European Union proposal to list Octamethylcyclotetrasiloxane (D4), Decamethylcyclopentasiloxane (D5) and Dodecamethylcyclohexasiloxane (D6) in Annex B to the Stockholm Convention on Persistent Organic Pollutants

1. Introduction

1. The cyclosiloxanes octamethylcyclotetrasiloxane (D4), decamethylcyclopentasiloxane (D5) and dodecamethylcyclohexasiloxane (D6) are cyclic volatile methyl siloxane (cVMS) substances with four, five and six siloxane groups, respectively. They have been grouped for the purposes of this proposal as they have a similar chemical structure and hazard profile and D4, D5 and D6 could substitute each other which could lead to regrettable substitution. There are no known natural sources of D4, D5 and D6. They are manufactured and used in a variety of sectors such as the construction (sealants, paints and coatings), automotive (parts and lubricants), electronics, pulp and paper, oil and gas, medical and aerospace/defence sectors.

2. D4, D5 and D6 have been identified as high production volume (HPV) chemicals by the Organisation for Economic Co-operation and Development (OECD, 2007) and the US Environmental Protection Agency (US EPA, 2007). According to US EPA (2022), total production volume of D4 in 2015 was between 750 million and 1 billion pounds (equivalent to 340,194−453,592 tonnes/year). In the European Union (EU), D4, D5 and, to a lesser extent, D6 are high tonnage substances. The three substances have been registered under the Registration, Evaluation and Authorisation of Chemicals (REACH) Regulation. D4 is manufactured and/or imported to the EEA at 100,000− 1,000,000 tonnes/year, D5 at 10,000−100,000 tonnes/year and D6 at 1,000−10,000 tonnes/year. In the EU, they are mainly used as monomers for the production of silicone polymers, in which they can remain as residual impurities. They are also used as substances on their own or in the formulation of various mixtures that are subsequently used in by consumers and professionals in wide-dispersive applications (e.g. cosmetic products, household cleaning products, medicinal products). Environment Canada, Health Canada (2008abc) indicated the use of silicone formulants containing D4, D5 and D6 in certain pesticide products. Their presence as intentional constituents or impurities in a very wide variety of consumer products and as residual impurities in silicone polymers means that they have significant potential for environmental release. According to Environment Canada, Health Canada (2008abc), the application of D4-, D5- and D6-containing pesticides on crops and the disposal of sewage sludge on agricultural lands, by incineration and by deposit in landfills will result in the release of D4, D5 and D6 to environmental media. Monitoring data indicate that D4, D5 and D6 are widely dispersed in the environment and are found in remote regions.

3. D4, D5 and D6 have been identified in the EU under REACH as Substances of Very High Concern (SVHC) and included in the Candidate List for Authorisation in June 2018 due to their Persistent, Bioaccumulative and Toxic (PBT) and/or very Persistent, very Bioaccumulative (vPvB) properties[1]. Furthermore, the use of D4 and D5 in wash-off cosmetic products has been restricted in EU under the REACH Regulation since 31 January 2020[2] and another REACH restriction for D4, D5 and D6 in consumer and professional products is under decision making by the European Commission (ECHA, 2016ab, 2019 and 2020).

4. This proposal specifically addresses the information requirements and screening criteria of Annex D in the Stockholm Convention on Persistent Organic Pollutants (POPs) and summarises relevant evidence relating to the screening criteria for persistence, bioaccumulation, long-range environmental transport and adverse effects. The proposal is based on the PBT/vPvB assessments performed at the EU level under the REACH Regulation (ECHA 2018a,b,c), information from peer-reviewed scientific journals as well as grey literature.

2. Chemical identity

5. Table 1 lists the substance identity and the structure of the cyclic volatile methyl siloxanes based on ECHA (2018a,b,c). Table 2 lists the available physical and chemical data for these substances based on ECHA (2018a,b,c). These substances are mono-constituent substances. For D4, small amounts of impurities can include other cyclic siloxanes such as D5 (less to up to ca. 4% w/w; Environment Agency,

[1] https://www.echa.europa.eu/candidate-list-table

[2] http://data.europa.eu/eli/reg/2018/35/oj

2013a). For D5, small amounts of impurities can include other cyclic siloxanes such as D4 (up to 1%) and D6 (up to 3%) (ECHA, 2018b). In addition, D6 contains D4 (<1% w/w) and/or D5 (<3% w/w) as impurities (ECHA, 2018c).

Table 1. Substance identity and structure of D4, D5 and D6

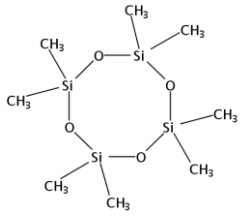
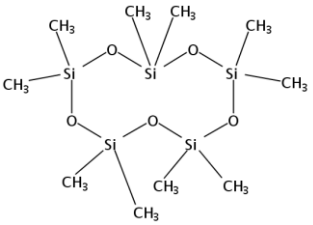
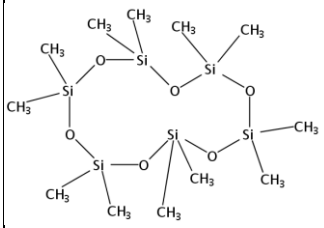
	D4	D5	D6
CAS number	556-67-2	541-02-6	540-97-6
IUPAC name	Octamethylcyclotetrasiloxane	Decamethylcyclopentasiloxane	Dodecamethylcyclohexasiloxane
EC number	209-136-7	208-764-9	208-762-8
Molecular formula	$C_8H_{24}O_4Si_4$	$C_{10}H_{30}O_5Si_5$	$C_{12}H_{36}O_6Si_6$
Molecular weight (g/mol)	296.62	370.77	444.92
Synonyms	D4 Cyclotetrasiloxane Cyclomethicone	D5 Cyclopentasiloxane Cyclomethicone	D6 Baysilone SF 1217 Silsoft 1217 Cyclohexasiloxane Cyclomethicone
Structural formula			

Table 2. Overview of physicochemical properties for D4, D5 and D6

	D4	D5	D6
Physical state at 20°C and 101.3 kPa	Liquid	Liquid	Liquid
Melting/ freezing point (°C)	17.7	-38	-3
Boiling point (°C)	175	210	245
Vapour pressure (Pa at 25 °C)	132	33.2	4.6
Water solubility (µg/L at 23 °C)	56.2	17.03	5.3± 0.48
Henry's Law Constant (Pa m^3/mol)	1.21×10^6 at 25 °C	3.34×10^6 at 24.6 °C	2.54×10^6 at 23.6 °C
Partition coefficient n-octanol/water, Kow (log value)	6.49 at 25.1 °C	8.02 at 25.3 °C	8.87 at 24 °C
Adsorption/desorption, Koc value in L/Kg, (log value)	1.7×10^4 (4.22)	1.5×10^5 (5.17)	2.2×10^5 to 1.5×10^6 (5.35 to 6.18)
Partition coefficient octanol-air, Koa (log value)	4.34 at 25 °C	4.96 at 24°C	5.86±0.12 at 24°C

Partition coefficient air-water, Kaw (log value)	2.69 at 21.7 °C	3.13 at 24.6 °C	3.01 at 23.6°C

Source: EU SVHC support documents for D4, D5 and D6 (ECHA 2018a,b,c), the EU background document to the Opinion on the Annex XV dossier proposing restrictions on D4, D5 and D6 (ECHA, 2020) and the Environment Agency risk assessment reports for D4, D5 and D6 (Environment Agency, 2009a,b,c)

3. Information on D4, D5, D6 and how they fulfil the Annex D screening criteria

3.1 Persistence

6. D4, D5 and D6 contain no chromophores that would absorb visible or UV radiation, so direct photolysis is not likely to be significant (ECHA, 2018c).

7. D4, D5 and D6 are poorly soluble in water, volatile and adsorb strongly to organic matter in sewage sludge, sediment and soil. The very low water solubility and high volatility of these substances also indicate that leaching from soil is not expected to be a significant process in the environment.

8. D4 can hydrolyse in pure water with a relatively short half-life (e.g. 16.7 days at pH 7 and 12 °C (freshwater) and 2.9 days at pH 8 and 9°C (marine water); the half-life is dependent on the pH and temperature of the water; Environment Agency, 2009a). Like for D4, hydrolysis of D5 is dependent on the pH and temperature of the water. D5 is more stable than D4 in water with a hydrolysis half-life of 315 days at pH 7 and 12 °C (freshwater), and 64 days at pH 8 and 9 °C (marine water) (Environment Agency, 2009b). D4 and D5 have a high tendency to adsorb to sediments and particles which hinders hydrolysis. The significance of hydrolysis was proven in clean water test systems but not under environmentally relevant conditions. As regards D6, the hydrolysis is unlikely to be a relevant degradative pathway in the environment with a half-life being >1 year at pH 7 and 25 °C (Kozerski, 2009 as cited in ECHA, 2018c).

9. Loss processes (volatilisation and hydrolysis) of D4, D5 and D6 are expected to be attenuated by adsorption to organic carbon (Whelan *et al.,* 2010) and a significant proportion is expected to distribute to sediment where persistence is expected.

10. D4, D5 and D6 are considered to be not readily biodegradable (D4: 3.7% degradation after 29 days (Springborn Smithers Laboratories, 2005) and D5: <1% degradation after 28 days (Environment Agency, 2009b; however, interpretation is complicated by the high volatility of the substances) and D6: 4.5% degradation after 28 days in an OECD TG 310 study by Springborn Smithers Laboratories (2005). In the freshwater sediment compartment (OECD TG 308 studies), D4 and D5 have degradation half-lives of 242–365 days (Xu, 2009a,b) and 1,200–3,100 days (Xu, 2010) under aerobic and anaerobic conditions at 24 °C, respectively. These half-lives are expected to be longer at lower temperatures. For D4, the sediment half-life appears to depend on the sediment characteristics (e.g. pH and organic carbon content) as a half-life of 47 days at 24°C (equivalent to a half-life of 123 days at 12°C) was found in a second sediment (Xu and Miller, 2008). Environment Canada, Health Canada (2008a) reported half-lives in sediments for D4 in the range of 49−588 days. No information on simulation tests in water and sediment is available for D6. Read-across from D4 and D5 to D6 has been considered appropriate for the assessment of D6 persistence (ECHA, 2018c). Based on the comparison of physico-chemical properties of D4, D5 and D6, D6 can be expected to be more persistent than D4 and D5 (ECHA, 2018c). Persistence of D4 and D5 in sediment is also supported by the sediment core data from Lake Pepin (USA) with an estimated degradation half-life of D4 up to 2.5 years in sediment (Powell, 2010). The degradation half-life for D5 cannot be estimated from the data, however, occurrence and levels of D5 found in sediments layers of Lake Pepin deposited in the early 1970s suggest that the degradation of D5 in the sediment core was slow.

11. In the soil compartment, the available data do not allow the derivation of reliable degradation half-lives for D4, D5 and D6. In a non-standard laboratory study (conducted at 22 ºC, Xu and Chandra, 1999 , Xu, 1999 and Xu, 2007a) D4, D5, and D6 have been measured to degrade fast in dry tropical soil (soil half-life estimated around 4.1−5.3 days for D4, 0.11−0.19 days for D5 and 1.8−3 days for D6 at 50-90% relative humidity; at a relative humidity of 32% the half-lives for D5 and D6 are 0.08 days (1.9 hours) and 1.38 days, respectively, compared with 58 minutes for D4 under the same conditions). However, half-lives have been observed to increase with increasing humidity of the soil (little or no degradation of D4, D5 and D6 occurred in the temperate soil at 100 per cent relative humidity and half-lives up to ca. 200 days have been obtained for D6 with 90% relative humidity). Degradation is thought to result from hydrolysis reactions catalysed by the surface activity of soil clays. The increase in moisture of the soil is thought to decrease the surface acidity and thus the hydrolysis rate. It is probable that under some situations, rapid degradation of D4, D5 and D6 may occur, but in other situations the degradation will be much slower. The relative half-lives in soil were D4 < D5 < D6.

12. There is some evidence that D4 is a transient degradation product of polydimethylsiloxane (PDMS) in contact with soil, while the principal degradation products are silanols prior to complete mineralisation (Herner *et al.* 2002). Thus, in addition to release of residual D4 from PDMS manufacture, there may be *de novo* synthesis of D4 occurring in landfills and agricultural lands where sewage sludge containing PDMS is spread (Environment Canada, Health Canada, 2008a).

13. Reaction products in all compartments are expected to be silanols (e.g. dimethylsilanediol). These are more hydrophilic than the parent substances and will therefore be removed from the atmosphere by wet deposition (either adsorbed onto particulates or dissolved) and undergo further degradation in the environment to ultimately form carbon dioxide and silicic acid and/or silica (ECHA, 2016a).

Conclusion on persistence according to the criteria in Annex D

14. The Annex D criteria for Persistence 1. (b)(i) and (ii) are considered to be met. D4, D5 and D6 (using a read-across from D4 and D5) have degradation half-lives in sediment greater than six months (180 days). Persistence of D4 and D5 in sediment is also supported by sediment core data.

3.2 Bioaccumulation

15. D4, D5 and D6 meet the screening criteria for bioaccumulation with a log kow of 6.49, 8.02 and 8.87, respectively.

16. For D4, a steady-state BCF of 12,400 L/kg based on total ^{14}C measurements (corresponding to a steady-state BCF ≥11,495 L/kg and a kinetic BCF≥12,422 L/kg based on parent compound alone (it is not reported if the BCF kinetic was growth corrected) was measured for Fathead Minnow *Pimephales promelas* (Fackler *et al.*, 1995). The corresponding kinetic BCF was 19,000 L/kg, or 14,900 L/kg when normalised to a fish containing 5% lipid (it is not indicated whether this value was corrected to take account of the contribution of metabolites and if it was growth corrected). Another bioconcentration study following OECD TG 305 for D4 indicated a steady-state BCF for Common Carp *Cyprinus carpio* in the range 3,000–4,000 L/kg (based on parent compound analysis, fish lipid content was closed to 5 per cent) in two studies (OECD TG 305; CERI, 2007 and 2010a). The depuration half-life was estimated to be between 6.5 and 8.8 days (CERI, 2007 and 2010a). The kinetic BCF in CERI (2010a) study was in the range 4,100 - 5,500 L/kg (without growth correction; the fish lipid content was closed to 5 per cent). For comparison, growth-corrected kinetic BCFs in the two studies were in the range 4,120–6,930 L/kg (CERI, 2007 and 2010a).

17. For D5, a steady-state BCF of 7,060 L/kg based on total ^{14}C measurements (corresponding to a steady-state BCF ca. 5,860 L/kg based on parent compound alone, it is not reported if this BCF was lipid normalised) was measured for Fathead Minnow *Pimephales promelas* (Drottar, 2005a; OECD TG 305 study). BCFs in the range 2,000-5,000 L/kg and above were also measured as part of a fish early life stage test with this species (Parrott *et al*., 2010); the fish were growing rapidly and normalisation to a "standard" lipid content of 5% would increase the reported BCFs by a factor of around 1.3-1.7 times. The steady-state BCF for Common Carp *Cyprinus carpio* was reported to be in the range 12,049–12,617 L/kg (based on parent compound analysis) or 10,550 – 11,048 L/kg when normalised to a 5 % lipid content (the kinetic lipid-normalised BCF is higher: 12,566-14,009 L/kg (not growth corrected)) (CERI, 2010b; OECD TG 305 study). A long depuration half-life between 19 and 22 days was estimated for D5 in CERI (2010b).

18. For D6, bioaccumulation studies via aqueous exposure were performed following OECD TG 305. These studies show that D6 is bioaccumulative with steady-state and kinetic BCFs of 1 160 L/kg based on total radioactivity (or a steady-state BCF ≥ 916 L/kg and a kinetic BCF ≥1 311 L/kg as parent substance when corrected for the fraction of the total radioactivity, it is not reported if these BCFs are lipid and growth corrected) in Fathead minnow *Pimephales promelas* (Drottar, 2005b) and kinetic BCFs of 4 419–12 632 L/kg (growth corrected, the fish lipid content was closed to 5 per cent) in common carp *Cyprinus carpio* (CERI, 2010c). The depuration half-lives for Fathead minnow and carp are also rather long (27–30 days for Fathead minnow (Drottar, 2005b) and around 25 days before growth correction for the sequential fit for the carp (CERI, 2010c)). High BCF values (up to ~2 400 L/kg; it is not indicated whether this value was corrected to take account of the contribution of metabolites) are also found in aquatic invertebrates (*Daphnia magna*) for D6 (Dow Corning, 1985).

19. In laboratory fish dietary studies, for D4 a dietary BMF of 4.6 (growth corrected kinetic value, lipid normalised; minus liver and digestive tract) was measured in Rainbow Trout (*Oncorhynchus mykiss;* Dow Corning, 2007), leading to significant whole body concentrations (up to 100 mg/kg ww; concentration in fish minus liver and digestive tract). A long growth-corrected depuration half-life was estimated as 105 days from this study, and whole-body autoradiography showed that a significant amount of radioactivity remained in the gall bladder, with moderate amounts remaining in the

gastrointestinal tract, liver, 42 days after exposure ceased (Dow Corning, 2006b). A growth-corrected and lipid-normalised BMF of 0.51 (or ~0.7 if the measured concentrations in fish during the uptake phase are used) for D4 has been measured in carp (*Cyprinus carpio)* (CERI, 2011). The growth-corrected depuration half-life was ~30 days. The predicted growth-corrected BCF values using method 1 models (as refer to in the OECD TG 305 guidance (OECD, 2017)) are in the range 1,667 to 9,667 L/kg. Furthermore, the low rate of depuration seen in the feeding studies with *O. mykiss* and *C. carpio* (growth-corrected depuration rate constant of 0.00659 day^{-1} *and* ~0.058 day^{-1}, respectively) is consistent with the BCF for D4 being >5,000 L/kg.

20. For D5, a dietary BMF up to 3.9 (lipid-normalised kinetic value minus the contribution from the digestive tract) was measured in Rainbow Trout *Oncorhynchus mykiss* (Dow Corning, 2006b), leading to significant whole body concentrations (up to 111 mg/kg ww minus digestive tract). The results are based on total ^{14}C measurements, although a similar value would be expected for the parent compound. A long growth-corrected depuration half-life was estimated as 74 days from this study, and whole-body autoradiography showed that a significant amount of radioactivity remained in the liver and in the intestinal content in the lower portion of the intestine 42 days after exposure ceased (Dow Corning, 2006b). A dietary BMF of 0.96−1.21 (growth-corrected and lipid-normalised kinetic value) has been measured in *C. carpio* (CERI, 2011). The mean measured concentration of D5 in fish was 21.4 mg/kg ww after 13 days of uptake. The growth-corrected depuration half-life was ~30 days. Steady-state does not appear to have been reached during the 13-day uptake phase. The predicted growth-corrected BCF values using method 1 models (as refer to in the OECD TG 305 guidance (OECD, 2017)) are in the range 4,244 to 24,620 L/kg. The low rate of depuration seen in the feeding studies with *O. mykiss* and *C. carpio* (growth-corrected depuration rate constant of 0.00939 day^{-1} and ~0.023 day^{-1}, respectively) is consistent with the BCF for D5 being >5,000 L/kg.

21. Laboratory accumulation studies with the sediment worm *Lumbriculus variegatus* gave biota-sediment accumulation factors (BSAF) of 19–28 for D4 (Krueger *et al.,* 2008a) and a bioaccumulation factor (BAF) of 0.53–4.1 for D5 (Krueger *et al.,* 2008b). The studies had limitations because no special measures were taken to avoid loss from volatilisation during the spiking of the sediment or the uptake phase, and the actual number of measurements was low. If it is assumed that exposure was mainly via pore water, the equivalent BCF for D4 and D5 is in the approximate range 7,000−11,000 L/kg and 2,400−10,000 L/kg, respectively, although there is considerable uncertainty in these estimates. Environment Canada, Health Canada (2008a) reported BSAF values ranging from 0.7 to 2.2 in *Chironomus tentans* for D4. However, it was not specified whether the gut contents of test organisms had been purged before calculation of BSAF values. A benchmarking study (Kierkegaard *et al.,* 2011) suggests that the BSAF for D4 and D5 is higher than that for PCB-180 in ragworm and flounder in a UK estuary. van Egmond (2010) has carried out a further analysis of these data. The BSAF values determined for D5 were in the range 0.6 to 4.3. Assuming a log Koc of 5.2 the estimated BCF for D5 (assuming exposure was via pore water only) was in the range 2,826 to 4,656 L/kg for the polychaetes on a whole-body weight basis. A similar benchmarking study carried out in lakes from Sweden indicated that the bioaccumulation of D5 in perch is similar to that of PCB-180 (Kierkegaard and McLachlan, 2010; Kierkegaard *et al.,* 2013). However, there are uncertainties in interpreting these 'benchmarking' studies.

22. Field BSAFs values above 1 have been found for D4, D5 and D6 for benthic invertebrates in Lake Pepin in the USA (Powell *et al.,* 2009a), for D5 in Atlantic cod (mean of 2.4 (range 0.6−4.9)) and sculpin (mean of 7.3 (range 0.7−30)) from Adventfjorden (Warner *et al.,* 2010; it is not clear from the paper if the BSAFs were calculated using liver concentrations or whole fish concentrations), for D4 (mean value in the range 1−2.6) and D5 (mean BSAF of 1.4) in fish from Tokyo Bay, Japan (Powell, 2012).

23. Field studies typically show that trophic dilution is occurring in many aquatic food webs for D4, D5 and D6. However, biomagnification or trophic magnification is possible for some pelagic food webs as reported below:

24. • Trophic magnification factor (TMF) of up to 2.7 for D6 in Lake Mjøsa and Lake Randsfjorden in Norway (Bårga *et al.,* 2013a and 2013b). Overall TMF from both lakes combined (Lake Mjøsa and Lake Randsfjorden) was determined to be 2.91 with a 95% confidence interval (CI) of 2.11−4.02 for D5 and an overall TMF of 2.3 with a 95% CI of 1.8−3.0 for D6 (Borgå *et al.,* 2013a and 2013b). In addition, the levels of D5 and D6 in the pelagic food chain correlated with reference substances that are known to biomagnify (PCB-153 and p,p'-DDE). Results of this study are uncertain considering that the number of samples analysed was relatively small. Furthermore, the fish samples analysed refer to fillets or livers rather than whole fish, and thus the levels found may not reflect the levels present in whole fish.

25. • TMF of 1.1 for D4 (95% CI 0.51−1.9; the probability of a TMF >1 is 49%), TMF of 1.2 for D5 (95% CI 0.64−1.9; the probability of a TMF >1 is 65%) and TMF of 0.97 for D6 (95% confidence interval 0.62−1.4; the probability of a TMF >1 is 40%) when both zooplankton and the top predator (Walleye) were excluded in one of the food web configurations in the western basin of Lake Erie, Canada (McGoldrick *et al.*, 2014). There are some uncertainties with this study resulting from the relatively small sample sizes and the inclusion of species with a relatively high contribution from pelagic carbon sources in what was essentially a benthic food web. This study suffers from a possible underestimation of the concentrations in fish at the higher trophic levels compared with lower trophic levels.

26. • TMF of 1.39−1.77 (D5) and 1.01−1.45 (D6) in a study in Dalian Bay in Northern China (Jia *et al*., 2015).

27. • TMF in the range 0.5−2.8 (with most estimates above 1) has been reported for D6 in a study in Lake Champlain in the USA (Powell *et al.*, 2014b),

28. • Biomagnification factor (BMF) of 1−20 for D4 in midge larvae, burrowing mayfly and two fish species; BMF of 1.1−5.3 for D5 in midge larvae and burrowing mayfly and a BMF of 1.6 for D6 in midge larvae in Lake Pepin in the USA (Powell *et al.*, 2009a). Interpretation of the BMF is complicated by the small sampling size and the low concentrations that were found. The plankton was not sampled and so concentrations were estimated, which introduces some uncertainty. Furthermore, the sediment and benthic macroinvertebrates were collected at a different point in time than the fish.

29. • Mean BMF of 1−1.4 for D4 (95% CI 0.4−2.1; the probability of a BMF>1 is 37% and 95% CI 0.4−4.2; the probability of a BMF>1is 55%), 0.7−0.9 for D5 (95% CI 0.3−1.5; the probability of a BMF>1 is 13% and 95% CI 0.2−2.8; the probability of a BMF>1 is 30%) and 1.7−1.8 for D6 (95% CI 0.6−3.6; the probability of a BMF>1 is 80% and 95% CI 0.6−4.9; the probability of a BMF>1 is 81%) for Atlantic cod-shrimp in Oslofjord, Norway (Powell *et al.*, 2009c and 2010b). Atlantic cod-herring relationship had a BMF of 1.0 for D4 (95% confidence interval 0.4−2.0; the probability of a BMF>1 is 39%) and 0.9 for D6 (95% CI 0.4−2.0; the probability of a BMF >1 is 29%). The number of samples was small, so the robustness of these estimates is unclear.

30. • Mean BMFs were estimated for the Lake Trout-Perch relationship (D4: 2.4 (95% CI 1.6−3.3), D5: 5.2 (95% CI 3.0−8.6) and D6:1.4 (95% CI 0.9−2.1)) and for the Lake Trout-Cisco relationship (D4: 1.9 (95% CI 1.3−2.7), D5: 2.3 (95% CI 1.5−3.5) and D6:1.5 (95% CI 0.9−2.2)) in Lake Opeongo in Canada (Powell *et al.*, 2009b and 2010a). Interpretation of these BMFs is complicated by the low levels found in the lowest parts of the food chain and by the high and variable analytical background concentrations which introduced some uncertainties into the data.

31. • BMFs for D4 were above one (up to 1.7) for three out of the four predator–prey interactions and involving Japanese Sea Bass (the probability of a BMF>1 is 57−79%) and BMFs for D5 equal to one for the red barracuda – white croaker and red baraccuda – juvenile dotted gizzard shad feeding relationships (95% confidence interval 0.2−2.8 and 0.2−2.5; the probability of a BMF>1 is 35−37%, respectively) in Tokyo Bay, Japan (Powell, 2012).

32. It is apparent that different conclusions can be drawn from some studies depending on the food chain configuration that is assumed. However, it is important to note that high bioaccumulation in a part of the food chain may have unpredictable effects throughout other parts of the food chain as well.

33. Furthermore, there is unequivocal evidence from field studies that D4, D5 and D6 can be found in a wide range of organisms (particularly fish and aquatic invertebrates but also birds and mammals) throughout aquatic food chains, including top predators. VMS have been detected in a variety of biota samples across the globe (Augusto, 2019). Their concentrations were found higher in aquatic and terrestrial biota from densely populated areas, though some studies also detected VMS in biota from remote regions (Augusto, 2019). Among the organisms studied so far, the highest levels of VMS were found in aquatic organisms (notably, fish). Field studies show a predominance of D5 in almost all samples, independently of their geographic origin or type of ecosystem (marine, freshwater, terrestrial).

34. D4 concentrations in the range 0.1–0.9 mg/kg ww have been reported in tissues of some fish species ((e.g. Roach *Rutilus rutilus*, Ide (or Orfe) *Leuciscus idus* and European Eel *Aguilla aguilla* in the River Rhine, Germany (EVONIK Industries, 2007; summarised in Environment Agency, 2009a) and also Cod liver from several localities (TemaNord, 2005; Schlabach *et al.*, 2007; Durham *et al.*, 2009)). For D5, concentrations have been reported up to 1−3 mg/kg ww in tissues of some fish species, for example Roach *Rutilus rutilus*, Ide (or Orfe) *Leuciscus idus* and European Eel *Aguilla aguilla* in the River Rhine, Germany (EVONIK Industries, 2007; summarised in Environment Agency, 2009b) and Atlantic Herring *Clupea harengus* and European Plaice *Pleuronectes platessa* in Oslofjord, Norway (Powell *et al*., 2009c and 2010b). For D6, concentrations have been reported up to 0.4 mg/kg ww in cod

liver from the inner Oslofjord (Durham *et al.*, 2009). The levels found for D6 were in agreement with those of previous studies in the area (e.g. TemaNord, 2005 and Schlabach *et al*., 2007) and confirm that elevated concentrations of D6 occur in biota taken from areas close to sources of release.

35. The maximum whole fish concentrations for D4, D5 and D6 in fish laboratory bioconcentrations studies exceeded 1 mg/kg ww. Concentrations in field and/or fish laboratory bioconcentration studies for D4, D5 and D6 are comparable to levels of other substances having PBT/vPvB properties under REACH (including POP substances such as HBCDD, SCCP, pentaBDE and UV-328) that are considered to meet the bioaccumulation criteria of Annex D (BCF>5000 L/kg) (ECHA, 2018c).

36. Furthermore, D4, D5 and D6 were detected in 11 out of 49 samples of human breast milk from 'normal' Swedish woman who had never had breast implants. The maximum levels found in 2004 were as follows: D4 10 µg/L; D5 4.5 µg/L; D6 4.8 µg/L. The highest level of total (D4, D5 and D6) siloxanes recorded was between 13 and 14 µg/L (13 −14 ppb) (Swedish Environmental Research Institute, 2005). cVMS were detected in the plasma samples from general population in northern China (n=519) in 2012–2014 at 1.98–6.22 ng/mL (detection frequency (df) = 3.7%), and 1.85–7.50 ng/mL (df = 1.7%) for D4, D5, and D6, respectively (Xu *et al.*, 2015). Concentrations of D4, D5, and D6 in abdominal fat of general population from China (n = 249) in 2012–2014 were 4.00–141 ng/g (df = 38%), 3.10–77.5 ng/g (df = 18%), and 4.08–77.2 ng/g (df = 35%), respectively (Xu *et al.*, 2015).

37. Humans can be exposed to VMS through their diet. For instance, consumption of fish containing cVMS is a potential exposure pathway for the general population. Sanchís and co-workers (Sanchís *et al.*, 2016) examined the presence of volatile methyl siloxanes in market seafood and freshwater fish from different sites at the Xuque River in Spain. cVMS were detected in almost all freshwater samples at a concentration between pg/g and ng/g. Market samples showed a significant greater concentration, which is consistent with the expected contamination during storage and handling.

38. The Toxcokinetic information on the substances is as follows:

39. **Absorption:** According to Environment Agency (2009abc), studies in the rat show that around 5% of inhaled D4, 3% of inhaled D5 is absorbed and it is likely that no more than 3% of inhaled D6 is absorbed; in humans 6–17% of D4 may be absorbed. In rats and humans around 1% of the applied dose of D4, around 0.1–1% of the applied dose of D5 and 0.003–0.1% of the applied dose of D6 is absorbed across the skin, with absorption being limited by evaporation from the skin (Environment Agency, 2009abc; ECHA's dissemination website for D4[3], D5[4] and D6[5]). In rats around 50−77% of D4, around 20% of D5 and 15% of D6 in an oral dose is absorbed (Domoradzki *et al.*, 2017 and Environment Agency, 2009abc). Absorbed D4, D5 and D6 is distributed widely throughout the body, with some preferential storage in fat for D4 and D5.

40. **Distribution:** In inhalation studies, higher concentrations of D4 were found in lung tissue and fat than other tissues. According to the opinion of the Scientific Committee on Consumer Safety (or SCCS), there is evidence that D4 accumulates in adipose tissue (SCCS, 2010). After oral exposure (gavage, single dose) to D4, female and male tissues of rats revealed the following distribution for D4: perirenal fat > digestive tract > lung or liver > spleen > blood (Domoradzki, 2017). Given orally, higher concentrations of D5 are located within the liver and spleen compared with those following inhalation exposures (Environment Agency, 2009b).

41. **Elimination:** After single and multiple inhalation exposures, the longest half-lives determined for parent D5 were in the lung, liver and fat. The values for males and females rats were 160.1−135.3 hours for lung, 96.9−124.1 hours for liver and 130.4−120.5 hours for fat. The data demonstrates that the fat has the longest half-lives of all the tissues, which is due to the lipophilicity of D5 (ECHA's dissemination website for D5).

42. **Metabolism:** D4 is metabolised – in rats the two major metabolites are dimethylsilanediol and methylsilanetriol, both of which were also identified in humans. Available studies in rats indicate that the liver is the site of the first step in the metabolism of D4. Human and rat metabolism of D4 are qualitatively similar with at least eight metabolites (dimethylsilanediol and methylsilanetriol were two major metabolites) identified in urine (ECHA's dissemination website for D4). D5 is metabolised, two major metabolites (dimethylsilanediol and methylsilanetriol) and five minor metabolites of D5 have been identified in urine (ECHA's dissemination website for D5). The identity of D6 metabolites in the urine are methylsilanetriol and dimethylsilanediol (ECHA's dissemination website for D6).

[3] ECHA's dissemination website for D4: https://echa.europa.eu/de/registration-dossier/-/registered-dossier/15289/7/2/1
[4] ECHA's dissemination website for D5: https://echa.europa.eu/de/registration-dossier/-/registered-dossier/14807/7/2/1
[5] ECHA's dissemination website for D6: https://echa.europa.eu/de/registration-dossier/-/registered-dossier/15811/7/2/1

43. **Excretion:** The main routes of elimination for D4 and its metabolites are in the urine and exhaled air, and faeces (ECHA's dissemination website for D4). Parent D5 is not excreted in urine. The majority of inhaled and orally ingested D5 that is absorbed is expired as volatiles. The rest is then excreted as metabolites in urine and as parent in faeces (ECHA's dissemination website for D5). After oral exposure in rats and rabbits, D6 is eliminated as parent in faeces, via exhaled air and in urines as metabolites (ECHA's dissemination website for D6).

44. For the oral route, D4 appears to be delivered via the lymphatics with the lipid core of chylomicrons and other lipoproteins. Given the route-specific nature of D4 pharmacokinetics, oral pharmacokinetic data collected is not as useful in understanding the bioavailability or tissue kinetics of D4. The oral pharmacokinetic data therefore, may not be practical for safety assessments and can lead to misleading or erroneous conclusions (as cited in SCCS, 2010). Additionally, toxicokinetic and pharmacokinetic modelling studies investigated the question how the exposure route (inhalation, dermal and oral) affects bioavailability of D4 and hence the biologically relevant internal dose: when absorbed through the lungs, D4 enters the arterial systemic circulation where it is distributed throughout the body to potentially all organ systems. When absorbed by the dermal route, D4 enters the venous circulation, which moves directly to the heart and lungs where the majority of the D4 is then eliminated via exhaled air and therefore unavailable systemically (as cited in SCCS, 2010). Regarding D5, it appears to enter the blood via the lymphatics within the lipid core of chylomicrons and other lipoproteins, which is in a form different from that for inhalation or dermal routes of exposure (ECHA dissemination website for D5).

45. Furthermore, the data indicate that oral or inhalation exposure to D4 and D5 caused an expression profile similar to phenobarbital in rat liver. While both compounds increased CYP2B1/2 in both sexes of Sprague-Dawley rats, differences in CYP3A1/2 and NADPH cytochrome P-450 reductase were observed with female rats being more sensitive to enzyme induction at low doses of both compounds (Zhang *et al.* 2000).

Conclusion on bioaccumulation according to the criteria in Annex D

46. The Annex D criteria for bioaccumulation 1. (c) (i)(ii)(iii) are considered to be met for D4, D5 and D6 as BCF values exceed 5000 L/kg and log kow are greater than 5. This is supported by monitoring data for D4, D5 and D6 indicating widespread uptake by biota (including in humans). Field studies typically show that trophic dilution is occurring in many aquatic food webs for D4, D5 and D6. However, biomagnification or trophic magnification (BMF or TMF>1) is possible for some pelagic food webs. It is important to note that high bioaccumulation in a part of the food chain may have unpredictable effects throughout other parts of the food chain as well. Furthermore, there is unequivocal evidence from field studies that D4, D5 and D6 can be found in a wide range of organisms (particularly fish and aquatic invertebrates but also birds and mammals) throughout aquatic food chains, including top predators. A benchmark approach shows that concentrations in field and/or fish laboratory bioconcentration studies for D4, D5 and D6 are comparable to levels of other substances having PBT/vPvB properties under REACH (including POP substances such as HBCDD, SCCP, pentaBDE and UV-328) that are considered to meet the bioaccumulation criteria of Annex D (BCF>5000 L/kg). Finally, toxicokinetic data indicate that there is evidence that D4 and D5 accumulate in adipose tissue/fat of rats.

3.3 Potential for long-range environmental transport

47. The atmospheric half-lives of the cVMS are 12.7 −16.9 days for D4 (Sommerlade *et al.*, 1993; Atkinson, 1991; Kim and Xu, 2017), 10.4−11 days for D5[6] (Atkinson, 1991; Kim and Xu, 2017) and 6.58 days for D6 (Kim and Xu, 2017) due to reaction with atmospheric hydroxyl radicals (OH) (assuming an average atmospheric OH concentration of 5×10^5 molecule/cm^3 reflecting a concentration in the northern hemisphere). Due to their relatively long atmospheric half-lives (>2 days) and combined with their volatility, the major portion of the environmental burden of D4, D5 and D6 will partition mainly in the air (ECHA, 2016a). Therefore, D4, D5 and D6 have the potential to undergo long-range transport to remote regions via the atmosphere. It is worth noting that above-mentioned atmospheric half-lives do not account for process of removal from the air due to the adsorption of cVMS to aerosols (organic and inorganic aerosols such as minerals and crystalline) and as further discussed in this section.

48. Chemical partitioning space plots as described by Wania (2003, 2006) predict that D4, D5 and D6 have a low Artic contamination potential (ACP). ACP use log Koa and log Kaw as input parameters.

[6] The half-life of D4 and D5 is probably shorter in urban and suburban areas (Xu and Kim, no year). A similar trend is expected for D6.

49. Several modelling studies have been performed, which suggest that the travel distance is high for the three siloxanes. The characteristic travel distance (CTD) predicted (Environment Canada, Health Canada, 2008a,b,c; Xu and Wania, 2013; Gouin, 2010 and Xu *et al.*, 2019) is in the range 1380−5284 km for D4; 1310−5000 km for D5 (including a high dispersion, ϕ1 for D5 as derived by Breivik *et al.*, 2022) and 1860−8640 km for D6. The upper boundary of predicted CTD for D4, D5 and D6 are close to or above the CTD of 5097 km for the reference compound PCB-28. The Transfer Efficiency (TE) (Environment Canada, Health Canada, 2008a,b,c; Gouin, 2010; Xu and Wania, 2013) is predicted to be very low for the three substances: $4.4x10^{-6}$–$1.6x10^{-2}$% for D4, $1.9x10^{-6}$–$1x10^{-2}$% for D5 (including Low transfer (ϕ2) and Low accumulation (ϕ3) as derived by Breivik *et al.*, 2022) and $1.6x10^{-6}$–$3.9x10^{-3}$% for D6. Those predicted TE values are below the reference value of 2.248% for PCB-28 and would suggest that the deposition to surface media is unlikely.

50. However, the CTD and TE values for D4, D5 (including ϕ1, ϕ2 and ϕ3) and D6 should be considered with caution considering uncertainties in the input parameters used in the models such as the half-lives in water and soil which are not available for D4, D5 and D6.

51. Furthermore, the OECD Pov and LRTP Screening Tool, GloboPOP model and ACP do not account for the deposition potential of cVMS from aerosols consisting of inorganic material such as minerals or crystalline particles (further discussed below).

52. Therefore, the transfer efficiency (TE), transfer potential, and ACP reported above (Wania, 2003, 2006; Environment Canada, Health Canada, 2008a,b,c; Gouin, 2010; Xu and Wania, 2013 and Breivik *et al.*, 2022) are considered to be underestimated for D4, D5 and D6.

53. Xu and Vogel (2021) investigated snow scavenging of cVMS and its potential effect on the cVMS concentrations in snowmelt water and surrounding soil under laboratory conditions. Measurements were made using a snow chamber and ^{14}C-labeled D4 and D5. In addition, the transfer of snow-bound cVMS to snowmelt water and surrounding soil was studied with ^{14}C-D4 and ^{14}C-D5-spiked snowpack placed both in a closed snow chamber and on top of a layer of frozen soil in an open chemical hood. Xu and Vogel (2021) measured the snow sorption coefficient (KiA) of D4 and D5 which is defined as the ratio of the interfacial concentration in units of mol/m^2 of snow surface and the gas phase concentration in units of mol/m^3 of air. KiA values measured in both sorption and desorption processes were small (<10^{-2} m). They increased with decreasing temperature and were higher for D5 compared to D4. Based on the total snow scavenging ratio (WT) values for D4 and D5, the concentrations of D4 and D5 in snow at 0°C were calculated to be in the range < 1−3.4 and 3.6−20.9 times (respectively) of their concentrations in the air (depending on surface area of snow flakes, given as a snow area index (SAI) in the range of 1000 to 6000). In snow at – 20 °C this was 2.99 to 17.5 times for D4 and 10.92 to 62.8 times of their concentrations in the air for D5. The measured snow-to-water transfer at 0°C in the closed soil chamber for D4 and D5 was ca. 0.1 % for D4 (mostly as dissolved in water) and ca. 12.3 % for D5 (mostly bound to particles in water) and the substances were removed from the snow by re-volatilisation (92.9 % for D4 and 82.8 % for D5) and hydrolysis (7 % for D4 and 4.9 % for D5). The snow-to-soil transfer determined in simulated snow melting at ~20°C in a chemical hood for D4 and D5 was estimated to be up to 8.7% and 3.9% respectively based on total radioactivity (degradation products were not investigated).

54. There are identified uncertainties with the study of Xu and Vogel (2021). The aluminum-lined bags used for gas preparation and dosing seemed to have increased the hydrolysis rate of the D4 and D5 under the open chemical hood experiment. Furthermore, only one benchmark compound (cyclopentanone) was used in the study, which has a known low snow sorption coefficient (KiA). The study could have been performed with several reference compounds having different snow sorption coefficients from low to high values. As a consequence, there is uncertainty associated with the derived snow sorption coefficient (KiA) values and snow scavenging ratios (WT) by Xu and Vogel (2021). Sanchís *et al.* (2015b), back-calculated the snow scavenging ratio (reported as WS) of D6 applying Mackay *et al.* (2015a) estimation method which considers a snow to air sorption coefficient for VMS which ranged from 8 x10^{-4} for the linear siloxane L3 to 0.56 m for D6 at -7°C (these values are predicted from polyparameter linear free energy model and the measured solute descriptors for VMS; Mackay *et al.*,2015a). Sanchís *et al.* (2015b) calculated snow scavenging ratios (WS) of 89, 62 000, and 120 for L3, D6, and naphthalene (having a similar vapor pressure as cVMS), respectively (derived by using a snow surface area of 0.37 m^2/g and assuming a snow density of 0.3 kg/L instead of an SAI of 1000). The derived WS for naphthalene is according to Sanchís *et al.* (2015b) three orders of magnitude lower than the field measures (4.6×10^5), suggesting that WS for VMS could be significantly higher than these estimates. Mackay *et al.* (2015a) also estimated a volume-based snow scavenging ratios of 0.8 for L3 to 557 for D6 using snow to air sorption coefficients of 8 x10^{-4} for L3 to 0.56 m for D6 at -7°C and an average snow area index (SAI) of 1000. The snow scavenging ratio for D6 derived by Mackay *et al.* (2015a) is much higher than the values derived by Xu and Vogel (2021) for D4 (WT=1.03) and D5

(WT=5.07) at comparable temperature and SAI (-6.8°C and SAI of 1000), thus further highlighting the uncertainty of the KiA and WT values derived by Xu and Vogel (2021) for D4 and D5.

55. Finally, Xu and Vogel (2021) discuss that based on the various measurements and calculations the concentrations of D4 and D5 in snowmelt would be expected to be very low, and therefore the snow scavenging could not be a valid deposition mechanism. However, the results of Xu and Vogel (2021) show that deposition from air to snow followed by a transfer from snow to water or soil is possible for D4 and D5. Considering the high global volumes of these substances even a low percentage of deposition and transfer to a receiving matrix (water (including sediment) or soil) is of potential concern for remote areas. Dry aerosol-bound deposition (from aerosols consisting of inorganic and organic particles, and water), wet deposition (via rain and snow) and gaseous deposition (in particular on foliage) are possible ways of deposition of D4, D5 and D6, as discussed below.

56. According to Navea *et al.* (2009), volatile methylsiloxanes are sorbed to atmospheric aerosols by partitioning. Kim and Xu (2016) investigated the sorption and desorption behaviours of D4 and D5 on nine major primary and secondary atmospheric aerosols at a relative humidity (RH) of 30% and at room temperature (21 ± 1 °C). Nine mineral aerosols were selected for the study including aerosols with three phyllosilicate minerals (kaolinite, illite and mica), with inorganic (mainly crystalline) particles of hematite, quartz, carbon black, sea salt, and with two sulfates (ammonium sulfate and ammonium hydrogen sulfate). It was found that sorption and desorption of VMS took place via a two-phase process, which included an initial rapid step, followed by slower subsequent step. The initial rapid step was favoured especially at low concentrations. Values of apparent aerosol–air partition coefficients (Kp) ranged 0.09–50.4 L/m^2 for D4 and 2.1–284 L/m^2 for D5 with carbon black having the largest values and sea salt having the least value. For all the aerosols, Kp values for D5 were 2.3–39 times larger than those for D4, indicating higher affinities toward D5. Aerosols such as carbon black and sea salts reversibly interacted with D4 and D5. The same reversible sorption trend was also observed for other sorption systems such as D4 on quartz, and D5 with illite, mica, hematite, and quartz for the entire range tested.

57. Other aerosols, such as those containing kaolinite and sulfates, showed irreversible sorption for the VMS, especially at low concentrations. However, for kaolinite as more D4 and D5 sorbed, the irreversible fraction decreased (or the reversible fraction increased) to 27% (at D5 ~1100 μg/m^2). Furthermore, for kaolinite and sulfates, it is important to note that more and more gas-phase D4 was produced when the gas phase D5 concentration decreased over time. The formation of D4 in this case was related to transformation of sorbed D5 on the aerosol surface into D4.

58. Although the cVMS concentrations used in this study were ~106 higher than the atmospherically relevant conditions, the authors argue that the observed sorption behaviours are still environmentally relevant. This is because aerosols used in the current study were also ~106 higher than the average aerosol concentrations in real atmosphere. Thus, the authors concluded that cVMS concentrations on aerosol surfaces could be similar to that in the real environment. Findings of Kim and Xu (2016) demonstrate that sorption of cVMS to atmospheric inorganic aerosols should be accounted for in the deposition potential of these substances as some aerosols such as carbon black, sea salt, quartz, illite, mica, hematite reversibility interacted with D4 and/or D5. Similar sorption and desorption behaviours are expected for D6 due to its similar physico-chemical properties compared to D4 and D5. Furthermore, modelling predictions (OECD Pov and LRTP Screening Tool, GloboPOP model, ACP) described above did not account for sorption on inorganic particles in aerosols, nor the possible formation of D4 following transformation of sorbed D5 on aerosol surface.

59. While modelling predict a potential long-range atmospheric transport of these substances with a low potential for deposition to surface media, monitoring data indicate that long-range environmental transport of D4, D5 to D6, with the potential for transfer to a receiving environment, is possible via air, water and migratory species.

60. Before presenting the monitoring data, it is worth noting that local sources of cVMS have been reported in the Arctic. The wastewater effluent from the communities Longyearbyen (Adventfjorden, approximately 2000 inhabitants) and Ny Ålesund (Kongsfjorden, 40−150 inhabitants) as well as cruise ship traffic during the summers are possible sources of human influence in Liefdefjorden (Warner *et al.*, 2010 and Campbell, 2010). As regards the Canadian Archipelago, some possible local sources have been reported by Panagopoulos Abrahamsson *et al.* (2020) for some of the data points, such as commercial and tourist boats, possible constructions activities, influence of the controlled oil spill region and the nearby river delta. Considering that in this study the detected concentrations of cVMS in sediment of Adventfjorden were lower than the ones in the Canadian Archipelago, even though there is a point source in Adventfjorden, it is unlikely that boat traffic, constructions and controlled oil spills alone can account for the detected higher concentrations in the Canadian remote areas. Hence, it cannot

be excluded that the long-range transport via river/oceanic currents and/or air may have contributed to the concentrations of cVMS found in the marine sediments. Furthermore, the statement of Panagopoulos Abrahamsson *et al.* (2020), that the 'nearby'[7] river delta may be a source of cVMS as well as the quantifiable concentrations of D4, D5 and D6 clearly indicate their potential for long range transport via adsorption onto suspended matter and subsequent transport to sediment via rivers and ocean currents.

61. Panagopoulos Abrahamsson *et al.* (2020) further stated that when comparing the wastewater concentrations of cVMS to the sediment concentrations of cVMS in Adventfjorden, it was observed that the concentrations of D4 in the sediment samples were slightly higher than what one would expect based on the wastewater emissions. The authors speculated that this observation could be the result of long-term emissions or emissions other than wastewater (e.g., industrial applications). However, another possibility is the contribution of atmospheric deposition of D4 and an enrichment of the sediment with D4 due to biota carcasses of organisms which bioaccumulate D4.

62. The monitoring data reported in the paragraphs below have been selected to represent places away from known point sources, having significant cVMS releases (such as wastewater effluent pipe) in the case that information on possible local sources was reported by the authors. Overall and as further discussed below, local sources alone cannot explain the concentrations of D4, D5 and D6 detected in remote areas, hence the contribution of the long-range transport via air, water in river/oceanic currents and/or migratory species to the observed concentrations cannot be ruled out.

63. D4, D5 and D6 have been detected in various media in the Arctic, including in the air at two remote sites (Zeppelin/Ny-Ålesund in Svalbard and Alert, Nunavut in Canada) between 2009 and 2021 (concentrations in the range of nd[8]–35.1 ng/m^3 for D4, nd–12.3 ng/m^3 for D5 and nd–5.61 ng/m^3 for D6, Genualdi *et al.*, 2011; Krogseth *et al.*, 2013; Rauert *et al.*, 2018; Warner *et al.*, 2020; NILU, 2014 to 2022 ; Saini *et al.*, 2023 and Wania *et al.*, 2023), in marine sediment from the Norwegian Arctic seawaters, the Canadian Archipelago, the Arctic Ocean, the Atlantic Ocean and the Pacific Ocean between 2009 and 2021 (concentrations in the range of nd–8.60 ng/g dry weight (dw) (or nd–1.87 ng/g wet weight (ww)) for D4 (and up to 61 ng/g dw or 13.26 ng/g ww in the Pacific), nd–11.5 ng/g dw (or nd–2.5 ng/g ww) for D5 (and up to 87.4 ng/g dw or 19 ng/g ww in the Canadian Archipelago with 'potential' local sources), nd–4.6[9] ng/g dw (or nd–1 ng/g ww) for D6 (and up to 12.42 ng/g dw or 2.7 ng/g ww in the Canadian Archipelago with 'potential' local sources); MAREANO programmes[10] between 2009 and 2021; Evenset *et al.*, 2009; ECCC unpublished and as cited in ECCC, 2022 and Panagopoulos Abrahamsson *et al.*, 2020), in avian and marine biota samples from Svalbard (Liefdefjorden, Billefjorden, Moffen, Nordkappsundet and Bjørnøya) and on the remote islands Sklinna and Røst of the Norwegian coast (concentrations in the range of n.d–9.2 ng/g ww for D4, n.d–19.1 ng/g ww for D5 and n.d–20.5 ng/g ww for D6 between 2008 and 2012 (Evenset *et al.*, 2009; Campbell, 2010; Warner *et al.*, 2010; Warner *et al.*, 2013; Huber *et al.*, 2015).

64. D4, D5 and D6 were also detected in phytoplankton and krill sampled from the Southern Ocean in 2009 (concentrations in the range 0.3–117 ng/g dw for D4, 0.3–63.1 ng/g dw for D5 and 0.1–72.7 ng/g dw for D6; Sanchís *et al.*, 2015a) and in soil and vegetation (lichens, grass, mosses) sampled from Antarctica in 2009 (concentrations in the range nd–23.9 ng/g dw for D4, nd–110 ng/g dw for D5 and nd–42 ng/g dw for D6 in soil and concentrations in the range nd–21 ng/g dw for D4, nd–55.4 ng/g dw for D5 and 0.86–88 ng/g dw for D6 in vegetation; Sanchís et al., 2015a). Sanchís *et al.* (2015a) consider that D4, D5 and D6 can undergo atmospheric deposition by snow scavenging during the Antarctic winter and accumulate in the Antarctic biota and soil after the summer snow melt. The reliability of this study was questioned in two publications (Mackay *et al.*, 2015a; Warner *et al.*, 2015) and responded to by the authors (Sanchís *et al.*, 2015b). The EU Committee for Risk Assessment (RAC) considers in its opinion (ECHA, 2016b) that the study of Sanchís *et al.* (2015a) should not be overlooked. The analytical procedures may be reliable even if background levels of D5 in the analysed samples are high, but consistent through all samples. Augusto (2019) further stated that the authors of the Antarctic study have already provided the scientific community with data showing the credibility of the results (Sanchís *et al.*, 2015b). Furthermore, McLachlan (2018) stated that it is possible that deposition with snow is the major process of removal from the air under conditions of heavy snowfall and low phototransformation. Lower concentrations of cyclic VMS in the air have been observed during major snow events in Toronto (Canada) (Ahrens *et al.*, 2014 as cited in McLachlan, 2018).

[7] It is worth noting that samples C1 and C10 are considered as 'close to the mouth of the Mackenzie River' by the authors while these samples are 180-190 km away from the river mouth/delta.
[8] 'nd' means non-detected.
[9] This value represents an underestimate of D6 concentration considering its low extraction recovery (64±13%).
[10] Link to the chemistry database: https://mareano.no/kart-og-data/kjemidata.

65. McLachlan (2018) further reported that the rate of gaseous deposition for VMS to foliage was higher compared to other deposition processes (however, the dry aerosol-bound deposition rates did not account for possible adsorption to aerosols with inorganic particles such as minerals and crystalline particles). Thus, the gaseous deposition of cVMS has likely contributed to the measured concentrations of cVMS found in vegetations from Antarctica (Sanchís *et al.*, 2015a).

66. In contrast to modelling studies predicting a low potential for subsequent deposition to surface media, the findings of Sanchís *et al.* (2015a) indicate that deposition to remote areas by D4, D5 and D6 is possible. Despite the fact that D4, D5 and D6 may ultimately degrade in the atmosphere during Antarctic summer, the concentration of OH radicals during the Antarctic winter is lower, resulting in slower degradation of D4, D5 and D6 in the atmosphere. Consequently, deposition of D4, D5 and D6 seems to be possible during periods of lower photolytic activity. In its opinions (ECHA, 2016b and 2019), RAC noted that due to the high volume of total emissions into air of D4 and D5 from all uses and dissipation from WWTP, even if deposition rates were low, this exposure route would be a potential source of concern (including in remote areas). Similar conclusions can be drawn for D6 due to its similar physico-chemical properties. RAC further noted that because of the PBT/vPvB properties of D4, D5 and D6, the atmospheric redeposition does not need to be a significant source of D4, D5 and D6 to cause concerns and to require minimisation of the emissions into the atmosphere (ECHA, 2019). For volatile compounds released to the air there will always be some partitioning between the air and surface media (ECHA, 2019). Furthermore, the decline in the D5/D4 ratio[11] away from source regions suggests the dominant role of long-range transport in delivering these chemicals to remote areas (Rauert *et al.*, 2018 and Saini *et al.*, 2023). The presence of D4, D5 and D6 at remote sites such as the Arctic and the Antarctic therefore indicates long-range transport. Presence of D4, D5 and D6 in the Arctic air indicates atmospheric transport. Measured concentrations in the Arctic air have been shown to be three orders of magnitude higher than most regulated POPs (NILU, 2022).

67. Measured levels of D4, D5 and D6 in deep marine sediments (up to a water depth of 1963 m) from the Norwegian Arctic seawaters, the Canadian Archipelago, the Arctic Ocean, the Atlantic Ocean and the Pacific Ocean away from point sources indicate the potential of D4, D5 and D6 for long-range transport via the adsorption onto suspended matter and subsequent transport to sediment via water in rivers and ocean currents. Moreover, sediments have also been suggested to undergo long-range transport with turbidity currents (Kneller *et al.*, 2016). As a consequence, it cannot be ruled out that sediments containing D4, D5 and D6 (where they are persistent) can be transported over long distances along the sea floor via turbidity currents. The long-range transport potential of D4, D5, and D6 via air and/or water in rivers and ocean currents is further supported by their presence in shorthorn sculpin (*Myxocephalus scorpius*) livers at a concentration of nd–0.35 ng/g ww for D4, nd–2.94 ng/g ww for D5 and nd–3.61 ng/g ww for D6 in Liefdefjorden, Svalbard (Campbell, 2010; Warner *et al.*, 2010 and 2013). According to Warner *et al.* (2010), sculpins are considered quite stationary and overwinter within the fjords on Svalbard, therefore observed concentrations are most likely due to uptake from this area. The authors further stated that no human settlements exist in Liefdefjorden, with cruise ship traffic during the summer being the only human influence impacting this fjord. These findings indicate that the long-range transport of D4, D5 and D6 (via air and/or water/oceanic currents) has contributed to the concentrations found in the sculpins.

68. Furthermore, the measurements of D4, D5 and D6 in fish and seabird migratory species such as polar cod (*Boreogadus saida*), liver and whole fish (nd–9.2 ng/g ww for D4, nd–19.1 ng/g ww for D5 and nd–10.7 ng/g ww for D6; Evenset *et al.*, 2009) and glaucus gull (*Larus hyperboreus*) liver and muscle (nd–6.5 ng/g ww for D4, 0.93–3.42 ng/g ww for D5 and 1.8–20.5 ng/g ww for D6; Campbell, 2010) in locations distant from known point sources such as Liefdefjorden, Billefjorden, Moffen and Bjørnøya in Svalbard indicate the potential for transfer of these substances to the remote environment via migratory species. The long-range transport potential of cVMS via migratory species is further supported by the findings of Warner *et al.* (2010) which noted that D6 concentration in Atlantic cod (*Gadus morhua*) liver from Kongsfjorden (having less human activity in the region compared to Adventfjorden) was higher compared to Atlantic cod from Adventfjorden ($p < 0.05$). Warner *et al.* (2010) indicated that although the local settlement of Ny-Ålesund was considered the most probable source of cVMS in Kongsfjorden, concentrations observed within Atlantic cod may also be a result of exposure to sources from southern populated regions. Furthermore, the findings of Warner *et al.*, (2010 and 2013), Campbell (2010) and Evenset *et al.* (2009) suggest that while the difference in D4, D5 and D6 concentrations in livers of shorthorn sculpin (*Myxocephalus scorpius*) and of polar cod (*Boreogadus*

[11] Due to the different half-lives of the two chemicals the D5/D4 ratio should be highest around localised emission (sources) and decrease as the air mass moves away from urbanised areas, as the D5 degrades at a faster rate.

saida) from Liefdefjorden might be explained by different bioaccumulation pattern, it cannot be ruled that it may also be attributed to fish migration patterns (migratory (polar cod) vs. stationary (sculpin)).

69. Finally, a benchmark exercise was performed in order to compare the concentrations of cVMS with the ones of known POP substances (before their inclusion to the Stockholm Convention) in marine sediment and in seabird eggs sampled at similar locations in remote areas. In marine sediment from the Norwegian Arctic sampled during the MAREANO programmes between 2009 and 2021, cVMS concentrations were up to 8.60 ng/g dw for D4, up to 0.17 ng/g dw for D5 and up to 0.8 ng/g dw for D6 while the concentrations of POP substances were up to 1.22 ng/g dw for PFOA, up to 1.20 ng/g dw for decaBDE or BDE-209, up to 0.25 ng/g dw for Dechlorane Plus (*syn* + *anti*) and <LOQ for PFHxS. In seabird pooled eggs from remote islands Sklinna and Røst on the Norwegian coast in 2012, cVMS concentrations were in the range nd–3.6 ng/g ww for D5 and nd–0.8 ng/g ww for D6 while the concentrations of POP substances were in the range of nd–1.61 ng/g ww for decaBDE (or BDE-209), 0.23–1.58 ng/g ww for PFHxS, 0.141–1.27 ng/g ww for PFOA and nd–0.080 ng/g ww for Dechlorane Plus (*syn* + *anti*) (Huber *et al.,* 2015). D4 was not detected (LOD of 2.1 ng/g ww) in the samples of seabird eggs. A LOQ of 0.5–2.7 ng/g ww for D4 was reported in NIVA (2022a) for the analysis of common eider eggs thus suggesting that the LOD determined in Huber *et al.* (2015) study is high, thus presence of D4 in the seabird eggs cannot be excluded. Overall, the benchmark approach indicates that cVMS concentrations are in similar ranges to concentrations of POP substances in marine sediment and seabird eggs.

Conclusion on long-range environmental transport according to the criteria in Annex D

70. D4, D5 and D6 have been measured in environmental and biota samples from remote regions (Arctic and Antarctic), indicating that the substances have the potential for long-range environmental transport. While modelling predict long-range atmospheric transport for these substances with a low potential for deposition to surface media, monitoring data indicate that long-range environmental transport of D4, D5 to D6, with the potential for transfer to a receiving environment, is possible via air, water and migratory species. The presence of D4, D5 and D6 in remote areas can be explained by atmospheric transport in the gas phase and bound to the atmospheric aerosols, followed by a possible deposition (wet deposition (via rain and snow), gaseous deposition (in particular on foliage) and dry aerosol-bound deposition (including on inorganic aerosols)) that cannot be ruled out. Furthermore, the measured levels of D4, D5 and D6 in deep marine sediments (up to a water depth of 1963 m) from the Norwegian Arctic seawaters, the Canadian Archipelago, the Arctic Ocean, the Atlantic Ocean and the Pacific Ocean indicate the potential of D4, D5 and D6 for long-range transport via the adsorption onto suspended matter and subsequent transport to sediment via water in rivers and ocean currents. These substances are persistent in sediments. Additionally, the presence of D4, D5 and D6 in migratory species in locations distant from known point sources such as Liefdefjorden, Billefjorden, Moffen and Bjørnøya in Svalbard indicate the potential for transfer of these substances to the remote environment via migratory species. It is therefore concluded that D4, D5 and D6 meet the Annex D criteria for potential long-range environmental transport 1. (d)(i), (ii) and (iii)).

3.4 Adverse effects

3.4.1 Adverse effects to the environment

71. D4 has a harmonised classification as a Reprotoxic category 2 (suspected of damaging fertility) and as Aquatic Chronic 1 (very toxic to aquatic life with long lasting effects).

72. As regards toxicity to aquatic organisms, D4 is toxic to fish (Rainbow Trout (*Oncorhynchus mykiss*)) with a long-term NOEC of around 4 – 6 µg/L (Sousa *et al.,* 1995). It is noted that this substance causes effects on mammalian reproduction, possibly involving an endocrine pathway and no data are available to determine whether it affects fish reproduction. D4 is also toxic to aquatic invertebrates (*Daphnia magna*) with a 21-day $NOEC_{survival}$ of 7.9 µg/L (Sousa *et al.,* 1995). A novel test method designed to test high volatile hydrophobic organic chemicals using headspace passive dosing (HS-PD) and following OECD TG 201 was performed with D4 (Trac *et al.,* 2018). The study shows that D4 induced a growth rate inhibition of 11% on algae (*Raphidocelis subcapitata)* when tested at the saturation level. This suggests an EC_{10} value very close to the solubility limit of D4 (around 51 µg/L) According to Trac *et al.* (2018) this result can be interpreted as a moderate chronic toxicity to algae. QSAR data in Environment Agency (2009a) further confirm that algae should not be more sensitive to D4 than fish or invertebrates. The available aquatic toxicity data for fish, invertebrates and algae show that D5 does not cause toxic effects in neither short- nor long-term studies at concentrations up to (or close to) its water solubility limit. No data are available to determine whether D5 affects fish reproduction. For D6, a long-term toxicity study on aquatic invertebrates *(Daphnia magna)* following OECD TG 211 (Springborn Smithers Laboratories, 2006) and a growth inhibition test on *Pseudokirchnerella subcapitata* following OECD TG 201 (Dow Corning, 2009) are available. In the

REACH registration dossier, the results of a bioaccumulation study (Drottar, 2005b) are used to fill the chronic toxicity in fish endpoint. No effects are seen in any of these studies up to the solubility limit of D6.

73. Radermacher *et al.* (2020) investigated the occurrence of D4, D5 and D6 in fillets of bream (*Abramis brama*) from major German rivers archived in the German Environmental Specimen Bank covering the period 1995 to 2017. The measured concentrations were assessed against the Environmental Quality Standard (EQS) values derived in the context of the Water Framework Directive 2000/60/EC implementation in Sweden (833 µg kg^{-1} for both D4 and D5 based on secondary poisoning risk for predators). When comparing the 5% fat-normalised data with the EQS, the following EQS exceedances for D5 were found: Rhine/Bimmen 2009, 2011; Saar/Güdingen 2017; Saar/Rehlingen 2003–2017; Saale 2007, 2009; Danube/Jochenstein 2005–2009. Thus, in these years feeding on fish caused a secondary poisoning risk to predators.

74. As regards toxicity to sediment organisms, the lowest NOEC for D4 is <0.73 mg/kg dry weight (dw), obtained in a 28-day study with *Lumbriculus variegatus* (OECD TG 225; Krueger *et al.*, 2009) (although a higher NOEC of 13 mg/kg dw was found for this species in a second study (Picard, 2009)). If the results are normalised to a standard organic carbon (OC) content of 5%, the $NOEC_{standard}$ is <1.5 mg/kg dw. In the REACH Restriction background document (ECHA, 2016a), a comparison was made with pelagic organisms (assuming that the effects occur due to exposure via pore water), and the equivalent pore water concentration was estimated to be around <2 µg/L (below its water solubility of 56.2 µg/L), thus indicating that D4 is toxic to sediment organisms. D5 is also toxic to sediment organisms. The lowest NOECs for long-term sediment toxicity studies for D5 are 70 mg/kg dw for *Chironomus riparius* (Krueger *et al.*, 2008) and 62 mg/kg dw for *Hyalella azteca* (Norwood *et al.*, 2010; a NOEC of 130 mg/kg dw was found for this species in a second study (Springborn Smithers, 2009)). No effects were seen in the sediment toxicity test for *Lumbriculus variegatus* with a NOEC ≥1272 mg/kg dw for D5 (test following guideline EPA OPPTS 850.1735; Wildlife International Limited, 2007). The lowest NOEC for D5 when normalised to a standard OC content of 5% is a $NOEC_{standard}$ of 109 mg/kg dw for *Ch. riparius*. For comparison with pelagic organisms (assuming that the effects occur due to exposure via pore water), the equivalent pore water concentration is estimated to be around 14 µg/L for D5 (below its water solubility of 17.03 µg/L), thus indicating that D5 is toxic to sediment organisms. As regards D6, the lowest NOEC for long-term sediment toxicity studies is < 22 mg/kg dw for *Chironomus riparius* (OECD TG 218, Wildlife International Limited, 2009). In a second study for the same species, no effects were seen with a resulting NOEC ≥620 mg/kg dw (OECD TG 218, Springborn Smithers Laboratories, 2010b). No effects were seen in the sediment toxicity test for *Lumbriculus variegatus* with a NOEC ≥420 mg/kg dw for D6 (OECD TG 225, Springborn Smithers Laboratories, 2010a). The lowest NOEC for D6 when normalised to a standard OC content of 5% is a $NOEC_{standard}$ < 41 mg/kg dw for *Ch. riparius*. For comparison with pelagic organisms (assuming that the effects occur due to exposure via pore water), the equivalent pore water concentration is calculated to be around <0.7 µg/L (below its water solubility of 5.3 µg/L), indicating toxicity of D6 to sediment organisms.

75. As regards toxicity to terrestrial organisms, limited toxicity test data are available for D4 and no data for D6, while D5 is concluded as toxic to soil organisms. D5 has been shown to cause effects in long-term toxicity tests on two plant species (barley *Hordeum vulgare* and durum wheat *Triticum durum*), springtails *Folsomia candida* and earthworms *Eisenia andrei*. The affected plants are monocots; no significant effects were noted with two dicot species (red clover *Trifolium pretense* and radish *Raphanus sativus*) (Soil Toxicology Laboratory, 2010; Velicogna *et al.*, 2012). The lowest reported IC_{50} was 209 mg/kg dw for barley (individual dry mass of barley roots after 14 days; other effects were noted at higher concentrations on shoot and root length). The organic carbon content of the soil used in the test was not given and so it is not possible to normalise the reported effect concentrations to a standard OC content of 2%, nor is it possible to estimate the equivalent pore water concentration at these exposure levels. The results are based on the initial concentration of D5 in soil. Significant loss through volatilisation would be expected in the test system used and so the actual exposure concentrations (and hence effect concentrations) may be significantly lower than those based on the initial concentration.

76. No relevant data for D4 and D6 are available for birds. For D5, no adverse effects have been observed in an avian reproduction test (OECD TG 206) using Japanese quail (*Coturnix coturnix japonica*) at concentrations up to 1,000 mg/kg feed (Stafford, 2012). However, the results should be used with care considering that it was a range finding tests with a possible low proportion of viable eggs for the control and not all endpoints were investigated (e.g. egg shell thickness).

3.4.2 Adverse effects to human health

77. The toxicity of D4, D5 and D6 has been evaluated by among others ECHA, US EPA, the Canadian ministries, Scientific Committee on Consumer Safety (SCCS), Danish Environment Protection Agency and UK Environment Agency. In the European Union, D4 has a harmonised classification as toxic to reproduction category 2 (H361f), meaning that it is suspected of damaging fertility, and included in Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation).

78. For D4 a two-generation reproductive toxicity study in rats performed similar to OECD TG 416 and according to GLP and five one-generation studies in rats and rabbits are available. For D5, there is a two-generation and one-generation study available in rats (see Appendix for details on the studies). In the studies for D4 and D5 the predominant route of exposure used was the inhalation route. According to toxicokinetic studies, D4 and D5 are not extensively absorbed by the oral route and therefore, the inhalation route of exposure is more suitable.

79. For D4 the main adverse effects observed were dose-dependent decreases in numbers of corpora lutea in three studies (Unpublished study report, 1998, Meeks *et al.*, 2007; Varaprath *et al.*, 1996) starting at 300 ppm (3640 mg/m³) with statistical significance at 700 ppm (8492 mg/m³), statistically significant increased pre- and post-implantation losses in two studies (Unpublished study report, 1998; Varaprath *et al.*, 1996) at a LOAEC of 700 ppm, decreased numbers of implantation sites in five studies (Unpublished study report, 1996b, 1997, 1998, ; Meeks *et al.*, 2007; Varaprath *et al.*, 1996) with a LOAEC of 500 ppm and statistically significant at 700 ppm (6066 and 8492 mg/m³, respectively) as well as statistically significant decreased mean live litter sizes in four studies (Unpublished study report, 1996b, 1997, 2001b; Siddiqui *et al.*, 2007a; Varaprath *et al.*, 1996) with a LOAEC of 500 ppm and lower number of pups born in three studies (Unpublished study report, 1997, 2001b; Siddiqui *et al.*, 2007a; Varaprath *et al.*, 1996) with a LOAEC of 500 and 700 ppm.

80. A possible mode of action for the fertility effects observed for D4 is that there might be an indirect action on hormonal control of the rat female reproductive system. The disturbance of ovulation through suppression of the luteinizing hormone (LH) surge was proposed as a plausible cause for the reproductive toxicity of D4 (CeHoS, 2018). In rats exposed to D4 via inhalation (whole body) for a single period of six hours a reduction in LH levels were observed (Unpublished study report, 2001a). Since LH surge is required for ovulation to occur, decreased fertility in rats being exposed to D4 on proestrus day may have been the result of a reduction in peak serum LH levels. This mechanism is analogous in both rats and humans; however, according to the Siddiqui *et al.* (2007a) humans do not have this critical short daily time window relevant for the pre-ovulatory LH surge. Barbiturates can also suppress LH release. Phenobarbital at a dose ≥ 100 mg/kg bw consistently blocks LH release (Alleva and Alleva, 1995). The clear absence of fertility effects in women treated with barbiturates, such as phenobarbital, could not be demonstrated given there is no such finding in numerous epidemiological studies, and a weak effect on fertility might be difficult to detect. In conclusion, it is unlikely but cannot be excluded that there is an effect of barbiturates on fertility (LGL, 2010).

81. No reproductive toxicity was observed for D5 in a two-generation reproduction study up to a concentration of 160 ppm (2496 mg/m³)(Unpublished study report, 1999b; Siddiqui *et al.*, 2007b ; Stump *et al.*, 2000) and in a one-generation study up to 132 ppm (2059 mg/m³) (Unpublished study report, 1996a; see Appendix for details on the studies). However, in a 90-day inhalation toxicity study in Fisher 344 rats a treatment-related increase in the incidence of ovarian interstitial gland hyperplasia and vaginal mucosal mucification and atrophy in female rats were observed at the top concentration of 233 ppm (3635 mg/m³) (Burns-Naas *et al.*, 1998). It is pertinent to note here that the concentration employed in the repeated dose toxicity study is a considerably higher than the maximum 160 ppm used in the reproductive toxicity study. This may account for the differences in effects on the reproductive system observed in the two types of studies.

82. D4 is considered to be an endocrine disruptor by CeHoS (Danish Centre on Endocrine Disrupters) (CeHoS, 2018 as cited in DEPA, 2021). This is based on a study undertaken to screen for potentially endocrine properties of D4 (i.e., estrogenic activity), which indicated that D4 had both a very weak estrogenic and anti-estrogenic activity. The potency of D4 in comparison to other estrogenic substances such as ethinylestradiol (steroid hormone used in p-pills) indicated that D4 is 585,000 times less potent than ethinylestradiol in the rat and 3.7 million times less potent than ethinylestradiol in the Fisher-344 rat strain. High oestrogen levels in the ovaries stimulate release of LH from the pituitary gland and stimulates ovulation. The two hormones interact via a feedback loop and therefore are physiologically linked. A relationship between the regulation of LH and oestrogen by D4 impacting effects on reproductive parameters cannot be excluded.

83. For D6, there is currently a combined screening study for reproductive/developmental toxicity available (Unpublished study report, 2005e). The increased number of non-gravid females at 1000

mg/kg bw/day was not statistically significant. The NOAEL for reproductive toxicity of D6 was established as ≥1000 mg/kg bw/day. An extended one-generation reproductive toxicity (EOGRTS, OECD TG 443) study is currently in development, but not yet completed or available for evaluation.

84. No evidence of D4-mediated developmental toxicity was reported in studies conducted in rats (Unpublished study report, 2001b; Siddiqui *et al.*, 2007; York and Schardein, 1994) and rabbits (Unpublished study report, 1994) with inhalation and oral exposure (see Appendix for details on the studies). In these studies, there were markedly increased post implantation losses and a reduction in the number of live foetuses was observed at the top dose of 1000 mg/kg bw/day. However, these effects were considered secondary to maternal toxicity (decreased food consumption).

85. For D5, no evidence of developmental toxicity was found in two studies according to OECD TG 414 in rats (Unpublished study report, 2020a) and rabbits (Unpublished study report, 2020b) and in a two-generation study in rats (Unpublished study report, 1999b; Siddiqui *et al.*, 2007b ; Stump *et al.*, 2000) with up to a concentration of 161 ppm (2412 mg/m³) via the inhalation route, which is the highest achievable vapour concentration (Unpublished study report,1999b; Stump *et al.*, 2000; SCCS, 2015; see Appendix for details on the studies).

86. For D6, no evidence of developmental toxicity was found in two studies according to OECD TG 414 in rats (Unpublished study report, 2017) and rabbits (Unpublished study report, 2018). Additionally, no developmental toxicity was observed in a reproduction/developmental toxicity screening test (OECD TG 422, GLP; Unpublished study report, 2005d; see Appendix for details on the studies) and a dose range finding study conducted on rats and rabbits up to the limit dose of 1000 mg/kg bw/day.

87. The carcinogenic potential of D4 was assessed in one study. In a combined chronic/carcinogenicity study (Unpublished study report, 2004a) (OECD TG 453, GLP) in which D4 (vapour) was administered to 60 Fischer 344 rats/sex/dose by inhalation route (whole body) at concentrations of 0, 10, 30, 150 and 700 ppm (equivalent to 0, 120, 360, 1820, 8490 mg/m^3) 6 hours/day, 5 days/week for 24 months. In this carcinogenicity study exposure to D4 at 700 ppm caused a statistically significant increase in incidence of uterine (endometrial) adenomas (7% at 700 ppm compared to 0% in control animals). The biological significance of these adenomas is unclear given that there does not appear to be a relationship between uterine weight increase, and histopathological changes and occurrence of tumours (as discussed below in relation to a repeated dose (inhalation) study for D4). Cystic endometrial hyperplasia was reported (78% at 700 ppm compared to 19% in control animals) at 700 ppm. In addition, considerable increases in absolute (46%) and relative (54%) uterus weight were seen at 700 ppm (Unpublished study report, 2004a). The NOAEL for D4 was established as 150 ppm based on increased occurrence of tumours in the uterus at 700 ppm by the SCCS (2010).

88. Since D4 is not genotoxic, a non-genotoxic mode of action is assumed for the tumour formation (SCCS, 2010, 2015). It was proposed that the endometrial adenomas and hyperplasia at 700 ppm in female rats could be attributed to a hormonal dysregulation resulting from dopamine-agonist activity of D4 (SCCS, 2010). D4 can act as a dopamine-agonist causing a reduction in prolactin. A reduction of prolactin in the rat causes luteolysis and new ovarian follicle stimulation resulting in oestrogen dominance, which leads to persistent endometrial stimulation and finally to uterine tumours (SCCS, 2010). Additionally, as discussed in Brott *et al.*, (2014) in maintaining dopaminergic inhibition of prolactin secretion, female reproductive senescence is delayed, which leads to prolonged stimulation of the endometrium and eventually tumours. However, differences in the reproductive ageing process between humans and rodents might mean that this mechanism is not relevant to humans. It is known that prolactin is not luteotropic (acting on the corpora lutea) in primates and humans (SCCS, 2010). However, it was concluded by SCCS that there is at present insufficient data to dismiss altogether the proposed neuroendocrine mode of action in rats as not relevant for humans (SCCS, 2010).

89. The carcinogenic potential of D5 was assessed in one study. In a combined chronic/carcinogenicity study (Unpublished study report, 2005a; EPA OPPTS 870.4300, GLP), D5 (vapour) was administered to 60 Fischer 344 male/female rats /dose by inhalation route (whole body) at doses of 0, 10, 40 and 160 ppm (0, 154, 616, 2464 mg/m^3) 6 hours/day, 5 days/week for 106 weeks. Exposure to D5 resulted in a statistically significant increase in the incidence of uterine endometrial adenocarcinomas at the highest concentration tested (160 ppm). The incidence of endometrial adenocarcinoma was 0, 1, 0 and 5 for female rats in the 0, 10, 40 and 160 ppm exposure groups, respectively. The SCCS derived a NOAEC of 40 ppm based on the occurrence of uterine endometrial adenocarcinomas in this study (SCCS, 2015). Similarly, to D4, D5 may act as a dopamine-agonist and affect prolactin secretion, thus contributing to the observed tumorigenic effects in female rats. The SCCS could not exclude this mode of action (MoA) as being relevant for humans given that a thorough MoA for this type of tumour has yet to be elucidated (SCCS, 2015).

90. The SCCS recognised that D4 and D5 may possibly act as dopamine 2-like receptors agonists, thus contributing to the observed tumorigenic effects in female rats (SCCS, 2010, 2015). The US EPA concluded that cancer hazard associated with D5 could not be completely excluded based on the data from available carcinogenicity study (US-EPA, 2003). The carcinogenic effects for both substances were significant only at highest concentrations tested and no clear MoA for tumour formation was postulated. The relevance of these effects to human is also uncertain (SCCS, 2010, 2015). Both substances are not genotoxic.

91. The human health effects of repeated oral exposure to D4, D5 and D6 have been evaluated in rats and rabbits and summarised in the Annex. The principal target organ for D4, D5 and D6 toxicity appears to be the liver with increased liver weight being the key systemic effect reported in five oral toxicity studies following exposure to D4 (one study)(Unpublished study report, 1990a; Environment Agency, 2009a; SCCP, 2010), D5 (two studies)(Unpublished study report, 1990b, 1991a; Environment Canada, 2008b; SCCP, 2015) and D6 (two studies) (Unpublished study report, 2005d; Environment Agency, 2009a)

92. The LOAEL for both D4 and D5 in relation to increased liver weight in subacute oral repeated toxicity studies in rats was 25 mg/kg bw/day (Environment Agency, 2009a and b) . The lowest NOAEL for increased liver weight based on subchronic oral toxicity studies in rats was 300 mg/kg bw/day for D6, with a LOAEL of 1000 mg/kg bw/day which is the highest tested dose in this study (Unpublished study report, 2005d; Environment Agency, 2009c).

93. Liver enlargement is considered to be relevant in humans. Liver weight increases greater than 10% were considered by the UK Environment Agency to be outside of normal human variation (in the absence of historical control data to compare with) and therefore to potentially affect human health. The incidence and severity of adverse effects observed appear to be greater in short term studies and in longer term studies the effects are generally similar to adaptive and/or reversible. Female animals were found to be more sensitive to the liver effects mediated by D5 following oral exposure compared to males.

94. Repeated inhalation toxicity studies of up to 2 years in rats are available for D4 (three studies), D5 (five studies) and D6 (one study) and summarised in Annex. A key effect reported in the inhalation studies was increased liver weights with accompanying hypertrophy (Unpublished study report, 2005b; ; Burns-Naas *et al.*, 1998; Environment Agency, 2009a; SCCS, 2010, 2015). Increased liver weight was observed for D4 (LOAEC 30 ppm) (Environment Agency, 2009a) and D5 (LOAEC 160 ppm in females only; Environment Agency, 2009b), but not for D6 following repeated inhalation exposures (Unpublished study report, 2013). Histopathological findings in the liver were reported for D4 (LOAEC 700 ppm)(SCCP, 2010) and D6 (LOAEC 10 ppm; Unpublished study report, 2013) only.

95. Levels of gamma-glutamyl transferase, a marker for liver damage, were increased following inhalation exposure to D5 (LOAEC 49.2 ppm in females and 233 ppm in males; Burns-Naas *et al.*, 1998). Hepatocyte hypertrophy could be attributed to cytochrome P450 enzyme induction in the liver. Significant dose and age dependent induction of liver microsomal CYP2B isoforms in rats following oral exposure to D4 has been reported, which may contribute to liver enlargement (Falany and Li, 2005; Zhang *et al*., 2000).

96. Liver effects were less pronounced in longer term studies (6, 12, or 24 months of exposure) suggesting that this effect may be a short-term, reversible effect. Female animals were found to be more sensitive to the liver effects mediated by D5 following inhalation exposure compared to males.

97. The lowest NOAEC for increased liver weight based on subchronic inhalation toxicity studies in rats is 10 ppm for D4 (Unpublished study report, 1991b; Environment Agency, 2009a; SCCP, 2005). The lowest NOAEC for liver enlargement is 28 ppm for D5 (Burns-Naas et al., 1998; SCCS, 2010, 2015).

98. The nasal cavity was a target organ for inhalation exposure to D5 and D6 (Unpublished study report, 2005c, 2013; Burns-Naas *et al.*, 1998; SCCS, 2010). The key findings in the respiratory tract were proliferation of goblet cells in the nasal cavity accompanied by submucosal inflammation, focal macrophage accumulation, and minimal to slight interstitial inflammation in the lungs (see Appendix for further details). These effects are considered adverse and are consistent with effects expected during chronic inhalation of irritating substances.

99. The lowest NOAEC for local nasal cavity effects is 1 ppm for D6 in rats (Unpublished study report, 2013) and 40 ppm for D5 in rats (Unpublished study report, 2005c). The effects in the nasal cavity when compared against the criteria for repeated dose inhalation toxicity in the CLP regulation, could mean that the data for D6 would meet the criteria for STOT RE (Category 1) for local effects on the nasal cavity.

100. Chronic interstitial inflammation in the lungs was increased in all treated groups for D4 following inhalation exposure for 90 days. The severity of this finding was increased in female rats of 480 ppm animals and both sexes of highest exposure (883 ppm) group. A NOAEC of 34 ppm was identified for the lung effects (Unpublished study report, 1995).

101. Histopathological analysis of the uterus following inhalation exposure to D4 showed hyperplasia together with increased absolute and relative uterus weight (Unpublished study report, 2004a). Uterine endometrial adenomas were also reported in the study, but the incidence was low, and the human relevance of the tumour is questionable as discussed above in relation to carcinogenic potential. Additionally, uterine tumours were reported to occur at lower concentrations of 30 ppm compared to uterine weight changes at 150 ppm. This may cast doubt on the relationship between uterine weight increase, histopathological changes and occurrence of tumours.

102. D4 mediated effects on the ovaries (LOAEC unknown given that the dose at which this effect occurred was not specified), with decreased ovary weight being reported following inhalation exposure (Unpublished study report, 1998; see Appendix for more information). These effects were not considered to be adverse given that there were no histopathological changes reported and this was not accompanied with adverse effects on fertility for D4. Therefore, any impact on fertility from ovary effects is likely to be negligible in the absence of fertility effects. Nevertheless, D4 has a harmonised classification as toxic to reproduction category 2 (H361f: suspected of damaging fertility) according to CLH.

Conclusion on adverse effects according to the criteria in Annex D

103. The Annex D criteria for Adverse effects 1.(e)(i) and (ii) are considered to be met for D4, D5 and D6.

104. The adverse effects to the environment are based on harmonised classification of D4 as Aquatic Chronic 1 (very toxic to aquatic life with long lasting effects). D4 is toxic to fish and to aquatic invertebrates. A novel test method using headspace passive dosing indicates that D4 has as a moderate chronic toxicity to algae. Information on D5 and D6 do not suggest their ecotoxicity towards fish, aquatic invertebrates and algae, when the information is available. D4, D5 and D6 are concluded toxic to sediment organisms (toxicity to *Lumbriculus variegatus* for D4 and to *Chironomus riparius* for D5 and D6). As regards toxicity to terrestrial organisms, limited toxicity test data are available for D4 and no data for D6, while D5 is concluded as toxic to soil organisms. D5 has been shown to cause effects in long-term toxicity tests on two monocot plant species (barley *Hordeum vulgare* and durum wheat *Triticum durum*), springtails *Folsomia candida* and earthworms *Eisenia Andrei*. No relevant data for D4, D5 and D6 are available for birds.

105. As regards adverse effects to human health, D4 has a harmonised classification as toxic to reproduction category 2 (H361f). Inhalation exposure to D4 caused adverse effects on fertility in rats. It is noted that D4 causes effects on mammalian reproduction, possibly involving an endocrine pathway (i.e., estrogenic activity). Disturbance of ovulation through suppression of the LH surge is proposed as a plausible MoA for the reproductive toxicity of D4. No reproductive toxicity effects were identified for D5 in the available studies; however, the available data is limited by the use of a suitable D5 dose range (the concentrations employed were not sufficiently high enough).

106. The available data indicates a carcinogenic effect (uterine tumours) for D4 and D5 in rats. Based on the absence of genotoxicity by D4 and D5, a non-genotoxic MoA is assumed for the tumour formation. A threshold for carcinogenicity is further supported by the available studies where lower concentrations of D4 and D5 did not elicit tumours. The MoA for uterine tumour development is unclear given that the tumours occurred at concentrations that did not impact on uterine weights or histopathology. The human relevance of these effects cannot be excluded.

107. There is sufficient evidence of adversity to human health related to exposure to D4, D5 and D6 by both the inhalation and oral exposure routes. The critical effects associated with these three substances is liver enlargement accompanied with histopathological findings. While histopathological findings in the liver were not reported for D5 this was a result of this parameter not being included for assessment. Effects in the lungs and nasal cavity are consistent with chronic inhalation of irritative substances. These local effects occur at lower doses than liver effects following inhalation exposure and can be considered as the critical effect for D4, D5 and D6. The effects in the nasal cavity when compared against the criteria for repeated dose inhalation toxicity in the CLP regulation, could mean that the data for D6 would meet the criteria for STOT RE (Category 1) for local effects on the nasal cavity.

4. Statement of the reasons for concern and need for global action

108. Based on the existing data, D4, D5 and D6 can be considered to meet the screening criteria in Annex D of the Stockholm Convention for persistence, bioaccumulation, long-range transport and adverse effects.

109. D4, D5 and D6 do not occur naturally in the environment. They are released to the environment mainly as a result of their presence as intentional constituents or impurities in a very wide variety of consumer products and as residual impurities in silicone polymers. The application of D4-, D5- and D6-containing pesticides on crops and the disposal of sewage sludge on agricultural lands, by incineration and by deposit in landfills will result in the release of D4, D5 and D6 to environmental media. D4, D5 and D6 are persistent, bioaccumulative, present adverse effects to the environment and to the human health and undergo long-range environmental transport, making emissions of these substances a transboundary pollution problem including in remote areas. Globally, the occurrence and distribution of D4, D5 and D6 is shown for humans, wildlife and the environment. Detections include measurements in the Arctic and Antarctica.

110. D4, D5 and D6 have been frequently detected in the environment and in biota globally. They have been detected in numerous environmental matrices worldwide including in the Arctic (in air, marine sediment and in biota samples (avian and marine)) and in Antarctica (in soil, in marine and terrestrial biota samples). D4, D5 and D6 have been detected in human: plasma, abdominal fat and breast milk. cVMS have also been detected in seafood intended for human consumption so that it cannot be ruled out that humans can be exposed to VMS through their diet.

111. The concern for adverse effects includes toxic effects on reproduction (D4), potential endocrine disruption (D4), carcinogenic effects in rats (uterine tumors; D4 and D5), effects in lungs and nasal cavity (D4, D5 and D6) and liver enlargement (D4, D5 and D6) with histopathological findings (D4 and D6). D4, D5 and D6 are toxic to aquatic organisms (including sediment) and D5 is toxic to terrestrial organisms such as plants. Due to their POP properties, concentrations of D4, D5 and D6 in biota from the Arctic and Antarctica and in humans indicate a potential for adverse effects in wildlife and humans.

112. Since D4, D5 and D6 demonstrate persistence and long-range transport, measures taken nationally or regionally are not sufficient to safeguard a high level of protection of the environment and human health, and therefore wider international action is necessary.

113. Based on the persistence, bioaccumulation, toxicity to aquatic organisms (including sediment) and in terrestrial organisms (including humans) and the widespread occurrence in environmental compartments including remote regions, it is concluded that the use of D4, D5 and D6 is likely to lead to significant adverse human health and environmental effects such that global action is warranted.

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Appendix

1. Additional information for Adverse effects to humans

1.1. Reproductive toxicity

1.1.1. In the two-generation reproduction study (Unpublished study report, 2001b and Siddiqui *et al.*, 2007a) conducted according to EPA OPPTS 870.3800, similar to OECD 416 and in compliance with GLP, D4 was administered to 30 male and female Sprague-Dawley rats (F0 and F1) per concentration by inhalation (whole body) at concentrations up to 700 ppm. Exposure period was for F0 and F1 males and females at least 70 days prior to mating, throughout mating, gestation (to GD 20), lactation, with the exception of lactation days 0-4, until euthanasia. Starting on postnatal day (PND) 22, F1 weanlings were exposed to D4 as described for the F0 generation. The F2 pups were not directly exposed to D4. Extended parturition and/or dystocia was observed and the following statistically significant effects were observed: reduction in fertility indices in first mating period, reduction in mating indices, reductions in mean live litter sizes and mean number of pups born. In addition, increased gestation length in F0 and F1 females and dose-related reduction in corpora lutea in F1 females were observed. The NOAEC for reproductive toxicity and systemic toxicity was established as 300 ppm.

1.1.2. In the one-generation reproductive toxicity study of Unpublished study report (1997) D4 was administered to 22 Sprague-Dawley female rats/dose by whole body inhalation at concentrations up to 700 ppm (no guideline followed). Female F0 were exposed to D4 daily for 6 h for period of at least 70 consecutive days prior to mating, during mating and gestation until day 21 and during lactation days 5 to 21 and pups on postnatal day 21 to 27. Males were unexposed. This study was conducted to identify adverse reproductive effects of D4 in female rats. Adverse effects comprised of reductions in mean live litter size and in the number of pups born and reduction in the number of implantation sites. The NOAECs for maternal and reproductive toxicity were 70 and 500 ppm, respectively.

1.1.3. In another one-generation reproductive toxicity study of Varaprath *et al.* (1996) D4 was administered to 22 male and female Sprague-Dawley rats/dose by inhalation (6 h/day; whole body) at 700 ppm, for at least 28 consecutive days prior to mating, during mating, until completion of breeding period (males) and until gestation day 20 (females). Adverse effects observed were reductions in mean live litter size, decrease in mean number of implantation sites, decrease in number of corpora lutea, increased pre-implantation losses and a numerical difference between the number of implantation sites and the number of offspring. The NOAEC was established as <700 ppm for reproductive effects.

1.1.4. In a one-generation reproductive toxicity study of Unpublished study report (1996b), D4 was administered to 20 male and female Sprague-Dawley rats/dose by inhalation (6 h/day; whole body) at concentrations up to 700 ppm for at least 28 consecutive days prior to mating, during mating and lactation day 21 (suspended from GD 21 through lactation day 4). Pups were exposed daily (6 h/day) on days 21 – 28. Mean body weight gain was reduced in males (weeks 1 – 6) and females (over the entire gestation period) at 700 ppm. Following adverse effects on reproduction were observed in the study: reduction in the mean live litter size and reduction in the number of implantation sites. The NOAEC was established at 70 ppm.

1.1.5. In a one-generation reproductive toxicity study of Unpublished study report (1998) and Meeks *et al.* (2007), D4 was administered to Sprague-Dawley female rats (F0 and offspring) by inhalation (6 h/day; whole body) at concentrations up to 700 ppm in the overall phase (28 days prior to mating until GD 19), in ovarian phase (31 days prior to mating until 3 days prior to mating), in fertilization phase (3 days prior to mating until GD3) and implantation phases (from GD 2 to GD 5). In the overall phase a statistically significant reduction in the mean numbers of corpora lutea was observed, increased pre- and post-implantation loss, significant reduction in the mean number of viable foetuses and statistically significant reduction in mean gravid uterine weight. In the fertilization phase the following statistically significant effects were observed: decrease in the mean number of corpora lutea, increase in the percentage of pre-implantation loss, reduction the mean number of implantation sites and reduction in the mean number of viable foetuses and gravid uterine weight. The NOAECs for parental and reproductive toxicity were 70 and 300 ppm, respectively.

1.1.6. Additionally, in a reproductive toxicity study (Unpublished study report, 1999a and Meeks *et al.*, 2007) female Sprague-Dawley rats were exposed via whole body inhalation to 700 ppm of D4 for 6 h/day by multiple or single exposure on different days prior or after mating. The main adverse effects were statistically significant reduction in the fertility index (pre-mating phase, exposed 1 day prior to mating), reduced numbers of corpora lutea and implantation sites and statistically significant reduction of the mean numbers of corpora lutea and in absolute mean uterine weights (pre-mating phase, exposure in the 3 days prior to mating until GD3 group).

1.1.7. In a developmental toxicity study (Unpublished study report, 1993b; Siddiqui *et al.*, 2007; York and Schardein, 1994) conducted similar to OECD 414 and in compliance with GLP, D4 was administered to female Sprague-Dawley rats by whole body inhalation at 0, 100 ppm, 300 ppm, or 700 ppm from GD 6-15. There were no treatment-related effects in mortality, clinical signs or caesarean parameters. Statistically significant reductions in body weight gain and maternal food consumption were noted in the highest exposure group (700 ppm) over the entire gestation period (gestation days 0 – 20). The maternal LOAEC is 700 ppm based on the reductions in body weight gain and food consumption. The maternal NOAEC is 300 ppm. There were no treatment-related developmental effects. There were no treatment-related malformations or developmental variations. The developmental NOAEC is ≥700 ppm.

1.1.8. In a developmental toxicity study (Unpublished study report, 1993a; York and Schardein, 1994) similar to OECD 414 and in compliance with GLP, which is referenced in the registration dossier, D4 was administered to female New Zealand White rabbits by whole body inhalation at concentrations of 0, 100 ppm, 300 ppm or 500 ppm from days 6 through 18 of gestation. There were no treatment-related effects in mortality, clinical signs, body weight or caesarean parameters. Statistically significant reductions in maternal food consumption were noted in the highest exposure group (500 ppm) during the first and second exposure intervals (gestation days 6-9 and 9-12). The maternal LOAEC is 500 ppm based on the reduction in food consumption. The maternal NOAEC is 300 ppm. There were no treatment-related effects in developmental parameters. There were no treatment-related malformations or developmental variations. The developmental NOAEC is ≥500 ppm.

1.1.9. In a one-generation reproduction study (Unpublished study report, 1996a) D5 was administered to Sprague-Dawley rats/group by whole body inhalation at concentrations of 26 or 132 ppm for at least 28 consecutive days prior to mating and through the day of necropsy for each F0 animal, except exposure of F0 females was suspended from gestation day 21 through lactation day 4. No adverse effects on body weights, body weight gain, food consumption, mortality and reproductive parameters (fertility, mating, days between pairing and coitus, gestation, parturition) were observed in the study. The NOAEC for maternal toxicity and reproductive/developmental effects was established at ≥132 ppm.

1.1.10. In a developmental toxicity study (Unpublished study report, 2020a) conducted according to OECD 414 and in compliance with GLP, Sprague-Dawley rats were exposed via whole body inhalation to 0, 32 ppm, 74 ppm and 161 ppm D5 (highest achievable vapour concentration). No adverse treatment related effects on maternal toxicity (mortality, clinical signs, body weight, food consumption), maternal developmental toxicity (pregnancy rates, resorption rates, litter size, numbers of corpora lutea or implantations, pre- and post-implantation loss or gravid uterine weights) and developmental toxicity (fetal body weight, number of live offspring, sex ratio, litter size and weights, skeletal and visceral malformations) were observed in the study. Dams in the 161 ppm group had a slight statistically significant increase in absolute (10.9%) and relative (9.3%) liver weights compared to controls. These were considered treatment related but non-adverse due to the small magnitude of change compared to controls. The NOAEC for maternal and developmental effects was >161 ppm.

1.1.11. Additionally, developmental toxicity of D5 was investigated in a two-generation reproduction study (Unpublished study report, 1999b; Siddiqui *et al.*, 2007b; Stump *et al.*, 2000) conducted according to EPA OPPTS 870.3800 and in compliance with GLP in Sprague-Dawley rats. No developmental neonatal toxicity or developmental neurotoxicity were observed in the study after exposure to D5 up to 160 ppm (highest concentration tested).

1.1.12. In the evaluation of the study (SCCS, 2015), a slight, but statistically significant, increase in the mean F1 male pup anogenital distance (AGD) at 160 ppm was noted. This effect could indicate an anti-estrogenic or androgenic effect of D5. However, the other studies available for D5 failed to show such hormonal activity (SCCS, 2015) and a NOAEC of 160 ppm was established for developmental toxicity of D5 based on the results of this two-generation study.

1.1.13. In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (Unpublished study report, 2005d) conducted according to OECD 422 and in compliance with GLP Sprague-Dawley rats were daily exposed to D6 via gavage at doses of 0, 100, 330 and 1000 mg/kg bw/day. No adverse effects on developmental parameters (fetal body weight, number of live offspring, sex ratio, litter size and weights, postnatal survival) were observed in the study. No external skeletal and visceral malformations were reported related to the treatment with D6. The NOAEL for developmental effects was established as least 1000 mg/kg bw/day.

1.1.14. In a developmental toxicity study (Unpublished study report, 2017) conducted according to OECD 414 and in compliance with GLP, D6 was administered to females RccHan:WIST rats via gavage at 0, 100, 330 and 1000 mg/kg bw/day from GD 6-20. No adverse treatment related effects on maternal toxicity. No adverse effects on developmental toxicity were reported in the study. The NOAEL for maternal and developmental effects was established as at least 1000 mg/kg bw/day.

1.1.15. In a developmental toxicity study (Unpublished study report, 2018) conducted according to OECD 414 and in compliance with GLP, D6 was administered to females New Zealand White rabbits via gavage at 0, 100, 300 and 1000 mg/kg bw/day from GD 7-27. No adverse effects on maternal toxicity, fertility and developmental toxicity were observed in the study. The NOAEL for maternal and developmental effects was established as at least 1000 mg/kg bw/day.

1.2. Repeated Dose Toxicity

1.2.1. In the study of Unpublished study report (2004b) male and female Fischer 344 rats were exposed via inhalation (whole body) to D4 vapour at concentrations of 0, 10, 30, 150 and 700 ppm for 6 months, 12 months, 12 months + 12 months recovery or 24 months (according to EPA OPPTS 870.4300, GLP). The main target organs affected were liver, lungs, and uterus. The NOAEC was 10 ppm for systemic effects (liver enlargement) after 6 months (Environment Agency, 2009a SCCP, 2010). Increased absolute and relative uterus weight was observed accompanied by hyperplasia at 700 ppm. Liver weight increases were accompanied by statistically significant centrilobular hypertrophy of hepatocytes. Increased incidence of goblet cell hyperplasia was seen in the nasal mucosa. Significant increases of the severity of chronic nephropathy compared to controls was seen from 30 ppm in males and from 150 ppm in females. The nephropathy observed was not considered relevant to humans.

1.2.2. In the study of Unpublished study report (1995) male and female Fischer 344 rats were exposed via inhalation (nose only) to D4 vapour at concentrations of 0, 34, 120, 480 and 883 ppm for 90 days (according to OECD TG 408, GLP). The main target organs affected were liver, lungs and ovary. The NOAEC for local effects on the lung was 34 ppm. The NOAEC was 122 ppm for a 20% increase in liver weight in females (Environment Agency, 2009a). Ovarian atrophy was observed at a slight to moderate degree and was not reversible at the highest tested concentration. A dose-dependent increase in group mean liver absolute weight and liver to body and brain weight ratios was noted. An increased incidence of goblet cell proliferation of the nasal cavity and nasopharyngeal tract was observed at the highest tested concentration. Chronic interstitial inflammation in the lungs was increased in all treated groups.

1.2.3. In the study of Unpublished study report (2005c) male and female Fischer 344 rats were exposed via inhalation (whole body) to D5 vapour at concentrations of 0, 10, 40 and 160 ppm for 2 years (according to OECD TG 453, GLP). The main target organs affected were liver and lungs. The NOAEC for effects on the lungs and liver was 40 ppm. Increased liver weights in females (11.6%) after 6 and 12 months and in males after 2 years was observed at 160 ppm. Histomorphological changes in the nasal cavity were consistent with chronic inhalation of irritating substances. A statistically significant increase in hyaline inclusions in the nasal respiratory/olfactory epithelium was noted in male and/or female rats of 160 ppm group.

1.2.4. In the study of (Burns-Naas *et al.,* 1998) male and female Fischer 344 rats were exposed via inhalation (nose only) to D5 vapour at concentrations of 0, 28.6, 49.2, 87.7 and 233 ppm for 90 days, with a recovery period of 1 month for a satellite control and top concentration group (according to OECD TG 413, GLP). The main target organs affected were liver and lungs. The NOAEC was 25 ppm for increased liver weight (15%) and increased gamma-glutamyl transferase levels. Reversible increases in absolute and relative liver weights (marginal to slight, but statistically significant) was observed at all concentrations ≥49.2 ppm. An increased incidence of subacute/chronic multifocal alveolitis was reported at the two highest doses in males and females, which was irreversible at the highest concentration of D5. Other local effects of focal interstitial inflammation on the lungs and minimal to slight goblet cell hyperplasia of the respiratory mucosa (Burns-Naas *et al.,* 1998).

1.2.5. In the study reviewed by (SCCS, 2010) Fischer 344 rats were exposed via inhalation (whole body) to D5 vapour at concentrations of 0, 10, 25, 75 and 160 ppm for 28 days, with a 14 day recovery period (no detail on OECD TG 413 or GLP status). The main target organs affected were liver and lungs. The NOAEC was 75 ppm for increased liver weight (15%). A statistically significant increase in liver weight of 15% above controls was observed in females exposed to 160 ppm without accompanying histopathology. Foci of alveolar macrophage accumulation and focal interstitial inflammation was not completely resolved by the end of the one month recovery period.

1.2.6. In the study of (Unpublished study report, 2013) Sprague-Dawley rats were exposed via inhalation (whole body) to D6 vapour at concentrations of 0, 1, 10 and 30 ppm for 90 days, with a 28 day recovery period (according to OECD TG 413, GLP). The main target organs affected were liver and lungs. The NOAEC was 1 ppm for increased liver weight and lung effects. An increased incidence of minimal alveolar macrophages was observed in the lung and mild periportal hepatocellular vacuolation in the liver of females, which resolved after a 28-day recovery period. The inflammation and hyperplasia of the nasal cavity is consistent with a mucosal irritant and were considered adverse and support classification as STOT RE (Category 1).

1.2.7. In the study of Unpublished study report (1990a) male and female Sprague-Dawley rats were exposed by gavage to D4 at doses of 0, 25, 100, 400 and 1600 mg/kg bw/day for 2 weeks. The NOAEL was 25 mg/kg bw/day based on 17% liver enlargement in females at the next dose. Statistically significant increases (10%) in relative liver weight in both males and female animals occurred (Environment Agency, 2009a). The liver weight increases are considered adverse.

1.2.8. In the study of Unpublished study report (1990b) male and female Sprague Dawley rats were administered D5 by gavage at dose of 0, 25, 100, 400 and 1600 mg/kg bw/day for 14 days (according to OECD TG 407, GLP). The LOAEL was 25 mg/kg bw/day based on liver weight increases of 31% (Environment Agency, 2009b). The liver weight increase was accompanied by liver lesions, but no detail about the nature of the lesions were provided by the study authors. The liver weight increases are considered adverse.

1.2.9. The liver effects observed in these studies were at times reversible and so considered to be adaptive and possibly caused by induction of xenobiotic metabolising enzymes such the cytochromes P450. A measurable enzyme induction (CYP2B1/2, PROD, EROD, CYP3A1/2) was reported at 5 mg/kg bw/day, with a NOEL of 1 mg/kg bw/day in Sprague Dawley rats when administered D5 accompanied by increases in relative liver weight (Environment Agency, 2009b).

1.2.10. In the study of Unpublished study report (2005d) male and female Crl:CD rats were administered D6 by gavage at dose of 0, 100, 330 and 1000 mg/kg bw/day for 28 days (according to OECD TG 422, GLP). The NOAEL was 300 mg/kg bw/day for this study based on a statistically significant increase in liver size at the top dose (Environment Agency, 2009c).