1) concluded that silicone administration does not enhance the development of skin fibrosis and production of characteristic autoantibodies in Tsk/+ mice. Silicone did not induce increased levels of circulating antibodies therefore it may not be involved in the development of the scleroderma-like syndrome.

Klykken *et al* (1991a; CoR 1) concluded that formation of a tissue capsule around PDMS fluid component of a mammary prosthesis did not represent an immunologically mediated event but a merely normal wound healing response to an alloplastic material.

In a *Listeria* host resistance assay, a PDMS mammary implant material did not alter the regulatory framework of the immune system. Under the conditions of the assay, PDMS fluid had no effect on immune competence (Klykken *et al*, 1991b; CoR 1).

A study was conducted in B6C3F_1 mice and in Sprague Dawley and Fischer 344 rats to investigate the adjuvancy potential of silicone mammary gel (PDMS). A normal immune response was noted when the antigen (BSA) was not blended with the silicone prior to immunisation and there did not appear to be any silicone induced adjuvant response (Klykken *et al*, 1996; CoR 1).

8.8 Special studies

PDMS 350 cSt was tested for cytotoxic potential in cultures of MRC-5 (human embryonic lung) cells using both direct contact and test article extract exposures. MRC-5 cells have been demonstrated to provide a sensitive model for evaluating cytotoxic potential.

The direct contact portion of the assay was performed by placing PDMS-soaked filter disks directly onto the MRC-5 cultures. Controls were treated by placing approximately 1 cm^2 pieces directly onto the MRC-5 cell monolayer and visually evaluating the condition of the cell

monolayers after a 24-hour exposure period. The extraction portion of the assay was performed by introducing a medium of the test material into wells containing the MRC-5 cultures, and visually evaluating the condition of the cell monolayer after a 48-hour exposure period. Finally, the cytotoxic potential of the PDMS extract was quantified by measuring the relative uptake of the vital dye, neutral red, in PDMS-treated cultures relative to negative control cultures.

Two trials of the direct contact assay were performed because the positive control, raw latex catheter, failed to produce sufficient toxic effects in the first trial.

The final results of the study showed that 350 cSt PDMS did not produce cytopathic effects in MRC-5 cultures, in either the direct contact or extract exposure models (Raabe, 1998; CoR 2c).

In an *in vitro* study, excised human skin samples were used to study the interaction of PDMS 350, 500, 1,000 or 20,000 cSt with the stratum corneum and its lipids. Making use of polarised light microscopy, transmission electron microscopy, small angle X-ray diffraction and differential scanning calorimetry, the authors found that the investigated PDMS did not change either the microstructure of the excised human stratum corneum or the structure of a specifically designed *in vitro* lipid system model containing typical stratum corneum fatty acids. They concluded that the compounds were unlikely to cause side-effects when topically applied (Glombitza and Müller-Goymann, 2001; CoR 2e).

8.9 Summary and evaluation

PDMS with viscosities ranging from 10 to > 100,000 cSt have been subjected to a very broad range of safety studies including: acute (oral, dermal and inhalation [aerosol]), *i.p.*, *s.c.*, intradermal, irritation (skin, eye and vaginal), sensitisation, subacute (oral and dermal), subchronic, chronic, carcinogenicity, genotoxicity, reproductive/developmental and immunological as well as oral and dermal pharmacokinetic studies. No adverse effects have been seen in virtually all of these studies and the NOAELs in these studies have always been greater than the highest dose tested in the study. Oral and dermal pharmacokinetic studies conducted with 10 and 350 cSt PDMS have shown essentially no potential for absorption.

9. EFFECTS ON HUMANS

9.1 Skin irritation

The local tolerance of PDMS with a viscosity of 350 cSt has been studied by simple patch test using Finn chambers (8 mm diameter; 50 mm^2 surface). Three other silicone products and a control substance were tested in parallel. An aliquot of 20 µl of each substance was applied onto the back of healthy volunteers (25/sex) aged between 18 and 37 years. The subjects were certified as normal following a comprehensive clinical assessment including a detailed medical history and a complete physical examination. A plug of ether was used to wipe the area of the back before applying the patches. After 24 hours of rest, the skin area was scored. No skin reaction following PDMS application was observed in this test. The authors concluded that the local tolerance of the substance was "considered as good" (Thébault *et al*, 1989; CoR 1a), i.e. PDMS 350 cSt was well-tolerated by human skin.

9.2 Skin sensitisation

In a repeated insult patch test in human subjects, a 5% (v/v) solution of a not specified substance in 12,500 cSt PDMS was evaluated; the PDMS was used as vehicle/control. Sodium lauryl sulphate (0.1% aqueous solution) served as the positive control. Based on inclusion criteria and exclusion criteria the test group was selected. One hundred and fifteen subjects between the ages of 18 and 70 were enrolled and 106 completed the study which was conducted over a 6 week period involving three phases: Induction, rest and challenge. Aliquots of 0.2 ml of the study material solution and the PDMS were applied under semi-occlusive dressing. The induction phase consisted of 9 consecutive applications. The subjects were required to remove the patches after 24 hours. The sites were evaluated after 48 hours, except after application on Friday (evaluation after 72 hours). After the ninth evaluation, the subjects were dismissed for a rest period of approximately 10 to 15 days. The challenge phase was initiated during the sixth week of the study. Substances were applied to sites previously unexposed. The patches were removed after 24 hours and the sites were graded after an additional 24-hour and 48-hour period. Under the conditions of this study, there was no evidence of sensitisation of the test material in 12,500 cSt PDMS and no evidence of sensitisation of the PDMS vehicle (Dosik, 2005; CoR 1).

9.3 Chronic exposure, medical and surgical use

9.3.1 Urology

Minimally invasive endoscopic techniques using PDMS have been reported as an efficient treatment and an alternative to standard surgical techniques. This technique dated back to the early 1980s when the sub-ureteral injection of polytetrafluoroethylene was first reported followed by the use of polyvinyl alcohol, but there were concerns regarding safety, efficacy, stability and long term efficacy. To avoid side effects Smith *et al* (1994; CoR 1) showed PDMS could be a more reliable product and that endoscopic subureteral injection of PDMS was technically feasible on animals. Therefore, PDMSs have been used since the mid-1990s with high success rates for reflux in an ambulatory setting with no short-term complications (Aboutaleb *et al*, 2003; CoR 1). This technique is less invasive than surgery with lower associated morbidity and is recommended as the first line of surgical therapy for primary low grade vesico-ureteral reflux in children (Aboutaleb *et al*, 2003; CoR 1). The success rate for PDMS intervention was lower than that of open surgery at 3 months and it was minimally invasive with lower associated morbidity. Dodat *et al* (1995; CoR 1) reviewed 785 cases of vesico-ureteral reflux over a 7-year period and found that a complete resolution of reflux was obtained in 93% of children treated with PDMS versus 86% with Teflon and 48% with collagen. PDMS provides the best results due to its higher viscosity and absence of retraction.

The use of PDMS is recommended by Hamid *et al* (2003; CoR 2e) as a safe and minimally invasive treatment for genuine stress urinary incontinence in males following a spinal cord injury with a stable compliant bladder. PDMS can be used as the first line of treatment in this difficult group of patients with a complex problem.

9.3.2 Ophtalmology

PDMS implementation into the eye-ball following vitrectomy has been used increasingly in human ophthalmology over the last 40 years for the repair of complicated retinal detachments. This is especially when a long-term endotamponade is required. Following injection into the rabbit eye, PDMS 1,000 or 3,000 cSt appeared to be the most biocompatible material for vitreous replacement (Versura *et al*, 2001; CoR 2e). After the invention of the vitrectomy instrument, the role of PDMS was expanded as a vitreous substitute and retina tamponade. Indications for PDMS injection include retinal detachment due to ocular trauma, proliferative diabetic retinopathy, giant retinal tears and cytomegalovirus necrotising retinitis vitreoretinopathy. Despite the progress and potential importance of PDMS and its clinical utilisation as an adjunct for the treatment of complicated retinal detachment, retinal tolerance and toxicity were still controversial issues. Soheilian *et al* (1995; CoR 1) evaluated retinal toxicity of low viscosity PDMS 100 cSt as a short-term postoperative tamponade. No toxic effects on the retina were

demonstrated in the rabbit up to 5 months. His study showed that 100 cSt PDMS can remain in the rabbit eye for 5 months without emulsification. One of the advantages of very low viscosity silicone is the ease of its administration into the eye. Although there is no agreement on when PDMS should be removed, authors (Papp *et al*, 2007; CoR 2) basically agree that it should be removed as soon as possible. It is noted that many surgeons still leave it permanently in the eye, especially in complicated cases.

Budde *et al* (2001; CoR 2) suggested that silicone oil may enter the optic nerve after long-term oil endotamponade and elevate intraocular pressure. In a histopathology analysis of 74 eyes enucleated after silicone oil endotamponade, these eyes showed that silicone oil in the optic nerve was surrounded by a granulomatous inflammatory reaction that may add to optic nerve damage. The risk of silicone oil-associated optic nerve degeneration is independent of the viscosity of the oil used. The authors concluded that the silicone oil should be removed as soon as retinal stability is achieved. The authors could not establish pre-existing glaucoma as a risk factor for migration of intraocular oil into the optic nerve. Agrawal *et al* (2002; CoR 2) noticed that Budde report reinforced two very important points: Maintaining strict intra-ocular pressure control in the postoperative period and early removal of oil after a certain period of time in most cases.

Auriol *et al* (2008; CoR 1) in a retrospective study including 27 patients showed that heavy silicone oil can be used as an effective endotamponade in complicated retinal detachment treated by a large inferior retinectomy. The authors believed that heavy silicone oil prevents fluid from accumulating under the inferior retina, thus limiting the rate of inferior reopening and that it seemed to limit the rate of reproliferation. It was also stressed that special attention must be paid to unusual adverse effects like inflammatory reactions and fibrin accumulation in the interior chamber which seemed to occur especially in large retinectomy.

As reported by Theelen *et al* (2004; CoR 1), silicone oil is an excellent tool in the surgical treatment of complicated retinal detachment. In some complex cases, high-density silicone oil must be used instead of regular silicone oil especially when the pathology is located inferiorly. Their effectiveness in terms of anatomic success as an intraocular tamponade in complicated retinal detachment was shown in a study evaluating 18 patients who underwent pars plana vitrectomy and intraocular tamponade even if in few cases an inflammatory response occurred.

Green *et al* (1994, 1998; CoR 1) emphasised that the increasing use of silicone oils as a tamponade in retinal detachment requires silicone oils with a high level of purity to eliminate toxic tissue reactions related to potentially toxic ingredients in these oils.

Silicone foldable intraocular lenses have been used in cataract and implant surgery since 1984. Key characteristics of silicone intraocular lenses are flexibility and compressibility of the optic, traits that enable surgeons to insert the lens through incisions. Other benefits resulting from the

combination of small incision surgery and foldable intraocular lenses include decreased postoperative inflammation, less operative astigmatism, reduced damage to corneal endothelium cell loss and faster vision rehabilitation (Steinert *et al*, 1997; CoR 1). Lenses made of silicone material demonstrated safe and effective performance through long-term follow-up. The performance was equivalent when compared to the better established standards for polymethacrylate lenses.

9.3.3 Dermatology

Liquid injectable silicone has been used for many years for soft tissue augmentation to effectively correct specific cutaneous atrophies. Its use has been controversial because of a history of problems such as product migration and granulomatous inflammation (Prather and Jones, 2006; CoR 1), which results probably from the presence of adulterants and impurities. The controversy remains particularly in some countries where there is an inadequate investigation and control of biomaterials used for soft tissue augmentation (Ficarra *et al*, 2002; CoR 1). Silicone oils may be employed with success and minimal complications when appropriate treatment principles are adhered to and a strict protocol is followed. Liquid injectable silicone is currently underway for the correction of HIV lipoatrophy as well as for the improvement of nasolabial folds, marionette lines, mild-malar depressions and the long-term correction of hypertrophic scars. This use requires extensive experience and precise technique in order to achieve optimal results.

Various adverse events have been reported in association with cosmetic injections. Most reported adverse effects have occurred after illegal silicone injections by unlicensed practitioners using formulations not intended for medical use and often administered in large volumes. These injections into body tissue eventually reach the bloodstream and cause an embolism in the lung or lead to acute renal failure. Few data are available regarding the incidence of adverse effects after administration of silicone oil soft tissue fillers by licensed medical provider using formulations intended for medical use (Price *et al*, 2006; CoR 1; Branton *et al*, 2008; CoR 4b,e).

Hypertrophic scars also can be treated with self-drying silicone gel. The gel helps to reduce, soften and flatten the scars while maintaining the moisture balance and elasticity of adjacent skin (Lacarrubba *et al*, 2008; CoR 1).

Rosa *et al* (2008; CoR 1) analysed the biological effect of polymethylmethacrylate-bovine collagen (Artecoll) and PDMS using a histopathological study in mice. These substances are used for treatment of scars, wrinkles and cutaneous defects, and they must be as biocompatible as possible. A prospective study was performed using 40 mice for each substance and was injected into the right ear. Artecoll produced an intense foreign body granulomatous reaction in the right ear, periportal and intralobular infiltrates in the liver as well as interstitial nephritis. Reactions with PDMS were only local and caused an eosinophilic reaction and phagocytosis considered as a

regular inflammatory reaction. Those findings are similar to those of authors who reported that foreign body reactions are with PDMS.

Due to its physical mode of action PDMS has been successfully used recently as a safe and efficacious pediculicide (Heukelbach *et al*, 2008; CoR 2e).

PDMS 10 and 350 cSt showed low a dermal absorption rate *in vitro.* The absorbed fractions were 0.5% and 0.3% in vaginal skin, and 0.2% and 0.11% in abdominal skin, for 10 or 350 cSt PDMS, respectively. The flux was below 0.5 µg/cm²/h at all times (Plotzke *et al*, 2000; CoR 2b).

9.3.4 Dietary studies

Silicone compounds have been widely used as additives in a wide variety of foods, drugs and cosmetics for many years. PDMS offers potential for use as a dietary substitute for animal and vegetable fats.

A study was developed to determine tolerance to and effect upon nutrient absorption of PDMS administered as 1% and 2% of the daily diet. No significant signs of adverse effects were seen among 6 healthy male volunteers. Evaluation of tolerance was based upon assessment of observed or reported changes in bowel habits, stool appearance and consistency and anal leakage. Blood samples, urine and faeces were collected to assess the absorption of selected nutrients. Clinical laboratory parameters and body weights were also monitored and faecal microflora was assessed (Breger *et al*, 1994; CoR 2*).*

Another study was designed to assess tolerance to higher levels of PDMS representing the maximum level up to 5% of a standard diet, that an individual might be expected to consume under normal conditions. Following a 3-day placebo period, 7 healthy male volunteers received the additive in ascending doses (2%, 3%, 4% and 5% of the diet by weight) for 5 consecutive 3-day periods. Evaluation of tolerance was based upon assessment of observed or reported changes in bowel habits, stool appearance and consistency and anal leakage. Blood samples were collected to assess the absorption of vitamin K as determined by prothrombin time and partial thromboplastin time evaluations. All subjects experienced flatulence during the study. No other significant discomfort was reported. There was no indication of clinically significant changes in vitamin K absorption as estimated by PT and PTP determinations. There were some minor changes in some biological parameters. There was an increase in percentage neutrophil count over pre-study values, which was accompanied by a decrease in percentage lymphocyte count with a slight decrease in total WBC count. Post-study medical examination revealed a slight weight loss among 3 subjects. The clinical significance of these findings is not known (Weigens *et al*, 1994; CoR 2).

9.4 Immunology

Because the developments of defined autoimmune disorders are rare events, epidemiological studies for many years were not definitive due to the lack of statistically significant numbers of patients studied. Many investigators have attempted to answer the questions raised when patients with silicone-related disorders developed clinical manifestations of scleroderma, lupus or other immune disorders. There is now a worldwide scientific consensus through a number of epidemiological studies that silicone based material is not associated with an increased risk of these diseases. Silicone elastomers have been extensively studied and scrutinised as a result of the breast implant debate. Three independent review panels have carefully assessed the specific issue of silicone immunogenicity. All three groups concluded that there is no convincing evidence to support an association of silicone breast implants with immune-related human health conditions (Klykken *et al*, 2008).

Pastor *et al* (2001; CoR 1) raised the issue of autoimmune disease and silicone antibodies in an ophthalmic surgery patient population (IgG binding to silicone detecting by Elisa) and speculated that a proportion of patients who had received silicone for retinal detachment surgery might have been sensitised to this material and the proportion is higher when silicone is used intraocularly. Klykken *et al* (2002) in a response to this report emphasised the weakness of the study and the failure of the authors to find an association between silicone implant exposure and/or symptoms and markers of immune disease. Klykken *et al* also pointed out that the enzyme-linked immunosorbent assay (Elisa) methodology used to measure antisilicone antibodies is flawed and the existence of antisilicone antibodies is biologically unlikely. In a response Pastor *et al* (2002) recognised that an association between autoimmune diseases and the exposure to silicone devices employed in ophthalmic surgery had not been established and that the publication was inconclusive regarding the possible repercussion of the presence of antisilicones antibodies in patients carrying silicone sponges, bands or intraocular silicone oil.

Bekerecioglu *et al* (2008; CoR 2) in a study of 15 patients undergoing reconstructive procedures for burn scars in which silicones were used, suggests that implants cause a negligible and non-specific foreign body reaction and that these antibodies against the silicone implants have little or no clinical importance. Elevations in serum immunoglobulin (IgE) and the presence of silicone antibodies in the capsular tissue for the silicone-implanted group were reported. Klykken *et al* (2008) in a response to the author pointed out that the elevation in serum IgE can also have other biologically plausible explanations. For example, a selective increase in serum IgE has been observed following surgical procedures and the magnitude of increase appears to correlate with the surgical injury intensity. Ethylene oxide has been used to sterilise a variety of silicone medical devices and residual ethylene oxide can react with endogenous proteins to create neo-antigens. In patients who have experienced silicone shunt malfunctions, there was no evidence of infection, but the patients presented with elevated eosinophil counts and serum IgE antibodies

specifically directed toward ethylene oxide protein conjugates. In their conclusion, Klykken *et al* believe that Bekerecioglu *et al* were too quick to reach their conclusions and were unaware of other more likely mechanisms and the extensive literature rebutting the hypothesis of a specific immune response to silicone.

9.5 Chronic exposure

9.5.1 Occupational

9.5.2 Non-occupational

For a discussion on human use and exposure, see Sections 3.4, 5.2 and 10.

Epidemiology of PDMS

Because of their stability and excellent biocompatibility, silicones are used in numerous medical applications (Berger, 1966; Silver, 1992; Colas and Curtis, 2004). Silicone materials, the most common of which is PDMS (Colas and Curtis, 2004) are extremely versatile and can have many physical forms, such as fluid, gel, gum, rubber, elastomer or resin. Medical applications have used silicone fluids for instrument and needle coating, injection (e.g. soft tissue filler) and gels, rubbers and elastomers to fabricate implantable medical devices to treat a variety of medical conditions, (e.g. intraocular tamponade, gel-filled implants, various shunts, joint implants).

Human data on the use of silicone fluids and gel-filled medical devices range from basic case reports to more controlled population-based observational studies as well as controlled clinical study designs. Case reports that rely on self-reported history of having received injected silicone fluid are not reliable for confirmed exposure to silicone. Evidence is lacking about whether it was medical grade, industrial grade, adulterated with additives or a substance other than silicone (Timberlake and Looney, 1986). These unidentified injected mixtures are erroneously referred to as silicone (Braley, 1964, 1970). To be useful for risk assessment or for evaluating causal association, human data should provide an estimate of the relative risk of an endpoint among an exposed population compared with an unexposed population. Case reports and case series are anecdotal reports or non-experimental human data (ECETOC, 2009) of adverse outcome following exposure. They are a useful communication tool to call attention to new or unusual findings. They may help to generate a hypothesis on the association between exposure and disease, but they are highly susceptible to over-interpretation (Fletcher *et al*, 1982). Similarly exposed individuals without an adverse outcome are not generally considered newsworthy and are not published, thus, leaving readers to learn only of the adverse events potentially associated with a particular exposure. In order to test an hypothesis, more rigorous study designs are

required. Furthermore, Hill (1965) offers nine criteria to assess causation; obviously the putative causal agent must be identifiable. Based on these criteria (Hill, 1965; ECETOC, 2009), a large number of the published case report studies do not meet these criteria and, being unreliable (CoR 3), have been dismissed from this report. A list of these published studies is included in the bibliography as not quoted (Section 11.2).

When a controlled clinical study substantiates the use of medical grade silicone fluid for injection and data are collected for specific endpoints of interest, then the data may contribute to the risk assessment. Non-experimental clinical studies reviewed in this effort are assigned CoR 2, reliable with restrictions.

Silicone fluid injection is approved for use in the USA as vitreous fluid replacement and tamponade in cases of retinal detachment and is also used in the treatment of hemifacial atrophy among more than 800 patients with human immunodeficiency virus. While no adverse effects were noted after several years, longer-term follow-up is needed to assess the efficacy, durability and long-term safety (Jones, 2005). Silicone fluid injection is widely available in Israel since its Health Ministry lifted the ban in 2000 (The State of Israel, 2000) and off-label use of silicone fluid occurs in Australia, England, France and USA (Siegel, 2000), primarily for soft tissue augmentation (Ashley *et al*, 1965; Orentreich and Orentreich, 1987; Benedetto and Lewis, 2003). Wilkie (1977) reported his ten-year experience with silicone facial injections among 92 patients. Granulomas developed among 13 injection sites between one and 7 years after the injections. Following 1,677 silicone injections to the face, Milojevic (1982) observed incomplete correction for deep wrinkles and scars, some cases where the injected fluid in the region of the eyelids or lips had a tendency to “descend and accumulate” up to 30% volume loss 3 weeks after the injection and 2 cases of granuloma formation. Balkin (2005) reported using silicone fluid to treat more than 4,000 foot ulcers in 1,585 patients over 41 years. No significant adverse response, e.g. inflammation, infection, allergy or granuloma, was observed in up to 20 years of follow-up. From this population, a total of 148 post-mortem and surgical specimens were obtained from 49 patients, the longest *in vivo* experience being 38 years (Wallace *et al*, 2004). There were no noticeable adverse effects other than occasional local disfigurement among patients with larger quantities of injected silicone. The tissue specimens showed a histologically stable and biologically tolerated host response (Wallace *et al*, 2004).

Webster *et al* (1984) reported their 20 year experience in treating 524 patients with facial injections of medical grade silicone fluid. The authors state, “None of us found any record of an adversity, complication or patient dissatisfaction, with four exceptions.” One patient experienced increased redness, itching and tightness at an injection site which disappeared in 2 days, a second patient became frightened after viewing a “scare” programme about silicone and wanted the silicone removed. A third patient reported erythema near the nose; the surgeons estimated this occurred in roughly 10% of nasal area injections and that it may have existed prior to treatment.

The fourth patient reported dissatisfaction with the additional treatment required to treat acne scars. As to the reliability and rigor of these data, the authors comment, "…there exist definite limitations on the scientific value of clinical reports of this nature…The surgeon's good and some of their worst results tend to drop out of follow-up before the surgeons are satisfied that they have truly good or complete long-term results." Reporting on ten years of follow-up among 73 patients with facial atrophy, Rees *et al* (1973) stated, "While an occasional treatment failure or complication has occurred, the overall results have been almost uniformly good." Despite good results with respect to facial contour, 4 patients experienced tissue firmness and one developed a hard nodule that required additional treatment (Rees *et al*, 1973). The one case of treatment failure was not due to silicone, but due to the advanced stage of underlying tissue atrophy. Assigning the cause of treatment failure to silicone would be an example of confounding by indication. That is, progression of the underlying condition for which silicone injection was administered, may be the root cause of the undesired outcome (Ashley, 1983).

Regarding a US FDA approved silicone injection clinical study among eight plastic surgeons (Braley, 1971), Edgerton (1977) stated that for the 1,300 original patients there was a "strikingly small number of complication." "A small number of patients did develop an unexplained recurrent nodular erythema in the injected sites." Lemperle *et al* (2003) injected ten filler materials intradermally to check biocompatibility and durability. One month following injection of silicone fluid, each micro-droplet was surrounded by a monolayer of fibroblasts and collagen fibres. At 9 months, granulomatous nodules in the dermis and *s.c.* tissue were surrounded by strands of fibrous tissue. The authors concluded, "…all substances…appeared to be clinically and histologically safe. None of the tested substances is without undesirable effects" Lemperle *et al*, 2003. Mutou (1970) reported unsatisfactory results from 16% of the 614 women in whom he had injected fluid silicone for mammary augmentation.

The pre-requisites for including human data in risk assessment are that exposure to the substance of interest must have occurred, the outcome or health effect should be adequately determined (ECETOC, 2009) and should meet the nine criteria as laid out by Hill (1965). Obviously the exposure should precede the effect and the effect should be determined by established criteria that are generally accepted as valid measures to determine disease endpoints or symptom definitions.

Epidemiology data to be considered reliable and useful without restriction would come from studies that employ accepted standards of rigor, e.g. population based cohort or case-control studies where exposure of interest and outcome are well-defined, temporality is known, treatment groups may be randomly assigned. The data are useful for quantifying a risk estimate for the likelihood of a particular exposure resulting in a particular outcome of interest (e.g. disease, injury). These experimental epidemiology studies (ECETOC, 2009) are assigned CoR 1, Reliable without Restriction (Appendix B). In a blind clinical study random assignment of three injection materials was used to treat 71 arthritic knees; 2 patients experienced increased pain (one received

silicone fluid) and no other side effects were observed (Corbett *et al*, 1970). Van Schie *et al* (2000) conducted a randomised double-blind trial among 29 diabetic neuropathic patients who received plantar injections of the active treatment (silicone) or placebo control (saline). Results confirmed the efficacy of silicone injections under metatarsal heads to reduce plantar pressures and thereby reduce the risk of foot ulceration (Van Schie *et al*, 2000). Chasan (2007) advised that the debate over the safety of silicone for soft tissue augmentation has spanned well over half a century and yet, no longitudinal study, with appropriate follow-up data, has been conducted.

Research and data pertinent to silicone gel is directly relevant to PDMS because the lightly cross-linked component of the gel is swollen with a high molecular weight PDMS fluid. The envelope for a breast implant is a polysiloxane elastomer composed of high molecular weight PDMS cross-linked between the polymer silicon atoms to form a 3-dimensional resin-like network of extremely high molecular weight (Lane and Curtis, 2005). A small amount of PDMS fluid will pass through the envelope (Barker *et al*, 1978). Since the 1994 assessment of linear PDMS many epidemiology studies have looked for potential associations between silicone materials and a variety of health outcomes and local complications.

Numerous epidemiology studies have examined a potential association between silicone gel-filled medical devices (primarily breast implants) and a variety of connective diseases, cancer and local complications. Since PDMS is the basic material for a variety of medical devices, these epidemiology studies are useful in examining the safety profile of PDMS.

Connective tissue disease

More than 30 epidemiology studies by investigators affiliated with prestigious institutions worldwide have addressed the question of whether silicone breast implants are associated with increased risks for various connective tissue diseases (CTDs) and other rheumatic disorders (Burns, 1994; Burns *et al*, 1996; Duffy and Woods, 1994; Dugowson *et al*, 1992; Edworthy *et al*,1998; Englert and Brooks, 1994; Englert *et al*, 1996; Friis *et al*, 1997; Gabriel *et al*, 1994; Giltay *et al*, 1994; Goldman *et al*, 1995; Hennekens *et al*, 1996; Hochberg *et al*, 1996; Lacey *et al*, 1997, Lacey, 1998; Laing *et al*,1996; McLaughlin *et al*, 1994, 1995a,b; Nyrén *et al*, 1998; Park *et al*, 1998a,b; Sánchez-Guerrero *et al*, 1995; Schusterman *et al*, 1993; Strom *et al*, 1994; Teel, 1997; Weisman *et al*, 1988; Wells *et al*, 1994; Wigley *et al*, 1992; Wolfe, 1995). When checking self-reported rheumatic conditions against medical records, Brinton *et al* (2004) found an over-report of rheumatic diseases among women with breast implants and among women without implants. They concluded that self-reporting of connective tissue disorders is influenced by reporting and surveillance biases (Brinton *et al*, 2004). Medical record verification of CTD diagnoses among 2,761 Danish women with breast implants found no significant increase in any definite CTD or combined CTDs (standardised rate ratio (SRR) 1.4, 95% CI 0.9, 2.0) among women with breast implants compared with women in the general population. Rates for

unspecified rheumatism were elevated among women with breast implants (SRR 1.9, 95% CI 1.6, 2.2) and among women who had undergone other plastic surgery procedures (SRR 1.5 95% CI 1.4, 1.7). There was no increased risk for confirmed diagnosis of fibromyalgia among women with breast implants compared with women who had undergone other plastic surgery procedures (hazard ratio 1.2, 95% CI 0.6, 2.1) (Fryzek *et al*, 2007). Hölmich *et al* (2003a) identified intact and ruptured breast implants via magnetic resonance imaging and found no difference in self-reported CTD among women with ruptured breast implants compared with women with intact implants.

Overwhelmingly the weight of medical and scientific evidence demonstrates that implants are not associated with these conditions. Case-control and cohort studies from Sweden, Denmark, Australia, Canada and the USA included a total of more than 550,000 women – 25,000 who had implants. Many sought to include every woman with breast implants in an entire country or a well-defined geographical area (Friis *et al*, 1997; Gabriel *et al*, 1994; Nyrén *et al*, 1998; Park *et al*, 1998a,b). About half of these studies had no funding from breast implant manufacturers; more importantly, the findings from all the studies were overwhelmingly consistent regardless of their funding source or geographic location.

Only one study reported a marginally increased relative risk (Hennekens *et al*, 1996). Since this study was based on self-reported data collected during the height of the controversy, the authors cautioned that their preliminary findings may be due to a reporting bias. Subsequent research to validate the self-reported diagnoses of CTD via medical record review, confirmed the diagnosis for CTD among 22.7% of women with implants and 24% among women without implants. After adjusting for confirmed cases, the relative risk of CTD associated with breast implants was 1.17 (95% CI 0.62, 1.90), i.e. not statistically significant (Karlson *et al,* 1999).

Several critical reviews and meta-analyses (Hochberg and Perlmutter, 1996; Silverman *et al*, 1996; Lamm 1998; Janowsky *et al*, 2000; Tugwell *et al*, 2001; Lipworth *et al*, 2004a), summarised the findings of the controlled epidemiology studies and concluded with remarkable consistency that breast implants are not causally associated with defined CTD or atypical CTD. A review of the epidemiology studies published prior to 1998 can be found in Chapter III of the National Science Panel report (Submission of Rule 706 National Science Panel Report, 1998) prepared by a US court-appointed scientific panel of four respected independent scientists in the areas of immunology, rheumatology, epidemiology and toxicology.

In addition, these studies were reviewed by a number of respected, independent bodies such as Health Canada (1998), Australian Therapeutic Goods Administration (1998), German Federal Institute for Medicine and Medical Products (1998), Gott and Tinkler (1994), UK Medical Devices Agency (1997), UK Independent Review Group (1998) and the US Institute of Medicine

(Bondurant *et al*, 2000). Consistently these independent bodies concluded there is no evidence of a link between breast implants and CTD or a constellation of symptoms referred to as atypical CTD.

Atypical connective tissue disease and other rheumatic conditions

With respect to atypical forms of CTD and other non-specific rheumatic conditions, the evidence suggests there is no condition unique to silicone breast implants (Friis *et al,* 1997; Edworthy *et al*, 1998; Nyrén *et al,* 1998; Wolfe, 1999). The 'atypical connective tissue disease' reported in women with implants appears to be fibromyalgia (sometimes called muscular rheumatism or fibrositis), a common condition known to the medical community long before the development of silicone breast implants (Wolfe, 1999).

The frequency with which fibromyalgia occurs is comparable among women with and without implants. For example, a Swedish study of more than 7,000 women with breast implants and 3,300 women with breast reduction surgery found no difference in the risk for fibromyalgia between these two groups of women (Nyrén *et al,* 1998). In a study of more than 14,000 Danish women who had breast reduction surgery, breast implants (about 2,500 of the 14,000 women) or breast cancer without implants, there was no association between breast implants and CTDs. The investigators did report an excess of muscular rheumatism among these women regardless of whether or not they had breast implants. The researchers concluded, "All cohorts in our study had an excess of the nonspecific diagnostic code of muscular rheumatism, which includes fibrositis and myalgia. A likely explanation of this finding would be that the excess of muscular symptoms is related to breast surgery per se, rather to any systemic effect of silicone breast implants."(Friis *et al,* 1997). In a review of six epidemiology studies concerning fibromyalgia among women with breast implants, Lipworth *et al* (2004b) concluded that the weight of epidemiologic evidence consistently failed to support an association between breast implants and fibromyalgia.

A Canadian study stated that women with implants self-reported more symptoms post-surgery than women in the control group. They acknowledged that this excess might be attributed to a selection or volunteer bias among women who participated in the study, to a recall bias due to the media surrounding the controversy, or to local complications such as capsular contracture that "…may lead to secondary symptoms such as muscle ache, numbness in the upper extremities, muscle tension headaches and the sensation of stiffness. It is plausible that these symptoms are mechanical in nature, rather than autoimmune." (Edworthy *et al,* 1998).

In a study of 533 patients with fibromyalgia, the author reported that "…FIB [fibromyalgia] is associated with SBI [silicone breast implants] when SBI both before and after FIB onset are considered together. Associations are not seen when only implants that preceded FIB are

considered…" (Wolfe, 1995). Temporality, was not established, that is, the adverse outcome must precede the suspected causal agent (Hill, 1965; ECETOC, 2009).

In its report, the National Science Panel concluded, "…many of these rheumatologic complaints reported are common in the general population… No distinctive features relating to silicone breast implants could be identified." (Submission of Rule 706, 1998).

The 1997 US National Institutes of Health workshop on atypical rheumatic diseases and silicone breast implants asked, "Given the current information, is there a reason to believe that a possible association may exist between atypical connective tissue disease and silicone breast implants?" The National Institutes of Health summary from the workshop stated: "Several studies have addressed the possible health impact of breast implants. The conclusion of these studies is that there is no association between implants and well-defined rheumatic disease such as rheumatoid arthritis, lupus erythematosus or scleroderma." Further, the panel concluded that "…before the existence of an association between atypical rheumatic disease and silicone breast implants can be substantively addressed, atypical rheumatic disease needs to be defined." Unless a condition can be defined, it cannot be measured and causality cannot be rigorously tested. If causality cannot be tested, the two events, i.e. exposure and outcome, are merely coincidental findings. The panel also recommended additional basic research on the components of silicone as well as biological responses to silicone (NIAMS, 1997).

As research continued to evaluate a potential association between silicone breast implants and autoimmune disease outcomes, findings were remarkably consistent with earlier reports (Breiting *et al*, 2004; Fryzek *et al*, 2001, 2007; Kjøller *et al*, 2001; Jensen *et al*, 2001a,b; Laing *et al*, 2001). For example, Fryzek *et al* (2001) found a wide range of self-reported symptoms among women with breast implants compared to women with breast reduction surgery but concluded: "…the lack of specificity and absence of dose-response relationships suggest that the excess of reported symptom is not causally related to cosmetic implants."

Breast cancer

In the plethora of legal claims regarding the potential health effects of silicone breast implants, it is instructive to remember that the first scientifically testable hypotheses involved breast cancer. Following a series of case reports and animal toxicology studies, it was postulated that women with silicone breast implants might be at increased risk for breast cancer. One theory held that implanted women might experience an increased incidence of carcinomas of the breast; another that there might be an increase in sarcomas of the breast; and still another that the implants might significantly delay cancer detection and thereby negatively impact the prognosis of those who did develop the disease. All three have been tested and none is supported by the data derived from controlled human health studies.

Parenthetically, there were three major reasons why it was possible to rigorously test the original hypotheses regarding silicone implants and breast cancer. One, breast cancer is a disease whose definition is well established in the medical and scientific community. This meant that different investigators could reliably study the same condition. Two, breast cancer is unfortunately a disease that strikes a significant number of women worldwide. According to Kelsey and Gammon, "it has been estimated by the American Cancer Society that 1 in 10 women will develop breast cancer at some time during her life" and many of these will ultimately die of the disease or its complications (Kelsey and Gammon, 1990). Three, because of its high frequency and fearful consequences, breast cancer has been and continues to be a condition of interest to a large number of investigators. As a consequence, it was possible to add questions regarding breast implants into ongoing research studies and thereby obtain answers relatively rapidly.

Breast Cancer Incidence

Numerous epidemiology studies report that the breast cancer experience among women with breast implants is equivalent to or more favourable than women who don't have these medical devices. One of the earliest was by Deapen and colleagues (Deapen *et al*, 1986). In a study of 3,111 women in Los Angeles, they observed 9 cases of breast cancer whereas 15.7 were expected (observed to expected was 57%). Additional years of follow-up for this group, yielded statistically significant reductions in breast cancer risk, 63% risk at 14.4 years (95% CI 42.8, 89.5) (Deapen *et al*, 1997) and 69% risk at 15.5 years of follow-up (95% CI 50, 93) (Deapen, 2007). Similar results were reported in a population-based study conducted by researchers affiliated with the U.S. National Cancer Institute (Brinton *et al*, 1996). In this case-control study of 2,174 breast cancer cases and 2,009 controls, the estimate of relative risk associated with silicone breast implants was quite low (0.6, 95% CI 0.4, 1.0) and even lower risk among those with breast implants for ten or more years (0.46, 95% CI 0.2, 0.9). In a retrospective cohort study to examine breast cancer rates among women with breast implants from 18 plastic surgery clinics in southern U.S., Brinton *et al* (2000) concluded that breast implants do not appear to alter the risk for breast cancer. Based on data from the Surveillance Epidemiology and End Results (SEER) Program of the National Cancer Institute, the researchers expected 152.2 cases of breast cancer but found 136 cases. The standardised incidence ratio (SIR) was 0.9 (95% CI 0.8, 1.1). In a state-wide study linking Connecticut hospital discharge files to the state tumour registry women who had received breast implants were at no greater risk for breast cancer than women who underwent tubal ligation surgery (Kern *et al*, 1997).

Findings based on data for 11,676 women who underwent cosmetic breast augmentation in the Canadian province of Alberta showed fewer than half the expected number of cases of breast cancer among women with breast implants (Berkel *et al*, 1992). Reanalysis of the data maintained a decreased risk estimate (Bryant and Brasher, 1995). A cohort study of 24,558 women with breast implants from two Canadian provinces, Ontario and Quebec, found

statistically significant reduced rates of breast cancer for women with implants compared with both the general population and women having other plastic surgery procedures (Brisson *et al*, 2006).

Statistically significant reduced rates for breast cancer were seen among patients in France who received breast reconstruction with silicone breast implants following breast cancer surgery (Petit *et al*, 1994). Research in Denmark evaluated the health outcomes for 1,135 women hospitalised for cosmetic breast implantation and reported equivalent rates for breast cancer; SIR was 1.0 (95% CI 0.4, 2.0) (Friis *et al*, 1997). With additional years of follow-up and inclusion of outpatient plastic surgery practices, breast cancer remained less than expected although not statistically significant (Mellemkjær *et al*, 2000; Friis *et al*, 2006). More than 2,000 Finnish women with breast implants had fewer than expected cases of breast cancer compared with the general population (SIR 0.9, 95% CI 0.6, 1.3) and even among those with more than 10 years of exposure, rates remained less than expected (SIR 0.5, 95% CI 0.2, 1.0) (Pukkala *et al*, 2003). Using a nationwide linked registry, investigators in Sweden identified women who had received breast implants for non-medical (cosmetic) reasons (McLaughlin *et al*, 1995a). With an average duration since implant of 11.7 years, they observed 7 breast cancers whereas 11.2 were expected (SIR 0.63, 95% CI 0.3, 1.3). With additional years of follow-up, they observed 18 cases and 25.0 expected (SIR 0.7, 95% CI 0.4, 1.1) (McLaughlin *et al*, 1998) and with up to 37 years of follow-up (mean 18.4 y, range 0.1 - 37.8 y) the incidence of breast cancer was below expectation (SIR 0.7, 95% CI 0.6, 1.0) (McLaughlin *et al*, 2006). In a pooled analysis of population-based studies from Sweden and Denmark, Lipworth *et al* (2009), reported a statistically reduced risk for breast cancer (SIR 0.73; 95% CI 0.58, 0.90).

In their review of silicone breast implants and cancer, Herdman and Fahey (2001) noted the strikingly consistent epidemiology studies that show no association of silicone implants and breast cancer. They concluded that "…there are sufficient studies of sufficient quality to support a finding that there is no relationship between breast implants and breast cancer." In their review of surgical implants and carcinogenic risk to humans, the International Agency for Research on Cancer (IARC, 1999) stated: "There is evidence suggesting a lack of carcinogenicity in humans of breast implants, made of silicone, for female breast carcinoma." In their review of the safety of breast implants, the Institute of Medicine (Bondurant *et al*, 2000) concluded that the "…available evidence does not support an association of silicone or silicone breast implants with experimental carcinogenesis (other than rodent solid-state; carcinogenesis), primary or recurrent breast cancer, breast sarcoma or other solid tumours, lymphoma or myeloma. If anything, evidence (though limited) suggests a lower risk of breast cancer in women with silicone breast implants."

Detection of breast cancer

In response to concerns about the opacity of the breast implant and the possibility that it could mask detection of breast tumours during mammography, several studies examined the size and stage of the tumour at the time of detection as well as the survival rates for women with breast implants and breast cancer. The studies consistently concluded that women with breast implants who are diagnosed with breast cancer do not present at a later stage and do not experience a poorer prognosis for survival (Birdsell *et al*, 1993; Clark *et al*, 1993; Brinton *et al*, 1996; Petit *et al*, 1998; Brinton *et al*, 2000; Deapen *et al*, 2000; Hölmich *et al*, 2003b; Handel and Silverstein, 2006; McLaughlin *et al*, 2006; Friis *et al*, 2006). While numerous studies have disproven a causal link between breast implants (and its component PDMS) and cancer, silicone fluid migration from the implant or from injection may lead to granuloma formation. Palpable granulomas may be indistinguishable from tumours without additional diagnostic measures.

Cancer at other sites

Among a Los Angeles cohort of women with breast implants (mean follow-up of 15.5 y), Deapen *et al* (2007) found a deficit for breast cancer and a significant increase in cancer of the lung and bronchus (SIR 2.14; 95% CI 1.42, 3.09) and vulvar cancer (SIR 3.47; 95% CI 1.39, 7.16). Brinton *et al* (2001a) identified statistically significant increased rates for cancers of the stomach, cervix, vulva and brain as well as for leukaemia among women with breast implants compared with the general population. When compared with women undergoing other types of plastic surgery procedures only respiratory and lung cancers were statistically elevated. In a pooled analysis of Scandinavian women with breast implants, follow-up ranged from 0.1 to 37.8 years (mean 16.6 y). Breast cancer incidence was statistically decreased and lung cancer was statistically increased (SIR 1.64; 95% CI 1.10, 2.36) (Lipworth *et al*, 2009). Previous studies of women in this population (Fryzek *et al*, 2000; Kjøller *et al*, 2003) showed a 2-fold increase in smoking among women with breast implants leading the authors to conclude cigarette smoking as the likely explanation for the excess lung cancer (Lipworth *et al*, 2009). Among 24,588 Canadian women from Ontario and Quebec, Brisson *et al* (2006) found a statistically reduced incidence of breast cancer (RR 0.64; 95% CI 0.53, 0.79) among women with breast implants when compared with women who had other types of plastic surgery. There were no other significant findings for any of the types of cancers included in the study. Cancer incidence among Finnish women with breast implants revealed no significant excess or deficit for any type of cancer and the authors found fewer than expected cases of breast cancer (Pukkala *et al*, 2002). Non-melanoma skin cancer was statistically elevated among women with breast implants (SIR 2.1, 95% CI 1.5, 2.7), but authors relate this to possible increased exposure to sun and indoor tanning facilities (Friis *et al*, 2006).

While Brinton *et al* (2001b) identified a significant increase in brain cancer among women with implants compared with the general population, no excess of brain or nervous system cancer was detected in a large Danish cohort (Mellemkjær *et al*, 2000) even when the cohort was followed for an average of 12.7 years, with the longest implant duration being 30 years (Friis *et al*, 2006). In addition, other cohorts showed no increased incidence of brain cancer (McLaughlin *et al*, 1998; Pukkala *et al*, 2002; Deapen *et al*, 2007; Lipworth *et al*, 2009). Use of death certificate data in the Brinton *et al* (2001b) study may have contributed to the apparent elevated risk for brain cancer since death certificates may reflect metastases from other sites rather than the brain as the primary site (McLaughlin and Lipworth, 2004).

Women who received implants in private clinics showed a statistically elevated risk for non-Hodgkin's lymphoma; none of the 6 cases involved the breast as a primary site and their histology was different. The variation in histology, primary site and elevated risk among women from the public hospital argue against a causal relation with silicone implants (Friis *et al*, 2006). A non-significant excess of non-Hodgkin's lymphoma was found among Finnish women with cosmetic breast implants (Pukkala *et al*, 2002), but three larger studies showed no elevation in risk (Deapen and Brody, 1992; McLaughlin *et al*, 1998, 2006; Brinton *et al*, 2000). Thus, chance is a likely explanation (Friis *et al*, 2006).

A small percentage of breast implants were manufactured with a polyurethane foam (PUF) textured external surface. The US FDA (1996) evaluated the metabolism of PUF to toluene diamine (TDA) and measurable, albeit extremely low, levels of TDA in the urine of women with polyurethane coated implants. Based on these findings, the FDA recommended that "women with polyurethane foam-covered breast implants should not have them removed based solely on concerns about cancer from TDA." There was one case of multiple myeloma in a study of Swedish women (McLaughlin *et al*, 1998, 2006). There were no cases found among women from Denmark (Friis *et al*, 1997, 2006), Finland (Pukkala *et al*, 2002) or the USA (Brinton *et al*, 2001a). Among 3,182 women in Los Angeles followed for 37,589 person-years there were no plasma cell tumours observed when 0.57 cases would be expected (Deapen and Brody, 1995).

Nine cases of non-Hodgkin's lymphoma (no case was in or near the breast) were identified among women with breast implants (Lipworth *et al*, 2009). Deapen *et al* (2007) identified a non-statistically elevated number of cases of non-Hodgkins lymphoma. Forty cases of anaplastic large-cell kinase (ALK)-negative, T-cell, anaplastic non-Hodgkin lymphoma (T-ALCL) have been reported among women with breast implants (Lechner *et al*, 2011). This case series suggests that implants with a textured envelope, using the lost salt method, may lead to increased risk for this rare malignancy. The US FDA (2011b) recently published a literature review investigating the case reports of ALCL among women with breast implants and recommended that health care providers report all cases to FDA.

Sarcoma

The Oppenheimer effect is a phenomenon that occurs in rodents (Oppenheimer *et al*, 1948); there is no evidence that it operates in humans. And it is not a phenomenon unique to silicone. Sarcomatous tumours occur at a fairly high frequency at the site of foreign bodies, up to 30 or 40%, when materials of a sufficient size and shape are implanted in rodents. This happens irrespective of the chemical composition of the implanted material. It has been observed with glass, gold, stainless steel, other metals used in medical devices, various types of non-silicone polymers and even money (Brand *et al*, 1976; Moore and Palmer, 1977). Over ten years ago, the Commissioner of the FDA concluded – vis-à-vis silicone breast implants – that these types of tumours "are unlikely to occur in humans" and that insufficient evidence exists "to establish an 'unreasonable and substantial risk' that could be attributed to the device." (Young, 1988; Wolfe, 1988). In their review of breast implants and cancer, Brinton and Brown (1997) note "... two expert committees commissioned by the FDA to review this issue concluded that the tumors were due to nonspecific solid-state carcinogenesis and that this phenomenon in rodents did not appear to be relevant in humans."

Epidemiology information indicates that humans are not at increased risk to solid state tumorigenesis as evidenced by the number of humans with *various* types of implanted pins, plates, staples, screws, sutures, shrapnel, shunts, tubes, pacemaker leads and other medical devices. For example, Morgan and Elcock analysed data from a case-control study based on military medical records (Morgan and Elcock, 1995). They found no statistically significant association between soft tissue sarcomas and various types of orthopaedic materials or other metal or plastic implants (odds ratio 0.5, 95% confidence interval 0.05 - 2.30).

Relative to breast implants, if the use of silicone materials resulted in the development of breast sarcomas, one would expect to see an increase in the occurrence of these tumours in conjunction with the increase in the use of breast implants over time. In such an ecologic study conducted in the USA and based on the Surveillance, Epidemiology and End Results (SEER) data, May and Stroup (1991) noted that the incidence rates for fibro-sarcoma and other soft-tissue sarcomas of the breast among women were very low and did not increase over time. Furthermore, no sarcomas of the breast were observed in various analytic epidemiology studies conducted in the USA (Deapen *et al*, 1997), Denmark (Friis *et al*, 1997), Sweden (McLaughlin *et al*, 1998), Canada (Birdsell *et al*, 1993) or Great Britain (Park *et al*, 1998a,b).

In summary, although solid state tumorigenesis is an interesting phenomenon that occurs in rodents, medical implants – irrespective of material composition– are not related to an increased risk of sarcomas in humans.

Silicone to silica

In his document to the European Parliament, Garry (1999) cited numerous reports that allege an immune response among women with silicone breast implants. In support of this contention, he suggested that silicone from the implants breaks down to silica in the human body. This hypothesis has been examined and discarded by numerous independent scientific bodies including the science panel convened by Judge Jones in Oregon (which subsequently excluded this work for consideration in litigation) (Stenzel-Poore, 1996), the IRG (1998) and the Submission of Rule 706 National Science Panel (1998) convened by Judge Samuel Pointer under the US Federal Rules of Evidence. Work by Shanklin and Smalley (1996) claimed to observe crystalline silica via optical microscopy in tissues surrounding breast implants. This claim has been refuted by Pasteris *et al* (1999) who state that, "Birefringent materials are common in breast tissue from women with and without breast implants." Further, they suggest that "…researchers should be held to a more rigorous standard than polarized-light microscopy for the identification of foreign materials in tissue."

In support of their hypothesis of the degradation of silicone to silica with a resulting cell-mediated immune response, Smalley *et al* (1995) developed a blood test to use as a screening and diagnostic tool among women with breast implants and their offspring (Shanklin, 1997). In a blind test of this procedure, Young (1996) submitted sera from women with and without breast implants. There were no discernible differences in the results, that is, the test results were not reliable based on the presence or absence of exposure to silicone.

In sharp contrast to the careful reviews of the scientific literature in this controversy, others have made unfounded recommendations, some of which are dangerous. For instance, some doctors suggest that women with breast implants have them removed before they get pregnant (Cohen, 1996). Carried to the extreme, this precautionary guidance led to further musing that women with breast implants who are pregnant consider getting an abortion (WNBC, 1994). One doctor recommended that children of mothers with breast implants be tested and treated with an antimalarial drug (Shanklin, 1997) that is also used in treatment of CTD. According to physicians with the Motherisk Team at the Hospital for Sick Children in Toronto, this drug was "…never approved for use in children and is highly toxic to them in overdose" (Koren and Ito, 1998).

10. HAZARD (RISK) ASSESSMENT

The total worldwide use of PDMS was estimated to be 238 kt in 2007, including 77 kt in the 27 member states of the EU ('EU-27'), 68 kt in the USA, 7 kt in Japan and 86 kt in the rest of the world. A percentage breakdown of uses in the EU-27 is given in Table 14. The fractions, apart from sealants, include the volumes sold via distributors (CES, 2010).

Table 14: Uses of PDMS in the EU-27 in 2007 (CES, 2010)

Fraction (%)	Use
	Processing aid
4.5	Defoamer / antifoam
3.5	Release agent
8.3	Detergent
	Cosmetic, toiletry, medicinal / pharmaceutical
0.2	Antiperspirant
17.6	Skin and hair care
1.9	Medicinal / pharmaceutical
1.4	Polish, coating
1.6	Paper coating
10.2	Textile
8.2	Chemical intermediate
	Other
6.4	Electrical
1.5	Mechanical fluid
22.9	Sealant
1.3	Reprography
0.4	Heat transfer fluid
10.1	Miscellaneous

PDMS fluids are colourless and their vapour pressure is not measurable. PDMS is stored under nitrogen and transported in closed containers. They are not classified as dangerous under European or other chemical laws or under international transport regulations. Special packaging and labelling is not required.

10.1 Environment

According to the EU guidance on risk characterisation, environmental risk assessment is conducted by comparing the predicted environmental concentration (PEC) with the predicted no effect concentration (PNEC) in order to determine a risk characterisation ratio (RCR). A RCR > 1 highlights a potential cause for concern (ECHA, 2008c).

For single substances, the computer model EUSES (European Union System FOR THE Evaluation of Substances) is normally used for calculating the RCR. This model is not suitable for polymers. Therefore the approach taken here has been to use measured concentrations as the PECs and to compare these with PNECs derived from the most environmentally relevant compartments. The PNEC is derived from the no observed effect concentration (NOEC) from a chronic study divided by an appropriate assessment factor. The assessment factor depends on the number of studies available at different trophic levels. Where three long-terms studies are available on three trophic levels, the assessment factor is 10. (ECHA, 2008b).

A series of studies measuring the concentrations of PDMS in different environmental compartments were made pre-1990 and are summarised in Fendinger *et al* (1997a). These studies tended to concentrate on likely worst case scenarios such as the outfalls of waste water treatment plants that had not been modernised and soils receiving high loadings of sewage sludge waste. The approach therefore taken has been to take a 90^{th} percentile concentration as being the PEC value as recommended by EPA (US EPA, 1989 cited by Powell *et al*, 1999).

10.1.1 PNEC calculations

Aquatic environment

As the solubility in water of PDMS is not measurable using currently available techniques and the substance is rarely if ever detected in water, aquatic toxicity testing using the aqueous phase has never been a priority. Thus most of the studies pre-date the need for GLP compliance and the use of recognised protocols. Furthermore the algal toxicity data are inadequate and the only available chronic fish study, the fish early life-stage test, was judged to be not reliable. The weight of evidence is that no adverse effects have been observed even at concentrations far in excess of the water solubility or via long-term feeding.

The feeding study is equivalent to a very high exposure, which could not be achieved via the water. Therefore, in the absence of chronic effects, it was not possible to calculate a PNEC and consequently a traditional RCR has not been derived for the aquatic phase. Even though a

RCR cannot be calculated, one can be estimated. Given the fact that the PNEC is greater than the water solubility and the PEC is less than water solubility, the RCR must therefore be < 1.

For the sediment phase, three long-term NOECs are available for the algivorous *Hyallela azteca*, the detritus-feeding *Chironomus tentans* and the worm *Nereis diversicolor* (Table 9). The studies performed to date have failed to show any adverse effects so it is therefore not possible to derive a NOEC. The estimated NOEC would be > 1,000 mg/kg. Since results on three trophic levels are available, then $PNEC_{Sediment}$ value can be estimated as being > 100 mg/kg.

Terrestrial environment

For risk assessment, chronic NOECs are available for three organisms, representing three trophic levels (Table 10). No effects were seen in the earthworm *Eisenia foetida* or soil microflora (NOEC > 1,000 mg/kg dry weight). An assessment factor of 10 is therefore applied to the lowest NOEC, in this case, for the springtail (*Folsomia candida*) of 230 mg/kg dry weight. The PNEC is therefore 23.0 mg/kg dry weight in soil.

10.1.2 PEC calculations

Aquatic environment

The aquatic environment has not been addressed as PDMS is effectively insoluble in water and no valid environmental measurements therefore exist.

Fendinger *et al* (1997a) plotted the concentration distributions of PDMS in sediments and the 90th percentile concentration determined by regression. This analysis demonstrates that at more than 90% of the locations, PDMS concentrations in sediment are < 26 mg/kg. The 90^{th} percentile concentration was selected for the basis of the exposure assessment, because it is considered a reasonable worst-case exposure concentration.

None of the values used in this assessment exceeded 100 mg/kg.

The sediment monitoring data used Fendinger in this assessment did not include samples collected from the New York Bight (Pellenbarg, 1979a) or samples collected by Powell *et al* (1999) from the Little Calumet River. The samples collected from the New York Bight (maximum concentration 125 mg/kg) were not included in this analysis, because the sediments from this location represent PDMS loadings that would occur from off-shore sludge disposal, which is no longer practiced. Samples collected by Powell *et al* (maximum concentration 314 mg/kg, mean 78 mg/kg) from the Little Calumet River were not included in the assessment, because some of these samples were collected from a man-made canal

whose only source of water is one of Chicago's primary WWTPs. The man-made canal directs effluent flow from the treatment site into the upper portions of the Calumet River and is not considered a natural waterway.

Terrestrial risk assessment

Fendinger *et al* (1997a) also plotted the concentration distributions of PDMS in soils and determined the 90th percentile concentration by regression. This analysis demonstrates that at more than 90% of the locations, PDMS concentrations in soils are < 17 mg/kg. The 90th percentile concentration was selected for the basis of the exposure assessment, because it is considered a reasonable worst-case exposure concentration.

In the analysis by Fendinger, monitoring information from locations representative of sludge amendment practices common at the time were used, along with sediments collected in the vicinity of treatment plants representative of current treatment practices. Measurements from pristine soils and sediments were not included in the analysis, because the intent was to evaluate the range of concentrations in soils and sediments influenced by sources of PDMS. Based on these criteria, sludge amended soils that had received cumulative sludge loadings of > 1,000 t/ha were not included as part of the assessment. The 1,000 t/ha cumulative sludge amendment level (which represents a 10 t/y amendment for 100 y) was chosen because this cumulative sludge amendment level is the same as that used in the US EPA (2002) risk assessment calculations for sludge disposal.

10.1.3 Risk characterisation ratio

Aquatic environment

The RCR for the water phase has not been calculated for reasons outlined above.

It is also not appropriate to calculate the RCR for sediment as no adverse effects have been observed, however it is possible to estimate that the PNEC is > 100 mg/kg.. The ratio of the PEC (26 mg/kg) to PNEC (> 100 mg/kg) is < 0.26. This value is below one and demonstrates that PDMS does not pose a threat to the sediment phase in the environment.

Terrestrial Environment

The RCR for the terrestrial environment is the ratio of the PEC (17 mg/kg) to PNEC (23 mg/kg), i.e. 0.74. This value is below one and demonstrates that PDMS does not present a risk to the

terrestrial environment. This can be regarded as a conservative value given that it is based on outdated sludge amendment practices

10.2 Animal/Human Health

PDMS has a low order of toxicity.

PDMSs ranging in viscosity from 10 cSt to over 100,000 cSt have been subjected to a wide range of safety studies. These studies include acute, subacute, subchronic, chronic and carcinogenicity studies as well as dermal and eye irritation, skin sensitisation, mutagenicity, developmental/reproductive and immunotoxicity studies. In all of these studies, PDMS exhibited a low order of toxicity.

In acute oral studies, the LD_{50} was > 2 g/kgbw in one study and > 5 g/kgbw in another study. The acute dermal and *i.p.* LD_{50} was > 2 g/kgbw and in an acute aerosol inhalation study, the median lethal concentration LC_{50} was > 696 mg/m^3 and > 11,582 mg/m^3 for 10,000 cSt and 100,000 cSt PDMS, respectively. PDMS was shown to be essentially non-irritating in both dermal and eye irritation studies and was considered a non-sensitiser in a Guinea Pig Maximisation Test.

No clinical signs of toxicity and no microscopic lesions were observed in selected tissues with 10 cSt or 350 cSt PDMS in subacute feeding studies at concentrations up to 10% (100,000 ppm) in the diet. The NOAEL for both of these materials in these studies was > 100,000 ppm. In a subacute dermal study with 350 cSt PDMS, the NOAEL was > 1 g/kgbw/d.

Four subchronic oral feeding studies have been conducted with 10, 35, 350 or 1000 cSt PDMS. Feed concentrations of PDMS in these studies ranged from 0.5% (5,000 ppm) to 5.0% (50,000 ppm). The NOAEL from these studies was > 50,000 ppm (5%).

A combined chronic/carcinogenicity feeding study with 10 cSt PDMS was conducted with doses ranging from 0 to 1,000 mg/kgbw/d. No test material pre-neoplastic or neoplastic changes were observed and the NOAEL for this study was > 1,000 mg/kgbw/d. Furthermore, PDMS with viscosities ranging from 50 cSt to 60,000 cSt are non-mutagenic.

No effects were seen in reproductive or developmental studies with 350 cSt PDMS. The NOAEL for these studies was > 1,000 mg/kgbw/d and no significant immunotoxicity effects have been observed.

Pharmacokinetic studies using oral doses of ^{14}C-PDMS 10 or 350 cSt up to 1,000 mg/kgbw, which included whole body autoradiography, showed no significant radioactivity outside of the gastrointestinal tract. Virtually all (99.6 - 99.8%) of the recovered dose was in faeces.

Pharmacokinetic studies with 10 or 350 cSt ^{14}C-PDMS indicated very little, if any, dermal absorption ($\leq$ 0.5%).

PDMS with a viscosity of 10 cSt has a number-average molecular weight of 1,300 and this material has been shown to have a very low or non-existent dermal or oral absorption ($\leq$ 0.5%). Therefore, any PDMS with a viscosity > 10 cSt would also have essentially no potential for percutaneous penetration. This has been shown to be true in virtually all of the safety studies conducted to date with any PDMS with a viscosity > 10 cSt. PDMS has a very low order of acute, subacute, subchronic, reproductive/developmental, chronic/carcinogenicity and immunological toxicity. The NOAELs in these studies have been shown to be greater than the highest dose tested. Likewise, these materials are non-irritating and are non-sensitisers. Therefore, PDMS in not expected to show a significant risk to human health when used in applications applied to the skin.

Table 15 provides a list of the NOAEL derived from the various safety studies conducted on PDMS of various viscosities.

Table 15: No observed adverse effect levels from PDMS studies

Viscosity (cSt)	Route	NOAEL		Reference
Subacute		(ppm)	(%)	
10	Oral	> 100,000	10	Tompkins, 1995a
350	Oral	> 100,000	10	Tompkins, 1995b
		(mg/kgbw)		
350	Dermal	> 1,000		Blee, 1999b
Subchronic		(ppm)		
35, 350, 1,000	Oral	> 100,000	10	Hoffman *et al*, 1989
35, 350, 1,000	Oral	> 100,000	10	Manston *et al*, 1989
10	Oral	> 50,000	5	Tompkins, 1995d
350	Oral	> 50,000	5	Tompkins, 1995c
35	Oral	> 50,000	5	King and Siddiqui, 1989
Chronic		(mg/kgbw)		
10	Oral	> 1,000		Mertens, 2003
Carcinogenicity		(mg/kgbw)		
10	Oral	> 1,000		Mertens, 2003
Reproductive		(mg/kgbw)		
350	Oral	> 1,000		Campbell and Sewell, 1969
350	Dermal	> 3,000		Campbell and Sewell, 1969
Gel	Implant	> 28,500		Siddiqui, 1994a,b
Developmental		(mg/kgbw)		
Gel	Implant	> 28,500		Siddiqui, 1994a,b
10, 350	Oral	> 1,000		Blee, 1999c,d

No adverse effects have been seen in virtually all safety studies conducted on PDMS ranging in viscosities from 10 to > 100,000 cSt. The NOAELs in these studies have always been greater than the highest dose tested in the study (Table 15). No PDMS with a viscosity > 10 cSt has shown eye or dermal irritation, or dermal sensitisation. All have been shown to be non-mutagenic. Both oral and dermal pharmacokinetic studies conducted with 10 cSt or 350 cSt PDMS have shown essentially no potential for absorption. Therefore, any PDMS with a viscosity > 10 cSt is not anticipated to pose an undue risk to human health.

10.3 Summary and Conclusion

Extensive environmental, animal and epidemiology studies have been conducted on PDMS. In all cases PDMS has been shown to pose little or no risk to the environment or human health.

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11.3 Databases consulted

The bibliography of the previous ECETOC review on linear PDMS was used as a starting point (ECETOC, 1994).

A search of the literature was made at the Royal Belgian Library (Brussels, Belgium), yielding a list of titles and abstracts of publications from 1994 to 2008. Databases used included Chemical Abstracts, Medline and Toxcenter, all provided on line by STN (Science and Technology Network International, Eggenstein-Leopoldshafen, Germany).

Additional information was obtained from CES (European Silicone Industry Association, Brussels, Belgium), SEHSC (Silicones Environmental Health and Safety Council, Herndon, Virginia, USA) and SIAJ (Silicone Industry Association of Japan, Tokyo, Japan).

APPENDIX A: SYMBOLS, UNITS AND ABBREVIATIONS

≈	Approximately
≥	More than or equal to
×	Multiplied by, fold
~	Estimated
<	Less than
>	More than
µ	Micro- (10^{-6})
·	multiplied by
·OH	Hydroxyl radical
^{1}H	Proton
AAS	Atomic absorption spectroscopy / spectrometer
AES	Atomic emission spectroscopy / spectrometer
BBA	Biologische Bundesanstalt für Land und Forstwirtschaft (Braunschweig, Germany)
bw	Body weight
CAS	Chemical Abstracts Service
CES	Centre Européen des Silicones
CoR	Code of reliability
cSt	Centistoke
CTD	Connective tissue disease
d	Day
D_4	Octamethylcyclotetrasiloxane
D_5	Decamethylcyclopentasiloxane
DMSD	Dimethylsilanediol
D-unit	Dimethylsiloxy unit
EC_{50}	Median effect concentration
EQC	Equilibrium criteria
FDA	Food and Drug Administration
FIB	Fibromyalgia
FID	Flame ionisation detection
g	Gramme
GC-MS	Gas chromatography-mass spectrometry
GPC	Gel permeation chromatography
h	Hour
ha	Hectare
hPa	Hectopascal
HPLC	High performance liquid chromatography
i.p.	Intraperitoneal

ICP	Inductively coupled plasma
IgE	Serum immunoglobulin
IUPAC	International Union of Pure and Applied Chemistry
JACC	Joint Assessment of Commodity Chemicals
k	Kilo- (10^3)
K_d	Solid-water distribution coefficient
K_{oc}	Partition coefficient (organic carbon-water)
K_{ow}	Partition coefficient (octanol-water)
l	Litre
LC_{50}	Median lethal concentration
LC-MS	Liquid chromatography-mass spectrometry
LD_{50}	Median lethal dose
ln	Natural logarithm
LOEC	Lowest-observed effect concentration
LOEL	Lowest-observed effect level
log	Common logarithm
LT_{50}	Median survival time
m	Metre, milli- (10^{-3})
M	Trimethylsilyl end group
min	Minute
mol	Mole
MS	Mass spectrometry
n	Number, nano- (10^{-9})
NIH	National Institutes of Health
NMR	Nuclear magnetic resonance
No.	Number
NOAEL	No observed adverse effect level
NOEC	No observed effect concentration
PDMS	Polydimethylsiloxane
PNEC	Predicted no effect concentration
P_{ow}	K_{ow}
ppb	Parts per billion (10^9), by volume
ppm	Parts per million (10^6), by volume
ppt	Parts per trillion (10^{12}), by volume
s	Second
s.c.	Subcutaneous
S9	Supernatant of centrifuged 9,000 × g liver homogenate
SBI	Silicone breast implants
SEHSC	Silicone Environmental, Health and Safety Council
SIR	Standardised incidence ratio

sp.	Species
t	Tonne, time
TDA	Toluene diamine
wk	Week
WWTP	Wastewater treatment plant
y	Year

APPENDIX B: CRITERIA FOR RELIABILITY CATEGORIES

Adapted from Klimisch *et al*, 1997

Code of Reliability (CoR)	Category of reliability
1	Reliable without restriction
1a	'Good laboratory practice' guideline study (OECD, EC, EPA, FDA, *etc*.)
1b	Comparable to guideline study
1c	Test procedure in accordance with national standard methods (AFNOR, DIN, etc.)
1d	Test procedure in accordance with generally accepted scientific standards and described in sufficient detail
2	Reliable with restrictions
2a	Guideline study without detailed documentation
2b	Guideline study with acceptable restrictions
2c	Comparable to guideline study with acceptable restrictions
2d	Test procedure in accordance with national standard methods with acceptable restrictions
2e	Study well documented, meets generally accepted scientific principles, acceptable for assessment
2f	Accepted calculation method
2g	Data from handbook or collection of data
3	Not reliable
3a	Documentation insufficient for assessment
3b	Significant methodological deficiencies
3c	Unsuitable test system
4	Not assignable
4a	Abstract
4b	Secondary literature
4c	Original reference not yet available
4d	Original reference not translated
4e	Documentation insufficient for assessment

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www.sciencedirect.com/science/journal/00275107

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Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis, Volume 600, Issues 1-2
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