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Quantitative weight-of-evidence analysis of the persistence, bioaccumulation, toxicity, and potential for long-range transport of the cyclic volatile methyl siloxanes

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ABSTRACT

Cyclic volatile methyl siloxanes (cVMSs) are highly volatile and have an unusual combination of physicochemical properties, which are unlike those of halocarbon-based chemicals used to establish criteria for identification of persistent organic pollutants (POPs) that undergo long-range transport (LRT). A transparent quantitative weight of evidence (QWoE) evaluation was conducted to characterize their properties. Measurements of concentrations of cVMSs in the environment are challenging, but currently, concentrations measured in robust studies are all less than thresholds of toxicity. The cVMSs are moderately persistent in air with half-lives ≤11 d (greater than the criterion of 2 d) but these compounds partition into the atmosphere, the final sink. The cVMSs are rapidly degraded in dry soils, partition from wet soils into the atmosphere, and are not classifiable as persistent in soils. Persistence in water and sediment is variable, but the greatest concentrations in the environment are observed in sediments. Based upon the measurements that have been made in the environment, cVMSs should not be classified as persistent. Studies in food webs support a conclusion that the cVMSs do not biomagnify, a conclusion that is consistent with results of toxicokinetic studies. Concentrations in air in remote locations are small and deposition has not been detected. Taken together, evidence indicates that traditional measures of persistence and biomagnification used for legacy POP are not suitable for cVMS. Refined approaches used here suggest that cVMSs are not classifiable as persistent, bioaccumulative, or toxic. Further, these chemicals do not undergo LRT in the sense of legacy POPs.

Silicone compounds in general are very widely used and are an essential component of the technological society that many of us live in. The cyclic volatile methyl siloxanes (cVMS) are a class of silicone compounds that have an unusual combination of physicochemical properties that results in their wide use in consumer products such as hair conditioners, deodorants, and cosmetics (Montemayor, Price, and Van Egmond 2013) and industrial applications including production of polymers, dry cleaning solvents, and industrial cleaning fluids (Horii and Kannan 2008; Wang et al. 2009). In many of their uses, these siloxanes may be released into the environment, either as a result of their direct use or from products that they are used to manufacture. The cVMSs have large vapor pressures (~5 to 130 Pa at 25°C), and low water solubility (5–56 μg/L), resulting in large air/water partition coefficients (K_{AW}) and octanol/water partition coefficients (K_{OW}). Table 1 presents more detailed information on the properties of the three principal cVMS compounds, octamethylcyclotetrasiloxane (D4, CAS 556–67-2), decamethylcyclopentasiloxane (D5, CAS 541–02-6), and dodecamethylcyclohexasiloxane (D6, CAS 540–97-6). Unlike other neutral organic chemicals, the water–soil partition coefficient (corrected for content of organic carbon, K_{OC}) is more than two orders of magnitude less than would be predicted from the K_{OW}.

Releases of cVMSs to the environment have raised concerns as to the fate and potential effects of these

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Table 1. Key physicochemical properties for D4, D5, and D6.

Name	MW (g/mol)	Log K_{OW}	Log K_{OC} (L/kg)	K_{OA} at 37.5°C	Water solubility (µg/L)	Henry's law constant H_C (atm-m^3/mol)
D4	296	6.49	4.22	4.1	56	11.8
D5	370	8.03	5.17	4.7	17	33.0
D6	444	9.0	6.03	5.3	5.1	48.8

Note. Data from Environment Agency (2010a; 2010b; 2010c), Xu and Kropscott (2012; 2013), and Xu, Kozerski, and Mackay (2014).

substances on humans and the ecosystem. The cVMSs have been the subject of several regulatory reviews in the United Kingdom (Environment Agency 2010a; 2010b; 2010c), Canada (Environment Canada [EC] and Health Canada [HC] 2008a; 2008b; 2008c), and Nordic States (IVL 2005; Nordisk Ministerråd 2005), a judicial review (Giesy et al. 2016; Siloxane D5 Board of Review 2011), and an evaluation for the European Chemicals Agency (ECHA) (Environment Agency 2014a; 2014b). In addition, several review papers have recently been published on the environmental and biological properties of D5 (Fairbrother et al. 2015; Gobas et al. 2015a; 2015b; Mackay 2015; Mackay et al. 2015a; 2015c); as these papers were reviews and not original experimental studies they were not included in the quantitative weight of evidence (QWoE) but provided a separate opinion on one of the cVMS. Since and during the time when these reviews were conducted, new information has been published in reports and in the scientific literature, and this led us to undertake a QWoE method to assess the properties of the cVMSs as a whole weight of evidence (WoE).

In carrying our risk assessments, a particular concern is that different scientific disciplines have adopted different methods for developing, analyzing, and combining information (Gough 2007). This provides a particular challenge in a complex multidisciplinary area such as environmental risk assessment. Weight of evidence (WoE) is a term that is widely used in the literature, but mostly in the metaphorical sense (Weed 2005). WoE offers a structured and transparent approach to risk assessments and is of particular value for assessments involving a number of different lines of evidence. To date, WoE has been used infrequently in a formal and quantitative sense for risk assessment in relation to persistent organic pollutants (POP) and long-range transport (LRT), with the possible exception of the Giesy et al. (2014) evaluation of persistent, bioacumulative, and toxic (PBT) properties of chlorpyrifos.

Weight of evidence

Hypothesis-based approaches to WoE have been used for assessing risks of substances with endocrine activity (Borgert et al. 2011; 2014), carcinogens (Rhomberg, Bailey, and Goodman 2010), various other mechanisms of toxicity, and chemicals in general (Becker et al. 2015; Lutter et al. 2015). Quantitative and semiquantitative methods have been used for sediment (Chapman 2007), for oil spills (McDonald et al. 2007), and for the herbicide atrazine (Van der Kraak et al. 2014). The evidence shows that a framework based on quantitative WoE is needed to characterize the PBT properties of data-rich chemicals such as cVMS.

In conducting a QWoE analysis, it is important to recognize that domains of evidence may be either independent or linked in dependent chains of responses. Independent domains of evidence are typically based on a single response such as toxicity of a single type (i.e., carcinogenicity). Dependent evidence is usually concatenated in a chain of events that is similar to an adverse outcome pathway (AOP; Figure 1) (Ankley et al. 2010; Becker et al. 2015) or some of the approaches for causality, such as those suggested by Hill (1965). Each of the links in a concatenated line of evidence may be tested experimentally, but if one of these is shown to not be

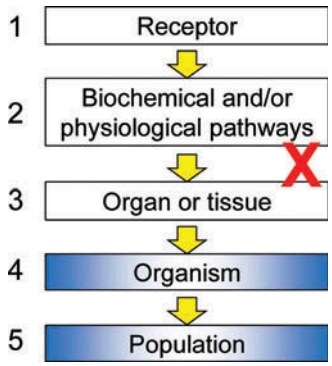

Figure 1. Illustration of linked or concatenated lines of evidence and the importance of continuity. The chain is broken if one of the lines of evidence is not true (red X).

relevant, that is, redundancy or resiliency in an organ or tissue that negates measured effects on physiology (red X in Figure 1), the chain is broken. In this case, the response is not propagated to the apical endpoint at the level of the organism or population and AOP is not relevant. This also applies to properties such as bioaccumulation. Thus, a model based on K_{OW} might predict that a chemical is able to biomagnify but in vivo measurements demonstrate that the chemical is completely metabolized and/or excreted, thus breaking the chain of evidence. Further measurements at higher levels of organization or closer to the apical endpoints therefore would override measures at lower levels.

Framework for analysis of quantitative weight of evidence

The methods that were used in this QWoE are illustrated in Figure 2. The process was a stepwise approach that began with searches to identify all relevant literature (publications and reports). These papers and reports were then grouped into lines of evidence for testing the risk hypothesis that the substance being considered had a property or effect that would result in exceedence of a threshold for persistence; bioconcentration, bioaccumulation, or biomagnification; and toxicity and/or LRT.

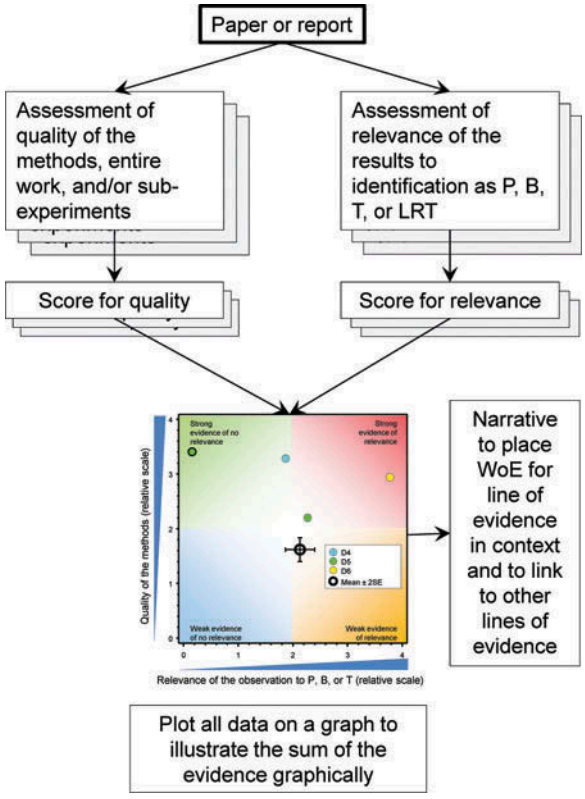

Figure 2. Illustration of the QWoE process used to assess the cVMSs for properties relevant to P, B, T, and LRT.

These papers and reports were then assessed in detail, using predefined criteria for quality and relevance to develop scores (on a relative scale) to separate those of greater quality from those of lesser quality and relevant from less relevant results. Inclusion of all papers and reports helped to reduce selection bias. It generally followed a process such as is outlined in ECHA (2010) and indicated in more detail in European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC 2014). It also drew on the Memorandum of the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) on WoE (SCENIHR 2013).

Objectives of the QWoE

The objectives of the QWoE analysis were to evaluate all of the studies on persistent, bioacumulative, and toxic (P, B, and T) properties and LRT of the cVMSs using a standardized scientifically robust process. This was done transparently, and the evaluations were fully documented. The process included all the available studies and, by using a graphical display of the results, was designed to bring all data from studies of varying quality and relevance together in such a way that the consistency and reliability of all the evidence could be clearly shown. Assessment of relevance of data also included consideration of the unique properties of the cVMSs that result in environmental behavior that is different from the legacy chemicals such as the halogenated aryl and aromatic hydrocarbons that have been identified as PBT and capable of LRT.

Methods

Prior to the assessment of publications and reports on cVMSs an identification of best practice for each type of method was conducted. These best practices were used to develop guides for scoring the quality of studies. From these, scoring sheets were developed and were used to score individual papers and reports for quality and relevance. These guides and scoring sheets are described in greater detail in the Supplemental Information (SI). The QWoE methodology for cVMSs utilized a staged approach beginning with

individual publications and reports and ending with the summation of all domains/lines of evidence. Characterization of substances for persistence (P), bioaccumulation (B), very bioacumulative (vPvB), or PBT inevitably involves a number of scientific judgments. The purpose of this methodology was to provide transparency and consistency and reduce bias in selecting and reviewing the sources of data. A description of the methods and the QWoE analyses of all studies that were included are provided in detail in the SI. It was not possible to capture all possible criteria for quality and/or relevance applicable to every publication and report in the scoring criteria (see later discussion). In situations where criteria for quality or relevance were not included a priori, expert judgment was used to assign a score and this was described in the WoE and the narrative.

Representation of the WoE findings

The next stage in the assessment of WoE was to separately consider the selected literature relating to P, B, toxicity (T), and LRT. In some cases, separate lines of evidence were used, such as, under the umbrella of B, bioconcentration, bioaccumulation, biomagnification, and trophic magnification factors (TMF). Procedures were followed for the graphical illustration of WoE as described by Van der Kraak et al. (2014). The results of the WoE analysis were summarized by drawing a graphical plot of score for quality against the score for relevance for each publication and report. The scoring was quantitative, making this a QWoE. The separate points showed clustering (if any) of data from all studies assessed (Figure 3).

Because all investigations were included, the distribution of the scores provided an easy visualization of the WoE for a particular line of evidence. In interpreting these graphs, it is important to remember that the scores are relative, not absolute. Their sole function was to separate studies and their data on the basis of relevance and quality. These studies were then discussed in the narrative and conclusions drawn. In addition, the graphical illustration (Figure 3) also included a mean value and variance of scores for quality and relevance. The mean represented the general trend of data, and variance indicated uncertainty in its quality and relevance. This information was used to identify areas of significant uncertainty.

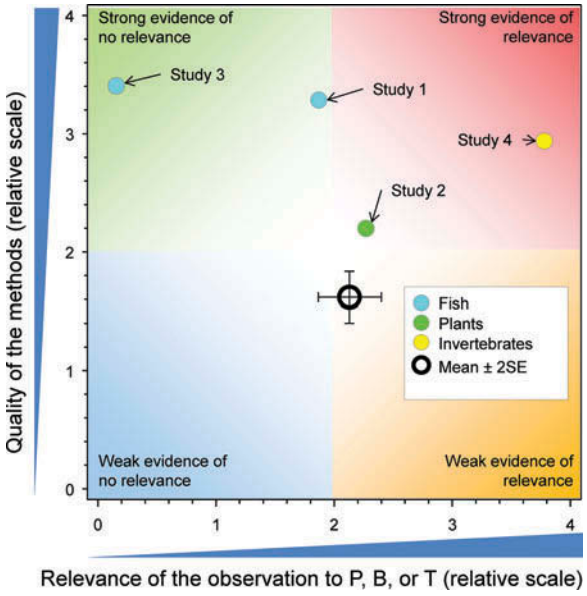

Figure 3. Illustration of the plotting of strength and relevance of studies included in the QWoE.

This article is a QWoE analysis of the environmental fate and toxicity of three principal cVMSs compounds, D4, D5, and D6. Formal QWoE analysis was conducted where sufficient studies were available; where fewer than four studies were available, analysis was by expert judgment and is presented in the narrative. The focus of the QWoE assessment was on the environment, and consideration of possible effects in humans arising from environmental exposure has been excluded. In terms of fate in the environment and toxicity, analysis is directed to determining whether these chemicals possess physical, chemical, and biological properties that would result in classification as POP and/or demonstrate LRT under the criteria of the Stockholm Convention (SC: United Nations Environmental Programme 2001) and United Nations Economic Commission for Europe (UNECE: United Nations Economic Commission for Europe 1998) or PBT, and/or vPvB under REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals: European Community 2011).

Problem formulation and hypothesis testing

Problem formulation (U.S. Environmental Protection Agency [EPA] 1998) is the first step in any risk assessment as it enables the sources of the chemicals in question to be described and their physical,

chemical, and biological properties to be characterized in relation to questions being raised and the reason(s) for the assessment (protection goals). This process allows the identification of assessment endpoints that are consistent with protection goals. It results in the development of conceptual models for exposure and effects, and narrows the focus to important queries. This provides the basis for the risk hypotheses and for an analysis plan to test the hypotheses with experimental data.

Protection goals are usually generic, are almost inevitably political in nature, and unquantified and/or unquantifiable. In this sense, they initiate regulation but rarely provide guidance for testing of risk hypotheses. In the context of POP and LRT, the protection goals focus on health of humans and the environment but none clearly states the level of protection and specific endpoints for assessment (see SI for more detail).

Assessment endpoints are those responses or attributes of receptor organisms that are used to determine the degree of harm that results from exposures to the chemicals being assessed (U.S. EPA 1998). Assessment endpoints are specific to the issues in hand, measurable or can be modeled, and might be tested with risk hypotheses. In ecotoxicology, assessment endpoints are generally aimed at apical endpoints related to sustainability of populations: survival, growth, development, and reproduction (Wheeler, Weltje, and Green 2014). This recognizes that there is resiliency in populations of organisms in the environment and that some effects at the individual level might be tolerated. In some cases, such as for threatened and endangered species, endpoints may be aimed at the survival of individuals.

There are 4 major lines of evidence that are used to identify POPs and PBTs (Figure 4). These are P, B, T, and LRT. The latter property is not considered in the REACH regulations but is under UNECE-LRT and the SC (Table 2). P and B are codependent in most cases; without significant P, B is unlikely to occur (Goss, Brown, and Endo 2013). As there are no formal assessment endpoints for T suggested for POPs and only one for PBTs, the following was utilized in our QWoE assessment. The generic assessment endpoint for toxicity was:

> Risk of unacceptable toxic effects in (humans and/or) organisms in an environment as a result of a combination of POP or PBT properties that result in internal (or external) exposures that exceed thresholds of adverse effects.

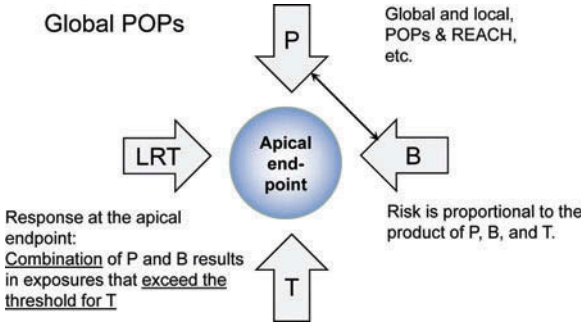

Figure 4. Illustration of the lines of evidence for identification of a compound as P, B, T and/or LRT. Co-dependence of P and B is indicated by the arrow.

With appropriate data and statistical approaches, the threshold of adverse effects might be expressed in terms of a probability that a certain proportion of a population or proportion of species would have its thresholds of adverse effects exceeded in a certain proportion of locations or scenarios of exposure. The null hypothesis is that:

> The combination of POP or PBT properties will not result in internal (or external) exposures that exceed thresholds of adverse effects.

In the context of assessing PBT and POP properties, the risk that exposures will exceed the threshold of adverse effects is proportional to the products of the risks of P, B, and T. Thus if the risk for any one of the properties is zero or very small (e.g., no B, P, or T) the product will be zero (or very small) and the substance should not be classified as a POP or PBT. Similarly, if a compound undergoes LRT and persists in environmental matrices in remote locations but is unable to bioaccumulate to the extent that internal exposures exceed thresholds of adverse effect, it does not present a risk.

The various global and regional frameworks for identification of POP and PBT use screening criteria to identify potentially problematic substances. The screening criteria vary between the SC, REACH, and similar classification schemes in other jurisdictions (Moermond et al. 2011). The criteria for classification of POP were developed from empirical measures of toxic organic compounds (legacy POPs) known to bioaccumulate in food chains and be transported to

Table 2. Criteria for the categorization of compounds as POPs and LRT substances under the Stockholm Convention, the UN Commission for Europe, and REACH.

Stockholm Convention, the UN Commission for Europe			
Persistence (P)	Bioaccumulation (B)	Toxicity (T)	Potential for long-range transport (LRT)
Water: DT_{50} ≥ 2 mo	BCF or BAF ≥5,000 or log K_{OW} ≥5	No specific criteria other than "significant adverse human health and/or environmental effects" (in Article 8, 7(a)).	Air: DT_{50} ≥ 2 d. Monitoring or modelling data that shows long-range transport via air, water, or biota.
Sediment: DT_{50} ≥ 6 mo	High bioaccumulation in other species, high toxicity or ecotoxicity.		Concentrations of potential concern detected in remote locations.
Soil: DT_{50} ≥ 6 mo Other evidence of persistence	Monitoring data in biota indicating that the bio-accumulation potential is sufficient to justify its consideration within the SC.		
REACH			
Marine water: t½ ≥ 60 d; Fresh water t½ ≥ 40 d, vP ≥ 60 d Marine sediment: t½ ≥ 180 d Freshwater sediment: t½ ≥ 120 d, vP ≥ 180 d Soil: t½ ≥ 120 d, vP ≥ 180 d	BCF ≥ 2,000 in aquatic species, vB ≥ 5,000	Chronic NOEC ≤ 0.01 mg/L or is a carcinogen, mutagen, or toxic for reproduction, or other evidence of toxicity.	NA

Note. From European Community (2011), United Nations Economic Commission for Europe (1998), and United Nations Environmental Programme (2001).

remote locations (Environment Canada 1995; Ritter et al. 1995). These criteria were designed to identify compounds of global significance. On the other hand, REACH makes use of stricter criteria for identification of PBT and very persistent and very bioacumulative (vPvB) substances. Criteria for classification of POPs under SC and PBT and vPvB under REACH are shown in Table 2.

Risks to air-breathing animals

In all of the regulatory assessments of the risks of B and T for cVMS, those to air-breathing animals are generally regarded as *de minimis* (EC & HC 2008a; 2008b; 2008c; Environment Agency 2010a; 2010b; 2010c; Environment Agency 2014a; 2014b; IVL 2005; Nordisk Ministerråd 2005; Siloxane D5 Board of Review 2011). The reason for this is that the cVMSs in question all have large vapor pressures, small octanol–air partition coefficients (K_{OA}), and large Henry's law constants (H_C) (Table 1). This results in rapid depuration, by exhalation, for air-breathing animals exposed to D4, D5, or D6 via ingestion, contact with skin, or inhalation (Andersen, Reddy, and Plotzke 2008).

The volatilization of cVMSs in air-breathing animal depends on the relative capacity of lipid (L) to retain the chemical relative to the tendency of volatilization from water (W). This volatilization should be predictable from the ratio of K_{LW} to K_{AW}, that is, $K_{LA,}$ where K_{LW}, K_{AW}, and K_{LA} are dimensionless lipid/water, air/water, and lipid/air partition coefficients. As discussed in Seston et al. (2014b), $K_{LW} \approx K_{OW}$ if all types of lipids are considered together. In this case, K_{LA} will be equal to K_{OA}. The measured log K_{OA} values and the temperature dependence of all VMS including D4, D5, and D6 are available and, at 37.5°C (close to the body temperature of mammals), are relatively small (4.1 for D4, 4.7 for D5, and 5.3 for D6) (Xu and Kropscott 2013). Based on an average content of lipid in plasma of 0.3%, plasma/air partition coefficients range from tens to hundreds, resulting in rapid depuration via respiration.

Therefore, in contrast to legacy pollutants such as polychlorinated biphenyls (PCB), the potential for bioaccumulation in warm-blooded air-breathing animals, including humans, is very limited. Birds may even be at a lesser risk because of the generally higher body temperature (42°C), which would favor excretion via respiration. Thus, these organisms were excluded from further consideration in this QWoE

analysis. The general focus is therefore on aquatic environment and, more specifically, on organisms exposed in matrices such as soil and sediment where cVMSs tend to accumulate.

Inherent properties of cVMSs in the context of WoE

Because silicon is a major component of D4, D5, and D6 (Figure 5), they possess unusual properties (Mackay et al. 2014), The K_{OW} of these compounds is large and solubility in water is small. In addition, for molecules of this size (Table 1), the Henry's law constant (H_C) is large and, consequently, molecules tend to partition from water and wet soil into air. Because the K_{OC}s are smaller (about 200-fold) than would be expected from the K_{OW} (Kozerski et al. 2014; Mackay et al. 2014), this further shifts the partitioning equilibrium from soil and sediments into air.

Constraints on exposures in the environment

The physicochemical (intensive) properties of the cVMSs (Table 1) result in marked constraints on concentrations that may occur in the environment. Because of the largely diffuse release of these chemicals in the environment (Montemayor, Price, and Van Egmond 2013; Wang et al. 2013a), there are few point sources that might result in concentrations of cVMSs that will not be in equilibrium between environmental compartments. By far the most important source of cVMSs to the aquatic environment is effluent from sewage treatment plants (STPs). Therefore, in almost all situations, concentrations of cVMSs in the environment are constrained by their physical properties and maximal absorptive capacity of the matrix within which they reside. This is highly relevant to testing for toxicity and bioaccumulation or assessing environmental persistence.

Maximum concentrations in water are constrained by solubility (Table 1). Maximum concentrations in dissolved or suspended organic matter in water, sediments, and soils are constrained by the sorption capacity of the matrix, which is governed by the K_{OC}, solubility in water, and the amount of organic carbon (OC) in wet soils or sediments (Kozerski et al. 2014). The fraction of OC varies from one soil or sediment to another and thus affects specific maximum sorption capacity.

The maximum sorption capacity, normalized to OC (noted as MSC in this article), for soil or sediment is calculated from the formula $MSC = C_W \times K_{OC} \times 0.001$, where C_W is the solubility in water and 0.001 kg/g is a correction factor for units. To calculate a sediment- or soil-specific MSC (SMCS), the MSC is multiplied by the fraction of OC in the matrix (f_{OC}). Values of dry weight (dw) are used for these calculations. The MSC values for the three cVMSs discussed here are shown in Table 3.

There is no evidence in reports from the literature that, under the environmental conditions tested, cVMSs partition strongly to clay particles in soil and sediment; however, their degradation products do (Xu et al. 1998). The cVMSs are not ionic and would not be expected to undergo ionic binding to charged binding sites on clay. However, under dry conditions and greater loading, they may undergo surface adsorption or fill micropores in clay minerals such kaolinite, illite, hematite, and silica (Xu, personal communication, 2015). This binding is usually less than partitioning to OC, which is the major determinant of adsorption of nonpolar organic chemicals in soils and sediments.

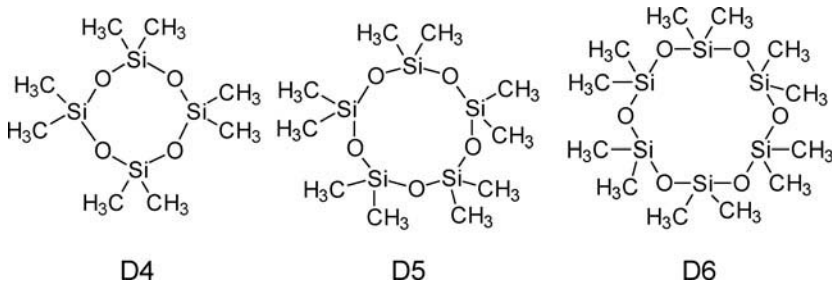

Figure 5. Chemical structures of the cVMSs D4, D5, and D6.

Table 3. Maximum concentrations of D4, D5, and D6 in water and maximum sorption capacity for soil or sediment.

cVMS	Maximum solubility in water (µg/L)	K_{OC} (L/kg)	Maximum sorption capacity (MSC) (mg/kg_{OC} dw)	Specific MSC for a soil or sediment with 3% OC (mg/kg dw)
D4	56	16,596	929	28
D5	17	147,911	2514	75
D6	5.1	1,071,519	5465	164

Relevance of physical and chemical properties of the cVMSs to testing for persistence, fate, and bioaccumulation

The large vapor pressures and small solubility of the cVMSs (Table 1) result in a strong tendency to partition into air, which apparently has implications for the fates of cVMSs in other environmental matrices, testing for P in water and water–sediment systems, and measuring concentrations in the environment. Conventional guideline tests for P (such as the OECD test 309: OECD 2004b) are not reliable for cVMSs because of the difficulty of preventing evaporative losses during the study, and thus sealed systems have been used. This questions the appropriateness of extrapolating from results obtained in hermetically sealed systems to the real environment, where no such barriers are present. In addition, although the K_{OC}s (Table 1) of the cVMSs are less than would be predicted from their K_{OW} values, they are still large and will affect bioavailability to organisms exposed via sediments or soil. This has implications for assessing P, B, and T, as it will affect rates of biodegradation and uptake in bioassays and in the environment.

The low solubility of cVMSs in water is relevant to toxicity testing. The strategy used in most toxicity tests is to use a range of concentrations or doses that includes values that exceed the threshold for biological activity. Thus, in most toxicity tests, effects are observed at larger exposures (such as the maximum tolerated dose [MTD] in toxicity tests in mammals); this is part of the experimental design. This has the advantage that the validity of the test to detect adverse effects is demonstrated and that values producing incipient responses, such as the lowest-adverse-effect level (LOAEL) and lowest-observed-effect concentration (LOEC), may be characterized for purposes of assessment of hazard or risk. However, these larger exposures may not be environmentally realistic or even thermodynamically attainable for substances, such as cVMS, that are poorly soluble in water, which results in slow uptake that might exceed feasible durations of tests (Fairbrother et al. 2015; Mackay, Powell, and Woodburn 2015c).

Under natural environmental conditions, the maximal concentration of a chemical in water cannot exceed maximum solubility. Thus, toxicity tests that make use of solvents to increase dispersion of substances in water may show toxicity at high concentrations that are unobtainable in the environment under normal conditions of use. Any effects observed under these conditions might be the result of physical effects (such as smothering of respiratory surfaces) by the chemical/solvent that cannot occur in the environment and are not representative of normal environmental conditions (spills excepted).

The same argument applies to toxicity measured in tests for sediments and soils where sorption capacity of the matrix is exceeded (Xu, Kozerski, and Mackay 2014). Because the cVMSs partition into organic matter, which varies in concentration from one location to another, toxicity values are sometimes normalized to the amount of OC in the sediment or soil. This normalization allows easy comparison to the MSC to characterize the appropriateness of the results of the test. This was addressed in the scoring scheme for the relevance of measures of toxicity in our QWoE assessment.

Results

Concentrations in the environment

The estimation or measurement of concentrations in various environmental matrices is critical for assessing toxicological relevance for use and release of cVMSs to the environment. The measurement of concentrations of cVMSs in environmental and biological matrices is difficult because of two factors: (1) Large volatility of the cVMSs results in losses during processing and handling of samples, and (2) widespread use in many consumer products

increases the likelihood of contamination during sampling, handling, and analysis. Materials and equipment used for analysis may contain cVMSs that contribute to background levels and thereby enhance uncertainty in interpretation of findings (Wang et al. 2013a).

Concentrations of cVMSs in environmental matrices were summarized in the literature, but most of these publications do not provide raw data and often combine values from different reports and papers without consideration for the quality of the study in relation to best analytical practices. For this reason, QWoE analysis was not applied to all studies. The well-conducted investigations are discussed in the narrative that follows, and QWoE assessments are provided in the SI. However, a review paper by Wang et al. (2013a) provided summary data for concentrations of D4, D5, and D6 in various environmental matrices from a number of countries and provided information on general trends in relation to sources of the cVMSs in the environment. These are discussed below.

Concentrations in the atmosphere

Concentrations of cVMSs were in the order D4 > D5 > D6 for air in the immediate vicinity of STPs and local ambient air (Wang et al. 2013a). However, for D4, D5, and D6, concentrations in biogas released from STPs were several orders of magnitude greater than in air in the immediate vicinity or local ambient air (10,000 to 400 μg/m^3, 60 to 0.01 μg/m^3, and 30 to 0.06 μg/m^3, respectively) (Wang et al. 2013a). The large concentrations in biogas and air close to STP are consistent with this being a major pathway of loss to the atmosphere during treatment. Mean efficiencies of removal of D4, D5, and D6 during treatment were large (>80%) regardless of location in North America or Europe (Wang et al. 2013a).

Concentrations in surface waters

Concentrations in surface waters receiving effluent from STPs were, in general D6 > D5 > D4 (Figure 5 in Wang et al. 2013a); importantly, none exceeded the maximal solubility in water (Table 3). Raw data were not available for concentrations of cVMSs in surface waters, but data from the review by Wang et al. (2013a) reported that maximum measured concentrations of D4, D5, and D6 were <1 μg/L. Therefore, for toxicity tests conducted in water, the maximal solubility of the cVMSs in water was used as a worst-case cutoff value for relevance of exposure. A second cutoff for concentrations in water was based on the maximum measured value reported in surface waters receiving effluents. These, based on the review by Wang et al. (2013a), were 0.02, 1.6, and 0.16 μg/L for D4, D5, and D6, respectively.

Concentrations in biosolids, soils, and sediments

As might be expected, concentrations of cVMSs in biosolids from STPs were greater than in sediments and soils amended with biosolids. Concentrations in biosolids were generally greater for D5 (100 to 0.07 mg/kg dw) than for D4 and D6 (10 to 0.03 mg/kg dw). Concentration of D4, D5, and D6 were similar in sediments and soils and ranged from 1 to 0.0015 mg/kg dw, with one outlier for D5 of about 6 mg/kg dw (Wang et al. 2013a).

Few publications in the peer-reviewed literature provided sufficient raw data for use in probabilistic characterization of the range of concentrations. However, one report provided information on concentrations of cVMSs in sediments and biota over several locations sampled from 2011 to 2013 (Seston et al. 2014a). Only the results of the sampling of sediments are discussed here, but these data are probably the most environmentally important, as sediments are a potential medium-term repository for cVMSs released into surface waters (see SI for QWoE analysis of the quality of the data). These raw concentration data were combined across subsites, years, and depths. If subsites were obviously different, such as in Lake Ontario where consistently large concentrations were observed in Hamilton Harbor, these were analyzed separately. Hamilton Harbor is a location with large inputs of effluents from STPs dealing with domestic and industrial sewage from the Greater Hamilton Municipality and has little exchange of water with Lake Ontario. Lake Pepin is located between Minnesota and Wisconsin about 100 km south of Minneapolis/Saint Paul. It is a flow-through site and receives inputs of effluents from Minneapolis/Saint Paul and other communities. Raw data for concentrations of D4, D5, and D6 were reported also from Tokyo Bay from samples

taken across several transects of the bay starting in November 2011 (Seston et al. 2014a). Values below the limit of detection (LOD) were included in the data set but not used to plot the cumulative distributions. They were, however, included in the ranking as they represent the proportion of values less than the LOD. Cumulative frequency distributions were constructed on $\log_{10}$-transformed data and plotted with SigmaPlot (Systat. 2011). Upper centiles were estimated from the linear regression of the transformed data (Solomon, Giesy, and Jones 2000).

The concentrations of D4, D5, and D6 in sediments from Lake Pepin (Figure 6) were in the rank order of D5 > D6 > D4, likely reflecting their use in the watershed. Because of lack of good fit to the linear regression model for the smaller values, the estimates of the upper centiles (>90th) were conservative. The 99.9th centile (Table 4) was selected as a worst-case value for characterizing exposures. As for Lake Pepin, the values for the concentrations of D4, D5, and D6 in sediments from Lake Ontario (Figure 7) were in the rank order of D5 > D6 > D4, also likely reflecting use in the watershed. Values were clearly bimodal, especially for D5. Concentrations in sediments from Hamilton Harbor were consistently greater than those in the open-water site locations. For this reason, only the values from Hamilton Harbor were used in the regression. Again, the upper centile values (>90th) were conservative. The 99.9th centile concentrations of D4, D5, and D6 from Hamilton Harbor (Table 4) were greater than those for Lake Pepin, most likely because this is not a flow-through site. The samples from Tokyo Bay (Figure 8) were taken across a large

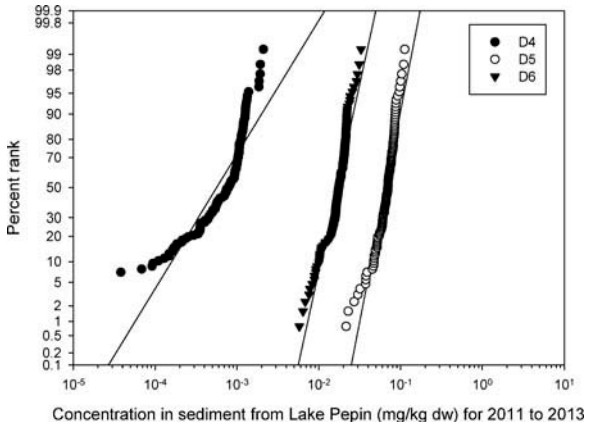

Figure 6. Concentrations of the cVMSs, D4, D5, and D6 in sediments from Lake Pepin (MN, USA) sampled once per year from 2011 to 2013.

Table 4. Regression equations and upper 99.9th centile concentrations of cVMSs in sediments from Lake Pepin, Lake Ontario, and Tokyo Bay between 2011 and 2013.

Data source	*n*	r^2	Slope	Intercept	99.9th centile (mg/kg dw)
D4 L Pepin	126	0.82	2.34	7.59	0.01
D5 L Pepin	126	0.89	7.34	8.68	0.17
D6 L Pepin	126	0.91	6.52	11.58	0.05
D4 L Ontario H Harbor	75	0.80	2.11	4.87	0.14
D5 L Ontario H Harbor	75	0.87	3.05	0.89	5.28
D6 L Ontario H Harbor	75	0.93	3.83	4.25	0.50
D4 Tokyo Bay	60	0.97	1.62	3.52	0.55
D5 Tokyo Bay	60	0.96	3.07	2.40	1.68
D6 Tokyo Bay	60	0.96	3.89	5.64	0.22

Note. *n* = number of samples; r^2 = the regression coefficient; and the slope and intercept were derived from log-probability transformed data.

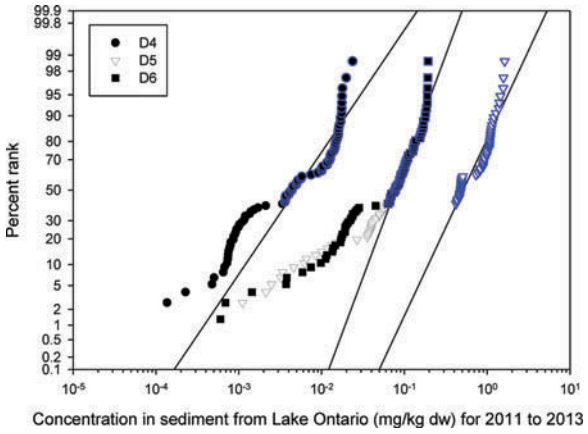

Figure 7. Concentrations of the cVMSs, D4, D5, and D6 in sediments from Lake Ontario sampled once per year from 2011 to 2013. The values outlined in blue are from Hamilton Harbor and were the only values used for the regression. The other values are from open-water sites.

area (500 km^2) and stratified into five regions representing distance from likely sources. Concentrations in zones 1 to 3 were generally greater than those in zones 4 and 5, furthest from the source. For this reason, regressions were performed on data from zones 1 to 3. Except for D4, the 99.9th centile concentrations from Tokyo Bay (Table 4) were less than those for Hamilton Harbor.

These upper centile concentrations, as discussed in the preceding, were used as cutoff values for assessment of the relevance of exposures used in toxicity tests carried out on sediment (see later discussion). The worst-case data for D5 and D6 from Hamilton Harbor and those for D4 from Tokyo Bay were used for this purpose. Thus, if the no-observed effect-

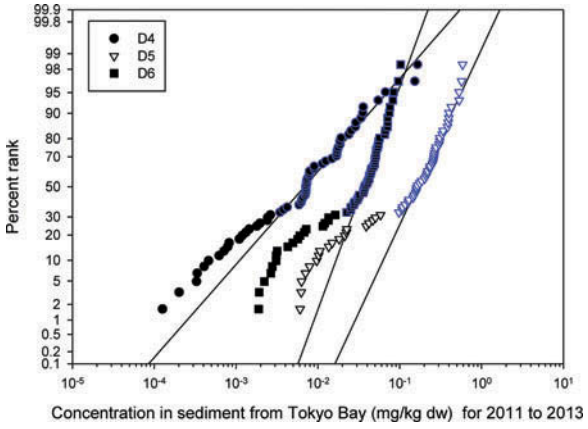

Figure 8. Concentrations of the cVMSs, D4, D5, and D6 in sediments from Tokyo Bay sampled once per year from 2011 to 2013. The values outlined in blue are from strata 1-3 closer to the source and were used for the regression. The other values are from more distant locations with smaller concentrations.

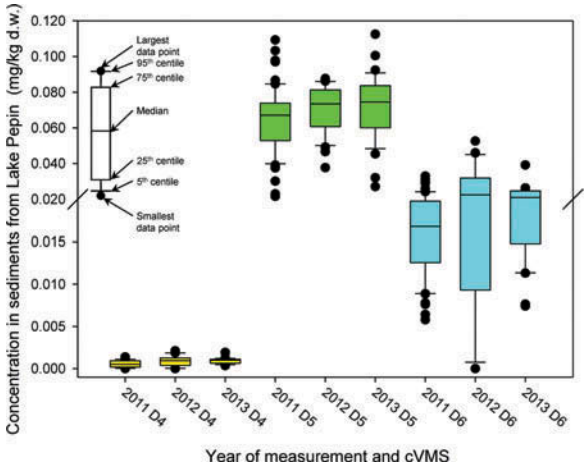

Figure 9. Box plots of concentrations of the cVMSs, D4, D5, and D6 in sediments from Lake Pepin (MN, USA).

concentration (NOEC) or LOEC from an acceptable test was greater than the 99.9th centile concentration measured in the environment, toxicity data were assigned a lesser score for relevance. For soils amended with biosolids, no raw data were available, but the maximum concentration reported by Wang et al. (2013a) was 1 mg/kg dw and was used as a cutoff value for relevance of exposure for toxicity tests in soil.

Temporal trends in concentrations

Data on concentrations of cVMSs in Lake Pepin, Lake Ontario, and Tokyo Bay were from the first 3 years of a long-term monitoring study. As illustrated for Lake Pepin (Figure 9), variance within each of the 3 years of measurement was large and there are too few years sampled to allow trends in concentrations to be discerned with confidence. There are also no records of inputs from STPs to determine whether differences in median or extreme values are related to variability between sites or to variation in amounts of the cVMSs entering the system.

Persistence (P)

The approach used in QWoE on persistence (P) of cVMSs made use of two domains of evidence: measurement in lab tests and under conditions in the field (Figure 10). As indicated, the inherent properties of the cVMSs are different enough from those of

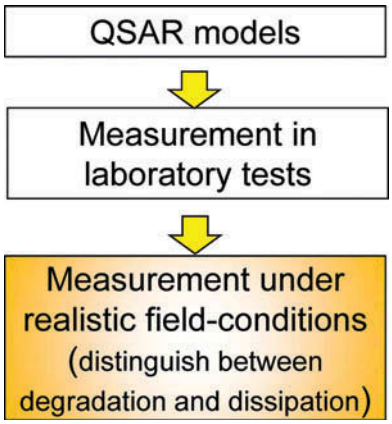

Figure 10. Illustration of concatenated lines of evidence for persistence in a particular environmental compartment.

most other chemicals used to calibrate quantitative structure–activity relationship (QSAR) models that such models are not reliable unless used with great caution (Mackay et al. 2014). For this reason, measured values were given greater credence than modeled values in our assessment.

The volatility of the cVMSs has implications for the measurement of P. Many of the early studies on P in water and water–sediment systems were confounded by the inability to obtain acceptable total recoveries at the end of the study. This was because of losses through evaporation from inadequately sealed test systems. Thus, special procedures were needed to reduce these losses and only a few tests have been conducted in these systems to date. These

considerations were included in the weighing of the evidence for P of cVMSs in water (see SI).

Persistence (P) in air

In air, the cVMSs are degraded by reaction with hydroxyl radical (•OH) to form hydroxy-substituted silanols, products that are less volatile and more soluble in water (Atkinson 1991), and have lesser potential for B and T. •OH is formed photochemically in the atmosphere, and concentrations vary diurnally and in relation to local concentrations of air pollutants (Madronich et al. 2015). Based on average concentrations of •OH in air, half-lives ($t_{½}$) for D4, D5, and D6 were estimated as 10.3, 6.7, and 5 d, respectively (SEHSC 2007b). While these half-lives are greater than the criterion of 2 d used to identify LRT substances such as PCB (Table 1), the inherent properties of the cVMSs are different, which greatly limits the extent to which they deposit and accumulate in surface matrices in remote regions (Xu and Wania 2013). Because cVMSs tend to remain in the atmosphere (the final sink), where they are degraded more rapidly than in other matrices, their presence in the global environment is ephemeral (months) and shorter than for classical POPs, where global lifetimes are longer (several years) (Xu and Wania 2013). Webster, Mackay, and Wania (1998) demonstrated that many chemicals partition into multiple environmental compartments but P in the major compartment or final sink is most appropriate for assessing P in the global context. Thus, overall persistence (P_{OV}) is more important for cVMSs than for other classes of chemicals, such as the classical POPs.

Persistence (P) in soil

The number of studies on dissipation of cVMSs from soil was limited (two studies conducted with radiolabeled products), probably because it is recognized that in wet soils there may be substantial losses of the cVMSs to air via volatilization. For this reason, a full WoE analysis was not conducted. No measurement of P in soil (Xu 1999; Xu and Chandra 1999), regardless of moisture or soil type, reached or exceeded the trigger values for P (Table 1). Measured $t_{½}$ for the D4, D5, and D6 varied between congeners, soil types, and amounts of moisture in soil. In dry soils, degradation followed first-order kinetics and $t_{½}$ for D4 ranged from 1 h to 3.54 d. In one soil, measured $t_{½}$ values of D5 and D6 were 2 2–1.38 days, respectively, at 32% moisture content (Xu and Chandra 1999). Rates of degradation fell with increasing content of water but partitioning to air rose at these greater levels of moisture. The measured $t_{½}$ values of the cVMSs in soil were smaller than the trigger values of classification as P, vP, or POP (120 or 180 d). The overall conclusion is that cVMSs should not be classified as P on the basis of P in soil.

Persistence (P) in water and sediment

Lab observations. Relatively few aquatic P investigations were conducted in the lab (Table 5) and some of these produced variable data; the QWoE analysis of these studies is provided in the SI. Because there were few studies, data are presented in a single graph (Figure 11). For D4, two hydrolysis studies in water and one in water–sediment, showed half-lives ($t_{½}$) less than the criterion for persistence for PBT ($t_{½}$ of 40 d [fresh water] or 120 d [sediment]), but another, in anaerobic water–sediment, displayed a $t_{½}$ of 365 d, greater than the criterion. One older aerobic water–sediment study with D4 (SEHSC 1991a) was not usable because the recovery in the system was poor. The rapid rates of hydrolysis and aerobic degradation show that, under environmentally realistic aerobic conditions, D4 does not trigger the criterion for P in sediment and water. Anaerobic sediments are invariably overlaid by aerobic sediments (Nilsson and Rosenberg 2000) where degradation is more rapid. Should diffusion or perturbation result in D4 entering the aerobic region of the sediment, it will degrade rapidly. In addition, the presence of D4 in anaerobic sediments would be less biologically relevant, as such sediments are less attractive to benthic organisms (Nilsson and Rosenberg 2000) and few organisms will be exposed. The quality of the studies was generally good; the mean score (SE) for quality of 4 usable studies was 3.3 (0.24). The mean score for relevance was 1 (1) and the variance was driven by the anaerobic persistence.

There were three studies of good quality (mean score (SE) of 3.4 (0)) on P of D5 in water and aquatic sediment (Figure 11, Table 5). In all cases, the $t_{½}$ was greater than the criterion value (108, 40, and 60 d) and the mean score (SE) for relevance was 3.7 (0.41). There was only one study of

Table 5. Summary of the WoE analysis of the persistence data for the D4, D5, and D6.

cVMS	Matrix	Measure	Value (d)	Q-score	R-score	Reference	Comment
D4	Aquatic Sed	t½ anaerobic	365 to 385	3.5	4	(CES 2009b)	The anaerobic t½ was greater than the trigger value for FW sediment of 120 d.
	Water	t½ hydrolysis	>29	3.4	0	(SEHSC 2005b)	Half-life was greater than 29 d but the test was compromised.
	Water	t½ hydrolysis	<17	3.7	0	(SEHSC 2005c)	The half-lives ranged from 12 min for pH 9 at 35°C to 23 d for pH 7 at 10°C. For pH 7.0 at 12°C (FW) predicted t½ = 16.7 d and for pH 8.0 at 9°C (SW) t½ = 2.9 d. All were less than the respective trigger values.
	Aquatic Sed	t½ aerobic	47	2.6	0	(CES 2008b)	The t½ was less than the trigger value for sediment (120 d).
	Aquatic Sed	t½ aerobic	>56	1.7	Not usable	(SEHSC 1991a)	Recovery was poor and it was not possible to determine half-life. Half-life >56 d but study was compromised.
D5	Water	t½ hydrolysis	455	3.4	3	(SEHSC 2006b)	The half-life at pH 6.99 and 10°C was > the trigger value of 40 d.
	Aquatic Sed	t½ aerobic	1200	3.4	4	(CES 2008a)	The aerobic t½ was > than the trigger value for FW sediment.
	Aquatic Sed	t½ anaerobic	3100	3.4	4	(CES 2008a)	The anaerobic t½ was > than the trigger value for FW sediment.
D6	Water	t½ hydrolysis	>365	2.9	4	(SEHSC 2009b)	Extrapolated t½ at pH 7 and ≤26°C was estimated to >365 d and exceeded all the trigger values.

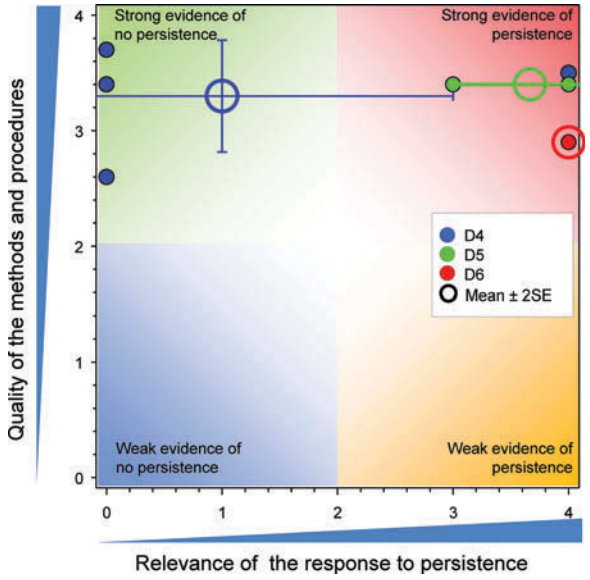

Figure 11. Graphical representation of the QWoE analysis of the studies on persistence of D4 (n=3), D5 (n=3), and D6 (n=1) in sediment-water and water in laboratory conditions.

moderate quality on P of D6 in water and the t½ was greater than the trigger value (SEHSC 2009b).

Field observations. As a subset of P (and LRT), concentrations measured in the environment may provide information on temporal trends (if appropriately sampled) and also on actual concentrations in the environment. These values are particularly important as they provide measures of exposures under realistic conditions. The three studies in Lake Ontario, Lake Pepin, and Tokyo Bay (see earlier discussion), which followed reliable sampling and good analytical practice, only provided data on concentrations in sediments for 3 yr (2011–2013; see Table 4 and Figure 9 for summaries of the data). Because of the large variability, data were judged insufficient to clearly discern a long-term trend.

Overall persistence (P_{OV})

Other than in modeling studies, it is not possible to assess global P of cVMSs across all matrices. The studies by Xu and Wania (2013) and Mackay et al. (2015a) provide useful insights. These studies have conducted with two widely accepted models for assessing LRT, the OECD P_{OV} and the LRTP Screening Tool, version 2.1.2 (the OECD Tool). The fate and distribution of cVMSs in the global environment was conducted using the GloboPOP model developed by Wania (2003; 2006). The results of the modeling demonstrated that, unlike legacy pollutants that are persistent in all media, rapidly transported to, and deposited into the Polar Regions, a large fraction of the cVMSs released into the environment tends to become airborne and removed from global environment by degradation in air. Although cVMSs are predicted to travel for large distances in the atmosphere, they have little potential (4 to 5 orders of magnitude less than legacy pollutants) for deposition to surface matrices in remote regions (Mackay et al.

2015a; Xu and Wania 2013). The models also illustrate that, unlike legacy POP, the cVMSs display short global residence times; the majority of the global mass is removed within 3 mo of the end of release. Persistence in matrices such as sediment occurs in a second phase, which is longer with first-order decay $t_{½}$s of 1, 1.9, and 2 yr for D4, D5, and D6, respectively (Xu and Wania 2013). Given the use of the cVMSs for some 30 yr, measured environmental concentrations are now in a state of quasi-equilibrium. If use of cVMSs were to cease, it is estimated that, within a few years, concentration in the environment would be undetectable (Xu and Wania 2013).

Strengths and uncertainties

The facts that reliable models are available (Mackay et al. 2015a; Xu and Wania 2013) and that physical and chemical properties of the cVMSs are well characterized provide support to the use of models to characterize the fate (and persistence of cVMS) in the environment. Because of the physical properties of the cVMS, traditional lab tests for P, even in sealed systems, are not appropriate for extrapolation to the environment because they do not consider rapid partitioning to air, the final sink in the environment. There were few data from long-term monitoring studies with repeated annual sampling in key sites, which limits the ability to accurately predict changes over time.

Bioaccumulation (B)

Bioaccumulation (B) is the process that results in an increased concentration of a chemical in an organism compared to that in the ambient environment. It is most likely to occur with chemicals that are lipid soluble, well absorbed, and poorly metabolized, thereby limiting clearance. In principle, if B is large enough, the organism will experience adverse effects.

As noted earlier, B is very unlikely to occur in air-breathing animals because they can readily clear any cVMSs taken up by the body through the lungs (Andersen, Reddy, and Plotzke 2008). In an aquatic compartment, for non-air-breathing organisms, clearance is likely to be poorer. For fish, the likely main route of exposure to cVMSs is through consumption of cVMSs contained in diet. The cVMSs bind to carbon-containing materials such as organic matter in sediment. The scenario that needs to be considered is as follows: Assuming that the bound chemical remains bioavailable, organisms feeding in contaminated sediment might bioaccumulate the chemical. Other organisms that feed on sediment-dwelling organisms might bioaccumulate cVMSs if the rate of ingestion is greater than the rate of clearance (biomagnification). Such an effect has been well documented for a number of legacy pollutants. This is termed trophic biomagnification (Figure 12). There have been many reviews of the procedures for studying bioaccumulation and biomagnification (Borgå et al. 2012b; Burkhard et al. 2012a; 2012b; 2013; Gobas et al. 2009).

A number of lines of evidence, ranging from physical properties to field studies of trophic magnification, were considered in assessing the potential of bioaccumulation and biomagnification of cVMS. Because of the unique combination of properties of the cVMS, the use of simple physical chemical properties, such as partition coefficient (K_{OW}), quantitative structure–activity relationships ((Q)SAR), and read-across to extrapolate to bioaccumulation, is inappropriate. Nonetheless, approaches that consider the unique properties of these superhydrophobic (log K_{OW} ≥7) compounds showed that, even with slow rates of biotransformation, these substances fail to bioaccumulate to toxic concentrations in aquatic

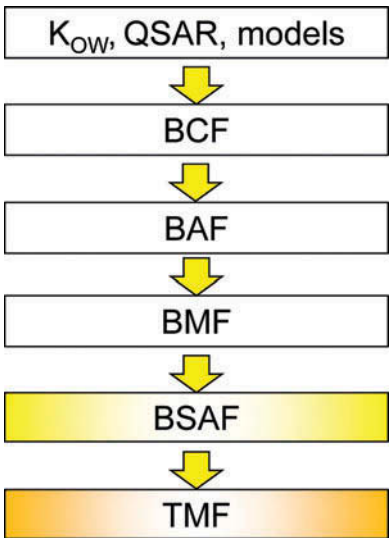

Figure 12. Illustration of the concatenation of lines of evidence for bioaccumulation.

organisms (Mackay, Powell, and Woodburn 2015c). In the QWoE, the greatest weighting among the relevant methodologies was given to high-quality field studies on trophic biomagnification (BMF, biomagnification factor). It should be noted that Annex XIII, Section 3.2.2 of REACH (European Community 2011) suggests that, in addition to bioconcentration factors (BCF), bioaccumulation factors (BAF), elevated concentrations in biota, and TMF may provide additional information (at least for chemicals that have been in widespread and consistent use for several years and are in a state of quasi-equilibrium in the environment). However, the integrative value of the averaging of individuals and trophic levels that are represented in a TMF appears to be completely ignored in the guidance for interpretation of field data and biomagnification by ECHA (2014, p 52), where it is recommended that "BMF and/or TMF values <1 cannot be used to disregard a valid assessment based on reliable BCF data indicating that a substance meets the numerical B/vB criteria in Annex XIII." This makes no scientific sense, as it is well known that BCF does not consider uptake via food (Gobas et al. 2009; Goss, Brown, and Endo 2013) and is not the best measure for superhydrophobic chemicals such as the cVMSs (Mackay, Powell, and Woodburn 2015c). Because BCF does not include a consideration of uptake from food, BMF, BAF, and TMF were selected as more realistic and appropriate measures of potential for biomagnification in the environment.

Lab studies (BCF, BAF, and BMF)

The studies examined utilized well-established standard protocols. In the case of the determination of BCF, a key consideration is whether the concentrations used exceeded the water solubility due to the use of solvents for the addition of the cVMSs to the test medium (water). Data examined confirmed that the BCF was large, with values ranging typically from 1,950 to 7,060 L/kg wet weight (ww) (Centre Europeen des Silicones [CES] 2006). However, this finding has little environmental relevance. The main source of cVMSs in the environment is from particles bound to effluent material emitted from STP. The cVMSs remain attached to particulate matter as they distribute in the water body. As a consequence, the concentrations in water remain below the solubility limit because of the unfavorable partitioning from sediment and loss of cVMSs from water to air. It is therefore reasonable to assume that uptake of cVMSs in an aquatic species at the base of the food chain is primarily from ingestion of sediment and/or ingestion of sediment dwelling organisms, rather than from any significant uptake from water through respiratory surfaces.

BMF. Estimates of BMF values were derived in two ways: using direct measurements of concentrations in species in a particular environmental matrix ($BMF_{experimental}$), or based on the uptake and elimination kinetics in fish ($BMF_{kinetic}$). The findings for the two methods differ significantly, with considerably greater BMF values being found using the kinetic method of calculation. Typically, the $BMFs_{experimental}$ were ≤1, whereas in 2 out of 9 studies the $BMFs_{kinetic}$ were significantly >1: D4 1.83 from SEHSC (2007a) and D5 1.39 from CES (2006). As all investigations were conducted following well-established guidelines and complied with good laboratory practice (GLP), the reason for the discrepancies in the findings is uncertain. A potentially significant issue with determination of a $BMF_{kinetic}$ is the growth correction (k_G) process used in these studies, which employ highly fed, rapidly growing rainbow trout as the test species. It is necessary to mathematically separate the kinetic processes of growth, metabolism, and depuration. Overestimation of the growth of the fish might result in an incorrect attenuation of the magnitude of the depuration rate, k_2, thereby falsely elevating the $BMF_{kinetic}$ values above the empirical $BMF_{experimental}$. The issues associated with kinetic versus empirical determination of BMF for D4/D5 were discussed in detail by Woodburn et al. (2013). Thus, in order to ascertain whether cVMSs behave in the real-world like legacy pollutants, such as PCB, in terms of bioaccumulation and biomagnification in food webs, reliance needs to be placed on findings from field studies.

Field studies (mmBAF, TMF)

For QWoE of field studies, specific considerations included the characterization of the sampling environment in terms of local sources of cVMSs and justification for each organism sampled,

including estimation of the potential impact of the greater range of habitat of top trophic species. Two types of metrics for B were used, multimedia bioaccumulation factor (mmBAF) and TMF.

mmBAF. The mmBAF is the quotient of the amount of chemical in an individual organism and the amount of compound in its environment (Czub and McLachlan 2004). Although it is not used in the regulatory context and cannot be directly compared to other measures of B, mmBAF is potentially appealing because of its simplicity and, in principle, less influence of variables such as temperature, composition of the food web, and so forth on the findings. However, this methodology is dependent on a crucial assumption that cVMSs and the reference compound (usually PCB180) are similarly distributed in the sediment. Two mmBAF studies were reported involving the Humber Estuary in the United Kingdom and a few Swedish lakes (Kierkegaard, Van Egmond, and McLachlan 2011; 2013). In both studies, mmBAF value greater than 1 was obtained, but in neither investigation was it demonstrated that PCB180 and the cVMSs were similarly distributed in the sediment. Indeed, such a finding would be unexpected since PCB180 is a legacy pollutant that has been evenly distributed in sediment from surface runoff and STP over many decades, and is no longer emitted in significant amounts. In contrast, cVMSs are continually emitted in small amounts from STP with limited contribution from surface runoff. Therefore, a concentration gradient for cVMSs in sediment with increasing distance from the STP is highly likely.

One additional important issue to consider with the concept of mmBAF is that it is most appropriately applied quantitatively when the partitioning behavior of the compound of interest is similar to that of the PCB180 congener. However, that is not the case here, as the cVMSs have a greater tendency than PCB180 to partition into lipids rather than OC (i.e., K_{OW}/K_{OC} >100). In contrast, PCB180 partitions roughly equally (i.e., $K_{OW}/K_{OC} \approx 1$). This difference in multimedia behavior explains the greater accumulation of D4 and/or D5 in biota versus sediment when compared to PCB180 in the mmBAF studies. A further problem with these studies is that they used the purge-and-trap analytical methodology before it was refined by Borgå et al. (2013). Consequently, these two studies cannot be utilized with any confidence to determine whether D4, D5, and/or D6 are bioaccumulative under field conditions.

TMF. There have been a number of investigations in different locations that have sought to determine TMF values and whether biomagnification or biodilution occurs, through the food web. The majority of such studies (see graphical presentation of the findings in Figures 13–15) conclude that D4, D5, and D6 do not biomagnify. The mean score (SE) for quality of the studies for D4, D5, and D6 was 2.42 (0.34). The mean score (SE) for relevance for D4 and D6 was 0 (0) and that for D5 was 0.05 (0.05), which was driven by one study (Kierkegaard, Van Egmond, and McLachlan 2011).

In the case of the study for Inner Oslofijord, the findings are supported by a dynamic modeling study (Whelan and Breivik 2013, not included in the QWoE). Modeling was not applied to the other sites, but analyses of bioaccumulation of D5-based chemical activity and fugacity (Gobas et al. 2015a, 2015b) reached a similar conclusion. One research group identified that biomagnification occurred in two investigations on Norwegian lakes (primarily Lake Mjosa) (Borgå et al. 2012a; 2013).

While the overall WoE assessment for TMF, in studies with cVMSs, clearly supports a conclusion

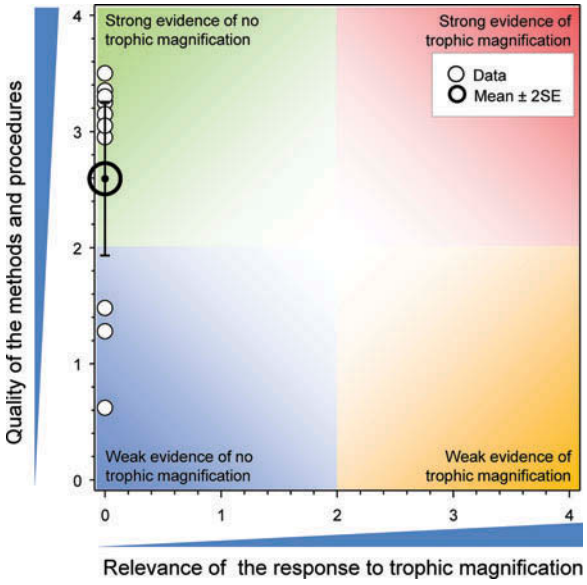

Figure 13. Graphical representation of the QWoE analysis of the studies on TMF of D4 (number of responses = 10).

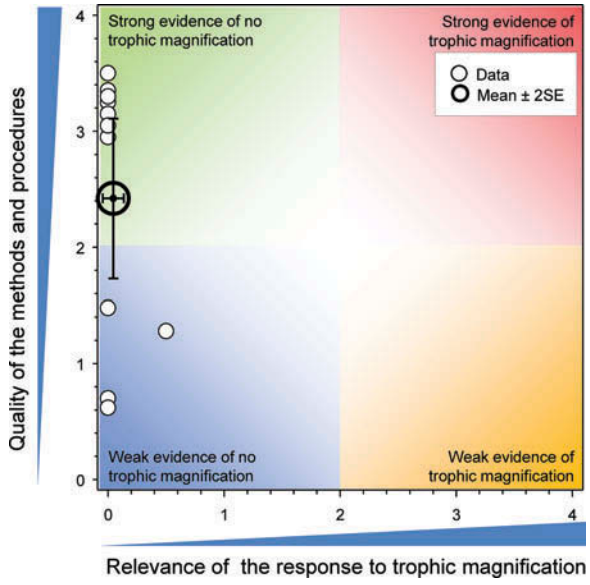

Figure 14. Graphical representation of the QWoE analysis of the studies on TMF of D5 (number of studies = 11).

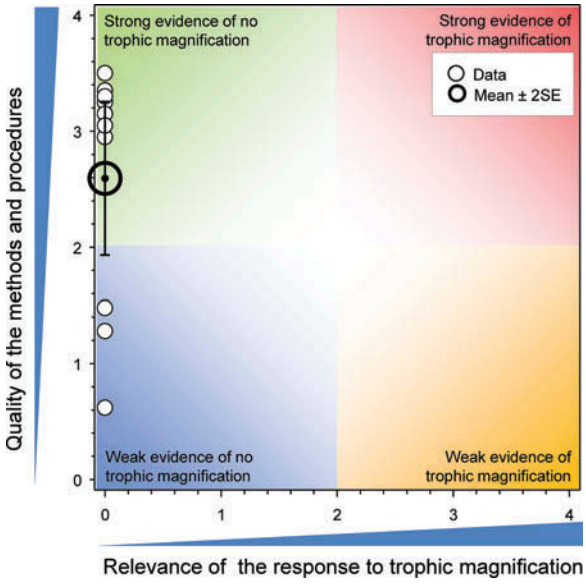

Figure 15. Graphical representation of the QWoE analysis of the studies on TMF of D6 (number of studies = 10).

that biodilution occurs between the bottom of the food web and the top predators, it is important to try to identify whether the different findings are due to different ecosystems investigated, choice of food web species surrogates, or other differences in methodology. Several differences were identified between the studies carried out by Borgå et al. (2012a) and those of the other TMF investigations. In particular:

(1) The assumption is made that the location the samples are taken from is not important because the fish species studied are migratory. This assumes a similar pattern of migration in an environment where there is inevitably a concentration gradient for each cVMSs due to STP discharge.
(2) Borga et al. (2013) measured cVMSs in skinless muscle fillets where lipid levels are small, whereas in the other studies, measurements were conducted in whole fish. Apart from the problem of the measurement of small amounts of lipid, the assumption is made that cVMSs distribute evenly in the lipid in the fish body. There is insufficient evidence to support this assumption.
(3) The number of fish of a particular species sampled is small and a sensitive and robust methodology is thus required, appropriate for the type of matrix being analyzed. The original purge-and-trap method used in Borgå et al. (2012a) appears to be less reliable than methods used by other labs, and consequently it was modified in the second paper from Borgå et al. (2013). Further, as a consequence of their experimental design, concentrations of D4, D5, and D6 in the top predators are significantly more variable than in other TMF studies.
(4) The assignment of the trophic levels of each species is highly dependent on the ratio $^{13}C/^{15}N$. The potential confounding of these values due to anthropogenic sources of N (STP and/or runoff of fertilizer) is not considered. The use of the isotope ratios results in a change in the expected assignment of trophic levels and consequently assumptions regarding feeding habits of each fish species. Expert judgment by ecologists familiar with the specific food web in question would provide useful information to supplement the isotopic ratio analyses.

Based on data available (including raw data), it is not possible to conclude that the findings by Borgå et al. (2012a; 2013) are invalid, only that the methodology differs significantly from the majority of the other studies on TMF of the cVMS. There is no indication, however, that these publications represent a more sophisticated study of

trophic magnification of the cVMS. Consequently, particular importance or emphasis cannot be attached to the findings.

The biodilution observed in the majority of investigations may be explained by less efficient uptake and/or increased ability to metabolize cVMSs in higher trophic level species. Studies of real-world variations in the uptake efficiency of cVMSs at different trophic levels are difficult to replicate in the lab. Use of gavage or spiked food may greatly overestimate the actual uptake rates that occur due to feeding on prey (Humberstone and Charman 1997; Versantvoort, Van De Kamp, and Rompelberg 2004). Assessment of the potential for biotransformation needs to be considered (Goss, Brown, and Endo 2013).

Several short-term and longer term lab uptake and depuration studies on cVMSs were conducted in fish administered ^{14}C-labeled material that meet the QWoE criteria for quality and relevance (see SI). The findings from these experiments are summarized as follows: In fish exposed via food in chronic uptake and depuration studies, D4, D5, and D6 were metabolized to a number of products that were more polar than the parent substance. It is likely, as a consequence, that these metabolites are more rapidly cleared from fish than parent material. For D4, one metabolite was identified in liver and 23 to 51% of the total radioactivity in the liver during depuration in a 77-d uptake and was attributable to metabolism (SEHSC 2007a). In a similar uptake and depuration investigation for D5, radioactivity was detected in liver and gall bladder (via whole-body autography), suggesting that D5 was metabolized but amounts of metabolite were not quantified (CES 2006). In an uptake (49 d) and depuration (98 d) study on fathead minnow, 79% of the total radiolabel was present as parent D6, 5% was associated with an unidentified metabolite, and the remaining 16% was unextractable and therefore likely also to be associated with conjugates or macromolecules (SEHSC 2005a). Concentrations in liver and digestive tract were large compared with other tissues throughout the study (Woodburn et al. 2013). Woodburn et al. (2013) concluded that this was consistent with significant biotransformation and clearance of D4 and D5.

Single-dose metabolism investigations were conducted for D4 and D5 in adult rainbow trout. Fish were dosed with ^{14}C-labeled material via gavage in corn oil and distribution in blood and urine followed for 96 h (see SI). For D4, metabolism was slow but 1.3% of the absorbed dose was converted to metabolites in the 96-h postexposure period (SEHSC 2008c). Measurements of concentrations in blood at different time points after administration showed a mean $t_{½}$ of 39 h. The urine contained only radiolabeled metabolites that were more polar than parent material (SEHSC 2008c). For D5, the proportion converted to metabolites in a similar study was 14% (CES 2007b), suggesting more rapid metabolism than D4. Measurements of concentrations in blood at different time points after administration of D5 showed a mean half-life of approximately 70 h. All radiolabel in urine was composed of metabolites more polar than D5. Based on these data, the $t_{½}$ for formation of metabolites was approximately 100 h and the rate constant was 0.0071/h. This value is, however, based on the assumption that the change in concentration in blood parallels alterations in concentration in whole body. This may significantly overestimate rate of metabolism. However, even if the overestimate is 10-fold greater, it is still compatible with the occurrence of biodilution. There were no similar data for D6, but using read-across, similar conclusions would be expected.

There were no specific data on biotransformation of other cVMSs in aquatic organisms in trophic levels lower than fish. However, studies on other chemicals generally indicated that lower trophic level aquatic organisms display reduced drug-metabolizing capacity (Van der Linde, Hendriks, and Sijm 2001), which is consistent with observations of relatively greater concentrations in benthic organisms.

Strengths and uncertainties

The various metrics for bioaccumulation and the observed metabolism of the cVMSs in vertebrates demonstrated a relatively reliable consistency, although there are some differences that need to be further resolved. The main gaps in data arise from insufficient understanding of predator prey relationships in the field and an undue reliance on

^{15}N–^{13}C relationships. Lab studies on uptake of cVMSs at environmentally relevant concentrations and rate of subsequent metabolism, distribution, and excretion for species representative of several trophic levels are needed to fully assess the impact of toxicokinetics on TMF. Lack of data on TMF for D6 is an uncertainty.

Toxicity (T)

In weighing evidence for T, a number of endpoints and targets were considered (Figure 16). Where data for LC/EC50, LOEC, and NOEC were available, the most sensitive measure was taken. Where multiple responses were measured, the most sensitive response was selected. QSAR data were judged to be least reliable, especially as the cVMSs have unusual properties that have traditionally not been included in the domain of QSAR models. Read-across from other cVMSs was preferred over other classes of compounds for the same reason. There is a hierarchy of responses from receptor to population in Figure 16 and responses at the organism and population level are most relevant to apical endpoints.

Toxicity tests for D4, D5, and D6 were evaluated for quality and relevance using the scheme illustrated in SI. Characterization of T incorporated an element of risk assessment as values were compared to maximum possible as well as environmentally relevant concentrations. Thus, relevance included two cut-off criteria based on concentration, solubility (water) and sorption capacity (sediment and soil). If no effects were observed at the maximum solubility or at the sorption capacity of the matrix, the relevance of observations to adverse effects was scored as zero. Where effects were noted at concentrations in the range of those measured in the environment, a greater score was assigned. Where effects were found at concentrations larger than those reported from the environment, lower scores were assigned. The cutoff for environmental concentrations was based upon the upper 99.9th centile of values measured in sediments in the environment (Table 4) and maximum values reported in receiving waters (Wang et al. 2013a). These cutoff values are summarized in Table 6, and their use is outlined in the scoring guide in the SI.

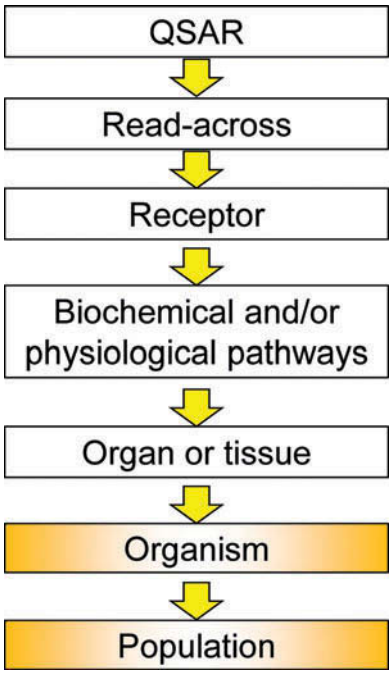

Figure 16. Illustration of the concatenation of lines of evidence for toxicity.

The QWoE analysis of individual studies is provided in SI. The overall results of the QWoE assessment of T data are presented graphically in Figures 17–19; and, because some points overlapped in the graphics, in Table 7.

Many of the responses measured in the T tests were only observed at concentrations considerably greater than the maximum water solubility or the MSC of soil or sediment (Table 7). These responses received an expert-judgment score for relevance of zero. Other responses that were only noted at concentrations >10-fold the worst-case maximum concentration measured in the environment (Table 6) also received an expert-judgment score for relevance of zero. Those responses that were reported at levels from 1- to10-fold greater than worst-case maximum concentration measured in the environment received an expert judgment for relevance of 0.5 to 0.

Table 6. The cutoff values for assessing the relevance of responses measured in toxicity tests.

cVMS	D4	D5	D6
Water, solubility cutoff (µg/L)	56	17	5.1
Water, concentration cutoff (µg/L)	0.02	1.6	0.16
Sediment, MSC cutoff	929	2,514	5,465
Sediment, concentration cutoff value (mg/kg dw)	0.55	5.28	0.5
Soil, MSC cutoff	929	2,514	5,465
Soil, concentration cutoff value (mg/kg dw)	1	1	1

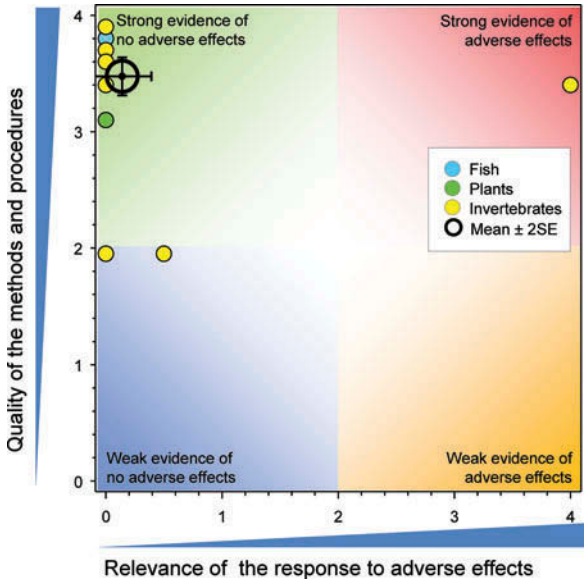

Figure 17. Graphical representation of the QWoE analysis of the toxicity data for D4 (number of responses = 32, several points overlap in the graphic).

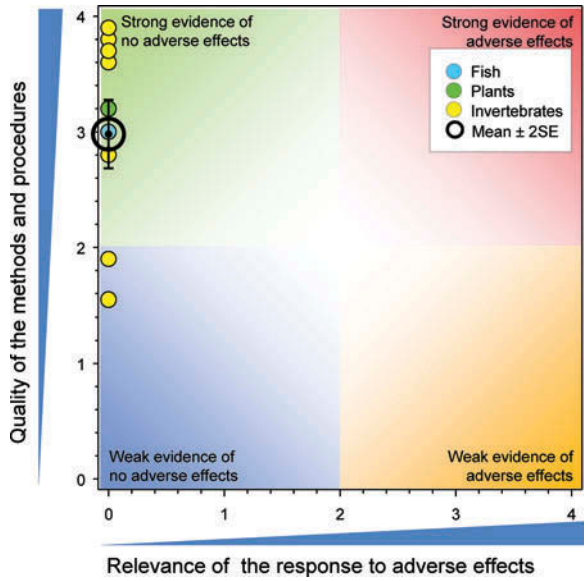

Figure 18. Graphical representation of the QWoE analysis of the toxicity data for D5 (number of responses = 36, several points overlap in the graphic).

Many of the studies were conducted under GLP with quality assurance (QA) and quality control (QC). The scores for quality of such investigations were thus relatively large unless a major weakness was identified in the design or methodology. Where major weaknesses were identified, these were noted in the QWoE (see SI) and are discussed in the narrative that follows.

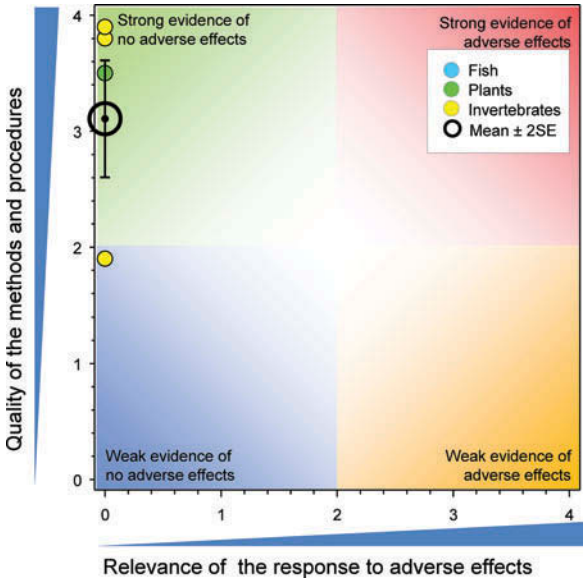

Figure 19. Graphical representation of the QWoE analysis of the toxicity data for D6 (number of responses = 14, several points overlap in the graphic).

D4

The scores for quality in the QWoE analysis for D4 (Figure 17) were close to 4 except for one of the tests for *Lumbriculus variegatus* (CES 2009e). This test was conducted using a protocol based on OECD Guideline 218 (OECD 2004a) employing an artificial sediment composed of approximately 10% peat, 20% kaolin clay, and 70% industrial quartz sand. The use of artificial sediment, with peat as the only source of organic matter, is a major potential weakness in this protocol. When using peat in artificial sediments, microbiological biomass and microbiological contributions to organic matter in artificial sediments are up to 10-fold less than in natural sediments, which might compromise the results of T tests (Goedkoop et al. 2005). Similar issues were described for T tests with *Tubifex tubifex* with other compounds (Arrate, Rodriguez, and Martinez-Madrid 2004). This indicates that sediments recommended in Organization for Economic Cooperation and Development (OECD) Test 218 are not suitable for chronic testing of benthic organisms. In the study on *L. variegatus* exposed to D4 (CES 2009e), controls were unaffected in terms of survival but the biomass of control worms at the end of the test was only 0.7 mg/worm dw. In a repeat test of D4 conducted in natural sediment (CES 2009c), the mean biomass in the control was double this value (1.6 mg/worm dw). Data suggest that husbandry was compromised in the artificial-sediment-based test

Table 7. Summary of the WoE analysis of the toxicity data for D4, D5, and D6.

cVMS	Test organism	Matrix	Response	Value	Units	Qscore	Rscore	Reference	Comment
D4	*O. mykiss*	Water	14-d survival	NOEC = 4.4	µg/L	3.8	0	(SEHSC 1990f)	NOEC 220-fold greater than the cutoff concentration of 0.02 µg/L
D4	*O. mykiss*	Water	14-d survival	NOEC = 6.8	µg/L	3.7	0	(Dow Corning Corporation 2008)	NOEC 220-fold greater than the cutoff concentration of 0.02 µg/L
D4	*O. mykiss*	Water	14-d weight	NOEC = 13	µg/L	3.7	0	(Dow Corning Corporation 2008)	NOEC 220-fold greater than the cutoff concentration of 0.02 µg/L
D4	*O. mykiss* ELS1	Water	30-d hatch	NOEC = 4.4	µg/L	3.9	0	(SEHSC 1991c)	NOEC 220-fold greater than the cutoff concentration of 0.02 µg/L
D4	*O. mykiss* ELS	Water	30-d embryo viability	NOEC = 4.4	µg/L	3.9	0	(SEHSC 1991c)	NOEC 220-fold greater than the cutoff concentration of 0.02 µg/L
D4	*O. mykiss* ELS	Water	93-d survival	NOEC = 4.4	µg/L	3.9	0	(SEHSC 1991c)	NOEC 220-fold greater than the cutoff concentration of 0.02 µg/L
D4	*O. mykiss* ELS	Water	93-d length & weight	NOEC = 4.4	µg/L	3.9	0	(SEHSC 1991c)	NOEC 220-fold greater than the cutoff concentration of 0.02 µg/L
D4	*C. variegatus*	Water	14-d survival	NOEC = 6.3	µg/L	3.7	0	(SEHSC 1990c)	NOEC was 300-fold greater than water concentration cutoff of 0.02 µg/L
D4	*S. capricornutum*	Water	96-h cell density	NOEC = 22	µg/L	3.1	0	(SEHSC 1990e)	NOEC was 1100-fold greater than water concentration cutoff of 0.02 µg/L.
D4	*S. capricornutum*	Water	96-h growth rate	NOEC = 22	µg/L	3.1	0	(SEHSC 1990e)	Rate of growth in cells exposed to an initial concentration of 22 µg D_4/L was 1% less than the controls but the concentration was >1100-fold greater than water concentration cutoff of 0.02 µg/L.
D4	*L. variegatus*	Sediment	28-d survival	NOEC = 13	mg/kg dw	3.9	0	(CES 2009c)	NOEC was ~80-fold less than the worst-case measured concentration in the environment.
D4	*L. variegatus*	Sediment	28-d growth	NOEC = 32	mg/kg dw	3.9	0	(CES 2009c)	NOEC was greater than the MSC
D4	*L. variegatus*	Sediment	28-d survival	NOEC ≤ 0.73	mg/kg dw	1.95	0.5	(CES 2009e)	NOEC was ~1.3-fold less than the worst-case measured concentration in the environment.
D4	*L. variegatus*	Sediment	28-d growth	NOEC = 38	mg/kg dw	1.95	0	(CES 2009e)	NOEC was greater than the MSC.
D4	*D. magna*	Water	21-d life cycle	NOEC = 7.9	µg/L	3.7	0	(SEHSC 1990d)	NOEC was 350-fold greater than water concentration cutoff of 0.02 µg/L.
D4	*D. magna*	Water	21-d life cycle	NOEC = 7.9	µg/L	3.7	0	(SEHSC 1990d)	NOEC was 750-fold greater than water concentration cutoff of 0.02 µg/L and the response was not adverse.
D4	*D. magna*	Water	96-h survival	NOEC = 15	µg/L	3.7	0	(SEHSC 1990a)	NOEC was 750-times greater than the water concentration cutoff of 0.02 µg/L.
D4	*M. bahia*	Water	96-h survival	NOEC = 9.1	µg/L	3.7	0	(SEHSC 1990b)	NOEC was 450–fold greater than water concentration cutoff of 0.02 µg/L.
D4	*C. tentans*	Sediment	14-d survival	NOEC = 54	mg/kg dw	3.6	0	(SEHSC 1991b)	NOEC was greater than the MSC.
D4	*C. tentans*	Sediment	14-d survival	NOEC = 170	mg/kg dw	3.6	0	(SEHSC 1991b)	NOEC was greater than the MSC.
D4	*C. tentans*	Sediment	14-d survival	NOEC = 130	mg/kg dw	3.4	0	(SEHSC 1991d)	NOEC was greater than the MSC.
D4	*C. tentans*	Sediment	14-d growth	NOEC = 65	mg/kg dw	3.4	0	(SEHSC 1991d)	NOEC was greater than the MSC.
D4	*C. tentans*	Sediment	14-d survival	NOEC = 120	mg/kg dw	3.4	0	(SEHSC 1991d)	NOEC was greater than the MSC.

(*Continued*)

Table 7. (Continued).

cVMS	Test organism	Matrix	Response	Value	Units	Qscore	Rscore	Reference	Comment
D4	*C. tentans*	Sediment	14-d growth	NOEC = 120	mg/kg dw	3.4	0	(SEHSC 1991d)	NOEC was greater than the MSC.
D4	*C. tentans*	Sediment	14-d survival	LOEC = 16	mg/kg dw	3.4	4	(SEHSC 1991d)	LOEC did not exceed the MSC, no concentration response, poor survival in all treatments except control.
D4	*C. tentans*	Sediment	14-d growth	NOEC = 200	mg/kg dw	3.4	0	(SEHSC 1991d)	NOEC was greater than the MSC.
D4	*C. tentans*	Water	14-d survival	NOEC = 15	µg/L	3.4	0	(SEHSC 1991d)	NOEC was 750-fold greater than the water concentration cutoff of 0.02 µg/L.
D4	*C. tentans*	Water	14-d survival	NOEC = 15	µg/L	3.4	0	(SEHSC 1991d)	NOEC was 750-fold greater than the water concentration cutoff of 0.02 µg/L.
D4	*C. riparius*	Sediment	28-d survival	NOEC = 44	mg/kg dw	3.4	0	(SEHSC 2008a)	NOEC was greater than the MSC.
D4	*C. riparius*	Sediment	28-d dev. time	NOEC = 131	mg/kg dw	3.4	0	(SEHSC 2008a)	NOEC was greater than the MSC.
D4	*C. riparius*	Sediment	28-d emerg. ratio	NOEC = 131	mg/kg dw	3.4	0	(SEHSC 2008a)	NOEC was greater than the MSC.
D4	*C. riparius*	Sediment	28-d emerg. rate	NOEC = 131	mg/kg dw	3.4	0	(SEHSC 2008a)	NOEC was greater than the MSC.
D5	*O. mykiss*	Water	45-d survival	NOEC = 17	µg/L	3	0	(Dow Corning 2009)	NOEC was greater than the maximum solubility in water in the study.
D5	*O. mykiss*	Water	45-d length & weight	NOEC = 17	µg/L	3	0	(Dow Corning 2009)	NOEC was greater than the maximum solubility in water in the study.
D5	*O. mykiss* ELS	Water	30-d hatch	NOEC = 14	µg/L	3.9	0	(CES 2009d)	NOEC was greater than the maximum solubility in water in the study.
D5	*O. mykiss* ELS	Water	30-d normal larvae	NOEC = 14	µg/L	3.9	0	(CES 2009d)	NOEC was greater than the maximum solubility in water in the study.
D5	*O. mykiss* ELS	Water	90-d survival	NOEC = 14	µg/L	3.9	0	(CES 2009d)	NOEC was greater than the maximum solubility in water in the study.
D5	*O. mykiss* ELS	Water	90-d length and weight	NOEC = 14	µg/L	3.9	0	(CES 2009d)	NOEC was greater than the maximum solubility in water in the study.
D5	*O. mykiss*	Water	14-d survival	NOEC = 16	µg/L	3.8	0	(SEHSC 2000)	NOEC was greater than the maximum solubility in water in the study.
D5	*O. mykiss*	Water	14-d length & weight	NOEC = 16	µg/L	3.8	0	(SEHSC 2000)	NOEC was greater than the maximum solubility in water in the study.
D5	*P. promelas*	Water	65-d survival	NOEC = 8.7	µg/L	3.6	0	(Parrott et al. 2013)	NOEC was greater than maximum solubility attainable in the study.
D5	*P. promelas*	Water	65-d length & weight	NOEC = 8.7	µg/L	3.6	0	(Parrott et al. 2013)	NOEC was greater than maximum solubility attainable in the study.
D5	*P. promelas*	Water	65-d survival CF	NOEC = 8.7	µg/L	3.6	0	(Parrott et al. 2013)	Effect was not considered adverse.
D5	*P. subcapitata*	Water	96-h cell density	NOEC = 12	µg/L	3.2	0	(SEHSC 2001)	NOEC was greater than the maximum solubility in water in the study.
D5	*P. subcapitata*	Water	96-h growth rate	NOEC = 2	µg/L	3.2	0	(SEHSC 2001)	NOEC was greater than the maximum solubility in water in the study.
D5	*D. magna*	Water	48-h survival	NOEC = 2.9	µg/L	3.6	0	(SEHSC 2002)	NOEC > 2.9 µg/L.
D5	*D. magna*	Water	21 d survival	NOEC = 15	µg/L	3.8	0	(SEHSC 2003a)	NOEC was greater than the maximum solubility in water in the study.
D5	*D. magna*	Water	21 d reproduction	NOEC = 15	µg/L	3.8	0	(SEHSC 2003a)	NOEC was greater than the maximum solubility in water in the study.

(*Continued*)

Table 7. (Continued).

cVMS	Test organism	Matrix	Response	Value	Units	Qscore	Rscore	Reference	Comment
D5	*D. magna*	Water	21 d length	NOEC = 15	µg/L	3.8	0	(SEHSC 2003a)	NOEC was greater than the maximum solubility in water in the study.
D5	*L. variegatus*	Sediment	28-d survival	NOEC = 1272	mg/kg dw	1.9	0	(CES 2007a)	NOEC was greater than the MSC of the sediment.
D5	*L. variegatus*	Sediment	28-d growth	NOEC = 1272	mg/kg dw	1.9	0	(CES 2007a)	NOEC was greater than the MSC of the sediment.
D5	*L. variegatus*	Sediment	28-d survival	NOEC = 336	mg/kg dw	1.9	0	(CES 2008c)	NOEC was greater than the MSC of the sediment.
D5	*H. azteca*	Sediment LE	28-d survival	NOEC = 100	mg/kg dw	2.8	0	(Norwood et al. 2013)	NOEC was greater than the MSC of the sediment.
D5	*H. azteca*	Sediment LE	28-d growth	NOEC = 300	mg/kg dw	2.8	0	(Norwood et al. 2013)	NOEC was greater than the MSC of the sediment.
D5	*H. azteca*	Sediment LR	28-d survival	NOEC = 300	mg/kg dw	2.8	0	(Norwood et al. 2013)	NOEC was greater than the MSC of the sediment.
D5	*H. azteca*	Sediment LR	28-d growth	NOEC = 600	mg/kg dw	2.8	0	(Norwood et al. 2013)	NOEC was greater than the MSC of the sediment.
D5	*H. azteca*	Sediment	28-d survival	NOEC = 130	mg/kg dw	3.7	0	(CES 2009a)	NOEC was greater than the MSC of the sediment.
D5	*H. azteca*	Sediment	28-d growth	NOEC = 130	mg/kg dw	3.7	0	(CES 2009a)	NOEC was greater than the MSC of the sediment.
D5	*H. vulgare*	Soil	14-d root d mass	IC50 = 209	mg/kg dw	1.55	0	(Velicogna et al. 2012)	Toxicity only observed at concentrations 200-fold greater than measured in the environment.
D5	*T. pratense*	Soil	14-d root d mass	IC50 = 4,054	mg/kg dw	1.55	0	(Velicogna et al. 2012)	All responses seen only at concentrations greater than MSC.
D5	*E. andrei*	Soil	28-d survival	LC50 = 4,074	mg/kg dw	1.55	0	(Velicogna et al. 2012)	All responses seen only at concentrations greater than MSC.
D5	*F. candida*	Soil	28-d prod juveniles	IC50 = 767	mg/kg dw	1.55	0	(Velicogna et al. 2012)	Toxicity only observed at concentrations 767-fold greater than measured in the environment.
D5	*C. riparius*	Sediment	28-d emergence	NOEC = 180	mg/kg dw	3.9	0	(SEHSC 2003b)	NOEC was greater than the MSC of the sediment.
D5	*C. riparius*	Sediment	28-d development	NOEC = 69	mg/kg dw	3.9	0	(SEHSC 2003b)	NOEC was greater than the MSC of the sediment.
D5	*C. riparius*	Sediment	28-d survival	NOEC = 160	mg/kg dw	1.9	0	(SEHSC 2008b)	NOEC was greater than the MSC of the sediment.
D5	*C. riparius*	Sediment	28-d time to dev.	NOEC = 160	mg/kg dw	1.9	0	(SEHSC 2008b)	NOEC was greater than the MSC of the sediment.
D5	*C. riparius*	Sediment	28-d emerg ratio	NOEC = 160	mg/kg dw	1.9	0	(SEHSC 2008b)	NOEC was greater than the MSC of the sediment.
D5	*C. riparius*	Sediment	28-d rate of dev	NOEC = 70	mg/kg dw	1.9	0	(SEHSC 2008b)	NOEC was greater than the MSC of the sediment.
D6	*P. subcapitata*	Water	96-h cell density	NOEC = 2 µg (nominal 5.1 µg/L)	µg/L	3.5	0	(SEHSC 2009a)	NOEC was greater than the maximum solubility in water in the study.
D6	*P. subcapitata*	Water	96-h growth rate	NOEC = 2 µg (nominal 5.1 µg/L)	µg/L	3.5	0	(SEHSC 2009a)	NOEC was greater than the maximum solubility in water in the study.
D6	*L. variegatus*	Sediment	28-d survival	NOEC = 484	mg/kg dw	1.9	0	(CES 2008d)	NOEC was greater than the MSC of the sediment.
D6	*L. variegatus*	Sediment	28-d survival	NOEC = 484	mg/kg dw	3.9	0	(CES 2010b)	NOEC was greater than the MSC of the sediment.
D6	*L. variegatus*	Sediment	28-d growth	NOEC = 484	mg/kg dw	3.9	0	(CES 2010b)	NOEC was greater than the MSC of the sediment.
D6	*D. magna*	Water	21 d survival	NOEC = 4.6	µg/L	3.8	0	(SEHSC 2006a)	NOEC was greater than the functional solubility in water in the study.

(*Continued*)

Table 7. (Continued).

cVMS	Test organism	Matrix	Response	Value	Units	Qscore	Rscore	Reference	Comment
D6	*D. magna*	Water	21 d reproduction	NOEC = 4.6	µg/L	3.8	0	(SEHSC 2006a)	NOEC was greater than the functional solubility in water in the study.
D6	*D. magna*	Water	21 d length	NOEC = 4.6	µg/L	3.8	0	(SEHSC 2006a)	NOEC was greater than the functional solubility in water in the study.
D6	*C. riparius*	Sediment	28-d survival	NOEC = 22	mg/kg dw	1.9	0	(SEHSC 2010)	Toxicity only observed at concentrations 100-fold greater than measured in the environment.
D6	*C. riparius*	Sediment	28-d time to dev.	NOEC = < 22	mg/kg dw	1.9	0	(SEHSC 2010)	Toxicity only observed at concentrations 100-fold greater than measured in the environment.
D6	*C. riparius*	Sediment	28-d emerg ratio	NOEC = 22	mg/kg dw	1.9	0	(SEHSC 2010)	Toxicity only observed at concentrations 100-fold greater than measured in the environment.
D6	*C. riparius*	Sediment	28-d rate of dev	NOEC = < 22	mg/kg dw	1.9	0	(SEHSC 2010)	Toxicity only observed at concentrations 100-fold greater than measured in the environment.
D6	*C. riparius*	Sediment	28-d survival	NOEC = 260	mg/kg dw	3.9	0	(CES 2010a)	NOEC was greater than the MSC of the sediment.
D6	*C. riparius*	Sediment	28-d rate of dev	NOEC = 260	mg/kg dw	3.9	0	(CES 2010a)	NOEC was greater than the MSC of the sediment.

[1]ELS = early life-stage toxicity test.

(CES 2009e), resulting in unrealistic responses in the test organisms. Because of this, the score for expert judgment for strength of the methods and procedures was reduced by a multiplier of 0.5. One study on *Chironomus tentans*, exposed via sediment, showed significantly reduced survival after a 14-d exposure (SEHSC 1991d). The LOEC of 16 mg/kg dw was detected at the smallest concentration tested and did not exceed the MSC. However, there was no concentration-response relationship in treatments and there was poor survival in all treatments (12 to 26%) versus 73% in pooled controls. The reason for this is unclear, but the result was different for other studies in the same species and also in the same investigation but with different sediment (see SI).

All but two of the tests with D4 showed T values of zero relevance, for example, effects only detected at levels greater than maximum solubility in water, MSC in soil or sediment, or greatest concentrations measured in the environment (mean score for relevance (SE) of 0.14 (0.13)). The mean score (SE) for quality of the studies was 3.48 (0.08). The QWoE of all the responses leads to the conclusion that concentrations of D4 measured, or expected to be in the environment, did not present an apparent hazard to aquatic or benthic organisms.

D5

The scores for quality of studies in the QWoE analysis for D5 (Figure 18) were close to 4 except for two T tests using *L. variegatus* (CES 2007a, 2008c) and tests for T to four soil organisms (Velicogna et al. 2012). The score for quality of the methods and procedures for the two T tests with *L. variegatus* and one with *C. riparius* was reduced by a factor of 0.5 for the same reasons discussed in the preceding section for D4: the potential problem resulting from the use of peat as the sole source of organic matter (CES 2007a; 2008c; SEHSC 2008b).

The major weakness in the tests on soil organisms (Velicogna et al. 2012) was that total organic carbon (TOC) in the test soil was not measured. Since TOC determines MSC (Table 3), this needs to be known to properly interpret the test results. In this case, TOC was estimated (see SI). Several responses were measured in the two terrestrial plants (barley and wheat): emergence, shoot length, root length, shoot dry mass, and root dry mass. Emergence is a conserved response in plants and is generally less sensitive than responses related to growth (Stephenson et al. 2000), and other responses are likely to be correlated. Because of this, only the most sensitive response was used in the assessment.

All T data indicated no relevance. The mean score (SE) for quality was 2.98 (0.15) and the mean score for relevance of the adverse effects in the environment was zero. As all the most sensitive responses were above the cutoff value based on the MSC, it was concluded that concentrations of D5 measured or expected to be in the environment did not present any apparent hazard to aquatic, benthic, or soil-dwelling organisms. Similar conclusions were reached in a review by Xu, Kozerski, and Mackay (2014), who indicated that large proportions of D5 in test soils were present as neat material, which would have physical effects on the organism and, spills excepted, would not be thermodynamically attainable in the environment.

D6

Toxicity of D6 was tested in only four species, all of which were aquatic organisms (Figure 19). However, 14 responses were available for QWoE analysis. As for D4 and D5, the test on *L. variegatus* (CES 2008d) and *C. riparius* (SEHSC 2010) made use of artificial sediment and received a reduced score for quality of methods. The repeat tests with natural sediments (CES 2010b; 2010a) provided more realistic values. The mean score (SE) for quality was 3.11 ± SE 0.25 and the mean score for relevance of adverse effects in the environment was zero. All the most sensitive responses were above the cutoff value for environmental levels or the MSC was exceeded, leading to the conclusion that concentrations of D6, as measured or expected to be in the environment, did not exceed T values for aquatic or benthic organisms.

Strengths and uncertainties

For the most part, T data for D4, D5, and D6 were of high quality. Almost all tests were conducted with clear protocols, GLP, QA/QC, and with raw data provided. That some tests may not have been identified as compromised by the use of artificial sediments is not problematic, as this additional stress would likely result in more sensitivity in the test species. This adds an additional level of conservatism to the conclusions.

There were relatively fewer T tests for D6 but an acceptable number for D4 and D5. This introduces some uncertainty; however, it does not negate the conclusion of lack of relevant toxicity. None of these tests investigated a mode or mechanism of action; however, this is true for most neutral (uncharged) molecules such as cVMSs. In these cases, toxic effects are considered to be induced by narcosis and interference with properties of cell membranes, which is dependent on inherent properties of the substances (Mackay, Powell, and Woodburn 2015c; Siloxane D5 Board of Review 2011). As D4, D5, and D6 are likely to share a common mode of action and, in lab tests, are without effects at concentrations greater than the maximum solubility in water, the MSC in soil or sediment, or the greatest concentrations measured in the environment, the lack of a large number of tests with each cVMSs is not problematic; it is possible to compare the findings between cVMSs and this increases the confidence in the conclusion that they are without hazard in the environment. Toxicity via exposures in food chains has not yet been tested in empirical experiments, but because of the volatility of the cVMS, these exposures would be difficult to maintain (see SI for examples of the difficulty of maintaining constant concentrations in simple T studies).

Long-range transport (LRT)

The output from models (Mackay et al. 2015a; Xu and Wania 2013) has been compared to measured values in areas close to major uses and in remote areas, and values for D5 were within an order of magnitude (Mackay et al. 2015a). Other lines of evidence applied to QWoE of LRT were verified presence in remote areas and rate of change of concentrations in local and remote areas (Figure 20).

In terms of environmental measurements of the cVMSs, it is vital to ensure that there are no local sources of cVMSs to confound the findings. Because the primary use of cVMSs is in personal-care products, it is often assumed that the absence of humans in these remote Polar Regions implies that there are no uncontrolled background releases to the environment. Use of cVMSs by personnel conducting sampling might be controlled, but the assumption that there are no additional sources

needs to be justified. For example, the use of silicone oils as drilling lubricants in ice coring is recommended (Talalay 2007). While these products are linear dimethyl siloxane oils (DSO), there may be contamination or mixing with cVMSs. In addition, cVMSs may have other uses as components of lubricants for equipment used on ships and other transportation. This raises the possibility that there may be unexpected sources and releases of cVMSs into remote environments or that the sampling equipment is contaminated with these substances.

There were three reports of concentrations in environmental matrices from remote locations where raw data were provided. All of these studies were in the northern hemisphere. In addition, one study from Antarctica provided summary data. There were no long-term temporal analyses reported from air, water, sediment, or soil in remote locations. There were too few studies to conduct a graphical analysis of QWoE; however, the quality of the methods of analysis was assessed and is provided in the SI. Relevant details are described here.

The review by Wang et al. (2013a) reported maximum concentrations close to areas of use and release for D4, D5, and D6 in outdoor air of 2.3, 1.8, and 0.45 μg/m^3, respectively. In measurements conducted between January and June 2009 that followed good analytical practices, concentrations of D5 measured in a rural location in Sweden were exceptionally small and ranged from 0.009 to 0.0005 μg/m^3 (McLachlan et al. 2010). These values were substantially smaller than those close to sources such as STPs and landfill sites (Wang et al. 2013a). Measurements of concentrations of cVMSs in air were made using passive air samplers in 20 locations around the globe in 2009 (Genualdi et al. 2011). Five of these locations were in the Arctic. Raw data were provided and maximum estimated concentrations of D4, D5, and D6 from the Arctic sites were 0.018, 0.004, and 0.00054 μg/m^3, respectively. Concentrations in air from the lower latitude sites were greater, and maximum estimated levels of D4, D5, and D6 from non-Arctic sites were 0.05, 0.28, and 0.053 μg/m^3, respectively.

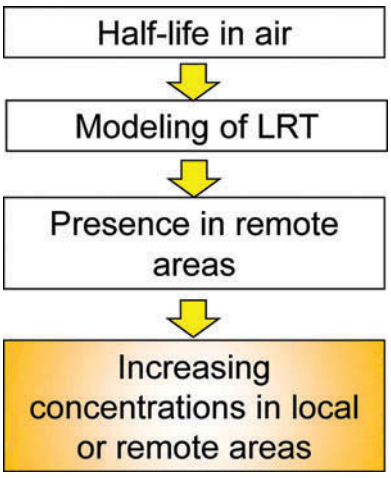

Figure 20. Illustration of the concatenation of lines of evidence for LRT.

Analysis of large-volume air samples taken in the late summer–autumn and winter of 2011 in the Zeppelin observatory in Svalbard, Norway (Krogseth et al. 2013), showed that D5 and D6, but not D4, were present in quantifiable amounts in air. A total of 24 duplicate samples were collected regularly with approximately 2-d intervals from August 23 to December 4 and raw data were provided. No consistent trend in values was noted, except that concentrations tended to increase in the winter. Concentrations were log-normally distributed. The 90th centiles of average levels of duplicate samples of D5 and D6 in late summer–autumn were 0.0011 and 0.0004 μg/m^3, respectively, and in the winter 0.004 and 0.0007 μg/m^3, respectively (calculated from data in Krogseth et al. 2013). The greater concentrations in winter were ascribed to lesser amounts of •OH produced in the absence of ultraviolet (UV) radiation in the Polar troposphere during the winter and hence less degradation in the troposphere.

A recent study reported measurement of cyclic and linear VMS (lVMS) in soil, in terrestrial plants, and in two components of the marine food web in the Antarctic (Sanchís et al. 2015). Samples were collected during a sampling expedition of the RV Hespérides in 2009, and were taken in the Drake Passage, Bransfield Strait, and the South Scotia, Bellingshausen, and Weddell seas in Antarctica. The analytical methods used in this experiment were seriously flawed (Mackay et al. 2015b; Warner, Krogseth, and Whelan 2015) and the score for quality of the study was 0.067 (see SI); however, the paper is published and is therefore discussed here.

It is most likely that the samples in the Sanchis et al. (2015) study were contaminated with cVMSs after collection. Maximum concentrations of D3,

D4, D5, and D6 in Antarctic soils were reported to be 25.2, 23.9, 110, and 42.0 μg/kg dw, respectively (Sanchís et al. 2015). In contrast, concentrations measured in agricultural soils in Ontario that were amended with biosolids containing cVMSs were similar and ranged from <8 (MDL) to 17, 221, and 711 μg/kg dw for D4, D5, and D6, respectively (Wang et al. 2013b). Given the large distances of sampling sites in the Antarctic from human activity, the fact that more than 95% of the release of cVMSs is in the northern hemisphere (Xu and Wania 2013), and the lack of a plausible pathway of deposition from the atmosphere (Mackay et al. 2015b), the similarity of these numbers is truly astonishing. That unexpectedly high levels also were reported for terrestrial vegetation, marine plankton, and krill (Sanchís et al. 2015) calls the analyses into question, and parsimony suggests that these were the result of demonstrably poor sampling and processing techniques and/or likely contamination of the samples (Warner, Krogseth, and Whelan 2015). This example further points to the need to exercise extreme care to avoid contamination when sampling and analyzing for cVMSs.

Strengths and uncertainties

Eliminating local sources of contamination in the assessment of potential for LRT of cVMSs is a major challenge because of ubiquity of their use. The analyses of cVMSs in air in Polar Regions were conducted with good analytical practice and there is little uncertainty in the values reported from pumped samples (Krogseth et al. 2013; McLachlan et al. 2010). Because passive samplers are deployed over longer periods of time than pumped samples, accidental contamination is more likely to occur and consequently true blank and field spike values are inherently less certain. Passive samplers may be calibrated to provide estimates of concentrations in air but these are averages over time of deployment. Passive samplers are less useful for characterizing short-term trends but may be useful for long-term trends.

Conclusions

Based on the use of QWoE methodology that was developed, the following conclusions were reached.

Persistence (P) in the environment

In air, half-lives for D4, D5, and D6, have been estimated as 10.3, 6.7, and 5 d, respectively. These half-lives are greater than the criterion for LRT (2 d). However, the cVMSs tend to remain in the atmosphere (the final sink), where they are degraded more rapidly than in other matrices; their presence is shorter (months) than for the classical legacy pollutants where global lifetimes in the troposphere are several years.

The cVMSs are not highly P in soils, where, depending on type of soil and content of water, they either dissipate rapidly into air or are degraded in soil. Rates of degradation of cVMSs in soil decrease with increasing content of water but partitioning to air rises at these greater moisture levels. The measured half-lives of the cVMSs in soil are smaller than trigger values for classification of chemicals as POP, PBT, or vP (120 or 180 d). The overall conclusion is that cVMSs should not be classified as P on the basis of persistence in soil.

The limited studies provide no clear conclusion on degradation of the cVMSs in water. Some investigators find values less than the criterion for P (half-life of 40 d [fresh water] or 120 d [sediment]), but other show half- lives that are greater. On their own, the values for sediment would trigger persistence or vP.

Overall persistence (P_{OV})

Because of their unusual physical and chemical properties and movement between matrices in the environment, with the final sink in the atmosphere, overall P_{OV} of cVMSs in the environment is the most appropriate measure to use for assessing P. There are no simple tests to use to measure this, but modeling tools are available to characterize P_{OV}. There are no guidelines for using P_{OV} to classify chemicals as P and vP; however, expert judgment of the results of global modeling demonstrate that global half-lives in air are short, and if use were to cease, partitioning into and then rapid degradation in the atmosphere would result in complete dissipation in a few years. As these processes are ongoing, this means that concentrations in the global environment are in a quasi-steady

state at this time and are unlikely to rise with continued use and release. Even in the event of increased use and releases, levels essentially cannot reach thresholds of T. A similar conclusion was reached for D5 alone by the Siloxane D5 Board of Review (2011), and similarities in properties and read-across allow extrapolation of these conclusions to D4 and D6.

Biomagnification (BMF) in the environment

Lab studies to determine BCF showed values between 1,950 and 7,060 L/kg ww. However, this finding has little relevance to the environment where concentrations in water are low and do not reach maximum solubility such as is typically used in lab studies. Typically, lab investigations to determine $BMF_{experimental}$ yielded values ≤1; however, in two studies, the $BMFs_{kinetic}$ provided values between 1 and 2. The reason for these discrepancies in findings is uncertain. The overall WoE for TMF studies with cVMSs clearly supports a conclusion that biodilution occurs between sediment dwellers at bottom of the food web and top predators, although there are some results from one lab that conclude that BMF occurs. Methodological differences may explain the discrepancies. Based on assessments for each line of evidence, it is evident that D4, D5, and D6 clearly do not meet criteria for BMF expressed in the lack of trophic magnification in the environment.

Assessment of the potential for adverse effects in the environment

Overall, QWoE analysis demonstrates that there is moderate to strong evidence of no adverse effects from concentrations of D4, D5, and D6 as measured or expected to be in the environment. The major drivers of this conclusion are lack of T of cVMS, even in chronic exposure tests that allow for bioaccumulation and BMF, and minimal levels measured in the aquatic or soil environments. Also relevant is the read-across consistency for low T across three cVMSs studied here.

Long-range transport (LRT) in the environment. cVMSs were detected in the air in local and remote locations. Concentrations near to regions of use were greater than those in Polar Regions, but all were small and of no toxicological relevance. Presence in air in remote (Polar) regions is indicative of LRT, although unexpected local sources may be an issue. However, the key question is whether these small amounts deposit and become adsorbed in surface matrices such as soil and water (ice) or enter the food chain. Based on the physical properties of the cVMSs, they are unlikely to partition into surface waters/ice and soils, and even if this occurs in small quantities, the equilibrium will result in movement back into air or degradation in dry soils. The cVMSs degrade relatively rapidly in air with $t_{½}$ values ≤11 days. Unlike legacy POP, there is no evidence that cVMSs are accumulating in remote regions.

Comparison of the findings with those of classical legacy pollutants. The cVMSs display different physicochemical properties from those of PCB and similar legacy pollutants. Although both possess limited water solubility, cVMSs are much more volatile, have greater K_{AW}s, and therefore air is the ultimate environment sink. The volatility of cVMSs explains why they do not bioconcentrate in air-breathing vertebrates, including humans. This is in complete contrast to pollutants such as PCB.

In the aqueous environment, PCB and cVMSs bind to sediment. The mode of entry to the environment for cVMSs is almost solely through release from STPs. Although, several decades ago, STPs were also a significant route of entry for PCB, this is no longer the case and was probably not the most important route by which PCB entered the aquatic environment even in the past. The consequence is that although PCB are widely and evenly distributed in sediments of lakes or estuaries, cVMSs tend to be bound only to surface and suspended particles and there is a clear concentration gradient in sediments with increasing distance from each STP. There also are distinct differences between PCB and cVMSs in the ratio of partitioning from water into OC in sediments and soil and partitioning from water into lipid. Biomagnification can occur in sediment-dwelling benthic invertebrates, but at higher trophic levels in the aquatic environment, biodilution generally occurs as a consequence of poor assimilation and metabolism. In contrast,

assimilation is better and metabolism poorer for the PCB.

Lab tests in aquatic species demonstrate that cVMSs are not toxic at environmentally relevant concentrations, even with exposures sufficient to enable potential occurrence of bioaccumulation. This contrasts with the situation for PCB and many other legacy pollutants.

The physicochemical properties of legacy pollutants have justifiably raised serious concerns regarding pollution of remote pristine areas. The physicochemical properties of the cVMSs provide a clear indication that transport of large amounts to remote regions and deposition to soils and water is highly unlikely.

Combining all of these lines of evidence shows that cVMSs display different physical, chemical, and biological properties from those of legacy POP. The traditional criteria of persistence and bioconcentration used to classify legacy POP are not suitable for the cVMS. Refined approaches are needed, and when they are applied, these demonstrate that these materials should not be classified as P, B, or T or as vP or vB.

Using the QWoE approach provided a transparent way to summarize the quality and relevance of the data from various studies on the cVMSs. The relevance of the data was determined from exceedence (or lack thereof) of criteria and use of thermodynamically appropriate concentrations in the studies. The quality of study shown provided a measure of confidence, and the clustering of data points on the graphs provided a measure of consistency and reliability of the data. The term WoE has been used in regulations such as REACH, but as of this time it has not been utilized in decision making in a transparent way. As demonstrated with assessment of bioaccumulation, QWoE also enables several lines of evidence (BMF, BSAF, and TMF) to be brought into question, and consistency across these lines of evidence provides corroborative observations to help better answer the question.

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Availability of unpublished reports

Unpublished study reports are available by request from the Silicones Environmental, Health, and Safety Center (SEHSC), a sector group of the American Chemistry Council (ACC), via e-mail to Tracy Guerrero, tracy_guerrero@americanchemistry.com.

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