Annex XV Report

PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE AS A CMR CAT 1 OR 2, PBT, VPVB OR A SUBSTANCE OF AN EQUIVALENT LEVEL OF CONCERN

Substance Name: 1,2,3-Trichlorobenzene

EC Number: 201-757-1

CAS Number: 87-61-6

Submitted by:	Germany
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PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE AS A CMR CAT 1 OR 2, PBT, VPVB OR A SUBSTANCE OF AN EQUIVALENT LEVEL OF CONCERN

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- *It is proposed to identify the substance as substance of equivalent concern according to Article 57 (f).*

Summary of how the substance meets the CMR (Cat 1 or 2), PBT or vPvB criteria, or is considered to be a substance of an equivalent level of concern

Taking into account all available information on persistent, bioaccumulative and toxic properties of 1,2,3-trichlorobenzene (1,2,3-TCB), it is concluded that 1,2,3-TCB is a PBT-substance. The PBT-properties of 1,2,3-trichlorobenzene have already been agreed in the TC NES subgroup on identification of PBT and vPvB substances in 2003 (and were supported by the TCNES and CA-Meeting), and as a result 1,2,3-trichlorobenzene was assessed as PBT-substance.

The substance is considered to fulfil the P criterion, and also the vP-criterion. In addition to that, also the B criterion is fulfilled. In case that lipid normalization to 5% is performed, 1,2,3-trichlorobenzene would not clear fulfil the B criterion. However, if doing so the maximum BCF will still be close to the B criterium of Annex XIII. Although 1,2,3-trichlorobenzene is highly toxic for aquatic organisms tested on the long-term, it does not formally meet the T-criterion. The overall conclusion is however drawn in a weight of evidence approach, taking supporting evidence into account relating to the very high long-range environmental transport potential of this substance. It raises an equivalent concern according to Article 57 (f).

Registration number(s) of the substance or of substances containing the substance:

PART I

JUSTIFICATION

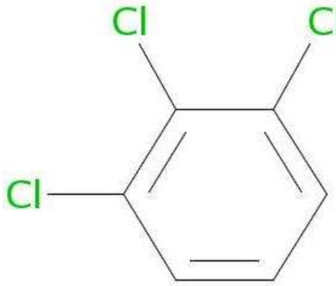
1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Chemical Name:	Benzene, 1,2,3-trichloro-
EC Name:	1,2,3-trichlorobenzene
EC Number	201-757-1
CAS Number:	87-61-6
IUPAC Name:	1,2,3-trichlorobenzene

1.2 Composition of the substance

The detailed composition of the substance is confidential and provided in the technical dossier.

Chemical Name:	Benzene, 1,2,3-trichloro-
EC Number:	201-757-1
CAS Number:	87-61-6
IUPAC Name:	1,2,3-trichlorobenzene
Molecular Formula:	$C_6H_3Cl_3$
Structural Formula:	
Molecular Weight:	181.45 g/mol
Typical concentration (% w/w):	Min. ≥ 99 % (w/w)
Concentration range (% w/w):	-

1.3 Physico-chemical properties

Table 1: Summary of physico- chemical properties

REACH ref Annex, §	**Property**	**IUCLID section**	**Value**	**[enter comment/reference or delete column]**
VII, 7.1	Physical state at 20°C and 101.3 kPa	4.1	Solid, white crystals or platelets from alcohol	HSDB, 2010
VII, 7.2	Melting/freezing point	4.2	51.3 °C	HSDB, 2010
VII, 7.3	Boiling point	4.3	218.5 °C	HSDB, 2010
VII, 7.5	Vapour pressure	4.6	0.21 mm Hg at 25 °C	HSDB, 2010
VII, 7.7	Water solubility	4.8	18 mg/L at 25 °C	HSDB, 2010
VII, 7.8	Partition coefficient n-octanol/water (log value)	4.7 partition coefficient	log K_{OW} = 4.05	HSDB, 2010
XI, 7.16	Dissociation constant	4.21	---	
VII, 7.4	Density	4.4	1.4533 g/m³ at 25 °C	HSDB, 2010
	Henry's Law Constant	5.4.2	282.16 Pa x m³ / mol	Calculation
VII, 7.9	Flash point	4.11	113 °C (close cup)	PTB-AG 3.43, CHEMSAFE, 2009
VII, 7.10	Flammability	4.13	Pyrophoric properties: The classification procedure needs not to be applied because the organic substance is known to be stable into contact with air at room temperature for prolonged periods of time (days). Flammability in contact with water: The classification procedure needs not to be applied because the organic substance does not contain metals or metalloids.	BAM, II.2 (2010) BAM, II.2 (2010):
VII, 7.11	Explosive properties	4.14	The classification procedure needs not to be applied because there are no chemical groups present in the molecule which are associated with explosive properties.	BAM, II.2 (2010)
VII, 7.12	Relative Self-ignition temperature for solids	4.12	The classification procedure needs not to be applied because the organic substance has a	BAM, II.2 (2010)

			melting point ≤ 160 °C,	
VII, 7.13	Oxidizing properties	4.15	The classification procedure needs not to be applied because contained chlorine atoms are chemically bonded only to carbon.	BAM, II.2 (2010)

2 HARMONISED CLASSIFICATION AND LABELLING

No entry in Table 3.1/3.2 of Annex VI of Regulation (EC) 1272/2008 as amended by the 1st ATP.

3 ENVIRONMENTAL FATE PROPERTIES

3.1 Degradation

3.1.1 Abiotic degradation

3.1.1.1 Hydrolysis

Due it’s chemical structure 1,2,3-trichlorobenzene (1,2,3-TCB) is not expected to hydrolyse under normal environmental conditions. This assumption is supported by the experimental data (Korte and Freitag, 1986) on hydrolysis of 1,2,4-trichlorobenzene (1,2,4-TCB) at 50°C, which has the same chemical composition and nearly the same chemical structure.

3.1.1.2 Phototransformation/photolysis

3.1.1.2.1 Phototransformation in air

Indirect photochemical degradation in the troposphere is considered to be very slow based on an estimated OH radical reaction rate of $0.282 \cdot 10^{-12}$ $cm^3 s^{-1} molecules^{-1}$, which corresponds to an atmospheric half-life of 57 days for the reaction with OH-radicals (AOPWIN v1.91; 24 h day^{-1}; OH radical concentration of $5 \cdot 10^5$ OH cm^{-3}). A QSAR Model Reporting Format and a QSAR Prediction Reporting Format are annexed to document the model prediction.

3.1.1.2.2 Phototransformation in water

The environmental exposure occurs in the whole water column. Because of the substance’s behaviour it will predominantly volatilize from water or adsorb at suspended organic matter and sediment. Photodegradation of 1,2,3-TCB is expected to be a relevant degradation process only in very shallow clear waters and in the first few centimetres layer of the water column. Therefore aquatic photodegradation is not considered to have relevant impact on the overall persistency of 1,2,3-TCB in the environment.

Summary

Based on the available data, 1,2,3-TCB has a low degradation rate in the atmosphere and is not expected to hydrolyse under environmental conditions.

3.1.2 Biodegradation

3.1.2.1 Screening tests

The ready biodegradability was studied with a method corresponding to the OECD TG 301C, Modified MITI (I) test (MITI-List, 2002). The test concentration was 100 mg/l and the activated sludge concentration was 30 mg/l. In the aerobic study, the degradation measured as Biochemical Oxygen Demand (BOD) was 0% after 14 days.

3.1.2.2 Simulation tests

The behaviour and fate of chlorobenzenes in spiked and sewage sludge-amended soil was tested by Wang and Jones (Wang and Jones, 1994). For testing the fate, four different experimental conditions were investigated: (1) normal; (2) sterilized; (3) sterilized and shaded; (4) sterilized, shaded and sealed. Under condition (4) no decrease of concentration was observed. Whereas under condition (1)-(3) the concentration of TCB decreased. This indicated volatilization as main loss process. The loss process in soil occurs in two steps (two step first order kinetic model). In the first step the TCB volatilize to the atmosphere over short periods. The second step was much slower and was presumably controlled by the rate of compound desorption from soil. A proportion of the TCB will stay in the soil for much longer periods. The concentration in spiked soil decreased faster than in sludge amended soil.

Table 2: Half-lives of TCB in the sewage sludge-amended soil and standard spiked soil in microcosm experiments (Wang and Jones, 1994)

Compound	First step				Second step			
	Sewage sludge-amended soil		Standard spiked soil		Sewage sludge-amended soil		Standard spiked soil	
	Loss (%)	DisDT$_{50}$ (d)	Loss (%)	DisDT$_{50}$ (d)	Loss (%)	DisDT$_{50}$ (d)	Loss (%)	DisDT$_{50}$ (d)
1,2,4-TCB	83.2	22.5	64.5	12.5	2.26	49500	19.8	194
1,2,3-TCB	88.6	22.2	73.0	15.0	4.45	1370	12.8	222
1,3,5-TCB	85.3	23.7	71.2	10.5	6.22	239	14.8	238

Additionally, a read-across approach was carried out, comparing 1,2,3-TCB with its structural analogues 1,2,4-TCB and 1,3,5-TCB. A reporting format is annexed to this document which contains a more detailed discussion of the read-across approach (reporting format for the analogue approach).

Biodegradability was assessed based on structural considerations, evaluation of the available data and evaluation of possible biodegradation pathways.

It is expected that environmental degradation of all three trichlorobenzene isomers proceeds via the same biodegradation pathways. The observed biodegradation is generally slow, with 1,3,5-trichlorobenzene being slightly more persistent than the other isomers. The most experimental results are available for 1,2,4-trichlorobenzene, which is persistent in soil and sediment. 1,2,3-trichlorobenzene is expected to show very similar properties with respect to biodegradability.

3.1.3 Summary and discussion on degradation

1,2,3-TCB has a low degradation rate in the atmosphere and is not expected to hydrolyse under environmental conditions. The substance was shown to be persistent in soil. Read-across shows that the biodegradability is expected to be similar to the close structural analogue 1,2,4-TCB, which is persistent in soil and sediment and which is considered to fulfil the P and the vP criterion.

In conclusion, 1,2,3-TCB is regarded to fulfil the P and the vP criterion of Annex XIII of the REACH regulation.

3.2 Environmental distribution

3.2.1 Adsorption/desorption

Based on model estimates a K_{OC} of 2402 L/kg has been estimated (ECHA, 2008). Therefore a high adsorption potential and a low mobility in soil is expected for 1,2,3-Trichlorobenzene. Due to the slow degradation in soil, the substance may contaminate groundwater by leaching through sandy soils with low organic carbon content.

3.2.2 Volatilisation

Calculation of the Henry constant using the equation HENRY=VP*MOLW/SOL from the Guidance document for Chemical Safety Assessment (ECHA, 2008) and the substance properties from table 1 results in a Henry constant of 282.16 $Pa*m^3*Mol^{-1}$. This indicates that the substance is highly volatile from water. Due to the high adsorption potential to organic matter, volatilisation from soil and sludge is expected to be lower.

The distribution coefficient $K_{air,water}$ (Henry coefficient) calculated from the Henry constant is 0.12.

3.2.3 Distribution modelling

Distribution in Waste Water Treatment Plant

The modelling of the distribution in a municipal Waste Water Treatment Plant was done with SimpleTreat 3.0 (debugged version, 7 Feb 1997) and the result of the Screening Test on ready biodegradation (substance is not biodegradable; k=0/h).

Table 3: Distribution in WWTP (Simple Treat 3.0)

Summary of distribution	(Percent)
To air	67.5
To water	14.9
Via primary sludge	16.1
Via surplus sludge	1.4
Degraded	0.0
Total	100

The result of the distribution modeling in a WWTP indicates that nearly 68 percent of the 1,2,3-TCB found in the influent waste water is emitted to air.

Long-range Transport

An important indicator for the environmental persistence can be the long-range transport to remote areas. For the calculation of the long-range transport potential of 1,2,3-Trichlorobenzene two different multimedia models have been used. On the one hand the OECD Pov and LRTP Screening Tool (OECD, 2006) has been used and on the other hand the model ChemRange (Scheringer, 1996) has been used. Both models require only a few input parameters. These are the partition coefficients octanol/water, Kow, the dimensionless Henry's Low Constant, Kaw and the environmental degradation half-lives in air, water and soil.

Unfortunately there is only one measured DisT50 available for 1,2,3-Trichlorobenzene. This is the DisT50 in soil. Although, it is well known that this DisT50 represents not only degradation this value was used in a calculation. 1,2,3-Trichlorobenzene is benchmarked as “non” biodegradable. According to TGD (ECHA 2008) the half-lives in soil and water have to be considered as infinite. However the models require a discrete value for the simulation. Due to this fact the half-lives according to the TGD for inherent biodegradation in water of 150 d and 3000 d in soil have been used. Furthermore, the half-lives in water have been calculated on the one hand according to Arnot (Arnot et al., 2005) and on the other hand using the QSAR-model CATALOGIC (OASIS Catalogic v5.10.7, 2009). Finally four calculations with different half-lives for water and soil have been carried out to show the influence of these half-lives on the long-range transport potentials of 1,2,3-Trichlorobenzene.

Table 4: Input parameters for both models

Input parameter	1,2,3-TCB (TGD)	1,2,3-TCB (Arnot)	1,2,3-TCB (Catalogic)	1,2,3-TCB (measured soil)
logKow	4,05	4,05	4,05	4,05
logKaw	-0,936	-0,936	-0,936	-0,936
$t_{½}$ (air) [d]	57	57	57	57
$t_{½}$ (water) [d]	150	91,025	82	150
$t_{½}$ (soil) [d]	3000	273,075	246	222

Results using the OECD P_{ov} and LRTP Screening Tool:

Figure 1 shows that all four calculations yield nearly the same values for characteristic travel distance (CTD) and overall persistency (P_{ov}). Substances with CTD and P_{ov} values of this magnitude are considered to show a high long-range transport potential.

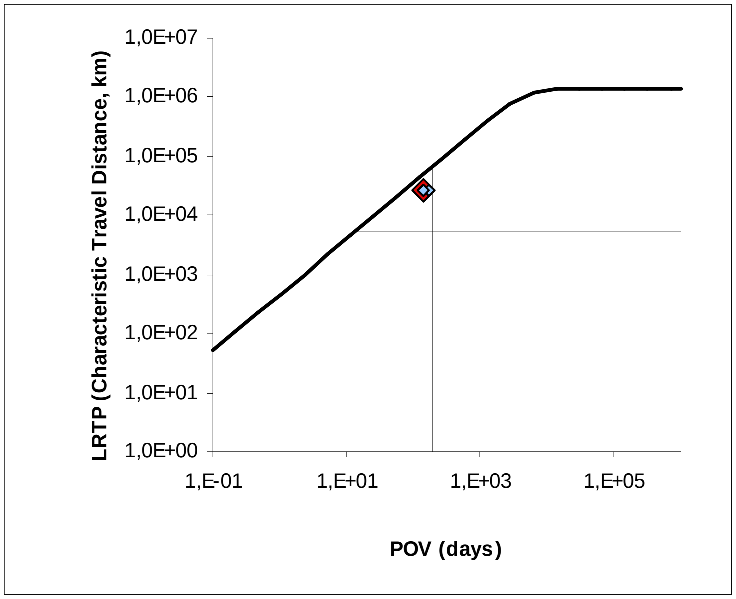


Figure 1: Characteristic Travel Distance (CTD) and overall persistence (P_{ov}) of 1,2,3-Trichlorobenzene

In order to bechmark the calculated long-range transport potential of 1,2,3-Trichlorobenzene the results have been compared with the long-range transport potential of the well known POPs PCB

28, PCB 101 and PCB 153, regulated under the Stockholm Convention. In Table 5, the characteristic travel distances (CTD) are listed:

Table 5: Characteristic Travel Distances [km]

Substance	CTD [km]
1,2,3-Trichlorobenzene (Arnot)	26992
1,2,3-Trichlorobenzene (Catalogic)	26951
1,2,3-Trichlorobenzene (measured soil)	27180
1,2,3-Trichlorobenzene (TGD)	27199
PCB 153	12629
PCB 101	8595
PCB 28	3298

Figure 2 illustrates that the long-range transport potential of 1,2,3-Trichlorobenzene is larger than the long-range transport potential of all three PCBs.

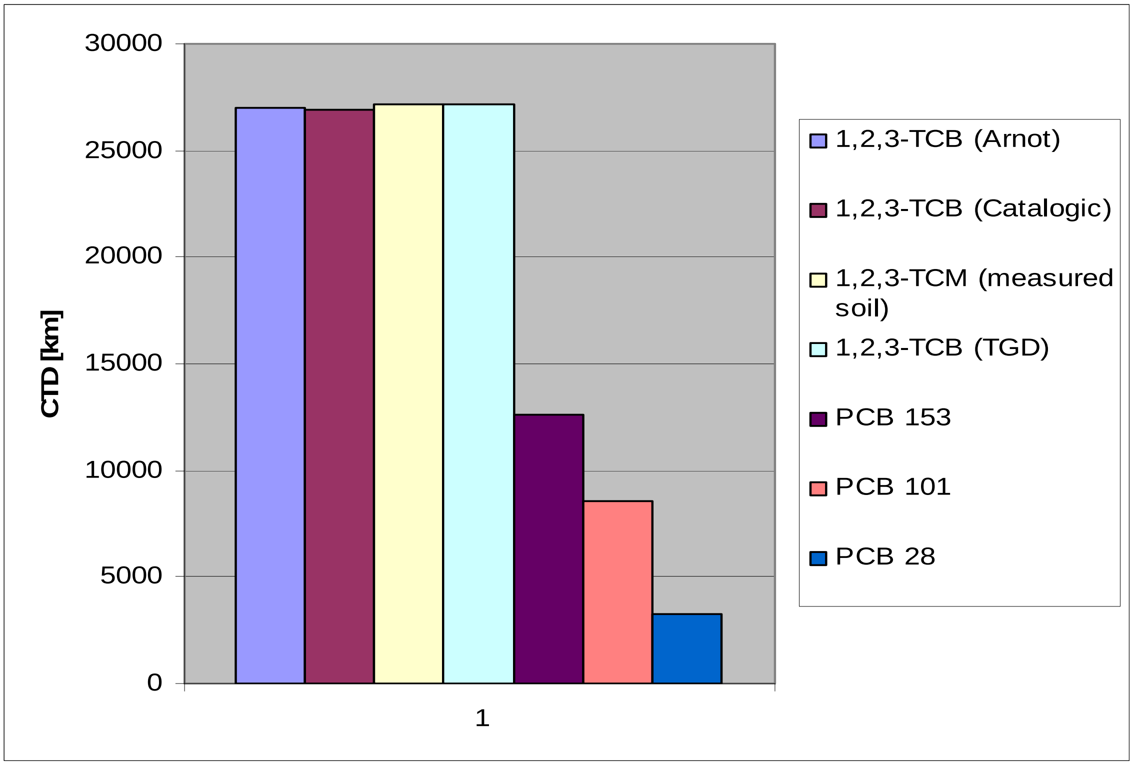


Figure 2: Characteristic Travel Distances of 1,2,3-TCB compared to PCB 28, PCB 153 and PCB 101

<u>Results using ChemRange:</u>

In contrast to the OECD P_{ov} and LRTP Screening Tool, ChemRange calculates the spatial range of a chemical. The spatial range is calculated as the fraction of earth circumference which can be reached by a substance. The long-range transport is calculated for the surface compartments soil and water and air. In order to benchmark the calculated long-range transport potential of 1,2,3-Trichlorobenzene the results have been compared with the long-range transport potential of the well known POPs PCB 28, PCB 101 and PCB 153, regulated under the Stockholm Convention. Using a release scenario to air the calculated spatial ranges are listed in Table 6.

Table 6: Spatial ranges

Substance	Range soil (Fraction of earth circumference)	Range water (Fraction of earth circumference)	Range air (Fraction of earth circumference)
1,2,3-Trichlorobenzene (Arnot)	0.55	0.55	0.55
1,2,3-Trichlorobenzene (Catalogic)	0.55	0.55	0.55
1,2,3-Trichlorobenzene (measured soil)	0.56	0.56	0.56
1,2,3-Trichlorobenzene (TGD)	0.56	0.56	0.56
PCB 28	0.29	0.30	0.29
PCB 101	0.32	0.33	0.32
PCB 153	0.40	0.40	0.40

Comparison of results

The calculated spatial ranges for 1,2,3-TCB using a release scenario to soil are very similar.

The high long-range transport potential of 1,2,3-Trichlorobenzene and PCB 28 is illustrated by Figure 3 and Figure 4. Both diagrams are similar and show a shape which is characteristic for substances with a high long-range transport potential. In case of a substance with a low long-range transport potential the shape of the plot would just a sharp peak at the source point.

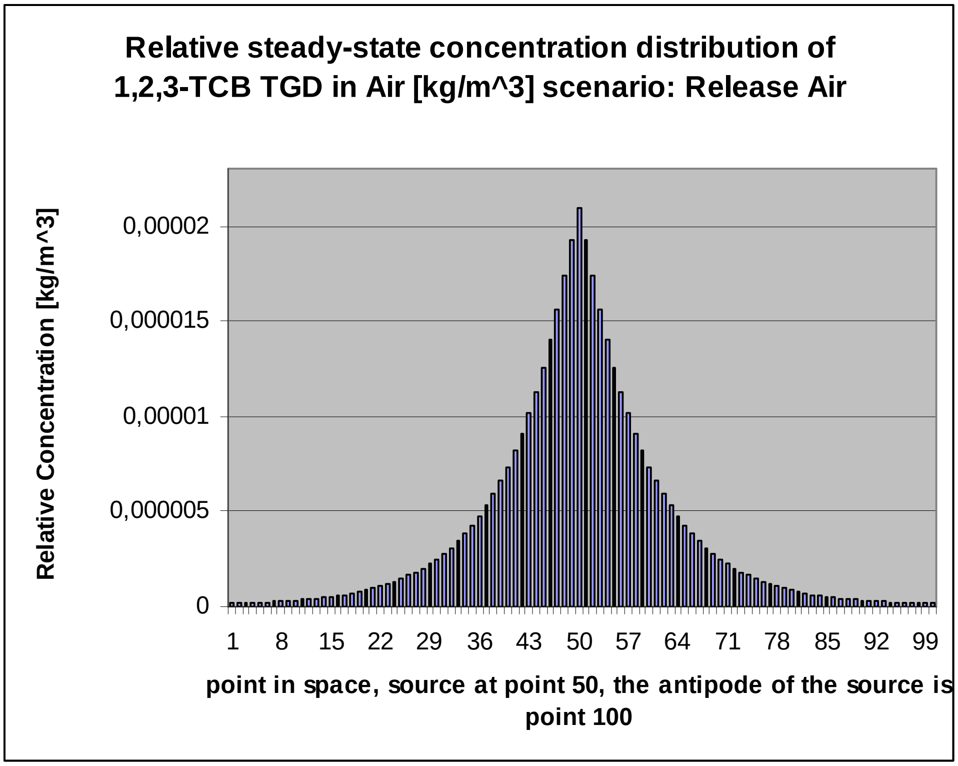


Figure 3: Relative steady-state concentration distribution of 1,2,3-Trichlorobenzene

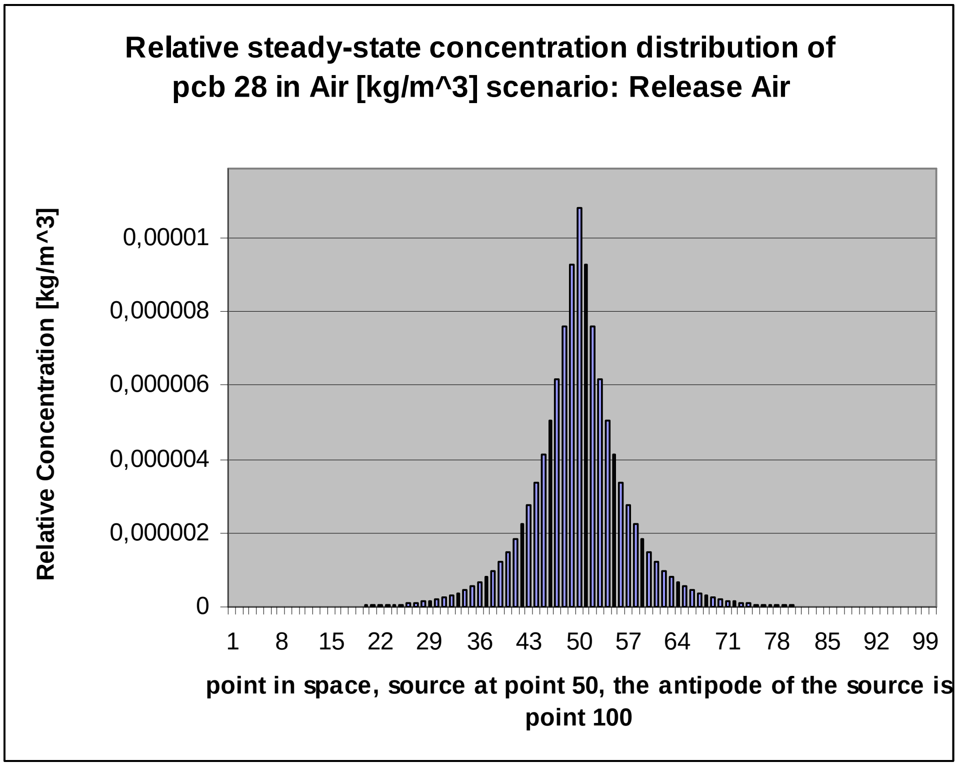


Figure 4: Relative steady-state concentration distribution of PCB 28

Conclusions:
Due to its high volatility (Henry constant of 282.16 Pa*m³*Mol^{-1}), 1,2,3-TCB is expected to be distributed from water to air. In the air, 1,2,3-TCB is persistent (estimated half life 57 days) and may be transported via air for more than several thousand kilometres. Distributed by this pathway also to remote areas, 1,2,3-TCB will be deposited there again to soil or water remaining where it may be even more persistent e.g. due to lower temperatures.

Model calculations confirm the expected potential for long-range transport, as both the OECD P_{ov} and LRTP Screening Tool and ChemRange yield a long-range transport potential that is higher for 1,2,3-Trichlorobenzene than for the POPs PCB 101, 153 and PCB 28. Thus, it can be concluded that 1,2,3-Trichlorobenzene is persistent in air and has a high long-range transport potential.

3.3 Bioaccumulation

3.3.1 Aquatic bioaccumulation

3.3.1.1 Bioaccumulation estimation

The log K_{ow} of 4.05 indicates that bioconcentration in aquatic organisms may occur.

3.3.1.2 Measured bioaccumulation data

Table 7: Available bioconcentration factors (BCF)

Organism	Exposure mg/L	Exposure days	BCF whole	Lipid content	Reference	Rel.
<u>Fish:</u> *Poecilia reticulata*	10% of LC$_{50}$	5	1860 (kin.)	5±2%	(van Hoogen and Opperhuizen, 1988)	4
Gambusia affinis (Mosquito fish)	0.038-0.132	4	430[1] (kin.)	3.1%	(Chaisuksant et al., 1997)	3
Salmo gairdneri (hatchling)	0.0038-0.0061	2	710[1] (kin.)	3.2%	(Galassi and Calamari, 1983)	3
Poecilia reticulata	note[2]	not given	702[2]	5.4%	(Geyer et al., 1985)	4
Salmo gairdneri	4.3 *10^{-6} 72 *10^{-6}	119 105	1200[3] (ss) 2600[3] (ss)	8.3% 8.8%	(Oliver and Niimi, 1983)	3
Cyprinus carpio	0.0025 0.025	42 42	130-1200[4] 350-980[4]	not given	(MITI-List, 2002)	2
<u>Invertebrates:</u> *Lymnaea stagnalis (Pond snail)*	0.025-0.05	10	4-9	0.5%	(Legierse et al., 1998)	2

Reliability scores: 1) reliable without restriction, 2) reliable with restriction, 3) not reliable, 4) not assignable.

[1] These studies were deemed not reliable as the exposure period lasting 2-4 days was insufficiently short; [2] Comparison of literature-reported BCF values for diverse fish species and varying lipid contents. Original literature not reviewed; [3] This study was rated not reliable because fish were exposed simultaneously to 12 substances and the overall concentration may have elicited adverse effects on fish (conc. of 1,2,3-trichlorobenzene = 4.3 / 72 ng/L, overall conc. = 116 / 2544 ng/L); [4] A mixture of three isomeric trichlorobenzenes was administered and the individual BCF were calculated. There is no further information given on lipid normalization of BCF.

There are only few data on bioaccumulation of 1,2,3-trichlorobenzene available. The study published by van Hoogen and Opperhuizen (1988) was intentionally designed to assess the lethal concentration of trichlorobenzenes for Guppy. For evaluating the bioconcentration the exposure concentration was set to 10% of LC$_{50}$ and the BCF was calculated for 1860 after exposure duration of 5 days. However, due to the short exposure period the calculation of BCF is solely based on kinetic parameters. Therefore and also because of the high exposure concentration the reliability of the study is considered to be not assignable.

The studies conducted by Chaisuksant et al. (1995) and Galassi et al. (1983) are considered to be not reliable as the exposure duration was short (2-4 days) and fish were not fed. In both studies the calculated BCF were derived from kinetic parameters. Additionally, in the experiment with mosquito fish specimen, the fish were exposed to a mixture of eight halogenated benzenes. For the highest of the three overall exposure concentrations each constituent was dosed at 1/20 of LC$_{50}$.

In a study conducted by Oliver and Niimi (1983) trout with an initial weight of about 250 g were exposed to two different overall concentrations of a mixture containing 12 chlorinated organic compounds. The uptake period was extended to 119 days and 105 days, respectively, and the trout reached a final weight of about 400 g. Food was also analyzed for contamination with trichlorobenzenes and blank values were considered in BCF calculation. For the accumulation study administering a higher exposure concentration a BCF of 2600 was reported. However, this study was deemed not reliable because 12 substances were simultaneously administered and effects regarding mixture toxicity influencing bioaccumulation can not be excluded due to the elevated level of background contaminants.

The MITI database also provides BCF values for 1,2,3-trichlorobenzene determined for carp using a standard test system. Although a mixture of all three isomeric trichlorobenzenes was administered in two different overall concentrations, the individual concentrations of each isomer in exposure medium as well as in fish were analyzed. The reported BCF values range between 130 and 1300 but no further information on lipid content or lipid normalization are given.

Bioaccumulation tests of 1,2,3-trichlorobenzene in pond snails led to apparently negligible BCF values below 10 (Legierse et al., 1998).

In summary, BCF values having at least reliability scoring 4 can be stated within the range from 130 to 1860. Notwithstanding the low reliability of the study by Oliver and Niimi a maximum BCF of 2600 was also observed. Therefore a BCF of > 2000 can be derived as a realistic worst case estimate. In case that a lipid normalization to 5% is applied the BCF may still range from 130 to 1860, indicating a high bioaccumulation potential of 1,2,3-trichlorobenzene.

However, as the most of the few available data are not reliable it is a peferable option to assess the bioaccumulation potential through read-across using the better suited data on 1,2,4-trichlorobenzene.

read across

From a mechanistic point of view the three trichlorobenzene isomers are expected to show similarly high BCF values. The vast majority of deviations in determined BCF may be attributed to the inherent variability of experimental studies (different fish species etc.) rather than different physico-chemical properties of these isomers. For each isomer the observed BCF values are of limited reliability. Nonetheless, the results indicate that all three isomers show a similar, high bioaccumulation potential. Furthermore, the data indicate that 1,3,5-trichlorobenzene is slightly more bioaccumulative than 1,2,4- and 1,2,3-trichlorobenzene. Most results are available for 1,2,4-trichlorobenzene. These data have already been evaluated in the EU Risk Assessment and the PBT Working Group. A BCF of >2000 was derived as a realistic worst case for this substance. In analogy to this approach, a BCF of >2000 is also expected for 1,2,3-trichlorobenzene. These estimates are considered reliable within the given variance of data.

3.3.2 Summary and discussion of bioaccumulation

The log K_{ow} of 4.05 is indicating that bioconcentration in aquatic organisms may occur. The few observed BCF values are of limited reliability. Most of the available BCF values range from 130 to 1860. Although of low reliability, in one study (Oliver and Niimi, 1983) a maximum BCF of 2600 was observed, so a BCF of > 2000 can be derived as a realistic worst case estimate. This is confirmed by the read-across approach, which indicates that all three trichlorobenzene isomers show a similar, high bioaccumulation potential. Hence, the variability of BCF can rather be attributed to the inherent variability of experimental studies (different fish species etc.) than to different inherent properties of these constitutional isomers. According to the read-across approach, 1,2,3-trichlorobenzene is as bioaccumulative as 1,2,4-trichlorobenzene, for which a BCF of >2000 was assumed.

In case that lipid normalization is additionally taken into consideration, the BCF may still reach 1860 indicating a high bioaccumulation potential.

4 HUMAN HEALTH HAZARD ASSESSMENT

Not relevant for this type of dossier.

5 ENVIRONMENTAL HAZARD ASSESSMENT

5.1 Aquatic compartment (including sediment)

5.1.1 Toxicity data

In this section only test results of long-term studies are reported as those are relevant for comparison with the aquatic T-criterion of Annex XIII of the Reach Regulation.

5.1.1.1 Fish

5.1.1.1.1 Long-term toxicity to fish

There are different long term toxicity test with 1,2,3-TCB: one Juvenile growth test, two Early life stage tests (ELS) and one full life cycle test (Exposure duration 147 days). From the Juvenile growth test with *Gambusia affinis* results the lowest effect concentration (Chaisuksant et al., 1998). The EC_{10} for growth rate reduction is 0.022 mg/L and the NOEC for length is 0.062 mg/L based on measured concentrations. The test is valid and plausible. The other species for which tests are available was *Danio rerio.* While results from two different ELS studies differed for this species (NOEC 0.25 and 0.077 mg/L respectively) results of the full life cycle tests showed that the most sensitive endpoint was female egg production with a NOEC below 0.04 mg/L.

Table 8: Long-term toxicity to fish.

Species	**Duration**	**EC_{50} (mg l^{-1})**	**NOEC (mg l^{-1})**	**Method, conditions**	**Reference**
Gambusia affinis	42 d	0.098	0.062 (length) 0.022 (EC_{10}) (growth rate reduction)	Juvenile growth test, 24 ± 1°C, pH 7.3, 7.9 – 9.2 mg O_2/L, semi-static, measured conc.	(Chaisuksant et al., 1998)
Danio rerio	28 d	0.99 (LC_{50})	0.25 (hatching, survival, growth)	ELS; $CaCO_3$ about 210 mg/l; dissolved oxygen 7.7 mg/l; 24 ± 2°C; photoperiod 12 h; semi-static; measured conc.	(Van Leeuwen et al., 1990)
Danio rerio	147d		0.276 (survival, growth) < 0.04 (average egg production per female)	Exposure starting with 2.5 months old fish; flow through system; 24°C; 12 h light photoperiod; 0.1 mL/L acetone; 2 duplicates; 20 animals per aquarium; fed commercial fish food; pH 7.9; 6.6 mg O_2/L; 193 mg $CaCO_3$/L; average recovery 79 ±	(Roex et al., 2001)

				12%	
Danio rerio	28 d		0.077 (hatching and total survival)	ELS; 24°C; 12h light photoperiod; 3 replicates; 10 eggs per replicate, measured conc.	(Roex et al., 2002)

5.1.1.2 Aquatic invertebrates

5.1.1.2.1 Long-term toxicity to aquatic invertebrates

The long-term toxicity to aquatic invertebrates was tested in two tests. The NOECs were in similar regions. Both studies are valid and plausible but the test conducted by (Kühn et al., 1989) is preferred for the assessment because the duration of the study by (Calamari et al., 1983) was only 14 days. The test conducted by (Kühn et al., 1989) resulted in a NOEC (real concentration) of 0.03 mg/L for the endpoint time to first offspring.

Table 9: Long-term toxicity to aquatic invertebrates.

Species	**Duration**	**EC_{50} (mg l^{-1})**	**NOEC (mg l^{-1})**	**Method, conditions**	**Reference**
Daphnia magna	14 days	0.20	0.08 (EC_{16})*	30 newborn animals; groups of 10; 20°C; 16 h light photoperiod; semi-static, analytical monitoring, nominal conc.	(Calamari et al., 1983)
Daphnia magna	21 d		0.03 (time to first offspring)	Provisional procedure proposed by the Federal Environmental Agency (UBA); open vessel, measured conc.	(Kühn et al., 1989)

* In the study the EC 16 is reported as no effect concentrations, due to the accepted hypothesis that a reproductive impairment ranging from 10 to 20% could be considered in the range of natural variability.

5.1.1.3 Algae and aquatic plants

There are three publications dealing with the toxicity of 1,2,3-TCB conducted with *Pseudokirchneriella subcapitata* with similar results. The tests were all carried out in closed systems. The EC_{50} was 0.9 mg/L and the NOEC was 0.2 mg/L. The tests with two other species were less reliable and resulted in less sensitive effect concentrations. Results are summarized in Table 10.

Table 10: Toxicity to algae

Species	**Duration**	**EC_{50} (mg l^{-1})**	**NOEC (mg l^{-1})**	**Method, conditions**	**Reference**
Pseudokirchneriella subcapitata (orig.: *Selenastrum capricornutum*)	96 h	0.9	0.22	U.S. EPA, Algal Assay Procedure - Bottle Test, National Eutrophication Research Program, Corvallis, 82 ppg (1971). Test vessels modified according to Galassi and Vighi, Chemosphere, 10, 1123 (1981).	(Calamari et al., 1983)
Pseudokirchneriella subcapitata (orig.: *Selenastrum capricornutum*)	96 h	0.9	0.22	U.S. EPA, Algal Assay Procedure - Bottle Test, National Eutrophication Research Program, Corvallis, 82 ppg (1971). Flasks closed by screw cap with both silicon rubber and Teflon gaskets;	(Galassi and Vighi, 1981)
Pseudokirchneriella subcapitata	48 h	0.85	0.2	Triplicate; closed-system with no headspace and low bicarbonate buffer content, analytical monitoring, nominal conc., biomass	(Chen et al., 2009)
Cyclotella meneghiniana strain CyOH2	48 h	6.42		15°C, 16 h light;, 10^5 cells/mL;	(Figueroa and Simmons, 1991)
Ankistrodesmus falcatus	4 h	5.99		5000 lux; 4-7 10^5 cells/mL; Acetone; flasks capped with rubber stoppers wrapped in aluminium foil	(Wong et al., 1984)

5.1.1.4 Sediment organisms

There are two tests which investigated the toxicity of 1,2,3-TCB to *Chironomus riparius*. However test duration of these tests was too short to assess long-term toxicity to this species.

Table 11: Toxicity to sediment organisms

Species	**Duration**	**LC_{50} (mg l^{-1})**	**Method, conditions**	**Reference**
Chironomus riparius	48 h	1.7 (real)	10 larvae per test conc.; 21°C; closed scintillation flasks	(Roghair et al. 1994)
Chironomus riparius	96 h	NOEC (real) = 0.018	3.0g cellulose fibres as artificial substrate; 19°C; semi-static; measured conc., types of behaviour	(Van der Zandt et al 1994)

6 CONCLUSIONS ON THE SVHC PROPERTIES

6.1 PBT, vPvB assessment

Not relevant for this dossier. See section 6.3.

6.2 CMR assessment.

6.3 Substances of equivalent level of concern assessment

6.3.1 Assessment of PBT/vPvB properties - comparison with criteria of Annex XIII

6.3.1.1 Persistence

1,2,3-trichlorobenzene (1,2,3-TCB) is not subject to hydrolysis. The screening biodegradation tests indicate that 1,2,4-TCB is not readily biodegradable. Based on data from soil degradation tests half-lives of more than 200 days have been determined.
Due to its high volatility (Henry constant of 282.16 Pa*m³*Mol^{-1}), 1,2,3-TCB is expected to be distributed from water to air. In the air, 1,2,3-TCB is persistent (estimated half life 57 days) and will be transported via air for more than several thousand kilometres. Distributed by this pathway also to remote areas, 1,2,3-TCB will then be dissipated again to soil or water remaining there persistent e.g. due to lower temperatures.
Thus, considering all information available, 1,2,3-TCB is concluded to fulfil the P-criterion and the vP criterion.

6.3.1.2 Bioaccumulation

The log K_{ow} of 4.05 is indicating that bioconcentration in aquatic organisms may occur. There are only few available data on the bioaccumulation of 1,2,3-trichlorobenzene. The high bioaccumulation potential is confirmed by several bioconcentration tests using different fish species. Available BCF values range from 130 to 1860 with an additional value of 2600, although of limited reliability. From these data a BCF of > 2000 can be derived as a realistic worst case estimate, but it is also possible to derive additional supporting BCF values via read-across from 1,2,4-trichlorobenzene.

From a mechanistic point of view the three trichlorobenzene isomers are expected to show similarly high BCF values. Hence, the variability of BCF can rather be attributed to the inherent variability of experimental studies (different fish species etc.) than to different inherent properties of these constitutional isomers. Most experimental data are available for 1,2,4-trichlorobenzene. A BCF of >2000 was derived as a realistic worst case for this substance, leading to the conclusion that the substance is bioaccumulative. In analogy to this approach, a BCF of > 2000 is also expected for 1,2,3-trichlorobenzene. Thus, based on a weight of evidence approach considering both the available data for 1,2,3-trichlorobenzene and data for its structural analogues, it is concluded that 1,2,3-trichlorobenzene fulfils the B-criterion of Annex XIII.

In case that lipid normalization to 5% is applied, the maximum BCF of 1,2,3-trichlorobenzene will still reach 1860 which indicates a high bioaccumulation potential. This high BCF still supports an equivalent concern according to Article 57 (f) of REACH regulation.

6.3.1.3 Toxicity

Aquatic ecotoxicity tests with long-term exposure are available for fish, aquatic invertebrates and algae. The lowest NOEC is 0.062 mg l-1 for *Gambusia affinis*. The long-term toxicity to aquatic invertebrates is in a similar range. The most sensitive organism is Daphnia magna with a NOEC of 0.03 mg/L. For algae, the lowest NOEC is 0.2 mg l^{-1}. Although these NOECs indicate a high toxicity for aquatic organisms on the long-term, the T-criterion is formally not fulfilled.

Long-range transport potential: Due to its volatility and persistence to atmospheric degradation, 1,2,3-TCB has a very high potential for long-range atmospheric transport. Based on model calculations, estimated travelling distances are several thousand kilometres.

6.3.2 Summary and overall conclusions on the PBT/vPvB properties

Taking into account all available information on persistent, bioaccumulative and toxic properties of 1,2,3-trichlorobenzene, it is concluded that 1,2,3-trichlorobenzene is a PBT-substance and needs to be controlled as such. The substance is considered to fulfil the P criterion, and also the vP-criterion. In addition to that, also the B criterion is fulfilled. In case that lipid normalization to 5% is performed, 1,2,3-trichlorobenzene would not clearly fulfil the B criterion. However, if doing so the maximum BCF will still be close to the B criterium of Annex XIII. Although 1,2,3-trichlorobenzene is highly toxic for aquatic organisms tested on the long-term, it does not formally meet the T-criterion. The overall conclusion is however drawn in a weight of evidence approach, taking supporting evidence into account relating to the very high long-range environmental transport potential of this substance. It raises an equivalent concern according to Article 57 (f).

The PBT-properties of 1,2,3-trichlorobenzene have already been agreed in the TC NES subgroup on identification of PBT and vPvB substances in 2003 (and supported by the TCNES and CA-Meeting), and as a result 1,2,3-trichlorobenzene was assessed as PBT-substance.

PART II

INFORMATION ON USE, EXPOSURE, ALTERNATIVES AND RISKS

INFORMATION ON MANUFACTURE, IMPORT/EXPORT AND USES – CONCLUSIONS ON EXPOSURE

1,2,4-TCB is mainly used as intermediate and as a process solvent in closed systems. In addition, the RAR identified the following minor uses that are by now restricted in the EU (Directive 2005/59/EC): solvent, dye carrier, corrosion inhibitor and lubricant. In the past, 1,2,4-TCB was used as an additive in dielectric fluids. 1,2,3-TCB and 1,3,5-TCB have a lower production volume, but are assigned to the same uses. As trichlorobenzenes are priority substances under the Water Framework Directive, their occurrence in rivers is controlled by monitoring programmes.

All substances are preregistered with an envisaged registration deadline of 2010. Though the preregistration data have to be interpreted cautiously, this indicates a potential production volume of more than 100 tons for 1,2,4-TCB (classified as R50-53 according to directive 67/548/EEC) and more than 1000 tons for 1,2,3-TCB and 1,3,5-TCB.

The main uses as an intermediate and as a process solvent in closed applications are not considered to result in a release of 1,2,4-TCB into the environment. All other uses are restricted.
Despite the extensive restriction on the marketing and use of 1,2,4-TCB in the EU, the substance may enter the EU market via imported articles. For example, textiles may contain 1,2,4-TCB from use as a dye carrier. However, there is no information on the amount of imported articles containing 1,2,4-TCB.

Furthermore, 1,2,3-TCB and 1,3,5-TCB are not restricted and may be used as substitutes for 1,2,4-TCB. Again, updated information would be helpful to clarify this concern.

With regard to the known uses of the three Trichlorobenzenes, current exposure is expected to be low, but trichlorobenzenes should be considered for further regulatory steps due to their SVHC properties: Both 1,2,4-TCB and 1,2,3-TCB have been identified as PBTs by the TCNES PBT subgroup. 1,3,5-TCB shows similar properties and should thus also be regarded as PBT. These substances pose a risk to human health and the environment that is not predictable in the long-term. Once released into the environment, adverse effects caused by PBTs cannot be remediated. Consequently, strong precautionary measures are necessary to prevent the release of these substances, though it is expected that only small amounts of trichlorobenzenes are emitted in the EU. As no safe concentration may be derived for PBTs, even low emissions give rise to concern and need to be limited further. Nonetheless, the production volume has to be considered when setting priorities for regulatory measures for concurrent SVHCs. In addition to that, the long-range transport potential of the trichlorobenzenes needs to be considered in a weight of evidence assessment of the PBT-properties including all available information.

CURRENT KNOWLEDGE ON ALTERNATIVES

RISK-RELATED INFORMATION

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ANNEX 1

Reporting Format for the analogue approach for 1,2,3-Trichlorobenzene and 1,3,5-Trichlorobenzene

CHEMICALS:	**1,2,3-Trichlorobenzene and 1,3,5-Trichlorobenzene**
EC No:	**201-757-1 and 203-608-6**
CAS No:	**87-61-6 and 108-70-3**

HYPOTHESIS OF THE ANALOGUE APPROACH

The analogue approach is mainly based on the structural isomer 1,2,4-trichlorobenzene, which was already evaluated in the EU Risk Assessment and the PBT Working Group. For 1,2,3-trichlorobenzene, read-across to 1,2,4-trichlorobenzene was already carried in the PBT Working Group. To support the approach, data on further chlorobenzenes were taken into account for some endpoints.

Mechanistic reasoning

Trichlorobenzenes have comparable structural features as they only differ in the substitution pattern of the three chlorine atoms and show very similar physico-chemical properties (see data matrix). For Trichlorbenzenes no specific metabolism or mode of action is expected for bioconcentration and aquatic ecotoxicity, respectively. Thus, these properties are assumed to depend mainly on physico-chemical properties like lipophilicity, which allows to read-across from 1,2,4-trichlorobenzene to its structural isomers.
The position of substituents may influence the chemical reactivity of aromatic compounds. For chlorine, the negative inductive effect (electron-withdrawal due to higher electronegativity) outweighs the mesomeric effect (electron-donation due to resonance effects), resulting in a weak electron-withdrawing effect, which decreases reactivity towards electrophiles. Furthermore, chlorine atoms are ortho- and para-directing substituents, i.e. substituents that direct electrophiles to attack preferably at the ortho- and para position. For 1,3,5-trichlorobenzene, each of the three unsubstituted carbon atoms is in ortho- or para-position to all three substituted carbon atoms. Contrary, for 1,2,4-trichlorobenzene and 1,2,3-trichlorobenzene, each of the three unsubstituted carbon atoms is in meta-position to either one or two substituted carbon atoms. Thus, the overall reactivity of chlorobenzenes depends primarily on the number, but also on the position of substituents, with the deactivating effect with respect to reaction with electrophiles being weaker for 1,3,5-trichlorobenzene as compared to the other trichlorobenzene isomers. Consequently, 1,3,5-trichlorobenzene is less susceptible to nucleophilic attacks as compared to the other two isomers.

Endpoint	Hypothesis
k_{OH}	All trichlorobenzene isomers show the same mechanism with respect to OH radical reaction, which is OH radical addition to the aromatic ring. Chlorine substituents are expected to reduce reactivity due to the electron-withdrawing-effect. Thus, reaction rate constants are expected to be smaller for the highly chlorinated benzenes. The varying position of the chlorine

	substituents is expected to cause only minor differences with respect to reaction rates. The reaction rate constant for 1,3,5-trichlorobenzene is expected to be slightly higher than the respective rate constants of the other two trichlorobenzene isomers. This assumption is supported by QSAR results.
DT50	Biodegradation of trichlorobenzenes proceeds via reductive dechlorination or hydroxylation; a slightly larger half-life for 1,3,5-trichlorobenzene is supposed due to its reduced susceptibility to both degradation pathways.
BCF	Increasing BCF, correlated with increasing $\log K_{ow}$ within a $\log K_{ow}$ range of 1- 6. All trichlorobenzene isomers show very similar $\log K_{ow}$ values. Experimentally determined BCF values of substances with a log Kow of about 6 and beyond repeatedly showed a levelling-off. This phenomenon, referred to as a "hydrophobicity cut-off", has been attributed to diminished gill permeation ability with increasing molecular dimensions (size exclusion). However, a proceeding linear correlation beyond $\log K_{OW}$ of 6 (to at least 7 or 8) has also been hypothesized. The trichlorobenzene isomers are expected to show only slight differences with respect to these factors. Furthermore, the impact of molecular size and metabolism on the bioaccumulation potential of trichlorobenzenes is expected to be minor as compared with lipophilicity. Thus, the three trichlorobenzene isomers are supposed to have very similar BCF values.
Aquatic toxicity	The trichlorobenzene isomers are expected to show unpolar baseline (narcosis) toxicity due to the lack of specific molecular interaction potential. Due to their similarity with respect to lipophilicity they are expected to be similarly toxic.

Endpoints for which read-across approach is applied

Read across is used in conjunction with QSAR results to support the validity of experimental data and QSAR results for the following endpoints:

- Persistence: biodegradation (DT50) and OH radical reaction (k_{OH})
- Bioconcentration: BCF
- Ecotoxicity (read across for 1,3,5 trichlorobenzene only)
  - Long-term toxicity to fish
  - Long-term toxicity to invertebrates

SOURCE CHEMICAL(S)

The following chemicals were used for the read-across approach:

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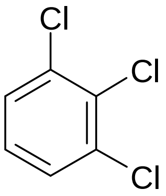
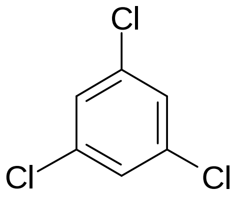
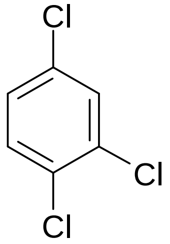
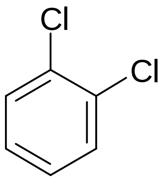
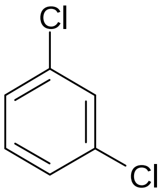
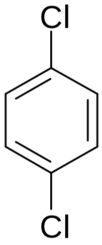
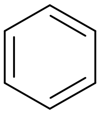
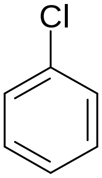
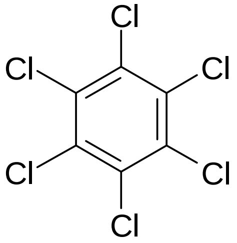
		
CAS 87-61-6	CAS 108-70-3	CAS 120-82-1

1,2-Dichlorobenzene	1,3-Dichlorobenzene	1,4-Dichlorobenzene
		
CAS 95-50-1	CAS 541-73-1	CAS 106-46-7

Benzene	Monochlorobenzene	Hexachlorobenzene
		
CAS 71-43-2	CAS 108-90-7	CAS 118-74-1

PURITY /IMPURITIES

Trichlorobenzenes are produced mainly by chlorination of benzene or dichlorobenzene. The mixture of trichlorobenzenes can be separated and purified by crystallization and distillation. Purity of the respective isomers is greater than or equal 99 %. The impurities expected for the individual trichlorobenzenes are tetrachlorobenzenes, respective other trichlorobenzene isomers, dichlorobenzenes, dichlorotoluenes and bromo-chlorobenzenes. Impurities are not expected to significantly influence results.

ANALOGUE APPROACH JUSTIFICATION

Due to mechanistic differences and available experimental data, approaches and substances used for read across differed between endpoints. Approaches and justifications are described below.

Reaction with OH radicals

ll trichlorobenzene isomers show the same mechanism with respect to OH radical reaction, which is OH radical addition to the aromatic ring. Chlorine substituents are expected to reduce reactivity due to the electron-withdrawing-effect. Thus, reaction rate constants are expected to be smaller for the highly chlorinated benzenes, which is confirmed by both the QSAR results and the available experimental data on other chlorobenzenes and benzene. The QSAR predictions for 1,2,3- and 1,3,5-trichlorobenzene are in accordance with this trend. The varying position of the chlorine substituents is expected to cause only minor differences with respect to reaction rates. This assumption is supported by both experimental data on dichlorobenzenes and QSAR results. However, as mentioned before, 1,3,5-trichlorobenzene is more susceptible to electrophilic attacks as compared to the other two trichlorobenzene isomers, which is also reflected by the QSAR results. A similar effect is observed for 1,3-dichlorobenzene which is more reactive towards OH radicals than 1,2- and 1,4-dichlorobenzene. Accordingly, all trichlorobenzene isomers are expected to show similar reactivity, with 1,3,5-trichlorobenzene being slightly more reactive. It is proposed to use the values predicted by EPISUITE's AOPWIN for 1,2,3- and 1,3,5-trichlorobenzene. A QSAR Model Reporting Format (QMRF) and a QSAR Prediction Reporting Format (QPRF) are given to document the reliability of the results (Annexes 2 and 3).

Biodegradation

The available data indicate that environmental degradation of all three trichlorobenzene isomers proceeds via the same biodegradation pathways. The observed biodegradation is generally slow, with 1,3,5-trichlorobenzene being slightly more persistent. Most results are available for 1,2,4-trichlorobenzene. These data were already evaluated in the EU Risk Assessment and the PBT Working Group. The substance was found to be persistent in soil and sediment.

In several studies, reductive dechlorination of trichlorobenzenes was observed. This biodegradation pathway is assumed to proceed via a nucleophilic aromatic substitution mechanism (Bosma et al., 1988; Marinucci and Bartha, 1979). Thus, biodegradation of 1,3,5-trichlorobenzene is expected to be more slowly as compared to the other two trichlorobenzene isomers, which are assumed to show similar degradation kinetics. This assumption is supported by the available data (Bosma et al., 1988; Marinucci and Bartha, 1979; Fathepure et al., 1988).

Another observed biodegradation pathway is hydroxylation through oxygenase enzymes (Ballschmiter and Scholz, 1980). Again, 1,3,5-trichlorobenzene is expected to be degraded more slowly than 1,2,4- and 1,2,3-trichlorobenzene, as the 1,3,5-substitution blocks the reaction site more effectively (Morita, 1977). 1,2,4- and 1,2,3-trichlorobenzene are expected to show very similar biodegradability.

Bioaccumulation

Only few data of limited reliability are available on the bioconcentration of trichlorobenzenes. For *Oncorhynchus mykiss*, *Poecilia reticulata* and *Cyprinus carpio*, data are available for two or three trichlorobenzene isomers. However, values for *Poecilia reticulata* differ strongly with respect to exposure time which complicates interpretation of the results. The values observed for *Oncorhynchus mykiss* and *Cyprinus carpio* are in the same range, with all three isomers showing a very similar, high bioaccumulation potential. Furthermore, the data indicate that 1,3,5-trichlorobenzene is slightly more bioaccumulative than 1,2,4- and 1,2,3-trichlorobenzene. Most results are available for 1,2,4-trichlorobenzene. These data were already evaluated in the EU Risk Assessment and the PBT Working Group. A BCF of > 2000 is derived as a realistic worst case for this substance.

Trichlorobenzenes are unpolar, lipophilic substances. Bioconcentration of these substances is expected to be mainly determined by their lipophility, which is reflected by the $\log K_{ow}$. Within a $\log K_{ow}$ range of 1- 6, bioconcentration of unpolar compounds is expected to show a linear increase with increasing $\log K_{ow}$. All trichlorobenzene isomers show very similar $\log K_{ow}$ values and thus, based on lipophilicity, their bioconcentration factors are expected to be in the same range. All trichlorobenzene isomers have a $\log K_{ow}$ about 4 and are thus potentially bioaccumulating based on lipophilicity.

Further factors like molecular size or metabolism are proposed to influence bioconcentration, though they are expected to be of minor importance as compared to lipophilicity. A large molecular size is proposed to decrease BCF due to reduced bioavailability. However, the molecular weight is clearly smaller than the cut-off values recommended in the technical guidance (MW>700 indicating not vB, MW>1100 indicating not B). Furthermore, the trichlorobenzene isomers are expected to show only marginal differences with respect to molecular size.

The metabolism of a substance may reduce or limit its bioaccumulation potential. A possible metabolism pathway for trichlorobenzenes is hydroxylation by oxygenase enzymes, following a similar pattern as the abovementioned biodegradation pathway. Analogously, 1,3,5-trichlorobenzene is probably metabolized slightly slower than 1,2,3-trichlorobenzene and 1,2,4-trichlorobenzene.

In summary it can be stated that with respect to the factors relevant for bioconcentration, there are no significant differences between 1,2,3-trichlorobenzene and 1,2,4-trichlorobenzene. For 1,3,5-trichlorobenzene, slight deviations with respect to metabolism are assumed. The impact of this factor on the BCF is expected to be minor or negligible as compared to lipophilicity. Thus, from a mechanistic point of view, the three trichlorobenzene isomers are expected to show very similar BCF values.

Thus, a BCF of >2000 is assumed for 1,2,4-trichlorobenzene and is also expected for 1,2,3- and 1,3,5-trichlorobenzene, with 1,3,5-trichlorobenzene potentially showing a slightly higher BCF.

Ecotoxicity

Toxic Mode of Action. Based on the chemical structure, all three trichlorobenzene isomers are expected to exhibit baseline (nonpolar narcosis) toxicity. This hypothesis is supported by various expert systems (so called profiler) implemented in the OECD QSAR Application Toolbox (beta Version 2.0, Mai 2010).

Toxicity of nonpolar narcotics is largely determined by lipophilicity and thus by the $\log K_{ow}$. As all trichlorobenzenes are isomers they show very similar $\log K_{ow}$ values and thus, based on lipophilicity, their ecotoxicity is expected to be very similar. Reactivity might influence ecotoxicity of these isomers. While the OECD QSAR Application toolbox gives some hints, that reactivity might be higher for 1,2,4 trichlorobenzene (expected mode of protein binding nucleophilic substitution) available data do not support this hypothesis (see data below).

Fish. Comparable experimental data on acute toxicity of 1,2,3 and 1,2,4 trichlorobenzene for *Danio rerio* and *Oncorhynchus mykiss*. show that toxicity of both compounds is in the same concentration range. Available data for 1,3,5, trichlorobenzene with *O.mykiss* are in the same range of toxicity. Small differences in toxicity (max. factor 8 between 1,2,3 and 1,3,5 trichlorobenzene) are expected to be due to interlaboratory variance (factor 3 between) resulting in 1,2,3 trichlorobenzene beeing slightly more toxic than 1,2,4 trichlorobenzene (factor 3 and between) , however data might indicate, that 1,3,5 trichlorobenzene is slightly less toxic than expected due to the hypothesis of similar toxicity (factor 3).

With respect to long-term toxicity, data for 1,2,4 and 1,2,3 trichlorobenzene again support hypothesis of comparable toxicity. No data for 1,3,5 trichlorobenzene are available, thus read-across needs to be applied.

Daphnia. Data on acute toxicity to *Daphnia magna* for 1,2,4-trichlorobenzene and 1,2,3-trichlorobenzene support similarity of toxicity of both chemicals.

With respect to long-term effects, available data for an exposure time of 14 days also indicate similar toxicity for 1,2,4-trichlorobenzene and 1,2,3-trichlorobenzene. However, considering data for an exposure time of 21 days, 1,2,4-trichlorobenzene and 1,2,3-trichlorobenzene differ to some extent (factor 13).

Algae. Comparable data on *Pseudokirchneriella subcapitata* are available for 1,2,4-trichlorobenzene and 1,2,3-trichlorobenzene. For an exposure time of 96 h, both isomers show very similar NOEC values with 1,2,3-trichlorobenzene being slightly more toxic. For 1,3,5-trichlorobenzene, an EC_{10} is given from a 48 h test, from which a maximum NOEC is derived. Comparing this result with a NOEC derived from a 48 h test on 1,2,3-trichlorobenzene, both 1,3,5-trichlorobenzene and 1,2,3-trichlorobenzene are in the same range of toxicity.

Summary on Ecotoxicity Available data for 1,2,4-trichlorobenzene and 1,2,3-trichlorobenzene show that toxicity of both isomers is very similar, with the most sensitive NOEC values being 0.04 mg/l and 0.03 mg/l. Results support the hypothesis of baseline toxicity for all three isomers and all organisms groups tested. Neither one of the isomers nor one of the organisms groups showed unexpected high toxicity.

For 1,3,5-trichlorobenzene, only few data of limited reliability are available. However, experimental results for 1,2,3 and 1,2,4 trichlorobenzene and similarity of the expected toxic mode of action for 1,3,5 Trichlorobenzene provide confidence, that a read-across for 1,3,5 trichlorobenzene based on data for 1,2,3 and 1,2,4 trichlorobenzene is reasonable. This is supported by experimental data for 1,3,5 trichlorobenzene for acute fish toxicity and algae toxicity showing toxicity comparable to those of 1,2,3 and 1,2,4 trichlorobenzene .

DATA MATRIX

	Target 1	**Target 2**	**Source 1**	**Source 2**	**Source 3**	**Source 4**	**Source 5**	**Source 6**	**Source7**
Chemical Name	1,2,3-Trichlorobenzene	1,3,5-Trichlorobenzene	1,2,4-Trichlorobenzene	1,2-Dichlorobenzene	1,4-Dichlorobenzene	1,3-Dichlorobenzene	Benzene	Monochlorobenzene	Hexachlorobenzene
CAS RN	000087-61-6	000108-70-3	000120-82-1	000095-50-1	000106-46-7	000541-73-1	000071-43-2	000108-90-7	000118-74-1
Physico-chemical data									
Molecular Weight	181,45	181,45	181,45	147.01	147.01	147.01	78.11	112.56	284.78
Partitioning Coefficient logKow	4.05	4.19	3.9-4.3[1] 4.7 [RAR]						
Fate									
k_{OH}									
-Exp. Value in 10^{-12} cm^{3}s^{-1}molecules^{-1}			0.532[RAR] 0.5[RAR] 0.6[RAR] 0.55[PysProp]	0.42[PhysProp]	0.32[RAR,PhysProp] 0.48[RAR]	0.72[PhysProp]	1.2[RAR] 1.23[PhysProp]	0.77[PhysProp]	0.027[PhysProp]
-Calc. value in 10^{-12} cm^{3}s^{-1}molecules^{-1}, AOPWIN	0.282	0.679	0.282	0.4	0.4	0.965-	1.95	1.372	0.0169
ready biodegradability screening test	not readily biodegradable (MITI)	not readily biodegradable (MITI)	not readily biodegradable (MITI)						
DT50									
-Exp. Value soil	DisT50 = 222 d	DisT50 = 238 d	DisT50 = 194 d						

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[1] The IUCLID file contains several experimental values, most of which are in the abovementioned range from 3.9 to 4.4. The overall range of values is 2.33 to 4.8.

[RAR] Taken from the respective EU Risk Assessment Report, recommended values, in some cases further data available

[PysProp] Taken from the PhysProp Database (PhysProp, 2001, US EPA, 2008)

	Target 1	**Target 2**	**Source 1**	**Source 2**	**Source 3**	**Source 4**	**Source 5**	**Source 6**	**Source7**
Chemical Name	1,2,3-Trichlorobenzene	1,3,5-Trichlorobenzene	1,2,4-Trichlorobenzene	1,2-Dichlorobenzene	1,4-Dichlorobenzene	1,3-Dichlorobenzene	Benzene	Monochlorobenzene	Hexachlorobenzene
	(259 d study, no significant bio-degradation)	(259 d study, no significant bio-degradation)	(259 d study, no significant bio-degradation)						
-Exp. Value sediment	DT50 = 202 d DT50 = 212 d (two sediment samples,)[RAR]								
BCF									
-Exp. value *Oncorhynchus mykiss (Salmo gairdneri)*	1200 (119 d) 2600 (105 d)	1800 (119 d) 4100 (105 d)	1300 (119 d) 3200 (105 d)						
-Exp. value *Poecilia reticulata*	1860 (4 d) 702 [2]	756 [2]	1139 (17 d)						
-Exp. value *(Brachy)danio rerio*			574-1412 (28 d)						
-Exp. value *Jordanella floridae*			2026 (28 d)						
-Exp. value *Cyprinus carpio*	130-1200 (42 d)	150-1700 (42 d)	120-1320 (42 d) 805-830 [3]						
Environmental Toxicity									
Mode of action									
-Verhaare scheme	Class 1 narcosis	Class 1 narcosis	Class 1 narcosis						
-ECOSAR Classification	Neutral organics	Neutral organics	Neutral organics						

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[2] test duration not given, original literature not reviewed

[3] test duration not given

	Target 1	**Target 2**	**Source 1**	**Source 2**	**Source 3**	**Source 4**	**Source 5**	**Source 6**	**Source7**
Chemical Name	1,2,3-Trichlorobenzene	1,3,5-Trichlorobenzene	1,2,4-Trichlorobenzene	1,2-Dichlorobenzene	1,4-Dichlorobenzene	1,3-Dichlorobenzene	Benzene	Monochlorobenzene	Hexachlorobenzene
-OASIS acute toxicity MOA	Basesurface narcotics	Basesurface narcotics	Basesurface narcotics						
-OASIS Protein binding	No binding	No binding	Nucleophilic substititution on aromatic halogens						
Acute Toxicity to Fish, LC_{50}, [mg/L]									
-Exp. value *Poecilia reticulata*	0.35 (96 h)								
-Exp. value *Danio rerio*	3.1 (24/48 h)		6.3 (24/48 h)						
-Exp. value *Oncorhynchus mykiss (Salmo gairdneri)*	0.71 (24/48 h)	5.48 (96 h)	1.95 (24/48 h) 1.32 (96h)						
-Exp. value *Leuciscus idus*		7.05 (96h)[4]	0.7 (48 h)						
-Exp. value *Solea solea*		1.96 (96 h)							
Long-term Toxicity to Fish NOEC, [mg/L]									
-Exp. value, *Danio rerio*	0.077 (28 d) 0.25 (28 d)		0.04 (21 d)						
-Exp. value, *Poecilia reticulata*		3.3 (14 d, EC_{50})	0.11 (14 d)						
- Exp. Value *Gambusia affinis*	0.022 (42d, EC_{10})								
Acute Toxicity to									

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[4] Test not validated because data not available

	Target 1	**Target 2**	**Source 1**	**Source 2**	**Source 3**	**Source 4**	**Source 5**	**Source 6**	**Source7**
Chemical Name	1,2,3-Trichlorobenzene	1,3,5-Trichlorobenzene	1,2,4-Trichlorobenzene	1,2-Dichlorobenzene	1,4-Dichlorobenzene	1,3-Dichlorobenzene	Benzene	Monochlorobenzene	Hexachlorobenzene
Aquatic Invertebrates, $L(E)C_{50}$, [mg/L]									
Exp. value *Daphnia magna*	1.66 (24-48h, arithmetic mean of 5 tests)		2.1 (48 h) geom. mean used in RAR						
Exp. value *Mysidopsis bahia*			0.45 (96 h)						
Long-term Toxicity to Aquatic Invertebrates. NOEC, [mg/L]									
Exp. value *Daphnia magna*	0.08 (14 d, $NOEC=EC_{16}$)		0.06 (14 d, $NOEC=EC_{16}$)						
	0.03 (21 d)		0.4 (21 d)						
Exp. value *Mysidopsis bahia*			≤ 0.064						
Toxicity to aquatic Plants. NOEC, [mg/l]									
Exp. value *Pseudokirchneriella subcapitata (Selenastrum capricornutum)*	0.22 (96 h)		0.37 (96 h)						
	0.2 (48 h)	< 0.73 (48 h, EC_{10} = 0.398)							
Toxicity to sediment organisms, [mg/l]									
Exp. value *Chironimus riparius*	1.7 (48 h, LC_{50})								

	Target 1	**Target 2**	**Source 1**	**Source 2**	**Source 3**	**Source 4**	**Source 5**	**Source 6**	**Source7**
Chemical Name	1,2,3-Trichlorobenzene	1,3,5-Trichlorobenzene	1,2,4-Trichlorobenzene	1,2-Dichlorobenzene	1,4-Dichlorobenzene	1,3-Dichlorobenzene	Benzene	Monochlorobenzene	Hexachlorobenzene
	0.018 (96 h, NOEC)								

Unless otherwise mentioned, all data are taken from the Annex V-Dossiers for 1,2,3-, 1,2,4- and 1,3,5-trichlorobenzenes. Choice of endpoints used for read-across: For the trichlorobenzenes, the key studies /most sensitive tests were reported respectively. Further tests were chosen if results are reported for more than one trichlorobenzene isomer and allow comparison between the substances. The other chlorinated benzenes and benzene were only used to support the estimation of log k_{OH} and thus, only calculated and experimental log k_{OH} values are considered for these substances.

CONCLUSIONS PER ENDPOINT

Reaction with OH radicals

All trichlorobenzene isomers are expected to show similar reactivity, with 1,3,5-trichlorobenzene being slightly more reactive. The values predicted by AOPWIN for 1,2,3- and 1,3,5-trichlorobenzene can be regarded as valid within the variation of the model for aromatic compounds. Results are additionally supported by experimental data from structural analogues. A QSAR Model Reporting Format (QMRF) and a QSAR Prediction Reporting Format (QPRF) are given to document the reliability of the results.

Biodegradation

The observed biodegradation is generally slow for all three trichlorobenzene isomers, with 1,3,5-trichlorobenzene being slightly more persistent. This assumption is supported by the evaluation of possible biodegradation pathways.
Most results are available for 1,2,4-trichlorobenzene. These data were already evaluated in the EU Risk Assessment and the PBT Working Group. The substance was found to be persistent in soil and sediment. As data are not standardized, default half-lifes for non biodegradable substances are applied in the assessment. 1,2,3-trichlorobenzene is assumed to be as persistent as 1,2,4-trichlorobenzene, whereas 1,3,5-trichlorobenzene is probably even more persistent. Thus, default half-lifes for non biodegradable substances can also applied for 1,2,3-trichlorobenzene and 1,3,5-trichlorobenzene.

Bioaccumulation

From a mechanistic point of view, the three trichlorobenzene isomers are expected to show high BCF values, with differences between the isomers being marginal. The vast majority of deviations in determined BCF may be attributed to the inherent variability of experimental studies (different fish species etc.) rather than different physico-chemical properties of these constitutional isomers. For each isomer the observed BCF values are of limited reliability. Nonetheless, the results indicate that all three isomers show a similar, high bioaccumulation potential. Furthermore, the data indicate that 1,3,5-trichlorobenzene is slightly more bioaccumulative than 1,2,4- and 1,2,3-trichlorobenzene.
Most results are available for 1,2,4-trichlorobenzene. These data were already evaluated in the EU Risk Assessment and the PBT Working Group and a BCF of 2000 was used as a realistic worst case for this substance. In analogy to this approach, a BCF of 2000 is also expected for 1,2,3- and 1,3,5-trichlorobenzene, with 1,3,5-trichlorobenzene potentially showing a slightly higher BCF. These estimates are considered as reliable within variation of the data.

Aquatic Toxicity

Long-term toxicity to fish
Taking into account data from all structural isomers, one of the most sensitive species is expected to be *Danio rerio*, for which long-term data on 1,2,4-trichlorobenzene and 1,2,3-trichlorobenzene are available. Based on structural considerations and the available data, the corresponding NOEC for 1,3,5-trichlorobenzene is expected to be in the same range, but potentially slightly higher. Thus, for the assessment, a NOEC of 0.077 mg/l is estimated.

Long-term toxicity to invertebrates

According to data available for 1,2,3 and 1,2,4 trichlorobenzene long-term toxicity of 1,3,5 trichlorobenzene to daphnia magna is expected to be in the range of 0.03 to 0.06 mg/L.

Based on data for 1,2,4 trichlorobenzene *Mysidopsis bahia* is expected to be more sensitive or in the same range as *Daphnia magna*.

As it is expected according to structural considerations and the available data that 1,3,5-TCB is potentially slightly less toxic, a NOEC of 0.06 mg/L (read across from 1,2,4-TCB) is used for 1,3,5-trichlorobenzene.

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ANNEX 2

QSAR Prediction Reporting Format (QPRF) (version 1.1, May 2008)

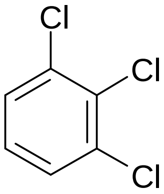
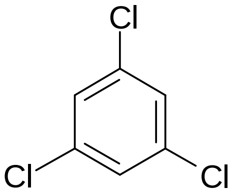
1. Substances

1.1 CAS number: 87-61-6 and 108-70-3

1.2 EC number:

1.3 Chemical name: 1,2,3-Trichlorobenzene and 1,3,5-Trichlorobenzene

1.4 Structural formula:

1,2,3-Trichlorobenzene	1,3,5-Trichlorobenzene
	
CAS 87-61-6	CAS 108-70-3

1.5 Structure codes:

a. SMILES:

1,2,3-Trichlorobenzene	1,3,5-Trichlorobenzene
c(c(c(cc1)Cl)Cl)(c1)Cl	c(cc(cc1Cl)Cl)(c1)Cl

(used for the model prediction)

b. InChI: *not available/ not used for the model prediction*

c. Other structural representation: *not available/ not used for the model prediction*

d. Stereochemical features: *the substance is no stereo-isomer*

2. General information

2.1 Date of QPRF: 7 May 2010

2.2 QPRF author and contact details:

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3. Prediction

3.1 Endpoint (OECD Principle 1)

a. Endpoint: OH-radical reaction rate constant (k_{OH}) of organic compounds

b. Dependent variable: log k_{OH} (AOPWIN equation for addition to aromatic rings))

3.2 Algorithm (OECD Principle 2)

a. Model or submodel name: AOPWIN[5] for k_{OH}
(references see corresponding QMRF)

b. Model version: AOPWIN v1.92

c. Reference to QMRF: The corresponding QMRF named 'AOPWIN for k_{OH}' has been newly compiled.

d. Predicted value (model result):

1,2,3-Trichlorobenzene	1,3,5-Trichlorobenzene
$0.282 \cdot 10^{-12}$	$0.679 \cdot 10^{-12}$

e. Predicted value (comments): k_{OH} given in $cm^3 s^{-1} molecules^{-1}$

f. Input for prediction: SMILES

g. Descriptor values: electrophilic substituent constants σ^+ for chlorine, referring to attack at the meta (σ^+_m) position and at the ortho or para position (σ^+_p)

σ^+_m	σ^+_p
0.399	0.114

1,2,3-Trichlorobenzene	1,3,5-Trichlorobenzene
$\sum\sigma^+ = 2\cdot\sigma^+_p + 1\cdot\sigma^+_m$	$\sum\sigma^+ = 3\cdot\sigma^+_p$

AOPWIN equation for addition to aromatic rings:

$$\log k_{OH} = -11.71 - 1.34\cdot\sum\sigma^+$$

3.3 Applicability domain (OECD principle 3)

a. Domains: 1,2,3-Trichlorobenzene and 1,3,5-Trichlorobenzene are considered to be in the applicability domain as described in the corresponding QMRF and the original Literature (Atkinson 1991).

i. *descriptor domain.* The molecular weight (MW) of both isomers is 181.45. This is in the range of the training set that was used to derive for the model equation for monocyclic aromatic compounds and biphenyls (Atkinson 1991).

Training set: $78.12 \leq MW \leq 204.01$, Average MW: 125.68

ii. *structural fragment domain*. The fragments of the chemical structure are three chlorine atoms, that are substituted to different positions of the benzene ring. These fragments were also included in the training set, which contains

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[5] US EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v 4.00. United States Environmental Protection Agency, Washington, DC, USA . http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm

1,2,4-trichlorobenzene, 1,2-dichlorobenzene, 1,4-dichlorobenzene, 1,3-dichlorobenzene and chlorobenzenes. Furthermore, their occurrence per molecule is in the range of the training set.

iii. *mechanism domain.* The mechanistic domain of the model can be defined clearly by the different reaction mechanisms that are accounted for by respective model equations: H-atom abstraction from C-H and O-H bonds; OH radical addition to double and triple bonds; OH radical addition to aromatic rings; and OH radical interaction with N-,S-, and P- atoms. Accordingly, Therefore, 1,2,3-trichlorobenzene and 1,3,5-trichlorobenzene can be considered to be in the mechanistic domain of the model.

iv. *metabolic domain.* Not relevant.

b. Structural analogues: Experimental data on structural analogues are given in tables 1 and 2.

Table 1: Calculated and experimental k_{OH} for structural analogues (experimental data taken from the PhysProp Database[6], k_{OH} given in $10^{-12} \cdot cm^3s^{-1}molecules^{-1}$).

CAS No.	Chemical Name	SMILES	Exp k_{OH}	Est k_{OH}	Training Set
000120-82-1	1,2,4-Trichlorobenzene	c(ccc(c1Cl)Cl)(c1)Cl	0.550	0.282	yes
000095-50-1	1,2-Dichlorobenzene	c(c(ccc1)Cl)(c1)Cl	0.420	0.400	yes
000106-46-7	1,4-Dichlorobenzene	c(ccc(c1)Cl)(c1)Cl	0.320	0.400	yes
000541-73-1	1,3-Dichlorobenzene	c(cccc1Cl)(c1)Cl	0.720	0.965	yes
000071-43-2	Benzene	c(cccc1)c1	1.230	1.950	yes
000108-90-7	Chlorobenzene	c(cccc1)(c1)Cl	0.770	1.372	yes
000118-74-1	Hexachlorobenzene	c(c(c(c(c1Cl)Cl)Cl)Cl)(c1Cl)Cl	0.027	0.017	no

Table 2: Calculated and experimental log k_{OH} for structural analogues.

CAS No.	Chemical Name	SMILES	Exp log k_{OH}	Est log k_{OH}	Training Set
000120-82-1	1,2,4-Trichlorobenzene	c(ccc(c1Cl)Cl)(c1)Cl	-12.26	-12.55	yes
000095-50-1	1,2-Dichlorobenzene	c(c(ccc1)Cl)(c1)Cl	-12.38	-12.40	yes
000106-46-7	1,4-Dichlorobenzene	c(ccc(c1)Cl)(c1)Cl	-12.49	-12.40	yes
000541-73-1	1,3-Dichlorobenzene	c(cccc1Cl)(c1)Cl	-12.14	-12.02	yes
000071-43-2	Benzene	c(cccc1)c1	-11.91	-11.71	yes
000108-90-7	Chlorobenzene	c(cccc1)(c1)Cl	-12.11	-11.86	yes
000118-74-1	Hexachlorobenzene	c(c(c(c(c1Cl)Cl)Cl)Cl)(c1Cl)Cl	-13.57	-13.77	no

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[6] Beauman, J. A.; Howard, P. H. Physprop database. Syracuse Research Corporation: Syracuse (NY, USA), 2001.

US EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v 4.00. United States Environmental Protection Agency, Washington, DC, USA . http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm

c. Considerations on structural analogues: Figure 1 shows calculated vs. experimental k_{OH} values for structural analogues. The correlation between calculated and experimental values is good ($r^2 \approx 0.89$). The largest deviation is observed for hexachlorobenzene, which was not used in the training set. Hexachlorobenzene is outside the molecular weight range of the training set and has more chlorine substituents per molecule than the substances in the training set. However both deviations from the training set range are not considered to affect model performance significantly. Note further that the prediction error for this substance is still small. Further, due to the rather small errors, the variation of experimental data also contributes to the observed deviations. As k_{OH} values of the training set cover several orders of magnitude, the model predicts k_{OH} values in logarithmic units and commonly, QSARs for predicting a wide range of k_{OH} values are evaluated in logarithmic units.

The predicted order of k_{OH} values is:

C_6H_6 > C_6H_5Cl > 1,3-$C_6H_4Cl_2$ > 1,3,5-$C_6H_3Cl_3$ > 1,2-$C_6H_4Cl_2$ = 1,4-$C_6H_4Cl_2$

1,4-$C_6H_4Cl_2$ > 1,2,4-$C_6H_3Cl_3$ = 1,2,3-$C_6H_3Cl_3$ > C_6Cl_6

Analysis of experimental data yields:

C_6H_6 > C_6H_5Cl > 1,3-$C_6H_4Cl_2$ > 1,2,4-$C_6H_3Cl_3$ > 1,2-$C_6H_4Cl_2$ > 1,4-$C_6H_4Cl_2$

1,4-$C_6H_4Cl_2$ > C_6Cl_6

Thus, the overall trends for calculated and experimental k_{OH} values are in good agreement. The only deviation is 1,2,4-trichlorobenzene, that shows a slightly higher experimental k_{OH} than expected from an analysis of the other experimental data. However, differences in reactivity are determined solely by the number of chlorine substituents and the substitution pattern, and thus, this deviation from the expected trend is assumed to result from variation of the experimental data.

Figure 1: Calculated vs. experimental k_{OH} for structural analogues. The dashed line indicates conformity between calculated and experimental results.

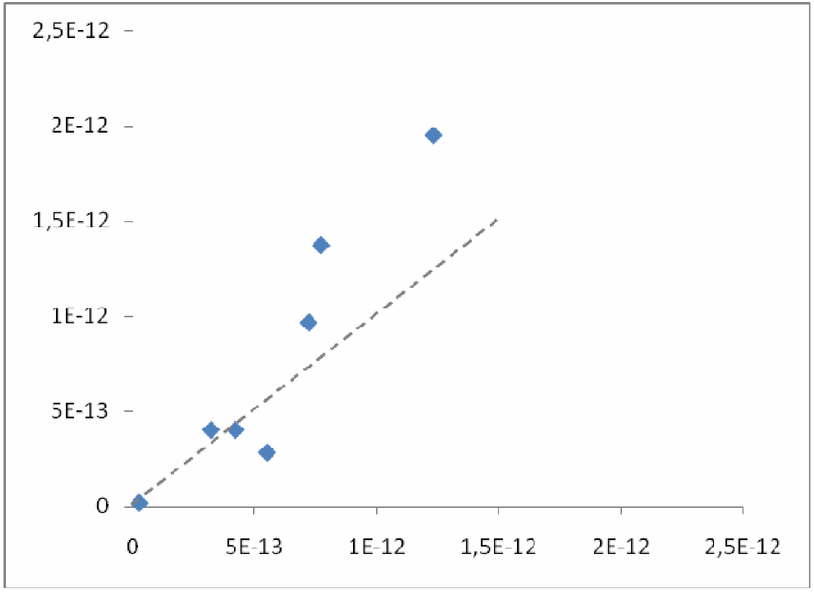


Figure 2 shows the resulting plot of calculated vs. experimental log k_{OH} values, giving a very good correlation between calculated and experimental values ($r^2 \approx 0.94$). With respect to log k_{OH}, all calculation errors are within a range of 0.3 and the mean absolute error is 0.15. This is in accordance with the very good performance for aromatics that is documented in the QSAR Model Reporting Format. As can be seen from figure 3, AOPWIN tends to overestimate k_{OH} slightly for lowly chlorinated structural analogues, whereas the highly chlorinated hexachlorobenzene is slightly underestimated. Given the small calculation errors and the fact that trichlorobenzenes can be considered to have a medium number of chlorine substituents, this finding is not considered to impact reliability for 1,2,3- and 1,3,5-trichlorobenzenes.

Figure 2: Calculated vs. experimental log k_{OH} for structural analogues. The dashed line indicates conformity between calculated and experimental results.

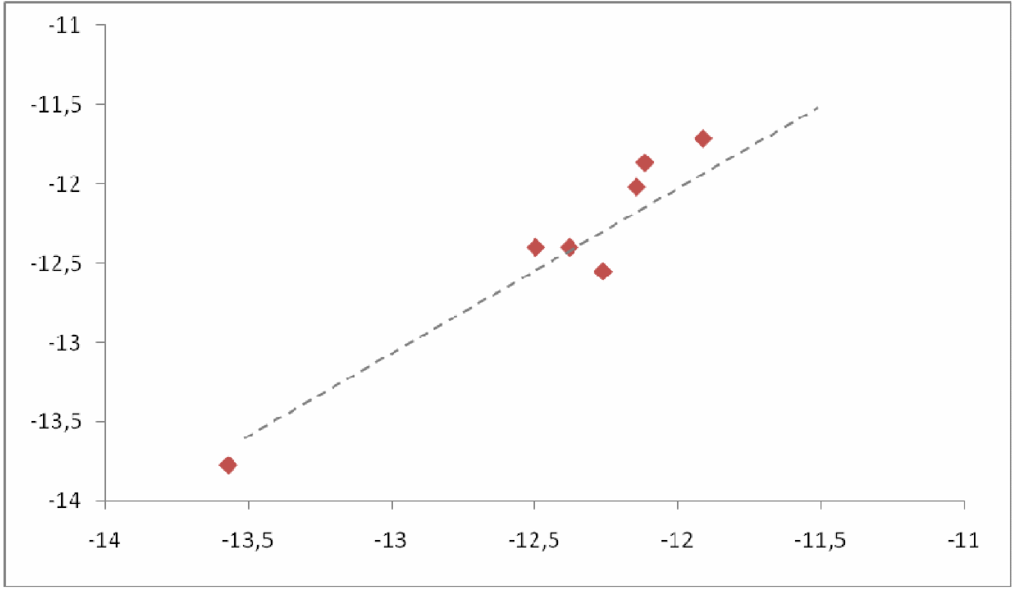
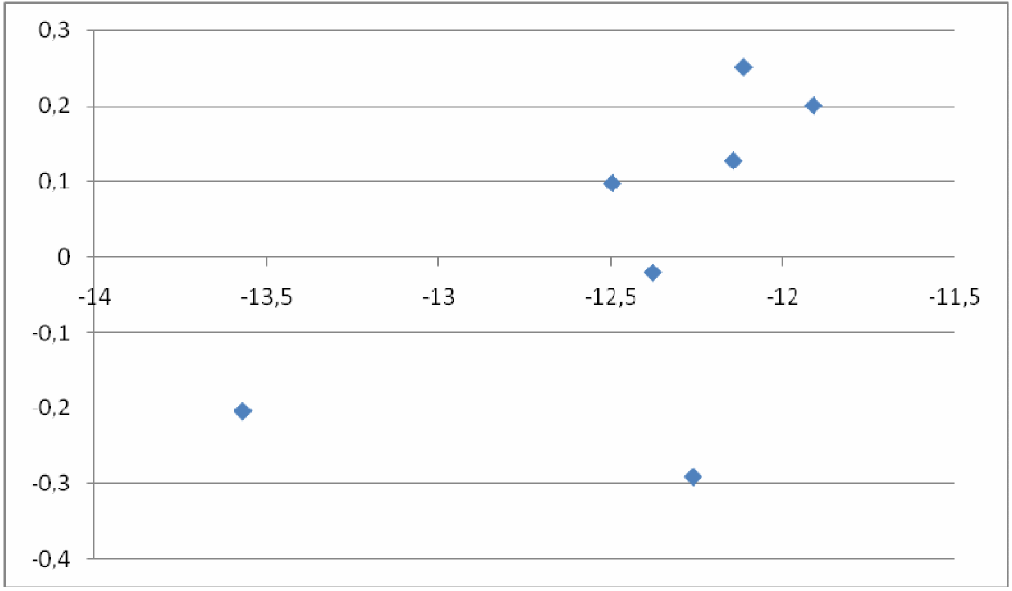


Figure 3: Calculation error vs. experimental log k_{OH} for structural analogues



3.4 The uncertainty of the prediction (OECD principle 4)

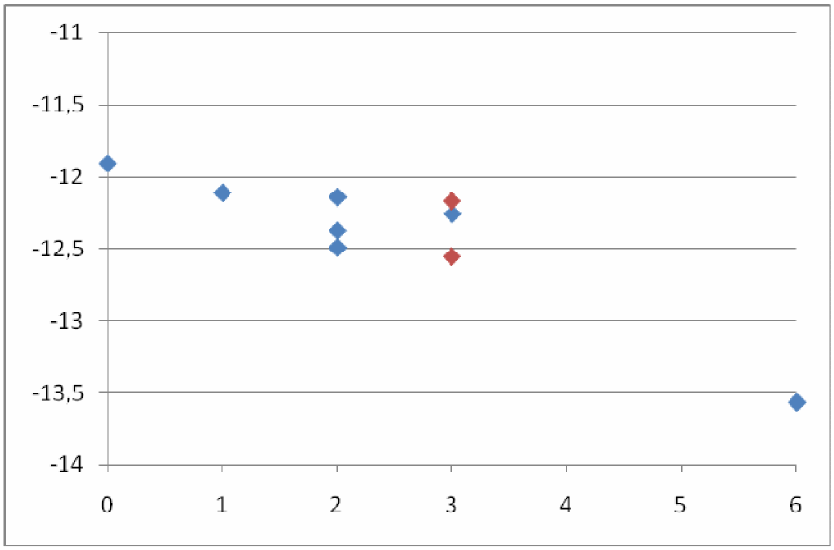
Given the calculation errors and the variability observed for the structural analogues, it is expected that the QSAR prediction is correct within a range of 0.3 (see 3.3c).

3.5 The chemical and biological mechanisms according to the model underpinning the predicted result (OECD principle 5).

The reaction of chlorobenzenes with OH radicals proceeds via addition of the OH radical to the aromatic ring. Due to their electron-withdrawing effect, chlorine substituents are generally expected to reduce reactivity towards OH radicals, resulting in decreasing log k_{OH} values with increasing chlorine content. Furthermore, the position of the substituents has an impact on susceptibility to electrophilic attacks. For example, 1,3-dichlorobenzene and 1,3,5-trichlorobenzene are expected to be more reactive than their respective isomers. This may lead to slight deviations from the aforementioned trend. Taking into account the experimental data from structural analogues, the predicted log k_{OH} values for 1,2,3-trichlorobenzene and 1,3,5-trichlorobenzene are in accordance with this trend.

This is illustrated in figure 4, which shows the experimental log k_{OH} values of the structural analogues and the predicted log k_{OH} values for 1,2,3-trichlorobenzene and 1,3,5-trichlorobenzene, plotted vs. the number of chlorine atoms.

Figure 4: Experimental log k_{OH} for structural analogues plotted vs. number of chlorine atoms. The red dots represent predicted log k_{OH} values for 1,2,3-trichlorobenzene and 1,3,5-trichlorobenzene.



4. Adequacy (Optional)

4.1 Regulatory purpose: REACH Annex XV Report. Proposal for Identification of a substance as a PBT.

4.2 Approach for regulatory interpretation of the model result: The model result is a key factor determining atmospheric residence time and thus an important input when modelling and assessing the atmospheric long-range transport potential of the substances.

4.3 **Outcome:** The k_{OH} values of 1,2,3-trichlorobenzene and 1,3,5-trichlorobenzene are $0.282 \cdot 10^{-12}$ and $0.679 \cdot 10^{-12}$ $cm^3 s^{-1} molecules^{-1}$. They are considered to be correct within a range of 0.3 logarithmic units.

4.4 **Conclusion:** The k_{OH} values of 1,2,3-trichlorobenzene and 1,3,5-trichlorobenzene are $0.282 \cdot 10^{-12}$ and $0.679 \cdot 10^{-12}$ $cm^3 s^{-1} molecules^{-1}$. These k_{OH} values can be used when assessing the atmospheric long-range transport potential of the substances. The resulting atmospheric half-lives depend on the underlying assumptions on the OH radical concentration.

ANNEX 3

QSAR Model Reporting Format (QMRF) for AOPWIN

Text version; original QMRF was generated in xml-Format, using the QMRF Editor v1.2, which is available free of charge http://ecb.jrc.ec.europa.eu/qsar/

1.QSAR identifier

1.1.QSAR identifier (title):
AOPWIN for k_{OH}

1.2.Other related models:
AOPWIN method for estimating k_{O3} (the rate constant for the gas-phase reaction between ozone and olefinic/acetylenic compounds)

1.3.Software coding the model:
EPISUITE Freely available software from the US EPA and the Syracuse Research Corporation
http://www.epa.gov/oppt/exposure/pubs/contact.htm
http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm

2.General information

2.1.Date of QMRF:
23.04.2010

2.2.QMRF author(s) and contact details:
Anna Böhnhardt
German Federal Environment Agency (UBA)
Wörlitzer Platz 1
06844 Dessau, Germany,
Phone: + 4934021033029
Anna.Boehnhardt@uba.de

2.3.Date of QMRF update(s):

2.4.QMRF update(s):

2.5.Model developer(s) and contact details:

Roger Atkinson
Air Pollution Research Center
Department of Environmental Sciences
University of California
Riverside, CA 92521
http://www.envisci.ucr.edu/faculty/atkinson.html

2.6.Date of model development and/or publication:
Original model published in the years 1986 and 1987, update published in 1995. Software is regularly updated.

2.7.Reference(s) to main scientific papers and/or software package:

[1] Atkinson R 1986. Kinetics and mechanisms of the gas-phase reactions of the hydroxyl radical with organic compounds under atmospheric conditions. Chemical Reviews 86 (1): 69-201. http://dx.doi.org/10.1021/cr00071a004

[2] Atkinson R 1987. A structure-activity relationship for the estimation of rate constants for the gas-phase reactions of OH radicals with organic compounds. International Journal of Chemical Kinetics 19 (9): 799-828. http://dx.doi.org/10.1002/kin.550190903

[3] Kwok ESC and Atkinson R 1995. Estimation of hydroxyl radical reaction rate constants for gas-phase organic compounds using a structure-reactivity relationship: An update. Atmospheric Environment 29 (14): 1685-1695. http://dx.doi.org/10.1016/1352-2310(95)00069-B

[4] US EPA 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v 4.00. United States Environmental Protection Agency, Washington, DC, USA. http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm

[5]US EPA. 2000. On-Line AOPWIN™ User's Guide (accessed on April 22nd, 2010). In: US EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v 4.00. United States Environmental Protection Agency, Washington, DC, USA. http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm

[6] Atkinson R 1991. Atmospheric lifetimes of dibenzo-p-dioxins and dibenzofurans. The Science of the Total Environment 104: 17-33. http://dx.doi.org/10.1016/0048-9697(91)90005-Y

2.8.Availability of information about the model:
The model equations and increments are documented in the original papers (Atkinson1986, Atkinson1987, Kwok&Atkinson1995) and in the On-Line AOPWIN User’s Guide that is included in the EPISUITE software package. The software and the user's guide are available free of charge (http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm). Most information given in this QMRF is taken from the original papers and the On-Line AOPWIN User’s Guide. According to the AOPWIN User's Guide, the complete training set is not available. However, the training set may be partly reconstructed by a careful analysis of the original papers and the literature cited therein. For example, the substances used to derive the regression equation for aromatic reactivity are given in a study on atmospheric lifetimes of dibenzo-p-dioxins and dibenzofurans (Atkinson 1991).

2.9.Availability of another QMRF for exactly the same model:
no other QMRF known

3.Defining the endpoint - OECD Principle 1

3.1.Species:

3.2.Endpoint:
2.Environmental fate parameters 2.Persistence: Abiotic degradation in air (Phototransformation) 2.2.b.Indirect photolysis (OH-radical reaction rate constant k_{OH})

3.3.Comment on endpoint:
k_{OH} values cover several orders of magnitude and are thus
evaluated as log k_{OH} in the section on validation

3.4.Endpoint units:
k_{OH} in $cm^3 \cdot molecule^{-1} \cdot s^{-1}$

3.5.Dependent variable:
log k_{OH} for aromatic reactivity; k_{OH} or log k_{OH} for other reaction mechanisms (probably k_{OH})

3.6.Experimental protocol:
Reaction rate constants can be determined directly by absolute rate techniques (pulsed photolysis, flow discharge techniques) or by relative rate methods.

3.7.Endpoint data quality and variability:
Data mainly taken from the PhysProp Database (SRC PhysProp Database.Syracuse Research Corporation) and the monographs of Atkinson (Atkinson 1989, Atkinson 1994). These sources contain collected experimental data from the scientific literature and have been carefully evaluated by atmospheric chemists.

4.Defining the algorithm - OECD Principle 2

4.1.Type of model:
QSAR estimating the OH-radical reaction rate (k_{OH}) of organic compounds

4.2.Explicit algorithm:

Determination of the overall reaction rate constant k_{OH}
Equation 1: Determination of the overall reaction rate constant (k_{OH}) by summation over the partial rate constants of all reaction sites *r* ($k_{mech,r}$), accounting for the respective reaction mechanisms.

$$k_{\mathrm{OH}} = \sum k_{\mathrm{mech}} = \sum \sum k_{\mathrm{mech,\,r}} \qquad (1)$$

Estimation of local reactivity I
Equation 2: Estimation of local reactivity for hydrogen abstraction & addition to double and triple bonds ($k_{mech,r}$) through group rate constants ($k_{mech,group}$) that reflect the basic reactivity towards OH. The influence of substituents (X) is accounted for by substituent factors (F(X)) that are specific for the respective mechanism. Both group rate constants and substituent values are incremental values and have been published in the original literature.

$$k_{\mathrm{mech,\,r}} = k_{\mathrm{mech,\,group}} \cdot \prod_X F(X) \qquad (2)$$

Estimation of local reactivity II
Equation 3: Estimation of local reactivity for addition to aromatic rings ($k_{aro,r}$) from sum of electrophilic substituent constants $\Sigma\sigma^+$

$$\log k_{\mathrm{aro,\,r}} = -11.71 - 1.34 \sum \sigma^+ \qquad (3)$$

4.3.Descriptors in the model:

- group rate constant ($k_{mech,group}$)
  increment; values given in the original literature and in the user's guide

- substituent factor (F(X))
  increment; values given in the original literature and in the user's guide
- electrophilic substituent constants σ^+
  increment; values given in user's guide

4.4.Descriptor selection:
Electrophilic substituent constants describe aromatic reactivity (Brown and Okamoto 1958) and were thus selected as descriptors for aromatic rings.

4.5.Algorithm and descriptor generation:
Values for group rate constants and substituent factors were derived partly from individual molecules and partly from a nonlinear least-squares fit. The model equation for aromatic reactivity was derived from a least-squares analysis on a set of monocyclic aromatics and biphenyls.

4.6.Software name and version for descriptor generation:

4.7.Chemicals/Descriptors ratio:

5.Defining the applicability domain - OECD Principle 3

5.1.Description of the applicability domain of the model:

The compound to be predicted should have similar structural features as the compounds from the training set (chemical domain). The chemical domain can be estimated from the group rate constants and substituent factors applied in the model. If it is not possible to describe all features of the chemical strucure by group rate constants and/or substituent factors, the compound is outside the applicability domain. However, this approach only allows for a rather coarse estimation of the chemical domain. For a more precise description, knowledge of the training set is required. Furthermore, the compound to be predicted should be in the so-called mechanistic domain. The latter can be defined clearly by the different reaction mechanisms that are accounted for by respective model equations: H-atom abstraction from C-H and O-H bonds; OH radical addition to double and triple bonds; OH radical addition to aromatic rings; and OH radical interaction with N-,S-, and P- atoms. Finally, the compound to be predicted should be shown to be in the same parameter range (parameter domain).

As the training set is not available, a precise description of the chemical and the parameter domain is not possible. However, subsets of the training set can be reconstructed by a careful analysis of the original papers and the literature cited therein. For example, the substances used to derive the regression equation for aromatic reactivity are given in a study on atmospheric lifetimes of dibenzo-p-dioxins and dibenzofurans (Atkinson 1991). This way, a "subdomain" may be derived from a set of substances that are verified to belong to the training set. For example, the regression equation for aromatic reactivity was derived from a set of monocyclic aromatic compounds and biphenyls. Thus, for applying this equation, the compound to be predicted should be chemically similar to the respective training set of monocyclic aromatic compounds and biphenyls. The reaction rate constants of these compounds are available in the PhysProp Database and range from $1.4 \cdot 10^{-13}$ $cm^3 \cdot molecule^{-1} \cdot s^{-1}$ (Nitrobenzene) to $1.13 \cdot 10^{-10}$ $cm^3 \cdot molecule^{-1} \cdot s^{-1}$ (3,5-Dimethylphenol). According to the user's guide, further substituent constants and increments, e.g. for condensed aromatics have been derived from experimental data to extend the applicability of the model.

5.2.Method used to assess the applicability domain:

As the training set is not available, the applicabiliity domain has to assessed by the user in a case-to case decision, e.g. by studying the original literature to find out whether subsances similar to the compound under study were included in the training set.

Subsets of the training set can be reconstructed by a careful analysis of the original papers and the literature cited therein. Thus, it would probably be possible to reconstruct large parts of the training set and thus derive a more comprehensive description of the applicability domain.

5.3.Software name and version for applicability domain assessment:

5.4.Limits of applicability:
If it is not possible to describe all features of the chemical strucure by respective increments (group rate constants and/or substituent factors), the compound is considered outside the applicability domain. Generally, the method can be considered to describe organic compounds that may contain the following atoms: carbon, hydrogen, oxygen, nitrogen, sulfur, phosphorous. A substance containing other atoms should be regarded as being outside the application domain. An exception are lead and mercury: In the user's guide, it is mentioned that additional substituent factors F(Pb) and F(Hg) were added. However, it should be checked carefully whether the chemical strucure can be adequately described by the respective increments.

6.Internal validation - OECD Principle 4

6.1.Availability of the training set:
No

6.2.Available information for the training set:
CAS RN: No
Chemical Name: No
Smiles: No
Formula:No
INChI:No
MOL file:No

6.3.Data for each descriptor variable for the training set:
No

6.4.Data for the dependent variable for the training set:
No

6.5.Other information about the training set:

6.6.Pre-processing of data before modelling:

6.Internal validation - OECD Principle 4

6.7.Statistics for goodness-of-fit:

6.8.Robustness - Statistics obtained by leave-one-out cross-validation:

6.9.Robustness - Statistics obtained by leave-many-out cross-validation:

6.10.Robustness - Statistics obtained by Y-scrambling:

6.11.Robustness - Statistics obtained by bootstrap:

6.12.Robustness - Statistics obtained by other methods:

7.External validation - OECD Principle 4

7.1.Availability of the external validation set:
No

7.2.Available information for the external validation set:
CAS RN:No
Chemical Name:Yes
Smiles:No
Formula:No
INChI:No
MOL file:No

7.3.Data for each descriptor variable for the external validation set:
No

7.4.Data for the dependent variable for the external validation set:
All

7.5.Other information about the external validation set:
partly published (Meylan and Howard 1993); refers to the original version of the model (before 1995 update)

7.6.Experimental design of test set:

7.7.Predictivity - Statistics obtained by external validation:
Overall dataset:
$n = 77$; $r^2 = 0.89$; stdv = 0.24; me = 0.17, mne = -2.56; mpe = 2.2 (referring to log k_{OH})
n = number of compounds; stdv = standard deviation; me = mean error; mne = maximum negative error (largest underestimation); mpe = maximum positive error (largest overestimation)

7.8.Predictivity - Assessment of the external validation set:

The published part of the test set contains 35 substances (5 aliphatic compounds, 19 oxygenated organic compounds, 8 aromatics, 1 alkyne, 2 substances containing N or S functional groups but no C-C multiple bonds).

The reaction mechanism represented best in this subset is hydrogen abstraction from C-H and O-H bonds (24 compounds), followed by aromatics. OH radical addition to double and triple bonds is only represented by one alkyne with no olefinic compounds reported. The unpublished part of the test set cannot be assessed.

7.9.Comments on the external validation of the model:

Model performance was also validated using a larger data set of 805 compounds (Böhnhardt et al 2008), referring to the updated AOPWIN model. However, it should be noted that this data set contains external data as well as data that were used for model development.The test set contains data from the PhysProp Database as well as further experimental reaction rates collected from literature. It covers the following reaction mechanisms: H-atom abstraction from C-H and O-H bonds; OH radical addition to double and triple bonds; OH radical addition to aromatic rings. The test set does only contain N, S and P containing functional groups that are substituted to aromatic rings and thus, model performance for other N, S and P containing compounds is not tested.

The following statistics are reported fort he overall dataset (referring to log k_{OH}):
n = 805; $r^2 = 0.93$; $q^2 = 0.92$; rms = 0.35; bias = 0; me = 0.2, mne = -2.56; mpe = 2.2

The test set was divided into subsets according to chemical compound classes and thus, compound-class specific statistics are also available in the original study (Böhnhardt et al 2008). The model performance was found to depend on the compound-class under consideration. The best performance is observed for the subset of alkynes ($r^2 = 0.99$), however, this data set contains only 7 substances (most of which were probably used to derive the model). This QMRF gives statistics for the compound classes with the weakest and the second best performance, respectively:

Alkenes:
n = 124; $r^2 = 0.62$; $q^2 = 0.51$; rms = 0.48; bias = -0.05; me = 0.23, mne = -2.56; mpe = 1.29

Aromatics:
n = 134; $r^2 = 0.94$; $q^2 = 0.94$; rms = 0.21; bias = -0.02; me = 0.14, mne = -0.65; mpe = 0.83

n = number of compounds; q^2 = predictive squared correlation coefficient; rms = root-mean-square error; bias = systematic error; me = mean error; mne = maximum negative error (largest underestimation); mpe = maximum positive error (largest overestimation)

8.Providing a mechanistic interpretation - OECD Principle 5

8.1.Mechanistic basis of the model:
The model is developed based on profound knowledge of the different reaction pathways and assigns incremental values that are specific for the mechanism under consideration. The overall reaction rate is assumed to be the sum of four reaction constants corresponding to the following reaction mechanisms: H-atom abstraction from C-H and O-H bonds; OH radical addition to double and triple bonds; OH radical addition to aromatic rings; and OH radical interaction with N-,S-, and Patoms. These mechanism-specific rate constants are assumed to be the sum of partial rate constants that can be assigned to the individual reaction sites and that are described by increment values.

8.2.A priori or a posteriori mechanistic interpretation:
a priori

8.3.Other information about the mechanistic interpretation:

9.Miscellaneous information

9.1.Comments:

9.2.Bibliography:

[1] Meylan WM and Howard PH 1993. Computer estimation of the atmospheric gas-phase reaction rate of organic compounds with hydroxyl radicals and ozone. Chemosphere 26: 2293-99. http://dx.doi.org/10.1016/0045-6535(93)90355-9

[2] Böhnhardt A, Kühne R, Ebert R-U, Schüürmann G 2008. Indirect photolysis of organic compounds – prediction of OH reaction rate constants through molecular orbital calculations. J. Phys. Chem. A. 112: 11391-11399. http://dx.doi.org/10.1021/jp8052218

[3] Brown HC and Okamoto Y 1958. Electrophilic Substituent Constants. Journal of the American Chemical Society 80 (18):4979-4987. http://dx.doi.org/10.1021/ja01551a055

9.3.Supporting information:

Training set(s)Test set(s)Supporting information

10.Summary (JRC Inventory)

10.1.QMRF number:

To be entered by JRC

10.2.Publication date:

To be entered by JRC

10.3.Keywords:

To be entered by JRC

10.4.Comments:

To be entered by JRC