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CASE STUDY ON THE USE OF AN INTEGRATED APPROACH FOR TESTING AND ASSESSMENT OF THE BIOACCUMULATION POTENTIAL OF DEGRADATION PRODUCTS OF 4,4'-BIS (CHLOROMETHYL)-1,1'-BIPHENYL

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IOMC INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS
A cooperative agreement among FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD

Environment Directorate
ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT
Paris 2016

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FOREWORD

OECD member countries have been making efforts to expand the use of alternative methods in assessing chemicals. The OECD has been developing guidance documents and tools for the use of alternative methods such as (Q)SAR, chemical categories and Adverse Outcome Pathways (AOPs) as a part of Integrated Approaches for Testing and Assessment (IATA). There is a need for the investigation of the practical applicability of these methods/tools for different aspects of regulatory decision-making, and to build upon case studies and assessment experience across jurisdictions.

The objective of the IATA Case Studies Project is to increase experience with the use of IATA by developing case studies, which constitute examples of predictions that are fit for regulatory use. The aim is to create common understanding of using novel methodologies and the generation of considerations/guidance stemming from these case studies.

This case study was developed by Japan for illustrating practical use of IATA in a regulatory context and submitted to the 2015 review cycle of the IATA Case Studies project. This case study was reviewed by the project team and revised to consider the comments from reviewers. The document was endorsed at the 9th Task Force on Hazard Assessment meeting in June 2016.

The following three case studies were also reviewed in the project in 2015 and are published with this case study:

1. CASE STUDY ON THE USE OF INTEGRATED APPROACHES FOR TESTING AND ASSESSMENT FOR IN VITRO MUTAGENICITY OF 3,3’ DIMETHOXYBENZIDINE (DMOB) BASED DIRECT DYES, ENV/JM/MONO(2016)49, Series on Testing & Assessment No. 251.

2. CASE STUDY ON THE USE OF INTEGRATED APPROACHES FOR TESTING AND ASSESSMENT FOR REPEAT DOSE TOXICITY OF SUBSTITUTED DIPHENYLAMINES (SDPA), ENV/JM/MONO(2016)50, Series on Testing & Assessment No. 252.

3. CASE STUDY ON THE USE OF AN INTEGRATED APPROACH TO TESTING AND ASSESSMENT FOR HEPATOTOXICITY OF ALLYL ESTERS, ENV/JM/MONO(2016)51, Series on Testing & Assessment No. 253.

In addition, a considerations document summarizing the learnings and lessons of the review experience of the case studies is published with the case studies:

REPORT ON CONSIDERATIONS FROM CASE STUDIES ON INTEGRATED APPROACHES FOR TESTING AND ASSESSMENT (IATA) -First Review Cycle (2015): Case Studies on Grouping Methods as a Part of IATA- ENV/JM/MONO(2016)48, Series on Testing & Assessment No. 250.

This document is published under the responsibility of the Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology.

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INTRODUCTION

Assessment of the bioaccumulation potential of the degradation products of 4,4'-bis (chloromethyl)-1,1'-biphenyl were performed by using an evaluation method for bioaccumulation potential of new chemical substances specified in Japan's Chemical Substance Control Law (CSCL). The degradation products were evaluated as "not highly bioaccumulative" by read-across based on the measured bioconcentration factors (BCFs) of the source chemical, by comparing the hydrophilicity between the parent chemical and its degradation products, and by using QSAR software to generate the estimated BCF values.

1. PURPOSE

1.1. Purpose of use

The safety assessment of industrial chemical substances in Japan is conducted based on Japan's Chemical Substance Control Law (CSCL). The manufacturers and importers of new chemical substances are required to notify the authorities of the safety assessment results, such as biodegradation, bioaccumulation potential, and 28-day repeated-dose toxicity. The persistence of a new chemical is evaluated by first conducting a biodegradation test (OECD TG 301C). The purpose of this test is to investigate the persistence (P) of a new chemical in the environment and the presence of the parent chemical and its degradation products in the environment. If the new chemical is judged "non-biodegradable" from this test result[1] under CSCL, the bioaccumulation potential (B)[2] and toxicity (T) of the new chemical and its degradation products are evaluated. The safety of a new chemical is judged from these PBT evaluation results. From the viewpoint of examination cost and animal protection, the analogue approach based on an expert evaluation by using experimental data of a similar chemical can be accepted in these PB evaluations under CSCL. B assessment on the degradation products having concentrations of ≥1% would occasionally be associated with technical difficulties in identifying chemical structures and testing/analyzing owing to the low concentration; therefore, historically, CSCL has been accepting the B assessment strategy on degradation products without chemical identity by using a measured bioconcentration factor of a parent chemical if any data (such as reverse-phase HPLC) show that the degradation products are more hydrophilic than the parent chemical.

Ministry of Economy, Trade and Industry in Japan (METI) announced the "Concerning the assessment of bioaccumulation of new chemical substances by analog approach, etc. (Announcement)" (bioaccumulative analogy rule) in September (Ministry of Economy, Trade and Industry in Japan, 2015) to clarify the criteria for the effectiveness of the analogue approach for determining the bioaccumulation potential under the CSCL. In case some of the criteria are not met (in other words, data gap filling is unsuccessful or uncertainty is very high), some experimental testing might be recommended to complete the assessment based on a case-by-case basis.

This case study describes the bioaccumulation evaluation results for the degradation products of 4,4′-bis (chloromethyl)-1,1′-biphenyl under the CSCL according to this analogy rule.

1.2. Target chemicals

The safety assessment of the 4,4′-bis-(chloromethyl)-1,1′-biphenyl (source chemical 1) under CSCL initially requires that a biodegradation test should be performed according to OECD TG 301C. The BOD value of source chemical 1 was equal to 0%, and the four degradation products (target chemicals 1–4) were identified in the test (see data matrix). Target chemical 1, 4,4-biphenyl dimethanol was generated in water (9%) and in active sludge (2%–3%). Further, a small amount of 4′-(hydroxymethyl)-[1,1′-biphenyl]-4-carboxylic acid (target chemical 2), biphenyl-4,4′-dicarboxylic acid (target chemical 3), and an unidentified chemical substance (target chemical 4) were only generated in active sludge. Therefore, abiotic degradation was presumed to be the major reaction, and the generation of target chemicals 2–4 were thought to occur via the biological oxidation of target chemical 1.

[1] BOD < 60% and more than 1% of degradation product in a biodegradation test (OECD TG 301C).

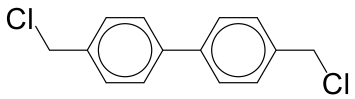
[2] CSCL defines "not highly bioaccumulative" as BCF < 5,000.

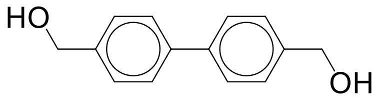
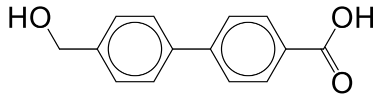
Since source chemical 1 was judged “non-biodegradable” under CSCL, evaluating its bioaccumulation potential and for its degradation products (target chemicals 1–4) was necessary. The bioaccumulation potential of source chemical 1 was assessed “not highly bioaccumulative” based on an experimental bioconcentration test performed according to the test method: OECD TG 305 determining a of BCF ≤48.

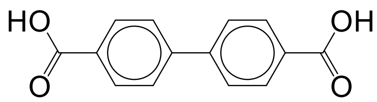
In this case study, we evaluated the bioaccumulation potential of the degradation products according to the bioaccumulative analogy rule.

The structures of source chemical 1 (parent chemical) and the target chemicals are shown in Table 1.

Table 1 Structures of Source chemical 1 and target chemicals assessed in this case study

	Source chemical 1 (Parent chemical)
Structure	
SMILES	ClCc1ccc(c2ccc(CCl)cc2)cc1
CAS No.	1667-10-3
Chemical name	4,4′-bis(chloromethyl)-1,1′-biphenyl

	Target chemical 1 (Degradation product 1)	Target chemical 2 (Degradation product 2)
Structure		
SMILES	OCc1ccc(c2ccc(CO)cc2)cc1	OCc1ccc(c2ccc(C(O)=O)cc2)cc1
CAS No.	-	-
Chemical name	4,4-biphenyl dimethanol	4′-(hydroxymethyl)-[1,1′-biphenyl]-4-carboxylic acid

	Target chemical 3 (Degradation product 3)	Target chemical 4 (Degradation product 4)
Structure		Unidentified
SMILES	OC(c1ccc(c2ccc(C(O)=O)cc2)cc1)=O	-
CAS No.	787-70-2	-
Chemical name	biphenyl-4,4′-dicarboxylic acid	-

1.3. Endpoint

The bioaccumulation potentials for target chemicals.

2. HYPOTHESIS FOR THE ANALOGUE APPROACH

The bioconcentration of chemical substances in fish: most chemical substances, with the exception of biomolecules such as inulin and dextran, are taken up by organisms by simple passive diffusion via the biomembranes of the gills (Hunn,1974; Veith,1979; Furspan, 1983; Isaia, 1982). The principal driving force for this permeability is thought to be the hydrophobicity of a chemical (Barron, 1990). Therefore, for the chemicals that are taken up by fish by passive diffusion, a good correlation is known to occur between logBCF and logPow (which is a parameter showing the hydrophobicity of a chemical) (Hunn, 1974; Meylan, 1999; McKim, 1985). If the logPow is below 7, logBCF tends to monotonically increase according to the increase in logPow. If logPow exceeds 7, logBCF has been experimentally shown to decrease (Barron, 1990; Dimitrov, 2005). Moreover, uptake and excretion as related to the bioconcentration of a chemical are expressed using a single-compartment model by using the following formula (Arnot, 2006):

$$\mathrm{BCF} = C_B/C_{WD} = k_1/(k_2 + k_E + k_M + k_G),$$

where C_B is the chemical concentration in the organism ($g \cdot kg^{-1}$); CWD is the freely dissolved chemical concentration in the water ($g \cdot L^{-1}$); k1 is the chemical uptake rate constant from the water at the biomembrane of the gills ($L \cdot kg^{-1} \cdot d^{-1}$); and k_2, k_E, k_M, and k_G are rate constants (d^{-1}) representing chemical elimination from the organism via the biomembranes of the gills, fecal excretion, metabolic biotransformation, and growth dilution, respectively. The molecular size of a chemical and the molecular interaction between the chemical and a biomolecule affect k_1 and k_2, since a chemical's molecular size influences its biomembrane permeability. A chemical having a molecular size exceeding a certain threshold value has a low risk of bioconcentration. The cutoff criteria between BCF and certain molecular size parameters such as molecular weight (MW), maximum diameter (Dmax), and effective diameter (Deff) have been experientially determined. For example, MW > 700, Dmax > 1.47 nm, and Deff > 0.95 nm have been proposed for screening the bioaccumulation potential (Arnot, 2010).

The difference in molecular interaction between the biomembrane and a chemical (for example, the hydrogen bond, an ionic interaction) also influences k_1 and k_2 (Barber, 1988; Saarikoski, 1986). This interaction is based on the difference in the thermodynamic stability of the chemical in the biomembrane and in water. The metabolism and protein binding of a chemical in the living body varies with its molecular structure and reactivity of its functional groups, which affect its bioconcentration potential. For example, a protein-binding chemical increases the bioconcentration potential in the living tissue, and the metabolic biotransformation of the chemical promotes the excretion of the chemical from the living body (Wolf, 1992; Arnot, 2008; Kolanczyk, 2003; Conder 2008).

These findings suggest that similar chemical substances i.e., those having similar structure, physicochemical properties (such as hydrophobicity and molecular interactions), and biological activities, will show similar bioconcentration potential behavior. Furthermore, if the bioconcentration data for similar chemical substances exist and their hydrophobicity is higher than the value for an untested chemical, the bioaccumulation potential of the untested chemical can be safely considered to be lower than that of the tested chemical.

A new guideline entitled "Concerning the assessment of bioaccumulation of new chemical substances by analog approach, etc. (Announcement)" (bioaccumulative analogy rule) developed based on the above hypothesis was released in September 2013 in Japan (Ministry of Economy, Trade and Industry in Japan, 2015).

According to this guideline, the bioaccumulation potential of an untested chemical is evaluated by using the following two evaluation methods by using the data on analogous chemical substances.

A) Bioaccumulation assessment by using QSAR and read-across
The bioaccumulation potential of a target chemical (Target) can be regarded as "not highly bioaccumulative" if the chemical fulfills the following three conditions.
A-1. Data suggest that the measured BCF value of the source chemical (Source) is below 500.

A-2. The Target and Source have a similar structure. (Specific conditions are (i) or (ii).)

(i) The Target is an isomer of the Source.

(ii) The Target and Source have the same basic skeleton, and both chemical substances have an identical structure apart from minor differences (including differences in the number of carbon atoms of the alkyl group).
(However, this does not include the case where the polarity (hydrophilicity) of the Target was lower than that of the Source and the BCF of the Target was likely higher than 500.)

A-3. The bioaccumulation potential of the Target can be logically assumed, based on their chemical structure, to be almost the same or lower than the Source. (Specific conditions are (i) or (ii).)

(i) The BCF value of the Target estimated using QSAR model is almost the same or lower than the measured and estimated BCF of the Source. (This is limited to only a case where the measured and estimated BCF values for Source were not significantly different from each other.)

(ii) There are two or more Sources whose measured BCF is below 100.

B) Bioaccumulation assessment based on a comparison of hydrophilicity (polarity) by using HPLC.
The bioaccumulation potential of the Target can be regarded as "not highly bioaccumulative" if the chemical fulfills the following three conditions.

B-1. Data show that the Source has BCF value of below 500.

B-2. The Target and Source have a similar structure.
The Target and Source have the same basic skeleton and both chemical substances have an identical structure apart from minor differences (including a case where the number of carbon atoms of alkyl group was changed.).
(However, this does not include the case where the polarity (hydrophilicity) of the Target was lower than that of the Source and the BCF of the Target was likely higher than 500.).

B-3. From the result of a polar (hydrophilic) comparison of Source and Target by using reverse-phase HPLC, the hydrophilicity of the Target was found to be higher than that of the Source.

(However, this approach was not applicable to highly lipophilic source chemicals [logPow > 6.0].)

3. SOURCE CHEMICALS

3.1. Identification and selection of source chemicals

We selected the parent chemical (Source chemical 1) as an analogue of the degradation products (Target chemicals 1–4). The parent chemical changes to the degradation products via hydrolysis and/or microbial reaction. It has a similar structure without any known additional functional groups that might increase its bioaccumulation potential.

Furthermore, other source chemicals corresponding to the following conditions were extracted from the database by using the Query function of OECD QSARToolbox ver. 3.2.

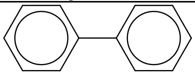
Two of the chemical substances identified using the above operation satisfied the following conditions and were selected as Source chemicals.

- The chemicals had a hydroxyl or carboxyl group
- The BCF value was known
- Test organism species: Fish[3]
- QA = high quality.

Table 2 Selection conditions for the Source chemical by using OECD QSARToolbox ver. 3.2 query function

Selected database	Physicochemical Properties • Chemical Reactivity COLIPA • ECHA CHEM • Experimental pKa • GSH Experimental RC50 • Phys-chem EPISUITE Environmental Fate and Transport • Bioaccumulation Canada • Bioaccumulation fish CEFIC LRI

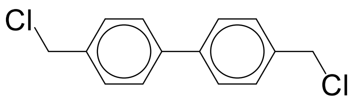
[3] Since different fish species might show different BCF values for the same chemical, data from the same test species were used in this evaluation (Veith, 1979). However, if no data were available in the same fish species, data from different fish species could be used to assess the bioaccumulation potential in fish.

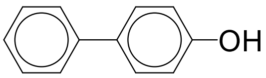
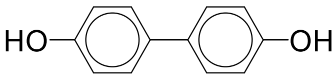
		• Bioaccumulation NITE • Biodegradation in soil OASIS • Biodegradation NITE • Biota-sediment Accumulation Factors US-EPA • ECHA CHEM • Phys-chem EPISUITE
Query condition	Subfragment	
	Parameters	Number of rings = 2 logPow ≤ 4.52[4]

3.2. List of source chemicals

The source chemicals used in this study are shown in Table 3.

Table 3 List of Source chemicals used in this case study

	Source chemical 1 (Parent chemical)
Structure	
SMILES	ClCc1ccc(c2ccc(CCl)cc2)cc1
CAS No.	1667-10-3
Chemical name	4,4′-Bis(chloromethyl)-1,1′-biphenyl

	Source chemical 2	Source chemical 3
Structure		
SMILES	Oc1ccc(-c2ccccc2)cc1	Oc1ccc(-c2ccc(O)cc2)cc1
CAS No.	92-69-3	92-88-6
Chemical name	p-Phenylphenol	4,4-Dihydroxydiphenyl

[4] 4.52 = 3.52 (maximum logPow value of target chemicals) + 1 (margin)

4. JUSTIFICATION OF DATA GAP FILLING

4.1. Data gathering

All the measured values for biodegradation, physicochemical properties, and BCF values were obtained using J-CHECK[5] and QSAR Toolbox ver. 3.2. The data for Source 1 were obtained using J-CHECK, and those for Sources 2–3 were obtained using QSAR Toolbox ver. 3.2. The polarity between Source 1 and Targets 1–4 was compared using reverse-phase HPLC as described in the biodegradation test report for Source 1. (The HPLC chromatogram obtained from METI. See Annex I for more detailed information.)

The values for the physicochemical properties and BCF were estimated using the QSAR software; they are listed in Table 4. In all, 58 biodegradation products of Source 1 were estimated using "microbial metabolism simulator" of OECD QSARToolbox ver.3.2. The estimated BCF values of these biodegradation products were less than 500. (See Annex II for more detailed information.)

Table 4 Data items and QSAR software versions used to calculate the estimated values

Parameters estimated	QSAR models	QSAR software name	Validation
logPow	KOWWIN	KOWWIN ver.1.68 (US EPA),	No
	log P Multicase	OECD QSARToolbox ver.3.2 (OECD)	No
	Clog P	ChemBioDraw Ultra ver.14 (PerkinElmer, Inc.),	No
BCF	BCFBAF ver.4.01	BCFBAF ver.3.01 (US EPA),	Yes[6]
	BCF-baseline model v.02.07	CATALOGIC ver.5.11.13 (OASIS LMC)	Yes[6]
Molecular weight, Dmax, Deff		OECD QSARToolbox ver.3.2 (OECD)	No

4.2. Data matrix

The data matrix of all chemical substances subjected to this analogue approach is shown in Annex III.

4.3. Justification

A) Source 2–3 and Targets 1–3 fulfilled three conditions of analogy rule A (as described on page 4–5). The detailed information for each condition (A-1 to A-3) is provided below.
The bioaccumulative evaluation of Targets 1–3 by rule A only use data for Sources 2–3 owing to

[5] J-CHECK (Japan CHEmical Collaborative Knowledge database): http://www.safe.nite.go.jp/jcheck/top.action

[6] Model validation was conducted by the QSAR expert committee hosted by the National Institute of Technology and Evaluation according to OECD principles.

the large difference between the measured and estimated values of Source 1[7].

A-1. The measured BCF values of Sources 2–3 were below 500, and the uncertainty of the estimation value of BCF based on the read-across was considered to be entirely permissible, because it had 10-fold margin of the criteria for “highly bioaccumulative (BCF ≥ 5,000)” under CSCL.

A-2. Sources 2–3 and Targets 1–3 have similar structures, in which a hydroxyl, hydroxyl methyl, or carboxyl group is present in the side chain of a biphenyl skeleton at the para position. The difference in the substituted groups is unlikely to significantly affect the bioaccumulation potential. For example, for chemical substances with the same basic skeleton (hydroxyl, hydroxyl methyl, or carboxyl group), measured logPow values are similar. (See Annex IV for more detailed information and an example.) Therefore, their substituted chemicals are thought to have similar bioaccumulation potentials. Hence, Sources 2–3 are relevant analogues for evaluating the bioaccumulation potentials of Targets 1–3.

A-3. From the following two sources of evidence, the bioaccumulation potentials of Targets 1–3 can be considered to be below those of Sources 2–3.

- The measured and estimated BCF values of Sources 2–3 were similar and below 100. The measured BCF values of Sources 2–3 tended to be similar to the estimated BCF values (see data matrix). The bioaccumulation potentials of Targets 1–3 were logically assumed to be almost the same or lower than the measured and estimated BCF values of Sources 2–3, because the estimated BCF values of Targets 1–3 were almost the same or lower than those of Sources 2–3.

- Based on the structural similarity between Sources 2–3 and Targets 1–3, the bioaccumulation potentials of Targets 1–3 were considered to be similar to those of Sources 2–3. Moreover, each measured BCF value of Sources 2–3 was below 100.

B) Source 1 and Targets 1–4 fulfilled three conditions of analogy rule B (as described on page 5). The detailed information for each condition (B-1 to B-3) is provided below.

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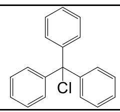
[7] Report on the difference between the measured and estimated BCF values of Source 1.

While searching for a benzyl chloride structure from the training data set in the BCFBAF model, only one derivative was identified (See Table for more detail). The chemical structure of the derivative was significantly different from that of source chemical 1; therefore, the discrepancy between the measured and estimated BCF values could be explained by the lack of training set for chemicals with a benzyl chloride structure.

Table. Information for benzyl chloride derivative is included in the training data set of the BCFBAF model

Structure	
CAS No.	76-83-5
Name	Benzene,1,1,1-(chloromethylidyne)tris-
Mw	278.78
logKow (measured value)	5.25
LogBCF (measured value)	2.63
LogBCF (estimated value)	3.13

B-1. The measured BCF value of Source 1 was below 500, and the uncertainty of the estimation value of BCF based on the read-across was entirely permissible, because it had a 10-fold margin for the criteria of “highly bioaccumulative (BCF ≥ 5,000)” under CSCL.

B-2. Source 1 and Targets 1–4 have relations as those between a parent chemical and degradation products, and structural similarities between them might be high, because the structure is partially retained during degradation.

B-3. The result of comparison of polarity between Source 1 with Targets 1–4 (obtained using reverse-phase HPLC) showed that Targets 1–4 were more hydrophilic than Source 1 (See Annex I for detailed information).

5. STRATEGY FOR AND INTEGRATED CONCLUSION OF DATA GAP FILLING

5.1. Integrated conclusion

When target and source chemicals fulfill the criteria for analogy rule either A or B, the bioaccumulation potential can be judged “not highly bioaccumulative” under CSCL.

In this case study, rules A and B were applied for Targets 1–3, and rule B was applied for Target 4. Based on the bioconcentration data of analogue Sources 2 and 3, the bioaccumulation potentials of Targets 1–4 were qualitatively evaluated as “not highly bioaccumulative” (i.e., BCF values of <500).

Since Targets 1–3 fulfilled the criteria for both the rules, the evaluation results of these chemicals were considered to have higher reliability than that of Target 4.

The following information also supports the assessment result mentioned above:

- The estimated logPow of Targets 1–3 were less than 4.5, which is used as a threshold value for the bioaccumulation criteria under REACH (ECHA, 2014).
- The BCF values of the estimated structures of the 58 biodegradation products of Source 1 were <500.

5.2. Uncertainty

A certain fixed margin needs to be considered for the evaluation of the measurement error for BCF values. Based on the criteria of “highly bioaccumulative (BCF ≥ 5,000)” under the CSCL, the results of evaluation in this analogy rule allowed a 10-fold margin of error.

In this case study, the bioaccumulation potential was evaluated based on the BCF values in accordance with the CSCL criteria; therefore, bioaccumulation via the oral route was not considered.

The results of OECD 301C biodegradation study were used to identify the degradation products of the parent chemical (i.e. Source 1).In this study, biodegradation products that were not observed in the 301C study could occur under different test conditions; however, these products were not included in this assessment.

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ANNEX I DETAILED INFORMATION OF THE BIODEGRADATION TEST DATA OF SOURCE 1 AND THE TEST RESULTS OF COMPARISON OF POLARITY (HYDROPHILICITY) BETWEEN SOURCE 1 AND TARGETS 1–4 BY USING REVERSE-PHASE HPLC

I-1. Detailed information of the biodegradation test data of Source 1

Administrative data	
Study period	2008-11-25 to 2009-03-16
Reliability	1 (reliable without restriction)
DATA SOURCE	
Testing laboratory	Chemical Evaluation and Research Institute, Japan
MATERIALS AND METHODS	
Test guideline	OECD Guideline 301 C (Ready Biodegradability: Modified MITI Test (I))
GLP compliance	yes (incl. certificate)
Test material (CAS No.)	1667-10-3
Test material (Chemical Name)	4,4′-Bis(chloromethyl)biphenyl
Details on test material	Purity: 95.6% (According to attached data)—Water solubility: 20.1 µg/L (20°C)
STUDY DESIGN	
Concentration of activated sludge	Concentration of activated sludge: 30 mg/L
Duration	4 weeks
Initial test substance concentration	100 mg/L
Details on analytical methods	Recovery ratio (Water + test substance) system: 96.1% (Activated sludge + test substance) system: 96.3%
TEST RESULTS	
Extent of degradation (BOD)	0% (-2, -2, -1)
Extent of degradation (HPLC)	3% (4, 7, -2)
Overall remarks	
Test substance partially hydrolyzed in water and formed 4,4′–biphenyldimethanol (log Kow = 2.33; note) and chloride ion. 4,4′–Biphenyldimethanol was oxidized by microbes in (activated sludge + test substance) system, and it formed 4,4′–biphenylcarboxylic acid (log Kow = 3.52; note) through 4′–hydroxymethylbiphenylcarboxylic acid (log Kow = 2.72 note). Further, biodegradation products with unclear structure were detected in (activated sludge + test substance) system. Note: calculated using Kowwin v. 1.67.	

I-2. The test results of comparison of polarity (hydrophilicity) between Source 1 and Targets 1–4 by using reverse-phase HPLC (an excerpt from the report).

Test condition

Composition of liquid chromatography mass spectrometry

Liquid chromatography:	Alliance 2695 (manufactured by Nihon Waters K.K.)
Mass spectrometer:	ZQ2000 (manufactured by Nihon Waters K.K.)
Multi-wavelength detector:	2996PDA (manufactured by Nihon Waters K.K.)

The condition of liquid chromatography

Column	L-column ODS (15 cm × 2.1 mm I.D., manufactured by Chemicals Evaluation and Research Institute, Japan)
Column temperature	40°C
Eluting solution	A: Tetrahydrofuran/Formic acid (500:1 v/v) B: Water/Formic acid (500:1 v/v) Condition of gradient Time (min) A (%) B (%) 0.0 5 95 2.0 5 95 12.0 65 35 25.0 65 35
Flow rate	0.2 mL/min
Injection volume	LC-MS sample 1 5 µL LC-MS sample 2 10 µL
Measuring wavelength	250–340 nm

Condition of mass spectrometry

Ionization method	Electrospray ionization method
Detection of ions	Positive and negative ions
Detection method	Scanning
Scan mass range (m/z)	150–600
Ion source temperature	120°C
Temperature of the desolvation system	400°C
Cone voltage	30 V

Test sample

Standard solution 1 (Test item)	One hundred milligram of 4,4′-Bis(chloromethyl)-1,1′-biphenyl is dissolved in tetrahydrofuran, and the solution having a concentration of 7.5–300 mg/L is prepared.
Standard solution 2 (Target chemical 1)	One hundred milligram of 4,4-biphenyl dimethanol is dissolved in tetrahydrofuran, and the solution having a concentration of 7.5–300 mg/L is prepared.
Sample solution: (Sludge + test item)	The residual liquid in the biodegradation test (OECD TG 301)

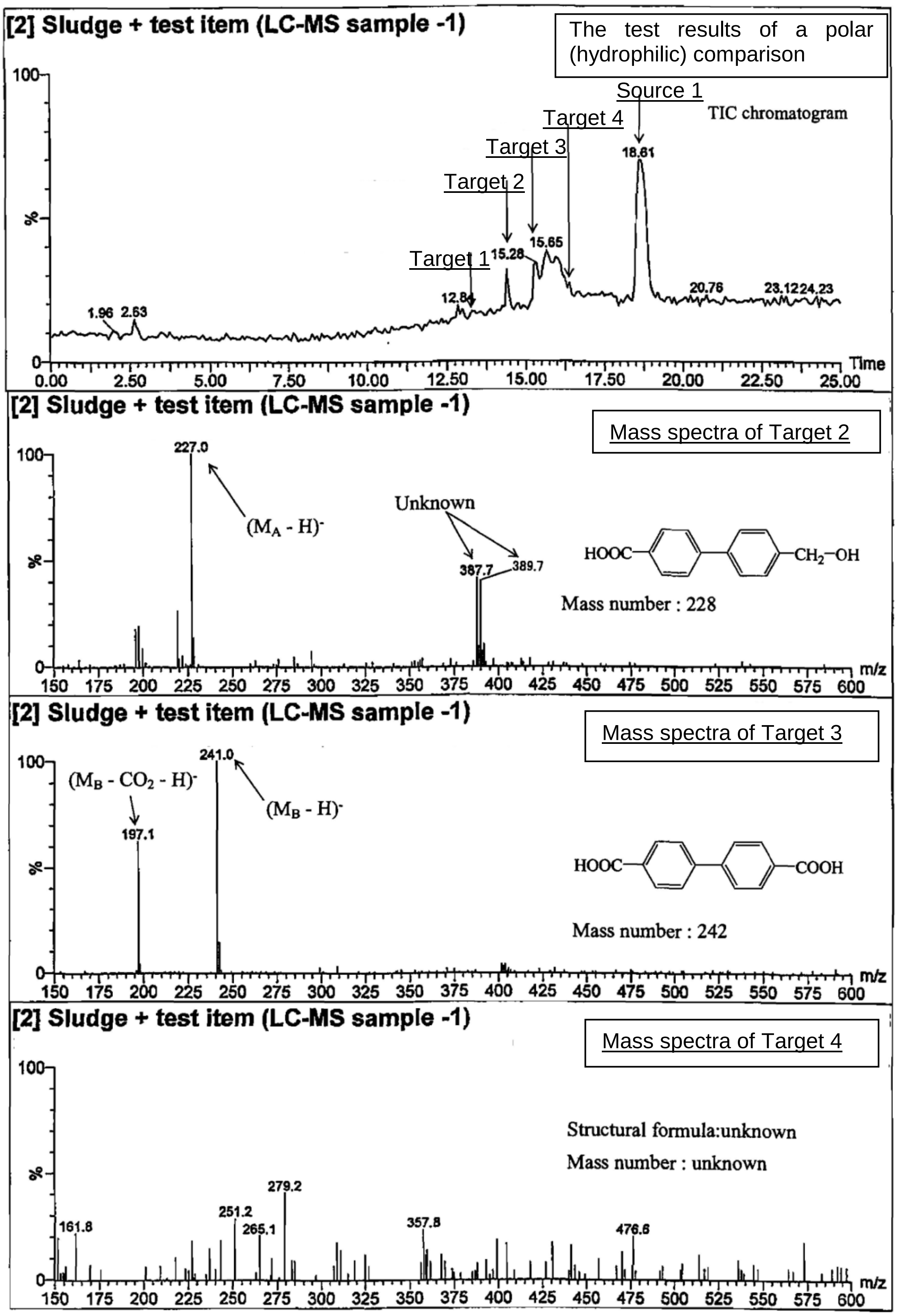
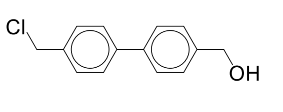
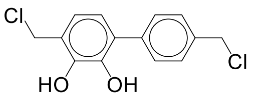
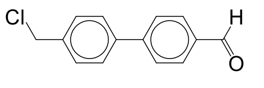
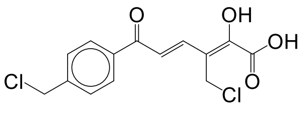
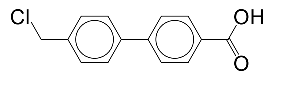


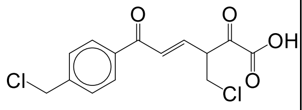
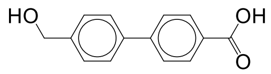
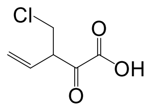
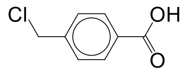
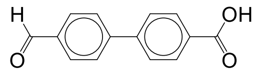
Fig.1 Test results of comparison of polarity (hydrophilicity) between Source 1 and Targets 1–4 by subjecting Targets 2–4 to reverse-phase HPLC and mass spectrometry.

ANNEX II ESTIMATION STRUCTURES OF THE BIODEGRADATION PRODUCTS OF SOURCE 1 IDENTIFIED USING "MICROBIAL METABOLISM SIMULATOR" OF OECD QSARTOOLBOX VER. 3.2

Chemical ID						
		Estimation structure 1	Estimation structure 2	Estimation structure 3	Estimation structure 4	Estimation structure 5
CAS						
Name						
Structure						
Experimental result						
Target endpoint (Bioaccumulation potential (*))						
Physical-chemical data						
logPow (measured value) [-]						
logPow (calculated value) [-]	KOWWIN	3.64	4.4	4.28	3	4.44
	logP Multicase	4.13	4.68	4.50	2.73	4.74
	ClogP	3.55	3.54	3.95	2.25	4.34
Molecular weight [-]		232.7	283.1	230.7	315.1	246.7
Diameter effective [Å]		6.5	7.4	6.5	8.6	6.5
Diameter maximum [Å]		14.5	15.0	14.5	14.7	15.1
Supporting data related to the target endpoint(s)						
		Estimation structure 1	Estimation structure 2	Estimation structure 3	Estimation structure 4	Estimation structure 5
In silico (Endpoint: BCF)	BCFBAF ver.3.01	65	372	309	3	3
	BCF base-line model v.02.07	8	6	91	4	5

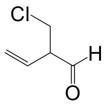
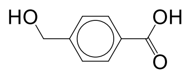
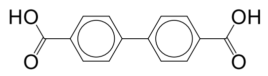
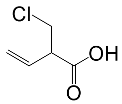
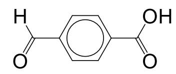
CSCL defines "not highly bioaccumulative" as a BCF of <5,000.

Annex II Estimation structures of the biodegradation products of Source 1 identified using "microbial metabolism simulator" of OECD QSARToolbox ver. 3.2 (Continued)

Chemical ID						
		Estimation structure 6	Estimation structure 7	Estimation structure 8	Estimation structure 9	Estimation structure 10
CAS						
Name			Target chemical 2			
Structure						
Experimental result						
Target endpoint (Bioaccumulation potential (*))						
Physical-chemical data						
logPow (measured value) [-]					2.12 (BIOBYTE (1995))	
logPow (calculated value) [-]	KOWWIN	1.84	2.72	0.27	2.68	3.36
	logP Multicase	2.41	3.21	0.47	2.12	3.58
	ClogP	1.74	2.74	-0.10	2.45	3.19
Molecular weight [-]		315.1	228.2	162.6	170.6	226.2
Diameter effective [Å]		8.4	6.5	7.1	6.5	6.5
Diameter maximum [Å]		14.4	14.7	8.9	11.0	14.8
Supporting data related to the target endpoint(s)						
		Estimation structure 6	Estimation structure 7	Estimation structure 8	Estimation structure 9	Estimation structure 10
In silico (Endpoint: BCF)	BCFBAF ver.3.01	3	3	3	3	3
	BCF base-line model v.02.07	4	4	3	4	5

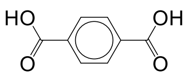
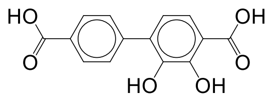
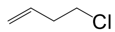
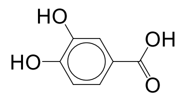
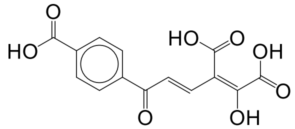
CSCL defines "not highly bioaccumulative" as a BCF of <5,000.

Annex II Estimation structures of the biodegradation products of Source 1 identified using "microbial metabolism simulator" of OECD QSARToolbox ver. 3.2 (Continued)

Chemical ID		Estimation structure 11	Estimation structure 12	Estimation structure 13	Estimation structure 14	Estimation structure 15
CAS						
Name				Target chemical 3		
Structure						
Experimental result						
Target endpoint (Bioaccumulation potential (*))						
Physical-chemical data						
logPow (measured value) [-]			0.93 (HANSCH,C ET AL. (1995))			1.76 (DA,YZ ET AL. (1992))
logPow (calculated value) [-]	KOWWIN	1.35	0.96	3.52	1.60	1.59
	logP Multicase	1.45	1.25	3.82	1.29	1.76
	ClogP	1.14	0.85	3.56	0.95	1.58
Molecular weight [-]		118.6	152.1	242.2	134.6	150.1
Diameter effective [Å]		6.7	6.5	6.5	6.9	6.5
Diameter maximum [Å]		8.1	10.5	14.9	8.3	10.1
Supporting data related to the target endpoint(s)						
		Estimation structure 11	Estimation structure 12	Estimation structure 13	Estimation structure 14	Estimation structure 15
In silico (Endpoint: BCF)	BCFBAF ver.3.01	4	3	3	3	3
	BCF base-line model v.02.07	3	3	5	3	3

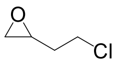
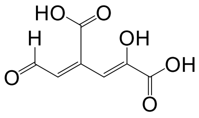
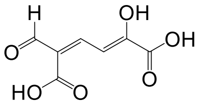
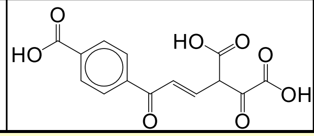
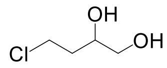
CSCL defines "not highly bioaccumulative" as a BCF of <5,000.

Annex II Estimation structures of the biodegradation products of Source 1 identified using "microbial metabolism simulator" of OECD QSARToolbox ver. 3.2 (Continued)

Chemical ID						
		Estimation structure 16	Estimation structure 17	Estimation structure 18	Estimation structure 19	Estimation structure 20
CAS						
Name						
Structure						
Experimental result						
Target endpoint (Bioaccumulation potential (*))						
Physical-chemical data						
logPow (measured value) [-]		2 (HANSCH,C ET AL. (1995))			0.86 (HANSCH,C ET AL. (1995))	
logPow (calculated value) [-]	KOWWIN	1.76	2.8	2.42	0.91	1.03
	logP Multicase	2.00	4.04	2.29	0.86	0.27
	ClogP	1.85	2.99	2.04	1.06	1.06
Molecular weight [-]		166.1	274.2	90.5	154.1	306.2
Diameter effective [Å]		6.5	7.4	5.3	7.2	8.4
Diameter maximum [Å]		10.7	14.9	8.1	9.8	14.4
Supporting data related to the target endpoint(s)						
		Estimation structure 16	Estimation structure 17	Estimation structure 18	Estimation structure 19	Estimation structure 20
In silico (Endpoint: BCF)	BCFBAF ver.3.01	3	3	19	3	3
	BCF base-line model v.02.07	4	5	9	3	3

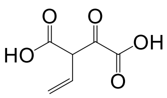
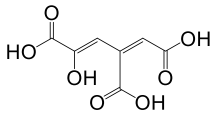
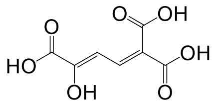
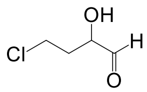
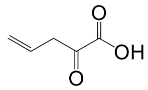
CSCL defines "not highly bioaccumulative" as a BCF of <5,000.

Annex II Estimation structures of the biodegradation products of Source 1 identified using "microbial metabolism simulator" of OECD QSARToolbox ver. 3.2 (Continued)

Chemical ID						
		Estimation structure 21	Estimation structure 22	Estimation structure 23	Estimation structure 24	Estimation structure 25
CAS						
Name						
Structure						
Experimental result						
Target endpoint (Bioaccumulation potential (*))						
Physical-chemical data						
logPow (measured value) [-]						
logPow (calculated value) [-]	KOWWIN	1.12	-0.69	-1.72	-1.16	-0.04
	logP Multicase	1.13	-0.94	-1.05	-0.10	-0.02
	ClogP	0.64	-1.40	-1.17	0.00	-0.67
Molecular weight [-]		106.6	186.1	186.1	306.2	124.6
Diameter effective [Å]		5.4	7.3	7.1	8.5	6.0
Diameter maximum [Å]		8.2	9.9	10.7	14.0	8.4
Supporting data related to the target endpoint(s)						
		Estimation structure 21	Estimation structure 22	Estimation structure 23	Estimation structure 24	Estimation structure 25
In silico (Endpoint: BCF)	BCFBAF ver.3.01	3	3	3	3	3
	BCF base-line model v.02.07	4	2	2	3	2

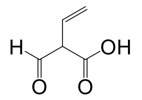
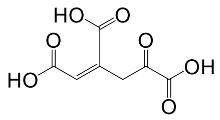
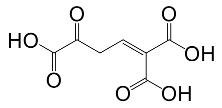
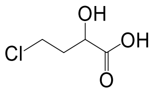
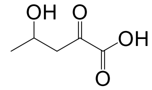
CSCL defines "not highly bioaccumulative" as a BCF of <5,000.

Annex II Estimation structures of the biodegradation products of Source 1 identified using "microbial metabolism simulator" of OECD QSARToolbox ver. 3.2 (Continued)

Chemical ID						
		Estimation structure 26	Estimation structure 27	Estimation structure 28	Estimation structure 29	Estimation structure 30
CAS						
Name						
Structure						
Experimental result						
Target endpoint (Bioaccumulation potential (*))						
Physical-chemical data						
logPow (measured value) [-]						
logPow (calculated value) [-]	KOWWIN	-1.8	-0.44	-1.47	-0.47	-0.4
	logP Multicase	-1.12	-1.61	-1.56	0.07	-0.31
	ClogP	-0.57	-1.04	-0.84	-0.29	-0.47
Molecular weight [-]		158.1	202.1	202.1	122.6	114.1
Diameter effective [Å]		7.0	7.8	7.0	5.9	5.8
Diameter maximum [Å]		8.9	10.4	10.7	8.1	8.7
Supporting data related to the target endpoint(s)						
		Estimation structure 26	Estimation structure 27	Estimation structure 28	Estimation structure 29	Estimation structure 30
In silico (Endpoint: BCF)	BCFBAF ver.3.01	3	3	3	3	3
	BCF base-line model v.02.07	3	3	3	2	3

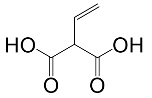
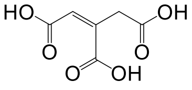
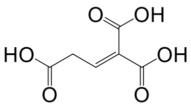
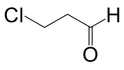
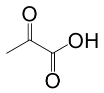
CSCL defines "not highly bioaccumulative" as a BCF of <5,000.

Annex II Estimation structures of the biodegradation products of Source 1 identified using "microbial metabolism simulator" of OECD QSARToolbox ver. 3.2 (Continued)

Chemical ID						
		Estimation structure 31	Estimation structure 32	Estimation structure 33	Estimation structure 34	Estimation structure 35
CAS						
Name						
Structure						
Experimental result						
Target endpoint (Bioaccumulation potential (*))						
Physical-chemical data						
logPow (measured value) [-]						
logPow (calculated value) [-]	KOWWIN	-0.14	-1.47	-2.5	0.1	-1.80
	logP Multicase	-0.12	-2.12	-2.24	-0.02	-1.36
	ClogP	0.24	-1.62	-2.12	-0.49	-1.42
Molecular weight [-]		114.1	202.1	202.1	138.6	132.1
Diameter effective [Å]		6.5	7.8	7.2	6.0	6.0
Diameter maximum [Å]		8.0	10.3	10.9	8.5	8.8
Supporting data related to the target endpoint(s)						
		Estimation structure 31	Estimation structure 32	Estimation structure 33	Estimation structure 34	Estimation structure 35
In silico (Endpoint: BCF)	BCFBAF ver.3.01	3	3	3	3	3
	BCF base-line model v.02.07	2	2	2	2	2

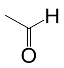
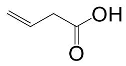
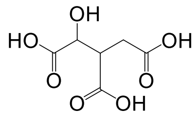
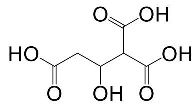
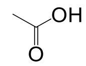
CSCL defines "not highly bioaccumulative" as a BCF of <5,000.

Annex II Estimation structures of the biodegradation products of Source 1 identified using "microbial metabolism simulator" of OECD QSARToolbox ver. 3.2 (Continued)

Chemical ID						
		Estimation structure 36	Estimation structure 37	Estimation structure 38	Estimation structure 39	Estimation structure 40
CAS						
Name						
Structure						
Experimental result						
Target endpoint (Bioaccumulation potential (*))						
Physical-chemical data						
logPow (measured value) [-]						
logPow (calculated value) [-]	KOWWIN	-0.47	-0.14	-1.17	0.58	-1.24
	logP Multicase	-0.25	-1.33	-1.37	0.76	-1.09
	ClogP	0.04	-0.85	-1.07	0.37	-1.24
Molecular weight [-]		130.1	174.1	174.1	92.5	88.1
Diameter effective [Å]		6.7	7.3	7.4	5.1	5.5
Diameter maximum [Å]		8.1	9.4	10.2	7.4	7.2
Supporting data related to the target endpoint(s)						
		Estimation structure 36	Estimation structure 37	Estimation structure 38	Estimation structure 39	Estimation structure 40
In silico (Endpoint: BCF)	BCFBAF ver.3.01	3	3	3	3	3
	BCF base-line model v.02.07	3	2	2	3	2

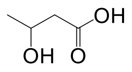
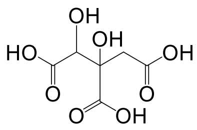
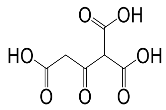
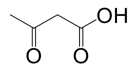
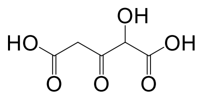
CSCL defines "not highly bioaccumulative" as a BCF of <5,000.

Annex II Estimation structures of the biodegradation products of Source 1 identified using "microbial metabolism simulator" of OECD QSARToolbox ver. 3.2 (Continued)

Chemical ID					
	Estimation structure 41	Estimation structure 42	Estimation structure 43	Estimation structure 44	Estimation structure 45
CAS					
Name					
Structure					
Experimental result					
Target endpoint (Bioaccumulation potential (*))					
Physical-chemical data					
logPow (measured value) [-]	-0.34 (TSCATS)				-0.17 (HANSCH,C ET AL. (1995))
logPow (calculated value) [-] KOWWIN	-0.17	0.93	-2.01	-2.62	0.09
logPow (calculated value) [-] logP Multicase	-0.34	0.56	-2.08	-2.00	-0.31
logPow (calculated value) [-] ClogP	-0.22	0.58	-2.07	-2.09	-0.19
Molecular weight [-]	44.1	86.1	192.1	192.1	60.1
Diameter effective [Å]	4.4	5.3	7.5	7.1	4.8
Diameter maximum [Å]	5.6	8.0	9.7	9.7	6.1
Supporting data related to the target endpoint(s)					
	Estimation structure 41	Estimation structure 42	Estimation structure 43	Estimation structure 44	Estimation structure 45
In silico (Endpoint: BCF) BCFBAF ver.3.01	3	3	3	3	3
In silico (Endpoint: BCF) BCF base-line model v.02.07	2	3	2	2	2

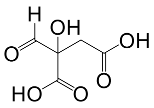
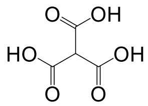
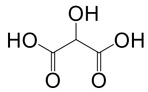
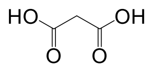
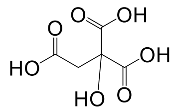
CSCL defines "not highly bioaccumulative" as a BCF of <5,000.

Annex II Estimation structures of the biodegradation products of Source 1 identified using "microbial metabolism simulator" of OECD QSARToolbox ver. 3.2 (Continued)

Chemical ID						
		Estimation structure 46	Estimation structure 47	Estimation structure 48	Estimation structure 49	Estimation structure 50
CAS						
Name						
Structure						
Experimental result						
Target endpoint (Bioaccumulation potential (*))						
Physical-chemical data						
logPow (measured value) [-]						
logPow (calculated value) [-]	KOWWIN	-0.47	-0.99	-3.13	-0.98	-2.62
	logP Multicase	-0.51	-3.04	-2.23	-0.65	-2.54
	ClogP	-0.64	-3.70	-0.79	-0.40	-1.21
Molecular weight [-]		104.1	208.1	190.1	102.1	162.1
Diameter effective [Å]		5.7	7.4	7.3	5.6	6.3
Diameter maximum [Å]		7.7	9.6	9.5	7.9	9.1
Supporting data related to the target endpoint(s)						
		Estimation structure 46	Estimation structure 47	Estimation structure 48	Estimation structure 49	Estimation structure 50
In silico (Endpoint: BCF)	BCFBAF ver.3.01	3	3	3	3	3
	BCF base-line model v.02.07	2	2	2	2	2

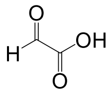
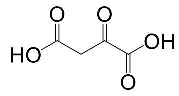
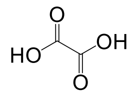
CSCL defines "not highly bioaccumulative" as a BCF of <5,000.

Annex II Estimation structures of the biodegradation products of Source 1 identified using "microbial metabolism simulator" of OECD QSARToolbox ver. 3.2 (Continued)

Chemical ID						
		Estimation structure 51	Estimation structure 52	Estimation structure 53	Estimation structure 54	Estimation structure 55
CAS						
Name						
Structure						
Experimental result						
Target endpoint (Bioaccumulation potential (*))						
Physical-chemical data						
logPow (measured value) [-]					-0.81 (HANSCH,C ET AL. (1995))	
logPow (calculated value) [-]	KOWWIN	-2.72	-2.06	-2.47	-1.25	-2.46
	logP Multicase	-2.29	-1.82	-2.10	-0.81	-2.39
	ClogP	-1.62	-1.45	-1.54	-0.71	-2.04
Molecular weight [-]		162.1	148.1	120.1	104.1	178.1
Diameter effective [Å]		6.8	6.8	5.8	5.5	7.1
Diameter maximum [Å]		8.5	8.1	7.5	7.7	8.8
Supporting data related to the target endpoint(s)						
		Estimation structure 51	Estimation structure 52	Estimation structure 53	Estimation structure 54	Estimation structure 55
In silico (Endpoint: BCF)	BCFBAF ver.3.01	3	3	3	3	3
	BCF base-line model v.02.07	2	2	2	2	2

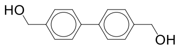
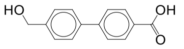
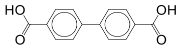
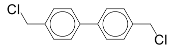
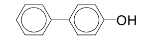
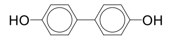
CSCL defines "not highly bioaccumulative" as a BCF of <5,000.

Annex II Estimation structures of the biodegradation products of Source 1 identified using "microbial metabolism simulator" of OECD QSARToolbox ver. 3.2 (Continued)

Chemical ID				
		Estimation structure 56	Estimation structure 57	Estimation structure 58
CAS				
Name				
Structure				
Experimental result				
Target endpoint (Bioaccumulation potential (*))				
Physical-chemical data				
logPow (measured value) [-]				
logPow (calculated value) [-]	KOWWIN	-1.40	-2.58	-1.74
	logP Multicase	-0.95	-1.90	-1.40
	ClogP	-1.76	-1.32	-1.75
Molecular weight [-]		74.0	132.1	90.0
Diameter effective [Å]		4.8	5.9	4.9
Diameter maximum [Å]		6.4	8.4	7.0
Supporting data related to the target endpoint(s)				
		Estimation structure 56	Estimation structure 57	Estimation structure 58
In silico (Endpoint: BCF)	BCFBAF ver.3.01	3	3	3
	BCF base-line model v.02.07	2	2	2

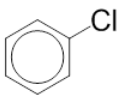
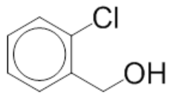
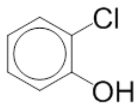
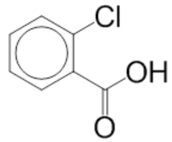
CSCL defines "not highly bioaccumulative" as a BCF of <5,000.

ANNEX III DATA MATRIX OF ALL CHEMICAL SUBSTANCES ANALYZED USING THIS ANALOGUE

Chemical ID								
		Target 1	Target 2	Target 3	Target 4	Source 1	Source 2	Source 3
CAS		-	-	787-70-2	-	1667-10-3	92-69-3	92-88-6
Name		4,4-Biphenyl dimethanol	4'-(hydroxymethyl)-[1,1'-biphenyl]-4-carboxylic acid	1,1'-Biphenyl-4,4'-dicarboxylic acid	-	4,4'-Bis(chloromethyl)-1,1'-biphenyl	p-Phenylphenol	4,4-Dihydroxydiphenyl
Structure					Unidentified			
Summary of data gap filling								
Target endpoint (Bioaccumulation potential (*1))	Experimental result (*2, 3)					Not highly bioaccumulative OECD TG305, GLP (Test term: 28 days) High concentration[0.01 mg/L] BCF≤5 Low concentration[0.001 mg/L] BCF≤48	Not highly bioaccumulative OECD TG 305, non-GLP (Test term: 42 days) High concentration[0.02 mg/L] BCF=39–57 Low concentration[0.002 mg/L] BCF=30–48	Not highly bioaccumulative OECD TG305, GLP (Test term: 28 days) High concentration[0.02 mg/L] BCF=11–34 Low concentration[0.002 mg/L] BCF=17–33
	Integrated conclusion (e.g. read-across) (*4)	**Not highly bioaccumulative (Read-across) [Comply with rules A and B.]**	**Not highly bioaccumulative (Read-across) [Comply with rules A and B.]**	**Not highly bioaccumulative (Read-across) [Comply with rules A and B.]**	**Not highly bioaccumulative (Read-across) [Comply with rule B.]**			
Physical-chemical data								
Melting point [^{o}C]							166	283
Boiling point [^{o}C, 760mmHG]							305	
Water solubility [mg/L] (Test temperature, Test method, GLP (*2))						0.0201 (20^{o}C, unknown, non-GLP)	38 (unknown, unknown, non-GLP)	32.1 (20^{o}C, OECD TG105, GLP)
logPow (measured value) [-] (Test method, GLP (*))						4.5 (OECD TG117, GLP)	3.2 (unknown, non-GLP)	2.75 (OECD TG117, GLP)
logPow (calculated value) [-]	KOWWIN	2.33	2.72	3.52		5.36	3.28	2.80
	logP Multicase	2.60	3.21	3.82		5.66	3.20	3.14
	ClogP	1.95	2.74	3.56		5.15	3.36	2.70
Molecular weight [-]		214.3	228.2	242.2		251.1	170.2	186.2
Diameter effective [Å]		6.5	6.5	6.5		6.5	6.5	6.5
Diameter maximum [Å]		14.1	14.7	14.9		15.0	12.1	12.7
Supporting data related to the target endpoint(s)								
		Target 1	Target 2	Target 3	Target 4	Source 1	Source 2	Source 3
In silico (Endpoint: BCF)	BCFBAF ver.3.01	9	3	3		1,585	60	32
	BCF base-line model v.02.07	4	4	5		2,045	16	4
Other data	Comparison result of polarity (hydrophilicity) between Sorce1 and Targets 1–4.	High Polarity Target 1 > Target 2 > Target 3 >Target 4 > Source 1 Low Polarity						
	Biodegradation test data (*2, 3)	Biodegradation product 1 of Source 1 in the biodegradation test. (Quantity in the biodegradation test: 2%–9%)	Biodegradation product 2 of Source 1 in the biodegradation test. (Quantity in the biodegradation test: unknown)	Biodegradation product 3 of Source 1 in the biodegradation test. (Quantity in the biodegradation test: unknown)	Biodegradation product 4 of Source 1 in the biodegradation test. (Quantity in the biodegradation test: unknown)	OECD TG 301C , GLP (Test term: 28 days) Extent of degradation BOD: 0% (-2%, -2%, -1%) HPLC: 3%(4%, 7%, -2%) Remarks: Test substance partially hydrolyzed in water and formed Target 1 and chloride ion. Target1 underwent microbial oxidation in (activated sludge + test substance) system and formed Target 3 through Target 2. Biodegradation products with unknown structure (Target 4) were detected in (activated sludge + test substance) system.	OECD TG 302C, non-GLP (Test term: 28 days) Extent of degradation BOD: 0% TOC: 3% HPLC: 15%	OECD TG 301C, GLP (Test term: 28 days) Extent of degradation BOD: 0% HPLC: 0%

*1 CSCL defines “not highly bioaccumulative” as a BCF of <5,000.
*2 "non-GLP" includes "The test method is unknown".
*3 Data used in this evaluation were assessed and judged by the expert committee through the official procedure under CSCL.
*4 If target chemicals comply with both the rules, the B assessment results are considered to have more reliability than for the target chemicals that comply with only one rule.

ANNEX IV REFERENCE DATA—BIOCONCENTRATION POTENTIAL AND LOGPOW VALUE OF CHLOROBENZENE SUBSTITUTES

Chemical ID					
		Refference 1	Refference 2	Refference 3	Refference 4
CAS		108-90-7	17849-38-6	95-57-8	118-91-2
Name		Benzene, chloro-		Phenol, 2-chloro-	Benzoic acid, 2-chloro-
Structure					
Experimental result					
Bioconcentration test data (*)		OECD TG305, non-GLP (Test term: 56 days) High concentration[0.15 mg/L] BCF=4.3–39.6 Low concentration[0.015 mg/L] BCF=3.9–22.8		OECD TG305, non-GLP (Test term: 42 days) High concentration[0.04 mg/L] BCF=14–24 Low concentration[0.004 mg/L] BCF=16–29	OECD TG305, non-GLP (Test term: 42 days) High concentration[1.25 mg/L] BCF≤1 Low concentration[0.125 mg/L] BCF≤10
Physical-chemical data					
logPow (measured value) [-]		2.89 (HANSCH,C ET AL. (1995))	1.89 (OECD TG117, GLP)	2.15 (HANSCH,C ET AL. (1995))	2.05 (HANSCH,C ET AL. (1995))
logPow (calculated value) [-]	KOWWIN	2.64	1.72	2.16	2.18
	logP Multicase	2.84	1.77	2.15	1.98
	ClogP	2.86	1.82	2.15	2.10
Molecular weight [-]		6.5	7.2	7.1	7.2
Diameter effective [Å]		8.3	8.5	8.3	9.2
Diameter maximum [Å]		112.6	142.6	128.6	156.6
Supporting data related to the target endpoint(s)					
In silico (Endpoint: BCF)	BCFBAF ver.3.01	35	4	12	3
	BCF base-line model v.02.07	14	4	5	4

* CSCL defines "not highly bioaccumulative" as a BCF of <5,000.
"non-GLP" includes "The test method is unknown".