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Bioconcentration and Aquatic Toxicity of Superhydrophobic Chemicals: A Modeling Case Study of Cyclic Volatile Methyl Siloxanes

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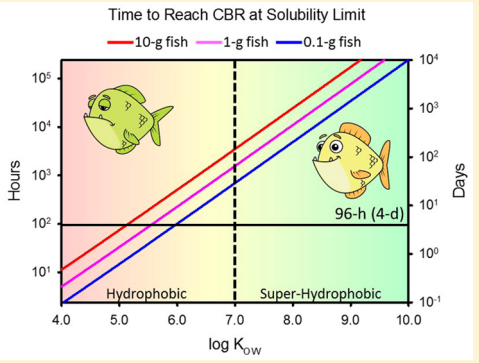
Supporting Information

ABSTRACT: Many chemicals in commerce are classified as "superhydrophobic", having log octanol–water partition coefficients (log K_{OW}) approaching or exceeding 7. Examples include long-chain alkanes, halogenated aromatics, and cyclic volatile methylsiloxanes (cVMS). We show that superhydrophobic chemicals present unique assessment challenges because of their sparing solubility in water and difficulties in empirical determinations of bioconcentration factors (BCFs) and aquatic toxicity. Using cVMS as an example, BCFs are considerably lower than expected due to biotransformation. Reviewed aquatic toxicity test data for cVMS in a range of aquatic organisms show little or no toxic effects up to solubility limits in water and sediment. Explanations for this apparent lack of toxicity of cVMS, and by extension to other superhydrophobic chemicals, are explored using a conventional one-compartment uptake model to simulate bioconcentration and toxicity tests using an assumed baseline narcotic critical body residue (CBR) and a range of organism sizes. Because of the low aqueous concentrations, equilibration times are very long and BCFs are sensitive to even very slow rates of biotransformation. Most organisms fail to achieve the assumed CBR during feasible test durations even at the solubility limit. Regulatory evaluation of superhydrophobic substances requires specially designed test protocols addressing biotransformation and dietary uptake.



INTRODUCTION

Many chemicals in commerce can be classified as "superhydrophobic", i.e., their octanol–water partition coefficients (K_{OW}) approach or exceed 7 on a base 10 logarithmic scale. Examples include long-chain alkanes, chlorinated alkanes or paraffins, certain organic dyes, halogenated aromatics such as PCBs, "dioxins", pesticides such as Mirex and toxaphenes, phthalate esters, and brominated fire retardants. One class of superhydrophobic materials is the polydimethylsiloxanes (silicones), which include the cyclic volatile methyl siloxanes (cVMS). Some 30 years ago, Bruggeman et al.[1,2] addressed the environmental chemistry of "superhydrophobic" chemicals that we define here as compounds with log K_{OW} > 7. They pointed out the difficulties inherent in testing for bioaccumulation and toxicity, including polydimethylsiloxanes.

Superhydrophobic substances are inherently problematic when evaluating criteria for persistence, bioaccumulation, and toxicity (PBT) in the context of chemical hazard or risk assessment because they are expected to have high bioconcentration factors (BCFs) in aquatic organisms and may biomagnify in aquatic food webs, because their log K_{OW} values exceed the conventional criterion of 5.0. A large K_{OW} value implies a low solubility in water, thus experimental determination of BCFs and acute aquatic toxicity (e.g., LC_{50}) of superhydrophobic substances can be difficult because of low concentrations, possible losses by evaporation and hydrolysis, decreased bioavailability in the water phase caused by the inevitable presence of organic matter and sorbing surfaces, and excessively long exposure times. These chemicals may tend to be persistent in the environment as a result of reduced bioavailability caused by their large molar masses and sorption to suspended solids and sediments. To simulate environmentally realistic conditions and overcome the inherent physical–chemical challenges presented by these chemicals, laboratory protocols have been modified to allow for dietary exposure as distinct from water exposure (e.g., Modified OECD 305 test[3]). Regulatory assessment of "superhydrophobic" substances requires reliable estimates of physicochemical properties such as vapor pressure, water solubility, and partition coefficients such as K_{OW}, as well as toxicity.

Obtaining toxicity data for "superhydrophobic" substances has proved to be problematic because even at the solubility limit in water or the corresponding maximum sorptive capacity in sediments, there may be little chemical in solution by which to express toxicity to fish and invertebrates.[4] Pioneering aquatic toxicity studies by Konemann and Veith and colleagues[5,6] suggested that in a series of chemicals of increasing hydrophobicity and decreasing solubility (S) the ratio LC_{50}/S increases until it reaches a "cutoff" of 1.0 in the range of log

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K_{OW} 6 to 7. Graphically this is because the regression plot of log LC_{50} vs log S has a slope of approximately 0.87 and crosses the diagonal of LC_{50} equal to S. At solubilities below this cutoff it may not be possible to expose the fish to acutely lethal conditions. This view has been challenged by Mayer and Reichenberg[7] who proposed an alternative explanation that the high melting points of more hydrophobic chemicals result in low fugacity ratios that cause low activities that are incapable of exerting baseline toxicity levels. These authors also suggested that slow uptake kinetics of sparingly soluble substances could play a role. Because the siloxanes addressed here as case studies are liquids, the high melting point explanation of low toxicity cannot apply, thus our focus is primarily on kinetic explanations and on the role of biotransformation, i.e. metabolism.

CYCLIC VOLATILE METHYL SILOXANES (CVMS)

The polydimethylsiloxanes consist of either linear or cyclic versions of permethylated siloxanes that have numerous industrial and commercial applications.[8,9] In particular, the cyclic volatile methylsiloxanes (cVMS) shown in Figure 1 have

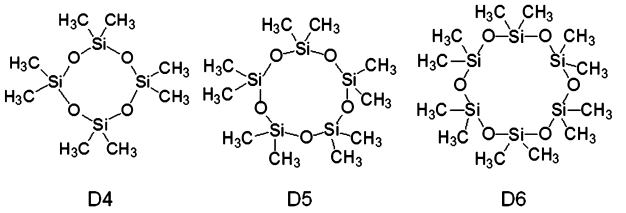

Figure 1. Chemical structures of the cyclic volatile methylsiloxanes (cVMS) D4, D5, and D6.

been used as major ingredients in formulations of personal care products, with an estimated annual production of several million tons over the past decade. The linear and cyclic methylsiloxanes may also be present as impurities in silicone fluids and elastomers. Allen et al.[8] estimated that greater than 90% of volatile methylsiloxanes (VMS) in personal care products are volatilized during use, the remainder being discharged to wastewater treatment systems. Only a very small fraction of cVMS used in personal care products (primarily D5) was available to go "down the drain" under conditions of domestic use.[10] Recent experimental measurements reviewed by Wang et al.[11] support the previous conclusions by Allen et al.[8] that during wastewater treatment the majority of cVMS partitions to air and sludge, with a small fraction (1−2%) being released to surface waters.[12] A fraction of the cVMS in sewage sludge is transferred by land application of biosolids to soil, where dissipation is fairly rapid.[13] Considering the potential environmental exposure to cVMS, scientific efforts have focused on potential adverse effects in the aquatic environment (Tables S1−S3 of the Supporting Information).

The difficulties of obtaining reliable cVMS physicochemical property data because of the extreme hydrophobicity have been discussed by Xu et al.,[14] while the challenges of measuring cVMS at trace-level concentrations that are used for aquatic toxicity testing have been discussed by Varaprath et al.[15] Obtaining aquatic toxicity data with these substances has thus proved problematic because even at the solubility limit in water or the corresponding maximum sorptive capacity in sediments, there may be an insufficient quantity of chemical in solution to induce toxicity to fish and invertebrates. Rücker and Kümmerer[16] have recently compiled a valuable critical review of the environmental chemistry of organo-silicon compounds, including the cVMS substances.

The cVMS substances have become the subject of scientific studies and regulatory scrutiny and controversy with numerous reports addressing environmental exposure and effects (Table S1 of the Supporting Information). Risk assessment reports have been compiled for the European Union[17−19] and by Environment Canada and Health Canada.[20−22] The latter risk assessment reports led to D4 and D5 being identified as Persistent (P) and Bioaccumulative (B) substances designated for possible regulation in Canada[23] and in Europe.[24] A subsequent Board of Review found that "present and future adverse environmental effects with D5 are minimal".[25]

The Canadian screening assessment of D5, triggered by a PBT evaluation, indicated that D5 was of concern because of its persistence in sediment and air (with half-lives exceeding the criterion of 2 days in air and 365 days in sediment) and high hydrophobicity or lipophilicity (log K_{OW} of 8.09).[20] D5 was thus expected to bioconcentrate in aquatic organisms and display at least baseline narcosis with a critical body residue (CBR) in the range of 2−8 mmol kg^{-1} ww, corresponding to approximately 40−160 mmol kg^{-1} lw at 5% lipid composition.[26] Using the simple rule of thumb that a bioconcentration factor (BCF) may be estimated as the product of total lipid content (typically assumed to be 5%) and K_{OW},[27] a BCF of over 10^6 L kg^{-1} ww is expected for D5. However, laboratory tests on D5[28] yield much lower BCF values that are close to the bioaccumulation criterion of 5000 L kg^{-1} ww, as reviewed by Gobas et al.[29,30] and summarized for D4, D5, and D6 in Table S2 of the Supporting Information. Clearly, other factors are influencing bioconcentration of cVMS. Redman et al.[4] reviewed aquatic toxicity data and conducted an aquatic risk assessment of cVMS by applying the Target Lipid Model (TLM) to fish and invertebrates. This model[31] evaluates the toxicity of nonionic chemicals that share a similar narcotic mode of toxic action. The authors[4] initially proposed a conservative acute mortality, lipid-based CBR of ∼100 mmol kg^{-1} lw for the nonmetabolizing freshwater pelagic invertebrate, *Daphnia magna*, which is consistent with the above CBR range for D5 (40−150 mmol kg^{-1} lw). An approximate CBR in D4-exposed *D. magna* cultures has been measured yielding a value of ∼7 mmol kg^{-1} ww or ∼450 mmol kg^{-1} lw (at 1.5% lipid), thus the suggested value for D5 appears conservative in nature.[32] The overall Predicted No-Effect Concentration (PNEC) for cVMS was about 3 mmol kg^{-1} lw from which Redman et al.[4] concluded that there was a low potential for risk to aquatic species at present-day rates of cVMS emissions. There remains, however, an incentive to determine the aquatic toxicity empirically to determine whether or not prevailing cVMS exposures are acceptable.

Several mechanisms have been hypothesized to explain the apparent lack of cVMS toxicity. The high molar masses and volumes may prevent or retard membrane transport, although this explanation has been disputed by Arnot et al.[33] Efficiencies of absorption of cVMS through gill and gut membranes may be low, resulting in low internal bioavailability.[4]They may also have a very low bioavailability from water because of sorption to suspended and dissolved organic matter.[34] Biotransformation may occur in organisms, yielding more water-soluble degradation products such as silanols.[17−19] Times to reach a CBR may be excessive by virtue of the low exposure concentrations. These rates can result in excessive exposure

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times to achieve critical toxic tissue concentrations. Finally, these cVMS substances may simply be "nontoxic".

The objective of this paper is to offer hypotheses to explain why superhydrophobic substances do not bioconcentrate to the expected extent and may appear to be nontoxic under typical test conditions, as is observed with cVMS. To accomplish this objective, we compile a series of conventional uptake equations and a simple accumulation model for aquatic organisms. The model is applied to cVMS under simulated conditions of standard toxicity tests (Table S1 of the Supporting Information), such as the OECD 203 acute fish assay.[35] We then discuss the reasons for the apparent lack of toxicity with cVMS and discuss their potential, and, by extension that of other superhydrophobic substances, to achieve toxic conditions under environmental conditions.

PHYSICAL–CHEMICAL PROPERTIES, BIOCONCENTRATION, AND TOXICITY

The physicochemical properties of D4, D5, and D6 are given in Table 1. They are liquids at ambient temperatures, with relatively large molar masses, high vapor pressures, low water solubilities, and very high K_{OW} values. Based on these properties, cVMS clearly fall into the category of being "superhydrophobic". Considering their molecular size, the air–water partition coefficients (K_{AW} values) for D4, D5, and D6 are large, and the compounds readily partition from water and soil into air.[12,14,36] Also, the organic carbon–water partition coefficients (K_{OC} values) for cVMS are smaller (about 200-fold) than would be expected from their K_{OW} values,[12,14,36] implying a further shift of partitioning equilibrium from soil and sediments into water, and eventually into air.

Table 1. Relevant Properties of D4, D5, and D6 at 25 °C[a]

property	D4	D5	D6
CAS no.	556-67-2	541-02-6	540-97-6
molecular formula	$C_8H_{24}Si_4O_4$	$C_{10}H_{30}Si_5O_5$	$C_{12}H_{36}Si_6O_6$
molar mass (g mol^{-1})	296.62	370.78	444.93
melting point (°C)	17.7	−38	−3
solubility in water (g m^{-3})	0.056	0.017	0.00515
solubility in water (μmol m^{-3})	188.8	45.8	11.6
Log K_{OW} (octanol–water)	6.98	8.09	8.87
Log K_{OC} (organic carbon–water, L kg^{-1})	4.22	5.17	6.03
Log K_{AW} (air–water)	2.74	3.13	3.01
Log K_{LW} (lipid–water; invertebrates)	6.48	7.60	8.40
Log K_{LW} (lipid–water; fish)	7.01	8.17	8.99
K_{LO} (lipid–octanol; invertebrates)	0.32	0.32	0.34
K_{LO} (lipid–octanol; fish)	1.1	1.2	1.3
half-life in air (d)	10.6	6.9	6.0, 4.4
half-life in soil (d)	5.29	12.6	
half-life in water (d)	3.9	70.4	400
half-life in sediment (d)	365	3100	

[a]The half-life in water is based on hydrolysis at pH 7. No biodegradation rates in water have been reported. Data sources are refs 4, 14, 16–19, and 58–67.

Bioconcentration and biomagnification data from laboratory studies on cVMS are compiled in Tables S2 and S3 of the Supporting Information. Reported fish BCFs are in the range 1700–13 400 L kg^{-1} ww, as summarized in the critical reviews on D5 by Gobas et al.[29,30] Because of the low water solubilities and the ready formation of micelles by these surface-active materials,[37] test organisms may be exposed to supersaturated conditions containing "neat" cVMS. Table S1 is a compilation of acute and chronic toxicity data of cVMS to aquatic organisms, showing a general lack of measurable toxicity up to the water solubility or sorptive capacity in sediment.[4,29,30,38] No effects have been observed with cVMS in standard 48- or 96-h acute toxicity tests. Effects were observed for D4 (reviewed by Hobson et al.[59]) in 14- and 18-d prolonged acute toxicity studies with rainbow trout (*Oncorhynchus mykiss*) but not sheepshead minnow (*Cyprinodon variegatus*), whereas no effects were observed for D5 (D6 was not tested) in any of the prolonged acute toxicity studies. In chronic aquatic exposures, D4 demonstrated some chronic reproductive effects on *D. magna* at 15 μg L^{-1} and a NOEC at 7.9 μg L^{-1}. No other chronic aquatic toxicity has been observed with D4, D5, or D6 in water or natural sediments, with NOECs often approaching water solubility limits for the respective materials. Chronic toxicity studies in artificial sediments could not be reproduced with natural sediments at the same or greater cVMS dose levels. This suggests that the lack of toxicity reported for natural sediments was likely due to mechanisms such as aging.

In sediment exposures, many of the conducted studies have been dosed at concentrations in excess of the maximum sorptive capacity for cVMS in sediment organic carbon.[38] For this reason, toxicity observed at concentrations in excess of the maximum sorptive capacity might have been due to "neat" cVMS. The maximum sorptive capacity of organic carbon (OC) may be calculated for a material as the product of the compound's water solubility (mg L^{-1}) and its K_{OC} value (L kg^{-1} OC). The maximum sorptive capacities of D4, D5, and D6 in organic carbon are 929, 2514, and 26520 mg kg^{-1} OC, respectively. Benthic organisms exposed to cVMS in artificial sediment demonstrated some chronic effects with D4 at 0.73 mg kg^{-1} dw (30 mg kg^{-1} OC) but these results were not reproducible on natural sediment, where the NOEC was 13 mg kg^{-1} dw (591 mg kg^{-1} OC) and the LOEC approached the maximum OC sorptive capacity at 19 mg kg^{-1} dw (864 mg kg^{-1} OC). For D5, chronic NOEC values are approximately equivalent to or in excess of the maximum sorptive capacity (2514 mg kg^{-1} OC) in both artificial and natural sediments with all tested species. With D6, chronic NOEC values are approximately equivalent to the maximum OC sorptive capacity (26 520 mg kg^{-1} OC) for organisms exposed on natural sediment. A chronic NOEC < 22 mg kg^{-1} dw (815 mg kg^{-1} OC) was reported with D6 and *Chironomus riparius* in artificial sediment but these results were not reproducible when natural sediment was used; the 28-d NOEC was the highest dose level of 620 mg kg^{-1} dw (19375 mg kg^{-1} OC).

MODEL AND PARAMETERS

To explore and suggest reasons for the difficulty in obtaining consistent toxicity values for superhydrophobic substances such as cVMS, we employ a conventional one-compartment first-order uptake model, as described by Arnot and Gobas[39] in their AQUAWEB model. We employ the conventional equation for dynamic uptake from water by respiration as it applies to standardized flow-through bioconcentration tests such as OECD 305[3] and US EPA 850.1730[40] and as used by Mackay et al.[41] Briefly the uptake equation is as follows, where t is time (h):

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$$C_F = C_W \times (k_1/(k_2 + k_M)) \times [1 - \exp(-(k_2 + k_M) \times t)] \quad (1)$$

Here, C_F is the concentration in the exposed fish (mol m^{-3} ww), C_W is the dissolved concentration in water (mol m^{-3}), k_1 is the uptake rate constant by respiration, estimated as $G \times E$ where G is the rate of water flow into the gills (m^3 water m^{-3} fish h^{-1}) and E is the respiration assimilation efficiency estimated from correlations with the chemical's octanol–water partition coefficient (K_{OW}). The rate constants for losses are k_2 (h^{-1}) by respiration (estimated as $k_1/(L \times K_{OW})$), where L is the fractional lipid content of the fish and k_M quantifies metabolism or biotransformation (h^{-1}). This equation implies that there is no chemical intake by food, and there are no losses by growth dilution and egestion. When $t \gg 1/(k_2 + k_M)$, a steady-state aquatic organism concentration, C_{FSS}, is approached:

$$C_{FSS} = C_W \times k_1/(k_2 + k_M) \quad (2)$$

C_{FSS}/C_W is the bioconcentration factor (BCF). When k_M is zero, C_F approaches $C_W \times (k_1/k_2)$ or $C_W \times BCF_E$ where BCF_E is a steady-state or equilibrium bioconcentration factor that can be estimated as $L \times K_{OW}$. If metabolism does occur, the lower steady state but nonequilibrium bioconcentration factor BCF_M is $k_1/(k_2 + k_M)$.

The aim of the standard BCF test[3,40] is to determine C_F/C_W after long exposure times when equilibrium is approached. Alternatively, if the test time to approach equilibrium is experimentally excessive, a "kinetic" BCF can be calculated using separate estimates of k_1 and k_2 and their ratio equated to the BCF_E or BCF_M. The aim of an aquatic acute toxicity LC_{50} test[35] is to determine the concentration in water that causes 50% mortality to the test organisms after a prescribed exposure time such as 96 h, i.e., the 96-h LC_{50} value. We assume that the LC_{50} occurs when C_F reaches a critical body residue (CBR) representing an effect on 50% of the organisms (CBR_{50}). The CBR_{50} selected here is a conservative 3 mol m^{-3} or equivalently 3 mmol kg^{-1} ww by assuming a fish density of 1 kg L^{-1}. This value corresponds to 60 mmol kg^{-1} lw and is in the range of CBRs for acute baseline neutral narcosis in small aquatic organisms, assuming ~5% lipid content.[26,42] This value is broadly consistent with the Redman et al.[4] analysis employing the Target Lipid Model. In the latter study, CBRs for the example cVMS substances were estimated for daphnia (*D. magna*) of 115 mmol kg^{-1} lw and for *C. tentans* of 28 mmol kg^{-1} lw. For invertebrate species, Landrum et al.[43] measured median effect residues (ER50) for several polycyclic aromatic hydrocarbons (PAHs) with the freshwater amphipod *Diporeia* spp. and found values ranging from 1.7 to 3.5 mmol kg^{-1} ww, consistent with a narcotic mode of action (i.e., ~ 3 mmol kg^{-1} ww), which has been proposed for PAH toxicity by DiToro et al.[31] A much lower baseline neutral narcosis CBR of 2.6 mmol kg^{-1} lw was employed as the PNEC.

Biochemically reactive chemicals such as pesticides and biocides likely exhibit specific modes of toxic action and have lower CBRs. Equation 1 can be rearranged to express the LC_{50} concentration C_W that yields a C_F or conservative CBR_{50} of 3 mol m^{-3} at a defined exposure time t.

$$LC_{50}\ (\text{mol m}^{-3}) = CBR_{50}/[(1 - \exp(-(k_2 + k_M)t)) \times k_1/(k_2 + k_M)] \quad (3)$$

When k_M is zero and k_2 is replaced by $k_1/(L \times K_{OW})$, where L is the fractional lipid content, eq 3 reduces to eq 4.

$$LC_{50}\ (\text{mol m}^{-3}) = CBR_{50}/[(1 - \exp(-(k_1 t/L \times K_{OW})) \times L \times K_{OW}] \quad (4)$$

The group $[1 - \exp(-(k_2 + k_M)t)]$ in eq 3 can be expressed as Φ, the fractional approach to steady state or equilibrium. At equilibrium, Φ is 1.0 and when t is zero, Φ is also zero, thus Φ is essentially a nondimensional time and $100 \times \Phi$ is the percentage approach to equilibrium. This gives an equation for LC_{50} as a function of CBR_{50}, Φ and BCF_E (for nonmetabolizing chemicals) or with BCF_M for metabolizing materials. The ratio CBR_{50}/BCF is the "Incipient Lethal Water Concentration" or ILC_{50}[44] or the "Threshold" LC_{50}.[45] The ILC_{50} is the concentration in water (mol m^{-3}) that results in the organism reaching its CBR after long exposure times when Φ equals 1.0. This is the minimum aqueous concentration necessary to cause toxicity. If the solubility is less than the ILC_{50}, then 50% mortality cannot be achieved. The estimation of a compound's LC_{50} value from an assumed narcotic CBR_{50} (3 mmol kg^{-1} ww) and its intrinsic properties eqs 3 and 4 may be validated using available property information and ecotoxicity data. To confirm that the model structure was valid for substances other than cVMS, calculations were also been performed for 1,2,4-trichlorobenzene (TCB; log K_{OW} = 4.02), naphthalene (log K_{OW} = 3.35), and di-*n*-butyl phthalate (DBP; log K_{OW} = 4.90) and the results are presented in Table S4 in the Supporting Information. It was assumed that a narcotic CBR_{50} (3 mmol kg^{-1} ww) applied to all three compounds.

Equation 4 can be rearranged to show the relationship among ILC_{50}, LC_{50} ,and Φ:

$$CBR_{50}/BCF = ILC_{50} = LC_{50} \times \Phi \quad (5)$$

Equations 3–5 capture the expected properties that control the LC_{50}, namely exposure concentration, time, and inherent toxicity. There is a hyperbolic relationship between the acute toxicity exposure concentration (LC_{50}) and time expressed by Φ, with their product being the ILC_{50}. It is noteworthy that when $k_2 \times t \ll 1.0$, as may apply to very slowly accumulating hydrophobic chemicals, Φ approaches $k_2 \times t$ or $(k_2 + k_M) \times t$.

METHODS

Estimates of effective water respiration rates G (L d^{-1}) for fish were obtained from the AQUAWEB correlations by Arnot and Gobas[46] as a function of fish mass W (kg), gill chemical transfer efficiency E (unitless), oxygen concentration in water C_{OX} (mg L^{-1}), the defined temperature T (°C), and fraction of oxygen saturation (S) to give k_1 (L kg^{-1} d^{-1}) and converted to L kg^{-1} h^{-1} for the present purposes. The numerical value of k_1 in units of h^{-1} is identical if the organism density is 1.0 g mL^{-1}.

$$G = 1400 \times W^{0.65}/C_{OX} \quad (6)$$

$$C_{OX} = S \times (14.04 - 0.24T) \quad (7)$$

$$1/E = 1.85 + 155/K_{OW} \quad (8)$$

$$k_1\ (\text{L kg}^{-1}\,\text{h}^{-1}) = E \times G/(24W) \quad (9)$$

The uptake efficiencies E for cVMS were essentially equal at 54% for D4, D5, and D6 because of the high values of K_{OW} in

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Table 2. Uptake Characteristics of D4, D5, and D6 in Organisms of Specified Masses, No Metabolic Conversion, Assuming a Water Concentration at the Solubility Limit, and a CBR_{50} of 3 mmol kg^{-1}[a]

organism mass (g)		5			0.05			0.001	
k_1 (L kg^{-1} h^{-1})		27.2			137			1000	
lipid content (%)		5.0			5.0			1.0	
chemical	D4	D5	D6	D4	D5	D6	D4	D5	D6
dimensionless time (Φ)	0.033	0.011	0.007	0.033	0.011	0.007	0.17	0.05	0.035
corresponding time (d)	24.7	101	397	4.9	20.2	79	0.72	2.8	11

[a]Φ is calculated from eq 5 as CBR_{50}/(BCF × solubility) and is the non-dimensional time required to reach the CBR at the substance's solubility limit. Additional details are provided in Table S4 of the Supporting Information.

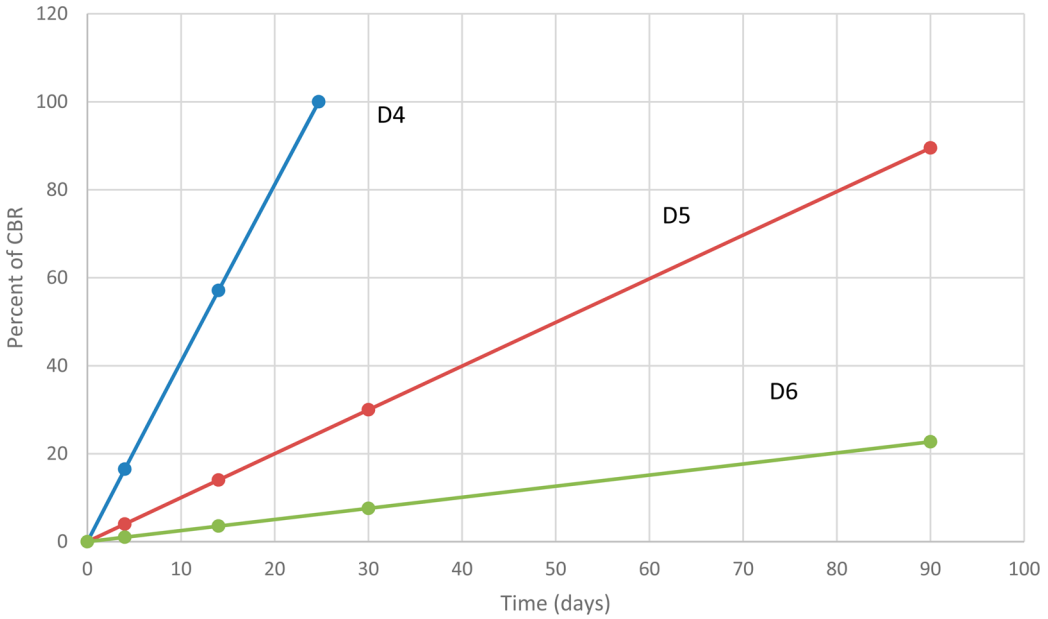

Figure 2. Estimated percent of LC_{50} critical body residue (CBR_{50}) for cVMS (D4, D5, D6) as a function time for a 5-g fish exposure at the respective chemical solubility limits.

eq 8. The respiratory loss rate constant k_2 was calculated as $k_1/(L \times K_{OW})$. We initially assume a fish mass of 5 g, a lipid content L of 0.05 or 5%, a temperature of 20 °C, an oxygen saturation of 80%, and a CBR_{50} of 3.0 mmol kg^{-1}. We then use eq 5 to determine how the measured LC_{50} is predicted to depend on K_{OW} for typical test durations for the cVMS substance D5 and later for D4 and D6. We then explore the effect of variation in body mass for fish using the allometric relation in eq 6.

For *Daphnia*, the above body size scaling is not valid and direct estimates of uptake rate constants are used. Evans[47] reported uptake rate constants for hydrophobic chemicals by *D. magna* (mass ~1 mg) ranging from 1.06 to 2.83 mL mg^{-1} ww h^{-1} with a mean value of 1.7 mL mg^{-1} ww h^{-1} for PCB 153 (log K_{OW} of 6.9) and cite a slightly lower value of 0.75 mL mg^{-1} ww h^{-1} for benzo[a]pyrene (BaP; log K_{OW} of 6.04). For amphipods (*Pontoporeia sp.*; mass ~83 mg) and marine crustaceans (*Mysis sp.*; mass ~43 mg), the uptake rate constants for BaP were 0.055 and 0.0575 mL mg^{-1} ww h^{-1}, respectively. Lipid contents of *Daphnia* were cited by Evans[47] to have ranged from 0.2 to 1.5%, suggesting a BCF for PCB 153 of 16 000 to 119 000 L kg^{-1} ww, a range consistent with values of measured k_1/k_2 ratios (BCF_E) of 45 000 to 120 000 L kg^{-1} ww. Depuration half-times were approximately 29 h. We conclude that while conventional uptake kinetic expressions such as eq 1 can be applied to *Daphnia*, organism-specific parameter values are essential. For the present purposes, *Daphnia* are treated as 1 mm^3 in volume with a mass of 1 mg, a lipid content of 1% and an uptake rate constant of 1 mL mg^{-1}-ww h^{-1}, corresponding to 1000 h^{-1} for an assumed density of 1000 mg mL^{-1} or 1 g cm^{-3}. The relatively large value of k_1 and the low lipid content result in a larger k_2, thus *Daphnia* approach equilibrium faster than fish.

RESULTS

Table S5 of the Supporting Information gives a detailed printout of sample results from the Microsoft Excel spreadsheet calculations. Model calculations were in excellent agreement with empirical data for TCB, naphthalene, and DBP used as less hydrophobic reference chemicals, as summarized for LC_{50} and BCF in Table S4. In the interests of clarity we first treat the role of hydrophobicity alone then consider the additional role of metabolism.

Role of Hydrophobicity. Values of log K_{OW} greater than 7 imply high BCF values that are well above the regulatory criterion of 5000 L kg^{-1} ww for a very bioaccumulative substance[48−52] unless there are substantial losses by biotransformation or growth dilution. We first consider uptake of D5 in a 5-g fish and assume no biotransformation losses. The uptake rate constant, k_1, is estimated to be 27.25 L kg^{-1} ww h^{-1}, k_2 is 4.43 × 10^{-6} h^{-1}, and the BCF_E is 6.15 × 10^6 L kg^{-1} ww. The half-time for uptake is ln2/k_2 or 156 000 h or 6520 days. Consequently, the BCF cannot be directly measured in a single

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laboratory study but must be estimated from two separate kinetic studies as the measured ratio of k_1 and k_2.

For D5, the estimated ILC_{50} in the absence of biotransformation is 4.88×10^{-7} mol m^{-3} or 0.181 μg L^{-1} and is the aqueous concentration in equilibrium with the CBR_{50}. Using these estimated concentrations, the likely toxic effect can be predicted for any combination of exposure concentrations and time. Three criteria or constraints must be satisfied for a successful toxicity test. First, the LC_{50} must equal or exceed the ILC_{50} which is a factor of ~100-fold lower than the water solubility limit of D5 (17 μg L^{-1}), suggesting that a toxicity test is feasible. Second, the half-time for uptake must be reasonable. For D5, with a half-time for uptake to equilibrium conditions of 6520 days (17.9 years), it is not feasible to approach equilibrium conditions in a conventional acute or chronic toxicity test. This time is long because k_1 implies that the fish respires only 27.2 times its volume of water per hour. To reach the BCF_E, a fish must accumulate chemical from a minimum volume of water, which is BCF times the fish volume, requiring a minimum time of BCF/k_1 or 226 000 h or 25.8 years. The time required to reach the CBR may, however, be reduced if a higher exposure concentration in water is used.

A third possible constraint for a successful toxicity assay is the solubility limit that for D5 is 4.58×10^{-5} mol m^{-3} (17 μg L^{-1}). Obviously, the LC_{50} cannot exceed this value. The time required to reach the CBR at the solubility limit is then shorter and requires that Φ is ILC_{50}/LC_{50} or 0.0106. The corresponding time is $-\ln(1\text{-}\Phi)/k_2$ or 2416 h (about 100 days) and is still too long to be experimentally feasible. Table 2 summarizes these results for the three cVMS substances and for smaller test organisms as discussed later.

A more direct approach for determining these constraints is to estimate the body burden as a percentage of the CBR at various times of exposure to a saturated solution. Illustrative results are given in Figure 2 for D4, D5, and D6 in 5-g fish. After 4 days of exposure to a saturated D5 solution, Φ is only 0.00043 and is approximately k_2t. The concentration in the fish is only $\Phi \times BCF_E$ or 0.12 mol m^{-3}, only 4% of the CBR_{50}. At longer test times this percentage increases, but the rate of increase is slow. For example, it is 14% of the CBR_{50} after 14 days, 30% after 30 days, and 89% after 90 days. For D4, the corresponding percentages for a saturated solution are 16% of the CBR_{50} after 4 days, 57% after 14 days, and the D4 CBR_{50} is reached at 25 days. The faster uptake of D4 is attributable to the higher concentration of D4 in water at the solubility limit and to the slightly lower fish BCF. For D6, uptake is slower than that of D5 and even after 90 days of exposure to a saturated solution the body burden is only 23% of the compound's CBR_{50}.

In summary, to achieve appreciable concentrations of a superhydrophobic substance in the organism requires respiration of a large volume of water, but the rate of respiration dictated by k_1 is very slow. The net result is an uptake half-time that is proportional to K_{OW} and can be excessive under typical test conditions. This conclusion may not be valid for smaller organisms, if metabolism occurs, or if the CBR is very low as a result of biochemical interactions, i.e., the chemical has a greater intrinsic toxicity corresponding to a specific mode of toxic action.

This resulting inability to achieve toxic conditions under standard laboratory conditions does not imply that there will be no ecosystem toxicity to fish. Toxicity in fish could occur if there is biomagnification as a result of dietary uptake from consumption of lower trophic level organisms. In the absence of biomagnification, toxic effects would most likely be observed in small, low-trophic-level organisms as discussed below.

Role of Organism Size. Faster uptake can be achieved by using a smaller organism with faster rates of uptake and elimination (i.e., k_1 and k_2). For illustrative purposes, we assume that volumetric respiration rates scale with body mass to a power of approximately 0.65 as suggested in eq 6. Thus k_1, which is normalized to body weight, scales with body mass to a power of −0.35. Reducing organism size by a factor of 100 increases k_1 by a factor of $100/100^{0.65}$ or 5.0-fold. This increase is significant, but modest in the context of typical test durations. Table 2 gives estimates of Φ and corresponding uptake half-times for fish of mass 5.0 and 0.05 g and an invertebrate of mass 0.001 g (typical of *D. magna*). The assumed invertebrate mass is a factor of 5000 smaller and has a lower lipid content of 1%. For D5, the daphnia (organism mass = 0.001 g) uptake half-time is much shorter than that of 5-g fish and 0.05-g fish, at 2.8 days versus 100 and 20 days, respectively. Smaller planktonic organisms may therefore approach equilibrium with D5 in the water column in days to weeks. This faster uptake half-time may contribute to the greater chemical sensitivity of plankton, daphnids, and early life stage organisms.

If k_1 and k_2 both increase by a factor of 5, then the BCF, the ratio CBR_{50}/BCF and the ILC_{50} are unaffected. There is more rapid initial uptake, a reduction in the uptake half-time, and a toxicity test may become feasible, especially for marginally less hydrophobic chemicals, such as D4. In the early stages of uptake, the percentages of the CBR increase. For example, for D5 after 4 days of exposure, the approach to CBR_{50} increases from 4% for a 5-g fish compared to 20% for a 0.05-g fish. Algebraically, the increase in k_1 and k_2 causes an increase in Φ (which is approximately equal to k_2t) for the specified time, a faster approach to the CBR and to equilibrium, but the same end point is eventually reached when Φ is 1.0.

The higher water concentration at the solubility limit of D4 causes a faster uptake rate and toxicity tests become more feasible. Ultimately, the test duration may be limited by the ability of the test organism, such as a daphnid, to maintain viability.

Role of Metabolism. Generally a whole-body metabolic or biotransformation rate constant of 0.01 day^{-1} is regarded as slow especially for short-term laboratory tests lasting 4 days, resulting in a ~ 4% loss of chemical mass. In longer tests and in environmental conditions even very slow rates of metabolism can have a profound effect, especially if the exposure time exceeds $1/k_M$ days. Introducing an assumed value of k_M has the dual effect of reducing BCF_E to BCF_M (increasing the ILC_{50}) and reducing the uptake half-time (increasing Φ). The net result is an increase in the approach to the toxic end point at a specified test time. For a specified CBR, these two effects cancel for superhydrophobic substances at shorter exposure times, as can be seen in eq 5. For metabolism to be significant in the long term, k_M must be comparable to, or larger than, k_2.

It may not be generally appreciated that even very slow rates of metabolism can significantly reduce BCFs, especially for superhydrophobic compounds. The factor by which the BCF is reduced is $(k_2 + k_M)/k_2$ and can be large when k_2 is small. For example, in a fish with an uptake rate constant (k_1) of 1000 h^{-1} (assumed fish density of 1 kg L^{-1}) or approximately 40 d^{-1} and a lipid content L of 5%, k_2 may be estimated[41] as $k_1/(L \times K_{OW})$ or $40/(0.05K_{OW})$. A metabolic half-life of 7 days ($k_M \sim 0.1$ d^{-1}) reduces the BCF for log K_{OW} compounds of 5 and 6 by modest

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factors of 1.02 and 1.2, respectively. For compounds of log K_{OW} 7 and 8 these factors are much greater, namely 3 and 23, representing a drop in log BCF of 0.49 and 1.34, respectively.

In the case of D5 in a 5-g fish, k_2 corresponds to a half-life of 6520 days, thus any k_M corresponding to a shorter half-life will be significant. Such a half-life is highly likely because the estimated half-life of D5 in water by abiotic hydrolysis alone is 70 days (Table 1). Bioconcentration studies on D5 by Drottar et al.[53] and Parrott et al.[28] show that the growth-corrected metabolic conversion half-life estimated from $(k_2 + k_M)$ is 24−36 days. These data suggest that the depuration of D5 is controlled not by respiratory losses, but by D5 biotransformation/metabolism. Additional evidence on the metabolic degradability of D5 with Fischer rats from Varaprath et al.,[54] shows extensive conversion of D5 to more polar metabolites. In long-term exposure of an aquatic organism, the BCF then approaches k_1/k_M, rather than k_1/k_2. A fish metabolism half-life range of 36 days for D5 corresponds to a k_M 0.019 d^{-1} or 0.0008 h^{-1}. For an estimated uptake rate constant (k_1) of 27.2 L kg^{-1} h^{-1} (Table 2, 5-g fish), a BCF_M of 34 000 L kg^{-1} ww is estimated and is orders of magnitude lower than the value estimated from K_{OW} alone. In the BCF tests by Drottar et al. (reviewed by Gobas[30]) with D5 and fathead minnow (*Pimephales promelas*), the measured uptake rate constant k_1 of D5 with fathead minnows was 16 L kg^{-1} h^{-1}. Analysis of the fish BCF data of Parrott et al.[28] reveals a comparable mean measured uptake rate constant (k_1) of D5 with fathead minnows of 30 L kg^{-1} h^{-1}. These experimental uptake rate values effectively bracket the modeled k_1 value of 27.2 L kg^{-1} h^{-1}, so the estimated D5 BCF_M values are slightly smaller and in the range 7000−13 000 L kg^{-1} ww.

Assuming a metabolism half-life such as 36 days, the effect of D5 metabolism is unimportant for short-term laboratory tests of up to a week. For longer-term laboratory tests and under environmental conditions, metabolism is important. To reach the CBR_{50} (3 mmol kg^{-1}) at the solubility limit of D5 (4.58×10^{-5} mol m^{-3}) implies a BCF of 65 000 L kg^{-1} ww, namely a concentration ratio of 3 mol m^{-3} in the fish to an exposure concentration of 4.58×10^{-5} mol m^{-3} in water. Adopting an uptake rate constant (k_1) of 27.2 L kg^{-1} h^{-1} at this BCF implies a total loss rate constant $(k_2 + k_M)$ of 4.2×10^{-4} h^{-1} or 0.01 d^{-1}. The estimated gill elimination rate constant, k_2, is 0.44×10^{-5} h^{-1} (0.0001 d^{-1}), thus k_M must be 4.1×10^{-4} h^{-1} or a 69-day metabolism half-life. Metabolism then accounts for 94% of the D5 losses. If the metabolism half-life is shorter than 69 days (i.e., $k_M > 0.01$ d^{-1}), it is impossible to achieve the CBR_{50} under test conditions. Under environmental conditions, dietary uptake will be the key determinant of concentration and possible toxicity in organisms that occupy higher trophic positions. Metabolism also affects toxicity (i.e., LC_{50}). A reduction in BCF causes the ILC_{50} to increase and the substance thus appears to be less toxic because higher water concentrations are needed to induce toxicity, i.e., the LC_{50} increases but this may not be feasible because of the solubility limit. A useful strategy for evaluating a new chemical is to estimate the CBR and BCF, then calculate their ratio, the ILC_{50}. This can be compared with the water solubility as was done earlier for D5 in which the ILC_{50} was a factor of ~100× lower than the solubility. Introducing metabolism increases the ILC_{50} because of the lower BCF, and the factor by which the solubility exceeds the ILC_{50} decreases until when this factor is less than 1.0, a toxicity test is not feasible. The metabolic half-life required to decrease this factor to 1.0 or less is readily calculated, databases exist for such half-lives.[55]

For toxicity evaluations, the direct inclusion of a metabolic rate constant implies that metabolites (e.g., silanols from the degradation of cVMS) are nontoxic, which may or may not be the case. Redman et al.[4] adopted the conservative approach that the metabolite is equi-toxic with the original cVMS substance, effectively doubling the total concentration of D5 plus metabolites for long-term environmental exposure. It is likely that, in general, oxygenated metabolites of superhydrophobic substances, such as D5, will be less hydrophobic and are thus excreted more readily.

The results show that for superhydrophobic chemicals such as cVMS, conventional aquatic toxicity tests with exposure from water respiration will often fail to reach a toxic end point. Toxicity of superhydrophobic chemicals may not be measurable as an LC_{50} in a reasonable test time, even for small organisms and especially if there is appreciable transformation of the substance by biological or abiotic hydrolytic mechanisms. Again we emphasize that this conclusion does not imply that superhydrophobic chemicals are nontoxic in the environment. It is possible that the CBR_{50} can be approached or exceeded if the organism consumes a diet containing high concentrations of these substances (i.e., the toxic end point is reached by bioaccumulation and biomagnification rather than bioconcentration). A comprehensive analysis of the effects of dietary intake under laboratory or ecosystem conditions is beyond our scope here, but some aspects are worthy of note. For superhydrophobic substances, uptake from the diet generally greatly exceeds the rate of respiratory uptake. Comparison of dietary uptake rate constants with those for egestion, metabolism, and growth, as in the AQUAWEB model[39] can reveal the extent of possible biomagnification. By designing dietary uptake tests such as OECD 305 using such a model it may be possible to achieve relatively high body residues approaching CBRs, resulting in toxic effects under controlled conditions.

In summary, the novelty of this study is that the previously puzzling low BCFs and lack of toxicity can be fully explained by applying an existing biouptake model, parametrized to account for the extreme hydrophobicity and the presence of even slow and approximate metabolic rates. We believe that these findings apply generally to superhydrophobic substances and indicate a need to reconsider and modify scientific and regulatory test methods.

SUPERHYDROPHOBIC SUBSTANCES: REGULATORY AND ECOLOGICAL IMPLICATIONS

It seems likely that concentrations of most superhydrophobic chemicals observed in aquatic organisms in the environment originated by dietary/prey uptake, except of course for phytoplankton and other low-trophic-level organisms that may approach equilibrium directly with dissolved chemical in the water column. If the superhydrophobic chemicals biomagnify, there is a possibility of increased concentrations at successively higher trophic levels that could result in toxic exposures being approached. The extent of possible biomagnification of a persistent substance is controlled by the chemical's hydrophobicity, dietary assimilation efficiency, elimination rates, and the nature of the diet. If there is even slow biotransformation such that k_M approaches or exceeds k_2, biomagnification is unlikely to be significant. The preferred approach for elucidating these possibilities is to obtain

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monitoring data for representative food webs and convert the concentrations to fugacities or chemical activities to reveal their relative equilibrium status. Activities are simply the ratio of concentration to solubility or fugacity to vapor pressure, i.e., the fraction of saturation.[29,56,57] For narcotic chemicals, acute lethality generally occurs in a range of chemical activities of 0.01−0.1; therefore, the proximity to potentially toxic conditions is readily evaluated by examining the absolute and relative activities in food web samples, as has been done for D5 by Gobas et al.[29]

For regulatory purposes, chemical toxicities are generally expressed either as external exposure concentrations (e.g., LC_{50} values) or internal concentrations in the organism (CBR values) that cause an adverse effect. For superhydrophobic chemicals, measuring and using LC_{50} values is challenging, and extrapolating them to environmental conditions is difficult because of the necessarily low exposure concentrations in water and the likely low bioavailability because of sorption to organic surfaces. The use of internal or body burden concentrations in organisms is clearly easier and more reliable, but it requires monitoring data for representative organisms to assess the proximity to levels of concern. Applying mass balance models to simulate exposures under test conditions both prospectively and retrospectively, as illustrated here by taking into account estimates of CBR, ILC_{50}, required exposure times, and solubility limits, can, even if the results are only approximate, assist in the design of more effective regulatory tests and avoid the excessive cost and animal usage incurred when tests prove to be fruitless.

Standard bioconcentration and toxicity tests have the considerable advantage that they can be conducted under reproducible conditions. In the case of superhydrophobic chemicals, a cautionary note is warranted because of the severe experimental difficulties with laboratory testing and it may be impossible to obtain the conventionally desired empirical data. Ultimately, the goal is to obtain and interpret monitoring data from impacted ecosystems, supplemented with laboratory data and consistent mass balance modeling of chemical fate and possible effects.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.5b03195.

Additional text, figures, and tables as noted in the text (PDF)

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