資料１－１

残留性有機汚染物質に関するストックホルム条約の新規対象物質を化審法第一種特定化学物質に指定することについて（案）

平成２５年６月２８日

厚生労働省医薬食品局審査管理課化学物質安全対策室
経済産業省製造産業局化学物質管理課化学物質安全室
環境省総合環境政策局環境保健部企画課化学物質審査室

１．背景

（１）残留性有機汚染物質に関するストックホルム条約（平成16年５月発効。以下「POPs条約」という。）においては、難分解性、生物蓄積性、毒性及び長距離移動性を有するPOPs（Persistent Organic Pollutants、残留性有機汚染物質）による人の健康の保護及び環境の保全を図るため、各国が国際的に協調して、POPs条約の対象物質について、製造及び使用を原則禁止する等の措置を講じることとしている。

我が国においては、平成17年に国内実施計画を定め、平成24年に改正を行った。対象物質に関する製造、使用、輸入及び輸出の規制については、化学物質の審査及び製造等の規制に関する法律（昭和48年法律第117号。以下「化審法」という。）、農薬取締法（昭和23年法律第82号）、薬事法（昭和35年法律第145号）及び外国為替及び外国貿易法（昭和24年法律第228号）に基づき、所要の措置が講じられているところである。化審法においては、現在のPOPs条約対象物質のうち、意図的に製造されることのないPCDD及びPCDFを除いた19物質について、第一種特定化学物質に指定し、製造、輸入の許可制（事実上禁止）、使用の制限及び届出制（事実上禁止）等の措置を講じている。

（２）POPs条約における対象物質の追加のための手続きとしては、締約国から提案のあった候補物質について、残留性有機汚染物質検討委員会（以下「POPRC」という。）において、締約国等から提供された科学的知見に基づき、POPs条約で定められた手順に基づく検討を行うこととされており、昨年秋までに８回のPOPRCが開催されている（我が国からは、委員として北野大　淑徳大学教授が第１回より第８回まで継続的に出席。）。第６回POPRCでは、６，７，８，９，１０，１０－ヘキサクロロ－１，５，５a，６，９，９a－ヘキサヒドロ－６，９－メタノ－２，４，３－ベンゾジオキサチエピン＝３－オキシド類（別名：エンドスルファン又はベンゾエピン、以下、エンドスルファン）を附属書Ａ（廃絶）へ追加する旨の勧告を締約国会議に対して行うことが決定された。また、第８回POPRCでは、ヘキサブロモシクロドデカンを同様に附属書Ａへ追加する旨の勧告を行うことが決定された。

（３）上記勧告を踏まえ、平成23年４月に開催された第５回締約国会議において、

エンドスルファン[1]を附属書Ａに追加することが決定された。また、本年４月～５月に開催された第６回締約国会議において、ヘキサブロモシクロドデカン[2]を附属書Ａに追加することが決定された。これらの物質については、今後、POPs 条約の下で、製造、使用等を廃絶・制限する措置等が講じられることとなる（改正される附属書の発効は、国連事務局による各国への通報から１年後）。

２．化審法による対応（案）

（１）附属書Ａに追加されたエンドスルファン及びヘキサブロモシクロドデカンについては、POPs としての要件を満たすことが POPRC により既に科学的に評価されており（別添１及び別添２参照）、これらの要件は化審法の第一種特定化学物質と同様に、分解性、蓄積性及び毒性等に基づくものであることから、すでに附属書Ａに掲げられている化学物質と同様に、化審法の第一種特定化学物質に指定することとする。同時に、ヘキサブロモシクロドデカンについては、平成 22 年度から化審法第 14 条第１項に基づく有害性調査を行った事業者に対して、同条第２項に基づき、第一種特定化学物質に該当すると判定し、通知することとしたい。

（２）また、化審法第 24 条に基づき、これらの物質を使用している製品については輸入を禁ずることとなっており、その具体的な措置についても今後検討する。特に、ヘキサブロモシクロドデカンについては、難燃剤として現在も広く使用されていることから、POPs 条約で認められた範囲で適用除外の登録等を行うことの可否や、その製造・輸入・使用等を禁止する時期についても今後検討する。

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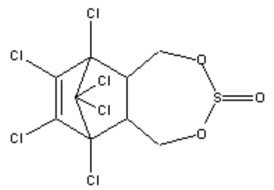
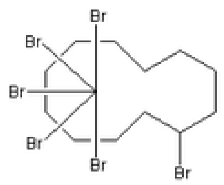
1 締約国会議における指定名称： Technical endosulfan (CAS No: 115-29-7) and its related isomers (CAS No:959-98-8 and CAS No: 33213-65-9)

2 締約国会議における指定名称： Hexabromocyclododecane” means hexabromocyclododecane (CAS No: 25637 99-4), 1,2,5,6,9,10-hexabromocyclododecane (CAS No: 3194-55-6) and its main diastereoisomers: alpha- hexabromocyclododecane (CAS No: 134237-50-6); beta-hexabromocyclododecane (CAS No: 134237-51-7); and gamma hexabromocyclododecane (CAS No: 134237-52-8)

POPs 条約への新規追加に伴い化審法第一種特定化学物質へ指定を行う物質（案）

No.	化学物質名	CAS 番号	化審法官報 公示整理番号
1	６，７，８，９，１０，１０－ヘキサクロロ－１，５，５ａ，６，９，９ａ－ヘキサヒドロ－６，９－メタノ－２，４，３－ベンゾジオキサチエピン＝３－オキシド類（別名：エンドスルファン又はベンゾエピン）  （構造式）	115-29-7 959-98-8 33213-65-9	
2	ヘキサブロモシクロドデカン  （構造式）	25637-99-4 3194-55-6 4736-49-6 65701-47-5 134237-50-6 134237-51-7 134237-52-8 138257-17-7 138257-18-8 138257-19-9 169102-57-2 678970-15-5 678970-16-6 678970-17-7	3-2254

別添１

エンドスルファンの有害性の概要

分解性	蓄積性	人健康影響関連	動植物への影響関連
【分解性】 好気的変換は、生物が媒介する酸化経由で起こり、主代謝物はエンドスルファンスルファートである。 これは、より極性の高い代謝物のエンドスルファンジオール、エンドスルファンラクトン、エンドスルファンエーテルへと分解される。 エンドスルファンスルファートは親物質エンドスルファンと同等の毒性がある。 【残留性】 ①大気 推定半減期(Atkinson法)：8.5day 実測半減期：75℃ α体：27day β体：15day ②水中 易分解性でない 水環境下：光分解性なし 加水分解性：pHが高い時のみ ③土壌 ・実験室(20℃) 好気的条件下半減期 ［α＋β体］：25～128day ［エンドスルファンスルファート］：123～391day ・温帯地域フィールド下半減期 ［α＋β体］：7.4～92day ・土壌中推定総半減期 ［α＋β体、及びエンドスルファンスルファート］：28～391 日 ④水／底質中 ・半減期： ［α＋β体及びエンドスルファンスルファート］：3.3～273day	【BCF（生物濃縮係数）】 ・魚類：1,000～3,000 ・無脊椎動物：12～600 ・藻類：2,682 ・ミジンコ：3,278 ・カキ（乾燥重量ベース） ［α＋β体、及びエンドスルファンスルファート］：375～1,776 【BAF（生物蓄積係数）】 ・イワナ、タラ及びサケの総計： 1,690～7,280 （湿重量ベース） ・水生生物の短期ミクロコズム試験 ［α＋β体、及びエンドスルファンスルファート］：375～1,776 ・野外水生生物のミクロコズム試験：［エンドスルファンスルファート］：1,000 （残留放射能ベース） 【魚類排泄試験】 ・半減期 ［α＋β体、及びエンドスルファンスルファート］：2～6 日 【log Kow】 α体：4.65 β体：4.34 エンドスルファンスルファート：3.77 ※ Risk Profileでは「エンドスルファンのBCF及びlog Kowは、ストックホルム条約のスクリーニングトリガーである5,000、及び5を下回っているものの、明確な生物濃縮性の可能性を示している。」とされている。	【反復投与毒性】 ・関連する最も低いNOECは ラット 0.6mg/kg bw/day （体重増加抑制、進行性糸球体腎炎、動脈瘤が2.9mg/kg bw/dayで観察） ・イヌの1年投与試験でも同程度 ・経口、経皮暴露で中枢神経系に影響あり 【発達神経毒性試験】 ・ラット：LOAEL:3.74mg/kg/day （仔の体重減少と体重増加抑制。神経毒性は10mg/kg/dayより下では見られていない） 【その他】 ・EU、米国、カナダの評価で発がん性はないとされている。 ・内分泌撹乱作用は両論あり。 【代謝物・異性体】 ・エンドスルファンラクトン混餌投与(90日） ラット:NOAEL 0.6mg/kg bw/day ・エンドスルファンスルファートは親物質と同程度の急性毒性を示す。 ・一般にα体のほうが毒性高い。	【水生生物への生態毒性】 ・関連する最も低いNOECは 魚類 0.05μg/L ・底生生物 NOECs：0.1～1mg/kg

※エンドスルファンは、化審法の第一種特定化学物質であるアルドリン系の化学物質と構造が類似していることから、それらと同様に生分解性が低いと考えられる。			

SC

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Persistent Organic Pollutants Review Committee
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Report of the Persistent Organic Pollutants Review Committee on the work of its fifth meeting

Addendum

Risk profile on endosulfan

At its fifth meeting, the Persistent Organic Pollutants Review Committee adopted the risk profile on endosulfan, on the basis of the draft contained in document UNEP/POPS/POPRC.5/3. The text of the risk profile, as amended, is set out below. It has not been formally edited.

K0953713 200110

ENDOSULFAN

RISK PROFILE

Adopted by the Persistent Organic Pollutants Review Committee
at its fifth meeting

October 2009

Annex

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Executive summary

Endosulfan is a synthetic organochlorine compound consisting of two isomers (α and β). It is commonly used as an agricultural insecticide. Technical endosulfan is a 2:1 to 7:3 mixture of the α- and β-isomers.

Endosulfan has been sold from the mid 1950s but it is now banned in at least 60 countries with former uses replaced and its production is decreasing. However, endosulfan is still used in different regions of the world.

Endosulfan aerobic transformation occurs via biologically mediated oxidation. The main metabolite formed is endosulfan sulfate. This compound is slowly degraded to the more polar metabolites endosulfan diol, endosulfan lactone, endosulfan ether. The combined median half-life DT_{50} measured in laboratory studies for α and β endosulfan and endosulfan sulfate, was selected as a relevant parameter for quantifying the persistence, it ranges typically between 28 and 391 days. In the aquatic compartment, endosulfan is stable to photolysis; a rapid hydrolysis is only observed at high pH values, and it is non-readily biodegradable. In water/sediment systems, DT_{50} > 120 d was demonstrated. There is a uncertainty on the degradation rate of endosulfan in the atmosphere, however it is expected that the half life exceeds the 2 days threshold.

The bioconcentration potential of endosulfan in aquatic organisms is confirmed by experimental data. The validated bioconcentration factor (BCF) values range between 1000 and 3000 for fish, from 12 to 600 for aquatic invertebrates; and up to 3278 in algae. Thus, reported BCFs are below the criterion of 5,000; and the log Kow is measured at 4.7, which is below the criterion of 5. However, measured BAF and BMF in Arctic organisms show that endosulfan has an inherent high bioaccumulation and biomagnification potential. Additionally, endosulfan was detected in adipose tissue and blood of animals in the Arctic and the Antarctic. Endosulfan has also been detected in the blubber of minke whales and in the liver of northern fulmars. Therefore, there is sufficient evidence that endosulfan enters the food chain and that it bioaccumulates and has the potential to biomagnify in food webs.

The potential of endosulfan for long range transport (LRT) has been confirmed from three main information sources: the analysis of the endosulfan properties, the application of LRT models, and the review of existing monitoring data in remote areas.

LRT has been confirmed by the presence of endosulfan in air and biota from remote areas. Most studies measure α- and β-endosulfan, and in some cases, endosulfan sulfate. Other endosulfan metabolites are only rarely quantified. The presence of endosulfan in remote areas, far away from intensive use areas, in particular, the Arctic and Antarctica has been confirmed. The potential for LRT seems to be mostly related to volatilization following by atmospheric transfer; deposition at high altitude mountain areas has been also observed.

The toxicity and ecotoxicity of endosulfan is well documented. Endosulfan is highly toxic for humans and for most animal taxa, showing both acute and chronic effects at relatively low exposure levels. Acute lethal poisoning in humans and clear environmental effects on aquatic and terrestrial communities has been observed under standard use conditions when the risk mitigation measures have not been followed. Several countries have found that endosulfan poses unacceptable risks, or has caused unacceptable harm, to human health and the environment, and have banned or severely restricted it. However, the information on its genotoxicity and its potential for endocrine disruption is not fully conclusive. Finally, the role of endosulfan metabolites other than endosulfan sulfate has received limited attention. Endosulfan lactone has the same chronic NOEC value as the parent endosulfan isomers. The assessment of the POP characteristics of endosulfan, including endosulfan sulfate, confirms the concern regarding endosulfan and its main metabolite; it should be also considered that other metabolites, formed through both environmental and biota transformations, maintains the chemical structure and in some cases have significant toxicity.

Based on the inherent properties, and given the widespread occurrence in environmental compartments and biota in remote areas, together with the uncertainty associated with the insufficiently understood role of the metabolites which maintain the endosulfan chemical structure, it is concluded that endosulfan is likely, as a result of its long-range environmental transport, to lead to significant adverse human health and environmental effects, such that global action is warranted.

1. Introduction

Endosulfan is a synthetic organochlorine compound. It is commonly used as an agricultural insecticide. It has been sold from the mid 1950s and it is still contained in pesticide products in some countries worldwide. Technical information about (eco)toxicity, environmental fate, residues in food and feedstuff, environmental concentrations, etc. of endosulfan is widely available from different sources around the world. Various reviews have been published during the last decade regarding every aspect related to our environment.

1.1 Chemical identity

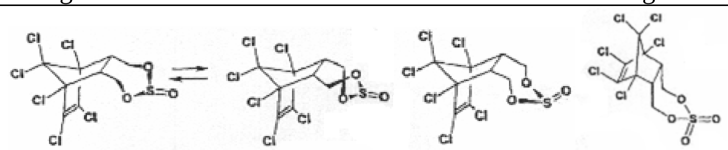
Names and registry numbers

Common name IUPAC Chem. Abstracts	Endosulfan 6,7,8,9,10,10-hexachloro-1,5,5a,6,9,9a-hexahydro-6,9-methano-2,4,3-benzodioxathiepin-3-oxide 6,9-methano-2,4,3-benzodioxathiepin-6,7,8,9,10,10-hexachloro-1,5,5a,6,9,9-hexahydro-3-oxide	
CAS registry numbers	alpha (α) endosulfan beta (β) endosulfan technical endosulfan * Endosulfan sulfate: * stereochemically unspecified	959-98-8 33213-65-9 115-29-7 1031-07-8
Trade name	Thiodan® , Thionex, Endosan, Farmoz, Endosulfan, Callisulfan	

* Technical endosulfan is a 2:1 to 7:3 mixture of the α- and the β-isomer.

Technical grade endosulfan is a diastereomeric mixture of two biologically active isomers (α- and β-) in approximately 2:1 to 7:3 ratio, along with impurities and degradation products. The technical product must contain at least 94% endosulfan in accord with specifications of the Food and Agricultural Organization of the United Nations (FAO Specification 89/TC/S) with content of the α-isomer in the range of 64-67% and the β-isomer of 29-32%. The α-isomer is asymmetric and exists in two twist chair forms while the β-form is symmetric. The β-isomer is easily converted to α-endosulfan, but not vice versa (INIA, 1999).

Structures

Molecular formula	$C_9H_6Cl_6O_3S$	$C_9H_6Cl_6O_4S$
Molecular mass	406.96 g·mol^{-1}	422.96 g·mol^{-1}
Structural formulas of the isomers and the main transformation product	 α-endosulfan β-endosulfan endosulfan sulfate	

Physical and chemical properties of endosulfan isomers and of endosulfan sulfate

	α isomer	**β isomer**	**Technical mixed isomers**	**sulfate**
Melting point, ºC	109.2	213.3	70-124	181 - 201
Solubility in water pH 5, at 25ºC, mg/L	0.33	0.32	0.05-0.99 Recommended value: 0.5	0.22
Vapour Pressure, Pa, at 25ºC	1.05 E-03	1.38 E-04	2.27E-5 – 1.3E-3 Recommended value: 1.3E-3	2.3 E-05
Henry’s Law Constant Pa m^3/mol, at 20ºC	1.1	0.2	1.09-13.2, recommended value: 1.06	0.041
logarithm of octanol-water partition coefficient (Log Kow) at pH 5.1	4.7	4.7	3.6	3.77
Dissociation constant	n.a. (no acidic protons)	n.a. (no acidic protons)	n.a. (no acidic protons)	n.a. (no acidic protons)

1.2 Conclusion of the Review Committee regarding Annex D information

The Committee evaluated Annex D information at its fourth meeting held in Geneva, from October 13th to 17th 2008, and decided that "it is satisfied that the screening criteria have been fulfilled for endosulfan" and concluded that "endosulfan met the screening criteria specified in Annex D".

1.3 Data sources

The primary source of information for the preparation of this risk profile was the proposal submitted by the European Community and its member States that are Parties to the Convention, contained in document UNEP/POPS/POPRC.4/14, and additional information submitted for Annex D evaluation. In particular:

- INIA 1999-2004. Monograph prepared in the context of the inclusion of the following active substance in Annex I of the Council Directive 91/414/EEC. Instituto Nacional de Investigación y Tecnología Agraria y Alimentaria (I.N.I.A.) including addenda.

In addition the following parties and observers have answered the October 2008 request for information specified in Annex E of the Convention: Albania, Australia, Bahrain, Bulgaria, Canada, China, Congo (RDC), Costa Rica, Croatia, Czech Republic, Ecuador, Egypt, Ghana, Honduras, Japan, Lithuania, Mali, Mauritius, Mexico, New Zealand, Nigeria, Norway, Romania, Slovakia, Switzerland, Togo, United States of America, Makteshim-Agan Industries (MAI), CropLife, Indian Chemical Council (ICC), Pesticide Action Network (PAN) International and the International POPs Elimination Network (IPEN). A more elaborated summary of the submissions is provided as separate informal document. *Summary of data submitted by Parties and observers for information specified in Annex E of the Convention.*

1.4 Status of the chemical under international conventions

Endosulfan is subject to a number of regulations and action plans:

- In March 2007 the Chemical Review Committee (CRC) of Rotterdam Convention on the Prior Informed Consent Procedure (PIC) for Certain Hazardous Chemicals and Pesticides in International Trade decided to forward to the conference of the parties of the Convention (COP) a recommendation for inclusion of endosulfan in Annex III. Annex III is the list of chemicals that are subject to the PIC procedure. Listing in Annex III is based on two notifications from different regions of regulatory action banning or severely restricting the use for health or environmental reasons that were found to meet the criteria listed in Annex II of the Convention. The COP in 2008 was not yet able to reach consensus on inclusion of endosulfan and decided to further consider the draft decision at the next COP. Meanwhile, the CRC has been evaluating further notifications of endosulfan.
- Endosulfan is recognized as one of the twenty-one high-priority compounds identified by UNEP-GEF (United Nations Environment Programme – Global Environment Facility) during the Regional Evaluation of Persistent Toxic Substances (STP), 2002. These reports have taken into account the magnitude of usage, environmental levels and effects for human beings and for the environment of this compound.
- The Sahelian Pesticides Committee (CSP) has banned all formulations containing endosulfan. The CSP is the structure for the approval of pesticides for CILSS member States (Burkina Faso, Cap Verde, Chad, Gambia, Guinea Bissau, Mali, Mauritania, Niger and Senegal). The deadline set for termination of the use of existing stocks of endosulfan was 31/12/2008.
- The UN-ECE (United Nations Economic Commission for Europe) has included endosulfan in Annex II of the Draft Protocol on Pollutant Release and Transfer Registers to the AARHUS Convention on access to Information, Public Participation in Decision-making and Access to Justice in Environmental Matters.
- UN-ECE task force concluded in June 2009 that endosulfan should be considered as POP. UNECE (2009)
- The OSPAR Commission has included endosulfan in the List of Chemicals for Priority Action (update 2002)
- In the Third North Sea Conference (Annex 1A to the Hague Declaration), endosulfan was agreed on the list of priority substances.

2. Summary information relevant to the risk profile

2.1 Sources

2.1.1 Production, trade, stockpiles

Endosulfan is synthesized via the following steps: Diels-Alder addition of hexachloro-cyclopentadiene and cis-butene-1,4-diol in xylene. Reaction of this cis-diol with thionyl chloride forms the final product.

Endosulfan was developed in the early 1950s. Global production of endosulfan was estimated to be 10,000 tonnes annually in 1984. Current production is judged to be significantly higher than in 1984. India is regarded as being the world's largest producer (9900 tonnes per year (Government of India 2001-2007)) and exporter (4104 tonnes in 2007-08 to 31 countries (Government of India)); followed by Germany (approximately 4000 tonnes per year); Production stopped at 2007 but export could continue until the end of 2010); China (2400 tonnes), Israel, Brazil and South Korea.

2.1.2 Uses

Endosulfan is an insecticide used to control chewing, sucking and boring insects, including aphids, thrips, beetles, foliar feeding caterpillars, mites, borers, cutworms, bollworms, bugs, white fliers, leafhoppers, snails in rice paddies, earthworms in turf, and tsetse flies.

Endosulfan is used on a very wide range of crops. Major crops to which it is applied include soy, cotton, rice, and tea. Other crops include vegetables, fruit, nuts, berries, grapes, cereals, pulses, corn, oilseeds, potatoes, coffee, mushrooms, olives, hops, sorghum, tobacco, and cacao. It is used on ornamentals and forest trees, and has been used in the past as an industrial and domestic wood preservative.

As recently as 2006 the US EPA has approved and registered the use of Endosulfan as a veterinary insecticide to control ectoparasites both in beef and lactating cattle. It is used as an ear tag in cattle.

The use of Endosulfan is now banned in at least 60 countries[1] with former uses replaced by less hazardous products and methods. More detailed information on current uses as informed by countries is provided as separate informal document. Summary of data submitted by Parties and observers for information specified in Annex E of the Convention.

Other countries are using of Endosulfan, including USA, Australia, Argentina, Brazil, Cameroon, Canada, Chile, Costa Rica, Ghana, Guatamala, India, Iran, Israel, Kenya, Madagascar, Mali, Mexico, Mozambique, China, Paraguay, Pakistan, Sierra Leone, South Africa, South Korea, Sudan, Tanzania, Uganda, Venezuela, Zambia, Zimbabwe.

Endosulfan is widely used in India for the last several years.

2.1.3 Releases to the environment

As a result of the use of endosulfan as an insecticide, endosulfan is released to the environment. No natural sources of the compound are known. From the manufacturing and formulation operations, local scale environmental releases to the air, waste water, or surface waters may also occur.

Global usage and emission of endosulfan, and the relationship between global emissions and the air concentration of endosulfan in the Canadian Arctic were reported in Li and MacDonald (2005). Cumulative global use of endosulfan for crops is estimated to be 338,000 tonnes. The average annual endosulfan usage in the world is estimated to have been 10,500 tonnes from 1980 to 1989 and 12,800 tonnes from 1990 to 1999. The general trend of total global endosulfan use increased continuously since the first year this pesticide was applied until at least the late 1990s. No recent figures, updated after the recent banning in at least 60 countries, are available. India is the world's largest consumer of endosulfan with a total use of 113,000 tonnes from 1958 to 2000. Total global endosulfan emissions have also increased continuously since the year when this pesticide was first applied presently amounting to an estimated total emission around 150,000 tonnes. Recent data on endosulfan usage and emissions in China indicate a total endosulfan usage of 24,000 t in the period from 1994 to 2004 and total endosulfan emissions of 1100 t (Jia et al. 2009a, 2009b). From 1998 to 2004, usage was about 2700 t/a and emissions were 1250 t/y; before 1998, values were lower.

A time trend of α-endosulfan air concentration at Alert, Canada between 1987 and 1997 (Li and MacDonald (2005)), compiled from several sources (Patton et al., 1989, Halsall et al., 1998 and Hung et al., 2002), shows this to be one of the few organochlorine pesticides with concentrations that were stable or were increasing slightly in Arctic air over the 1987-1997 time period. The data for emissions of α-endosulfan exhibit high variability but demonstrate a generally increasing trend at least up until the late 1990s. Canadian Arctic air sampling data similarly exhibits high variability but the few available data are not inconsistent with the emission data, suggesting the atmosphere is an important transporting medium. More recently, the long-term trend of endosulfan in arctic air - derived using Digital Filtration, a statistical time-series model that filters out regular seasonal fluctuations to reveal the underlying trend - does not show a decline over the period 1993 to 2006, unlike other OC pesticides (e.g.,γ-HCH and p,p'-DDT) (Hung et al., 2009).

1 Austria, Bahrain, Belgium, Belize, Benin, Bulgaria, Burkina Faso, Cambodia, Cape Verde,Chad, Colombia, Cote d'Ivoire, Croatia, Cyprus, Czech Republic, Denmark, Egypt, Estonia, Finland, France, Gambia, Germany, Greece, Guinea Bissau, Hungary, Indonesia, Ireland, Italy, Jordan, Kuwait, Latvia, Lithuania, Liechtenstein, Luxembourg, Malaysia, Mali, Malta, Mauritania, Mauritius, Netherlands, New Zealand, Niger, Nigeria, Norway, Oman, Poland, Portugal, Qatar, Romania, Saudi Arabia, Senegal, Singapore, Slovakia, Slovenia, Spain, Sri Lanka, St Lucia, Sweden, Switzerland, Syria, the United Arab Emirates, United Kingdom.

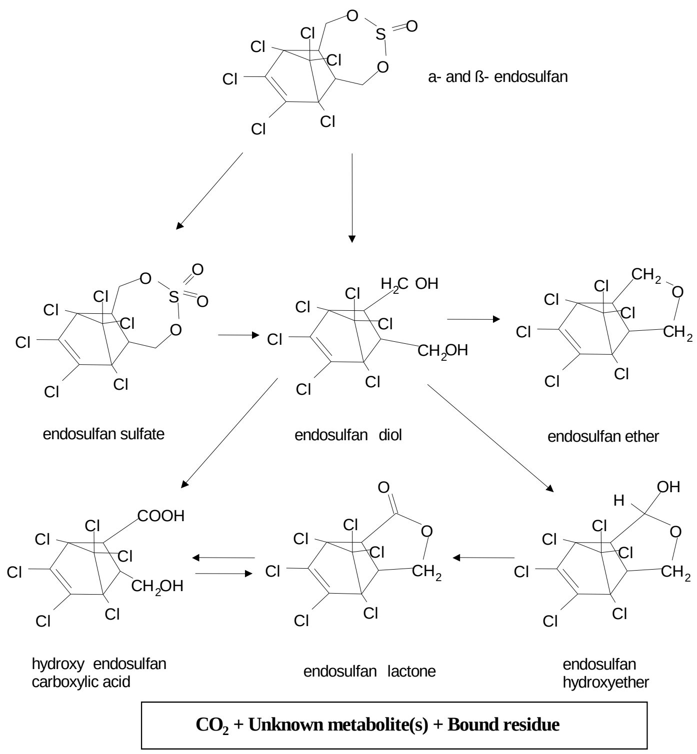
2.2 Environmental fate

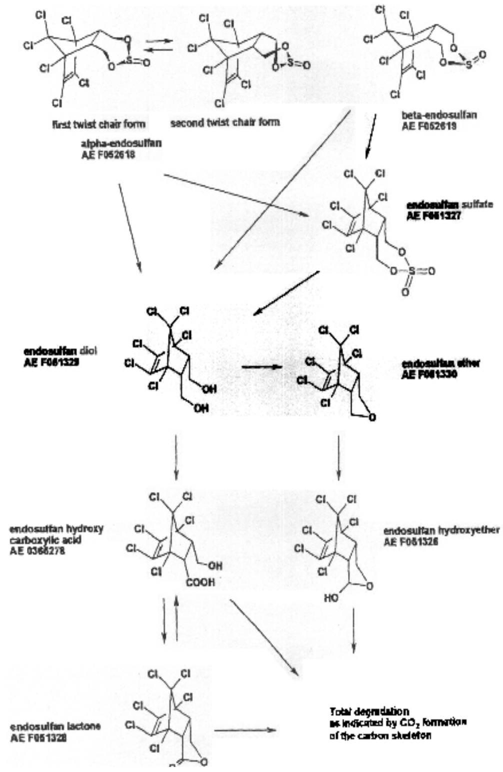
2.2.1 Persistence

Endosulfan aerobic transformation occurs via biologically mediated oxidation. The main metabolite formed is endosulfan sulfate. This compound is slowly degraded to the more polar metabolites endosulfan diol, endosulfan lactone, endosulfan ether. Formation of endosulfan sulfate is mediated essentially by micro-organisms, while endosulfan-diol was found to be the major hydrolysis product. Microbial mineralisation to carbon dioxide under laboratory conditions at 20ºC was 1.01 – 13.08% after 100 days for the parent endosulfan and for endosulfan sulphate 1.01 – 13.08% at 120 days and 5 – 35% at 365 days is in a range of depending on the type of soil.

Endosulfan sulfate also has insecticidal activity. Given the comparable toxicity of the sulfate metabolite a number of authors make use of the term "endosulfan (sum)" which includes the combined residues of both parent isomers and endosulfan sulfate. However, this term does not consider that in reality all the metabolites of endosulfan retain the backbone of the structure with the hexachloronorbornene bicycle.

The following degradation patterns for soil (right figure) and water (left figure) are proposed in the European Union risk assessment. In both cases, the parent isomers are transformed in endosulfan diol, either directly or through endosulfan sulfate. Endosulfan diol is then degradated into a set of related metabolites, including endosulfan ether, endosulfan hydroxyether, endosulfan carboxylic acid, and endosulfan lactone.





This environmental fate complicates the assessment of persistence as DT_{50} values. Most studies suggest that α-endosulfan has a faster degradation than β-endosulfan, and that endosulfan sulfate is much more persistent (INIA, 1999-2004). There is high variability in the reported DT_{50} values for these substances. The aerobic soil degradation studies reported in the EU assessment covered a range of soil types (sandy loam, loamy sand, clay and silt loam soils, pH ranging from 4.7 to 7.4, organic carbon ranging from 0.5 to 2.9%, and between 30 and 50% maximum water holding capacity) and were conducted following the USEPA or the Biologische Bundesanstalt (BBA) guidelines at 20ºC., The reported DT_{50} for aerobic soil degradation under laboratory conditions, ranged from 25 to 128 days for the α + β isomers, and from 123 to 391 days for endosulfan sulfate. The rapid field dissipation of endosulfan following its application under normal conditions is mostly related to volatilisation and varies largely; the European Union assessment reported, for the temperate regions, field DT_{50s} ranging from 7.4 to 92 days for the α + β isomers. A fast dissipation has been observed for tropical climates; volatilization, particularly for the α and β isomers, is considered the major process for endosulfan dissipation in tropical environments (Ciglasch et al., 2006; Chowdhury et al., 2007). In field studies conducted in India, the reported dissipation half lives ranged from 3 days (isomer not reported) (Raikwar, et al., 2003) to 100 and 150 days for α- and β-endosulfan respectively (Jayashree and Vasudevan 2007). Field aging increases the persistence in soil and is particularly relevant for endosulfan, with a 3-fold increase in the apparent organic carbon partition coefficient K_{OC} within 84 days in a tropical fruit orchard under natural weather conditions (Ciglasch et al., 2008).

At POPRC 4, the combined DT_{50} measured in laboratory studies for α and β endosulfan and endosulfan sulfate, was selected as a relevant parameter for quantifying the persistence of endosulfan. A large variability in the rate of this degradation has been observed. The estimated combined half-life in soil for endosulfan (α, β isomers and endosulfan sulfate) ranges typically between 28 and 391 days; but higher and lower values are reported in the literature under specific conditions.

In the aquatic compartment, endosulfan is stable to photolysis. A rapid hydrolysis is only observed at high pH values, and it is non-readily biodegradable. In water/sediment systems (Jones, 2002; 2003 reported in the EU dossier) DT_{50}s for the alpha, beta isomers and endosulfan sulfate ranging between 3.3 and 273 days, were presented. These specific values were not validated but DT_{50} > 120 d was demonstrated. Endosulfan diol, maximum 63.5%, and under acidic conditions (pH= 4.5 in water and 4.9 in sediment) endosulfan lactone, maximum 14.8%, were also observed.

There is a high uncertainty regarding the degradation rate of endosulfan in the atmosphere. Buerkle (2003) has presented a set of estimations based on Structure Activity Relationship and experimental values. A half life estimation in atmosphere using the Atkinson method was conducted in 1991, resulting in a value of 8.5 d. Experimental figures are presented for α-endosulfan (27 d at 75ºC for gas phase reaction with OH radicals generated by flash photolysis) and β-endosulfan (15 d based on the reaction with OH radicals in liquid Freon-113). The AOPWIN calculation method indicates a half life of 47.1 hours assuming a constant diurnal OH concentration of 5 $x10^5$ $cm^{-3.}$. It should be noted that for complex molecules like endosulfan, AOPWIN tends to under estimate the atmospheric half-life according to OH radical degradation (Atkinson et al., 1999)

It is concluded that, considering endosulfan and its related transformation products, the persistence of endosulfan in soil, sediments and air is confirmed.

2.2.2 Bioaccumulation

Three complementary sources of information have been analysed for assessing the bioaccumulation and biomagnification potential of endosulfan and its degradation products: the screening assessment based on physical-chemical properties, the analysis of experimental data, including bioconcentration, bioaccumulation and toxicokinetic studies, and the analysis of field collected information. The key elements of these assessments are presented below.

Screening assessment based on physical-chemical properties

The reported log K_{ow} for α- and β-isomers and endosulfan sulfate range between 3 and 4.8. New studies (Muehlberger and Lemke 2004) using the HPLC-method indicates a log K_{ow} of 4.65 for α-endosulfan, 4.34 for β-endosulfan and 3.77 for endosulfan sulfate. The other metabolites included in the K_{ow} determination have lower K_{ow} than endosulfan sulfate. These values indicate potential for bioconcentration in aquatic organisms, although they are below the screening trigger of 5 for the Stockholm Convention.

Recently, the role of the octanol/air partition coefficient (K_{oa}) for the screening assessment of the biomagnification potential of POPs in terrestrial food chains is receiving significant attention. Kelly & Gobas (2003) and Kelly *et al.* (2007) have proposed that the biomagnification of endosulfan in the terrestrial food chain is particularly relevant, because it has a high log K_{oa}. A high K_{oa} causes slow respiratory elimination. The proposed log K_{oa} for α- and β-endosulfan is 10.29; and for endosulfan sulfate is 5.18. Although there are no specific screening thresholds for the K_{oa} the authors suggests that chemicals with a log K_{ow} higher than 2 and a log K_{oa} higher than 6 have an inherent biomagnification potential in air-breathing organisms of terrestrial, marine mammalian, and human food chains provided that chemical metabolic transformation rates are not extensive. Endosulfan α- and β isomers clearly fall within this category; its primary metabolite endosulfan sulfate is very close. However, reservation was made by a few members on the use of log K_{oa} values for the purpose of biomagnification assessment as it was their view that this parameter is not included in the convention.

Bioconcentration and bioaccumulation studies in aquatic organisms

The reported BCF values for fish ranged from approximately 20 to 11,600 (L kg^{-1} wet wt.); however, the 11,600 value (Johnson and Toledo, 1993) is considered of low reliability because the elimination half-life derived from K2 is not consistent with observed data and therefore the Kinetic-based BCF is questionable. A 21-d BCF (ratio method) of 5670 is calculated based on total endosulfan (α, β, sulfate). A BCF of 5,670 has been proposed from the US-EPA re-evaluation of this study, but the uncertainty is still high and the data should not be considered as reliable. The USEPA re-evaluated in 2007 the bioconcentration studies (U.S.EPA 2007). The two highest quality studies indicate that the BCF range for fish is 1,000 (striped mullet; Schimmel et al. 1977) to 3,000 (sheepshead minnow; Hansen and Cripe 1991). Depuration half-lives in fish for α- and β-endosulfan and endosulfan sulfate were 2–6 days. Bioconcentration studies were available for five species of invertebrates in which BCF ranged from 12 to 600. An average BCF of 2,682 and 3,278 (dry weight) was determined for freshwater green algae and *Daphnia magna*, respectively (DeLorenzo et al. 2002). It should be noted that *D. magna* neonates accumulated little endosulfan when exposed via the ingestion of contaminated phytoplankton.

Weber et al. (2009) have published new information for Arctic food chains. Bioaccumulation factors (BAFs) and biomagnifications (BMFs) was limited to endosulfan results determined by GC-MS only, to avoid uncertainties associated with different analytical techniques (e.g. GC-ECD vs GC-MS). BAFs for endosulfan were estimated using concentrations measured by GC-MS in Arctic char, salmon, arctic cod, ringed seals and beluga coupled with concentrations measured in seawater or lake water (char). Wet weight BAF (ww) values for sum-endosulfan in char, cod, and salmon ranged from 1690 to 7280. Given the uncertainty of endosulfan measurements at low levels in biota and the possible spatial and temporal variation in water concentrations of endosulfan species, these BAFs should be viewed with caution. However, it is appropriate to evaluate the BAFs based on the sum-endosulfan concentrations since some of the body burden in these biota could be due to biotransformation to endosulfan sulfate. The average BAFwws for sum-endosulfan in 3 species of fish (4080) do not exceed the 5000 criteria, however, BAFs for sum-endosulfan based on concentrations in beluga and ringed seal blubber (where BAFlw=BAFww) averaged 3.95×10^5. These elevated BAFs are mainly due to high β-endosulfan reported by Kelly (2005).

BMFs in selected predator/prey species are based on results from Kelly (2005) and Kelly et al. (2007) as these were the only published data for endosulfan in marine mammals based on GC-MS analysis. BMFs > 1 were apparent for sum-Endosulfan for beluga (Delphinaterus leucas) preying on arctic cod (Arctogadus glacialus) and on salmon (Salmo sp), resulting in an overall mean BMF of 1.5 for fish to marine mammals.

The assessment of parent and metabolite bioconcentration is particularly relevant. The study by Pennington et al., (2004) offers a good example of the complexity of these estimations. Oysters were exposed to endosulfan in an estuarine mesocosm for 96h. Within this short exposure period, a significant bioaccumulation of α- and β-endosulfan in oysters is observed, but the quantification, even under mesocosm controlled conditions, is very different depending on how the water and organisms concentrations are compared. The authors suggest BCF values between 375 and 1766 (dry weight) for total (α-, β- and endosulfan sulfate). An outdoor aquatic microcosms study has been presented in the CropLife dossier (Schanne, 2002). The study was conducted outdoors in order to simulate the conditions in natural systems as closely as possible. For that purpose, sediment, water and other biota were collected from a large, shallow water natural reserve area of the Austrian side of Lake Constance. Concentrations of radio-labelled endosulfan lactone, and two unknown metabolites, M1 and M4, in water increased constantly during the study, whereas endosulfan sulfate was more or less constant at a low level or slightly decreasing at both entry routes. The total radioactive sediment residue was increasing during the study to maximum 13.8 µg radioactivity equivalents/kg. The total radioactive residue in macrophytes increased with time reaching a maximum of 2236 µg radioactivity equivalents kg^{-1} fresh weight. Like for macrophytes, the total radioactive residue in surviving fish reached a maximum of 3960 µg radioactivity equivalents kg^{-1} fresh weight.

This study clearly demonstrates that endosulfan is found in the sediment, fish and macrophytes up to study termination and is also degraded to metabolites that maintain the chlorinated cyclic structure of endosulfan. These metabolites have the potential to bioaccumulate in fish and macrophytes, and some of them have demonstrated their potential for persistence in the environment. In addition to this, the study reveals that there are other unknown metabolites with the same potential for bioaccumulation. The bioaccumulation factors (BAF) for spray-drift and run-off routes were estimated as: BAF total radioactivity ca.1000; BAF endosulfan-sulfate 4600-5000 (spray-drift). It should be noted that these BAFs should be taken with care as the tested concentrations provoked clear effects on aquatic organisms or were too close to toxic concentrations; therefore, the estimated bioaccumulation potential could be different to that expected due to the toxic effects of the tested concentrations.

Toxicokinetic and metabolism studies

Following oral administration of endosulfan, either via single oral dose or dietary administration, elimination of the parent compound and its metabolites is extensive and relatively rapid in a range of species of experimental animals. The metabolites of endosulfan include endosulfan sulfate, diol, hydroxy-ether, ether, and lactone.

A physiologically based pharmacokinetic model for endosulfan metabolism in the male Sprague-Dawley rats has been developed by Chan et al. (2006). Recently, the accumulation and elimination kinetics of dietary endosulfan in Atlantic salmon has been published (Berntssen et al., 2008). Dietary β-endosulfan showed a higher biomagnification factor (BMF) (0.10±0.026 vs. 0.05±0.003, $p<0.05$) than α-endosulfan, with higher uptake (41±8% vs. 21±2%) and lower elimination ($26 \pm 2 \times 10^{-3}$ day^{-1} vs. $40 \pm 1 \times 10^{-3}$ day^{-1}) rate constants,. Endosulfan sulphate levels remained unchanged during the depuration period, whereas the parental isoforms were rapidly eliminated. Based on the decrease in diastereomeric factor over time, biotransformation was estimated to account for at least 50% of the endosulfan elimination. The formation of the metabolite endosulfan sulfate comprised a maximum 1.2% of the total accumulation of endosulfan. No other metabolites were measured, and therefore a BMF for endosulfan plus all metabolites cannot be estimated from this study.

Assessment of field data and biomagnification models

A large number of studies offering information on measured levels of endosulfan in biota all over the world are available. Endosulfan and its metabolite endosulfan sulfate are frequently found in crops and in the vicinity of treated sites, as well as in remote areas where the presence of this pesticide must result from medium and long range transport from those areas in which endosulfan has been used.

Quantitative estimates of biomagnification can be obtained through the use of mathematical models calibrated with field data (Alonso et al., 2008). Several published models indicate the potential biomagnification of endosulfan through the food chain. A model of the lichen-caribou-wolf food chain predicts biomagnification of β-endosulfan. The BMFs for wolf range from 5.3 to 39.8 for 1.5 to 13.1 year old wolves (Kelly et al. 2003).

A particularly relevant piece of information was published in 2007 (Kelly et al., 2007). The model predicts a significant BMF for β-endosulfan in air-breathing species, ranging from 2.5 for terrestrial herbivores to 28 for terrestrial carnivores; and BMF below 1 for water-respiring organisms.

Also in the Canadian Arctic concentrations of α-, and β-endosulfan and endosulfan sulfate in ice-algae, phytoplankton, zooplankton, marine fish and ringed seal have been presented. Concentrations ranged from 0.1 – 2.5 ng g^{-1} lipid. Calculated trophic magnification factors were less than 1, suggesting no biomagnification in the ringed seal food chain (Morris et al. 2008). However a trophic magnification factor >1 was calculated for the Southern Beaufort Sea and Amundsen Gulf food webs if marine mammals are included in the food web (Mackay & Arnold (2005).

The comparison of reported concentrations of endosulfan in biota, and particularly in top predators, with those observed in the same organisms and ecosystems for other POPs, also offer indirect indications of bioaccumulation potential. Although the numerical BCF threshold is not exceeded in the standard laboratory studies, there is information demonstrating that the bioaccumulation potential of endosulfan exists.

2.2.3 Potential for long-range environmental transport

The potential of endosulfan for long range transport can be evaluated from three main information sources the analysis of the endosulfan properties, the application of LRT models, and the review of existing monitoring data in remote areas.

Screening of physical-chemical properties

There is enough information on the volatility of α and β endosulfan to support the potential for atmospheric transport. Atmospheric transport over long distances requires a minimum level of persistence in the atmosphere; as presented above, there is uncertainty on the real degradation rate of endosulfan in the atmosphere but the threshold half life of 2 days seems to be exceeded. Taking into account the much lower temperatures of the troposphere, the environmental half-life of endosulfan under real situations is likely to be even longer. Therefore, it should be concluded that the combination of volatility and sufficient atmospheric persistence results in a significant potential for long range transport.

LRT model predictions

Several models have been developed for estimating this potential according to the characteristics of the POP candidates. Becker, Schenker and Scheringer (ETH, 2009 Swiss submitted information) have estimated the overall persistence (POV) and LRT potential (LRTP) of α- and β-endosulfan and two of their transformation products, endosulfan sulfate and endosulfan diol with two multimedia box models, the OECD POV and LRTP Screening Tool and the global, latitudinally resolved model CliMoChem. The OECD Tool yields POV and LRTP for each compound separately, whereas the CliMoChem model calculates the environmental distribution of the parent compounds and the formation and distribution of the transformation products simultaneously. Results from the CliMoChem model show that POV and LRTP of the endosulfan substance family (α, β and sulfate) are similar to those of acknowledged POPs, such as aldrin, DDT, and heptachlor. The results also show that POV and LRTP of the substance family, i.e. including the transformation product, are significantly higher than those of the parent isomers alone (430 d compared to 33 d (α-endosulfan individually) and 65 d (β-endosulfan individually) Becker et al. (2009)). Additional results obtained with the CliMoChem model (Scheringer et al. 2000) indicate that all latitudinal zones in the Northern hemisphere contribute to the presence of endosulfan found in the Arctic but with different shares. The contribution of the tropical region (0–20 °N) is approximately 2%, whereas this region accounts for 12% of the endosulfan emissions in 2000. The northern temperature zone (40–70 °N) contributes about 60% of the endosulfan found in the Arctic but represents only 16% of the emissions. The northern subtropical region (20–40°N), finally, has similar shares of emissions and contribution to endosulfan in the Arctic (35%). However, this model has not been validated for endosulfan specifically but for other comparable molecules, and one member is of the view that the predicted values may not be realistic.

The US (USEPA 2007) concludes that recent studies suggest that desorbed residues of endosulfan volatilize and continue to recycle in the global system through a process of migration and re-deposited via wet and dry depositions as well as air-water exchange in the northern hemisphere. Dust dispersion and translocation also contribute endosulfan into the atmosphere as adsorbed phase onto suspended particulate matter, but this process does not appear to be a major contributor like volatilization. Transport of endosulfan in solution and sediment bound residues also can potentially contribute in the long-range and regional distributions of endosulfan.

Brown and Wania (2008) have recently published a model based on two parallel screening methodologies: one methodology screens chemicals based on substance properties and the other screens chemicals based on a structural profile of known Arctic contaminants. According to the model, endosulfan was found to have high Arctic contamination and bioaccumulation potential and matched the structural profile for known Arctic contaminants. These results are in agreement with the empirical estimations of Arctic contamination potential reviewed by Muir et al (2004) which concluded that endosulfan is subject to LRT as predicted by models and confirmed by environmental measurements.

Confirmation based on measures in remote areas

This potential has been confirmed by monitoring data; there is a significant amount of information as endosulfan has been measured in combination with other organochlorine insecticides. Several publications indicate the potential for long-range transport of endosulfan residues, and report findings of endosulfan in the Arctic at increasing levels in water, air and biota.

2.3 Exposure

2.3.1 Environmental monitoring data

Although endosulfan has only recently been included in formal POP monitoring programs, the chemical is frequently measured in studies on organochlorine pesticides, and therefore there is abundant but highly variable information on measured levels of endosulfan in environmental samples. Most studies include α- and β-endosulfan, and in some cases, endosulfan sulfate is also measured. Other endosulfan metabolites are only rarely quantified. The information has been compiled in three main categories:

- Medium range transport: Collects the information in untreated areas in the vicinity of areas for which endosulfan has been used or has been potentially used (areas with intensive agricultural activity).
- Potential for long range transport: Collects information in areas at significant distance from use areas, where the presence of endosulfan can only be explained by atmospheric transfer and deposition; includes high altitude mountain areas.
- Long range transport: Collects information in remote areas, far away from intensive use areas, in particular, the Arctic and the Antarctic.

A summary of relevant monitoring values is presented below. This summary is mostly based on the recent reviews by the European Communities and the USA submitted within their information dossiers, and completed by additional information presented by other parties/observers and the review of recent literature data.

POTENTIAL FOR LONG-RANGE TRANSPORT: MOUNTAINOUS REGIONS

The effect of "global distillation" is believed to account for transport of POPs whereby a compound volatilizes from warmer regions, undergoes long-range atmospheric transport, and subsequently re-condenses to an accumulation of these substances in the temperate, higher mountainous and Arctic regions. Wania and Mackay (1993) suggested that, through “global distillation” organic compounds could become latitudinally fractionated, “condensing” at different temperatures according to their volatility, so that compounds with relative low vapour pressures might accumulate preferentially in polar regions. Endosulfan was found in the atmosphere of European mountain areas (Central Pyrenees and High Tathras). Like hexachlorocyclohexane (HCH), endosulfan was found in higher concentrations in the warm periods (4-10 pg m^{-3}) in both the gas and particulate phase, reflecting its seasonal use pattern (van Drooge et al. 2004*)*. Endosulfan was found, along with many other POP substances, in snowpack samples collected at different altitudes of mountains on western Canada. The levels of contaminants in snow and in snowpack increased with the altitude, showing a 60-100 fold increase in net deposition rates of contaminants to snowpack over a 2300 meter rise in elevation (Blais et al., 1998). The concentration range of α-endosulfan was 0.06–0.5 ng L^{-1} in the sampling altitude range of 700 – 3,100 m. Aerial transport also caused contamination of snow (Sequoia National Park) and water (Lake Tahoe basin) of the Sierra Nevada Mountains in California, a region adjacent to California’s Central Valley which is among the heaviest pesticide use areas in the U.S. Levels of α-endosulfan found in rain were in a range of < 0.0035 ng L^{-1} to 6.5 ng L^{-1} while β-endosulfan was measured at concentrations of < 0.012 ng L^{-1} up to 1.4 ng L^{-1} McConnell et al. (1998). In 1997, LeNoir et al. (1999) reported concentrations of endosulfan (sum of alpha and beta isomers) measured in remote lakes of Sequoia National Park of California’s Sierra Nevada Mountains. Specifically, concentrations in 3 lakes at elevations between 2,000 and 3,300 meters ranged from 1.3 to 120.3 ng/L. The maximum level (120 ng/L) levels exceed the chronic NOAEC for freshwater fish of 56 ng/L (Dionne 2002). Concentrations of 71.1 pg m^{-3} of α-endosulfan were measured in the Himalayas; backward trajectory analysis indicted that it arrived there from the Indian subcontinent on westerly winds, driven by the Asian monsoon (Li et al 2006). However, one member is of the view that it is not clear whether some finger printing or source apportionment studies were carried out to reach this conclusion.

For mountain lakes in the Alps, Pyrenees (Estany Redò) and Caledonian Mountains (Øvre Neådalsvatn (Norway)), atmospheric deposition of endosulfan was estimated between 0.2 and 340 ng m^{-2} per month (Carrera et al., 2002). Unlike other chemicals, endosulfan showed a more uniform geographical distribution, the lakes in the South were much more exposed to endosulfan impact, reflecting the impact of agricultural activities in southern Europe. In the northern lakes only the more persistent endosulfan sulfate was measured. Endosulfan sulfate concentrations were 1000, 92 and 120 pg L^{-1} in the Pyrenees, Alps and Caledonian mountains respectively (Vilanova et al. 2001).

LONG-RANGE TRANSPORT: POLAR REGIONS

The US review summarizes information by GFEA (2007); Ngabe and Bidleman 2001, and Endosulfan Task Force (ETF) report MRID 467343-01.

Long range atmospheric transport of α- and β-endosulfan to the Arctic was first reported in 1986 (Patton et al. 1989). A "brown snow" event occurred in the central Canadian Arctic during the year 1988. The snow was coloured by dust that appeared to be transported from Asia. Endosulfan was detected in the dust at a maximum concentration of 22 pg L^{-1}. Since then endosulfan has been routinely found in the Canadian Arctic air monitoring program, from 1993 up to the present (Halsall et al., 1998; Hung et al., 2001). Extensive monitoring data on endosulfan from the Arctic are available for the atmosphere, snowpack, surface water and biota (Bidleman et al., 1992; De Wit *et al*., 2002; Halsall et al., 1998; Hobbs *et al*, 2003; Jantunen and Bidleman, 1998).

Long-range transport: Arctic Air

Endosulfan was reported as a widely distributed pesticide in the atmosphere of northern polar region. Unlike for most other organochlorine pesticides, the concentrations of which have declined average concentrations of endosulfan in the Arctic did not change significantly during the last 1990s (Meaking, 2000). Concentrations of α-endosulfan from Arctic air monitoring stations increased from early to mid-1993 and remained at roughly 0.0042-0.0047 ng m^{-3} through to the end of 1997. No clear temporal trends of endosulfan concentrations in the arctic atmosphere were observed (Hung et al., 2002). Measurements taken in air at Alert in Nunavut, Canada resulted in annual average concentrations between 3 and 6 pg m^{-3} during 1993 to 1997. Fluctuating values mirror the seasonal applications in source regions.

Concentrations of endosulfan in Arctic air were found to be exceeded only by those of ΣHCH-isomers and hexachlorobenzene (HCB) (Halsall et al., 1998). In comparison to monitored concentrations in the Great Lakes region, atmospheric levels in the Arctic were less dependent on temperature, although seasonal variations were apparent as well. For example α-endosulfan concentrations ranged by a factor of 3-5 from spring to fall periods. This infers a more blurred bimodal seasonal cycle with growing distance from areas of application. Hung et al. (2002) used temperature normalization, multiple linear regression, and digital filtration to analyze the temporal trends of an atmospheric dataset on organochlorine pesticides collected at the Canadian high Arctic site of Alert, Nunavut.

Seasonal variation of concentrations was also reported from Sable Island (240 km east of Nova Scotia, Canada, at 43°57´N, 60°00´W). In summer, aerial endosulfan concentrations (α- and β-isomers) were determined between 69 and 159 ng m^{-3} while for wintertime values dropped to 1.4-3.0 pg m^{-3} (only α–isomer) (Bidleman et al., 1992).

Similar data on α-endosulfan have been reported from Resolute Bay (Cornwallis Island, 75 N lat.) where air concentrations of approximately 4 pg m^{-3} have been measured (Bidleman et al., 1995) and from air samples taken on an iceberg that calved off the Ward Hunt Ice Shelf on the northern shore of Ellesmere Island, Canada, (approx. 81°N, 100°W). Mean concentration of α-endosulfan in summer 1986 and 1987 were 7.1 and 3.4 ng m^{-3}, respectively (Patton et al., 1989). Additional evidence for airborne long-range transport is provided by data from Newfoundland showing mean concentrations of 20 pg m^{-3} in summer 1977 (Bidleman et al., 1981).

Further air concentrations of endosulfan were reported from Amerma (eastern Arctic region of Russia) between 1–10 pg m^{-3} (De Wit et al., 2002; Konoplev et al., 2002). Endosulfan was detected in around 90% of all samples displaying a significant correlation with atmospheric temperature. Unlike other organochlorines where seasonal enhancements are hypothesized to be due to (re)volatisation from secondary sources, fresh applications were assumed to be responsible for endosulfan concentrations of 3.6 pg m^{-3} in winter and 5.8 pg m^{-3} in summer (mean values). Spatially, the annual concentrations at the various circumpolar sites did not show remarkable differences, indicating a degree of uniformity in contamination of the Arctic atmosphere.

Long-range transport: Arctic Freshwater

Endosulfan (isomer unspecified) was measured also at Amituk Lake on Cornwallis Island, NV, Canada. The ranges were (in ng L^{-1}) 0.135 – 0.466 in 1992, 0.095 – 0.734 in 1993, and 0.217 – 0.605 in 1994 (quoted in Ngabè and Bidleman 2001). Annual summertime peaks in endosulfan concentrations observed were attributed to fresh input from snow melt via influent streams.

Long-range transport: Arctic Freshwater Sediment

Laminated cores collected from Arctic Lake DV09 on Devon Island, in Nunavut, Canada, in May 1999 were analysed *inter alia* for endosulfan. Only α-endosulfan was present in the sediment of that lake. The concentration was highest at the sediment surface, and rapidly decreased to below detection limits in core slices dated prior to 1988.

Long-range transport: Arctic Seawater

Endosulfan was repeatedly detected in Arctic seawater during the 1990s. Mean concentrations were similar to those of chlordane and ranged from 2-10 pg L^{-1}. Seasonal trends displayed increasing concentrations during the open water season suggesting fresh input from gas exchange and runoff. This trend parallels seasonal trends observed in Arctic air and Amituk Lake (USEPA, 2007).

A survey of several pesticides in air, ice, fog, sea water and surface micro-layer in the Bering and Chukchi Seas in summer of 1993 (Chernyak et al., 1996) identified α-endosulfan in air and subsurface seawater at levels around 2 pg L^{-1}. In melted ice <9 pg L^{-1} and for the sea water surface micro-layer <40 pg L^{-1} were detected. For fog condensates from several sites of that region concentrations of <10 to <0.5 ng L^{-1} were reported. β-endosulfan was found in several atmospheric samples, e.g. from the Central Bering or Gulf of Anadyr at concentrations around 1 pg m^{-3}. Similar concentrations of endosulfan have been reported from seawater surface layer (40-60 m) collected in the Bering and Chukchi Seas, north of Spitzbergen and the Greenland Sea (Jantunen and Bidleman, 1998).

Arctic seawater concentrations of endosulfan were measured from 1990s to 2000 in different regions of the Arctic Ocean (Weber et al., 2006). Surface seawater concentrations for α- and β-endosulfan ranged from <0.1 to 8.8 pg L^{-1} and 0.1 to 7.8 pg L^{-1} respectively. Morris et al (2008) have reported α-endosulfan and endosulfan sulfate in Barrow Strait averaging 1.4 and 4.6 pg L^{-1} at 2m depth. Geographical distribution for α-endosulfan revealed the highest concentrations in the western Arctic, specifically in Bering and Chukchi Seas with lowest levels towards the central Arctic Ocean. The results of air-water fugacity ratio indicate that α-endosulfan has been undergoing net deposition to surface waters across all the regions of the Arctic Ocean since 1990s. The authors concluded that the net deposition through air-water transfer may be the dominant pathway into the Arctic Ocean for α-endosulfan, particularly during the ice free periods.

Long-range transport: Arctic Snow and Snowpack

Concentrations of α-endosulfan in snow samples collected in the Agassiz Ice Cap, Ellesmere Island, Canada in 1986 and 1987 ranged from 0.10 to 1.34 ng m^{-3} (Gregor and Gummer, 1989). The concentrations of α- endosulfan in snowpack in Agassiz Ice Cap were 0.288 ng L^{-1} in 1989 and 0.046 ng L^{-1} in 1992 (Franz et al., 1997). From measured snowpack concentrations and snowfall amounts, minimum winter deposition rates of 0.03 µg m^{-2} were estimated for the years 1986 and 1987 (Barrie et al., 1992).

Long-range transport: Arctic and Antarctic Biota

α-Endosulfan was found in 40% of samples of Antarctic krill. The geometric mean level detected was 418 pg g^{-1} lw, the maximum was 451 pg g^{-1} lw (Bengston et al., 2008).

Endosulfan (α- and β-isomer) was found in many different species in Greenland. The highest median and maximum concentrations in ng g^{-1} lw for various tissues and locations per species are summarized here: Terrestrial species: ptarmigan (median 1.9 and max 3.0 in liver), hare (median 0.55 and max 0.64 in liver), lamb (median n.d. and max 0.65 in liver), caribou (median 0.17 and max 0.39 in muscle), muskox (median 0.016 and max 1.8 in blubber). In freshwater fish: Arctic char (median 21 and max 92 in muscle tissue). In marine organisms: shrimp (median 3 and max 5.2 in muscle), snow crab (median 19 in muscle and max 95 in liver), Iceland scallop (median 0.36 and max 1.6 in muscle) capelin (median 50 ng g^{-1}). In seabirds: common eider (median 4.9 and max 8.6 in liver), king eider (median 3.7 in liver and max 10 in muscle), kittiwake (median 62 and max 130 in muscle), thick-billed murre (median 8.8 and max 15 in liver). In marine mammals: ringed seal (median 5.6 in liver at Qeqertarsuaq and max 25 in muscle at Ittoqqortoomiit), harp seal (median 12 and max 45 in blubber), minke whale (median 12 and max 29), beluga (median 45 and max 83 in skin), and narwhal (median 81 and max 120 in skin (Vorkamp et al., 2004).

Blubber samples from male beluga were collected over 20 years at five time points in Cumberland Sound, Canada. Only endosulfan sulfate was detected. But unlike other organochlorines, levels appear to have increased steadily (3.2 fold) over that 20 year time period from 1982 reaching ca. 14 ng g^{-1} lw in 2002 (USEPA 2007). α-endosulfan concentrations in blubber of minke whale populations from distinct parts of the North Atlantic were sampled in 1998 (Hobbs et al., 2003). The highest mean concentrations were found for minke whales in the North Sea/Shetland Islands (34 ng g^{-1} lipid for females and 43.0 ng g^{-1} for males), the Barents Sea (7.74 ng g^{-1} lw for females and 9.99 ng g^{-1} lw for males) and Norway's Vestfjorden/ Lofotes (4.51 ng g^{-1} lw for females and 9.17 ng g^{-1} lw for males). Lower concentrations of < 1 ng g^{-1} lw and 5 ng g^{-1} lw were reported for whales from Jan Mayen (territory of Norway) and Greenland. The differences were attributed to distinctions based on genetics, fatty acid profiles, etc.

Endosulfan was detected in adipose tissue and blood of polar bears from Svalbard (Norway). Mean values found for α-endosulfan were 3.8±2.2 ng g^{-1} wet weight (min-max: 1.3-7.8 ng g^{-1}) and 2.9 ± 0.8 ng $g^{-1}$for β-endosulfan (min-max: 2.2-4.3 ng g^{-1}). While the α-isomer was detectable in all samples (15/15) the β-isomer was found in just 5 out of 15 samples.

Alpha-endosulfan ranged between <0.1 and 21 ng g^{-1} wet weight fat, (<0.1-36 ng g^{-1}lw) in the fat of polar bears sampled along the Alaskan Beaufort Sea coast in spring, 2003 (Bentzen et al., 2008).

In liver of northern fulmar from Bjørnøja endosulfans were detected for just two individuals out of fifteen at low levels of 0.28 and 0.50 ng kg^{-1} lw (Gabrielsen, 2005).

Levels in murre eggs sampled in 2003 at St. Lazuria Island ranged from 3.04 to 11.2 ng g^{-1} (mean 5.89 ng g^{-1}) for β-endosulfan while and from 0.116 to 0.428 ng g^{-1} (mean 0.236 ng g^{-1}) for α-endosulfan. At Middleton Island in the Gulf of Alaska, measured levels in 2004 in murre eggs for β-endosulfan ranged up to 11.8 ng g^{-1} (mean of 6.74 ng g^{-1}). α-and β-endosulfan were also found in common murre eggs at East Anatuli Island, Duck Island, Gull Island, Cape Denbigh, Cape Pierce, Sledge Island, Bluff and Bogoslov Island (Roseneau et al., 2008).

Endosulfan levels in Chinook and sockeye salmon, Cook Inlet Alaska ranged from 252 to 1610 ng kg^{-1} (USEPA, 2003).

In ringed seals from Alaska, the highest levels were found in the western Arctic Ocean off Barrow (geometric mean in ringed seal blubber combined males and females of 22.6 ng g^{-1} α-endosulfan with the upper concentration at 43.39 ng g^{-1}) (Mackay and Arnold, 2005).

Endosulfan has been detected in biota in the Arctic (5 terrestrial, 1 freshwater and 13 marine species with maximum levels between 0.39 to 130 pg g-1 lw) and Antarctic (a seal species and krill with maximum levels of 451 pg g-1 lw). Monitoring data have detected endosulfan (and endosulfan sulphate) in the air, the freshwater, the marine water and the sediment of the Arctic and/or Antarctic regions. Therefore, there is evidence that endosulfan is transported at long distances and bioccumulates in biota in remote areas though one member considered the concentration encountered to be very low.

2.4 Hazard assessment for endpoints of concern

Endosulfan is highly toxic for most invertebrates and vertebrates, including humans. The insecticidal properties are shared, with some differences in potency, by the α and β isomers and the metabolite endosulfan sulfate. The toxicity of endosulfan has been evaluated by several organizations, including among others JMPR in 1998 (FAO/WHO, 1998); ATSDR in 2000 (ATSDR, 2000); the EU in 1999 with addenda up to 2004 (EC dossier submitted as additional information); an EFSA Scientific Panel in 2005 (EFSA, 2005), Australia in 2005 (submitted as additional information), Canada in 2007 (PMRA's REV2007, submitted as additional information), US EPA in 2007 (submitted as additional information), and New Zealand in 2008 (submitted as additional information).

The toxicity of other endosulfan metabolites has also been demonstrated for different species including humans.

Adverse effects on aquatic organisms

Endosulfan α, β and sulfate are highly toxic to aquatic invertebrates and fish. Acute median lethal concentrations (LC_{50}s) for several species at levels below 1µg L^{-1} have been reported. Chronic no observed effect concentrations (NOECs) below 0.1 µg L^{-1} have been reported for fish and aquatic invertebrates. A significant toxicity for aquatic organisms has been also observed for other metabolites; unfortunately, no chronic aquatic toxicity data are available for these metabolites, but the acute LC_{50}s for endosulfan lactone and ether are lower than 1 mg l^{-1} (highly toxic to aquatic organisms according to the UN-GHS classification), with reported K_{ow} higher than the GHS trigger for chronic classification in the case of endosulfan ether, and are not expected to be readily biodegradable..

The NOEC for sediment dwelling organisms tend to be between 0.1 and 1 mg kg^{-1}, with equivalent pore water concentration of about 1µg L^{-1}. The dietary toxicity of endosulfan to fish has been studied in Atlantic salmon (*Salmo salar*) histopathological effects were observed after 35 d of exposure to a diet containing 4 µg kg^{-1} of endosulfan, and the condition factor was significantly reduced in fish exposed for 49 d to 500 µg kg^{-1} (Petri et al., 2006; Glover et al., 2007).

Additional sublethal effects of particular concern, including genotoxicity and endocrine disrupting effects have been reported. Associated genotoxic and embryotoxic effects have been observed in oysters exposed to endosulfan (Wessel et al., 2007). Endosulfan sulfate has been shown to be an anti-ecdysteroidal compound for *Daphnia magna* delaying the molting process (Palma et al., 2009). The ecdysteroid system is used by crustaceans and other arthropods as the major endocrine signalling molecules, regulating processes such as moulting and embryonic development. Neurotoxicity has been observed in common toad (*Bufo bufo*) tadpoles (Brunelli et al., 2009), and developmental abnormalities on anuran *Bombina orientalis* embryos (Kang et al., 2008). In ovum exposure at a critical period for gonadal organogenesis provoked post-hatching effects in *Caiman latirostris* (Stoker et al., 2008). Immunotoxicity has been observed in Nile tilapia (Tellez-Bañuelos et al., 2008; Girón-Pérez et al., 2008). Toxic effects have also been observed on non-animal species, including cyanobacteria (Kumar et al., 2008) and aquatic macrophytes (Menone et al., 2008).

Adverse effects on terrestrial organisms

In laboratory animals, endosulfan produces neurotoxicity effects, which are believed to result from over-stimulation of the central nervous system. It can also cause haematological effects and nephrotoxicity. The α-isomer was generally found more toxic than the β-isomer (ATSDR, 2000).

The lowest relevant NOEC for endosulfan in terrestrial vertebrates is 0.6 mg kg^{-1} bw day^{1} based on reduced body-weight gain, increased marked progressive glomerulonephritis, and blood vessel aneurysm in male rats at 2.9 mg kg^{-1} bw day^{-1}; the same value was reported in a 1-year dog study. Reproductive effects on mallard ducks (*Anas platyrhynchos*) where observed at low dietary levels, the reported NOEC was 30 ppm in the diet. The acute median lethal dose (LD_{50}) value in this species is of 28 mg kg^{-1} bw (see INIA, 1999).

Toxicity has been shown for bees, beneficial arthropods and soil dwelling invertebrates in the laboratory and field studies (i.e., INIA, 1999, New Zealand dossier, Vig et al., 2006; Bostanian and Akalach 2004).

Adverse effects on human health

Endosulfan is highly acutely toxic via oral, dermal and inhalation routes of exposure and it is associated to human poisoning (Moon and Chun, 2009; Satar et al., 2009). Exposure through certain conditions of use (e.g. lack of protective equipment), and 'bystander' exposure has been considered a risk (Beauvais et al., 2009) and has been linked to congenital physical disorders, mental retardations and deaths in farm workers and villagers in developing countries in Africa, Asia and Latin America (Kishi 2002; NIOH 2003; Wesseling et al 2005; Glin et al 2006). A survey conducted by PAN Africa in Mali in 2001 of villages in 21 areas of Kita, Fana and Koutiala found a total 73 cases of pesticide poisoning and endosulfan was the main pesticide identified (Glin et al 2006). Endosulfan was found among the most frequently reported unintentional intoxication incidents, adding further evidence to its high toxicity for humans (Glin et al 2006).

The primary effect of endosulfan, via oral and dermal routes of exposure, is on the central nervous system (CNS). Effects in laboratory animals as a result of acute, subchronic, developmental toxicity and chronic toxicity studies indicate that endosulfan causes neurotoxic effects, particularly convulsions, which may result from over stimulation of the CNS. Possible mechanisms of neurotoxicity include (a) alteration of neurotransmitter levels in brain areas by affecting synthesis, degradation, and/or rates of release and reuptake, and/or (b) interference with the binding of neurotransmitters to their receptors. Additional effects were noted in the liver, kidney, blood vessels and haematological parameters following repeated exposure to endosulfan. The evaluation by the USEPA (2006) of a rat developmental neurotoxicity study conducted by Gilmore et al in 2006, indicates a LOAEL for developmental effects of 3.74 mg kg-1 day-1 based on decreased pup weight and deceased weight gain, no NOAEL for pups could be established in that study. No neurotoxic effects were observed at doses below 10 mg kg-1 day-1. Only minor effects were observed in the dams. An Australian study indicated that endosulfan is not genotoxic (Australia (1998)).

Acute exposure to high doses of endosulfan results in hyperactivity, muscle tremors, ataxia, and convulsions. The LD_{50} of endosulfan varies widely depending on the route of administration, species, vehicle, and sex of the animal. Female rats are clearly more sensitive to endosulfan than male rats, and, on the basis of a single study, this sex difference appears to apply to mice also. The lowest oral LD_{50} value is 9.6 mg kg^{-1} bw in female Sprague-Dawley rats (*Ratus norvegicus*), and the lowest inhalation LC_{50} is 0.0126 mg L^{-1} (2.13 mg kg^{-1} bw) in female Wistar rats (*R. norvegicus*). The lowest relevant NOAEL for endosulfan in laboratory animals is 0.6 mg kg^{-1} bw day^{-1}.

Regarding the metabolites, a particularly relevant study is the 90d toxicity study in rat dietary exposure on endosulfan-lactone, conducted by Langrand-Lerche (2003) and included in the EU dossier. The NOEC reported in this study is 0.6 mg kg^{-1} bw day^{-1}, although mild effects in liver and kidney were observed at this dose.

Evidence regarding genotoxicity is inconclusive. The assessments conducted by the EU, Canada or the USA concluded that endosulfan is not carcinogenic. However, Bajpayee et al., (2006) found that exposure to sublethal doses of endosulfan and its metabolites induce DNA damage and mutation. Although the contribution of the metabolites to the genotoxicity of the parent compound in bacteria *(Salmonella spp.)* and mammalian cells was unclear, and the pathways leading to bacterial mutation and mammalian cell DNA damage appeared to differ.

Contradictory opinions on the potential for endocrine disruption have been presented. Recent information indicates that endosulfan mimics non-uterotrophic E(2) actions, strengthening the hypothesis that endosulfan is a widespread xenoestrogen (Varayoud et al., 2008), acts via a membrane version of the estrogen receptor-α on pituitary cells and can provoke Ca^{++} influx via L-type channels, leading to prolactin (PRL) secretion (Watson et al., 2007), and is also anti-progestative (Chatterjee et al., 2008).

It should be noticed that the toxicological reviews have been mostly conducted in the framework of the pesticides registrations in various countries. As a consequence, some specific issues, of particular relevance in the long-term exposure assessment of POP related characteristics received little attention. For example, in the rat chronic study, females from the high dose group had a reduced survival rate after 26 weeks (93% in controls, 74% in high dose) and 104 weeks (88% in controls, 46% in high dose). The deaths were predominantly associated with respiratory infections. This effect could be associated to the potential immunotoxicity of endosulfan that has been hypothesized in some studies. As the study was not designed for the specific assessment of these endpoint, relevant effects at low doses could remain unobserved and only dramatic effects (over 50% mortality was observed in this case) are evidenced.

In some chronic toxicity studies, the concentrations of endosulfan and its metabolites were measured at the end of the study, but the limit of detection levels were too high and only endosulfan sulfate and occasionally endosulfan lactone, were above the quantification level. These limitations increase the uncertainty in the comparison of measured values in biota with the reported toxicological information.

Weber et al., 2009, have recently compared measured biota data in the Artic with toxicity endpoints. The maximum measured concentrations of α- and β-endosulfan for several species were just within one order of magnitude of the lowest valid mammalian NOAEL. These results add to the concern for adverse effects. It should be noted, that the role of metabolites is not considered in these calculations. Endosulfan sulfate and other metabolites have been detected in some mammalian toxicity studies, unfortunately, the limit of detection employed in these studies were too high, and do not allow the estimation of relevant internal concentrations to be compared to measured data.

There are toxicity and ecotoxicity data available for both endosulfan isomers and several metabolites. Endosulfan is a very toxic chemical for many kinds of biota. Metabolism occurs rapidly, but the oxidised metabolite endosulfan sulfate shows an acute toxicity similar to that of the parent compound. Endosulfan may cause endocrine disruption in both terrestrial and aquatic species. Degradation studies indicate that endosulfan is degraded into a large number of other metabolites, all of them retaining the endosulfan structure, and some of them showing significant toxicity while others do not. Therefore, there is sufficient evidence that endosulfan causes adverse effects to human health and the environment.

As additional information, a benchmark approach has been performed with lindane having similar toxicity than endosulfan. This approach shows that lindane and endosulfan are found in similar concentration in remote area biota.

Table: Comparative analysis of the toxicity and biota monitoring data in the remote areas for endosulfan and lindane. The NOEC and NOAEL for endosulfan can be found in the document UNEP-POPS-POPRC-END-08-EU-V1-1.

COMPARISON OF THE TOXICITY OF ENDOSULFAN AND LINDANE			
TOXICITY TO AQUATIC ORGANISMS	Lowest aquatic NOEC (fish)	Endosulfan : 0.05 µg/l (Knacker et al., 1991)	Lindane: 2.9 µg/ l (lindane risk profile)
TOXICITY TO MAMMALS	Lowest NOAEL for mamals	Endosulfan 0.6 mg/kg bw day Rats (Ruckman et al., 1989) Dogs (Brunk 1989-1990)	Lindane: 0.8 mg/kg bw day Rabbit (lindane risk profile)
COMPARISON OF MEASURED CONCENTRATIONS IN ARTIC AND ANTARCTIC BIOTA (for endosulfan: ∑ = α-endosulfan+ β-endosulfan + endosulfansulfate; sum of indicated isomers in other cases)			
Reference & Location	**Organism (tissue)**	**Endofulfan Mean (range)**	**Lindane Mean (range)**
Bengtson Nash et al 2008. Antarctica	Invertebrate: Antarctic krill	∑ 419 (<LOQ-451) pg/g lw	127 (<LOQ-127) pg/g lw
EPA 910-R-01-003. 2003 Alaska	Fish: Chinook salmon Fish: Chum salmon Fish: Sockeye salmon	∑ (<273-780) ng/kg ∑ (<273)ng/kg ∑ (<273-1610) ng/kg	(<124-203) ng/kg (<124-186) ng/kg (<124-793) ng/kg
Bentzen et al 2008 Alaska	Mammal: Polar Bear (fat)	α+ β 8 ng/g lw	8 ng/g lw
Roseau et al. 2008 Alaska	Bird: Common murre (eggs)	∑3.15 ng/g ww	0.19 ng/g ww

Miranda-Filho et al.2007 Antarctica	Marine mammals: elephants seals: Adult males Adult females Juveniles Pups	 ∑ 3.02 ng/g lw ∑ 2.68 ng/g lw ∑ 1.99 ng/g lw ∑ 0.90 ng/g lw	 1.04 ng/g lw 0.65 ng/g lw 0.34 ng/g lw 0.28 ng/g lw
Hobbs et al 2003 North Atlantic	Marine Mammals minke whales (blubber)	α (<1 -33.6) ng/g lw	(<1 - 86.6) ng/g lw

3. Synthesis of information

The potential health and environmental risks of endosulfan associated with its use as a pesticide are well documented and have resulted in banning the compound or imposition of use restrictions in many countries around the world. Human fatality and chronic poisoning cases, and severe environmental problems have been reported (Durukan et al., 2009; Jergentz et al., 2004). The assessment of the POP characteristics of endosulfan, including endosulfan sulfate, confirms the concern regarding endosulfan and its main metabolite; it should be also considered that other metabolites, formed through both environmental and biota transformations, maintains the chemical structure and in some cases have significant toxicity.

The persistence of endosulfan should be assessed in terms of a dual evaluation. First, the persistence of the "active" molecules, with insecticidal activity: the isomers α- endosulfan and β-endosulfan, and the main metabolite endosulfan sulfate. Second, the overall persistence of the number of transformation products which maintain a similar chemical structure with the hexachloronorbornene bicycle: endosulfan diol, endosulfan lactone, endosulfan ether; endosulfan hydroxyether; endosulfan carboxylic acid.

This environmental fate complicates the assessment of persistence using DT_{50} values. At POPRC 4, the combined DT_{50} measured in laboratory studies for α and β endosulfan and endosulfan sulfate, was selected as a relevant parameter. A large variability in the rate of this degradation has been observed. The estimated combined half-life in soil for endosulfan (α, β isomers and endosulfan sulfate) ranges typically between 28 and 391 days; but higher and lower values are reported in the literature under specific conditions. In the field, volatilization from soil and plant surfaces is expected to be a main dissipation route.

In the aquatic compartment, endosulfan is stable to photolysis; a rapid hydrolysis is only observed at high pH values, and it is non-readily degradable. The dissipation of endosulfan and the abundance of one or other degradation products is influenced by the pH and other properties of the water/sediment system. The accumulation of endosulfan sulfate in the sediment and of endosulfan hydroxy carboxylic acid in water has been seen throughout the studies. The degradation rate could not be estimated, but $DT_{50} > 120$ d has been demonstrated. Under acidic conditions endosulfan lactone seems to accumulate in the sediment not reaching a plateau after one year. The persistence of endosulfan and other pesticides in aquatic ecosystems of the tropics is not substantially lower than during summer in temperate regions.

There is a high uncertainty on the degradation rate of endosulfan in the atmosphere. However, there is enough information on the volatility of α and β endosulfan, and therefore the persistence in the atmosphere is essential for supporting the potential for atmospheric transport. The atmospheric transport at long distances requires a minimum level of persistence in the atmosphere; despite the uncertainty on the real degradation rate of endosulfan in this compartment the threshold half life of 2 days seems to be exceeded. Therefore, it should be concluded that the combination of a high volatility and sufficient atmospheric persistence may result in a significant potential for long range transport.

Several models have been developed for estimating this potential according to the characteristics of the POP candidate molecules. Results from the CliMoChem model show that POV and LRTP of the endosulfan substance family are similar to those of acknowledged Persistent Organic Pollutants, such as aldrin, DDT, and heptachlor. The results also show that POV and LRTP of the entire substance family, i.e. including the transformation products, are significantly higher than those of the parent compounds alone. However, this model has not been validated for endosulfan specifically but for other comparable molecules, and one member is of the view that the predicted values may not be realistic.

Several authors have suggested that endosulfan is subject to LRT as predicted by models and posses a high arctic contamination and bioaccumulation potential; matching the structural profile for known arctic contaminants. The US concludes that desorbed residues of endosulfan volatilize and continue to recycle in the global system through a process of migration and are re-deposited via wet and dry depositions as well as air-water exchange in the northern hemisphere.

These suggestions are confirmed by measured data. The presence of endosulfan in remote areas, including the Arctic and Antarctic, confirms that endosulfan has enough persistence and transport potential to move around the planet, representing a potential concern at the global level.

Three complementary information blocks have been analysed for assessing the bioaccumulation and biomagnification potential of endosulfan and its degradation products: the screening assessment based on physical-chemical properties; the analysis of experimental data, including bioconcentration, bioaccumulation and toxicokinetic studies; and the analysis of field collected information.

The reported log K_{ow} for α- and β-isomers and endosulfan sulfate range between 3 and 4.8. These values indicate potential for bioconcentration in aquatic organisms, although are below the screening trigger of the Stockholm Convention. Recently, the role of the octanol/air partition coefficient K_{oa} for the screening assessment of the biomagnification potential of POPs in terrestrial food chains is receiving significant attention. Although there are no specific screening thresholds for the K_{oa}, the authors suggest that organic chemicals with a log K_{ow} higher than 2 and a log K_{oa} higher than 6 have an inherent biomagnification potential in air-breathing organisms of terrestrial, marine mammalian, and human food chains. However, reservation was made by a few members on the use of log K_{oa} values for the purpose of biomagnification assessment as it was their view that this parameter is not included in the convention. Endosulfan clearly falls within this category along with other known POPs such as beta-hexachlorocyclohexane, dieldrin, hexachlorobenzene, mirex and pentachlorobenzene.

The bioconcentration potential of endosulfan in aquatic organisms is confirmed by experimental data. The validated BCF values range between 1000 and 3000 for fish; from 12 to 600 for aquatic invertebrates; and up to 3278 in algae. These values, measured in conventional studies, are in line with those expected from the K_{ow}, indicating a clear bioconcentration potential but below the screening trigger of 5000. However, due to the complex degradation and metabolism pattern of endosulfan, the potential for bioconcentration requires additional considerations.

The data obtained in the estuarine and freshwater microcosm experiments confirms that the assessment of parent and metabolite bioconcentration is particularly relevant. In the short-term estuarine experiment, the authors suggest BAFs between 375 and 1776 for total (α-, β- and endosulfan sulfate); but BAFs over 5000 could be obtained for α-endosulfan based on the concentrations measured at the end of the experiment. An outdoor aquatic microcosms study estimated bioaccumulation factors of about 1000, based on total radioactivity but up to 5000 for endosulfan sulfate. A similar situation is observed in the dietary exposure experiments with aquatic organisms. The initial “standard” assessment indicates a low bioaccumulation from food in cladocerans exposed to contaminated algae and in fish exposed to contaminated food. However, an in-depth analysis of the results in terms of the comparative assessment of the long-term toxicokinetics of endosulfan and its degradation products reveal some concerns, for example, the endosulfan concentrations in the fish exposed to endosulfan in the diet were low but remained unchanged during the whole depuration phase.

The biomagnification potential of endosulfan has been recently associated with its high K_{oa}, and model estimations, based on measured concentration of key elements from remote Arctic food chains, indicates a significant biomagnification of endosulfan in terrestrial ecosystems. However, reservation was made by a few members on the use of log K_{oa} values for the purpose of biomagnification assessment as it was their view that this parameter is not included in the convention.

This complex situation has been confirmed by the presence of endosulfan in biota from remote areas. Most studies include α- and β-endosulfan, and in some cases, endosulfan sulfate is also measured. Other endosulfan metabolites are only rarely quantified. The presence of endosulfan in biota including top predators has been confirmed for situations representing medium range transport; potential for long range transport, including atmospheric transfer and deposition at high altitude mountain areas; and in remote areas, far away from intensive use areas, in particular, the Arctic and the Antarctic.

Regarding the potential of endosulfan for producing adverse effects, the toxicity and ecotoxicity of this pesticide is well documented. Endosulfan is highly toxic for humans and for most animal groups, showing both acute and chronic effects at relatively low exposure levels. Acute lethal poisoning in humans and clear environmental effects on aquatic and terrestrial communities have been observed under standard use conditions when the risk mitigation measures have not been followed. A large number of countries have found that endosulfan poses unacceptable risks, or has caused unacceptable harm, to human health and the environment, and as a result have banned or severely restricted it.

Regarding environmental exposure, the potential risk of endosulfan is not limited to zones in the vicinity of the areas with extensive use. Concentrations of potential concern have been observed in areas at significant distances, due to medium-range atmospheric transport.

As expected for a currently used pesticide, the concentrations in remote areas tend to be orders of magnitude below those predicted/observed in crop areas. However, the assessment of POP and POP-like chemicals requires a very specific evaluation, which strongly differs from that employed in the local risk assessment employed by regulatory bodies for supporting the registration of pesticides. Regulatory risk assessments for pesticides focus on the health and environmental consequences of local episodic exposures, consider the expected benefits of the application, and the acceptability criteria differ dramatically from those relevant for assessing persistent pollutants. POPs have potential for distributing around the world, reaching remote areas, and bioconcentrating along the food-chain resulting in a long term exposure of human and wildlife populations. Thus, concentrations assumed to be acceptable at the local level in pesticide regulatory programmes should not be considered acceptable in a POP assessment. Such an assessment should be conducted based on the scientific evidences on the potential adverse effects to human health or to the environment resulted by long-range transport of the chemical.

The long-term concern for chemicals with POP characteristics is associated with its distribution to remote areas, which obviously are expected to lead to low but potentially relevant concentrations, followed by biologically dominated concentration processes through specific ecological pathways (biomagnification). Although traditionally it has been considered that these processes are dominated by the fugacity potential associated with very high lipophilicity and very low aquatic solubility, it is now clear that there are other mechanisms and routes which may lead to equivalent health and environmental concerns, as demonstrated for other POP candidates such as PFOS or HCH isomers.

Additional information on the likelihood of endosulfan for causing environmental effects in remote areas has been obtained through two complementary methods: benchmarking with related POPs and comparison of measured biota concentrations with endpoints of ecotoxicological concerns. Lindane has been selected for benchmarking, due to the similarities in terms of toxicity (being endosulfan slightly more toxic) and marketing (only recently identified as a POP). Monitoring endosulfan data show biota concentrations in several Arctic and Antarctic species in the same range than those observed for lindane, suggesting similar levels of concerns regarding health and environmental adverse effects. In addition, the upper range of the measured data for several species is within one order of magnitude when compared to the validated mammalian NOAEL; adding to the potential risk associated to long-range transport of endosulfan.

Finally, the role of endosulfan metabolites other than endosulfan sulfate has received limited attention. Endosulfan lactone has the same chronic NOEC value as the parent endosulfan isomers. The lactone is produced from the degradation of the carboxylic acid and/or the hydroxyether. If the toxicity of each metabolite is integrated into the degradation/metabolism process, the result is a biphasic curve. The initial degradation step, to endosulfan sulfate, increases the bioaccumulation potential and maintains or slightly reduces the toxicity; the further degradation steps provoke a clear reduction in the toxicity and bioaccumulation potential, but then further steps, with the formation of the lactone, increase again the toxicity and the bioaccumulation potential.

4. Concluding statement

Endosulfan has been banned or restricted in a number of countries but it is still extensively used in other countries.

Endosulfan has been reported throughout the atmosphere of northern Polar Regions. Concentrations of endosulfan (isomers unspecified) from Arctic air monitoring stations increased from early to mid-1993 and remained at that level through the end of 1997. Unlike most other organochlorine pesticides that have decreased over time, average concentrations of endosulfan in the Arctic have not changed significantly during the last five years.

The rapid field dissipation of the endosulfan isomers is related to volatility and it is then subject to atmospheric long-range transport. Persistence, in particular in colder regions, and bioaccumulation potential are confirmed through the combination of experimental data, models and monitoring results. Endosulfan is highly toxic to the environment and there is evidence suggesting the relevance of some effects on humans. However, the information on its genotoxicity and potential for endocrine disruption is not fully conclusive. Based on the inherent properties, and given the widespread occurrence in environmental compartments and biota in remote areas, together with the uncertainty associated with the insufficiently understood role of the metabolites which maintain the endosulfan chemical structure, it is concluded that endosulfan is likely, as a result of its long-range environmental transport, to lead to significant adverse human health and environmental effects, such that global action is warranted.

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別添２

ヘキサブロモシクロドデカンの有害性の概要

分解性	蓄積性	人健康影響関連	動植物への影響関連
【加水分解性】 環境中での重要な分解経路ではない （根拠：水溶解度が低く、有機炭素への吸着性が高く、加水分解される官能基無し） 【分解速度】 α−HBCDはβ及びγ−HBCDより分解が遅い 【残留性】 ・α−HBCDはβ及びγ−HBCDより残留性が高く、生物濃縮しやすい ・北極圏の最上位の捕食者において高濃度で検出	【BCF（生物濃縮係数）】 ・ファッドヘッドミノー：18,100 ・ニジマス：13,085 ・水生生物の総 PCB：18,100 【log Kow】 実験値：5.625	【神経系への影響】 ・聴覚機能の減弱（閾値の上昇と反応の低下） BMDL ＜1 ～ 10mg/kg bw 【生殖・発生への影響】 ・原始卵胞数の減少 NOAEL:10mg/kg/day ・マウス出生仔、単回経口：行動影響あり NOAEL:0.9mg/kg/day ※1500ppm(100mg/kg bw/day相当)でも一過性の変化しか現れなかったとする報告もある。 ・仔ラットの体重減少等 30～100 mg/kg/dayで影響あり ・仔ラットの大脳皮質におけるoligodendroglial developmentの減弱、甲状腺重量の増加と血清T3の減少等 NOAEL:100ppm (8～21mg/kg/day) 【代謝・内分泌系への影響】 ・ラット代謝機能（脂質、テストステロン、エストロゲン等）の変化 3～100mg/kg bw ・甲状腺ホルモンへの影響が懸念されるが、試験により結果はまちまち（影響なし～血清T4の減少）	【鳥類への繁殖毒性】 ・ニホンウズラ NOEC：5ppm（6週試験） （0.7mg/kg/day） ・アメリカチョウゲンボウ 0.8ppmの餌中投与により、求愛行動、産卵期の早期化、雛の成長速度の遅れが見られた。 ※POPRC8にて北野委員から御紹介、POPs条約webサイトにも掲載されている情報 ・ニホンウズラ NOEC：125ppm(20週試験） （16mg/kg/day） NOEC：<1ppm (6週試験） （0.14mg/kg/day） 1,5,25ppmで影響が見られたエンドポイントがあったが、濃度相関性がなくNOECを設定できなかった。（6週試験、α−HBCDのみ）

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Geneva, 11–15 October 2010

Report of the Persistent Organic Pollutants Review Committee on the work of its sixth meeting

Addendum

Risk profile on hexabromocyclododecane

At its sixth meeting, the Persistent Organic Pollutants Review Committee adopted a risk profile on hexabromocyclododecane, on the basis of the draft risk profile contained in document UNEP/POPS/POPRC.6/10. The text of the risk profile, as amended, is set out in the annex to the present addendum. It has not been formally edited.

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Annex

HEXABROMOCYCLODODECANE

RISK PROFILE

Draft prepared by the ad hoc working group on hexabromocyclododecane
under the POPs Review Committee
of the Stockholm Convention

October 15, 2010

TABLE OF CONTENTS

Executive summary

1. The commercially available brominated flame retardant hexabromocyclododecane (HBCD) is lipophilic, has a high affinity to particulate matter and low water solubility. Depending on the manufacturer and the production method used, technical HBCD consists of 70-95% γ-HBCD and 3-30 % of α- and β-HBCD. HBCD has attracted attention as a contaminant of concern in several regions, by international environmental forums and academia. In the EU, HBCD has been identified as a Substance of Very High Concern (SVHC) meeting the criteria of a PBT (persistent, bioaccumulative and toxic) substance pursuant to Article 57(d) in the REACH regulation. In December 2009, HBCD was considered by the Executive Body (EB) of the UNECE Convention on Long-Range Transboundary Air Pollution (LRTAP) to meet the criteria for POPs, set out in EB decision 1998/2.

2. HBCD is used as a flame retardant additive in polystyrene and textile products. Its main use is in the production of expanded and extruded polystyrene (EPS and XPS). It is also used in the production of high impact polystyrene (HIPS) and as a textile coating. HBCD is reported to be produced in the United States of America, Europe, and Asia and the main share of the market volume is used in Europe. There is information available about several HBCD suppliers in China, but information about amounts imported or produced in China is not available. The demand for HBCD is increasing as are the levels in the environment.

3. There are releases to the environment at all the different stages of the HBCD life cycle. The total releases are increasing in all regions investigated. The largest releases are estimated to be to water from production of insulation boards, to water and air from textile coating and there are also diffuse releases during the life cycle of insulation boards and textiles. HBCD is found to be widespread in the global environment, with elevated levels in top predators in the Arctic. In biota, HBCD has been found to bioconcentrate, bioaccumulate and to biomagnify at higher trophic levels. Several trend studies show an increase of HBCD in the environment and in human tissues from 1970/1980s until recent years. Its increased presence in the environment is likely attributed to the increased global demand. The general trend is to higher environmental HBCD levels near point sources and urban areas. High concentrations have been identified in Europe and in coastal waters of Japan and south China, near production sites of HBCD, manufacturing sites of products containing HBCD and waste disposal sites including those whose processes include either recycling, landfilling or incineration. The simulation test half-lives, together with field data on HBCD in sediments showing persistency over time, persistency in biota and levels and trends in the Arctic, document that HBCD is sufficiently persistent to be of global concern. α-HBCD seems to be subject to slower environmental degradation than β- and γ-HBCD.

4. HBCD has a strong potential to bioaccumulate and biomagnify. Available studies demonstrate that HBCD is well absorbed from the rodent gastro-intestinal tract. Of the three diastereoisomers constituting HBCD, the α-form is much more bioaccumulative than the other forms. HBCD is persistent in air and is subject to long-range transport. HBCD is found to be widespread also in remote regions such as in the Arctic, where concentrations in the atmosphere are elevated.

5. HBCD is very toxic to aquatic organisms. In mammals, studies have shown reproductive, developmental and behavioral effects with some of the effects being trans-generational and detectable even in unexposed off-spring. Besides these effects, data from laboratory studies with Japanese quail and American kestrels indicate that HBCD at environmentally relevant doses could cause eggshell thinning, reduced egg production, reduced egg quality and reduced fitness of hatchlings. Recent advances in the knowledge of HBCD induced toxicity includes a better understanding of the potential of HBCD to interfere with the hypothalamic-pituitary-thyroid (HPT) axis, its potential ability to disrupt normal development, to affect the central nervous system, and to induce reproductive and developmental effects.

6. In humans HBCD is found in blood, plasma and adipose tissue. The main sources of exposure presently known are contaminated food and dust. For breast feeding children, mothers' milk is the main exposure route but HBCD exposure also occurs at early developmental stages as it is transferred across the placenta to the foetus. Human breast milk data from the 1970s to 2000 show that HBCD levels have increased since HBCD was commercially introduced as a brominated flame retardant in the 1980s. Though information on the human toxicity of HBCD is to a great extent lacking, and tissue concentrations found in humans are seemingly low, embryos and infants are vulnerable groups that could be at risk, particularly to the observed neuroendocrine and developmental toxicity of HBCD.

7. Based on the available evidence, it is concluded that HBCD is likely, as a result of its long-range environmental transport, to lead to significant adverse human health and environmental effects, such that global action is warranted.

1 Introduction

8. On June 18th 2008, Norway, as a Party to the Stockholm Convention, submitted a proposal to list the brominated flame retardant hexabromocyclododecane (HBCD; some authors prefer HBCDD) as a possible Persistent Organic Pollutant (POP) under Annex A of the Convention. A summary of the proposal may be found in document UNEP/POPS/POPRC.5/4 and a copy of the proposal itself in document UNEP/POPS/POPRC.5/INF/16.

1.1 Chemical identity of the proposed substance

9. Commercially available HBCD is a white solid substance. Producers and importers have provided information on this substance under two different names; hexabromocyclododecane (EC Number 247-148-4, CAS number 25637-99-4) and 1,2,5,6,9,10-hexabromocyclododecane (EC Number 221-695-9, CAS number 3194-55-6). The structural formula of HBCD is a cyclic ring structure with Br-atoms attached (see Table 1). The molecular formula of the compound is $C_{12}H_{18}Br_6$ and its molecular weight is 641 g/mol. 1,2,5,6,9,10-HBCD has six stereogenic centers and, in theory, 16 stereoisomers could be formed (Heeb et al. 2005). However, in commercial HBCD only three of the stereoisomers are commonly found. Depending on the manufacturer and the production method used, technical HBCD consists of 70-95 % γ-HBCD and 3-30 % of α- and β-HBCD (European Commission 2008; Nordic Council of Ministers (NCM) 2008). Each of these stereoisomers has its own specific CAS number i.e. α-HBCD, CAS No: 134237-50-6; β-HBCD, CAS No: 134237-51-7; γ-HBCD, CAS No: 134237-52-8. Two other stereoisomers, δ-HBCD and ε–HBCD have also been found by Heeb et al. (2005) in commercial HBCD in concentrations of 0.5 % and 0.3 %, respectively. Other information pertaining to the chemical identity of HBCD is listed in Table 2, 3, and 4.

10. Technical HBCD has a log K_{ow} of 5.625 and is a lipophilic substance. The water solubility of the technical mixture is low and ranges from 46.3 µg/l in saltwater to 65.6 µg/l in freshwater at 20 ºC based on the sum of the water solubilities of the individual diastereoisomers (Wildlife International 2004a and 2004b). The solubility of the individual diastereoisomers also differs, with solubilities ranging from 2.4 µg /l for γ-HBCD to 48 µg /l for α- HBCD in freshwater at 20 °C.

Table 1. Information pertaining to the chemical identity of HBCD

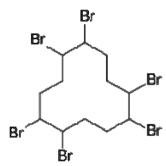
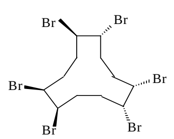
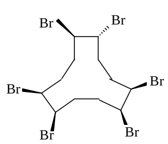
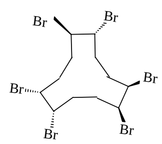
Chemical structure			
Structural formula of HBCD[1]: [1]Structural formula for 1,2,5,6,9,10-HBCD, i.e., CAS no 3194 55-. Note that CAS no 25637-99-4 is also used for this substance, although not correct from a chemical point of view as this number is not specifying the positions of the bromine atoms. As additional information, the structures and CAS numbers for the diastereomers making up 1,2,5,6,9,10-HBCD are given below, although these diastereomers always occur as mixtures in the technical product.			
Chiral components of commercial HBCD:	 alpha-HBCD, CAS No: 134237-50-6	 beta-HBCD CAS No: 134237-51-7	 gamma-HBCD CAS No: 134237-52-8

Table 2. Chemical identity

Chemical identity	
Chemical Name:	Hexabromocyclododecane and 1,2,5,6,9,10 -hexabromocyclododecane
EC Number:	247-148-4; 221-695-9
CAS Number:	25637-99-4; 3194-55-6
IUPAC Name:	Hexabromocyclododecane
Molecular Formula:	$C_{12}H_{18}Br_6$
Molecular Weight:	641.7
Trade names/ other synonyms:	Cyclododecane, hexabromo; HBCD; Bromkal 73-6CD; Nikkafainon CG 1; Pyroguard F 800; Pyroguard SR 103; Pyroguard SR 103A; Pyrovatex 3887; Great Lakes CD-75P™; Great Lakes CD-75; Great Lakes CD75XF; Great Lakes CD75PC (compacted); Dead Sea Bromine Group Ground FR 1206 I-LM; Dead Sea Bromine Group Standard FR 1206 I-LM; Dead Sea Bromine Group Compacted FR 1206 I-CM.
Stereoisomers and purity of commercial products:	Depending on the producer, technical grade HBCD consists of approximately 70-95% γ-HBCD and 3-30 % of α- and β-HBCD due to its production method (European Commission, 2008). Each of these has specific CAS numbers. Two other stereoisomers, δ-HBCD and ε–HBCD have also been found by Heeb et al. (2005) in commercial HBCD in concentrations of 0.5 % and 0.3 %, respectively. These impurities are regarded as achiral at present. According to the same authors, 1,2,5,6,9,10-HBCD has six stereogenic centers and therefore, in theory, 16 stereoisomers could be formed.

Table 3. Summary of physical chemical properties (adopted from European Commission 2008)

Property	**Value**	**Reference**
Chemical formula	$C_{12}H_{18}Br_6$	
Molecular weight	641.7	
Physical state	White odourless solid	
Melting point	Ranges from approximately: 172-184 °C to 201-205 °C 190 °C, as an average value, was used as input data in the EU risk assessment model EUSES. 179-181 °C α-HBCD 170-172 °C β-HBCD 207-209 °C γ-HBCD	Smith et al. (2005)
Boiling point	Decomposes at >190 °C (see also text below)	Peled et al. (1995)
Density	2.38 g/cm^3 2.24 g/cm^3	Albemarle Corporation (1994) Great Lakes Chemical Corporation (1994)
Vapour pressure	$6.3 \cdot 10^{-5}$ Pa (21 °C)	Stenzel and Nixon (1997)
Water solubility (20 ^{O}C)	see Table 4	
Partition coefficient n-octanol/water	Log Kow = 5.62 (technical product) 5.07 ± 0.09 α-HBCD 5.12 ± 0.09, β-HBCD 5.47 ± 0.10 γ-HBCD	MacGregor and Nixon (1997) Hayward et al. (2006)
Henry's Law constant	0.75 Pa×m^3/mol Calculated from the vapour pressure and the water solubility (66µg/l)	
Flash point	Not applicable	
Auto flammability	Decomposes at >190 °C	
Flammability	Not applicable-flame retardant	
Explosive properties	Not applicable	

Oxidizing properties	Not applicable	
Conversion factor	1 ppm = 26.6 mg/m^3 1 mg/m^3 = 0.037 ppm	

Table 4. Summary of the results of valid water solubility studies using generator column method, as evaluated by European Commission (2008) and listed in NCM 2008.

Test substance	Water	Water solubility (µg/l)*	Reference
α -HBCD	Water	48.8±1.9	MacGregor and Nixon (2004)
β -HBCD		14.7±0.5	
γ -HBCD		2.1±0.2	
HBCD technical product, sum of above		65.6	
α -HBCD	Salt-water medium	34.3	Desjardins et al. (2004)
β -HBCD		10.2	
γ -HBCD		1.76	
HBCD technical product, sum of above		46.3	
γ -HBCD	Water	3.4±2.3**	Stenzel and Markley (1997)

*20 °C, **25 °C

1.2 Conclusion of the Review Committee regarding Annex D information

11. The POP Review Committee evaluated Annex D information for HBCD at its fifth meeting in October 2009 (UNEP/POPS/POPRC.5/10) and concluded that the screening criteria have been fulfilled (Decision POPRC-5/6).

1.3 Data sources

12. This risk profile was developed using Annex E information submitted by countries and observers, national reports from environment protection agencies in different countries, the brominated flame retardants industry, the Co-operative Programme for Monitoring and Evaluation of the Long-Range Transmission of Air Pollutants in Europe (EMEP) and the Arctic Monitoring and Assessment Programme (AMAP). Recent relevant information from the open scientific literature is also included. The available literature is comprehensive. References that are cited in this risk profile are listed under the heading “References”, while additional references that were also considered but not cited, are listed under the heading “Additional references”.

13. Twenty-one countries have submitted information (Australia, Bulgaria, Burundi, Canada, China, Costa Rica, Croatia, Czech, Finland, Germany, Japan, Lithuania, Mexico, Norway, Poland, Romania, Serbia, Sweden, Switzerland, Ukraine and USA). Two observers submitted information - European HBCD Industry Working Group and the International POPs Elimination Network (IPEN). All submissions are available on the Convention web site.

14. Several international environmental assessments of HBCD have been conducted. Three of these have assessed experimental data and field data against the POP criteria in the Stockholm Convention. These were performed by the NCM, the Task Force on POPs under the Convention on Long-Range Transboundary Air Pollution (LRTAP) (ECE/EB.AIR/WG.5/2009/7) and the European Brominated Flame Retardant Industry Panel (EBFRIP). EBFRIP commissioned a body/tissue based assessment and a total daily intake based assessment, where estimated effect levels and no-effect levels calculated for body/tissue-residue and TDI (total daily intake) are compared with estimates of exposure in the environment (EBFRIP 2009b). EMEP under LRTAP has made a model assessment of the potential for long-range transboundary atmospheric transport and persistence of HBCD. The European Commission risk assessment (European Commission 2008) is the most extensive of the existing assessments, examining the data on environmental fate, effects and exposure levels in depth. In Canada, Australia and Japan national assessments of HBCD are under preparation. Norway has completed their national assessment and has included HBCD in its national action plan for brominated flame retardants. USA has made an initial screening assessment and an interim evaluation of the risk of HBCD (U.S. Environmental Protection Agency, US EPA 2008).

15. The Arctic Monitoring and Assessment Programme (AMAP) identifies Arctic pollution risks, their impact on Arctic ecosystems and assesses the effectiveness of international agreements on pollution control. Scientific findings obtained under the AMAP (AMAP 2009) have shown HBCD to be one of the pollutants of the Arctic.

16. In the EU, HBCD has been identified as a Substance of Very High Concern (SVHC), meeting the criteria of a PBT (persistent, bioaccumulative and toxic) substance pursuant to Article 57(d) in the REACH regulation (ECHA 2008b). In May 2009, HBCD was included in the European Chemicals Agency (ECHA) recommendation list of priority substances to be subject to Authorisation under REACH, based on its hazardous properties, the volumes used and the likelihood of exposure to humans or the environment. A proposal on classification and labeling of HBCD as a possible reprotoxic substance is currently under discussion within the EU (Proposal for Harmonised Classification and Labelling, Based on the CLP Regulation (EC) No 1272/2008, Annex VI, Part 2 Substance Name: Hexabromocyclododecane Version 2, Sep. 2009) (KEMI 2009)**.** In Ukraine the substance is registered on the hazardous chemical list based on health effects.

17. An OECD SIDS Initial Assessment Profile has been compiled (OECD 2007). The OECD SIAM 24 agreed that HBCD possesses properties indicating a hazard for human health with regard to repeated dose toxicity and possible developmental neurotoxicity and for the environment with regard to acute aquatic toxicity to algae, chronic toxicity to Daphnia, and a high bioaccumulation potential.

1.4 Status of the chemical under international conventions

18. HBCD is included as part of the brominated flame retardants group in the List of Substances for Priority Action of The Convention for the Protection of the Marine Environment of the North-East Atlantic (the OSPAR Convention). The OSPAR Convention is made up of representatives of the Governments of 15 Contracting Parties and the European Commission.

19. In December 2009, HBCD was considered by the Executive Body of the UNECE Convention on Long-Range Transboundary Air Pollution (LRTAP) based on a technical review (ECE/EB.AIR/WG.5/2009/7) to meet the criteria for POPs as defined under the POPs protocol. In 2010 the possible management options for HBCD are being assessed to give a basis for later negotiations.

2 Summary information relevant to the risk profile

2.1 Sources

2.1.1 Production, trade, stockpiles

20. The production of HBCD is a batch-process. Elemental bromine is added to cyclododecatriene at 20 to 70°C in the presence of a solvent in a closed system. Although technical HBCD primarily contains γ –HBCD, thermal isomerization of HBCD can occur and may result in the enrichment of α– HBCD and to a lesser extent β-HBCD both during the polymer extrusion process, and during incorporation of HBCD in textiles (Peled et al. 1995, Larsen and Ecker 1986, Heeb et al. 2008, Kajiwara et al. 2009). HBCD powder or pellets, HBCD masterbatches, HBCD containing EPS beads and high impact polystyrene (HIPS) pellets are often exported and imported downstream in the production chain for the manufacturing of end-products for further professional use or sales to consumers.

21. According to the Bromine Science and Environment Forum (BSEF 2010) HBCD is produced in the United States of America, Europe, and Asia. There is information available about suppliers and producers in China, but information on amounts of HBCD imported or produced in China is not available. According to the global demand reported by the industry in 2001, more than half of the market volume (9,500 of 16,500 tonnes) was used in Europe. Total global demand for HBCD increased over 28% by 2002 to 21,447 tonnes, and rose again slightly in 2003 to 21,951 tonnes (BSEF 2006). In the US EPA assessment the sum of manufactured and imported HBCD is reported to lie between 4,540 tons to 22,900 tons in 2005 (US EPA 2008). The authorities in Japan have reported the sum of manufactured and imported HBCD to be 2,744 tonnes in 2008. The consumption in Japan reached 700 tonnes/year in the beginning of the 1990s (Managaki et al. 2009), and has increased approximately four times since then. The total volume of HBCD used in the EU was estimated to be about 11,580 tonnes in 2006. The demand of HBCD within the EU is bigger than the production and a net import to the EU was expected to have been around 6,000 tonnes in 2006. (ECHA 2008a). Several national authorities report an import of HBCD as a pure compound or in products; Canada (100-1,000 tonnes), Australia (<100 tonnes), Poland (500 tonnes imported from China annually), Romania (185 tonnes) and Ukraine.

2.1.2 Uses

22. HBCD is used as a flame retardant additive, providing fire protection during the service life of vehicles, buildings or articles, as well as protection while stored (BSEF 2010). The main uses of HBCD globally are in expanded and extruded polystyrene foam insulation while the use in textile applications and electric and electronic appliances is

smaller (ECHA 2008a, US EPA report, OECD 2007, INE-SEMARNAT 2004, Lowell Center For Sustainable Production (LCSP 2006), BSEF 2010). HBCD has been on the world market since the 1960s. The use of HBCD in insulation boards started in the 1980s. To manufacture flame retarded end products, a masterbatch, a concentrated mixture of HBCD encapsulated into a carrier resin such as polystyrene, is used (European Commission 2008).

23. According to the industry, the main application of HBCD is in polystyrene foam that is used in insulation boards, which are widely used in the building and construction industry. These polystyrene foams exist in two forms, as expanded polystyrene (EPS) and extruded polystyrene (XPS) foams, with HBCD concentrations ranging from 0.7% to 3.0% The manufacture of EPS, XPS and HIPS involves polymerisation and extrusion processes where HBCD is added in the process as one of the additives used (ECHA 2008a).

24. The second most important application is in polymer dispersion on cotton or cotton mixed with synthetic blends, in the back-coating of textiles where HBCD can be present in concentrations ranging from 2.2 – 4.3% (Kajiwara et al. 2009). Back-coating to textiles is applied by adding a dispersion containing a polymer and HBCD among other additives as a thin coating film (ECHA 2008a). A further smaller application of HBCD is in high impact polystyrene (HIPS) which is used in electrical and electronic equipment and appliances at levels ranging from 1 – 7% (ECHA 2008a). HBCD may also be added to latex binders, adhesives and paints (Albemarle Corporation 2000, Great Lakes Chemical Corporation 2005). The use of HBCD in EPS in packaging material is believed to be very small and HBCD is not used in food packaging according to the technical report developed in the EU (ECHA 2008a). The US EPA (2008) has reported uses in crystal and high-impact polystyrene, styrene-acrylonitrile resins, adhesives and in coatings. Costa Rica has reported use of HBCD in the construction sector. In Mexico HBCD has been used in EPS foams and in back-coating of textiles since the 1980s (INE-SEMARNAT 2004). In the EU the main use is in XPS and EPS, and the use in HIPS and in textiles are each at ca 2% (ECHA 2008a). In Japan 80% of the consumption of HBCD is in insulation boards (including tatami mat) and 20% in textiles (Managaki et al. 2009). In Switzerland construction materials are the most important component of HBCD consumption (84%) (Morf et al. 2008).

25. HBCD is used in a wide range of end products (ECHA 2008a, US EPA 2008, OECD 2007, INE-SEMARNAT 2004, LCSP 2006). Insulation boards with EPS foam or XPS foam with HBCD may be found in transport vehicles, in buildings and in road and railway embankments. HBCD-containing HIPS is used in electric and electronic appliances, such as in audio visual equipment cabinets, in refrigerator lining as well as in distribution boxes for electrical lines and certain wire and cable applications. Another use of HBCD is in textile coating agents, mainly in upholstery fabrics, but also in bed mattress ticking, upholstery in residential and commercial furniture, vehicle seating upholstery, draperies and wall coverings, interior textiles (roller blinds) and automobile interior textiles. According to the submission of Germany, HBCD is used in EPS filling in nursing pillows and bean bags used as easy chairs. Granulated EPS waste is also used to improve the texture of agricultural and horticultural soil.

2.1.3 Releases to the environment

26. There are no natural sources of HBCD. HBCD is released into the environment during the manufacturing process, in the manufacture of products, during their use and after they have been discarded as waste. The production process of HBCD and industrial use processes are described in the EU technical report (ECHA 2008a). In the EU, Japan, and Switzerland, releases from different sources and life stages of HBCD have been estimated based on measurements of releases and modelling (ECHA 2008a, Managaki et al. 2009, Morf et al. 2008). The two national studies are substance flow analyses based on studying the flow of HBCD through different lifecycle stages over periods of several years. Some of the differences between studies are caused by the method used, different use scenarios, differences in ways that releases are accounted for and in the estimation factors used. The use category 'insulation boards' in the substance flow analysis in Japan, for example, also covers the use in the traditional tatami mat, that could have a higher release potential than insulation boards.

27. There are direct emissions to air, direct discharges to waste water and to surface water from industrial point sources. The total releases to the environment are increasing in Japan and Switzerland. Also in the EU total releases are increasing in spite of the decrease in the releases from textile back-coating since 2004. In the EU the releases to water were the largest (air; 665 kg/year, waste water; 1,553 kg/year, surface water; 925 kg/year) (ECHA 2008a), while in Switzerland (Morf et al. 2008) and Japan the releases to air were largest (air; 571 kg/year, water; 41 kg/year) (Managaki et al. 2009).

28. Losses to soil were considered minor in Japan, Switzerland, and the EU since waste with HBCD was disposed of in controlled landfills or incinerated. However, an industry survey (EBFRIP 2009a) revealed that potential losses to land may be higher than previously understood, due to disposal practices for HBCD packaging waste and that this loss due to packaging waste can be rapidly reduced by the introduction of appropriate handling and disposal practices. The survey included a selection of HBCD producers, warehouses and first line direct users of HBCD in Europe including only the first stages in the HBCD life cycle. Packaging waste was found to be the main contributor to potential releases to soil due to uncontrolled landfill or compost, recycling of empty paper packaging, substances going to unknown destinations and the unprotected storage of packaging. Annual losses to soil were estimated at 1,857 kg HBCD /year. Implementing best practices in handling reduced the total potential releases from 2,017 kg/year in 2008 to 309 kg/year

in 2009 in the survey. Industry producing and using HBCD has in 2006 introduced a voluntary programme to reduce direct emissions from industrial sources in the EU (EBFRIP 2009a).

29. According to the Swiss substance-flow analysis, construction materials are responsible for the majority of the releases and half of the total releases were estimated to come from diffuse atmospheric emissions from installed EPS and XPS insulation boards (Morf et al. 2008). In the EU technical report, however the releases of HBCD during the service life of insulation foams were assumed to be low (ECHA 2008a), but the releases from manufacture and use of insulation boards (1,628 kg/year) were still estimated to represent more than half of the total releases (3,142 kg/year) in 2006. According to the EU technical report, the estimated total releases of HBCD from manufacture and use of insulation boards (95% consumption) and manufacture and use of textiles (2% consumption) were in the same magnitude. Total releases from manufacture and use of electronic devices was considered minor (12.6 kg/year) (ECHA 2008a and table. 3 in ECHA 2008b). In Japan the releases from use in textiles represents the largest releases and atmospheric emissions of HBCD from textile coating in the industry accounts for more than half of the total releases from 1985 to 2001 (Managaki et al. 2009).

30. In the substance flow analysis made in Japan (Managaki et al. 2009) and the estimation of releases done in EU the releases from industrial point sources were the largest (ECHA 2008a; industrial point sources; 2,559 kg/year, releases during service life of products; 98.9 kg/year).

31. HBCD is used solely as an additive in physical admixture with the host polymer and can migrate within the solid matrix and volatilize from the surface of articles during their service life (Swerea 2010, ECHA 2008a, European Commission 2008). There will also be particulate releases and leaching of HBCD during the service life of flame retarded end-products. There are experiments revealing emissions of HBCD from various products (European Commission 2008, Miyake et al. 2009, Polymer Research Centre 2006 and Kajiwara et al. 2009). There are also several studies showing the occurrence of HBCD in indoor air and house dust (Abdallah et al. 2008a and b, Abdallah 2009, Goosey et al. 2008, Stapleton et al. 2008, Stuart et al. 2008, Takigami et al 2009 a and b). However HBCD emissions to indoor air from disturbance of products made from EPS or XPS during service life is estimated to be very low (ECHA 2008a). Industry data on an installed PS foam board containing HBCD showed a stable HBCD level after 25 years of use (EBFRIP 2009c). Although technical HBCD primarily contains γ –HBCD, in light-exposed dust, a photolytically-mediated shift from γ-HBCD to α-HBCD may occur (Harrad et al. 2009).

32. Estimates of releases from insulation boards during their service life have been based on the results of experiments measuring the loss of HBCD from a sample of foamed polystyrene, assuming a service life of 30 years (ECHA 2008a). Release estimates have been developed for the service life of textiles using the results of wearing and leaching tests on aged samples of treated textiles (ECHA 2008a-and references therein). There are no estimates on releases of HBCD from HIPS in articles. The total estimations for releases of HBCD from diffuse sources are probably underestimated in all analyses, since information is lacking on releases from some products, as well as the HBCD content in imported articles.

33. At the end of their service life, products containing HBCD are likely to be disposed of in landfills, incinerated, recycled, or remain as waste in the environment. Insulation boards form the majority of HBCD containing waste. It is understood that most of this material goes to landfill or incineration. The use of HBCD in insulation boards and the HBCD built into buildings and constructions is increasing. There will be some releases of HBCD in dust when buildings insulated with flame retarded insulation boards are demolished. Releases from insulation boards becoming waste were estimated at 8,512 kg HBCD per year in 2006 (ECHA 2008a). It is likely that those releases will be more significant in the future; particularly from about 2025 onwards, as increasing number of buildings containing HBCD will be refurbished or demolished. This turn-over will be different in different regions of the world, and range from 10-50 years.

34. Electrical and electronic appliances containing HIPS treated with HBCD are sometimes recycled. In the substance flow analysis in Switzerland (Morf et al. 2008) emissions from the recycling of vehicles, insulation panels and electrical and electronic equipment were estimated to account for about 2% of the total releases of HBCD and the emissions from incineration were estimated to account for 0.1%. In developing countries, electrical and electronic appliances containing HBCD and other toxic substances are often recycled under conditions which results in a relatively higher release of HBCD to the environment and contamination of the sites (Zhang et al. 2009), and exposure of workers (Tue et al. 2010). Open burning and dump sites are common destinations for HBCD-containing articles and electronic wastes (Malarvannan et al. 2009, Polder et al 2008c).

35. The substance flow analysis in Japan also indicates that emissions from construction materials will continue for several decades and be potentially long-term sources of HBCD leaching or volatizing to the environment, as well as representing larger releases when demolished or renovated in the future (Managaki et al. 2009). Additionally, the increasing HBCD stock seen in the study indicates possible problems arising in the recycling of construction materials in the future, when buildings of the present period are renovated or destroyed. This is also supported by the results from the substance flow analysis in Switzerland. The Swiss study also high-lights the stock in waste management and landfills as long-term sources of HBCD releases (Morf et al. 2008). The significance of those sources depends however

on the waste management strategies chosen in the country, if the wastes are incinerated, or disposed of to an uncontrolled or controlled landfill. The overall figures of municipal waste within the EU from 2006 are that 68% goes to landfill and 32% is incinerated (ECHA 2008a).

36. From both industrial point sources and diffuse sources there are releases to waste water and sewage systems (ECHA 2008a; Morf et al. 2008; Institut Fresenius 2000a and b; Kupper et al. 2008; Remberger et al. 2004; Sellström et al. 1999; Law et al. 2006b). The sewage sludge is either applied on agricultural land, incinerated or land filled (ECHA 2008a; Morf et al. 2008). There are releases of HBCD to surface water and soil, leaching from landfills (Morf et al. 2008; Morris et al. 2004) and sewage sludge (Morf et al. 2008; Morris et al. 2004).

2.2 Environmental fate

2.2.1 Persistence

37. To evaluate the persistency of HBCD a compilation of data on experimentally measured half-lives in different environmental compartments, data on half-lives derived from modeling, and field data have been undertaken. Results of the estimation model, BIOWIN (v4.10, EPI Suite v4.0), which estimates the probability for aerobic biodegradation in the presence of mixed populations of environmental microorganisms suggest that HBCD is not readily biodegradable; the expected time of primary degradation is in the order of weeks. Moreover, an early biodegradation study using Closed Bottle Test systems that were conducted in accordance with OECD Guideline 301D, found no biodegradation of HBCD over a 28 day study period (Wildlife International 1996). It should be noted that while the studies were performed using accepted test guidelines, the concentrations tested were about three orders of magnitude greater than the water solubility of HBCD (7.7 mg/L *vs* 66 μg/L).

38. Japanese authorities conducted a 28-day biodegradation study of 1,2,5,6,9,10-hexabromocyclododecane based on the OECD Test Guideline 301C. The degradation of the test substance, a mixture containing different stereoisomers, was assessed by high performance liquid chromatography. The percentage biodegradation of two HBCD isomeric forms (A and B), were calculated to be 5 and 6%, respectively. (Chemicals Inspection and Testing Institute, 1990).

39. The rate of degradation of HBCD is slower in the presence of oxygen. Davis et al. (2005) reported on the biodegradation of technical HBCD (t-HBCD) in freshwater sediments and soils. Using OECD test guidelines 307 and 308, the authors demonstrated that the rate of loss of HBCD at $20^{o}C$ was appreciably faster under anoxic conditions in both media. Relative to biologically sterile controls, biotransformation of HBCD was faster in the presence of microorganisms and DT50 values ranged from 11 to 32 days (aerobic) and 1.1 to 1.5 days (anaerobic) in sediment. In soil, half-lives under aerobic and anaerobic conditions were 63 and 6.9 days, respectively. However, in this study only the degradation of γ-HBCD was studied since the test concentration was too low to allow detection of α- and β-HBCD. It was also not possible to detect transformation products.

40. In the EU Risk Assessment, the degradation half-lives in aerobic sediment were calculated at 20 °C to be 113, 68 and 104 days for α-, β- and γ-HBCD, respectively (European Commission, 2008). In sediment, technical-HBCD was observed to be subject to primary degradation with half-lives of 66 and 101 days in anaerobic and aerobic sediment at 20 °C, respectively. The EU Risk Assessment notes that the study was conducted at HBCD concentrations much greater (mg/kg) than Davis et al. (2005) (μg/kg), so the degradation kinetics may be limited by the mass transfer of chemical into the microbes. The main transformation product was 1,5,9-cyclododecatriene (CDT) which was formed via a step-wise reductive dehalogenation of HBCD. No CO_2 was detected during the study. However, in a study performed according to OECD guideline 301F (Davis et al. 2006b), it was shown that t,t,t-CDT can be degraded to $CO_{2.}$

41. Degradation rate constants of HBCD, under anaerobic conditions in sewage sludge have also been reported (Gerecke et al. 2006). Experiments were conducted by adding individual target compounds or mixtures to freshly collected digested sewage sludge. The sewage sludge was amended with yeast and starch. Experiments, performed at 37 °C, with racemic mixtures of individual diastereoisomers showed that (+/-)-β-HBCD and (+/-)-γ-HBCD degraded faster than (+/-)-α-HBCD by an estimated factor of 1.6 and 1.8, respectively. Based on the investigations of Davis et al. (2006a) and Gerecke et al. (2006), α-HBCD seems to be subject to a slower degradation than β- and γ-HBCD.

42. There are no reliable empirical data on the degradation kinetics of HBCD in water. The hydrolysis of HBCD has not been studied. Hydrolysis should however, not be considered as a significant route of environmental degradation for this substance due to the low water solubility, the high partitioning to organic carbon, and the lack of hydrolysable functional groups (OECD 2007). According to calculations in the EMEP report on HBCD, the physical-chemical properties of the technical mixture and γ-HBCD stereoisomer give a half-life in water of about 5 years (EMEP 2009). According to EBFRIP (2009b) the half life for water and soil derived from comparing different model estimations lies in the range 8.5 – 850 days, with a median of 85 days and confidence factor (CF) of 10. The half life in freshwater and marine sediments lies in the range 6 – 210 days, with a median of 35 days and CF of 6. EBFRIP (2009b) does not differentiate between fresh water and marine sediment.

43. Several studies using sediment cores show that HBCD congeners deposited in marine sediments in Asia and in Europe at the beginning of the 1970s/1980s are still present in significant amounts (Minh et al. 2007, Tanabe 2008, Kohler et al. 2008, Bogdal et al. 2008), indicating a higher persistency in sediments than derived from experimental studies.

44. The trophic transfer of chemicals in terrestrial or aquatic food webs can also be used to assess persistence. Chemicals that are slow to break down by biologically mediated processes will increase in concentration with increasing trophic level, i.e. biomagnify. The measured field data from various surveys show that HBCD biomagnifies in some aquatic food chains. The α-HBCD appears to be the more persistent of the HBCD isomers, and to biomagnify more than β-HBCD and γ-HBCD. The findings in the Arctic provide additional evidence that HBCD can persist in the environment long enough to be transported over long distances (EBFRIP 2009b, NCM 2008).

2.2.2 Bioaccumulation

45. Several studies in laboratory, in local food webs and local ecosystems confirm the potential for HBCD to bioaccumulate and biomagnify. The field studies show a general increase of concentrations in biota with increasing trophic level in aquatic and Arctic food webs. No field studies in the terrestrial environment have been identified, but two laboratory studies show that HBCD has a potential to bioaccumulate in terrestrial mammals. Veith et al. (1979) estimated a steady-state bioconcentration factor (BCF) of 18,100 for technical HBCD in fathead minnow (*Pimephales promeas*) in a 32-day flow-through test. Thirty fish were exposed in the test system and five fish were sampled and analysed on days 2, 4, 8, 16, 24 and 32. The mean test concentration of *t*-HBCD was 6.2 µg/L which was below its aqueous water solubility and the test temperature was 25 ± 0.5 °C.

46. Accumulation of HBCD was also observed in rainbow trout (*Oncorhynchus mykiss*) exposed to nominal concentrations of 0.34 and 3.4 µg/L in a flow-through system for 35-days (Wildlife International 2000). The study adhered to the OECD 305 test method and included a 35-day depuration period following exposure. Trout exposed to the higher test concentration did not reach steady-state tissue concentrations over the duration of testing and calculated BCFs were considered less reliable than those determined at the lower test concentration. A steady-state BCF value of 13,085 was calculated for the whole fish exposed to technical HBCD at the lower concentration. Based on the studies by Wildlife International 2000 and Veith et al. (1979), an overall bioconcentration factor (BCF) for aquatic organisms of 18,100 was chosen in the EU risk assessment (European Commission 2008).

47. A study of 1,2,5,6,9,10-HBCD in carp was conducted by Japanese authorities, based on the OECD Test Guideline 305C for 14 weeks. As the supplied test substance was a mixture, it was separated by high performance liquid chromatography (HPLC) into 5 components which are referred to as components A-E according to the order of the peak appearance. The three main components B, C and E whose isomer identifications were not established but whose molecular formulae were the same as that of the test substance were analysed in this study. For component B, BCFs were 834-3,070 and 3,390-16,100 at 24 and 2.4 µg/L, respectively. For component C, BCFs were 816-1,780 and 3,350-8,950 at 20.2 and 2.02 µg/L, respectively. For component E, BCFs were 118-418 and 479-2,030 at 144 and 14.4 µg/L, respectively (Chemicals Inspection and Testing Institute 1995).

48. Law et al. (2005) measured the biomagnification factors (BMF) of individual isomers under a controlled laboratory environment. By exposing juvenile rainbow trout to food intentionally fortified with each isomer the authors were able to calculate BMFs of 9.2, 4.3 and 7.2 for α-, β- and γ-isomers, respectively. The authors also noted that bioisomerization *i.e.*, conversion of one isomer into another, can occur *in vivo* with this fish species.

49. Haukås et al. (2009) reported on the dietary exposure of juvenile rainbow trout to HBCD. The authors noted that bioaccumulation of HBCD was significant 6 hours after the single oral exposure and concentrations peaked after 4-8 days. After 48 h, the rank order of the relative distribution of the isomers in the fish were liver > muscle >> brain. The greater distribution to the liver was thought to be due to the greater blood supply to this organ from the stomach and intestine. After 21 days, the relative concentrations of the isomers decreased in the liver and brain, whereas no significant change in HBCD concentration was observed in muscle. It was hypothesized that the delay in elimination of the isomers from the muscle was due to the lower metabolic activity and circulation of blood to the muscle.

50. Two studies in the laboratory have examined the bioaccumulation of HBCD in mammals (WIL 2001; Velsicol Chemicals 1980). In a 90-day repeated dose (technical-HBCD, 1,000 mg/kg bw/day) toxicity study with rats, WIL (2001) found that concentrations of the α-isomer were much greater than that of the β- and γ-isomers at all sampling time points. The relative percentage of the isomers measured in the rats (α-: 65-70%; β-: 9-15% and γ-: 14-20%) was markedly different to the proportions in the HBCD formulation used (α-: 8.9%; β-: 6.6% and γ-: 84.5%). Velsicol Chemicals (1980) studied the pharmacokinetics of radiolabelled HBCD (^{14}C-HBCD, purity > 98%) administered to rats as a single oral dose. The authors found that the test substance was distributed throughout the body with the greatest amounts measured in fat tissue, followed by liver, kidney, lung and gonads. Rapid metabolism to polar compounds occurred in the blood, muscle, liver and kidneys, but HBCD remained mostly unchanged in the fatty tissue. The study concluded that HBCD accumulated in fatty tissues following repeated exposure.

51. There are numerous reports showing BMFs > 1 for HBCD in aquatic ecosystems. For example, in the Lake Ontario food web, lipid normalized BMFs for both the α- and γ-isomer were greater than one for many of the feeding relationships (Tomy et al. 2004a). In some instances, BMFs for the HBCD isomers were greater than those of other known persistent organic pollutants, for example, a BMF of 10.8 for the α-isomer was reported for the smelt:Mysis feeding relationship and was ca. two times greater than that of *p,p*-DDE and ΣPCBs. The trophic magnification factor (TMF), defined as the slope of the regression of log concentration *vs* trophic level, was 6.3 ($p<0.001$) and greater than that of ΣPCBs (5.7) (Tomy et al. 2004). In Lake Winnipeg, a freshwater lake in central Canada, BMFs of greater than one were also reported for all three HBCD isomers for many of the established predator to prey feeding relationships (Law et al. 2007). The calculated TMF-values were 1.4, 1.3 and 2.2 for α-, β-, and γ-HBCD respectively.

52. Similar findings have been made in the Norwegian Arctic. Sørmo et al. (2006) analyzed representative species from different trophic levels of the polar bear food chain, using samples collected from 2002 to 2003 at Svalbard in the Norwegian Arctic. HBCD was below detection limits (minimum 0.012 ng/g lw) in the amphipod, *Gammarus wilkitzkii*. HBCD biomagnified strongly from polar cod (*Boreogadus saida*) to ringed seal (BMF of 36.4, based on whole body wet weight concentrations), but did not biomagnify from ringed seal to polar bear (BMF of 0.6). Lower levels in the polar bear samples were considered to indicate possible enhanced metabolic capability in the bears. In East Greenland the comparative bioaccumulation, biotransformation and/or biomagnification from East Greenland ringed seal (*Pusa hispida*) blubber to polar bear (*Ursus maritimus*) tissues (adipose, liver and brain) of HBCD and legacy POPs was investigated by Letcher et al. (2009). α-HBCD was found to only bioaccumulate in the polar bear adipose tissue. The ringed seal blubber to polar bear adipose BMF for total-(α)-HBCD >1. The authors concluded that even if the metabolism of HBCD in polar bears was enhanced compared to other species, the high exposure of HBCD ensures biomagnification.

53. Morris et al. (2004) reported on biomagnification of HBCD in the North Sea food web. Although individual BMFs were not reported, the authors suggested that because concentrations of HBCD were higher in species in the top of the food chain it implied that HBCD was biomagnifying. For example, HBCD concentrations in top predators such as harbour seals (*Phoca vitulina*) and harbour porpoise (*Phocoena phocoena*) were several orders of magnitude greater than those measured in the aquatic macroinvertebrates such as sea-star and common whelk. Similarly, HBCD concentrations were high in liver samples from cormorant, a predator bird-species and in eggs of the common tern, while lower levels of HBCD were detected in their prey, cod and yellow eel (*Anguilla Anguilla)*.

54. Haukås et al. (2009) found the concentration ratio of the diastereoisomers of HBCD to range between 3:1:10 (α:β:γ) in sediments to 55:1 (α:γ) in the highest trophic level species, suggesting a diastereoisomer-specific bioaccumulation in the organisms. The study was conducted in a HBCD-contaminated Norwegian fjord in a marine food chain, measuring levels from sediments and sediment-dwelling organisms to sea birds. This corresponds with the results of Zhang et al. (2009) in two contaminated streams in China. In this study γ-HBCD was found to be the dominant diastereoisomer in the sediments (63% of total HBCDs), while α-HBCD was selectively accumulated in the biotic samples and contributed to 77%, 63% and 63% of total HBCDs in winkle (*Littorina littorea)*, crucian carp (*Carassius carassius)* and loach, respectively.

55. Tomy et al. (2008) investigated isomer-specific accumulation of HBCD at several trophic levels of an eastern Canadian Arctic marine food web. There was a significant positive relationship of α-HBCD with trophic level, with a TMF of 7.4 ($p<0.01$), indicative of biomagnification throughout the food web, while a significant negative relationship was observed between concentrations of γ-HBCD and trophic level (i.e. trophic dilution). α-HBCD contributed greater than 70% of the total HBCD burden in shrimp (*Pandalus borealis, Hymenodora glacialis)*, redfish (*Sebastes mentella)*, arctic cod (*Boreogadus saida)*, narwhal (*Monodon monoceros*) and beluga (*Delphinapterus leucas)*, while γ-HBCD was greater than 60% of total HBCD in zooplankton (mix), clams (*Mya truncata, Serripes groenlandica*), and walrus (*Odobenus rosmarus)*. The observed differences in diastereoisomer predominance were attributed in part to differing environmental fate and behaviour of the isomers, with the least water soluble γ-isomer more likely to diffuse passively from the water column into zooplankton, which have proportionately high lipid content. Similarly, as benthic filter feeders, clams may be more likely to absorb a higher proportion of the γ-isomer from sediment. The presence of higher proportions of α-HBCD, such as with the beluga and narwhal, may indicate enhanced metabolic capability based on evidence of stereoisomer-specific biotransformation of the γ-isomer to the α-form (Zegers et al. 2005, Law et al. 2006d). This also corresponds with the findings of Tomy et al. (2009) where the α-isomer accounted for >95% of the overall burden of HBCDs in the beluga, while the Arctic cod, the primary prey species of beluga in the western Canadian arctic marine food web, had a HBCD-profile dominated by the γ-isomer (>77%). The authors concluded that this was further evidence that beluga can bioprocess the γ- to the α-isomer.

2.2.3 Potential for long-range environmental transport

56. HBCD is persistent in air, with an estimated half-life of more than two days. Studies of and modeling of environmental fate and environmental transport of HBCD, as well as field data provide further evidence of the potential for long-range transport of HBCD. The detected levels in the Arctic atmosphere, biota and environment are strong indicators of HBCD's potential for long-range transport.

57. The atmospheric degradation half-life of HBCD by gas-phase reaction with hydroxyl radicals (OH) has not been experimentally measured but can be modeled, providing an estimate (by AopWin v1.91) of 76.8 hours (3.2 days). The estimate was obtained by assuming a concentration of 5×10^5 OH molecules.cm^{-3} and that the reaction takes place 24 hours a day (these are values used in the European Union risk assessments). It is noted that the model is sensitive to the chosen OH-concentration (NCM 2008).

58. Bahm and Khalil (2004) derived a 24 hour global annual average OH concentration of 9.2×10^5 molecules·cm^{-3}, with a value of 9.8×10^5 molecules·cm^{-3} for the northern hemisphere and 8.5×10^5 molecules·cm^{-3} for the southern hemisphere. These values are consistent with Prinn et al. (1995) and Montzka et al. (2000) who deduced OH concentrations from atmospheric measurements of methyl chloroform, reporting 24 hour global annual average values of $9.7(\pm0.6)\times10^5$ and $1.1(\pm0.2)\times10^6$ molecules·cm^{-3} respectively. Considering the uncertainty in the model estimates of k_{OH}, the half-life for photochemical degradation of HBCD ranges from 0.4 to 4 days and 0.6 to 5.4 days for the northern and southern hemisphere respectively (EBFRIP 2009b).

59. BSEF (2003) examined the long-range transport potential (LRTP) of HBCD using four LRTP assessment models (TaPL3-2.10, ELPOS, Chemrange-2.0 and Globo-POP), and concluded that HBCD has a low potential to reach remote areas. LRTP indicators were expressed as the overall characteristic travel distance (CTD) for TaPL3 and ELPOS, the spatial range for Chemrange, and the Arctic contamination potential after 10 years of steady emissions (ACP10) for Globo-POP. CTDs of 760 and 784 km in air were predicted using TaPL3 and ELPOS, respectively, while Chemrange estimated a spatial range for HBCD in air of 11% of the earth's circumference. An ACP10 of 2.28% was estimated from Globo-POP. The results were comparable with those obtained for brominated diphenyl ether flame retardants, in particular the penta- through decaBDE congeners that also are detected in the Arctic (Wania and Dugani 2003). BSEF (2003) concludes, that based on the properties of HBCD, its long-range transport is likely to be regulated by transport of aerosols. Overall, the low volatility of HBCD was predicted to result in significant sorption to atmospheric particulates, with the potential for subsequent removal by wet and dry deposition. The transport potential of HBCD was considered to be dependent on the long-range transport behaviour of the atmospheric particles to which it sorbs.

60. HBCD's physico–chemical properties suggest that it may experience active surface–air exchange as a result of seasonally and diurnally fluctuating temperatures. Subsequently, this may result in the potential for long-range transport of HBCD through a series of deposition/volatilization hops, otherwise known as the ''grasshopper effect", described by Gouin and Harner (2003). This assumption is supported by environmental data. The concentrations of HBCD in bulk samples collected in urban and remote sites in Sweden and Finland had a clear seasonal and diurnal flux rate with higher concentrations in winter and lower in summer and fall. (Remberger et al. 2004). Precipitation samples collected from the Great Lakes Basin contained as much as 35 ng HBCD/L, with the highest levels occurring in the winter months (Backus et al. 2005). The researchers hypothesized that observed winter peaks resulted from increased scavenging efficiency of snow compared with rain, as well as higher concentrations in the particle phase during winter. In the study by Yu et al. (2008) in Southern China a large variable percentage of HBCD (69.1–97.3%) existed in the particle phase, suggesting that long-range transport of HBCDs is governed by environmental conditions.

61. Based on model estimates HBCD seems to have a "low" to "moderately-low" long-range transport potential. Using the bench-marking approach, HBCD's potential for long-range transport is in the range of the legacy POPs (EBFRIP 2009b). Detectable levels in remote regions suggest that long-range transport is occurring on a larger scale than predicted by the models. The models do not include the full potential of transport by the "grass-hopper effect" and some of the environmental conditions typical for the wind systems of the Arctic, for example the Arctic haze events.

62. According to the AMAP report from 2009, transport of less volatile brominated flame retardants (BFRs) does take place when there are large numbers of particles in Arctic air, during the Arctic haze. Therefore, periods of strong winds and no precipitation may lead to longer transport distances than the models predict for BFRs (AMAP 2009). Brown and Wania (2008) identified HBCD as a potential Arctic contaminant based on an atmospheric oxidation half-life of greater than two days and structural similarities to known long range transported Arctic contaminants. The authors explain the discrepancy between the model results and long-transport behaviour of HBCD with the possibility that particle-bound atmospheric transport may be more efficient in delivering contaminants to the Arctic than is currently estimated in global transport calculations; one reason may be because the effect of intermittent rain is ignored in the models. EMEP modeling reached the same conclusion (EMEP 2009). This is also supported by field studies and environmental monitoring. In the Norwegian pollution monitoring programme, HBCD concentrations were found to be higher (Birkenes 30.8 pg/m^3 and Zeppelin 26.39 pg/m^3) in the atmosphere over the Norwegian Arctic when the air transport came from polluted areas on the continents and lower (Birkenes 1.03 pg/m^3 and Zeppelin 0.26 pg/m^3) when the air transport came from the North Pole Sea and Scandinavia (Climate and Pollution Agency, Norway (KLIF 2008)). The monitoring data also demonstrated that the air from polluted regions can reach the remote areas on a short time basis (Manø et al. 2008). In a recent review, HBCD has been found to be ubiquitous in the Arctic and Western Europe and the eastern parts of North America were found to be important source regions via long range transport (de Wit et al. 2009). HBCD was monitored for the first time in the European Arctic atmosphere in 1990 (5-6 pg/m^3; Bergander et al. 1995) and in the Canadian and Russian Arctic in 1993 (1,8 pg/m^3; PWGSC-INAC-NCP 2003 and 1-2 pg/m^3 (2006 and

2007); Xiao et al. 2010), The ∑HBCD air concentrations in the Canadian Arctic was similar to the air concentrations of BDE-99 (Xiao et al. 2010).

2.3 Exposure

2.3.1 Environmental levels and trends

63. HBCD is widespread in the global environment, with high levels in the top predators. According to Covaci *et al*. (2006) high concentrations have been measured in marine mammals and birds of prey. Zegers et al. (2005) published data on HBCD concentrations in two species of marine top predators, the harbor porpoise and the common dolphin (*Delphinus delphis*), from different European seas. The highest HBCD concentrations were measured in porpoises stranded on the Irish and Scottish coasts of the Irish Sea (median concentration 2,900 ng/g lw, maximum 9,600 ng/g lw) and the northwest coast of Scotland (5,100 ng/g lw). The median concentrations in porpoises from other areas were 1,200 ng/g lw on the south coast of Ireland, 1,100 ng/g lw on the coasts of the Netherlands, Belgium, and the North Sea coast of France, 770 ng/g lw for the east coast of Scotland, and 100 ng/g lw for the coast of Galicia (Spain). The median HBCD concentrations in the common dolphin, a pelagic marine mammal species feeding primarily over the continental shelf and in offshore waters, were 900 ng/g lw on the west coast of Ireland, 400 ng/g lw in the English Channel coast of France, and 200 ng/g lw in Galicia (Zegers et al. 2005). Law et al. (2006d) studied HBCD in the blubber of harbour porpoises from the UK during the period 1994–2003. Eighty-five animals were analysed for HBCD. α-HBCD dominated over the other isomers and was detected in all samples at concentrations ranging from 10 to 19,200 µg/kg wet weight (11–21,300 µg/kg on a lipid basis) (see paragraph 71 for follow-up study).

64. de Boer et al. (2004) have analysed HBCDs in eggs of peregrine falcons (*Falco peregrinus*) (71 ng/g lw – 1,200 ng/g lw) and muscle in sparrowhawks (*Accipiter nisus*) (84-19,000 ng/g lw) from the U.K., with detection frequencies of 30% and 20%, respectively. Levels of 330-7,100 ng/g lw were in 2001 found in eggs from the common tern (*Sterna hirundo*) in the Netherlands in a study by Morris et al. (2004) and levels of 34-2,400 ng/g lw were found in eggs of peregrine falcons in Sweden sampled 1991-1999 (Lindberg et al. 2004).

65. Due to their high position in the food chain and the elevated exposure in the aquatic environment, fish often exhibit high residues of contaminants. Not surprisingly, HBCDs have been detected in many studies in both freshwater and marine biota (Covaci et al. 2006). Concentrations of HBCDs in fish downstream of an HBCD manufacturing plant on the River Skerne (Durham, U.K.) were very high, with levels up to 10,275 ng/g lw (Allchin and Morris 2003). Concentrations of HBCDs were mostly between 10 and 1,000 ng/g lw in urban/suburban regions of Europe, while levels in the North American Great Lakes were lower by approximately one order of magnitude (3-80 ng/g lw) (Covaci et al. 2006). The wide spread spatial occurrence of HBCD in the aquatic environment was illustrated by Ueno et al (2006) that measured HBCD in the muscle of skipjack tuna (*Katsuwonus pelamis)* (1997-2001) in the Asia-Pacific area. Levels ranged between 0.28 ng/g lw in the waters outside Brazil to 45 ng/g lw in the waters outside Japan. The study by Xian et al. (2008) in the Yangtze River in China in 2006 examined HBCD levels in fresh water fish. Levels ranged between 12 ng/g ww in the muscle of grass carp (*Ctenopharyngodon idella)* to 330 ng/g ww in the muscle of mandarin fish (*Siniperca chuatsi).*

66. HBCD is ubiquitous in the Arctic environment and has been found to be widespread in the Arctic food webs (de Wit et al. 2006, 2009). The top predators in the Arctic are especially vulnerable due to environmental changes and a high burden of persistent contaminants (AMAP 2009). During periods when fat reserves are used up because of environmental stress, contaminants accumulated in the fat reserves are released and transferred to vital organs (KLIF 2007). Muir et al. (2004) detected ΣHBCD concentrations in the blubber of beluga whales (*Delphinapterus leucas*) in the Canadian Arctic in 2001, a species protected by the Convention on migratory species. The concentrations were in the range of 9.8-18 ng/g lw. Muir et al. (2006) detected levels of HBCD in adipose tissue of polar bears (*Ursus maritimus*) in several populations in the Arctic region in 2002. The highest levels were detected in the female bears from the Svalbard area (109 ng/g lw). Polar bears are listed on the IUCN Red List of threatened species. Miljeteig et al. (2009) compared levels of contaminants in eggs between four Arctic colonies of ivory sea gull (*Pagophila eburnea*), one in the Norwegian Arctic (Svalbard) and three in the Russian Arctic (Franz Josef Land and Severnaya Zemlya). The contaminant levels presented are among the highest reported in Arctic seabirds and were identified as an important stressor in a species already at risk due to environmental change. The population of ivory gulls in the Arctic is decreasing and the species is on the IUCN Red List of Threatened Species (www.iucnredlist.org/)**.** The levels of HBCD in the study ranged between 14 and 272 ng/g lw HBCD. In the report of KLIF (2007) glaucous gulls (*Larus hyperboreus*) and great black-backed gulls (*Larus marinus*) found dead at Bjørnøya in the Norwegian Arctic between 2003-2005 were analysed for contaminants, such as legacy POPs, mercury and emerging pollutants in the Arctic. The levels found for some of the contaminants, including HBCD, were higher than previously reported for glaucous gulls from Bjørnøya and other bird species in the Arctic and in Europe. The α-HBCD concentrations in the brain and liver samples of the glaucous gulls ranged from 5,1 ng/g lw to 475 ng/g lw, and from 195 ng/g lw to 15,027 ng/g lw, respectively. The levels in samples from the two great black-backed gulls were 44.7 and 44.8 ng/g lw in the brain samples and 1,881 - 3,699 ng/g lw in the liver samples. For a comparison, the levels found in cormorant liver (*Phalacrocorax carbo)* sampled in England in 1999-2000 were in the range 138-1,320 ng/g lw (Morris et al. 2004).

Some 40-45% of the sea birds were found to be completely or severely emaciated. There were also observations of dying glaucous gull on Bjørnøya with apparently abnormal behavior. According to KLIF (2007) this may indicate that high levels of contaminants, including high levels of HBCD, may have been a contributing factor to the birds' death, directly or indirectly.

67. According to the reviews done by Covaci et al. (2006), Law et al. (2008b) and Tanabe et al. (2008) the HBCD levels in the environment are generally increasing in all matrices in the environment, and seem to correlate with the increasing use of HBCD. The reviews cover over 100 published scientific studies (up to 2007) performed in North America, Europe, the Arctic, Asia and the South Pacific region. The reviews cover a variety of environmental compartments (atmosphere, indoor and outdoor air, sewage sludges, soils and sediments) and a variety of biological samples and food chains. In the review by de Wit et al. (2009) the few available temporal studies in the Arctic indicated an increase in biota of HBCD, no or unclear trend, depending on species and locality. According to Managaki et al. (2009), the increasing trend in releases of HBCD are in agreement with concentration data from sediment cores (Minh et al. 2007) and historic trends of HBCD levels in human blood in Japan (Kakimoto et al. 2008).

68. Several sediment core analyses performed in Asia and Europe show higher levels of HBCD in the top layers and lower concentrations in the deeper layers. These findings correlate with the trend in use of HBCD. HBCD was present in three sediment cores and six surface sediment samples collected in 2002 from Tokyo Bay, Japan (Minh et al. 2007). HBCDs first appeared in the mid-1970s and concentrations observed in the cores have increased since then. Based on the data, Tanabe (2008) estimated concentration doubling times of 7 to 12 years for HBCD in the sediment. HBCD was first detected in sediments from Lake Greifensee in the mid-1980s (Kohler et al. 2008). HBCD concentrations in the cores then increased in an exponential manner with a peak in 2001 (2.5 ng/g, dry weight). Bogdal et al. (2008) reported increasing HBCD concentrations up to the surface layer in two sediment cores from Lake Thun.

69. A temporal trend study of HBCD and PBDEs in eggs of herring gulls (*Larus argentatus*), Atlantic puffins (*Fratercula arctica*), and black-legged kittiwakes (*Rissa tridactyla*) in northern Norway (Helgason et al. 2009) showed that levels of α-HBCD increased in all species from 1983-2003. The mean levels increased from 16-108 ng/g lw in Herring gulls, 12-58 ng/g lw in Atlantic puffins and 30-142 ng/g lw in black-legged kittiwakes at Røst and Hornøya (Northern Norway). The same result was achieved in a similar study (KLIF 2005) in eggs from the same bird species sampled in 1983, 1993, and 2003 in northern Norway. The median levels increased from 7.9-110 ng/g lw in Herring gulls, 8.4-72.3 ng/g lw in Atlantic puffins and 15.9 – 161.3 ng/g lw in Black-legged kittiwakes at Røst and Hornøya. The increase in median levels was 25.3-81.4 ng/g lw in Glaucous gulls at Bjørnøya (Svalbard) (KLIF 2005). Esslinger et al. investigated the temporal trends and enantiomeric patterns of HBCD in stored pooled egg samples of herring gulls *(Larus argentatus)* collected between 1988 and 2008 from three geographically isolated colonies near the German coast (Dioxin 2010a). The temporal trend at Trischen island showed no trend or unclear trend, at Mellum island the trend was increasing until the beginning of 1990, where the levels in the eggs was leveling off, followed by a steep increase until the beginning of 2000, where the levels fluctuated and showed a decrease the last four years. The same temporal pattern was shown at the Heuwiese island, but here the data was limited to the last ten years. However, it is not possible to do a regression analysis since the analysis was based on single and pooled egg samples. No standard deviation was given and the significance of the variations in the levels was not possible to determine.

70. Recent monitoring data from for fish (bream and sole) that show concentration changes of HBCD in fish tissue is only based on data from three years (2007-2009) so any conclusion on trends can only be preliminary. Different trends were found, two increasing, two decreasing and one with no clear trend (Fraunhofer, 2010).

71. Stapleton et al. (2006) have shown an exponential increase in HBCD concentrations with a doubling time of approximately two years in California sea lions (*Zalophus californianus)* stranded between 1993 and 2003. Law et al (2008a,b) have continued their analysis of HBCD in UK harbor porpoises, which now includes 223 animals spread over 13 years (1994-2006). The within year variation is 4-6 orders of magnitude, which makes any conclusions uncertain. However, the mean values indicate increasing concentrations from the mid-1990's (30-70 µg/kg lipid weight) with a steep and statistically significant increase between 2000 and 2001 resulting in a mean concentration of 5,450 µg/kg in 2003. The steep increase was followed by a corresponding steep decrease between 2003 and 2004, resulting in a concentration of 817 µg/kg in 2006. Concentrations of PBDEs and HBCDs in marine mammals from Japanese and Chinese coastal waters have drastically increased during the last 30 years (Tanabe et al. 2008). In the samples from Japan, temporal changes in BFR levels were associated with trends in production/use of the commercial formulations. Since the withdrawal of some PBDE products from the Japanese market in the 1990s, concentrations of HBCDs appear to exceed those of PBDEs, reflecting increasing usage of HBCDs.

72. The concentrations in the European environment are often higher than those measured in biota in North America and the Asia-Pacific region (Hoh and Hites 2005; Tomy et al. 2004; Peck et al. 2008; Stapleton et al. 2006; Janák et al. 2005; Morris et al. 2004; Zegers et al. 2005; Yu et al. 2008; Kajiwara et al. 2006; Isobe et al. 2008; see reviews by Tanabe et al. 2008 and Law et al. 2008b). The levels in the Asia-Pacific region and North America are found to be in the lower range of the levels detected in sea mammals in Europe (Covaci et al. 2006). The results likely reflect the substantially higher market demand for HBCD in Europe relative to other regions of the world (Law et al. 2008b;

Tanabe et al. 2008). However, according to the review by Tanabe et al. (2008) HBCDs are also widespread in the Asia-Pacific region. The review concluded that HBCDs were detected in all the matrices examined - mussels, fish, marine mammals, human breast milk, house and office dust. The highest concentrations of BFRs were observed in the samples from Korea, South China, and Japan. A similar pattern emerges from other Asian studies. Assessing HBCD levels in skipjack tuna samples collected from thirteen offshore locations in the Asia-Pacific region during 1997–2001 (Ueno et al. 2006) found HBCD levels that were higher in mid-latitude areas of the Far East, as relatively high concentrations were detected in samples collected around Japan, the East China Sea and the North Pacific. In two other field studies the spatial distribution of HBCDs in the Asia-Pacific region were assessed by analyzing fat tissue of marine mammals from Japan and Hong Kong (Kajiwara et al. 2006; Isobe et al. 2008). The detected HBCD levels were higher in cetaceans from Japan than in cetaceans from Hong Kong, probably due to intensive usage in Japan in recent years. HBCD levels in mammals from Hong Kong and Japan ranged from 21 to 380 ng/g lipid wt and from 330 to 940 ng/g lipid wt, respectively. For comparison, measured levels in blubber sampled from white-sided dolphins at the eastern coast of US between 1993-2004 were in the range of 19-380 ng/g lw (14-280 ng/g ww) (Peck et al. 2008). Tanabe et al. (2008) concluded that the high levels of BFRs, including HBCD, in marine mammals found in coastal waters of Japan and south China could be due to the presence of a number of electronics manufacturing industries in this region.

73. According to Covaci et al. (2006) there is a general trend to higher environmental HBCD concentrations (air, sediment, and fish) near point sources (plants producing or processing HBCDs) and in urban areas, than in locations with no obvious sources of HBCDs. Concentrations of HBCDs are often elevated by at least one order of magnitude in the vicinity of plants either producing or using HBCDs. Several hot spots have been identified in Europe: the rivers Viskan (Sweden), Tees and Skerne (U.K.), Cinca (Spain), and the Western Scheldt estuary (Netherlands) (Covaci et al. 2006). All of these sites were related to present or former production facilities for HBCDs or HBCD retarded materials. Higher HBCD concentrations are also frequently found near urban centers and industrial sites (Janak et al. 2005; Remberger et al. 2005; Petersen et al. 2005; Minh et al. 2007; Morris et al. 2004; Sellström et al. 1998; Eljarrat et al. 2009; Hoh and Hites 2005). In a study by Remberger et al. (2004) the depositional fluxes measured in the urban region of Sweden were between 5.5 and 366 ng/m^2. Fluxes measured in more remote locations of Sweden and Finland were generally smaller and ranged from 0.02 to 13 ng/m^2. Air concentrations at sites near potential point sources ranged from 0.013 to 1,070 ng/m^3 while those at the urban stations were 0.076 to 0.61 ng/m^3. In the study by Remberger et al (2004) the highest air concentration (1,070 ng/m^3), was recorded close to the exhaust for the air ventilation system of the XPS manufacturing facility. In particular, soil samples collected near HBCD-processing factories are found to have high levels of HBCD. Remberger et al. (2004) and Petersen et al. (2005) measured HBCDs, ranging between 111 and 23,200 ng/g dw, in soil samples collected outside an XPS producing plant. Highest concentrations (1,100 and 680 ng/g lw α-isomer in sole, Solea solea, muscle and liver, respectively) in the study by Janak et al (2005) were measured nearest to a HBCD production plant at Terneuzen (ICL-IP Terneuzen formally known as, Broomchemie 7,500 tons HBCD/year). The levels fell with increasing distance to the point source.

74. The findings of Heeb et al. (2008) are also important to the issue of bioavailability. Heeb et al. (2008) documented conversion of the γ-isomer into α-HBCD at temperatures exceeding 100°C. In a wider context, this finding suggests that finished products subjected to high temperatures during processing, and the releases during the service life of HBCD containing articles, as well as the releases from the industrial use of HBCD in textiles and polystyrene, may carry a higher proportion of the α-isomer than is present in the original formulation. This in turn may increase the potential for organism exposure to the α-isomer, and may in part explain the predominance of α-HBCD in biota. Compared to α-HBCD, the γ- and β- isomers are commonly present at lower levels or below detection limits (European Commission, 2008).

75. In the study by KLIF (2008) the dominating isomer at the two local sites monitored in the Norwegian Arctic was γ-HBCD (71 - 72%). In the precipitation samples at the Great Lakes Basin in the study by Bakkus et al (2005) the dominating diastereoisomer was α-HBCD; the average percent distribution was 77%, 15% and 8% for α-, β- and γ-HBCD respectively. In the study by Yu et al. (2008), air samples were collected from four sites in the city of Guangzhou, a typical fast developing metropolitan city of South China, The analysis indicated that α-HBCD (59–68%) was the dominant isomer and β-HBCD was a minor isomer in all air samples. For gas-particle distribution on each diastereoisomers the percentage of β-HBCD in gas phase was higher than those in particle phase whereas the percentage of α and γ-HBCD in gas phase was lower than those in particle phase at all sites. This might be caused by slightly different physicochemical properties of three diasteroeoisomers. The stereoisomeric profile of HBCDs in most sediments have been found to be similar to that of commercial HBCD formulations, with γ-HBCD being the most abundant stereoisomer (Morris et al 2004). However, near production facilities using HBCD (Morris et al. 2004, Schlabach et al 2004a, b), the contribution of α-HBCD was higher than in the technical mixture.

76. Generally, the isomeric pattern observed in biota varies with species. This may reflect species differences in the external exposure situation, uptake, metabolism or depuration of the three isomers. Whilst several studies show that both α-HBCD and γ-HBCD have a tendency to bioaccumulate in organisms, α-HBCD reportedly has a higher potential to biomagnify than γ-HBCD (see section 2.2.2). The α-isomer of HBCD therefore dominates especially at higher trophic levels in the food webs. Selective biotransformation and bioisomerization, whereby the other stereoisomers are

preferentially converted to α-HBCD, contributes to this pattern (Law et al. 2006d; Janák et al. 2005; Zegers et al. 2005; see European Commission 2008 for overview). Another mechanism of importance can be a selective uptake of α-HBCD and/or differences in the stereoisomeric and enantiomeric profile of prey organisms. In peregrine falcons and white-tailed sea eagle only α-HBCD was detected, and in terns and guillemots it was the predominant diastereoisomer (Janák et al. 2008). This is in agreement with other studies of HBCD diastereoisomers in birds (Leonards et al. 2004; Morris et al. 2004; KLIF 2005). At the bottom of the food chain a different exposure pattern emerges. For example, in a study by Tomy et al. (2008), the main isomer in bottom dwelling filter feeders and zooplankton was found to be γ-HBCD. As illustrated by Roosens et al. (2009), such environmental changes are reflected in the human tissue samples, but may in addition be influenced by *in vivo* bioisomerization of β- and γ-HBCD to α–HBCD and a more rapid biotransformation of β- and γ-HBCD than α–HBCD (Zegers et al. 2005, Law et al. 2006c). *In vivo* studies with rats suggest that HBCD is also debrominated to PBCDe and TBCDe. In total, five different species of hydroxylated HBCD metabolites have been found by LCQ and GC-MS; monohydroxy- and dihydroxy-HBCD, monohydroxy- and dihydroxy-PBCDe and monohydroxy-TBCDe (Brandsma et al. 2009).

2.3.2 Human exposure

77. Humans, like other organisms, are exposed to HBCD via multiple sources: food, dust, air, textiles, polystyrene products and electronic equipment (for overview see NCM 2008; European Commission, 2008; AMAP 2009; Covaci et al. 2006; Harrad et al. 2010a,b). Human exposure to HBCD may be either dermal or oral, and may also result from inhalation of vapor and particles (European Commission, 2008). In the work environment direct dermal exposure and inhalation of fine HBCD dust or particles are particular concerns. In a study by Thomsen et al. (2007) industrial workers at plants producing EPS with HBCD were found to have elevated HBCD levels in their blood (i.e. 6-856 ng/g lw serum). Serum/blood levels in non-occupationally exposed individuals are typically much lower (i.e. 0.005-6.9 ng/ g lw) though the data indicates potentially significant sources of exposure (see KEMI 2008 for overview).

78. In non-occupationally exposed individuals indirect exposure via the environment or products, be it oral, dermal or by inhalation, is the main concern. In a study by Stapleton et al. (2008) HBCD levels in dust samples from indoor environments ranged from <4.5 ng/g to a maximum of 130,200 ng/g with a median value of 230 ng/g. A study by Abdallah et al (2009) found HBCD in household air (median concentration 180 pg m^{-3}), household dust (median concentration 1,300 ng/g), offices (median concentration 760 ng/g), and cars (median concentration 13,000 ng/g). Reported dietary exposure levels in humans vary globally and regionally (Shi et al. 2009, Roosens et al. 2009). Surveys in Europe and the US reveal dietary exposure levels for HBCD in the range of <0.01-5 ng/g w/w (see Roosens et al. 2009 for overview). Fatty foods of animal origin such as meat and fish are likely a major source of dietary human exposure, and the exposure situation closely depends on the consumption of those products in the population (e.g. Shi et al. 2009; Remberger et al 2004, Lind et al 2002, Driffield et al 2008). Among all dietary samples, the highest HBCD concentrations (up to 9.4 ng/g w/w) are reported for fish (Knutsen et al. 2008, Remberger et al. 2004, Allchin and Morris 2003). Accordingly in Norway, where fish is an important part of the diet, intake of fish has been found to closely correlate with serum HBCD levels (Thomsen et al. 2008; Knutsen et al. 2008). Eggs are another potential source of human exposure (Hiebl et al. 2007, Covaci et al. 2009). A survey of home-grown chicken eggs sampled near contaminated sites in developing countries showed eggs to contain <3.0-160 ng/g lipid weight (IPEN, 2005). HBCD levels in eggs were high in Mexico (91 ng/g lipid), Uruguay (89 ng/g lipid), Slovakia (89 ng/g lipid), relatively high in Turkey (43 ng/g lipid), and extremely high in Kenya (160 ng/g lipid). That vegetables may contain HBCD at similar concentrations as have been reported for meat and fish, was shown by Driffield et al. (2008), who assessed 19 different food groups representing the UK diet for 2004 for brominated flame retardants. The presence of HBCD in vegetables and vegetable oils and fats may arise from the presence of this substance in sewage sludge and the subsequent use of sewage sludge as a food crop fertilizer (Kupper et al. 2008, Brändli et al. 2007). Stereoisomeric patterns in food samples suggest both global and regional variation, as well as stereoisomeric differences depending on food type (Roosens et al. 2009; Shi et al. 2009).

79. Although fish and meat are the major dietary sources in Europe, USA and China (Covaci et al. 2006; Schecter et al. 2008; Thomsen et al. 2008; Shi et al. 2009), two British studies assessing HBCD exposure in humans also highlight indoor air, and in particular dust, as important sources of exposure in both adults and toddlers (Abdallah et al. 2008a and b). For a toddler of 10 kg who ingests an estimated 200 mg dust/ day (HBCD contamination at the 95^{th} percentile) the intake via dust may exceed by 10 times the levels received via diet alone (Abdallah et al. 2008a). In the study of Roosens et al. (2009), daily exposure from food and dust was found to be approximately similar in magnitude, and HBCD concentrations in serum only correlated significantly with estimates of exposure via dust. As postulated by the authors, exposure to dust may be an important exposure route because exposure remains more constant over time compared to exposure from food which depends on the more periodic intake of contaminated food items (Roosens et al. 2009). However, as fish and meat are common food commodities in many regions, diet could cause potentially higher exposures than dust, depending on consumption rates, dietary patterns and geographic distribution.

80. As a result of continuous exposure in homes, offices and cars, HBCD is found in human adipose tissue (Pulkrabová et al. 2009; Johnson-Restrepo et al. 2008; Antignac et al. 2008; Abdallah and Harrad 2009) and blood (Weiss et al. 2004; Weiss et al. 2006; Lopez et al. 2004; Brandsma et al. 2009; Thomsen et al. 2007; Meijer et al. 2008;

Roosens et al. 2009). Exposure occurs at an early stage of development as HBCD is transferred across the human placenta to the fetus (Mejier et al. 2008), and is also transferred from mother to child via breast milk. HBCD has been detected in breast milk in Europe (Covaci et al. 2006; Lignell et al. 2009; Eljarrat et al. 2009, Colles et al. 2008; Polder et al. 2008a; Polder et al. 2008b; Fängström et al. 2008; Antignac et al. 2008), in Asia (Kakimoto et al. 2008; Shi et al. 2009; Malarvannan et al. 2009; Tue et al. 2010), in Russia (Polder et al. 2008b), Mexico (Lopez et al. 2004) and in USA (Schecter et al. 2008). Hence exposure to HBCD occurs at critical stages of human development, both during pregnancy and postnatally via breast milk. Reported concentrations of HBCD in breast milk range from below detection limit to 188 ng HBCD/g lw (for overview see European Commission 2008). According to EBFRIP 2009b the typical range of total HBCD concentrations in human breast milk in populations inhabiting industrialized areas appears to be <1 to 5 ng/g lw. Geographically, the highest HBCD levels have been found in mothers' milk from two areas in Northern Spain (Catalonia and Galicia). The reported HBCD levels from these studies ranged from 3-188 and 8 -188 ng/g lw, with median values of 27 and 26 ng/g lw, respectively (Eljarrat et al. 2009; Guerra et al. 2008a).

81. As documented by a Japanese study (Kakimoto et al. 2008), HBCD levels in human milk appear to mirror the market consumption of HBCD. In mothers' milk from Japanese women (age 25–29) HBCD levels were below the detection limit in all samples collected during the 10-year period from 1973-1983, but then increased from 1988 onwards. In the period 1988-2006, α-HBCD was detected in all 11 pooled milk samples with levels ranging from 0.4-1.9 ng/g lw. Mean total HBCD concentrations over the period 2000 – 2006 ranged from 1-4 ng/g lw. The levels reported from this Japanese study are higher than values reported for women from Northern Norway where HBCD was detected in only 1/10 samples, at a concentration of 0.13 ng/g lw (Polder et al. 2008a). In a study from Stockholm, Sweden, temporal trends show an increase in HBCD levels in milk up to 2002 after which a levelling occurs.

82. The extent of oral absorption of HBCD in humans is largely unknown (ECHA 2008a). Estimations suggest that the uptake of HBCD via this exposure route ranges from 50-100% (ECHA 2008a, European Commission 2008). According to calculations made in the EU risk assessment (European Commission 2008) intake of HBCD via breast milk is 1.5 ng/ kg bw/ day for 0-3 month olds and 5.6 ng/ kg bw/ day in 3-12 month old babies. However, with the levels found in mothers' milk from some locations in northern Spain (A Coruña), Eljarrat et al. 2008 calculated the intake to be 175 ng/ kg bw/day for 1 month olds. This is 12 times higher than the estimated daily intake (EDI) for 0-3 month old infants as determined in the EU risk assessment (European Commission 2008) and 25-1,458 times higher than the EDI for adults in Sweden, Netherlands, United Kingdom and Norway (KEMI, 2009; Eljarrat et al. 2009, Roosens et al. 2010). A Flemish dietary study suggests that the age group between 3 and 6 years seems to be the highest exposed with an EDI for ΣHBCD of 7 ng/kg bw day. Newborns and adults are less exposed with EDI's of 3 and 1 ng/kg bw day, respectively (Roosens et al. 2010). In all instances, however, children appear to be more exposed than adults.

83. Data from China, which are based on α-HBCD levels in the range of <LOD to 2.78 ng/ g as measured in mothers' milk from 1,237 donors from 12 different provinces, suggest an EDI of 5.84 ng / kg bw/ day when assuming a body weight of 7.8 kg and a milk consumption for 6-month-olds as specified by the U.S. Environmental Protection Agency (Exposure Factors Handbook US EPA). This value is approximately 3 to 10 times lower than the calculated EDI for infants in the EU region which were proposed to be 15 and 56 ng/ kg bw/ day for 0-3 month and 3-12 month old infants, respectively (European Commission, 2008). Still, the EDI for infants in China is estimated to be 14 times that of Chinese adults, where an EDI of 0.432 ng/kg bw/day was given for a "reference" man (Shi et al. 2009).

84. Although α-HBCD, followed by γ- and β-HBCD, appears to be the predominant diastereoisomer in all biota, including humans (European Commission 2008), the profiles of α-, β-, and γ-HBCD isomers in human tissues are not consistent and differ somewhat between studies (Weiss et al. 2006, Thomsen et al. 2007, Roosens et al. 2009, Shi et al. 2009, Schecter et al. 2008, Eljarrat et al. 2009, Guerra et al. 2008a). The external exposure situation (time, dose and stereosisomeric pattern), toxicokinetics, biotransformation, and time of sampling may all be important.

2.4 Hazard assessment for endpoints of concern

85. The hazard potential of HBCD has been assessed in several reports (European Commission 2008, ECHA 2008b, US EPA 2008 and EBFRIP 2009b). In the EU, HBCD has been identified as a substance of very high concern based on its persistency, bioaccumulation and toxicity. In the US an initial screening assessment of HBCD concluded that there is a high concern for aquatic organisms from environmental releases, based on the bioaccumulation potential of HBCD, the high acute toxicity for aquatic plants and chronic toxicity for aquatic invertebrates, and also the potential for exposure and presence in remote regions (US EPA 2008).

86. Most toxicological studies with HBCD focus on HBCD mixtures and the available data on stereoisomer specific toxicity is very limited. It is difficult to draw any firm conclusions regarding the risks posed by the different stereoisomers and enantiomers at this point since partly contrasting results have been obtained that may depend on differences in the endpoints and methods used in the different studies (Dingemans et al. 2009, Zhang et al. 2008, Hamers et al. 2006, Palace et al. 2008).

2.4.1 Ecotoxicity to aquatic organisms

87. Ecotoxicity testing of HBCD in aqueous media is complicated by its very low water solubility and high adsorption potential (EBFRIP 2009b, NCM 2008). HBCD has a low acute toxicity to aquatic organisms owing in part to its limited solubility in aqueous media (Wildlife International 1997, Walsh et al. 1987, CEPA 2007 and ACCBFRIP 2001 for overview). Regarding the long-term toxicity of HBCD it was concluded to be very toxic to aquatic organisms in the EU Risk Assessment (European Commission 2008). This conclusion was based on the long-term ecotoxicity test with *Daphnia magna* (28d-NOEC 3.1 µg/l; Wildlife International 1998) and on the growth inhibition test with *Skeletonema costatum* (72h-EC50 52 µg/L; Wildlife International 2005). In both tests calculated NOEC and EC_{50} values were below the water solubility of the technical mixture of HBCD (66 µg/L). Based on the effects in long-term tests with *Lumbriculus variegates*, HBCD is known to cause adverse effects to aquatic sediment organisms at exposure level relevant for the environment (Institute of Hydrobiology 2001).

88. Fish-feeding studies indicate effects on key biological processes. For example an interference of HBCD with the HPT-axis and liver biotransformation enzymes were reported in rainbow trout exposed to individual HBCD diastereoisomers via food for 56 days followed by a depuration period of 112 days when fish were fed a reference diet (Palace et al. 2008). Lipid corrected concentrations of α-, *β*-, *γ*-isomers in the food were 29.14 ± 1.95, 11.84 ± 4.62, and 22.84 ± 2.26 ng/g, respectively (means ±SEM). Liver detoxification processes (P450 CYP1A activity) were inhibited by all HBCD stereoisomers after 7 days of dosing, and also after 56 days of dosing but then only in α- and β- exposed fish. Thyroid follicle epithelial cell heights were significantly greater in *γ*-HBCD exposed fish at day 56 of the uptake phase and in fish from the α- and *γ*-HBCD exposed groups at day 14 of the depuration phase. More recent studies also support that HBCD may interfere with the fish thyroid system (Palace et al. 2010). The link between HBCD induced disturbances in the HPT-axis and the importance of such effects to smoltification in Atlantic salmon has also been examined (Lower and Moore 2007). To assess this, Lower and Moore (2007) exposed juvenile salmon to 11 ng/L of a HBCD mixture for 30 days during the peak smoltification period in freshwater. The fish were then transferred to clean seawater for 20 days. Throughout the HBCD-dosing and saltwater exposures, 5-8 fish were sampled every 7 days and gill and blood tissues were collected. In addition, electro-olfactrograms were recorded in an additional 5 fish every 10 days using urine from salmon from the same stream (considered to be the cue for returning smolts) as an effector. The exposure to HBCD was not observed to affect seawater adaptability, although the peak of thyroxine was shifted and occurred one week earlier in HBCD exposed fish than in controls. A reduction in olfactory function, as evidenced by attenuated olfactory responses during early freshwater transition, was also observed. This latter effect is important as it can affect successful homing, and thereby ultimately also reproductive capacity in adult salmon. In contrast to the above findings, in a third reported study assessing TH effects in European flounders (*Platichtys flesus)*, no effects neither on the liver's biotransformation capacity or TH-levels were reported, even though HBCD accumulated dose-dependently (Kuiper et al. 2007). The fish were in this instance exposed to HBCD in food (µg/g lipid) and sediment (µg/g total organic carbon) in the following combinations; 0+0 (control); 0.3+0.08; 3+0.8; 30+8; 300+80; 3,000+800; and 0+8,000 for 78 days. Lastly, HBCD may also interfere with amphibian metamorphosis, a process that is tightly regulated by TH-hormones. As shown *in vitro*, HBCD at 10, 100 and 1000 nM potentiates T3 induced tadpole tail regression in a concentration dependent manner (Schriks et al. 2006). *In vivo* such effects may result in precocious metamorphosis.

89. Recent studies with fish models suggest that HBCD may also induce oxidative stress and apoptosis. Deng et al. (2009) examined oxidative stress and the apoptosis pathway in four-hour post-fertilization zebrafish (*Danio rerio*) embryos by exposing them to waterborne HBCD at concentrations of 0, 0.05, 0.1, 0.5, and 1.0 mg/ L for 92 hours. Survival was reduced at the three middle doses equivalently, but was elevated at the highest dose (1mg/L). Hatching rate was only affected at the highest dose (1 mg/L) with a 10 % reduction from controls. Malformation rates (including epiboly deformities, yolk sac and pericardial edema, tail and heart malformations, spinal curvatures and improper inflation of the swimbladder) increased dose dependently, and heart rate and body length both also decreased with exposure to HBCD. The levels of reactive oxygen species (ROS) also increased dose dependently in fish exposed to HBCD concentrations above 0.05 mg/L. With regard to apoptosis, HBCD elevated expression of the pro-apoptotic genes p53, Bax, Puma, Apaf-1, and caspase-9 and caspase-3, of which the response of the latter two was verified at the enzyme level. The anti-apoptotic genes Mdm2 and Bcl-2 were both significantly down regulated at the highest HBCD exposure concentration. The overall results demonstrate that waterborne HBCD may produce oxidative stress in zebrafish embryos and lower survival at doses below the water solubility of technical HBCD. The latter effect is important since HBCD has been documented to be maternally transferred to off-spring in oviparous animals, hereunder also fish (Nyholm et al. 2008, Jaspers et al. 2005, Lundsted-Enkel et al. 2006). The potential of HBCD to induce oxidative stress in zebra fish embryos has also been demonstrated by Hu et al. (2009). Here, the oxidative stress, assessed by lipid membrane damage (effects at 0.5, 2.5 and 10 mg /L) was also accompanied by delays in hatching (≤0.5 mg HBCD/ ml), dose-independent changes in superoxide dismutase enzyme activity (higher at 0.1, lower at 2.5 and 10 mg/ L) and an elevation of heat shock proteins (Hsp70) activity (≥0.1 mg/L), the latter effect likely indicating increased protein repair activity. Moreover, in a study with Chinese rare minnows (*Gobiocyprinus rarus*) Zhang et al. (2008) observed a consistent increase in oxidative stress and cellular macromolecules in brain (ROS, carbonylation, TBARS) and erythrocytes (DNA) by waterborne HBCD in the 100-500 µg/l range (42 days). Protective enzymatic-

(superoxide dismutase) and non-enzymatic antioxidant glutathione were compromised even at concentrations of 10 and 1 ug /L respectively. A shorter 28 day exposure resulted in somewhat higher effect concentrations. However, since most test concentrations in these studies are above the water solubility of HBCD, the studies may not be suited to derive dose-response relationships and to set thresholds of toxicity.

90. In fish proposed novel mechanisms of HBCD toxicity are decreased protein metabolism and changes in cytoskeleton dynamics and cellular defense mechanisms (Kling and Förlin 2009). Recently, HBCD was also demonstrated to have a genotoxic potential and to increase cell death in benthic clams (*Macoma balthica*) (Smolarz and Berger 2009).

2.4.2 Toxicity in soil organisms and plants

91. Long-term toxicity of HBCD to earthworms has been assessed by ABC (2003), who measured survival and reproduction in *Eisenia fetida* (clittelate adults) following 56 day exposure to a technical HBCD mixture. HBCD was mixed dry into artificial soil media at concentrations of 78.5 to 5,000 mg/kg dry soil weight. In this study, the NOEC for survival and reproduction were determined to be 4,190 and 128 mg HBCD/kg dry soil respectively. The NOEC for reproduction was later recalculated to 59 mg/kg dry soil weight because the soil that was used contained a higher amount of organic matter than standard soil (NCM 2008).

92. Assessments of the toxicity of HBCD in the terrestrial ecosystems have also been conducted with plants (Wildlife International 2002). This study, yielding a NOEC of > 5,000 mg HBCD/ kg dry soil for the test species corn (*Zea mays*), cucumber (*Cucumis sativa*), onion (*Allium cepa*), ryegrass (*Lollium perenne*), soybean (*Glycine max)* and tomato (*Lycopersicon esculentum*), was determined using a technical HBCD mixture in a seedling emergence test. For effects on soil micro-organisms, the only conducted study reports a NOEC of ≥ 750 mg HBCD/ kg dw using nitrate production as an endpoint for assessment (ECT 2007).

2.4.3 Toxicity in birds

93. A recent study with American kestrels indicates that a technical HBCD mixture administered to birds via the diet is readily taken up and distributed to internal organs (BFR 2009a; SETAC 2009). The main stereoisomer detected in liver, fat and egg was α-HBCD, followed by γ-HBCD and β-HBCD. According to these observations, HBCD is preferentially stored in fat and is transferred to eggs during development. Tissue concentrations were such that fat>>eggs>liver>plasma (SETAC 2009). In this study, administration of 800 ng/g ww of technical HBCD formulation in safflower oil for 21 days followed by a 25 day depuration period, resulted in environmentally relevant internal doses, i.e., ∑ HBCD 934.8 ng/g lw (20 ng/g ww) in liver and 4216.2 ng/g lw (181. 5 ng/g ww) in eggs) with the level of α-HBCD being 164 ng/g ww in egg) (BFR 2009b). In a parallel study, and) assessed reproductive effects of HBCD in American kestrels (*Falco sparverius*) (BFR 2009b; Dioxin 2010b). Also here kestrels were exposed daily to 800 ng/g ww of a technical HBCD mixture in safflower oil from three weeks prior to pairing until two days before hatching. α-HBCD dominated in eggs, where it was found at a concentration of 164 ng/g ww following exposure. While clutch size (number of eggs per female) was greater in the treated kestrels, hatchling numbers were comparable to that of controls (Dioxin 2010b). Treated kestrel nestlings were smaller in weight and had a slower growth rate than controls as determined by overall body weight. Behavioural parameters related to parental care were also affected by HBCD exposure (BFR 2009b; Dioxin 2010c). Collectively, the findings from these studies suggest that there is reason for concern of reproductive and developmental effects in wild birds, because the 800 ng/ g ww dose that elicited effects in the studies by Marteinson and Fernie (see BFR 2009 for overview) are similar to what have previously been observed in wild birds in Central Europe and the Norwegian Arctic, i.e., (cormorant (liver): 138-1,320 ng/g lw and tern (egg): 330-7100 ng/g lw (Morris et al. 2004); glaucous gulls (liver):195-15,027 ng/g lw and great black- backed gulls (liver): 1,881 - 3,699 ng/g lw (KLIF 2007); glaucous gulls (liver): 75.6 ng/g ww (Verreault et al. 2007).

94. The avian developmental and reproductive toxicity of HBCD was also examined in a Japanese study in 2009. In this study the Japanese quails (*Coturnix coturnix japonica*) that were fed diets containing 0, 125, 250, 500 or 1,000 ppm of HBCD (a mixture of isomers: α-, 27%; β-, 30%; γ-, 43%) for 6 weeks. HBCD caused a reduction in hatchability at all concentrations examined. A statistically significant reduction in egg shell thickness was also observed at concentrations above 125 ppm. Decreases in egg weights and egg production rate and an increase in the number of cracked eggs were observed at 500 and 1,000 ppm of HBCD. Adult mortality increased at 1,000 ppm. Additional tests were conducted with concentrations of 0, 5, 15, 45 or 125 ppm of HBCD to confirm no-observed-effect concentration (NOEC) on reproductive performance. Survival of chicks hatched from eggs of HBCD fed hens was significantly reduced at 15 ppm (2.1 mg/kg bw/day) and more. A tendency to reduced hatchability with increasing concentration of HBCD was also observed at 15 ppm and more. The NOEC for reproductive performance of quails was considered to be 5 ppm (0.7 mg/kg bw/day) of HBCD (Ministry of the Environment, Japan, 2009, Japanese submission).

95. When technical HBCD was injected into the air cell of chicken eggs prior to incubation, a lowering of hatching success was observed at concentrations of 100 and 10,000 ng/g (Crump et al. 2010). In the same study, effects on the mRNA expression of CYP2H1, CYP3A37, UGT1A9, deoiodinase 2, liver fatty acid binding protein and insulin-growth factor 1 in chicken were also documented (both doses). The observation that HBCD may interfere with key metabolic

pathways in chickens is further supported by Crump et al. (2008), who assessed effects on mRNA expression in chicken embryonic hepatocytes exposed to 0.01 to 30 µM α-HBCD or a technical mixture of HBCD. α-HBCD, but not technical HBCD, induced Phase I (CYP2H1 and CYP3A37) and Phase II (UGT1A9) metabolizing enzymes in a dose dependent manner. The Phase II metabolic enzyme, UGT1A9 is an avian ortholog to mammalian UGT1A1. These enzymes facilitate the excretion of the thyroid hormone thyroxine (T4) by glucuronidation. Hence, the up-regulation of this enzyme provides a mechanism by which T4 may be depleted in exposed organisms (i.e. through more rapid conjugation and excretion). Crump et al. (2008) also observed that the gene encoding transthyretin (TTR) was down-regulated by technical mixture of HBCD and α-HBCD at concentrations of >1µM. TTR is a serum and cerebrospinal fluid carrier of T4 and retinol. The observed down-regulation of TTR could therefore add to the effect caused by UGT1A9, and lead to even more lowering of T4 in blood/ serum.

2.4.4 Toxicity in terrestrial mammals

96. Available studies demonstrate that HBCD is rapidly absorbed from the rodent gastro-intestinal tract. The highest concentrations are subsequently reached in adipose tissue and muscles, followed by the liver. At long-term exposure, higher concentrations are achieved in females than in males, but the substance is bioaccumulating in both sexes, with the time to reach steady-state concentrations in the order of months. Of the three diastereoisomers constituting HBCD, the α-form is much more accumulating than the others (the relative bioaccumulation factor was in one study 99:11:1 for α-, ß-, and γ-HBCD, respectively). HBCD can be slowly metabolised and eliminated mainly via faeces (European Commission 2008).

97. In mammals HBCD primarily targets biotransformation processes in the liver and also affects the HPT-axis (see NCM 2008; European Commission 2008, ECHA 2008b). Induction of oxidative stress and interference with apoptotic programmes and hormone signalling could possibly be the initial toxic effects of HBCD exposure (e.g. Zhang et al. 2008; Reistad et al. 2006; Dingemans et al. 2009; Fery et al. 2009; Yamada-Okabe 2005; Hamers et al. 2006; Deng et al. 2009; Kling and Förlin 2009; Hu et al. 2009). In rats daily oral HBCD exposure of 3 to 100 mg/ kg bw affects key metabolic pathways including metabolism of lipid, triacylglycerol, androstenedioene, testosterone, estrogen and cholesterol, as well as Phase I and II biotransformation (Canton et al. 2008; van der Ven et al. 2006). In *in vitro* studies HBCD acts as an antagonist of important hormone receptors such as the androgen, thyroid hormone and progesterone receptors (Yamada-Okabe 2005, Hamers et al. 2006). Together with available *in vivo* data (see NCM 2008, European Commission 2008 and ECHA 2008b for overview), these studies indicated HBCD as a likely endocrine disruptor of both the hypothalamus-pituitary-thyroid hormone axis and of sex-steroid regulated processes in mammals. The thyroid hormone effects of HBCD have hitherto received most attention and a series of studies have been undertaken. The results from *in vivo* subchronic tests with rats range from no observed effects to increase in thyroid- and overall body weight, decreased serum T4 and increased serum TSH (WIL 2001, van der Ven et al. 2006, Ema et al. 2008, van der Ven et al. 2009, see KEMI 2009 for overview). Effects have been observed in both sexes but have also been limited to females only. Though the results may appear inconsistent, there is now considerable consensus that HBCD, like other brominated flame retardants, can interfere with the HPT-axis (KEMI, 2009, European Commission 2008, NCM 2008). The mechanism for the thyroid effects is not clear, but a mode of action has been proposed where changes in hepatic metabolism of thyroid hormone (TH) precedes changes in circulating TH levels, the pituitary, increased TSH levels and activation of thyroid with hypothyroidism and with secondary effects on lipoprotein synthesis and cholesterol- and fatty acid homeostasis as possible outcomes (van der Ven et al. 2006, KEMI 2009, Canton et al. 2008).

98. Besides their role as major regulators of body metabolism (Norris, 2007), thyroid hormones are required for normal development of the nervous system, as are retinoids (Forrest et al. 2002, Maden 2007), and disturbances in these systems may therefore result in long term neurotoxic effects in off-spring. For HBCD, a neurotoxic potential has previously been indicated both *in vivo* and *in vitro* with rodent models (Reistad et al. 2006, Mariussen and Fonnum, 2003, Dingemans et al. 2009, Eriksson et al. 2006, Lilienthal et al. 2009). In the *in vivo* study of Eriksson et al. (2006) neonatal direct exposure of pups to a single oral dose of HBCD (0.9 mg/ kg or 13.5 mg/ kg bw on postnatal day 10), induced alterations in spontaneous behavior with initial hypo-reactivity, followed by impaired habituation in adult mice. This study also reported effects on spatial learning and memory as assessed in a Morris water maze test with exposed mice. In contrast, in their two-generation study with rats where exposure of pups occurred indirectly via human breast milk, Ema et al. (2008), only observed transient changes in the performance of F1 males in a water-filled T-maze test at an exposure level of 1,500 ppm and higher and no effects on other parameters (locomotor activity). According to Ema et al. (2008), the discrepancy in their results from the results obtained in previous studies could be explained by differences in exposure regime and/or by differences in species sensitivity. Results from *in vitro* studies suggest that HBCD may be cytotoxic to nerve cells and possibly also interfere with neuronal signalling events such as Ca2+ and neurotransmitter uptake (Reistad et al. 2006, Mariussen and Fonnum 2003, Dingemans et al. 2009).

99. The *in vivo* neurotoxic potential of HBCD has also been studied by Lilienthal et al. 2009. In a one generation reproduction feeding study, they showed that HBCD-induced loss in hearing function was paralleled by changes in dopamine dependent behaviour (Lilienthal et al. 2009). Loss of hearing function was attributed to a cochlear effect of HBCD that resulted in increased thresholds and moderate prolongations of latencies in the lower frequency range from 0.5 to 2 kHz and after clicks. Both observed effects were dose-dependent with lower bounds of bench mark doses

(BMDL) between ≤1 and 10 mg/ kg bw. Saegusa et al. (2009) on the other hand detected weak hypothyroidism with increases in thyroid weight, thyroid follicular cell hypertrophy and serum TSH concentrations as well as a decrease in serum T3 levels in rat off-spring exposed to 10,000 ppm HBCD in a soy-free diet from gestation day 10 to day 20 after delivery. The TH changes were accompanied by a reduced density of CNPase-positive oligodentrocytes, which is indicative of impaired oligodendroglial development. Increased thyroid weights and decreased serum T3 concentrations were also observed in the adult stage from 1,000 ppm. Though the above data suggest that HBCD induced disturbances in TH-signalling is linked to effects on the nervous system in rodents, changes in behaviour and cognition may also be impacted by a decrease in apolar retinoids as observed in female rat livers following HBCD exposure (van der Ven et al. 2006, van der Ven et al. 2009). Moreover, the interferences of HBCD with sex-steroid hormones and their receptors should not be neglected as these hormones also exert non-genomic effects on brain functions such as learning and memory, fine motor control, pain perception and mood (Boulware and Mermelstein 2005, Chakraborti et al. 2007, Meaney et al. 1983, Schantz and Widholm 2001).

100. There are several studies on reproductive effects of HBCD. Saegusa et al (2009) performed a one-generation developmental toxicity study in rats, with maternal dietary exposure to 0, 100, 1,000 or 10,000 ppm HBCD from gestation day 10 until weaning of the offspring. In this study thyroid effects were observed both in dams (thyroid weight increase and follicular cell hypertrophy at 10,000 ppm) and offspring (thyroid weight increase, decreased serum T3 and increased serum TSH at 1,000 and 10,000 ppm). The thyroid effects together with the impaired oligodendroglial development in the brain cortex (statistically significant at the high dose (-24%) supported by a dose-dependent trend in the mid (-12%) and low (-8%) dose groups) and the decreased female body weight (9% in the high dose group) could indicate developmental hypothyroidism. The LOAEL of this study is 1,000 ppm (81-213 mg/kg/day), and the NOAEL 100 ppm (8-21 mg/kg/day). The long continuous exposure study of van der Ven et al. (2009) suggest that male reproductive organs are particularly sensitive to HBCD exposure i.e. a decreased testicular weight was observed at a BMDL of 52 µg/ g bw in F1 males. A weight reduction in other male organs; prostate, the adrenals, heart and brain as well as in F1 males' total weight was also observed. The observed body weight loss makes it impossible to say whether any of these effects on organs' weights are specific or secondary to the general body weight loss. In females the cytochrome P450 19 enzyme activity, based on group averages, showed a correlation to the internal concentration of γ-HBCD (linear correlation coefficient of 0.90). The cytochrome P450 19 enzyme converts androgens to estrogens (Norris 2006), and is essential for differentiation and development of gonads and brains of higher vertebrates, maintenance of reproductive tissues, and sexual behavior (Conley and Hinshelwood, 2001, Simpson et al. 2002). In females the time to vaginal opening was also delayed, but only at the top dose (BMDL 82.2 µg/ g bw at a benchmark critical effect (BMR) of 10%).

101. Like the studies of van der Ven et al. (2009) and Saegusa et al. 2009, Ema et al. (2008) document reproductive and developmental effects (decreased pup viability, fewer primordial follicles), and also changes in organ weights (e.g. liver and thyroid), and thyroid hormone levels. Several effects were trans-generational and affected both F0 parents and F1 and F2 parents and offspring. From the point of view of reproductive toxicology, the general decrease in viability in F2 pups on post-natal days 4 and 21 at 1,500 and 15,000 ppm and the decrease in primordial follicles at 1,500 and 15,000 ppm HBCD exposure in F1 females were the most severe effects. A reduced number of primordial follicles suggests that reproductive potential of the female may be reduced, and is generally regarded as sensitive biomarkers for adverse reproductive effects (Parker et al. 2006). It should be noted however that the highest dose used by Ema et al. (2008) may be considered to be very high. However, dosing was in this study done by mixing HBCD particles into an appropriate amount of powdered basal diet for each dietary concentration. The absorption kinetics of HBCD likely depends on both the particle size and amount of particles administered, and is expected to be lower than for dissolved HBCD. The actual tissue doses from this study are therefore presumably lower than the original dose would suggest, as may also be assumed from the findings of similar studies such as that of WIL 2001 who only observed reversible effects at doses up to 1,000 mg/kg bw/day in their 90-day oral exposure study.

2.4.5 Human toxicity

102. The EU risk assessment of HBCD completed in 2008 provides the most comprehensive assessment of toxic effects and risks of HBCD exposure to human health and welfare (European Commission 2008). This assessment concludes that HBCD may cause reproductive toxicity and long term toxicity, whereas there is no concern for acute toxicity, irritation, sensitization, mutagenicity and carcinogenicity. It moreover states that HBCD poses no risk to adult consumers or to workers when standard industrial hygiene measures are applied (current EU practice). These conclusions are founded on an extensive list of toxicity studies and on a comprehensive selection of exposure and risk assessments that consider not only workers and adult consumers, but also indirect exposure of humans via the environment (European Commission 2008). The EU risk assessment documents that currently in the general (human) population, HBCD tissue concentrations are much below those reported to induce adverse effects in other mammals (European Commission 2008).

103. In the EU, the proposal to classify and label HBCD for reproductive and developmental toxicity is currently under discussion. The substance is suspected of damaging fertility and the unborn child (CLP: Repr 2; H361fd), and the substance may cause harm to breast-fed children (CLP: Lact. Effects H362) (KEMI 2009).

2.4.6 Comparison of exposure levels and effect data

Near point sources and source regions

104. A comparison of measured concentrations in the tissues and organs of species of prey (fish) with the predicted no-effect concentration (PNEC) for secondary poisoning reveals that the concentrations in fish exceed the PNEC of 5 mg HBCD/ kg food for predators (mammals and birds) both near local point-sources and source regions. In the vicinity of point sources such as the river Skerne in the UK and the river Scheldt basin in Belgium, HBCD concentrations above 5 mg/kg wwt have been measured in fish (eel and brown trout). Also in marine mammals, concentrations higher than the PNEC have been measured, the highest being 6.4 mg/kg wwt whole body weight in harbour porpoise from the UK (European Commission 2008). The potential risk of HBCD to wild life near local point-sources and source regions is further supported by the body/tissue residue based risk assessment made by EBFRIP (2009b). Notably the upper third of the monitoring data used in the assessment exceeds the specific-toxicity residue-based PNEC for freshwater fish and for mammals. The upper limit of the monitoring data for birds also enters this range.

105. Further indications for concern come from recent preliminary data obtained with captive American kestrels which suggest a risk for reproductive and developmental effects in source regions. The findings from Marteinson et al. (Dioxin 20~~09~~10c) and Fernie et al. (Dioxin 2010~~c~~b) suggest that there is reason for concern of reproductive and developmental effects in wild birds, not only because of the seasonal changes in fat stores experienced by wild birds and the observed transfer to eggs, but also because the 800 ng/g ww dose and the subsequent *in ovo* HBCD concentrations that elicited effects in these studies are similar to what has previously been observed in wild birds in Central Europe, i.e., cormorant liver, 138-1,320 ng/g lw; and, tern eggs, 330-7100 ng/g lw (Morris et al. 2004). In the study, administration of 800 ng/g ww of technical HBCD formulation in safflower oil for 21 days followed by a 25 day depuration period, resulted in environmentally relevant internal doses, i.e., ∑ HBCD, 934.8 ng/g lw (20 ng/g ww) in liver; and, 4216.2 ng/g lw (181. 5 ng/g ww) in eggs (with the level of α-HBCD being 164 ng/g ww in eggs) (BFR 2009b; SETAC 2009).

Remote regions

106. HBCD has been detected in many Arctic species (invertebrates, birds, fish, terrestrial and marine mammals). Levels in Polar cod from Svalbard (Arctic Norway) have been reported at 1.38-2.87 ng/g lipid weight (see levels and effects tables in UNEP/POPS/POPRC.6/INF/25). The findings of HBCD in fish in remote regions suggest a potential for endocrine effects considering the laboratory studies done by Lower and More (2007), Palace et al. (2008 and 2010) showing effect on the thyroid axis for salmoid fish. Endocrine disruptor effects may arise from low dose exposure and are highly dependent on the timing of exposure (WHO and IPCS, 2002). The study on American kestrels (BFR 2009b; Dioxin 2010c) also suggests a risk for reproductive and developmental effects in wild birds in remote regions, where the internal doses (164 ng/g ww of α-HBCD) that elicited effects in the studies by Marteinson and Fernie (BFR 2009b) is exceeded by internal doses observed in wild birds in the Norwegian Arctic, i.e. glaucous gulls (liver), 195-15,027 ng/g lw; and, great black- backed gulls (liver), 1,881 - 3,699 ng/g lw (KLIF 2007); glaucous gulls (liver): 75.6 ng/g ww (Verreault et al. 2007). Muir et al. (2004) detected ΣHBCD concentrations in the blubber of beluga whales (*Delphinapterus leucas*) in the Canadian Arctic in 2001, a species protected by the Convention on migratory species. The concentrations were in the range of 9.8-18 ng/g lw. Muir et al. (2006) detected levels of HBCD in adipose tissue of polar bears (*Ursus maritimus*) in several populations in the Arctic region in 2002. The highest levels were detected in the female bears from the Svalbard area (109 ng/g lw Effects on polar bears and other marine mammals were not investigated in these studies.

Human health

107. Regarding the risk associated with human exposure to HBCD, it is important to note that the environmental background levels of HBCD have increased over the last decades (Law et al. 2008b, Law et al. 2006d), and that HBCD is found in most human tissues, including serum and blood of pregnant women as well as in mothers' milk (e.g. European Commission 2008; NCM 2008; ECHA 2008b). The increasing environmental levels are also mirrored in mothers' milk (Fängstrøm et al. 2008; Kakimoto et al. 2008) and in some instances the reported levels in human milk have been quite high (Eljarrat et al. 2009; Guerra et al. 2008). As demonstrated by its presence in cord serum and mothers' milk, HBCD is transferred from mothers to their children (Meijer et al. 2008; European Commission 2008). Young children may additionally ingest more HBCD via their environment than adults (Abdallah et al. 2008b) and generally have a higher intake of HBCD than adults (Roosens et al. 2010). Prenatal exposure to HBCD may lead to subtle behavioural changes in rodents, particularly motor activity and cognition are affected (Eriksson et al. 2006). No negative effects of this sort have been confirmed in humans (Roze et al. 2009). Early phases of human development are tightly controlled by hormones and intracellular signalling processes such as apoptosis, of which the latter is necessary for normal embryonic- and tissue differentiation (Oppenheim, 1991; Davies 2003; Barres et al. 1992). Thus, the developmental- and neurotoxic potential of HBCD observed in animal studies give cause for concern, particularly for unborn babies and young children.

3 Synthesis of information

108. HBCD is persistent in the environment and has a strong potential to bioaccumulate and biomagnify in food chains. α-HBCD appears to be the more persistent of the isomers of HBCD and to biomagnify more than β-HBCD and γ-HBCD. HBCD is widespread in the global environment and biota; elevated levels are found in top predators and other threatened species in the Arctic. Releases of HBCD to the environment are increasing in all regions investigated. The increasing standing masses of construction materials are potentially long-term sources of HBCD to the environment, as well as representing larger releases when demolished or renovated in the future. Releases during recycling of construction materials and electronic appliances can be of importance and are likely to increase in the future. A general trend seems to be that α-HBCD dominates in the upper trophic levels while the main isomer in the lower levels appears to be γ-HBCD. In human tissue α-HBCD seems to predominate in the general population. Most toxicological studies with HBCD focus on HBCD mixtures and the available data on stereoisomer specific toxicity is very limited.

109. HBCD is considered very toxic to aquatic organisms. There is a risk of adverse effects in marine mammals and fish in the vicinity of point sources and in regions with elevated background levels. The measured concentration levels in biota exceed the PNEC for secondary effects of 5 mg/kg wwt in the EU risk assessment of HBCD (European Commission 2008). Levels in birds from European regions with elevated back ground levels or near local point sources are concluded to lie near the threshold levels for adverse effects. In avian species, preliminary data from recent studies report effects such as reduced eggshell thickness, growth and survival. Further indications for concern come from recent preliminary data obtained with captive American kestrels which suggest a risk for reproductive and developmental effects also in wild birds in remote regions.

110. Both older and recent available literature suggest that HBCD can induce effects in mammals and that both chronic and subchronic, high and low dose exposure to HBCD may have wide ranging and potentially severe effects, particularly to the neuroendocrine system and to offspring during early phases of development. HBCD has a potential to interfere with the hypothalamic-pituitary-thyroid (HPT) axis and cause reproductive and developmental effects. Many effects were trans-generational and affected both parents and offspring. HBCD is maternally transferred to offspring, both in humans and in wildlife. Significant levels of HBCD in human milk and exposure through food has been reported near local sources. In humans the main risks of HBCD exposure are possible neuroendocrine and developmental disturbances from exposure during the early developmental phases of the child. Within the EU, a proposal to classify HBCD for reproductive and developmental toxicity is under discussion.

111. In addition to the findings in the *in vivo* animal studies, there are a large number of recent *in vitro* studies that document how HBCD upon adsorption may act on, and possibly interfere with biological processes such as cell homeostasis, protein repair, metabolism, intracellular signalling and neuroendocrine processes. Such studies add to the understanding that exposure to HBCD has various effects on human health and the environment, and should also be regarded when considering the toxicity of HBCD.

Table 5. POP characteristics of HBCD

Criterion	Meets the criterion (Yes/No)	Remark
Persistence	Yes	Dated sediment cores indicate very slow degradation rates of HBCD. HBCD is found to be widespread in the global environment, with high levels in Arctic top predators. Temporally increasing concentrations found in biota support the picture of HBCD as a persistent substance. The half-life of HBCD in water exceeds 60 days.
Bio-accumulation	Yes	Found in elevated concentrations in top predators. Log K_{ow} is estimated to 5.62. Fish studies document a BCF of 18,100 (Wildlife International 2000, Veith et al. 1979) (European Commission 2008). BMFs > 1 in aquatic ecosystems (Tomy et al 2004a,b, 2009, Sørmo et al. 2006)
Potential for Long-Range Environmental Transport	Yes	HBCD is found in the Arctic air and is widespread in the Arctic environment. Modelling data show an estimated atmospheric half-life of two to three days.

Criterion	Meets the criterion (Yes/No)	Remark
Adverse effects	Yes	Highly toxic for aquatic species with a 72h EC_{50} of 52 µg/l for *Skeletonema costatum* and a NOEC of 3.1 µg/l for *Daphnia magna*. HBCD exerts reproductive, developmental and neurotoxic effects in mammals and birds with a NOEC/NOAEL in the order of 1 mg/kg/day. *In vivo* data include: • Decreased pup survival and fewer primordial follicles in rats at 100 mg/kg/day, NOAEL 10 mg/kg/day (Ema et al. 2008). • Decreased pup weight, decreased testis and prostrate weights, impaired hearing, and reduction in female bone mineral density in rat offspring at 30-100 mg/kg/day (van der Ven et al. 2009, Lillienthal et al. 2009). • TH imbalance and impaired oligodendroglial development in the brain cortex of rat offspring at 1,000 ppm (81-213 mg/kg/day), NOAEL 8-21 mg/kg/day (Saegusa et al. 2009). • Behavioural effects in mice exposed to 13.5 mg/kg/day at day 10, NOAEL 0.9 mg/kg/day (Eriksson et al. 2006). • Bird egg/chick survival was decreased in quails exposed via the feed to 15 ppm HBCD (2.1 mg/kg/day), NOEC 5 ppm (0.7 mg/kg/day) (Ministry of the Environment, Japan, 2009). • Differences in courtship behaviour, earlier egg-laying, and a slower growth rate were observed in American kestrels exposed daily to 800 ng/g HBCD, internal dose of 164 ng/g ww α-HBCD (Dioxin 2010b and Dioxin 2010c).

4 Concluding statement

112. HBCD is a synthetic substance with no known natural occurrence that continues to be used in many countries including in imported articles and products. Releases of HBCD to the environment are increasing in all regions investigated, i.e., Europe and in Asia (Japan). HBCD is persistent in the environment and bioaccumulates and biomagnifies in fish, birds and mammals. A number of measured levels in biota, including higher trophic levels such as birds and mammals, in source and remote regions are of significant concern for human health and the environment.Therefore it is concluded that HBCD is likely, as a result of its long-range environmental transport, to lead to significant adverse human health and environmental effects, such that global action is warranted.

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