ACES REPORT 22

Octamethylcyclotetrasiloxane (D4)

EQS data overview

Sara Sahlin, Marlene Ågerstrand

Department of Environmental Science and Analytical Chemistry (ACES)

Stockholm University

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Preface

The Department of Environmental Science and Analytical Chemistry (ACES) at Stockholm University was commissioned, by the Swedish Agency for Marine and Water Management and the Swedish Environmental Protection Agency, to perform a literature overview and possible EQS derivation for the specific pollutant Octamethylcyclotetrasiloxane (D4). The work was performed under the Water Framework Directive (2000/60/EC) using the European Communities's guidance document "Technical Guidance for Deriving Environmental Quality Standards".

The report was prepared by Sara Sahlin and Marlene Ågerstrand. Michael McLachlan provided input on a draft version of the report.

Stockholm, April 23rd, 2018
The Department of Environmental Science and Analytical Chemistry (ACES)
Stockholm University

Förtydligande från Havs- och vattenmyndigheten

Havs- och vattenmyndigheten planerar att ta med oktametylcyklotetrasiloxan (D4) bland de ämnen som regleras i Havs- och vattenmyndighetens föreskrifter (HVMFS 2013:19) om klassificering och miljökvalitetsnormer avseende ytvatten[1]. Stockholms Universitet har därför på uppdrag av Havs- och vattenmyndigheten och Naturvårdsverket tagit fram beslutsunderlag för att kunna etablera bedömningsgrunder för D4. Utifrån litteratursökning och granskning av underlag har förslag på värden beräknats utifrån de riktlinjer som ges i CIS 27 (European Communities, 2011). Slutgiltigt val av värden att utgå ifrån vid statusklassificering har föreslagits av Havs- och vattenmyndigheten och efter dialog med deltagare i en arbetsgrupp (representanter från Kemikalieinspektionen, Naturvårdsverket och Läkemedelsverket). Då stor del av underlaget har varit sekundär information (dvs. inte offentligt tillgänglig) har det för Stockholms universitet inte varit möjligt att granska studiernas tillförlitlighet och relevans.

I enlighet med detta föreslås för limniska respektive marina sediment **15 µg/kg torrvikt respektive 1,5 µg/kg torrvikt**. Båda värdena avser sediment med 5% TOC. För biota och skydd av topp-predatorer föreslås värdet **830 µg/kg våtvikt.** Vid omräkning av biotavärdet till limnisk vattenfas erhålls värdet 0,06 µg/L. En jämförelse med det värde som skulle vara motiverat för vattenlevande organismer (0,44 µg/L) tyder på att det är organismer högre upp i näringskedjan är mer känsliga än pelagiska organismer. Vid statusklassificering är det därför lämpligt att huvudsakligen utgå från uppmätta halter i biota eller sediment. På grund av begränsat dataunderlag har alla värden tagits fram genom deterministisk beräkning.

Notera att bedömningsgrunder för D4 ännu inte har beslutats.

[1] https://www.havochvatten.se/hav/vagledning--lagar/foreskrifter/register-vattenforvaltning/klassificering-och-miljokvalitetsnormer-avseende-ytvatten-hvmfs-201319.html

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1. METHOD CONSIDERATIONS

Legal frameworks

The work was performed under the Water Framework Directive (2000/60/EC) using the European Communities's (2011) guidance document "Technical Guidance for Deriving Environmental Quality Standards".

Quality Standards (QS) for pelagic communities are derived to cover long-term (Annual Average: AA-QS) and short-term (Maximum Acceptable Concentration: MAC-QS) exposure. Risks for benthic communities and secondary poisoning for predators and human consumption of fishery products are addressed in the derivations of $QS_{sediment}$, $QS_{biota\ sec\ pois}$ and $QS_{biota\ hh}$, respectively. The critical QS compartment (converted to water concentration) is used to set the overall Environmental Quality standard (EQS). This dossier, however, propose QS expressed for specific compartments.

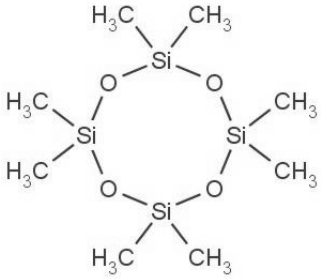
Data sources

The environmental information regarding properties and (eco)toxicity of D4 have been collected from the scientific literature (literature search conducted in March 2017), several reports from regulatory agencies, including the REACH registration dossier (ECHA 2017a), the CLP report (ECHA 2017b), the PBT evaluation (ECHA 2012), the Annex XV restriction report (ECHA 2015), the report from the Scientific Committee on Consumer Safety (SCCS 2010), and in assessments performed by UK, Canada and Netherlands (EA 2009; Environment Canada 2008; RIVM 2012). Most of the available information was collected from secondary literature and only a few (eco)toxicity studies were publicly available.

Due to the lack of publicly available studies, reliability evaluations (based on Klimisch score) were collected from the UK risk assessment (EA 2009), REACH Registration Dossier (ECHA 2017a) and the CLP report (ECHA 2017b). The studies were assigned as: (1) Reliable without restrictions, (2) Reliable with restrictions, (3) Not reliable or (4) Not assignable.

The following databases were used: Scopus; Web of science; Google Scholar; ETOX; Ekotoxzentrum; UBA; INERIS; RIVM; The following keywords were used: Octamethylcyclotetrasiloxane* OMCTS * Cyclomethicone* D4 and ecotoxicity* toxicity* sediment toxicity*mammal toxicity* avian toxicity.

2. CHEMICAL IDENTITY

Common name	**Octamethylcyclotetrasiloxane**
Chemical name (IUPAC)	2,2,4,4,6,6,8,8-octamethyl-1,3,5,7,2,4,6,8-tetraoxatetrasiloxane
Synonym(s)	D4; 2,2,4,4,6,6,8,8-octamethyl-1,3,5,7,2,4,6,8-tetroxatetrasilocane
Chemical class (when available/relevant)	Cyclic volatile methyl siloxanes (cVMS)
CAS number	556-67-2
EU number	209-136-7
Molecular formula	C8H24O4Si4
Molecular structure	
Molecular weight (g.mol^{-1})	296.61

3. EXISTING EVALUATIONS AND REGULATORY INFORMATION

Annex III EQS Dir. (2008/105/EC)	Not included
Existing Substances Reg. (793/93/EC)	Not included
Pesticides(91/414/EEC)	Not applicable
Biocides (98/8/EC)	Not applicable
PBT substances	PBT assessment under the previous EU chemical legislation (under REACH): D4 is under evaluation.
Substances of Very High Concern (1907/2006/EC)	No
POPs (Stockholm convention)	Proposed for the listing of additional chemicals in Annex A, B and/or C.
Other relevant chemical regulation and restriction proposals	Regulated under Cosmetic products Regulation 1223/2009/EC (not included in any Annex). *"Shall not be placed on the market in wash-off cosmetic products in a concentration equal to or greater than 0.1 % by weight of either substance, after 31 January 2020. "* Commission Regulation (2018/35/EU) amending Annex XVII to Regulation (EC) No 1907/2006. *"Shall not be included in the product, neither as part of the formulation nor as part of any mixture included in the formulation"* Establishing the ecological criteria for the award of the EU Ecolabel for rinse-off cosmetic products (2014/893/EU). "Leave- on" personal care products and other consumer/professional products (e.g. dry cleaning, waxes and polishes, washing and cleaning products) containing D4/D5 in concentrations > 0.1% shall not be placed on the market." (expected submission on 13/04/2018) (REACH).
Endocrine disrupter	Not listed on the PACT list as ED. ED (cat 1) on the SIN list.
CLP-Harmonised hazard classification (1272/2008/EC)	- H361: Reproduction 2 (suspected of damaging fertility) - H410: Aquatic chronic 1 (very toxic to aquatic life with long lasting effects)

4. PROPOSED QUALITY STANDARDS (QS)

Protection objective	Unit	Value	Comments
Pelagic community (freshwater)	[µg.L^{-1}]	0.44	See section 8.1
Pelagic community (marine waters)	[µg.L^{-1}]	0.044	See section 8.2
Benthic community (freshwater)	[µg.kg^{-1} $_{dw}$]	15	see section 8.3
	[µg.L^{-1}]	Not derived	
Benthic community (marine)	[µg.kg^{-1} $_{dw}$]	1.5	
	[µg.L^{-1}]	Not derived	
Predators (secondary poisoning)	[µg.kg^{-1} $_{biota\ ww}$]	833	See section 8.4
	[µg.kg^{-1} $_{lipid\ ww}$]	16 660	
	[µg.L^{-1}]	0.06 (freshwaters)	
Human health via consumption of fishery products	[µg.kg^{-1} $_{biota\ ww}$]	15 200	See section 8.4
	[µg.L^{-1}]	1	
Human health via consumption of water	[µg.L^{-1}]	Not derived	

5. MAJOR USES AND ENVIRONMENTAL EMISSIONS

5.1 Summary of Uses and Quantities

According to the REACH registration dossier (ECHA 2017a), 100 000 - 1 000 000 tonnes of D4 is manufactured and/or imported yearly in the European Economic Area. Application areas of D4 include detergents products, polishes (e.g. car cleaning products) and waxes, cosmetics and personal care products (PCP), semiconductors, non-metal-surface treatment products, lubricants and greases, textile treatment products and dyes, leather treatment products and laboratory chemicals. D4 is industrial used as an intermediate monomer in the production of silicone polymers, resins and other organosilicons. D4 is used in formulations of mixtures and/or re-packaging and used for the production of chemicals, rubber products, plastic products, mineral products and electronic and optical products (ECHA 2017a; ECHA 2015).

The mayor use is as monomers for silicone polymers (in which D4 can remain as residual impurities) and less than 5% of the produced D4 is used in PCPs. The use of D4 in PCPs has declined since the beginning of the 2000s because of substitution to D5, however, D4 may still be present in PCPs as an impurity in D5 and other polymers (ECHA 2015).

5.2 Summary of Estimated Environmental Emissions

D4 is emitted to the environment from industrial processes and from the use of products, both emitted to air and to the aquatic environment via wastewater. D4 emissions from PCPs accounts for 80% of the total WWTP emissions to EU surface waters (“wash-off” PCPs is of most significant contribution). The contribution of the total WWTP emissions of D4 to EU surface waters was estimated to 40 times less compared to the amount of D5 (ECHA 2016). Removal efficiency in WWTPs was estimated to 96%, with approximately 48 % distributed to air and 48% to sludge (ECHA 2015). Allen et al. (1997) estimated that 92% of D4 used in PCPs is released to the atmosphere. The estimated emissions of D4 from production and as a chemical intermediate were confidential in EA (2009). Currently, ECHA calls for evidence to identify the current uses of D4 in consumer and professional productions, the content of the substance, and emission rates from these articles.

6. ENVIRONMENTAL BEHAVIOUR

6.1 Environmental distribution

D4 has a relative high K_{AW}, suggesting that the substance is likely accumulated in the atmosphere rather than aquatic systems. D4 is highly volatile from both water and soil (vapour pressure of 132 Pa at 25°C and Henry´s law constant of 1.21 x10^6 at 21.7°C see table 1) and the estimated volatilization from river and shallow lakes was 1.8 and 164 hours, respectively (EA 2009). D4 sorbs well from water to soil and sediments, which may limit the volatilization of the substance from aqueous phases.

D4 meets the bioaccumulation (B) and very bioaccumulative (vB) criteria in REACH with fish BCF >10 000 L/Kg (the B and vB criteria is 2000 and 5000 respectively). Kierkegaard et al. (2011) showed that if you defined the bioaccumulation factor in fish as the concentration in the fish normalized to the chemical concentration in the water body (as opposed to the freely dissolved concentration), then D4 was even much more bioaccumulative than suggested by the bioconcentration factor in fish, with a bioaccumulation behaviour 6 to 14 times higher (for polychaetes and flounder, respectively) compared to PCB 180. Trophic magnification factors have been measured in several systems for D4, resulting in TMF below 1 or with results that could not be evaluated since the majority of samples were below limit of quantification (Bergå et al. 2013; Powell et al. 2010; Bergå et al. 2012). However, these TMFs should be treated with cautions due to the variability in TMF between systems (ECHA 2016). Wang et al. (2013) reviewed field and laboratory studies suggesting that D4 may have some potential to bioaccumulate by exposure via sediment (BSAF>1).

D4 can undergo long-range transport in the atmosphere to remote areas. However, D4 has low potential for deposition to surface media and is therefore expected to remain in the atmosphere until degraded (degradation half-life: 14 days) (ECHA 2016).

In the report with QS proposals by the Netherlands (RIVM 2012), environmental distribution was calculated (according to level III fugacity model in EpiSuite 4.1). The calculation was based on the assumption that 1000 kg of D4 was 100% released either to air, water or soil. The results showed that emissions to the water were likely to be distributed in water (52.8%) and sediment (38.3%) while emissions to the air remained in air (table 2).

Table 1. Chemical properties of D4.

		Master reference
Water solubility ($mg.L^{-1}$)	0.056 at 23°C (pH 7)	ECHA 2017b
Volatilisation		
Vapour pressure (Pa)	132 at 25°C	ECHA 2017b
Henry's Law constant ($Pa.m3.mol^{-1}$)	1.21 $x10^6$ at 21.7 °C	ECHA 2015
n-Octanol/air partition coefficient (Log K_{OA})	4.34 at 25°C	
	4.22 at 24°C	
Air/water partition coefficient (Log K_{AW})	2.69 ± 0,13 at 21.7°C	
Adsorption		
Organic carbon – water partition coefficient (Log K_{OC})	4.22 at 24°C (OECD)	Miller 2007
Suspended matter – water partition coefficient ($K_{suspwater}$)	Not found	
Bioaccumulation		
Octanol-water partition coefficient (Log K_{ow})	6.49 at 25°C	ECHA 2017b
BCF (measured) ($L.kg^{-1}$)	≥11 495	ECHA 2015
	1090 (*Carassius auratus*)	Opperhuizen et al. 1987 (assessed as "invalid" in EA 2009)
	1875-10 000 ww *(Pimephales promelas)*	Annelin and Frye 1989 (assessed as "use with care" in EA 2009)
	12 400[a] ww (*P. promelas*)	Fackler et al. 1995 (assessed as "valid" in EA 2009)
	4300-7000[b] ww (*P. promelas*)	Fackler et al. 1995 (assessed as "use with care in EA 2009)
	3000-4000[a] (*Cyprinus carpio*)	CERI, 2007 and 2010 (in ECHA 2012)
	4100-5500[b] (*C. carpio*)	CERI, 2007 and 2010 (in ECHA 2012)
BMF	0.5-4.6	ECHA 2015
	0.18 – 0.47[ac] (*Oncorhynchus mykiss*)	Dow Corning 2007 (in assessed as "valid" in EA 2009)
	1.8- 4.6[bc] (*O. mykiss*)	
	0.25[a] (*O. mykiss*)	Woodburn et al. 2012
	1.7[b] (*O. mykiss*)	
	0.58[ac] (*O. mykiss*)	
	4.0[bc] (*O. mykiss*)	
	1.0 (field cod-herring) (field)	Powell et al. 2010 (in ECHA 2012)
	1-1.4 (cod-shrimp) (field)	
	0.06 (*P. reticulata*)	Opperhuizen et al. 1987 (assessed as invalid in EA 2009)
BSAF (Biota-sediment accumulation)	2.2; 1.3; 0.7 (low, medium and high organic carbon content)	Kent et al. 1994 (assessed as "use with care" in EA 2009)
	>1	Powell et al. (2009) (in Wang et al. 2013)
TMF	0.55 (marine food web)	Powell et al. 2010 (in Wang et al. 2013)
	0.7[d] (pelagic food web)	Borgå et al. 2013

a= steady-state. b= kinetic. c= lipid adjusted. d= Marked with uncertainties since the majority of samples were below LOQ.

Table 2. Calculations of environmental distribution (EpiSuite 4.1) collected from RIVM (2012).

Matrix released to (1000 kg.h^{-1})	Partitioning into (%)			
	Air	**Water[a]**	**Soil**	**Sediment**
Air	100	0.000324	0.0163	0.000235
Water	8.82	52.8	0.00144	38.3
Soil	89.6	0.00196	10.4	0.00142

a = Including suspended matter.

6.2 Abiotic and biotic degradations

The main degradation process for D4 in water is through hydrolysis, which is pH and temperature dependent, with minimum rate minimum near natural pH (7) and increased rate at higher and lower pH. Additionally, the hydrolysis rate decreases with decreasing temperature. The hydrolysis rate of D4 in pure water (with relatively short half-life) can potentially be reduced by adsorption to organic matter. The main degradations product from abiotic degradation is expected to be dimethylsilanediol, which may undergo further degradation to carbon dioxide and silicic acid and/or silica (ECHA 2012).

D4 meets the Annex XIII criteria for persistent (P) and very persistent (vP) (120 and 180 days, respectively) on the basis for sediment degradation studies with half-time of 245-365 days (ECHA 2015). However, for natural waters it was not possible to determine the criteria for persistence in the assessment due to lack of definitive data. The atmospheric degradation was estimated to 12.7-15.8 days (expected to be shorter in urban areas) and was induced by reaction with atmospheric hydroxyl radicals. Expected half-life is reported in table 3.

Table 3. Abiotic and Biotic degradation of D4.

		Master reference
Hydrolysis	DT_{50} (pH 4)= 1.77h at 25 °C DT_{50} (pH 7)= 69-144h at 25°C DT_{50} (pH 9)≈1h at 25°C DT_{50} (pH 7)= 400h at 12 °C (freshwater) DT_{50} (pH 8)= 79h at 9 °C (marine water)	ECHA 2017b
Photolysis	Not significant	Wang et al. 2013
Biodegradation	$DT_{50\ (sediment,\ aerobic)}$= 245d $DT_{50\ (sediment,\ anaerobic)}$= 365d (OECD 308, modified)	ECHA 2017a
Phototransformation in air	DT_{50}= 15.8d (mean)	ECHA 2017a

7. AQUATIC ENVIRONMENTAL CONCENTRATIONS

7.1 Predicted concentrations

Predicted environmental concentrations (PEC) derived by the EA (2009) (using EUSES 2.0.3) are presented in table 4. Concentrations were predicted based on different scenarios, with highest concentrations at production and on-site use as an intermediate (UK site), and lowest at off-site use as an intermediate (UK and EU) (given in PEC range). The predicted environmental concentrations of the use of PCP (by general public) are also summarized. PECs of surface water and sediment from the use of PCPs estimated (using EUSES v2.1) in ECHA (2016) are presented in table 5.

Table 4. Predicted environmental concentrations of D4 (as range and as a result of use of PCP) (EA 2009).

Compartment	**PEC (range)**	**PEC (by the use of PCP)**
Surface water (µg/L)	0.0024- 3.9	0.009
Marine waters (coastal and/or transitional) (µg/L)	0.00016-0.099	0.00082
Sediment (µg/kg ww)	0.88-1500	3.3
Sediment (marine) (µg/kg ww)	0.05-37	0.3
Biota (fish, freshwater) (µg/kg)	170-112 000	390
Biota (marine top predators) (µg/kg)	62-3200	88

Table 5. Predicted environmental concentrations of D4 from the use of PCPs (ECHA 2016).

Compartment	**Continental PEC**	**Regional PEC**	**Local PEC**
Surface water (µg/L)	0.00021	0.0019	0.023
Sediment (µg/kg ww)	0.11	0.95	8.39

7.2 Measured concentrations

D4 has been detected in sediment, freshwater and marine fish and benthic organisms and marine predators in concentrations reaching up to 900 ng/g ww (in Eels from River Rhine). The only aqueous matrixes with detectable concentrations were in effluents and at sites located close to WWTP discharges.

In a Swedish screening D4 was not detected in the water, fish muscle or sediment samples analysed. However, D4 was detected in 37 out of 54 municipal sludge samples in concentrations ranging from 130- 2300 ng/g dw (sewage treatment plants in Henriksdal, Borås and Göteborg). D4 was the siloxane that occurred in highest concentration in almost all air samples and was measured at concentrations up to 0.3 µg/m^3 (measured in a background sample). Additionally, the substance was found in 3 out of 49 breast milk samples with maximum concentration of 10 µg/L (Kaj et al. 2005). In a Nordic environmental screening, siloxanes (cyclic and linear) were analysed in air, biota, sediment, sludge, soil and water samples. D4 was detected in all sludge samples, in one out of 24 sediment samples (LOD 4-65 ng/g dw), in 6 out of 37 water samples (LOD 0.05-0.12 µg/L) and in 9 out of 28 biota samples (LOD 0.3-0.5 ng/g ww). Neither of the investigated siloxanes was detected in the two analysed soil samples or in seabird egg (LOD 5 ng/g ww) samples. D4 was the dominant siloxane in air samples (detected in all samples: 0.08-4.0 µg/m^3). In general, siloxanes in biota were primarily detected in fish liver samples from urban sites (diffuse sources) and only in a few background samples. Most often the siloxanes were detected in samples from incoming water to STPs and only a few in effluents (LOD 0.05-0.12 µg/L) (TemaNord, 2005). Schlabach et al. (2007) analysed concentrations of D4 in biota (common mussels,

flounder fillet, flounder liver, cod liver and cod stomach contents) from the Inner Oslofjord, with highest concentration present in cod liver. Kierkegaard et al. (2013) detected D4 in Herring from Baltic Sea at concentrations 18 times lower compared to those of D5. Monitoring data found in the literature are presented in table 6.

Table 6. Measured environmental concentrations of D4.

Compartment	**Measured environmental concentration (MEC)**	**Master reference**
Freshwater (µg/L)	<0.06 (Sweden)	Kaj et al. 2005
	<0.03 (Norway)	Schlabach et al. 2007
	0.06-0.99 (downstream of WWTP, Spain)	Sanchís et al. 2013
	1 and 1.2 (downstream industrial WWTP, UK)	Boehemer and Gerhards, 2003 (in EA 2009)
Marine waters (coastal and/or transitional) (µg/L)	<0.02 (Norway)	Schlabach 2007
Landfill leachate	<0.07 (Sweden)	Kaj et al. 2005
	1.1 (Northern[a])	TemaNord 2005
WWTP/STP effluent (µg/L)	<0.07 (Sweden)	Kaj et al. 2007[b]
	0.06-0.28 (Sweden, Borlänge)	Kaj et al. 2007
	<0.04-0.11 (Northern)	TemaNord 2005; NILU 2007
	0.31 and 0.16 (UK)[c]	Boehemer and Gerhards, 2003 (in EA 2009)
	<0.1 (Germany)[c]	Boehemer and Gerhards, 2003 (in EA 2009)
	0.5 (Germany)	IUCLID, 2005 (in EA 2009)
WWTP industrial effluent (µg/L)	<0.06 (Sweden)	Kaj et al. 2005
	0.5- 16.4 (Germany)[d]	Boehemer and Gerhards, 2003 (in EA 2009)
	0.65-1 (France)[d]	
	2.9-5.2 (UK)	
Sludge (µg/kg dw)	300 (Sweden)	Kaj et al. 2005
	460 (Sweden, Borlänge)	Kaj et al. 2007
	1000-2700 (Norway)	Schlabach 2007
	96-960 (Northern)	TemaNord 2005
Sediment (µg/kg dw)	229 ng/g OC, 4.4 ng/g ww (mean Marsh) 186 ng/g OC, 3.9 ng/g ww (mean June) (Norway)	Krogseth et al. 2016
	<4 (Norway)	Schlabach 2007
	84 (one sample, Denmark)	TemaNord 2005
	<3-12 (River Rhine)	Boehmer and Gerhards, 2003 (in EA 2009)
	5-7 (3,5km downstream from WWTP in Hall Dike Creek)	
	15-45 (coast of Scotland)	
	5.33-679 (downstream of WWTP, Spain)	Sanchís et al. 2013
Biota (µg/kg ww)	<5 (fish muscle, Sweden)	Kaj et al. 2005
	<1.5 (Arctic char, Sweden)	Kierkegaard et al. 2010
	0.6-30 lipid weight (Herring muscle)	Kierkegaard et al. 2013
	<5-70 (marine fish, Northern)	TemaNord 2005
	<5- 8,9 (freshwater fish, Northern)	
	1.3-2.3 (Common mussel, Norway)	Schlabach et al. 2007

	2.6 (Flounder liver, Norway)	
	1.9 (Flounder fillets, Norway)	
	5-9.3 (Cod stomach, Norway)	
	134.4 (Cod liver, Norway)	
	2.6-9.2 (Cod liver, Svalbard)	Evenset et al. 2009
	170 (Roach, River Rhine)	EVONIK Industries, 2007 (In EA 2009)
	100 (Ide, River Rhine)	
	400-900 (Eel, River Rhine)	
	<20 (fish from Germany, Denmark, North East Atlantic)	
	<6 (Blue mussel, North Sea)	Bohemer et al. 2007 (in EA 2009)
Biota (marine predators) (µg/kg ww)	<5 (seabird eggs, Northern)	TemaNord 2005
	12 (Seal blubber, Denmark)	
	<2.3- <3.0 lipid weight (Seal blubber, Sweden)	Kierkegaard et al. 2013
	<1.1- 3.5 (Kittiwake, Svalbard)	Evenset et al. 2009
	<1 lipid weight (fat, liver and muscle in mink)	Woodburn and Durham 2009 (in ECHA 2012)

a = Denmark, Faroe Islands, Finland, Iceland, Norway and Sweden. b = Not detected in influent samples (n=4). c = Influent concentrations of 2.2-3.8 µg/L (UK) and 0.23-4.2 µg/L (Germany). d = Influent concentrations of 1090 (Germany) and 2828-6400 µg/L (France), downstream samples were below detection limit of 0.02 µg/L.

8. EFFECTS AND QUALITY STANDARDS

8.1 Freshwater aquatic ecotoxicology

Several of the available ecotoxicity studies reported effect values higher than the tested concentrations or effect values well above the water solubility (56 µg/L). All acute and chronic ecotoxicity studies are presented in supporting information table S1 and S2, respectively. No additional aquatic ecotoxicity studies were found compared to previous risk assessments of D4 (EA 2009; RIVM 2012; Environment Canada 2008). There was not sufficient studies or taxonomic groups to derive QS based on the probabilistic method (i.e. SSD).

Sousa et al. (1995) (in ECHA 2017a; EA 2009) investigated the toxicity of D4 to *O. mykiss* at durations of 96 hours which showed no observed effect up to 22 µg/L while prolonged acute toxicity test of 14 days yielded 20 % mortality (observed on day 14) at 6.9 µg/L, giving a NOEC of 4.4 µg/L and LC_{50} of 10 µg/L. The same study also investigated chronic toxicity (embryo viability, hatching, survival and growth) during 93 days without mortality (NOEC >4.4 µg/L). Since this was the highest measured concentration, effects at higher concentrations cannot be ruled out (the 14 days test resulted in mortality at 6.9 µg/L). The same study also investigated toxicity of D4 to *D. magna* with EC_{50} and NOEC of >15 and 7.9 µg/L, respectively. There was one available reliable algae study, summarized in ECHA (2017), with EC_{50} and NOEC of >22 and <22 µg/L, respectively for endpoint cell density. However, the effect values were based on initial measurements, which corresponded to 6 µg/L of the mean measured concentration. According to ECHA (2017), it was not possible to determine a classification regarding acute aquatic toxicity (based on 49-96h LC_{50} showing no effect). Based on NOEC of 7.9 (*D. magna*) and 4.4 µg/L (*O. mykiss*) including the properties of bioaccumulation and degradation, it was concluded that D4 fulfils the criteria of chronic aquatic toxicity (Aquatic Chronic 1, based on CLP regulation, 1272/2009/EC). D4 also meets the REACH "Toxicity" criteria based on NOEC/EC10 less than 0.01 mg/L and due to toxic to reproduction (category 2) (ECHA 2015).

Derivation of MAC-QS_{fw}

8 species and 20 effect values were available for derivation of MAC-QS_{fw} (supporting information table S1). Critical data for three trophic levels are presented in table 7. MAC-QS was based on *O. mykiss* with LC_{50} of 10 µg/L (Sousa et al. 1995) which was the only effect value in the dataset that resulted in an effect of D4 exposure. The *Daphnia* and algae studies suggest that these trophic levels are not as sensitive as fish. QSAR calculations, based on Log K_{OW} 6.49, suggest that algae and Daphnia were more sensitive although QSAR, based on Log K_{OW} 5.09 revealed toxicity higher than the water solubility of D4 (EA 2009) (supporting information table S1). AF 10 was applied on LC_{50} of 10 µg/L which was in accordance to European Communities (2011). The MAC-QS_{fw} was set to 1 µg/L. Although, there are some uncertainties regarding the algae study (due to decreased concentrations during the test) and that QSAR calculations of Daphnia and algae suggest equal or higher toxicity.

Table 7. Lowest effect values of D4 for three trophic levels from acute freshwater studies.

Species (life stage)	Endpoint & Duration	Effect value (µg/L)	Reliability evaluation	Reference
Oncorhynchus mykiss	14d LC_{50}	10	2[ab]	Sousa et al. 1995 (in ECHA 2017a)
Daphnia magna	48h EC_{50}	>15	1[a] 2[b]	Sousa et al. 1995 (in ECHA 2017a)
Pseudokirchnerella subcapitata	96h EC_{50}	>22[c]	2[d]	ECHA 2017b

a = Reliability evaluation from REACH Registration Dossier (ECHA 2017a). b = Reliability evaluation from EA (2009). c = Measured concentration decreased over time. d = Reliability evaluation from ECHA (2017b).

Derivation of AA-QS_{fw}

5 species and 7 effect values were available for derivation of AA-QS_{fw} (supporting information table S2). Critical data for three trophic levels are presented in table 8. The lowest effect data of studies with durations meeting the requirements for a chronic study was *D. magna* with a NOEC of 7.9 µg/L (Sousa et al. 1995). However, the prolonged acute toxicity of 14 days for *O. mykiss* yielded higher toxicity with NOEC of 4.4 µg/L (Sousa et al. 1995). QSAR calculations, based on Log K_{OW} 6.49, suggest higher toxicity to daphnia and fish with EC_{50} and NOEC of 0.64 and 2.1 µg/L, respectively (table S2). The AA-QS_{fw} was based on NOEC of 4.4 µg/L and AF of 10 was used in accordance with European Communities (2011), resulting in AA-QS of 0.44 µg/L.

Table 8. Lowest effect values of D4 for three trophic levels from chronic freshwater studies.

Species (life stage)	Endpoint & Duration		Effect value (µg/L)	Reliability evaluation	Reference
Oncorhynchus mykiss	Embryo viability, hatching, survival, growth	93d NOEC	>4.4	2[ab]	Sousa et al. 1995 (in ECHA 2017a)
Oncorhynchus mykiss	Mortality	14d NOEC	4.4	2[ab]	Sousa et al. 1995 (in ECHA 2017a)
Daphnia magna (≤24h)	Survival, reproduction	21d NOEC	7.9	1[a] 2[b]	Sousa et al. 1995 (ECHA 2017a)
Pseudokirchnerella subcapitata	Growth	96h NOEC	<22[c]	2[d]	ECHA 2017b

a = Reliability evaluation from REACH Registration Dossier (ECHA 2017a). b = Reliability evaluation from EA (2009). c = measured concentration decreased over time. d = Reliability evaluation from ECHA (2017b).

8.2 Marine aquatic ecotoxicity

The available marine acute studies are presented in table 9. None of the available studies showed an effect. Two of the fish studies were assessed as reliable with restriction/use with care in EA (2009). Studies of additional taxonomic groups (e.g. echinoderms or molluscs) were not available. No chronic marine aquatic studies were found.

Table 9. Available marine acute ecotoxicity studies for D4 including one EPI (v.3.12) calculation.

Species	Endpoint & Duration	Effect value (µg/L)	Reliability Evaluation	Reference
Fish				
Cyprinodon variegatus	14d LC_{50}	>6.3	2^{ab}	Sousa et al. 1990 (in ECHA 2017a)
Fundulus heterolitus	96h LC_{50}	>1 000 000	2^{a} 3^{b}	Firmin et al. 1984 (in ECHA 2017a)
Crustacean				
Artemia salina	96h EC_{50}	>500 000	3^{ab}	Firmin et al. 1984 (in ECHA 2017a)
Crangon crangon	96h EC_{50}	>1 000 000	3^{ab}	Firmin et al. 1984 (in ECHA 2017a)
Mydisopsis bahia	96h LC_{50}	>9.1	$1^{a}2^{b}$	Sousa et al. 1995 (in ECHA 2017a)
USEPA EPI (v.3.12)				
Fish	96h LC_{50}	280		EA 2009

a = Reliability evaluation from REACH Registration Dossier (ECHA 2017a). b = Reliability evaluation from EA (2009).

Derivation of MAC-QS_{sw}

None of the acute studies of marine fish or crustacean showed effect from the D4 exposure. Therefore, the lowest acute freshwater data of 10 µg/L was used in the derivation (Sousa et al. 1995). AF of 100 was applied since the dataset includes three trophic levels resulting in MAC-QS of 0.1 µg/L.

Derivation of AA-QS_{sw}

There were no chronic studies for marine species. The lowest chronic effect data for freshwater species was *O. mykiss* with a NOEC of 4.4 µg/L. AF of 100 was used since the dataset includes chronic data from three freshwater species representing three trophic levels (European Communities, 2011), resulting in AA-QS of 0.044 µg/L.

8.3 Sediment toxicity

The evidence of sorption potential (Log K_{OC} >3) was met and available environmental measurements supports the possibility for D4 to end up in sediment (table 6). Six ecotoxicity studies were found, of which one was public available (Kent et al. 1994), including two species from two taxonomic groups (Annelida and Diptera) (supporting information table S3). In the REACH registration dossier, read-across from D5 for *H. azteca* was used, resulting in a lower assessment factor (ECHA 2017a). However, in this dossier data for D5 is not considered.

All results were normalised to standard organic carbon content of 5% accordingly to European Communities (2011). Kent et al. (1994) showed that the toxicity of D4 increased with decreased organic matter content due to increased bioavailability. It is therefore likely that D4 exhibit higher toxicity in sediment with low content of organic matter.

According to the REACH registration dossier (ECHA 2017a) there was a general trend that ecotoxicity studies using natural sediment with pH below 8 showed no effect or reported higher NOEC compared to those with formulated sediment. The lowest NOEC of <1.5 mg/kg dw (EC_{50} of 19.5) was obtained in a 28-day study of *Lubriculus variegatus* using formulated sediment (Krueger et al. 2009). In REACH registration dossier (ECHA 2017a) it is stated that there were uncertainties in the study by Krueger et al. (2009) regarding that equilibration between the organic phases of the sediment may not have been reached because of the insufficient equilibration time. In addition, it was assumed that the sediment with peat based carbon source and the high pH-values interfered with the test system to exhibit toxicity. The study was not included in the sediment derivation in the REACH registration dossier based on these arguments. Instead, a NOEC of 27 mg/kg dw for the same species and natural sediment was used (Picard et al. 2009, in ECHA 2017a). Both studies are summarized in table 8. According to the OECD 225 guideline, formulated sediment should preferably be used over natural sediments, and the pH used in Krueger et al. (2009) seems to be within the range recommended in the guidance. Also, the organisms were added 48h after water was added to the sediment similar to the equilibration period of 48h recommended in OECD 225. In addition, there is a D5 study available on *L. variegatus* conducted under similar conditions (13% peat and pH of 7.1 and 7.9-8.3 in sediment and water, respectively) which was assessed as “Reliable without restrictions” in the REACH Registration Dossier of D5 (Krueger et al. 2007). Based on these argument, the effect value reported by Krueger et al. (2009) was used as critical data in the derivation.

Table 8. Test-set up for the two *Lumbriculus variegatus* studies (In ECHA 2012).

	Krueger et al. 2009	**Picard et al. 2009**
Species	*Lumbriculus variegatus*	*Lumbriculus variegatus*
Endpoint	Survival and reproduction (the total number of organisms at the end of the test)	Survival (the mean number of surviving organisms)
Guideline	OECD 225	OECD 225
Test system	Flow-through for the overlying water	Static
Sediment	Formulated (70% industrial sand, 10% peat, 20% kaolin clay)	Natural (93% sand, 6% slit, 1% clay)
pH sediment	7.3	6.5
pH water	8.4-8.6	7.2-8.2
Organic Carbon	2.4%	2.2%
Results (mg/kg dw)	Based on measured concentrations. Significant differences were found at all concentrations, results showing dose-response. EC_{50} 19.5 LOEC 1.5 NOEC <1.5 (30% reduction)	Based on measured concentrations. Significant different in the two highest concentrations EC_{50} >72.5 NOEC 27 LOEC 39.5

Derivation of $QS_{sediment}$

The dataset does not fulfil the criteria for AF 10 since only two species was available (table 9). AF 50 was therefore used to derive QS for freshwater sediment and AF 500 for marine sediment. According to the European Communities (2011), NOEC or EC_{10} are preferred when deriving QS for sediment toxicity. In this case the lowest effect value was LOEC of 1.5 mg/kg dw (NOEC < 1.5), resulting in 31% reduced survival (Krueger et al. 2009). It was not possible to determine a EC_{10} from the data reported by Krueger et al. (2009), therefore the NOEC was calculated by dividing LOEC by 2 (0.75 mg/kg dw).

Using the NOEC of 0.75 mg/kg for *L. variegatus* (Krueger et al. 2009) and applying AF of 50 and 500 (European Communities, 2011) gives QS_{sed} of 0.015 and 0.0015 mg/kg dw for freshwater and marine sediment, respectively.

Table 9. Studies with lowest effect values for two different species (two taxonomic groups). N= natural sediment, F= formulated sediment.

Species (life stage)	**Endpoint & Duration**		**Effect value at 5% OC** (mg/kg dw)	**Reliability Evaluation**	**Reference**
Lumbriculus variegatus (F)	Survival and reproduction	28d EC_{50} (NOEC)	19.5 (0.75)	2[a]	Krueger et al. 2009 (in ECHA 2017a[b]).
Chironomus riparius (F)	Survival and emergence rate	28d NOEC	54	2[c]	Krueger et al. 2008 (In ECHA 2017a)

a = Reliability evaluation from REACH registration dossier (ECHA 2017a). b= Study disregarded in ECHA (2017a). c = Reliability evaluation from EA (2009).

8.4 Secondary poisoning

The evidence of bioaccumulation potential (BMF>1 and BCF≥100) was convincing for D4 (European Communities, 2011). D4 has been detected in human breast milk samples (3 out of 49) with maximum concentration of 10 μg/L (Kaj et al. 2005). According to the proposals for Harmonised Classification and Labelling, the available data was conclusive but not sufficient for classification regarding: acute toxicity via oral route, cell mutagenicity and carcinogenicity. Reproduction toxicity was assessed to be from damaging fertility (ECHA 2017b). The most likely exposure route to humans is through dermal or oral contact from the use of PCPs (ECHA 2015). Under the Cosmetic Regulation (EC 1223/2009), the Scientific Committee on Consumer Safety (SCCS) concluded that D4 used in cosmetic products are not coupled with risks for human health (other exposures were not considered in the assessment) (SCCS 2010; ECHA 2015). Regarding exposure through the environment, D4 was assessed as not giving rise to any risks of concerns in EA (2009).

There were several available toxicological studies, however, most of them investigates inhalation as administration route. In total, six studies and 13 effect values of oral toxicity for rats and rabbits were available (supporting information table S4). Of these, one study was a peer-review study and the other six were cited and summarized in SCCS (2010) and EA (2009).

General toxicity

There was no evidence on acute toxicity via oral, inhalation or dermal administration routes (EA 2009; SCCS, 2010). Oral acute exposure showed no effect up to 4800 mg/kg (Löser 1979 in EA 2009).
D4 caused increased liver weight in repeated dose studies on rats through oral and inhalation routes. The increase of liver weights appears to be associated with induction of hepatic metabolizing enzymes, like those that are induced in the presence of phenobarbital (Franzen et al. 2017). A four-fold increase of enzymatic activation (CYP2B1/2) was observed in rats exposed to 1 mg/kg/day.

Repeated oral studies were available for doses up to 1600 mg/kg/day and durations up to 14 days (table S4). Dow Corning (1990, in EA 2009; SCCS 2010) reported 17% increase of liver weight in females at doses of 100 mg/kg/day and more than 10% in males treated with 400 mg/kg/days (treated for five days per week for 14 days), giving a NOAEL of 25 mg/kg/day for females. The liver weights were not affected in a 14 days rabbit study; instead oral doses caused reduced food consumption and reduced bodyweight at doses of 500 mg/kg/day (Dow Corning, 1992 in EA 2009). According to EA (2009), reduced food consumption may be a result of pharmacological effects due to the dopamine-like effects of D4. There were no available chronic (>12 month) oral toxicity studies, although, a whole-body inhalation study confirmed effects on liver weight with a NOAEL of 150 ppm based on increased liver weighs and centrilobular hypertrophy of hepatocytes in male rats (Dow Corning 2004, in SCCS 2010). According to ECHA (2015), increased liver weight by more than 10% is considered an adverse effect for human health. A larger increase in liver weight may compress other abdominal organs, and the enzyme induction can modify the normal response to other xenobiotics. Changes of liver weight through D4 exposure was considered reversible and not related to overt hepatotoxicity in the review by Franzen et al. (2017).

Genotoxicity and Carcinogenicity

There was no evidence on mutagenic or genotoxic potential of D4 in *in vitro* (bacteria and mammal cells) or in *in vivo* (oral rat study investigating chromosomal damage in germinal tissues up to 1000 mg/kg/day) (EA 2009; ECHA 2015; SCCS 2010). A 2-year rat study reported evidence on carcinogenicity in the uterine at inhalation doses of 700 ppm (NOAEL 150 ppm). These effects were not assessed as

relevant to humans because of different reproductive ageing process compared to rodents. Since the carcinogenic effect occurred late in life it was assumed to not cause effects on a population level (ECHA 2015). However, it remains unclear if these tumours may be relevant to other species exposed through the food web.

Reproduction and developmental toxicity

D4 is classified, based on mammalian inhalation studies, as:

- Hazard class and category: Reproduction 2
- Hazard statement: H361f Suspected of damaging fertility

Reproduction effects of D4 have been investigated through one-generation and two-generation inhalation studies on rats and rabbits. The concentrations ranged from 70-700 ppm for exposures of 28 or 70 days prior to mating and through gestation and lactation in females. The mainly adverse effect observed in females treated with 500 ppm or higher concentrations were reductions in corpora lutea, uterine implantation sites, total number of pups born, and mean live litter size (ECHA 2015). According to ECHA (2015), the mechanisms of reproductive effects may be relevant to human health. Effects on sperm production, motility or morphology and histopathological changes of male reproductive organs was not seen (ECHA 2015). Meeks et al. (2007) concluded that D4 exerted reproductive effects in female rats during critical phases of the reproductive cycle, around the time of ovulation and fertilization. The study showing lowest effect values was a two-generation whole body inhalation study by Siddiqui et al. (2007), with significant decrease of mean live litter size with a NOAEL of 300 ppm. The NOAEL was extrapolated to an oral NOAEL of 105 mg/kg/day in EA (2009).

Embryo-foetal development inhalation studies conducted on rats (gestation days 6-15) and rabbits (gestation days 6-18) with exposure of 10-700 ppm were reported in SCCS (2010). Teratogenicity was not observed, however, maternal toxicity occurred at 700 ppm and 500 ppm for rats and rabbits, respectively.

An oral rabbit study, with D4 administrated on gestation day 7-19, resulted in maternal toxicity at doses of 500 and 1000 mg/kg/day (increased spontaneous abortion and loss of post-implantation). Reductions in the number of live foetuses and gravid uterine weights were observed at 1000 mg/kg/d. However, these affects were assumed to be a result of reduced food consumption (loss in weight and stress) and not triggered directly by D4 (IRDC 1993b in EA 2009; SCCS, 2010).

Endocrine disruptions

Several studies have examined the ability of D4 to potentially disrupt endocrine pathways. Quinn et al. (2007a) showed that D4 significantly reduced the levels of proestrus LH hormones in female rats, causing a significantly decrease in the portion of ovulation, with 42% and 31% ovulating at inhalation concentrations of 700 and 900 ppm, respectively (compared to control of 79%). According to Franzen et al. (2017), this delay of LH hormones could explain the reproductive toxicity showed in Siddiqui et al. (2007).

D4 showed low affinity for estrogen receptor-α (ERα) in *in vitro*, suggesting weak estrogenic activity (Quinn et al. 2007b; He et al. 2003). Lee et al. (2015) investigated the estrogenicity of D4 in *in vitro* and *in vivo* using calcium-binding protein 9K (CaBP-9K) as a biomarker. D4 showed estrogenic potential in *in vitro* of rat cells. The uterotrphic *in vivo* (1000 mg/kg/ bw/d subcutaneosly in rats) assay showed no increase in uterine weight i.e. estrogenic effect was not shown. However, the estrogenic biomarker

(CaBP-9K) showed a significantly dose-dependent increase. In contrast, McKim et al. (2001) observed increased uterine weight and epithelial cell height in an uterotropic assay, indicating a weak estrogenic activity of D4 (orally administrated in rats). The results were dose-dependent with a NOAEL of 100 mg/kg/day. D4 was also single-dose administrated of 500 mg/kg/day, which showed evidence on weak anti-estrogenic properties. However, the authors concluded that D4 was several orders of magnitude less potent than ethinylestradiol used as positive control for detecting anti-estrogenic activity. Likewise, it was shown in a similar *in vivo* study that D4 increased the uterine weight and exhibited weak estrogenic activity from 250 mg/kg in mice (He et al. 2003).

$QS_{biota\ sec\ pois}$ derivation

The oral study showing lowest effect value was a 14 days rat study with a NOAEL of 25 mg/kg/day for the endpoint increased liver weight (Dow Corning, 1990 in EA 2009a). Although, it is unclear whether this effect should be considered adverse.

According to European Communities (2011) the following conversion factors (CF) should be used:

1. Age/study >6 weeks= CF 20
2. Age/study< 6weeks= CF 10

Since no details regarding age of rats were available and due to the short duration (14 days) CF of 10[2] was used (to convert NOAEL to NOEC) as precaution. Applying AF of 300 based on the duration of 14 days (no oral chronic or 90-day reproduction study available) gives a QS of 833 µg/kg biota ww [3] (European Communities, 2011). This QS corresponds to 0.06 µg/L in freshwater using BCF of 12400 and field BMF of 1.2 for cod-shrimp in the study by Powell et al. (2010).

$QS_{biota\ hh}$ derivation

There were no available acceptable daily intake (ADI) or tolerable daily intake (TDI), therefore a human toxicological standard (TL_{hh}) was calculated using the lowest NOAEL (25 mg/kg/day) and AF of 100, giving a TL_{hh} of 0.25 mg/kg/day (European Communities, 2011). Using this TL_{hh}, a body weight of 70 kg and a daily fish consumption of 115 g the QS_{hh} was set to 15.2 mg/kg biota ww (corresponding to 1 µg/L in freshwater). Using the DNEL of 5 mg/kg/d (table 10) the QS_{hh} was calculated to 304 mg/kg biota ww.

There is no existing drinking water standard for D4 (Directive 98/83/EC). QS for drinking water was not undertaken in this dossier.

[2] CF 20 was used in EA (2009).

[3] Corresponds to 16 660 µg/kg lipid ww, normalized to 5% lipid weight (QS_{biota} divided by 0.05).

9. EXISTING ECOTOXICOLOGICAL THRESHOLD VALUES

Results from previous assessments of D4 are presented in table 10 and are compared to the proposals from this dossier. PNEC results for freshwater and saltwater in the UK assessment (EA 2009) and Netherland assessment (RIVM 2012) were consistent with AA-QS in this dossier. PNEC for freshwater in Environment Canada (2008) was derived using LC_{50} of 10 µg/L for *O. mykiss* and AF 50. The PNEC for sediment was derived using NOEC of 54 mg/kg for *C. riparius* (Krueger et al. 2008) with AF 100 (and additional 10 for saltwater) in EA (2009). In the REACH registration Dossier (2017a) PNEC for sediment was derived using *L. variegatus* with a NOEC of 27 mg/kg (Picard et al. 2009) due to uncertainties of the *L. variegatus* study by Krueger et al. 2009). AF was lowered to 10 (100 for saltwater) based on read across from available D5 study on *Hyallela azteca* (28d EC50 > 135.4). Although, D4 and D5 share analogous structure it should be noted that D4 exhibit higher toxicity to *L. variegatus* and *C. riparius* compared to D5. PNEC for secondary poisoning was derived based on the same key-study as in this dossier using CF 20 and AF 300 in EA (2009).

Table 10. Ecotoxicological threshold values from previous and present assessments.

	REACH registration Dossier (ECHA 2017a)	**UK assessment (EA 2009)**	**Netherland assessment (RIVM 2012)**	**Canada assessment (Environment Canada 2008)**	**Proposals from this dossier**
$PNEC_{fw}$ (µg/L)	1.5	0.44	0.44	0.2	0.44
$PNEC_{sw}$ (µg/L)	0.15	0.044	0.044	-	0.044
$PNEC_{fw}$ sediment (mg/kg dw)	3.0 (AF 10)	0.54 (AF 100)	-	-	0.015 (AF 50)
$PNEC_{sw}$ sediment (mg/kg dw)	0.3 (AF 100)	0.054 (AF 1000)	-	-	0.0015 (AF 500)
PNEC sec pois (mg/kg)	41 (AF 90)	1.7 (AF 300)	-	-	0.83 (AF 300)
$DNEL_{oral}$ (mg/kg bw/d)	3.7 (AF 100)	-	-	-	-
QS_{hh} (mg/kg $_{bitoa\ ww}$)	-	-	-	-	15.2 (AF 100)

10. IDENTIFICATION OF ISSUES RELATING TO UNCERTAINTY IN RELATION TO THE QSs DERIVED

Since (eco)toxicity data were collected from secondary literature it has not been possible to evaluate studies for their reliability and relevance.

Uncertainties in relation to MAC- and AA-QS for pelagic ecosystems

Sorption and volatilization properties and the low water solubility (56 µg/L) of D4, challenge the assessment of D4 in standard aquatic toxicity tests. Due to the reproduction effects in mammal's uncertainties of long-term exposures to fish may be reduced if data on reproduction effects in fish were available (e.g. OECD 229: Fish short term reproduction assay).

Uncertainties in relation to $QS_{sediment}$

The lowest sediment effect value found (Krueger et al. 2009) was used to calculate the QS_{sed} although some uncertainties were recognized in the REACH registration dossier. It is however, believed that it is justified to include this data as precautionary measure. The QS_{sed} of 15 µg/kg dw is in the same range as the available environmental measurements in sediment (table 6). Further studies of *L. variegatus* could reduce uncertainties of the derived QS i.e. additional studies either supporting the results reported by Krueger et al. (2009) or Picard et al. (2008). Investigating effects of life-long exposure of D4 can also reduce possible uncertainties regarding sediment toxicity (e.g. OECD 233 for Chironomus sp., during >44 days which covers the 1st generation and the early part of the 2nd generation). In addition, sediment toxicity studies for *H. azteca* and macrophytes (OECD 239: Water-Sediment Myriophyllum Spicatum Toxicity test) could also provide data for additional taxonomy for comparisons of species sensitivity.

Uncertainties in relation to $QS_{sec\ pois}$

These QSs are coupled with uncertainties since they are derived from a non-chronic study (14 days) and consequently, a large AF is required. The ecological or human health consequences caused by increased liver weight is not well defined. Therefore, it remains unclear if the derived QS for secondary poisoning and human health are over- or underestimated. Increased liver weight by more than 10% is considered an adverse effect for human health. A larger increase of liver weight may compress other abdominal organs, and the enzyme induction can modify the normal response to other xenobiotics (ECHA 2015). However, according to Franzen et al. (2017) increased liver weight caused by inhalation of D4 is considered reversible and not related to overt hepatotoxicity. Uncertainties coupled with secondary poisoning can be reduced by chronic mammal toxicity studies investigating effects through oral exposure. It is also believed that further oral mammal toxicity studies investigating toxicity to reproduction (one study available with D4 administrated on gestation day 7-19) is necessary to reduce uncertainties. According to ECHA (2015), the mechanisms of reproductive effects through inhalation (prior to mating and through gestation and lactation in females) may be relevant to human health.

Uncertainties in relation to mixture effects

The homologous structure and similar effects of D4 and D5 in mammals raise concerns regarding their mixture effect.

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12. SUPPORTING INFORMATION

Table S1. All acute freshwater ecotoxicity studies of D4 including QSAR and EPI (v. 3. 12) calculations.

Species	Endpoint & Duration	Effect value (µg/L)	Guideline & Comments	Reliability Evaluation	Reference
Fish					
Brachydanio rerio	96h LC_{50}	>500 000		3[a]	Firmin et al. 1984 (in EA 2009)
Lepomis macrochirus	96h LC_{50}	>1 000 000		3[a]	Firmin et al. 1984 (in EA 2009)
Leuciscus idus	96h LC_{50}	>1 041 000		3[a]	IUCLID 2005 (in EA 2009)
Oncorhynchus mykiss (eggs)	14d LC_{50}	17	OECD 204; mortality observed at 14 days		Dow Corning 2008 (in ECHA 2017a)
Oncorhynchus mykiss (eggs)	14d NOEC	6.8	OECD 204		Dow Corning 2008 (in Fairbrother et al. 2016 and Mackey et al. 2015)
Oncorhynchus mykiss (eggs)	14d LOEC	13	OECD 204		Dow Corning 2008 (in ECHA 2017a)
Oncorhynchus mykiss	96h/14d LC_{50}	>51.7	OECD 204	2[b]	ECHA 2017a[c]
Oncorhynchus mykiss	14d NOEC	16.9	OECD 204	2[b]	ECHA 2017a[c]
Oncorhynchus mykiss	96h LC_{50}	1 000 000		3[a]	Firmin et al. 1984 (in ECHA 2017a)
Oncorhynchus mykiss (juvenile, 1 g)	18d LC_{80}	23	Single-test concentration of 23 µg/L, 80% mortality; observed mortality at days 5−18	4[a]	IUCLID 2005 (in ECHA 2017a)
Oncorhynchus mykiss (juvenile, 5 g)	18d NOEC	>31	Single-test concentration of 31 µg/L; no observed mortality	4[a]	IUCLID 2005 (in ECHA 2017a)
Oncorhynchus mykiss	96h LC_{50}	>22	EPA OTS 797.1400; GLP	1[b]	Sousa et al. 1995 (in ECHA 2017a)
Oncorhynchus mykiss	14d LC_{50}	10	EPA OTS 797.1400; GLP	1[b]2[a]	Sousa et al. 1995 (in ECHA 2017a)
Oncorhynchus mykiss	14d NOEC	4.4	20% mortality at 6,9 µg/L (LOEC); GLP	1[b]2[a]	Sousa et al. 1995 (in ECHA 2017a)
Oryzias latipes	96h LC_{50}	>5.6			CERI 2007 (in ECHA 2012)
Fish QSAR	96h LC_{50}	37	Based on Log K_{OW} 6.49		EA 2009
Fish QSAR	96h LC_{50}	560	Based on Log K_{OW} 5.1		EA 2009
Fish USEPA EPI (v.3.12)	96h LC_{50}	270	Based on Log K_{OW} 5.09		EA 2009
Crustacean					
Daphnia magna	48h EC_{50}	>15	EPA OST 797.1300; GLP	1[b]2[a]	Sousa et al. 1995 (in ECHA 2017a)
Daphnia magna	24h EC_{50}	25 200		3[ab]	IUCLID 2005 (in ECHA 2017a)
Daphnia QSAR	48h LC_{50}	9.7	Based on Log K_{OW} 6.49		EA 2009
Daphnia QSAR	48h LC_{50}	200	Based on Log K_{OW} 5.1		EA 2009

Species	Endpoint & Duration	Effect value (µg/L)	Guideline & Comments	Reliability Evaluation	Reference
Daphnia USEPA EPI (v.3.12)	48h LC_{50}	72	Based on Log K_{OW} 5.09		EA 2009
Algae and Cyanobacteria					
Pseudokirchnerella subcapitata	96h EC_{50}	>22	EPA 797.1050; initially measured concentration, corresponds to 6 µg/L.	2[b]	ECHA 2017b
Pseudokirchnerella subcapitata	72h EC_{50}	>22	Single-test concentration	3[a]	IUCLID 2005 (in EA 2009)
Green algae QSAR	72-96h EC_{50}	5.7	Based on Log K_{OW} 6.49		EA 2009
Green algae QSAR	72-96h EC_{50}	140	Based on Log K_{OW} 5.1		EA 2009
Green algae USEPA EPI (v.3.12)	96h EC_{50}	270	Based on Log K_{OW} 5.09		EA 2009

a = Reliability evaluation from EA (2009). b = Reliability evaluation from REACH registration dossier (ECHA 2017a). c = Ref. 005 (short-term toxicity to fish) in REACH registration dossier (ECHA 2017a).

Table S2. All chronic freshwater ecotoxicity studies of D4 including QSAR and EPI (v3. 12) calculations.

Species	Endpoint & Duration		Effect value (µg/L)	Guideline & Comments	Reliability Evaluation	Reference
Oncorhynchus mykiss	Embryo viability, hatching, survival, growth	93d NOEC	>4.4	EPA 797.1600; GLP	1[a]2[b]	Sousa et al. 1995 (ECHA 2017a)
Pimephales promelas	Mortality, behaviour, condition	28d NOEC	>0.26	EPA 797.1520		Springborn Laboratories 1991 (in Fairbrother and Woodburn 2016)
Fish QSAR		28 NOEC	2.1	Based on Log K_{OW} 6.49		EA 2009
Fish QSAR		28 NOEC	380	Based on Log K_{OW} 5.1		EA 2009
Crustacean						
Daphnia magna (≤24h)	Survival, reproduction	21d NOEC	7.9	EPA OST 797.1300; GLP; 16% reduced survival at 15	1[a] 2[b]	Sousa et al. 1995 (ECHA 2017a)
Daphnia magna (≤24h)	Survival	21d LC_{50}	>15	EPA OST 797.1300; GLP	1[a] 2[b]	Sousa et al. 1995 (ECHA 2017a)
Daphnia QSAR		16d EC_{50}	0.64	Based on Log K_{OW} 6.49		EA 2009
Daphnia QSAR		16d EC_{50}	19	Based on Log K_{OW} 5.1		EA 2009
Daphnia USEPA EPI (v.3.12)		16d EC_{50}	14	Based on Log K_{OW} 5.09		EA 2009
Insecta						
Chironomus tentans (2nd instar)	Growth/survival	14d NOEC	>15		2[b]	Kent et al. 1994
Algae						
Anabaena flos-aquae	Growth	14d EL_{50}	>2000		3[b]4[a]	Firmin et al. 1984 (in ECHA 2017a)
Pseudokirchnerella subcapitata	Cell density	72h NOEC	<22	EPA 797.1050; initially measured concentration, corresponds to 6 µg/L; cell density decreased with 18%	2[c]	ECHA 2017b
Pseudokirchnerella subcapitata	Cell density	96h EC_{10}	≥22		1[a]	ECHA 2017a[d]
Green algae USEPA EPI (v.3.12)		72-96h MATC	160	Based on Log K_{OW} 5.09		EA 2009

a = Reliability evaluation from REACH Registration Dossier (ECHA 2017a). b = Reliability evaluation from EA (2009). c = Reliability evaluation from ECHA (2017b). d = Ref. 001 (toxicity to algae and cyanobacteria) in REACH registration dossier (ECHA 2017a).

Table S3. All freshwater sediment toxicity studies of D4.

Species	Endpoint & Duration		Effect value (mg/kg dw)	Guideline/ Comments	OC (%)	Effect value at 5 % OC (mg/kg dw)	Evaluation	Reference
Annelida								
Lumbriculus variegatus	Reproduction, survival	28d NOEC	< 0.73	OECD 225; Formulated sediment; Study disregarded in ECHA (2017a)	2.4	<1.52	2[a]	Krueger et al. 2009 (in ECHA 2017a; ECHA 2012)
Lumbriculus variegatus	Survival, reproduction	28d EC_{50}	9.32	OECD 225; Formulated sediment	2.4	19.42	2[a]	Krueger et al. 2009 (in ECHA 2017a; ECHA 2012)
Lumbriculus variegatus	Survival	28d EC_{50}	>32	OECD 225, GLP; Natural sediment	2.2	>72.73	1[a]	Picard 2009 (in ECHA 2017a; ECHA 2012)
Lumbriculus variegatus	Survival, reproduction	28d NOEC	13	OECD 225, GLP; Natural sediment	2.2	27.08	1[a]	Picard 2009 (in ECHA 2017a; ECHA 2012)
Lumbriculus variegatus	Survival, reproduction	28d LOEC	19	OECD 225, GLP; Natural sediment	2.2	39.60	1[a]	Picard 2009 (in ECHA 2017a: ECHA 2012)
Insecta								
Chironomus tentans (2nd instar)	Growth	14d NOEC	65	ASTM, GLP; Formulated sediment	0.27	1200	1[a]2[b]	Kent et al. 1994
Chironomus tentans (2nd instar)	Survival	14d NOEC	≥130	ASTM, GLP; Formulated sediment	0.27	>24 000	1[a]2[b]	Kent et al. 1994
Chironomus tentans (2nd instar)	Growth	14d NOEC	≥250	ASTM, GLP; Formulated sediment	2.3	>543	1[a]3[b]	Kent et al. 1994
Chironomus tentans (2nd instar)	Survival	14d NOEC	120	ASTM, GLP; Formulated sediment	2.3	260	1[a]3[b]	Kent et al. 1994
Chironomus tentans (2nd instar)	Growth	14d NOEC	≥170	ASTM, GLP; Formulated sediment	4.1	>207	1[a]2[b]	Kent et al. 1994
Chironomus tentans (2nd instar)	Survival	14d NOEC	54	ASTM, GLP; Formulated sediment	4.1	65,85	2[b]	Kent et al. 1994
Chironomus tentans (larvae)	Survival	14d LC_{50}	>170	ASTM, GLP; Natural sediment	4.1	>207	1[a]	McNamara 1991 (In ECHA 2017a)
Chironomus tentans (larvae)	Survival	14d NOEC	54	ASTM, GLP; Natural sediment	4.1	66	1[a]	McNamara 1991 (In ECHA 2017a)

Species	Endpoint & Duration		Effect value (mg/kg dw)	Guideline/ Comments	OC (%)	Effect value at 5 % OC (mg/kg dw)	Evaluation	Reference
Chironomus tentans (larvae)	Survival	14d LOEC	170	ASTM, GLP: Natural sediment	4.1	207	1[a]	McNamara 1991 (In ECHA 2017a)
Chironomus tentans (larvae)	Survival	14d NOEC	<16	Significant reduced survival at all concentrations	3.9	<26	3[b]	Walker, 1993 (in EA 2009)
Chironomus riparius (larvae)	Survival	28d LC_{50}	114	OECD 218, GLP; Formulated sediment.	4.1	139	1[ab]	Krueger et al. 2008 (in ECHA 2017a; ECHA 2012)
Chironomus riparius (larvae)	Survival, emergence rate	28d NOEC	44	OECD 218, GLP; Formulated sediment.	4.1	53.66	1[ab]	Krueger et al. 2008 (in ECHA 2017a; ECHA 2012)
Chironomus riparius (larvae)	Development rate	28d NOEC	131	OECD 218, GLP; Formulated sediment.	4.1	159.76	1[ab]	Krueger et al. 2008 (in ECHA 2017a: ECHA 2012)
Crustacean								
Hyalella azteca (Read across from D5)	Survival	28d NOEC	130	Read across	4.8	135	1[a]	ECHA 2017a[c]

a = Reliability evaluation from REACH Registration Dossier (ECHA 2017a). b = Reliability evaluation from EA (2009). c = Ref. 006 (sediment toxicity) in REACH registration dossier (ECHA 2017a).

Table S4. All mammal toxicity studies of D4.

Species	Endpoint & Duration		Effect value (mg/kg bw)	Comments	Reference
Rat	Survival	LC_{50}	>4800		Löser 1979 (in EA 2009; SCCS 2010)
Rat (Fischer 344, immature female)	Liver weight	3d NOEL (LOEL)	250 (100)	GLP; uterotrophic assay; increased liver weight	Dow Corning 1999 (in EA 2009; SCCS 2010)
Rat (Sprague-Dawley, immature female)	Liver weight	3d NOEL	100	GLP; uterotrophic assay; increased liver weight	Dow Corning 1999 (in EA 2009; SCCS 2010)
Rat (Sprague-Dawley and Fischer 344, immature female)	Bodyweight	3d NOEL	100	GLP; uterotrophic assay; increased liver weight; Decreased bodyweight was observed at 250 mg/kg	Dow Corning 1999 (in EA 2009; SCCS 2010)
Rat (Sprangue-Dawley, female)	Liver weight	4d LOEL (NOEL)	20 (5)	Liver to body weight ratio; Increased liver weight; low no of rats used per group and limited data presented.	Zhang et al. 2000
Rat (Sprangue-Dawley, male)	Liver weight	4d LOEL (NOEL)	100 (20)	Liver to body weight ratio; 20 and 100 mg/kg/day D4 increased liver weight by approximately 20 per cent; low nr of rats used per group and limited data presented.	Zhang et al. 2000
Rat (Sprangue-Dawley, female)	Liver weight	14d NOEL	25	GLP; In females, liver weights increased by 8, 17, 24, and 24 per cent at 25, 100, 400, and 1600 mg/kg, respectively	Dow Corning, 1990 (in EA 2009; SCCS 2010)
Rat (Sprangue-Dawley, male)	Liver weight	14d NOEL	100	10% increased liver weight at 400 and 1600 mg/kg/d	Dow Corning, 1990 (in EA 2009; SCCS 2010)
Rat (Sprangue-Dawley)	Bodyweight	14d NOEL	400	GLP; At 1600 mg/kg/day the bodyweight in males and females was significantly reduced to 83 and 89% of the control weights, respectively.	Dow Corning, 1990 (in EA 2009; SCCS 2010)
Rats (Sprague Dawley)	Bodyweight	28d NOEL	< 200-300	Single-test dose encapsulated in diet; Signs of stress, reduced food consumption and reduced bodyweight	Dow Corning 1988 (in EA 2005; SCCS, 2010)
Rabbit (New Zealand White, female)	Liver weight	14d NOEL	>1000	GLP; No observed effect on liver weight	Dow Corning, 1992 (in EA 2009; SCCS 2010)
Rabbit (New Zealand White, female)	Food consumption ; Bodyweight	14d NOEL	< 500	GLP; Reduced food consumption and body weight at 500 and 1000 mg/kg/d	Dow Corning 1992 (in SCCS 2010)
Rabbit (New Zealand White, female)	Maternal toxicity	Treated on gestation day 7-19.	500	Dose range-finding study. Treatment related abortions at doses of 500 and 1000 mg/kg/d (NOEL 100 mg/kg/d). Reduced food consumption was observed, which was thought to cause increased spontaneous abortion and loss of post-implantation. No teratogenicity.	Global Silicone Producers Association, 1993 (in SCCS 2010)

Department of Environmental Science and Analytical Chemistry (ACES)

Stockholms universitet 106 91 Stockholm Tel 08-16 20 00
www.su.se info@su.se

Stockholm University