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Risk Assessment and Regulation of D5 in Canada

BIOACCUMULATION OF DECAMETHYLPENTACYCLOSILOXANE (D5): A REVIEW

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Abstract: Decamethylpentacyclosiloxane (D5) is a widely used, high–production volume personal care product with an octanol–water partition coefficient (log K_{OW}) of 8.09. Because of D5's high K_{OW} and widespread use, it is subject to bioaccumulation assessments in many countries. The present study provides a compilation and an in-depth, independent review of bioaccumulation studies involving D5. The findings indicate that D5 exhibits depuration rates in fish and mammals that exceed those of extremely hydrophobic, nonbiotransformable substances; that D5 is subject to biotransformation in mammals and fish; that observed bioconcentration factors in fish range between 1040 L/kg and 4920 L/kg wet weight in laboratory studies using non-radiolabeled D5 and between 5900 L/kg and 13 700 L/kg wet weight in an experiment using C^{14} radiolabeled D5; and that D5 was not observed to biomagnify in most laboratory experiments and field studies. Review of the available studies shows a high degree of internal consistency among findings from different studies and supports a broad comprehensive approach in bioaccumulation assessments that includes information from studies with a variety of designs and incorporates multiple bioaccumulation measures in addition to the K_{OW} and bioconcentration factor. *Environ Toxicol Chem* 2015;34:2703–2714. © 2015 The Authors. *Environmental Toxicology and Chemistry* Published by Wiley Periodicals, Inc. on behalf of SETAC.

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INTRODUCTION

Decamethylpentacyclosiloxane (D5) is a high–production volume substance that is widely used globally in personal care products such as suntan lotions and shampoos [1,2]. Because of widespread use and hydrophobicity, D5 is subject to environmental evaluations in many countries [3,4]. A comprehensive evaluation of the environmental behavior of D5 in Canada was recently completed by the Siloxane D5 Board of Review established under section 333(1) of the Canadian Environmental Protection Act 1999 [5]. The final conclusion reached by the Board of Review and accepted by the Minister of the Environment [6] was that D5 does not pose a danger to the environment or its biological diversity. This conclusion ran counter to the initial assessment by Environment Canada [7], which considered D5 persistent, bioaccumulative, inherently toxic, and toxic as defined by the Canadian Environmental Protection Act. This illustrates the challenges that can be encountered in the use and interpretation of scientific information in the regulatory process and emphasizes the need for development of practices that improve the evaluation of environmental fate and toxicity data, including collaborative efforts between industry and regulators to generate accurate and consistent data when needed [8].

Although evaluations of commercial chemicals vary among jurisdictions, most include an assessment of the persistence, bioaccumulation, toxicity, and risk of the chemical. The goal of this review is to compile and review empirical studies of the bioaccumulation behavior of D5 with the aim of providing information that is useful in the categorization of D5 for bioaccumulation. Similar efforts addressing persistence, toxicity, and risk of D5 are discussed in accompanying studies in the present issue of *Environmental Toxicology and Chemistry* [8–10].

Several international and national regulations address the bioaccumulation of substances and provide criteria to determine whether a substance is bioaccumulative in a regulatory context. At the international level, the United Nations Stockholm Convention on Persistent Organic Pollutants (POPs) [11] provides 3 criteria to identify a substance as being bioaccumulative in Annex D: 1) evidence that the bioconcentration factor or bioaccumulation factor in aquatic species for the chemical is greater than 5000 L/kg wet weight or, in the absence of such data, that the octanol–water partition coefficient (log K_{OW}) is greater than 5; 2) evidence that a chemical presents other reasons for concern, such as high bioaccumulation in other species, high toxicity, or high ecotoxicity; or 3) monitoring data in biota indicating that the bioaccumulation potential of the chemical is sufficient to justify its consideration within the scope of the Convention.

In Canada, the United States, the European Union, and Japan, bioaccumulation is addressed in, respectively, the Canadian Environmental Protection Act [12]; the Toxic Substances Control Act [13]; Regulations on the Registration, Evaluation, Authorization and Restriction of Chemicals [14]; and the Japanese Chemical Substances Control Law [15] (Table 1). The regulations identify criteria for bioaccumulative substance that are expressed in terms of the bioconcentration factor (BCF), the K_{OW} value, and (in Canada) the bioaccumulation factor (BAF; Table 1). Table 1 illustrates that the criteria values for the BCF and K_{OW} in Canada, the United States, the European Union, and Japan mimic those in the United Nations

All Supplemental Data may be found in the online version of this article.

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Table 1. An overview of selected regulations for bioaccumulation assessment of commercial chemicals, including bioaccumulation measures, criteria, and references

Regulation	Bioaccumulation measure	Criteria	Reference
Canadian Environmental Protection Act	K_{OW}	≥100 000	Government of Canada [12]
Canadian Environmental Protection Act	BCF	≥5000	Government of Canada [12]
Canadian Environmental Protection Act	BAF	≥5000	Government of Canada [12]
Regulations on the Registration, Evaluation, Authorization and Restriction of Chemicals	BCF	≥2000[a]	Annex XII [14]
Regulations on the Registration, Evaluation, Authorization and Restriction of Chemicals	BCF	≥5000[b]	Annex XII [14]
Toxic Substances Control Act and Toxic Release Inventory program	BCF	1000–5000[c]	TSCA [13]
Toxic Substances Control Act and Toxic Release Inventory program	BCF	≥5000[d]	TSCA [13]
UNEP Stockholm Convention on Persistent Organic Pollutants	K_{OW}	≥100 000	UNEP [11]
UNEP Stockholm Convention on Persistent Organic Pollutants	BCF	≥5000	UNEP [11]
Japanese Chemical Substances Control Law	BCF	1000–5000[e]	Japanese Ministry of the Environment [15]
Japanese Chemical Substances Control Law	BCF	<1000[f]	Japanese Ministry of the Environment [15]
Japanese Chemical Substances Control Law	K_{OW}	<3200[f]	Japanese Ministry of the Environment [15]

[a]Criteria values for "bioaccumulative" substances.
[b]Criteria values for "very bioaccumulative" substances.
[c]Criteria values for "bioaccumulative" substances.
[d]Criteria values for "very bioaccumulative" substances.
[e]Judgment considering other bioaccumulation potential tests.
[f]Not highly bioaccumulative.
K_{OW} = octanol–water partition coefficient; BCF = bioconcentration factor; BAF = bioaccumulation factor; TSCA = Toxic Substances Control Act; UNEP = United Nations Environment Programme.

Stockholm Convention on POPs, although alternate criteria values are also used. Regulations for bioaccumulative substances in Canada, the United States, and the European Union do not include criteria similar to the second and third criteria in the Stockholm Convention on POPs.

The practice of relying only on the BCF and K_{OW} to determine the bioaccumulative potential of a chemical substance can have some consequences of concern. For example, Kitano [16] reported that 5 of the current 21 chemicals listed as POPs by the United Nations exhibit a BCF less than 5000 L/kg wet weight but were considered bioaccumulative by the United Nations because these substances met the 2 non-K_{OW} and BCF criteria in the Convention (Table 1). This indicates that the BCF and K_{OW} are not always sufficient for correctly identifying bioaccumulative substances. Kelly et al. [17] showed that, as a result of their high octanol–air partition coefficient values, some chemicals that have a log K_{OW} less than 5 and BCFs less than 5000 L/kg wet weight and that do not biomagnify in water-breathing organisms can be highly bioaccumulative in food webs that include air-breathing organisms. Modeling studies by Czub and McLachlan [18], Kelly et al. [19], and others have further substantiated the limitations of K_{OW} and the BCF in correctly identifying a chemical's bioaccumulation behavior in diverse food webs. These studies indicate that the bioaccumulation behavior of many chemicals may not be adequately assessed by the BCF and K_{OW} alone. The studies further suggest that it is important to take a more comprehensive approach in evaluating the bioaccumulation behavior of chemicals in bioaccumulation assessments. Such an approach includes information on the BCF and K_{OW} but also on other bioaccumulation metrics, such as the biomagnification factor (BMF), the biota–sediment accumulation factor (BSAF), trophic magnification factors (TMF), and elimination and biotransformation rates. This broader approach was also adopted by the Board of Review for D5 in its evaluation of the bioaccumulation behavior of D5. Incorporating all available data in risk assessment can be expected to increase the weight of evidence of the risk assessment. The latter also has been recognized by Burkhard et al. [20], who have proposed methods to accomplish this.

Although a more comprehensive approach to the use of scientific information in bioaccumulation assessments may lead to better assessments, the application of this approach has some significant challenges. The first challenge is to ensure that the studies are of good quality and are recognized for their contributions to enhancing understanding of bioaccumulation as well as their limitations and to take into account that studies are conducted for different purposes, use various methods, and apply technologies characteristic of their times. The second challenge is to compare and evaluate data of different kinds and find internal consistency among a variety of data. In the present study, we have compiled and reviewed studies on the bioaccumulation of D5. This involved an in-depth, independent review of all available (known to us) and publicly accessible bioaccumulation data for D5, including a reanalysis of original data whenever possible. The goal of the present study was to develop a coherent and internally consistent profile of the bioaccumulation behavior of D5. We hope that this approach will contribute to a comprehensive approach to the bioaccumulation assessment of D5. In an accompanying study [10], we have applied a fugacity- and activity-based analysis to further evaluate and characterize the bioaccumulation of D5.

METHODS

Review

All studies of the bioaccumulation of D5 (known to us) were compiled, reviewed, and evaluated following guidelines described in Arnot and Gobas [21] for water analysis methodology, use of radiolabeled test chemicals, exposure concentrations in relation to the aqueous solubility, duration of exposure, tissue analysis method, application of Organisation for Economic Co-operation and Development (OECD) guideline 305 [22], the use of co-solutes and/or co-solvents, and the use of reference chemicals (Supplemental Data, Table S1). When possible, bioaccumulation metrics were recalculated

from the original data (when available). This involved determination of the uptake (k_1) and depuration (k_T) rate constants and derivation of the BCF and BMF at steady state by calculating the degree (in %) to which steady state was attained at the end of the uptake phase (t) of the experiments (as SS%)

$$SS\% = (100\%) \times (1 - \exp[-k_T \times t]) \quad (1)$$

Because no studies provided measurements of the bioavailable concentration in the water, reported concentrations in water were not corrected for bioavailability. Given D5's organic carbon–water partition coefficient ($\log K_{OC}$) of 5.17, it can be estimated (following Arnot and Gobas [21]) that, at the maximum accepted concentration of total organic carbon in water of 2 mg/L in an OECD 305 bioconcentration testing protocol, the fraction of freely dissolved D5 in water is approximately $1/(1 + 2.10^{-6} \times 10^{5.17}) = 0.77$, or 77%, and higher if total organic carbon concentrations in water are less than 2 mg/L.

As part of the present review, TMFs were calculated from wet weight–based concentrations, lipid contents, and trophic positions provided by the authors. The TMFs were derived using all reported concentrations for all samples or mean reported concentrations for each sampled species. The first method (all reported concentrations) tends to increase statistical power required to detect a TMF greater than 1 [23], whereas the second method reduces experimental artifacts caused by "unbalanced" sampling designs attributable to unequal replication in which certain species of the food web are sampled at a greater frequency than other species [24,25]. In the calculation of the TMF, all reported concentration data were used in the regression; concentrations below the detection limit were not considered in the regression; an increase in the N^{15}/N^{14} nitrogen isotope ratio of 0.34% was considered to correspond to an increase in trophic level by 1 trophic position; a simple linear regression in Excel was used to derive the TMF; statistical significance was assessed by the p value ($p = 0.05$) of the slope of the linear regression of the logarithm of the lipid-normalized concentration and trophic position.

Reports not yet published in the peer-reviewed scientific literature are provided in the Supplemental Data.

Bioaccumulation modeling

Bioaccumulation models formalize the mechanistic understanding of the bioaccumulation process. A comparison of model predictions with experimental data can help to gain further insights into the bioaccumulation behavior of D5. We therefore applied the AquaWeb model [26] to estimate the depuration rate constant, BCF, BMF, BSAF, and TMF of D5, assuming that D5 does not biotransform in biota. To be able to compare the model calculations with the experimental data, we parameterized the model to represent organisms of the same weight and lipid content and held under the same environmental conditions as those used in the experimental studies. The model input parameters are detailed in Supplemental Data, Table S2. To calculate the TMF, the AquaWeb model was parameterized to represent a food web used by the US Environmental Protection Agency in its K_{OW}-based Aquatic BioAccumulation Model [27] to evaluate the bioaccumulation of pesticides in aquatic systems. This food web consists of phytoplankton, zooplankton, 2 benthic invertebrate species, and 3 fish species of different sizes and spans trophic positions, calculated according to the trophic position model of Vander Zanden and Rasmussen [28], from 1 to 5. The model parameters that were used are summarized in Supplemental Data, Tables S2 to S7.

RESULTS

Bioconcentration

Bioconcentration is the process of chemical bioaccumulation from the water via the respiratory and dermal surfaces of the animal. Bioconcentration studies are conducted under laboratory conditions in which organisms are exposed to test chemicals in water but not the diet. Information on the bioconcentration of D5 is available from 4 experimental studies: Opperhuizen et al. [29], Annelin and Frye [30], Drottar [31], and Parrott et al. [32]. An overview of the evaluation of the studies using guidelines developed by Arnot and Gobas [21] is presented in Supplemental Data, Table S1. The studies differed considerably in terms of their objectives, methodologies, and reporting details. All studies were deemed to provide useful information on the bioconcentration of D5 and were considered in the present review.

Opperhuizen et al. [29] conducted a bioconcentration test of D5 in the presence of a mixture of linear and cyclic siloxanes in 0.17-g (± 0.03 g standard deviation [SD]) guppies (*Poecilia reticulata*) with a lipid content of 6.5% (± 2.5% SD) for 20 d. The study methodology did not conform with OECD guideline 305 [22] in terms of study duration, chemical concentration dosing, and reporting of experimental test conditions. However, the study design included an experiment with 2,2′,5,5′-tetrachlorobiphenyl (polychlorinated biphenyl [PCB]-52), which because of its well-known bioaccumulation behavior can act as a reference compound. Also, concentrations of chemicals were determined by gas chromatography with mass spectrometric detection (GC/MS), which distinguishes between parent D5 and its metabolites. The study involved very small fish, which can be expected to achieve steady state quickly, justifying the exposure duration of 20 d for D5 and 13 d for PCB-52, which are shorter than the 28 d recommended by the OECD guideline. The authors reported that their continuous-flow saturation experiment produced apparent supersaturated concentrations for mixtures of siloxanes but not for individual siloxanes. The authors report a half-life time of D5 ($\log K_{OW} = 8.09$ [8]) in the fish of 3.9 d, corresponding to a depuration rate constant of ln(2)/3.9, or 0.18 d^{-1}, whereas in the same study but in a different experiment, the half-life time of PCB-52 ($\log K_{OW} = 5.9$ [33]) was more than 40 d, corresponding to a depuration rate constant of ln(2)/40, or less than 0.017 d^{-1}. The experimental feeding rate of 2.5% of the body weight of the fish per day, or 0.025 d^{-1}, can be expected to produce a maximum possible growth rate (assuming a food assimilation of approximately 50% [34] and no energy allocation for animal maintenance) of 0.5×0.025, or 0.0125 d^{-1}, which accounts for less than 7% of the depuration of D5 in the fish. The data illustrate that the depuration rate of D5 is much faster than that of PCB-52.

The depuration rate constants for D5 and PCB-52 indicate that, at the end of the 13-d exposure period, approximately (1–exp[–0.18 × 20]), or 97%, of steady state was achieved for D5 and (1–exp[–0.017 × 13]), or 20%, of steady state was achieved for PCB-52. These percentages can be used to correct the reported BCFs to 1040 L/kg wet weight and 27 000 L/kg wet weight for D5 and PCB-52, respectively. The corresponding BCFs, normalized to fish with a 5% lipid content, are 800 L/kg for D5 and 21 000 L/kg wet weight for PCB-52. The BCF of D5 determined in the test is much smaller than that of PCB-52. The

difference between the BCFs of D5 and PCB-52 appears to be consistent with the difference in depurations rates of D5 and PCB-52 as expressed by the half-life times, which are approximately 3.9 d and more than 40 d, suggesting that differences in depuration rates may have been the main cause of the difference in the observed BCFs. The study further reported the detection of possible metabolites of D5 while emphasizing that observations of the apparent formation of unknown chemicals cannot be treated as proof of the occurrence of biotransformation by fish.

The study by Annelin and Frye [30] involved a 28-d bioconcentration study of D5 in 0.9-g to 1.7-g rainbow trout (*Oncorhynchus mykiss*), using a continuous-flow system to deliver D5 (in absence of a surfactant) to the water and using gas chromatography with flame ionization detection for chemical analysis. The study methodology did not conform with OECD guideline 305 [22]. The authors did not report BCF values but discussed attainable uptake values due to the experimental difficulty of accurately measuring concentrations in water. In the bioconcentration test, the D5 concentration in the water decreased from the initial concentration of 20 μg/L, which is in good agreement with the reported aqueous solubility of D5 of 17 μg/L, to approximately 4 to 5 μg/L and then increased to between 10 μg/L and 20 μg/L after 28 d exposure.

Concentrations of D5 in the fish increased over time and reached an apparent steady state value at a reported concentration of approximately 19 500 ± 8400 μg/kg wet weight after approximately 10 d. An estimate of the BCF can be derived from these observations at a value of approximately 19 500/5.5 or 3500 L/kg wet weight. The half-life time, determined as the time to achieve 50% of the steady state D5 concentration in the fish, was approximately 8 d, indicating a depuration rate constant of approximately 0.09/d. Hence, at the end of the 28-d exposure period, approximately 92% of steady state was achieved to give an adjusted BCF for D5 of 3800 L/kg wet weight. A BCF for a fish with a 5% lipid content could not be calculated because the lipid content of the fish was not reported. The authors further reported being skeptical of the ability of fish to biotransform methyl siloxanes suggested by Opperhuizen et al. [29], because they found no evidence of biotransformation. However, the gas–liquid chromatographic assays used by Annelin and Frye [30] for making measurements of siloxane metabolites in this study were developed for siloxane metabolites within the mg/kg range [35], whereas concentrations of D5 in water were in the μg/kg range, with siloxane metabolites to be expected at even lower concentrations. Therefore, any possible D5 metabolites may have been below the detection limit.

Drottar [31] conducted a bioconcentration test of C^{14}-labeled D5 in 1.4-g fathead minnows (*Pimephales promelas*), with an initial 2.9% lipid content using a flow-through system for the delivery of D5. The study followed OECD guideline 305E [22] and included 2 duplicate independent experiments using concentrations of D5 in the water of approximately 17 μg/L (i.e., equal to the aqueous solubility of D5) and 1.7 μg/L. Constant aqueous D5 concentrations and dissolved oxygen concentrations (5.6–7.2 mg O_2/L) were maintained at 22.5 °C. Liquid scintillation counting was used as the method for determining the D5 concentrations in water and fish. This method of analysis does not distinguish between D5, D5 metabolites, and assimilated C^{14} by the fish. However, further metabolite characterization indicated that approximately 83% of the radioactivity in the fish samples was in the form of parent D5 [31]. Because hydrolysis of D5 in water at neutral pH is slow and the replacement rate of water in the test was high, the authors assumed that the radioactivity determined in the water samples was predominantly from D5. Throughout the duration of the bioconcentration experiment, the fish did not increase in weight (Supplemental Data, Figure S1). This implies that any depuration of D5 from the fish cannot be attributed to growth dilution. Despite the lack of somatic growth, the fish lipid content increased throughout the duration of the test from 2.9% to 5.2% in a linear fashion (Supplemental Data, Figure S2). Because the lipid content can affect the depuration rate, the overall depuration rate constant was derived from both wet weight and lipid-normalized D5 concentration data. In the bioconcentration experiment conducted at the lower exposure concentration of 1.7 μg/L, the overall depuration rate constant of D5 in fish was 0.024 d^{-1} (± 0.004 d^{-1} standard error [SE]) based on the wet weight concentrations and 0.029 d^{-1} (± 0.004 d^{-1} SE) based on lipid-normalized concentrations. The change in lipid content in the fish only appeared to have a small effect on the determination of depuration rate constant. The depuration rate constant of 0.029 d^{-1} indicates that at the end of the 35-d uptake period only (1–exp[–0.029 × 35]), or 64%, of steady state was achieved. Hence, the BCF of 7060 L/kg wet weight calculated from total concentrations measured at the end of the bioconcentration test can be considered an underestimate of the true steady state BCF. Nonlinear regression of the apparent combined concentrations of D5 in the fish during the uptake phase produced an uptake rate constant for D5 of 394 L kg^{-1} d^{-1} and an estimate of the kinetic BCF (k_1/k_2) for D5 (adjusted for an average lipid content of 3.8%) of 13 700 L/kg wet weight, very close to the value of 13 300 L/kg wet weight reported in Drottar [31]. This BCF represents not only D5 but also the combined sum of D5, D5 metabolites, and assimilated ^{14}C in the fish. The D5 concentration data in the depuration phase of the bioconcentration experiment conducted at the higher exposure concentration of 17 μg/L show that the overall depuration rate constant of D5 in fish was 0.014 d^{-1} (± 0.003 d^{-1} SE) based on wet weight concentrations and 0.019 d^{-1} (± 0.003 d^{-1}SE) based on lipid-normalized concentrations. The depuration rate constant of 0.019 d^{-1} indicates that only 48% of steady state was achieved at the end of the uptake period. Nonlinear regression of the concentration data during the uptake phase produced an uptake rate constant for D5 of 110 L kg^{-1} d^{-1} and a kinetic BCF for D5 (adjusted for average lipid content of 3.8%) of 5900 L/kg wet weight, very close to the value reported in Drottar [31] of 5300 L/kg wet weight.

The BCFs of D5 were also measured by Parrott et al. [32] in an extended fathead minnow embryo-larval stage assay involving 65-d exposures—5-d exposure in the egg stage and 60-d exposure in the larval stage to D5 at 5 different aqueous concentrations in the presence of 20 μL/L dimethylsulfoxide. Concentrations of D5 were kept relatively constant and below the aqueous solubility of D5 throughout the test. Concentrations of D5 in water were measured and were 35% of nominal concentrations. The authors used GC/MS as the method for detection. No depuration phase was associated with this experimental design. The authors reported "few effects" of D5 in fathead minnow embryos, larvae, or juveniles. Survival and hatching of eggs and survival of fish was within the normal range. The study methodology did not follow OECD guideline 305 [22]. The BCFs reported for the various aqueous concentrations of D5 were between 2330 and 5970 after 28 d, 2060 and 5490 after 48 d, and 2919 and 8190 after 65 d. The authors concluded that the BCF in fathead minnows was 4450 for the lowest environmentally relevant concentrations of D5 in water and 4920 for all D5 exposure concentrations tested.

Because lipid content can be an important factor affecting the BCF, the authors also reported lipid-normalized BCFs between 91 000 and 460 000 and estimated an average BCF for a 5% lipid fish of 11 600. At the mean concentration of D5 in water of 0.864 μg/L, reported BCFs for D5 were 5010 (± 1600), 5180 (± 2600), and 3320 (± 690) for fish with lipid contents of, respectively, 1.08%, 2.36%, and 3.2% (Supplemental Data, Figure S3); at a mean concentration of 3.10 μg/L, reported BCFs for D5 were 5970 (± 2300), 4770 (± 1700), and 7950 (± 3500) for fish with lipid contents of, respectively, 1.64%, 1.89%, and 4.65% (Supplemental Data, Figure S4). The apparent lack of a simple proportional relationship between the BCF of D5 and lipid content of the fathead minnow in Parrott et al. [32] (Supplemental Data, Figures S3 and S4) indicates caution in the use and interpretation of the BCF normalized to 5% lipid content. A summary of the depuration rate constants and BCFs from the bioconcentration studies is illustrated in Figures 1 and 2.

Biomagnification

The BMF is defined as the ratio of the chemical concentrations in an animal and the animal's diet. Most authors prefer the use of ratios of appropriately normalized chemical concentrations, such as lipid-normalized concentrations for lipophilic substances (such as D5), because it provides a simple method to determine whether biomagnification occurred in a thermodynamic sense as an increase in chemical potential in the predator compared with that in the prey. A concentration ratio greater than 1 indicates the occurrence of biomagnification. Biomagnification factors can be determined in laboratory tests and in field studies. When measured in laboratory-based biomagnification experiments, BMFs represent dietary uptake only because the water in the test does not contain the test chemical. In contrast, BMFs measured in field studies represent uptake via all possible uptake routes, including uptake from water. Laboratory-based biomagnification studies of D5 in fish have been carried out by Opperhuizen et al. [29] and Drottar [36], with additional re-analyses by Woodburn and Domoradzki [37] and published in Woodburn et al. [38]. A BMF based on a field study of D5 was derived by Kierkegaard et al. [39] and is discussed in the section *Bioaccumulation in nonaquatic organisms*.

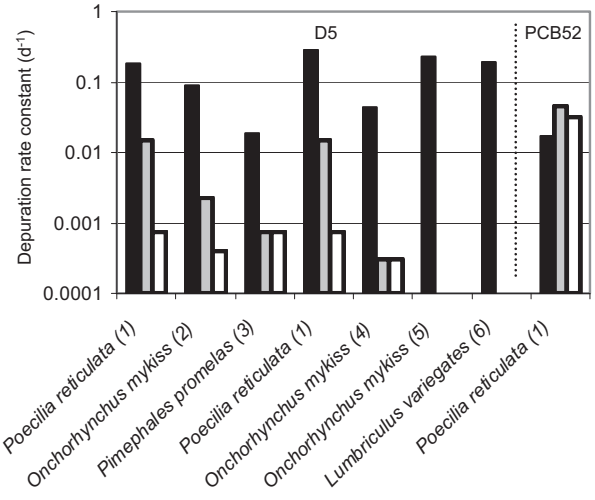

Figure 1. Depuration rate constants (d^{-1}) of decamethylpentacyclosiloxane (D5) and polychlorinated biphenyl (PCB)-52 in several fish and 1 invertebrate species observed in laboratory tests (solid black bars) and calculated by the AquaWeb model for the experimental conditions in the test assuming no D5 biotransformation. Gray bars include growth dilution, whereas white bars exclude growth dilution in model calculated depuration rate constants. Animal body weight is given in Supplemental Data, Table S2. Experimental data are from the following sources: 1 = Opperhuizen et al. [29]; 2 = Annelin and Frye [30]; 3 = Drottar [31]; 4 = Drottar [36]; 5 = Springer [48]; 6 = Krueger et al. [43].

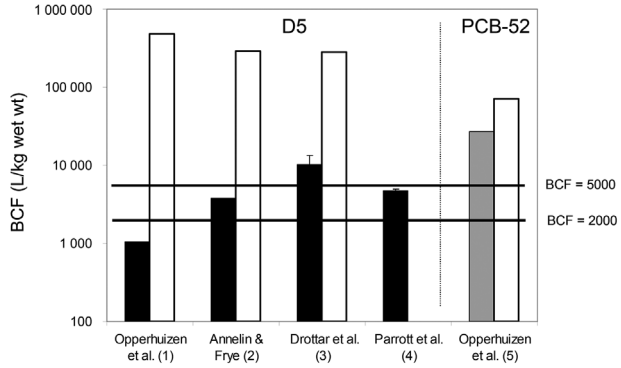

Figure 2. Bioconcentration factors (BCFs; L/kg wet wt) of decamethylpentacyclosiloxane (D5) and polychlorinated biphenyl (PCB)-52 observed in laboratory tests with different fish species (solid black bars for D5, gray bar for PCB-52) and calculated by the AquaWeb model for the experimental conditions in the test assuming no D5 biotransformation (white bars). The solid lines represent the bioconcentration criteria values of 2000 L/kg and 5000 L/kg wet weight. AquaWeb model calculations could not be carried out for the fathead minnow embryo–larval stage in the Parrott et al. study [32] because it is not within the model's domain. The error bar illustrates the range of experimental data. Experimental data are from the following sources: 1 = Opperhuizen et al. [29]; 2 = Annelin and Frye [30]; 3 = Drottar [31]; 4 = Parrott et al. [32]; 5 = Opperhuizen et al. [29].

Opperhuizen et al. [29] reported several dietary bioaccumulation studies. One experiment involved a 67-d dietary exposure of goldfish to a mixture of polydimethylsiloxanes that included both linear and cyclic polydimethylsiloxanes, including D5. A second 12-wk study investigated the dietary bioaccumulation of a mixture of polydimethylsiloxanes including D5 in guppies with PCB-52 added as a reference chemical. Chemical analysis was by GC/MS. The BMF of D5 derived from the concentrations of D5 in fish and food was 0.05 kg food/kg fish or 0.08 kg lipid/kg lipid, and in the same experiment the BMF of PCB-52 was determined to be 1.4 kg food/kg fish or 2.2 kg lipid/kg lipid. The authors suggested that the low BMFs of all polydimethylsiloxanes (including D5) in the study were attributable to rapid clearance rather than slow uptake. The results of the study by Opperhuizen et al. [29] were consistent with reported results of an earlier preliminary study by Bruggeman et al. [40].

The study by Drottar [36] published in Woodburn et al. [38] involved a laboratory-based experiment in which rainbow trout (lipid content, 5.64 ± 1.5%) were fed 458 ± 5.8 μg D5/g contaminated food (lipid content, 14.8%) at a rate of 0.03 g food/g fish/ d for 35 d while being exposed to clean water without detectable D5 concentrations. In a subsequent elimination experiment, concentrations of D5 in the fish decreased exponentially over time in accordance with a fish–water 2-compartment model. The authors reported an empirical steady state BMF based on an empirical elimination rate constant calculated from a period of no significant fish growth in the depuration phase (days 0–7) of 0.85 ± 0.26 kg lipid/kg lipid and a kinetic BMF of 3.4 ± 1.4 kg lipid/kg lipid. The authors reported a growth-corrected half-life time for D5 of 69 d, corresponding to a depuration rate constant of 0.010 d^{-1}. The reported growth dilution rate constants were 0.0351 d^{-1}

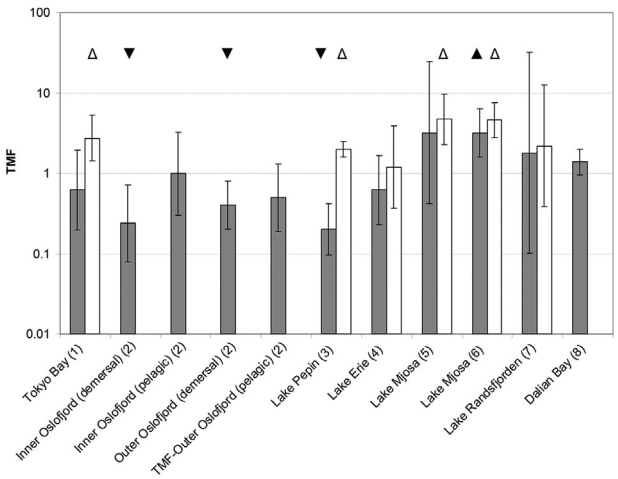

Figure 3. Trophic magnification factor (TMF) of decamethylpentacyclosiloxane (D5; gray bars) and polychlorinated biphenyl (PCB)-153 or PCB-180 (for Lake Erie only) (white bars) in various aquatic food webs. Error bars represent 95% confidence intervals. The TMFs presented are based on mean concentrations (data listed in Table S1). Trophic magnification factors less than 1 represent trophic dilution; TMFs greater than 1 represent biomagnification in the food web. Filled symbols represent an observed TMF for D5 that is significantly ($p < 0.05$) less than 1 (solid triangle pointing down) or greater than 1 (solid triangle pointing up). Open symbols represent an observed TMF for a PCB congener that is significantly ($p < 0.05$) greater than 1(open triangle pointing up). The empirical data are from the following sources: 1 = D.E. Powell et al., Dow Corning, Midland, MI, USA, unpublished manuscript; 2 = Powell et al. [61]; 3 = Powell et al. [60]; 4 = McGoldrick et al. [59]; 5 = Borgå et al. [57]; 6 = Borgå et al. [58]; 7 = Borgå et al. [58]; 8 = Jia et al. [62].

for the uptake phase and 0.0264 d^{-1} [38]. The depuration rate constant including an average growth dilution rate constant of 0.031 d^{-1} can then be estimated at approximately $0.01 + 0.031 = 0.041$ d^{-1} or a half-life time of 17 d. Including growth dilution for inter-comparison with other BMFs from other studies produces a kinetic BMF of 0.83 kg lipid/kg lipid. The BMFs are illustrated in Figure 3.

Bioaccumulation

Bioaccumulation factors are ratios of steady state concentrations of chemicals in aquatic organisms and water determined under conditions in which the organisms are exposed to the chemical of interest through all sources of exposure, including water and diet. A BAF is different from a BCF in that bioconcentration tests do not involve dietary exposure but only exposure via the water. Bioaccumulation factors are typically measured in the field, where animals are naturally exposed to the chemical via the water and diet. They also can be measured in the laboratory, but creating chemical concentrations in water and diet representative of those in the field can be difficult.

Norwood et al. [41] report BAFs of D5 determined in a study of the chronic toxicity and bioaccumulation of D5 in the amphipod *Hyalella azteca* exposed to D5 in spiked freshwater sediments with the main goal of determining the toxicity of D5 to *H. azteca*. *Hyalella azteca* were exposed for 28 d to 6 concentrations of D5 in 2 different natural sediments containing 0.5% and 11% organic carbon. The D5 concentrations in the sediments ranged from 40 000 μg/g organic carbon dry weight to 600 000 μg/g organic carbon dry weight and exceeded the apparent sorption capacity of D5 in organic carbon, estimated from the K_{OC} of D5 of $10^{5.17}$ L/kg organic carbon, as 17 μ/L × $10^{5.17}$ = 2500 μg/g organic carbon dry weight [8]. It is therefore likely that undissolved liquid D5 was present in the test system, perhaps coating sediment surfaces. This may explain the authors' conclusion that "the BAFs for siloxane D5 were not reliable" [41]. We therefore have not further considered the reported BAFs in Norwood et al. [41] in this review.

Biota sediment accumulation

Decamethylpentacyclosiloxane also has been the subject of bioaccumulation studies in sediment-dwelling benthic invertebrates. The magnitude of chemical bioaccumulation from sediments is often expressed by the BSAF, which has units of kg sediment dry weight/kg organism wet weight or kg organic carbon/kg lipid. Organic carbon has an average sorptive capacity for many chlorinated organic chemicals (such as PCBs) that is approximately 35% of that of octanol [42], a surrogate for lipids. As a result, a BSAF of 1/0.35 or 2.9 kg organic carbon/kg lipid indicates a thermodynamic equilibrium between concentrations in sediment and organism. The K_{OC} of D5 of $10^{5.17}$ L/kg organic carbon indicates that D5 has a much lower sorption capacity for organic carbon than many other hydrocarbons of similar K_{OW} [8]. In essence, D5 is $10^{8.09}/10^{5.17}$ (K_{OW}/K_{OC}), or 832 times more soluble in octanol than in organic carbon. In comparison, PCBs are only approximately 3 times more soluble in octanol than in organic carbon. This implies that thermodynamic equilibrium between concentrations in sediment and organisms is achieved when the BSAF is 832 kg organic carbon/kg lipid. A BSAF greater than 832 kg organic carbon/kg lipid indicates biomagnification.

Krueger et al. [43] reported on a laboratory-based bioaccumulation test of D5 in *Lumbriculus variegatus* exposed to sediments spiked with D5 following OECD guideline 218 [44]. The study involved a 28-d sediment uptake phase followed by a 22-d depuration phase. Two sublethal test concentrations of 20 μg/g dry weight and 336 μg/g dry weight were used. The authors analyzed D5 concentrations using gas chromatography with flame ionization detection. Both experiments showed depuration half-life times of 3.6 d and 3.4 d, corresponding to depuration rate constants of 0.19 d^{-1} and 0.20 d^{-1}, respectively. This illustrates that the 28-d uptake period was sufficiently long to achieve steady state (SS % = 99.6%). Although depuration rates of D5 in the 2 experiments were similar, the uptake rate constants measured in the 2 experiments differed substantially—0.83 kg dry weight kg^{-1} wet weight d^{-1} in the experiment with the lower D5 concentration and 0.092 kg dry weight kg^{-1} wet weight d^{-1} in the experiment with the higher D5 concentration. This difference is likely attributable to the fact that the higher D5 concentration in the sediment of 336 μg/g was greater than the apparent sorption capacity of D5 in the test sediment of 75 μg/g dry weight, or the product of the aqueous solubility of D5 (17 μg/L), the K_{OC} of D5 ($10^{5.17}$), and the fraction of organic carbon (3%) in the sediment [8].

Therefore, it is possible that undissolved D5 was present and the experimental exposure was not representative of most environmental exposures. The BSAF determined in the experiment with the lower 20 μg/g concentration is therefore 0.83 kg dry weight kg^{-1} wet weight d^{-1} / 0.19 d^{-1} or 4.4 kg dry weight sediment/kg wet weight. Because the organic carbon content in the sediments was 3% and the lipid content of the oligochaetes was 1.86%, the lipid- and organic carbon–normalized BSAF was $4.4 \times 0.03/0.0186 = 7.1$ kg organic carbon/kg lipid, which is below the thermodynamic equilibrium value for the BSAF of 832 kg organic carbon/kg lipid. The lack of attaining equilibrium might have been caused by a

combination of biotransformation and growth dilution. For very hydrophobic substances, such as D5 ($\log K_{OW} = 8.09$), which are also less sorptive in organic carbon than in lipids, diffusively controlled elimination rate constants (e.g., 0.0001 d^{-1}) are likely very small, causing even a low biotransformation rate constant (e.g., 0.01 d^{-1}) to result in a major departure (approximately 100-fold in this example) from equilibrium.

Bioaccumulation in nonaquatic organisms

Although assessment of bioaccumulation is typically limited to water-breathing aquatic organisms such as fish, it is important to consider bioaccumulation in air-breathing organisms such as marine and terrestrial mammals and birds. Kelly et al. [17,19] have demonstrated that the bioaccumulation behavior of neutral hydrophobic organic substances in air-breathing organisms is often related to the octanol–air partition coefficient (K_{OA}) of the substance. Substances with low octanol–air partition coefficients can be exhaled quickly and hence exhibit a lower potential for bioaccumulation. Andersen et al. [45] found that D5 was quickly depurated in rats and humans by exhalation as a result of D5's high vapor pressure and relatively low K_{OA}. In addition, Varaprath et al. [46] showed extensive biotransformation of D5 in Fisher 344 rats that were intravenously and orally exposed to D5. The high rate of depuration of D5 through exhalation and biotransformation indicates that D5 does not have a potential for biomagnification in air-breathing organisms or terrestrial food webs. Based on concentrations of D5 in 2 samples of herring (*Clupea harengus*) and 3 blubber samples from drowned gray seals (*Halichoergus grypus*) from the Baltic Sea, Kierkegaard et al. [47] concluded that D5 did not biomagnify in gray seals because of rapid metabolism and pulmonary elimination.

Biotransformation

Biotransformation (i.e., the transformation of substances in biota) of D5 has been studied in fish and rats. Springer [48] conducted a 96-h study of the elimination and biotransformation of orally gavaged radiolabeled D5 in 3 mature 1- to 1.4-kg rainbow trout. Samples of blood from fish were collected via an aortic cannula at selected points after an oral bolus dose of C^{14} radiolabeled D5 in corn oil. The highest concentrations of C^{14} were found in the bile of the fish, with only 4% of the total C^{14} being parent D5. In the liver, 46% of the measured radioactivity was parent D5, whereas in the intestinal tract 50% of the radioactivity was identified as parent D5. All radioactivity detected in the urine was attributable to biotransformation products of D5. The study reported a half-life of radioactivity of 2.9 d corresponding to a rate constant of 0.23/d and that 14% of recovered dose of D5 in the fish were metabolites of D5. Based on the results of this study [48], Woodburn and Domoradzki [37] calculated a whole-fish biotransformation rate constant of 0.17/d from the measured concentrations of D5 in blood over time, based on the assumption that the chemical exchange kinetics in the blood reflect those in the whole fish.

Jovanovic et al. [49] reported that of the 20% radiolabeled D5 absorbed in rats after administering an oral (gavage) dose of ^{14}C-D5 in corn oil, 50% to 60% was eliminated as parent D5 in exhaled air and 20% of eliminated as water-soluble metabolites of D5. Varaprath et al. [46] identified a number of metabolites of D5 in the urine of Fisher 344 rats that were intravenously and orally exposed to D5, including $Me_2Si(OH)_2$, $MeSi(OH)_3$, $MeSi(OH)_2OSi(OH)_3$, $MeSi(OH)_2OSi(OH)_2Me$, $MeSi(OH)_2OSi(OH)Me_2$, $Me_2Si(OH)OSi\text{-}(OH)Me_2$, $Me_2Si(OH)OSiMe_2OSi(OH)Me_2$ (where Me represents a methyl group), nonamethylcyclopentasiloxanol, and hydroxymethylnonamethylcyclopentasiloxane. No parent D5 was observed in the urine. The authors concluded that certain metabolites such as $Me_2Si(OH)_3$ indicate demethylation of the silicon–methyl bonds. The same metabolites were observed in a study by Springer [48] with D5 in rainbow trout.

Trophic magnification studies

The TMF can be viewed as an average food chain BMF of a chemical for each single trophic step in the food chain. The TMF is determined from field-derived chemical concentration data in a number of different species across a defined food web. The TMF is calculated from the slope (m) of a linear regression of the logarithm of the concentration of the chemical in the organisms of the food web and the estimated trophic position of the organism; i.e., $TMF = 10^m$. For lipophilic chemicals, such as D5, concentrations are normalized for lipid content because organisms with higher lipid content are expected to contain higher concentrations than organisms with lower lipid content when subjected to the same exposure concentration and environmental conditions.

Trophic position can be determined by conducting analyses of the intestinal contents of organisms. A trophic positioning model is then used to assign a numerical value for the trophic position. Stable N^{15}/N^{14}-isotope ratios in animal tissues provide an alternative method to determine trophic status. Typically, N^{15}/N^{14} isotope ratios in animal tissues increase with increasing trophic position in food webs and thus provide a useful and inexpensive empirical measure or surrogate for trophic position. Several authors have suggested that increases in the N^{15}/N^{14} nitrogen isotope ratio of 0.34% to 0.38% correspond with a 1-unit increase in trophic position [23,50,51]. Guidelines exist for the derivation of TMFs from food web concentration data [21]. However, challenges remain in the determination of the TMF. Differences in sample size among organisms of the food web (unequal replication) can produce an "unbalanced" sampling design that requires the application of appropriate statistical methods to determine the TMF [24,25]. Migration of species between areas of different contamination levels and sampling from locations with different concentrations also can introduce error in TMF measurements [52]. Also, an insufficient time for concentrations in biota to respond to environmental exposure concentrations can affect the accurate measurement of the TMF. Despite these challenges, the TMF is an insightful metric of chemical bioaccumulation because it provides a real-world measure of the actual bioaccumulation profile in a food web [53]. Trophic magnification factors can be applied broadly across ecosystems [54–56]. When using the TMF as a measure of biomagnification, an appropriate criterion for identifying bioaccumulative substances is a $TMF > 1$. This criterion is met if the slope (m) of the line regressing the logarithm of normalized chemical concentrations on trophic position is significantly ($p < 0.05$) greater than 0 (i.e., if $m > 0$, then $10^m > 1$). A TMF greater than 1 indicates that the chemical is able to biomagnify in a thermodynamic sense and increase in chemical potential with increasing trophic level.

Studies have reported on the trophic magnification of D5 in freshwater and marine food webs (Supplemental Data, Table S8) [57–62]. Several studies also reported concentration data to determine the TMF of PCB-153 or PCB-180 in the same food web used to investigate the trophic magnification of D5. Both PCB-153 and PCB-180 are known for their ability to biomagnify in aquatic food chains. The TMFs of PCB-153 and PCB-180 therefore can be used as a reference value with which

the TMFs of D5 can be compared. In one study [62], a brominated diphenylether (BDE-99) was used as a reference compound. However, BDE-99 is not recognized for its biomagnification capacity and has not been observed to produce TMFs significantly greater than 1 [63,64], likely because of the debromination of BDE-99 to BDE-47, which has been observed in fish [65].

Figure 3 illustrates the TMFs of D5 in relation to those of PCB-153 or PCB-180 (for Lake Erie), and Supplemental Data, Table S8 documents the data and associated statistical details. Figure 3 illustrates that the TMF of PCB-153 is significantly greater ($p < 0.05$) than 1 in Tokyo Bay, Lake Pepin, and Lake Mjøsa. This is in good agreement with many similar findings for these PCB congeners [66] and indicates that these studies are capable of detecting food web biomagnification. The TMFs of PCB-153 in Lake Randsfjorden [58] and PCB-180 in Lake Erie [59] were not significantly greater than 1, suggesting that the sampling schemes for the food webs in these studies may not have been suitable to measure a reliable TMF. Possible reasons might be the small range in trophic positions of the sampled species (e.g., 1.7 in Lake Randsfjorden vs the recommended 3 [23]) and small sample size. Borgå et al. [23] note that, based on the level of variability associated with past experimental designs, large sample sizes (e.g., $n = 60$–100) can be expected to consistently detect significant regression slopes for contaminants with apparent TMFs in the range of 1.5 to 2.0. The lack of a reference compound with a recognized biomagnification capacity in trophic magnification studies (e.g., Inner and Outer Oslofjord and Dalian Bay studies) makes it difficult to assess the ability of the study design to determine the TMF and to compare the TMFs between studies.

Supplemental Data, Table S8 shows that the method of calculation of the TMF for D5—that is, using individual concentration data versus mean concentrations for each species—had only minor effects on the TMF value. However, the method of calculation did have a substantial effect on the statistical significance (p value) of the TMF being different from 1 in 2 of 11 studies. In studies in the Outer Oslofjord and Lake Mjøsa, TMFs were statistically different from 1 when using individual concentrations but not when using mean concentrations for each species. In the other 9 studies, the p values for testing the hypothesis that TMF$\neq$1 using individual concentration data were generally greater than those for regressions using mean concentrations, but the fundamental outcome of the statistical test (i.e., significant or not) was not affected by the method of calculation. The effect of experimental design on testing the hypothesis of a TMF$\neq$1 illustrates the importance of both large sample size and a balanced design in TMF studies. Figure 3 shows that the TMFs of D5 are significantly less than 1 ($p < 0.05$) in Lake Pepin and the marine demersal food webs of the Inner and Outer Oslo fjord and the marine pelagic food web of the outer Oslofjord. The TMFs of D5 in Tokyo Bay, Lake Randsfjorden, Lake Erie, and Dalian Bay (China) are not significantly different ($p > 0.05$) from 1 (Supplemental Data, Table S8). Supplemental Data, Table S8 shows that statistical significance levels for the TMF of D5 (as expressed by the p value of the slope of the logarithm of the lipid-normalized concentration vs trophic position) exceed the statistical significance criterion of $p = 0.05$ by a large margin in the studies in Tokyo Bay, Lake Randsfjorden, and Lake Erie but only by a small margin in the study in Dalian Bay. In all 3 studies, D5 concentrations in species at all trophic positions exhibit large overlaps, illustrating the challenges of TMF studies and emphasizing the need for an appropriate experimental design. The TMF of D5 in Lake Mjøsa is greater than 1 ($p < 0.05$). The observations of the TMFs of D5 being both significantly greater and smaller in some studies and not significantly different from 1 in other studies suggest that the effect of trophic position on the lipid-normalized D5 concentration may be small and that confounding variables and limitations of TMF study designs may exert a large effect on the determination of the TMF. Uncertainty in the measurements of the TMF [67] or knowledge gaps [21] might be the main factors that cause the differences among TMFs and the lack of a clear indication of the trophic distribution of D5 in food webs. For example, the lack of common sampling areas for the species considered in the TMF calculation (e.g., Lake Mjøsa) and the presence of point sources such as a wastewater treatment plant that can cause concentration gradients in the sampling area (e.g., Lake Randsfjorden) can have a significant impact on study outcomes. Warner et al. [68] observed that concentrations of D5 in sediment decreased with increasing distance from a wastewater outlet in Adventfjorden in the Svalbard archipelago. McLeod et al. [52] used the AquaWeb model to illustrate that large variations in the TMF of PCBs can occur because of spatial gradients in concentration. Spatial gradients in concentration may produce mixed signals regarding the bioaccumulation behavior of chemicals that are not strong biomagnifiers. The effect of spatial gradients in concentration on the TMF suggests that the bioaccumulation behavior of contaminants is most clearly revealed in studies that confirm the lack of spatial concentration gradients in the study system (e.g., Mackintosh et al. [69]). To better characterize the bioaccumulation in food webs of chemicals such as D5, the statistical power of trophic magnification studies may need to be substantially improved.

Modeling studies

Whelan and Breivik [70] applied the ACC-HUMAN model to assess the food chain transfer of D5 in the Inner Oslofjord food web. The authors predicted "trophic dilution" of D5 between zooplankton and herring (*Culpea harengus*) and between herring and cod (*Gadus morhua*), principally caused by a combination of biotransformation and reduced gut absorption efficiency attributable to the high K_{OW} of D5.

The results of the AquaWeb modeling for D5 assuming no biotransformation of D5, carried out as part of the present review, are presented in Figures 1, 2 and 4. Figure 1 shows that model-calculated depuration rate constants for both growing and nongrowing fish of the same body weight and lipid content as the fish used in the various D5 bioaccumulation experiments were much smaller than the observed depuration rate constants. In contrast, predicted and observed depuration rate constants of the poorly biotransformable PCB-52 were in reasonable agreement. Figure 2 illustrates that model-predicted bioconcentration factors of D5 (assuming no biotransformation) were, in all cases, much greater than the observed values. Figure 4 illustrates that model-calculated BMFs and TMFs of D5 (assuming no D5 biotransformation) exceeded the upper 95% confidence interval of the observed values in all cases, with the exception of TMFs in Lake Mjøsa. The modeling results indicate that the empirically determined bioaccumulation metrics were in almost all cases less than those predicted by the AquaWeb model for a nonbiotransformed substance of the same log K_{OW} as D5. The modeling results point toward the important role that biotransformation plays in the depuration, bioconcentration, dietary bioaccumulation, and food web distribution of D5.

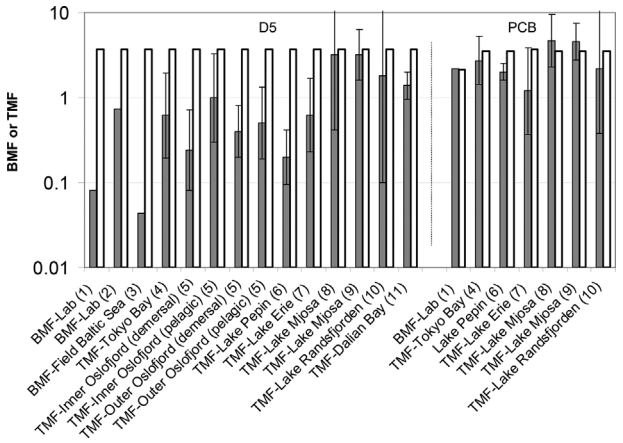

Figure 4. Biomagnification factors (BMF; kg lipid/kg lipid) and trophic magnification factors (TMF) of decamethylpentacyclosiloxane (D5) and reference chemicals polychlorinated biphenyl (PCB)-52 (for study 1), PCB-153 (for studies 4, 6, 8, 9, 10), and PCB-180 (for study 7) as observed in laboratory tests (for BMF) or field study (for TMF) (gray bars) and calculated by the AquaWeb model for the experimental conditions in the test (for BMF) and for a model food web (TMF) assuming no D5 biotransformation (white bars). Empirical TMFs presented are based on mean concentrations (Data listed in Supplemental Data Table S1). The error bars illustrate the 95% confidence intervals of the mean. The empirical data are from the following sources: 1 = Opperhuizen et al. [29]; 2 = Drottar [36]; 3 = Kierkegaard et al. [47]; 4 = D.E. Powell et al., Dow Corning, Midland, MI, USA, unpublished manuscript; 5 = Powell et al. [61]; 6 = Powell et al. [60]; 7 = McGoldrick et al. [59]; 8 = Borgå et al. [57]; 9 = Borgå et al. [58]; 10 = Borgå et al. [58]; 11 = Jia et al. [62].

DISCUSSION

The present review shows that a number of studies can provide insights into the bioaccumulation behavior of D5. Despite differences in approach, test species, methods, and measurement endpoints used, several characteristics of the bioaccumulation behavior of D5 are evident in all studies. First, all experimental studies indicate a high D5 depuration rate that is uncharacteristic for an extremely hydrophobic organic chemical with a log K_{OW} of 8.09. Measured depuration rates of D5 are much greater than those estimated by the AquaWeb model for a nonbiotransformable substance with a log K_{OW} of 8.09 (Figure 1). The measured depuration rates of D5 are also greater than those of poorly biotransformable PCB congeners (Figure 1). The relatively high depuration rate of D5 is an important observation, because the measurement of the depuration rate is least affected by experimental artifacts in dosing. Biotransformation of D5 is likely the main reason for the relatively high depuration rates in the tested fish and invertebrate species, because rates of excretion of parent D5 to fecal matter and respiration to water are very low as a result of the very high K_{OW}. Biotransformation of D5 is known to occur in rats, where demethylation plays a key role in the breakdown of D5 [46]. A similar breakdown pathway likely exists for D5 in fish given that demethylation products of D5 also have been observed in fish [48].

Second, the observed BCFs of parent D5 range among the various studies between 1040 L/kg and 4920 L/kg wet weight and are much smaller than those predicted by the AquaWeb model for a nonbiotransformable substance with a log K_{OW} of 8.09 and those of PCB reference compounds (Figure 2). These findings are consistent with the measured depuration rates of D5, which exceed those predicted by the AquaWeb model and those of the PCB reference compounds (Figure 1). The higher than expected depuration rates of D5 can be explained by biotransformation of D5, which is confirmed by the detection of metabolites of D5 in the studies of Springer [48], Drottar [31], Woodburn et al. [38], and Opperhuizen et al. [29]. In experiments using C^{14}-labeled D5, BCFs ranged between 5900 L/kg and 13 700 L/kg. These BCFs are also smaller than those predicted by the AquaWeb model and those of PCB reference compounds but greater than those of parent D5 in the other studies. The difference in BCFs between studies that use C^{14}-labeled and nonradiolabeled test chemical is generally recognized [22]. Organisation for Economic Co-operation and Development guideline 305 [22] emphasizes that BCF or BMF values based on total radioactive residues are not directly comparable to BCFs or BMFs derived by chemical-specific analysis of the parent substance only. In studies using C^{14}-labeled D5, concentrations in fish represent the combined concentration of parent D5, D5 metabolites, and assimilated radiolabeled carbon. Hence, BCFs using radiolabeled D5 can be expected to be greater than those in studies that did not use radiolabeled D5. In regulatory circles, reporting BCFs for the combined concentration of parent substance and metabolites is sometimes preferred. However, when relying on studies using C^{14}-radiolabeled test chemicals, this practice can lead to error in the determination of the BCF because of assimilation of carbon by the organism. The latter is relevant to D5, which is subject to demethylation [46]. The BCFs measured based on scintillation counts of C^{14}-labeled D5 and metabolites in fish tissues are therefore not representative of the actual BCF of D5.

Third, experimental steady state BMFs of D5 range from 0.08 kg lipid/kg lipid to 0.85 kg lipid/kg lipid, indicating a lack of dietary biomagnification. These experimental BMFs agree with a field-derived BMF in the Baltic Sea and field-derived TMFs in Lake Pepin and the marine demersal food webs of the Inner and Outer Oslo fjord (Supplemental Data, Table S8). These findings also point to the role of biotransformation as a key characteristic of the bioaccumulation behavior of D5 because TMFs and BMFs less than 1 can occur only if D5 is biotransformed. The reported TMF of D5 in Lake Mjøsa, which was found to be significantly greater than 1, is the only observation that does not fit bioaccumulation profile supported by other studies. The finding that 11 trophic magnification studies were not able to reach a unanimous conclusion with regard to the bioaccumulation behavior of D5 also may provide some insights. It suggests that the TMF study designs may not have had sufficient statistical power to detect the likely small food web distribution effect of D5, causing confounding variables to obscure the bioaccumulation behavior of D5. This possible explanation emphasizes the need for improving the design of trophic magnification studies. It also emphasizes the importance of reaching conclusions with regard to bioaccumulation based on as broad a database as possible.

Fourth, the only measured BSAF of D5, 7.1 kg organic carbon/kg lipid, was measured at concentrations of D5 in the sediment that exceeded the maximum sorption capacity of D5 in sediments by many fold. Despite difficulties interpreting this BSAF, the BSAF is much lower than the BSAF of D5 of 210 derived by the AquaWeb model, which assumed that D5 is not biotransformed and that D5 has a sorption affinity for organic carbon that is 0.12% of that in octanol. The finding that the measured BSAF of D5 of 7.1 kg organic carbon/kg lipid is less than that estimated by the model also indicates the ability of sediment-dwelling invertebrates to biotransform D5. The unusual relationship between the organic carbon–water partition coefficient and the K_{OW} of D5 is a special intrinsic property

of D5 (and possibly other silicone-based substances) that should be considered when comparing sediment bioaccumulation patterns of D5 with those of PCBs and other organic compounds.

The available bioaccumulation studies on D5 generally appear to be internally consistent and provide near unequivocal evidence of the important role of biotransformation in the bioaccumulation profile of D5. This high degree of internal consistency among bioaccumulation studies of various kinds indicates that the bioaccumulation profile of D5 can be assessed using the results from a variety of studies and that it is not necessary to rely on a single study or bioaccumulation measure, such as the BCF, to assess the bioaccumulation behavior of D5. In fact, this analysis suggests that because of the impossibility of recognizing and removing all experimental artifacts in a bioaccumulation assessment, there is considerable advantage of using a broad data set to derive a bioaccumulation profile. The practice of using data from multiple studies reduces the chance that recognized or unrecognized experimental artifacts or design flaws of a particular study unduly affect conclusions and decisions.

It is also interesting to observe that different kinds of studies can contribute information on the bioaccumulation behavior of D5. Older studies that may not be considered state-of-the-art can contribute to the development of a bioaccumulation profile in addition to newer state-of-the-art studies. For example, the Drottar [31] bioconcentration study is an example of a relatively recent study following OECD 305 [22] guidelines for bioconcentration studies, and the Opperhuizen [29] study is an older study that predated the OECD guidelines. Both studies reveal aspects of the bioaccumulation behavior of D5 and can contribute to the understanding of the bioaccumulation behavior of D5. It is often counterproductive to eliminate data from evaluation because of study type, age, technology, or lack of meeting protocol specification, because such elimination reduces the evidence in an analysis. Only erroneous data should be removed from analysis. The consistency among the findings of many studies observed in this analysis supports the application of a comprehensive approach to the development of a bioaccumulation profile for a chemical, where data from a range of relevant studies are considered. A comprehensive approach can be challenging, because it requires considerable expertise to evaluate studies for their contributions to knowledge as well as their limitations. However, this comprehensive approach will likely produce greater confidence and scientific support for decisions compared with a more selective approach.

Another interesting observation is that the Board of Review of Environment Canada considered properties other than the K_{OW}, BCF, and BAF included in the Bioaccumulation and Persistence regulations of the Canadian Environmental Protection Act [12]. This approach is consistent with the modus operandi in science, law, and public policy, which recognize a broad range of efforts that contribute to the advancement of knowledge, laws, and regulations. For example, the United Nations Stockholm Convention on Persistent Organic Pollutants specifies a broad range of scientific information that can be used to identify bioaccumulative substances. This approach proved instrumental in identifying "false negatives" in the bioaccumulation assessment process [16]. The Canadian Environmental Protection Act also includes provisions for considering properties other than the K_{OW}, BCF, and BAF by referring to the need for "...taking into account the intrinsic properties of the substance, the ecosystem under consideration and the conditions in the environment." Hence, the Canadian Environmental Protection Act is sufficiently flexible to consider bioaccumulation properties of various kinds and will likely become more effective when doing so. A more comprehensive regulatory approach likely befits D5 and possibly many other chemical substances with unique properties that do not match those of the substances that have historically provided the impetus for the development of the bioaccumulation regulations.

Finally, the Board of Review's decision on the bioaccumulative nature of D5 relies heavily on the absence of biomagnification of D5 across food webs rather than on D5's hydrophobicity and bioconcentration behavior recognized in the Bioaccumulation and Persistence regulations. (It should be noted that, at the time of the Board of Review's evaluations, the trophic magnification studies in Lakes Erie, Mjøsa, and Randsfjorden, and Dalian Bay had not been completed.) This makes good scientific sense, because the ability of chemicals to biomagnify elevates exposure and potential risk of health effects in organisms at higher trophic levels and humans, whereas trophic dilution, the opposite of biomagnification, reduces exposure and potential risks. The BCF is not always the best descriptor of the biomagnification process because it does not consider dietary exposure. The TMFs from field studies and BMFs derived from laboratory studies often provide more direct evidence of biomagnification. The Board's focus on biomagnification also finds support in international public policy, because the United Nations Stockholm Convention on Persistent Organic Pollutants specifically recognizes and acknowledges "that the Arctic ecosystems and indigenous communities are particularly at risk because of the biomagnification of persistent organic pollutants and that contamination of their traditional foods is a public health issue." The acknowledgement of the risk to indigenous peoples due to biomagnification of pollutants is of particular relevance to Canada, because it is home to many indigenous communities which often rely on country foods for sustenance. The Board's decision on the bioaccumulation behavior of D5 opens the door to more comprehensive evaluations of the bioaccumulation behavior of commercial substances that recognize not only bioconcentration in fish but also dietary biomagnification in food webs.

SUPPLEMENTAL DATA

Tables S1–S8.
Figures S1–S4. (253 KB PDF).

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