# Proposal for soil remediation values for 2,2',4,4',5-pentabromodiphenyl ether (BDE-99)

Wouter Gebbink, Mirja van Holderbeke, Kaat Touchant, Yentl Pareja Rodriguez, Anthony Purece, Eef De Clercq, Ingeborg Joris

Study accomplished under the authority of OVAM
Reference: 2025/EI/R/3456
September 2025

# Proposal for soil remediation values for

# 2,2',4,4',5-Pentabromodiphenyl ether (BDE-99)

**VITO**
Boeretang 200
2400 MOL
Belgium
VAT No: BE0244.195.916
vito@vito.be – www.vito.be
IBAN BE34 3751 1173 5490 BBRUBEBB

**Kaat Touchant**
Project Manager
+32 14336784 / kaatje.touchant@vito.be

**Wouter Gebbink**
Researcher
+31 14336903 / wouter.gebbink@vito.be

# AUTORS

Wouter Gebbink, VITO
Mirja van Holderbeke, VITO
Kaat Touchant, VITO
Yentl Pareja Rodriguez, VITO
Anthony Purece, VITO
Eef De Clercq, VITO
Ingeborg Joris, VITO

Distribution: limited I Ref.: 2025/EI/R/3456

# DISTRIBUTION LIST

Griet Van Gestel, OVAM
Laetitia Six, OVAM

# SUMMARY

The present report covers the proposed soil remediation values (SRV) for 2,2',4,4',5-Pentabromodiphenyl ether (BDE-99). The SRV were estimated following the guidelines stated by Cornelis and Touchant (2016). The estimation was performed using the S-Risk model (v 3.4.4) with the adjustment that BCF values were based on dry weight concentrations in the soil and not on porewater concentrations.

*Table 1: Proposed Soil Remediation Values (mg/kg dw) and the target value for BDE-99. The proposed values are highlighted in bold. The SRVs are reported based on two significant figures.*

| Scanenario | II | III | IV | V |
|---|---|---|---|---|
| Vlarebo | - | - | - | - |
| Proposed SRV based on human health toxicity | **0,0040** | **0,038** | 51 | **420** |
| Proposed values based on ecotoxicity | 0,38 | 0,38 | **0,38** | |
| POPs Regulation | | | | 580 |
| Background value (limit of detection) | 0,00055 | 0,00055 | 0,00055 | 0,00055 |

The SRV for groundwater is based on a human health toxicity evaluation and matches the drinking water standard (Cornelis & Touchant, 2016b). The proposed SRV for groundwater is 0,6 µg/L, while the background value for groundwater is based on the limit of detection and is 0,01 µg/L.

The proposed target value for soil is 0,0032 mg/kg dm which equals 80% of the SRV Type II. The proposed SRV value for the use of excavated soil for building sites is determined at 0,54 mg/kg dm.

.

# TABLE OF CONTENTS

# LIST OF FIGURES

# LIST OF TABLES

# LIST OF GRAPHS

**No table of figures entries found.**

Distribution: limited X Ref.: 2025/EI/R/3456

# LIST OF ACRONYMS

| | |
|---|---|
| ABSd | dermal absorption |
| AF | Assessment factor |
| atm | Atmosphere |
| BCF | Bioconcentration factor |
| BDE | Brominated diphenyl ether |
| BDE-47 | 2,2',4,4'-Tetrabromodiphenyl ether |
| BDE-99 | 2,2',4,4',5-Pentabromodiphenyl ether |
| BDE-100 | 2,2',4,4',6-Pentabromodiphenyl ether |
| BDNF | brain-derived-neurotrophic factor |
| BFR | Brominated Flame Retardant |
| BMD | benchmark dose |
| BMDL | benchmark dose (lower confidence limit) |
| BTF | Biotransfer factor |
| bw | Body weight |
| CLP | Classification, Labelling and Packaging |
| CONTAM | EFSA Panel on Contaminants in the Food Chain |
| COR | Carry-over rates |
| CYP | cytochrome P450 |
| $D_a$ | Diffusion coefficient in air |
| $D_{pe}$ | Permeation through water drinking pipes of polyethylene |
| $D_{pvc}$ | Permeation through water drinking pipes of polyvinylchloride |
| $D_w$ | Diffusion coefficient in water |
| dw | Dry weight |
| EFSA | European Food Safety Authority |
| ENEV | Estimated No-Effect Value |
| FR | Flame retardant |
| GD | gestation day |
| GSH | glutathione |
| H | Henry coefficient |
| K | Degrees Kelvin |
| Kd | Distribution coefficient |
| Koa | Octanol – air partition coefficient |
| Koc | Organic carbon – water partition coefficient |
| Kow | Octanol – water partition coefficient |
| LB | Lower bound |
| LOAEL | lowest-observed-adverse-effect level |
| LOEL | Lowest Observed Effect Concentrations |
| LOD | Limit of detection |
| LOQ | Limit of quantitation |
| lw | Lipid weight |
| Mw | Molecular weight |
| MB | Medium bound |
| MLOQ | Method Limit of Quantification |
| MOE | margin of exposure |
| MOET | margin of exposure total |
| MOS | Margin of Safety |
| MRL | minimal risk level |

| | |
|---|---|
| NOAEL | no-observed-adverse-effect level |
| NOEC | No Observed Effect Concentrations |
| OH-PBDE | Hydroxy-polybrominated diphenyl ether |
| OM | Organic matter |
| Pa | Pascal |
| PBDD | Polybrominated dibenzodioxin |
| PBDE | Polybrominated diphenyl ether |
| PBDF | Polybrominated dibenzofuran |
| PCB | Polychlorinated biphenyl |
| pKa | Acid dissociation constant |
| PND | Postnatal day |
| PNEC | Predicted No Effect Concentration |
| POP | Persistent organic pollutant |
| PUF | Polyurethane foam |
| Q | Risk quotient |
| QSAR | Quantitative structure–activity relationship |
| R | Universal gas constant |
| RBA | relative bioavailability |
| RfD | reference dose |
| S | Solubility |
| SRV | Soil Remediation value |
| SVOC | semi-volatile organic compounds |
| TDHI | total daily human intake |
| TDI | tolerable daily intake |
| UB | Upper bound |
| UF | uncertainty factor |
| Vp | Vapor pressure |
| ww | Wet weight |

# 1 INTRODUCTION

## 1.1 Background

The present report covers a proposal for soil remediation values for the Pentabromodiphenyl ether, BDE-99. The input information needed for the evaluation using the S-Risk model (www.s-risk.be) is listed in the Substance Data sheet (Annex A). Using the model, soil remediation values are estimated for the solid part of the soil. The data gathering needed for the evaluation follows guidelines as stated in "Basisinformatie voor risico-evaluaties: werkwijze voor het opstellen van bodemsaneringsnormen en toetsingswaarden, richtwaarden en streefwaarden" (Cornelis & Touchant, 2016b).

## 1.2 Approach

### 1.2.1 Physicochemical properties

Information on the physico-chemical properties of BDE-99 were collected from various databases (e.g. Pubchem databank, Reach registration dossier) and from the peer-reviewed scientific literature.

### 1.2.2 Occurrence in the environment

Data on the occurrence of BDE-99 in environmental compartments (soil, indoor and outdoor air, drinking water) and food is collected from the peer-reviewed literature as well as from various national and international authorities. This data is used to estimate background concentrations in the mentioned environmental compartments and food as well as for the estimation of the background exposure to BDE-99.

### 1.2.3 Toxicology

Toxicological data is gathered from reports from research institutions and from the peer-reviewed scientific literature. Chapter 9 provides an overview of the toxicokinetics of BDE-99 and described the most important toxicological effects. Toxicological reference values published by various authorities are reviewed and evaluated.

### 1.2.4 Transfer to animal and plant

Data on the transfer of BDE-99 from soil to plants and animals was collected from the peer-reviewed literature. In the absence of data for specific plants/crops, read-across from related plants/crops were used.

### 1.2.5 Calculations

The calculations for the proposed remediation values for the soil are done using the S-Risk model (v3.4.4). Application I within the model is used to estimate the soil remediation values, whereas Application II allows for the assessment of the importance of the different exposure pathways. An adjustment of the buffer space to 0.75 m is made in Application II in order to have comparable model settings compared to Application I.

Soil concentrations are calculated corresponding to a Risk index equal to 1 for non-carcinogenics and/or until the risk of cancer is equal to $1/10^5$ for carcinogenic endpoints. Estimations are also being made for soil concentrations resulting in concentrations in food, drinking water, indoor and outdoor air being equal to the regulatory limits in these foods/compartments. When no such regulatory limits exist, a safety limit is used. S-Risk is being used to estimate the soil remediation values with the following adjustment: BCFs

estimating the transfer from soil to plant are based on concentration in the soil, whereas normally BCFs for organic chemicals are based on pore water concentrations.

The estimation of the remediation values for groundwater are based on Cornelis and Touchant (Cornelis & Touchant, 2016b). When existing, legal limits for drinking water are included in the proposed remediation values.

### 1.2.6 Ecotoxicological Reference Values

For the evaluation of ecotoxicological effects, original sources, scientific reports and databases were consulted in order to derive new ecotoxicological soil remediation standards based on these sources. The methodology described in Cornelis and Touchant (Cornelis & Touchant, 2016b) was not employed for the actual derivation, as it did not meet the usage conditions of that methodology. Instead, the PNEC (Predicted No Effect Concentration) for the soil is proposed as the reference value.

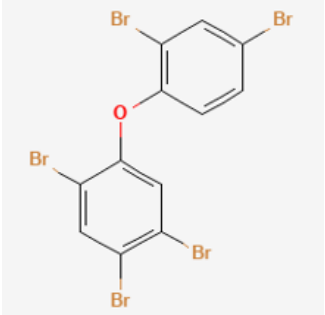
## 1.3 Reader's Guide

This report covers the proposal of the soil remediation value of 2,2',4,4',5-Pentabromodiphenyl ether (BDE-99).

Chapter 3 of this report covers the sources of BDE-99, and Chapter 4 described the behaviour of BDE-99 in soil. Physico-chemical properties are described in Chapter 5, whereas the presence of BDE-99 in the environment (soil, air, drinking water) and in food is described in Chapter 6. The transfer of BDE-99 from soil to plants and soil to animal products are described in Chapter 7 and 8, respectively. Information on toxicokinetics, effects of BDE-99 on animals and humans and toxicological reference values are summarized in Chapter 9. Chapter 10 covers the ecotoxicology of BDE-99. Regulatory limits of BDE-99 in air, water and food are stated in Chapter 11. Finally, Chapter 12 covers the estimation of the proposed soil remediation values.

Annex A contains the Substance Data sheet containing the values used as input for the S-Risk modelling.

# 2 IDENTIFICATION

| Substance | |
|---|---|
| **name English** | 2,2',4,4',5-Pentabromodiphenyl ether; 2,2',4,4',5-PentaBDE; BDE-99 |
| **name Dutch** | 2,2',4,4',5-Pentabroomdifenylether; 2,2',4,4',5-PentaBDE; BDE-99 |
| **CAS number:** | 60348-60-9 (BDE-99)<br>32534-81-9 (diphenyl ether pentabromo derivatives, pentaBDEs) |
| **EINECS number:** | 690-282-7 (BDE-99)<br>251-084-2 (pentaBDEs) |
| **EC index number:** | 690-282-7 (BDE-99)<br>602-083-00-4 (pentaBDEs) |
| **formula:** | $C_{12}H_5Br_5O$ |
| **Chemical structure:** |  |
| **Molecular weight:** | 564.7 g/mol |
| **Conversion:** | PentaBDE (commercial mixture): 1ppm = 23.48 mg/m$^3$ (20°C) (EU-RAR, 2001; ATSDR, 2017a) |

# 3 SOURCES OF BDE-99

BDE-99 is one of the major constituents in commercial pentaBDE mixtures (~42% in commercial mixtures such as DE-71 and Bromkal 70-SDE), which were sold as flame retardants. Production of commercial pentaBDE ceased in the EU in 1997, and global production decreased since the late 1990s and ended in 2004 (Jinhui *et al.*, 2017). By far the greatest use of pentaBDE has been for treatment of polyurethane foam (PUF) (90-95% of total uses). The PUF were mainly used in upholstery and automotive applications (Jinhui *et al.*, 2017). Minor uses of pentaBDE included textiles, printed circuit boards, insulation foam, cable sheets, conveyor belts, lacquers, and possibly oil drilling totalling to approximately to 5% of the total uses.

PentaBDE are additive flame retardants, meaning that they are added to the material and not chemically bound (such as reactive FRs). This means that there is a higher chance of BDE-99 being released from the products containing the flame retardant compared to reactive FRs.

BDE-99 was historically released into the environment from industrial processes as manufacturing of the FR or formulation of products containing pentaBDE. It can also be released from (consumer) products to the indoor environment and to the outdoor environment.

An indirect source of BDE-99 in the environment could be from degradation (debromination) of higher brominated PBDEs. For example, BDE-153 was degraded by microbes to form BDE-99 (1-7% conversion ((Robrock *et al.*, 2008). It should be noted that BDE-99 itself can undergo debromination as well to form lower brominated BDE congeners. Robrock et al. (Robrock *et al.*, 2008) showed the microbial degradation of BDE-99 to form the tetraBDE congeners BDE-47, -48, -49 and -66 with a conversion ranging from 0.1% to 22%. Also, within biota higher brominated BDE congeners can be dibrominated to form BDE-99 as was shown in fish (Roberts *et al.*, 2011).

As there has not been any production of pentaBDE (and thus BDE-99) in the EU since 1997 and globally since 2004, the presence of BDE-99 in the Belgian environment results from historical releases of BDE-99 during manufacturing and use, releases of products still containing BDE-99, or from higher brominated congeners released (historically) into the environment that can undergo debromination to form BDE-99.

# 4 BEHAVIOUR IN SOIL

## 4.1 Fate of Substance in soil

Due to its chemical properties (high log Kow), BDE-99 is expected to have strong sorption to particles such as soil or sediment (i.e., to the organic matter fraction) and negligible evaporation from soil surfaces to the air. Although penta-BDE is listed as a persistent substance, degradation can occur in the soil. Further details on the distribution and degradation of BDE-99 are described below.

## 4.2 Chemical form

The occurrence of BDE-99 in soil would be as solid.

## 4.3 Distribution

The binding of PBDEs to soil generally increases with increasing level of bromination as well as with increasing level of organic carbon in the soil (Liu, 2010). BDE-99 has log Koc value of 6.4 so strong sorption to soil is expected with negligible migration to groundwater.

Evaporation of PBDEs from soil to the air is expected to be very limited due to the low vapour pressure and high binding affinity to soil. With a vapour pressure of 4.3E-05 Pa (see Section 5.3) and the already mentioned log Koc value, evaporation of BDE-99 from soil to the air would be negligible.

## 4.4 Transformation

Although pentaBDE is listed as a persistent substance, degradation can occur. Both abiotic and biotic processes are responsible for the breakdown of PBDEs in the environment to e.g. lesser brominated PBDEs. Photolysis is a degradation mechanism by which PBDE congeners can be degraded in the atmosphere and at soil surfaces. To our knowledge, photodegradation of PBDEs in soil has only been studied for BDE-209, however, there are several other studies that showed photodegradation of PBDE congeners in other media, including BDE-99.

In controlled laboratory experiments or field -based studies, the photodegradation of BDE-99 dissolved in various organic solvents, water or air has been shown (Fang *et al.*, 2008; Pan *et al.*, 2016). Identified degradation products included the lower brominated BDE congeners BDE-28, -47, -49 and -66. Other chemicals such as OH-PBDEs, PBDDs, PBDFs, chlorinated-BDEs were identified as degradation products of BDE-99 itself and/or other BDE congeners (Pan *et al.*, 2016).

Photolysis of PBDEs on solid surfaces has also been studied, including surfaces such as TV casings, house dust, personal vehicles, textiles, and ice (summarized by (Pan *et al.*, 2016). One study focused on the photodegradation of BDE-209 on sand, soil and sediment (Söderström *et al.*, 2004). BDE-209 was spiked to these matrices and photodegradation was studied under natural conditions with outdoor sunlight. A range of nona-, octa-, hepta-, hexa- and penta-BDE congeners were identified as degradation products in sand, soil and sediment samples. Although BDE-99 itself or its degradation products (e.g. BDE-47) were not identified as degradation products in the soil experiments, it can be expected that given the evidence

that BDE-99 can be degraded by photolysis, this is a plausible degradation mechanism for BDE-99 present in the top layer of soil.

Microbial debromination is also an identified degradation pathway for PBDEs. Zhao et al. (Zhao *et al.*, 2018) published a review on microbial degradation of PBDEs. It provides an overview of studies that reported on the degradation of PBDEs by microbes identified in soil and sediment among other matrices. Ding et al. (Ding *et al.*, 2013) showed the degradation of BDE-99 using microbes obtained from soil samples to the lower brominated BDE-48 and BDE-49 (both tetra BDEs).

Lee et al. (Lee Lip & He, 2010) studied the microbial degradation of a commercial octa-BDEs mixture (BDE-203, -196 and -197) in soil collected from China, Singapore and US. Hexa-, penta-, tetra- and tri-BDE congeners were found as degradation products (without identifying the exact individual congeners).

# 5 PHYSICOCHEMICAL PROPERTIES

To better understand and model the transport and distribution of BDE-99 across different environmental compartments, it is crucial to have knowledge of the main physicochemical properties of this substance. The selection of the properties will primarily be based on experimental data on BDE-99. In case no such data can be found, modelled data or experimental data of other penta-BDE isomers will be used, given that the relative binding location of the bromine-atoms is not expected to influence the physicochemical properties significantly.
Table 2 summarizes the physicochemical properties that are needed to determine the transport behaviour of these substances in the environment.

*Table 2: Overview of relevant physicochemical properties*. Adapted from Cornelis *et al.* (2007).

| Property | Symbol | Unit |
|---|---|---|
| Water solubility (at 298 K) | $S$ | $mg/l$ |
| Acid dissociation constant | $pK_a$ | - |
| Vapor pressure (at 298 K) | $V_P$ | $Pa$ |
| Henry coefficient (at 298 K) | $H$ | $Pa \cdot m^3/mol$ |
| Octanol-water partition coefficient | $K_{OW}$ | - |
| Organic carbon – water partition coefficient | $K_{OC}$ | l/kg |
| Octanol – air partition coefficient (at 293 K) | $K_{OA}$ | - |
| Permeation through water drinking pipes of polyethylene | $D_{PE}$ | $m^2/day$ |
| Permeation through water drinking pipes of polyvinylchloride | $D_{PVC}$ | $m^2/day$ |
| Diffusion coefficient in air | $D_a$ | $m^2/day$ |
| Diffusion coefficient in water | $D_w$ | $m^2/day$ |

## 5.1 Water solubility (S)

BDE-99 is an aromatic halogenated compound and is consequently poorly soluble in water. Table 3 provides an overview of the different water solubility values found at 25°C found in literature.

*Table 3: Overview of BDE-99 solubility values in water at 25°C found in literature.*

| Water solubility [mg/l] | Experimental or modelled value | Reference |
|---|---|---|
| 0.0094 | Experimental | (Tittlemier *et al.*, 2002) |
| 0.00437 | Experimental | (Kuramochi *et al.*, 2007) |
| 0.0024 | Experimental[a] | (Stenzel, 1997) & (EC-JRC, 2002) |
| 0.0035[b] | Modelled | VEGA QSAR *(IRFMN 1.0.2)*[1] |
| 0.000394 | Modelled | EPI Suite *(v4.00 – v4.11)*[2] |
| 0.001[b] | Modelled | US EPA CompTox tool[3] |
| 0.009 | Not specified | (Salih Al-Omran, 2019) |
| 0.0024 | Not specified[c] | (Stenzel, 1997) |

[a]According to the EC (2002), this value is experimental, Stenzel and Markley (1997) also report this value, though was mentioned about the value being experimentally determined.
[b]Low reliability value according to VEGA QSAR-model.
[c]Consensus value based on hierarchical clustering, group contribution and nearest neighbor modelling.

The (ATSDR, 2017b), (NICNAS, 2020), (EnvironmentCanada, 2004), and the (EPA, 2008) provide water solubility values for BDE-99 of 0.0024 – 0.0133 mg/l at 25°C. These values are based on initial reports by the (EC-JRC, 2002), in which 0.0133 mg/l is reported for the broader pentabromodiphenyl ether group. On the other hand, 0.0024 mg/l was reported by Stenzel (Stenzel, 1997) for BDE-99, specifically. Finally, De Boer et al. (de Boer *et al.*, 2000) also reports a water solubility of 0.0009 mg/l for penta-BDE, though without explicitly mentioning for which isomer.

The different experimental and modelled results reported in literature are rather consistent, ranging from approximately 0.001 to 0.01 mg/l. For the calculation of an average water solubility, only the experimental values explicitly derived for BDE-99 (so not the broader penta-BDE group) will be considered. This leads to an average solubility in water of 0.0054 (± 0.0036) mg/l for BDE-99 at 25°C.

## 5.2 Acid dissociation constant (pKa)

This parameter is not relevant for BDE-99 under normal environmental conditions seeing that the hydrogen atoms that are present, are all part of the aromatic structure of the congeners, thus making H-transfer exceptionally unfavourable from a thermodynamic point of view. Therefore, BDE-99 does not ionize under environmental conditions (NICNAS, 2020).

[1] VEGA QSAR – VEGA HUB
[2] EPI Suite™-Estimation Program Interface | US EPA
[3] CompTox Chemicals Dashboard | US EPA

## 5.3 Vapour pressure ($V_P$)

The vapour pressure of a chemical compounds gives an indication of the volatility; with the VOC-directive defining an organic compound as volatile if the vapour pressure is greater than 10 Pa at 20°C (Olsen, 2001).
Table 4 provides an overview of the different vapour pressures reported in literature. A QSAR-model is also provided by (Wania & Dugani, 2003) for polybrominated diphenyl ethers, with which the vapour pressure [Pa] at 25°C can be estimated ($R^2$ of 0,9962):

$$\log(V_p) = -0.0099 \times M_W + 1.1962$$

This model relies on the molecular weight as the single input for $V_P$-estimation. Consequently, $V_P$-values can only be estimated for the broader penta-BDE group ($M_W$ of 564,7 g/mol). Nevertheless, the difference in $V_P$ between penta-BDE isomers is rather small, as demonstrated by the $V_P$-values[4] of $4.57 \times 10^{-5}$ Pa for BDE-99 (calculated average value based on a more limited literature search than below) and $3{,}99 \times 10^{-5}$ Pa for BDE-100 (Wania & Dugani, 2003). The model can therefore be used to accurately estimate $V_P$-values for BDE-congeners.

*Table 4: Overview of BDE-99 vapour pressures at 25°C reported in literature.*

| Vapor pressure [Pa] | Experimental or modelled value | Reference |
|---|---|---|
| $1.76 \times 10^{-5}$ | Experimental | (Tittlemier *et al.*, 2002) |
| $3.63 \times 10^{-5}$ | Experimental | (Kuramochi *et al.*, 2007) |
| $6.82 \times 10^{-5}$ | Experimental | (Wong *et al.*, 2001) |
| $5.1 \times 10^{-5}$ | Experimental | (EC-JRC, 2002) |
| $3.3 \times 10^{-6}$ | Estimated | (EC-JRC, 2002) |
| $7.94 \times 10^{-6}$ | Not specified | (Salih Al-Omran, 2019) |
| $1.44 \times 10^{-4}$ | Modelled | EPI Suite *(v4.00 – v4.11)* |
| $1.55 \times 10^{-5}$ | Modelled[a] | VEGA QSAR *(IRFMN 1.0.2)* |
| $4.22 \times 10^{-6}$ | Modelled | US EPA CompTox tool |

[a]Good reliability according to VEGA QSAR-model; modelled data of -9.814 (log [atm]) closely resembles experimental data of -10.389 (log [atm]). However, reference for experimental value is not mentioned.

EFSA (2011) reported a vapour pressure of $2.46 \times 10^{-7}$ without explicitly providing units and referring to the EPI estimation program by the (EC-JRC, 2002). However, in the (EC-JRC, 2002) study, a measured value of $2.9 - 7.3 \times 10^{-5}$ Pa (taken as an average of 5.1 in Table 4) and an EPI-estimated value of $3.3 \times 10^{-6}$ Pa were reported. Therefore, the EFSA (EFSA, 2011b) value will not be considered.

Given the sufficient number of experimental values and the great variability in modelled values (ranging from $10^{-4}$ to $10^{-6}$), only the experimental values will be used to calculate an average vapour pressure (Wong *et al.*, 2001; EC-JRC, 2002; Tittlemier *et al.*, 2002; Kuramochi *et al.*, 2007). This leads to an average vapour pressure of $4.3\ (\pm 2.2) \times 10^{-5}$ Pa at 25°C for BDE-99; from this, it can be concluded that BDE-99 is not considered a volatile organic compound.

[4] Average $V_P$-values based on several experimental measures, all of which are also considered in Table 4.

## 5.4 Henry coefficient (H)

The Henry-coefficient gives an impression of the volatility of a chemical substance from water, and as such, gives an indication on the potential environmental partitioning. The Henry-coefficient is defined as the ratio of a chemical concentration in the gas phase to that in the aqueous phase at a reference temperature (298 K) at equilibrium (US-EPA, 2012a). In case the Henry coefficient is unknown, it can be calculated from the vapour pressure of a chemical relative to its solubility in water (Cornelis *et al.*, 2022):
The greater the H-value, the more volatile a compound is from water. The US EPA (US-EPA, 2012a) provides the following Henry coefficients – volatility classification:

- Very volatile from water: > $10^{-1}$ $\mathrm{atm \cdot m^3/mol}$
- Volatile from water: $10^{-1}$ – $10^{-3}$ $\mathrm{atm \cdot m^3/mol}$
- Moderately volatile from water: $10^{-3}$ – $10^{-5}$ $\mathrm{atm \cdot m^3/mol}$
- Slightly volatile from water: $10^{-5}$ – $10^{-7}$ $\mathrm{atm \cdot m^3/mol}$
- Non-volatile: < $10^{-7}$ $\mathrm{atm \cdot m^3/mol}$

In Table 5, an overview of the different Henry coefficients at 25°C found in literature are reported. A QSAR-model based on experimental data is furthermore provided by Cetin and Odabasi (Cetin & Odabasi, 2005), with which the Henry-coefficient can be estimated ($R^2$ of 0.97) for BDE-99 over a temperature range of 5 – 40°C:

$$H = R \times T \times exp\left(20.3 - \frac{8513}{T}\right)$$

This model relies on the temperature [K] as sole input variable. For a temperature of 25°C (i.e., 298 K) this leads to an estimated H-value of 0.635 $\mathrm{Pa \cdot m^3/mol}$, which corresponds with the measured experimental data of 0.60 (Table 5).

*Table 5: Overview of different Henry coefficients at 25°C reported in literature.*

| Henry Coefficient [$Pa \cdot m^3/mol$] | Experimental or modelled value | Reference |
|---|---|---|
| 0.23 | Experimental | (Tittlemier *et al.*, 2002) |
| 0.60 | Experimental | (Cetin & Odabasi, 2005) |
| 0.79 | Experimental | (Kuramochi *et al.*, 2007) |
| 0.94 | Calculated[a] | (Wania & Dugani, 2003) |
| 6.82 – 17.21 (average: 12.02) | Calculated[b] | (EC-JRC, 2002) |
| 0.50 | Calculated[c] | (Salih Al-Omran, 2019) |
| 0.36[d] | Modelled | EPI Suite *(v4.00 – v4.11)* |
| 1.10 | Modelled[e] | VEGA QSAR *(IRFMN 1.0.2)* |

[a]Calculated based on reported solubility of $4.87 \times 10^{-5}$ $\mathrm{mol/m^3}$ and $V_P$ of $4.57 \times 10^{-5}$ Pa.
[b]Calculated based on reported solubility of 2.4 µg/l and $V_P$ of $(2.9 - 7.3) \times 10^{-5}$ Pa.
[c]Calculated based on reported solubility of 0.009 mg/l and $V_P$ of $7.94 \times 10^{-6}$ Pa.
[d]Group method estimate is reported given its preference over the bond contribution method estimate (US-EPA, 2012a).
[e]Moderate reliability according to VEGA QSAR-model

For the calculation of an average Henry coefficient, all the experimental values reported in Table 5 will be considered. The H-value by Wania and Dugani (Wania & Dugani, 2003) will not be considered in this calculation, since the solubility- and $V_P$-values used to calculate the H-value were already average values based on literature findings; findings which are also considered separately in Table 5. The H-value of the EC (EC-JRC, 2002) will be included given that the solubility and $V_P$, on which the H-value was based, were also considered in

Chapters 5.1 and 5.3. Furthermore, the H-values based on solubility and $V_P$-values by Salih Al-Omran (Salih Al-Omran, 2019) will not be considered given that it was not mentioned how the water solubility and vapour pressure values were determined (experimentally vs modelled). Finally, a geometric mean will be calculated of all considered values, so that the final result is not skewed by the EC (EC-JRC, 2002) value. This leads to a geomean Henry coefficient of $1.07\ (\pm 1.67)\ Pa \cdot m^3/mol$ at 25°C (i.e., $1.07 \times 10^{-5}\ atm \cdot m^3/mol$); from which, it can be concluded that BDE-99 is slightly volatile from water.

## 5.5 Octanol water partition coefficient (log $K_{OW}$)

The octanol-water partition coefficient is defined as the ratio of the concentration at equilibrium of a given substance ($C_i$) in n-octanol and water at a specific temperature.

$$K_{OW} = \frac{[C_i]^{eq}_{n-oct}}{[C_i]^{eq}_{water}}$$

As such, it serves as measure for determining the lipo- or hydrophilicity of a substance. The greater the log $K_{OW}$-value, the more lipophilic the substance, with log $K_{OW}$-values typically varying between -3 (very hydrophilic) and +10 (very hydrophobic) (Cumming & Rücker, 2017). Since the log $K_{OW}$ is also closely linked to the bioaccumulation of a substance, the octanol-water partition coefficient can also be used as a proxy for bioaccumulation potential, with a log $K_{OW} \geq 4$ ((EC, 2008) or log $K_{OW} > 5$ (Mackay *et al.*, 2013) often being used as the criterion for bioaccumulation.

**Error! Reference source not found.**6 provides an overview of the different log $K_{OW}$-values f ound in literature. From this, it can be concluded that BDE-99 is very hydrophobic and possesses a significant bioaccumulation potential. Moreover, a QSAR-model based on experimental data is provided by Braekevelt et al. (Braekevelt *et al.*, 2003), with which the log $K_{OW}$ can be estimated ($R^2$) based on the number of bromine atoms ($n_{Br}$) in BDE-congeners:

$$\log(K_{OW}) = 0.621 \times n_{Br} + 4.12$$

*Table 6: Overview of different log $K_{OW}$-values found in literature.*

| Log $K_{OW}$ | Experimental or modelled value | Reference |
|---|---|---|
| 7.32 | Experimental | (Braekevelt *et al.*, 2003) |
| 7.39 | Experimental | (Kuramochi *et al.*, 2007) |
| 6.46 – 6.97[a] | Experimental | (EC-JRC, 2002) |
| 7.13 | Modelled[b] | VEGA QSAR *(IRFMN 1.0.2)* |
| 7.66 | Modelled | EPI Suite *(v4.00 – v4.11)* |

[a]Measured value determined for commercial mixture of penta-BDE isomers.
[b]Moderate reliability according to VEGA QSAR-model (AlogP-model).

NICNAS (NICNAS, 2020)(2020), EFSA (EFSA, 2011b), ATSDR (ATSDR, 2017b), Yue and Li (Yue & Li, 2013), and Salih Al-Omran (Salih Al-Omran, 2019) rely on the experimental value of 7,3 reported by Braekevelt et al. (Braekevelt *et al.*, 2003). Other values reported by a.o. Environment Canada (EnvironmentCanada, 2004), Wania and Dugani (Wania & Dugani, 2003) are based on commercial mixtures, estimated values or on experimental studies that could not be found online. Moreover, according to the EC (EC-JRC, 2002) the log $K_{OW}$-range

of 6.46 – 6.97 was measured for BDE-99, though the same range is reported by the Michigan Department of Environmental Quality (MichiganDepartmentofEnvironmentalQuality, 2008) belonging to a commercial mixture of penta-BDEs, for this reason, this range will not be considered. Even though the log $K_{OW}$ is not expected to differ significantly between penta-BDE isomers, only experimental values determined specifically for BDE-99 will be considered for the calculation of an average value; therefore, only Braekevelt et al. (Braekevelt *et al.*, 2003) and Kuramochi et al. (Kuramochi *et al.*, 2007) will be considered, leading to an average log $K_{OW}$ of 7.36. This average value is furthermore in good agreement with the modelled values provided in **Error! Reference source not found.**6.

## 5.6 Organic carbon-water partition coefficient (log $K_{OC}$)

The organic carbon – water partition coefficient measures how strongly a chemical is sorbed to soil particles (or other organic material) relative to its concentration in water, both at equilibrium and at a certain temperature. Additionally, the $K_{OC}$ can furthermore be defined as the distribution coefficient ($K_d$) normalized to the total organic content ($C_{org}$), with the distribution coefficient being defined as the concentration of a chemical absorbed per unit mass of soil to its concentration in the water phase at equilibrium and at a certain temperature (O'Sullivan & Megson, 2014).

$$K_d = \frac{[C_i]^{eq}_{soil}}{[C_i]^{eq}_{water}}$$

$$K_{OC} = \frac{K_d}{C_{org}}$$

The higher the $K_{OC}$-value, the more tightly a chemical is bound to soil, which complicates degradation since less substance is available for microbial action. Similarly to high $K_{OW}$-values, high $K_{OC}$-values are also linked to an increased soil persistency, with a log $K_{OC}$ > 4.5 l/kg indicating very strong sorption to soil with negligible migration to groundwater, while log $K_{OC}$-values of 2.5 – 3.4 l/kg and < 1.5 l/kg indicate a moderate sorption (slow migration to ground water) and low sorption to soil (rapid migration to groundwater), respectively (US-EPA, 2012b). The log $K_{OC}$-values of BDE-99 found in literature are provided in **Error! Reference source n ot found.**; based on which, it can be concluded that BDE-99 exhibits very strong sorption to soil with negligible migration to ground water.

Cornelis et al. (Cornelis *et al.*, 2022) also provides a QSAR-model for predominantly hydrophobic chemicals, according to which BDE-99 would have a log $K_{OC}$ of 6.06 l/kg based on a log $K_{OW}$ of 7.36 (Chapter 5.5):

$$log(K_{OC}) = 0.81 \times log(K_{OW}) + 0.1$$

This estimated log $K_{OC}$ is in line with the experimental data reported in **Error! Reference s ource not found.**. The other two modelled values shown in **Error! Reference source not found.**7 exhibit more significant deviation from the experimental values. However, VEGA QSAR also mentioned a low reliability for the modelled log $K_{OC}$-value.

*Table 7: Overview of different log $K_{OC}$-values found in literature.*

| Log $K_{OC}$ [l/kg] | Experimental or modelled value | Additional information | Reference |
|---|---|---|---|
| 6.5 | Experimental | - | (Streets *et al.*, 2006) |
| 5.75 | Experimental | - | (EC-JRC, 2002) |
| 6.92 | Experimental | Jordan Lake Reservoir sediment (Chatham County, NC) | (Wang *et al.*, 2011a) |
| 6.19 | | Greasy Creek sediment (Benton County, OR) | |
| 6.27 | | Leaf Lake sediment (El Dorado County, CA) | |
| 6.25 | | San Diego Creek Sediment (Orange County, CA) | |
| 6.52 | Experimental | River Mustio sediment (Finland) | (Kuivikko *et al.*, 2010) |
| 6.82 | | Tammisaari sediment (Finland) | |
| 6.53 | | Hermansö sediment (Finland) | |
| 6.33 | | Västergädden sediment (Finland) | |
| 6.06 | Estimated via QSAR-model[a] | - | (Cornelis *et al.*, 2022) |
| 5.64 | Modelled[b] | - | VEGA QSAR *(IRFMN 1.0.2)* |
| 4.34 | Modelled[c] | - | EPI Suite *(v4.00 – v4.11)* |

[a]Based on log $K_{OW}$ of 7.36 using QSAR-model of Cornelis et al. (2022).
[b]Low reliability according to VEGA QSAR-model.
[c]Modelled via MCI-method.

Only experimental values will be included in the calculation of an average log $K_{OC}$. For this reason, the log $K_{OC}$-results reported by the ATSDR (ATSDR, 2017b) and NICNAS (NICNAS, 2020) will not be included. Based on the results of Streets et al. (Streets *et al.*, 2006), EC (EC-JRC, 2002), Wang et al. (Wang *et al.*, 2011a) and Kuvikko et al. (Kuivikko *et al.*, 2010), an average log $K_{OC}$ of 6.4 (± 0.3) l/kg is estimated.

## 5.7 Octanol-air partition coefficient ($K_{OA}$)

The n-octanol – air partition coefficient is defined as the ratio of the concentration of a chemical in n-octanol to its concentration in air, at a specific temperature and pressure, and at equilibrium. This measure is often used to indicate the ease with which a substance volatilizes from environmental matrices (such as soil and vegetation) into the air. Lower $K_{OA}$-values indicate a higher volatility, and as a consequence, a higher tendency to partition into air. While a high $K_{OA}$-value indicates a preference for the soil matrix (Meylan & Howard, 2005). The $K_{OA}$-value can be calculated as the ratio of $K_{OW}$-value to the dimensionless Henry-coefficient (i.e., the Henry-coefficient normalized relative to the temperature (T, in [K]) and gas constant (R, equal to [8.314 $m^3 \cdot Pa/mol \cdot K$]).

$$K_{OA} = \frac{K_{OW}}{\frac{H}{R \times T}}$$

Harner and Schoeib (Harner & Shoeib, 2002) reported an experimentally measured log $K_{OA}$ of 11.31 at 25°C for BDE-99. Using EPI Suite, a log $K_{OA}$ of 11.157 is estimated at 25°C, while VEGA QSAR estimates a log $K_{OA}$ of 11.55, according to which the reliability is good. However, the log $K_{OA}$ can also be calculated based on $K_{OW}$- and H-values. Based on an average log $K_{OW}$ of 7.36 and a Henry-coefficient of 0.92 $Pa \cdot m^3/mol$ (calculated in Chapters 5.4 and 5.5), a log $K_{OA}$ of 10.79 can be calculated at 25°C (298 K). This value is in agreement with the aforementioned results and is therefore put forward as the log $K_{OA}$-value of choice.
The $K_{OA}$-values for chemical substances are often calculated at 293 K instead of 298 K. This leads to a more conservative estimate seeing that a lower temperature implies less volatilization and thus more substance residing in the soil. Moreover, 293 K is also a more realistic depiction of soil temperatures. To this end, the log $K_{OA}$ temperature-dependency formula is used to calculate the log $K_{OA}$ at the desired temperature (Van Holderbeke et al., 2023):

$$K_{OA}(T) = K_{OA}(T_0) \times \exp\left(-\frac{\Delta H_{AO}}{R} \times \left(\frac{1}{T} - \frac{1}{T_0}\right)\right)$$

In which:
- $K_{OA}(T_0)$ is the $K_{OA}$-value at reference temperature $T_0$ (in this case, at 298 K)
- $\Delta H_{AO}$ is the enthalpy change related to the volatilization from n-octanol to the air; a value of 91.1 kJ/mol was measured by Harner and Schoeib (Harner & Shoeib, 2002)
- R represents the universal gas constant, equal to 8.314 $J/mol \cdot K$
- $K_{OA}(T)$ represents the $K_{OA}$ value at the desired temperature (in this case 293 K)

This then leads to a log $K_{OA}$ of 10.52 at 293 K.

## 5.8 Permeation through drinking water pipes ($D_{PE}$, $D_{PVC}$)

There were no values found in literature for the permeation of BDE-99 through drinking water pipes of polyethylene or polyvinylchloride. In the Netherlands, a standard $D_{PE}$-value of $1 \times 10^{-7}$ m²/day is used in CSOIL in case no experimental data can be found. This choice is justified by the fact that $D_{PE}$ lies in the range of $0.10 \times 10^{-7} - 35 \times 10^{-7} m^2/day$ for most common contaminants (Vonk, 1985). In case no data can be found in literature for the substance of interest, it is recommended to use a permeation coefficient of a substance of similar molecular structure (van den Berg, 1997). If no such data can be found, a default value of $10^{-7}$ m²/day can be used for calculations (Lijzen *et al.*, 2018). For permeation through PVC water pipes, a default value of $D_{PE}/1000$ is used in S-risk (Cornelis *et al.*, 2017). For these reasons, the permeation coefficients for BDE-99 through PE- and PVC-pipes are assumed to be $1 \times 10^{-7}$ and $1 \times 10^{-10}$ m²/day, respectively.

## 5.9 Diffusion for organic substance in air (Da) and water (Dw)

The gas diffusion coefficient in air can be estimated based on the molecular weight ($M_W$) of a substance using the following formula (Cornelis *et al.*, 2022):

$$D_a = 0.035 \times 24 \times \sqrt{\frac{76}{M_w}}$$

For BDE-99 ($M_W$ of 564.7 g/mol), this would lead to a $D_a$-value of 0.308 m²/day.

The gas diffusion coefficient in water can also be estimated based on the molecular weight of a substance, using the following formula (Cornelis *et al.*, 2022).

$$D_w = 3.6 \times 10^{-6} \times 24 \times \sqrt{\frac{76}{M_w}}$$

For BDE-99 ($M_W$ of 564.7 g/mol), this would lead to a $D_w$-value of $3.17 \cdot 10^{-5}$ m²/day.

## 5.10 Conclusion physicochemical properties

For risk assessment purposes, an overview of all relevant physiochemical properties is given in **Error! Reference source not found.**8.

*Table 8: Overview physicochemical properties of BDE-99*

| Property | Value |
|---|---|
| Solubility (S) at 298 K | 0.0054 mg/l |
| Acid dissociation constant ($pK_a$) | N.A. |
| Vapor pressure ($V_P$) at 298 K | $4.3 \times 10^{-5}$ Pa |
| Henry coefficient (H) at 298 K | $1.07\ \mathrm{Pa \cdot m^3/mol}$ |
| Octanol-water partition coefficient ($K_{OW}$) | $10^{7.36}$ |
| Organic carbon– water partition coefficient ($K_{OC}$) | $10^{6.4}$ l/kg |
| Octanol – air partition coefficient ($K_{OA}$) at 293 K | $10^{10.52}$ |
| Permeation through drinking water pipes of polyethylene ($D_{PE}$) | $10^{-7}$ m²/day |
| Permeation through drinking water pipes of polyvinylchloride ($D_{PVC}$) | Calculated in S-risk as $10^{-10}$ m²/day |
| Diffusion coefficient in air ($D_a$) | 0.308 m²/d |
| Diffusion coefficient in water ($D_w$) | $3.17 \times 10^{-5}$ m²/d |

# 6 OCCURENCE IN THE ENVIRONMENT AND HUMAN EXPOSURE VIA FOOD

The production and use of pentaBDE was phased out in the mid 2000s world-wide, resulting in declining concentrations in environmental media over time (Abbasi *et al.*, 2019). In order to estimate current human exposure to BDE-99 via various environmental media, food and/or drinking water best, only the most recent studies for each media are discussed below.

Preference is given to data obtained from samples taken in Belgium, however, when no such data is available, data from other European countries are being used.

## 6.1 Soil

Data on the presence of BDE-99 in soil in Belgium is limited. A study published in 2009 reported on PBDEs in home-grown eggs and analysed soil as a potential source (Covaci *et al.*, 2009). Soil samples from the perimeter surrounding the chicken run were collected in autumn 2006 and spring 2007 from 10 locations throughout Belgium. Median concentrations of BDE-99 in soil collected in 2006 and 2007 were 0.03 µg/kg dw and 0.02 µg/kg dw, respectively.
BDE-99 was detected in 8 samples in 2006 and in 4 samples in 2007. The maximum concentration reported was 2.49 µg/kg dw in soil collected in 2006.

Vermeulen et al. (Vermeulen *et al.*, 2010) reported on PBDEs in soil collected in 2005/2006 in two recreation parks near Antwerp, i.e. in Hoboken and Brasschaat. A total of 16 soil samples from grassland and open woodland were collected at each site and combined into 4 pooled samples per site. Soil concentrations of BDE-99 in grassland were reported to be 0.05 and 0.08 µg/kg dw for the two sites and 0.04-0.05 µg/kg dw in open woodland soil from both sites (this is an estimation as the study only reported sum-PBDE concentrations and percent contribution of BDE-99 was estimated from a figure, i.e. 40% for grassland and 50% for open woodland).

In a more recent report (OVAM, 2020), soil samples were collected from 50 location across Flanders in 2020. BDE-99 was only reported to have concentrations >LOQ in 6 of the 50 samples. The concentrations for the six locations varied from 0.06 to 0.09 µg/kg dw, with the LOQ being 0.05 µg/kg dw.

More recent data from other European countries showed that BDE-99 was detected in all 8 collected soil samples from urban and rural sites near Stockholm, Sweden in 2012. The concentrations ranged between 0.2 and 1.1 µg/kg organic matter - equals to 0.04 to 0.9 µg/kg ww) (Newton *et al.*, 2015). Similarly, Drage et al. (Drage *et al.*, 2016) showed that BDE-99 concentrations in soil collected at 8 sampling sites along a 60 km transect near Birmingham, UK in 2012/2013 ranged between 0.55 and 1.6 µg/kg OM. Both studies reported soil concentrations on the bases of ng/g organic matter and additional information to convert these concentrations to µg/kg dw were not provided.

**Selected value for background concentration**
The most recent data from Belgium shows very low detection frequency and if detected, concentrations are just above the LOQ.

This indicates that there is no general diffuse pollution of BDE-99.

## 6.2 Air

For the presence of BDE-99 in air, a similar criteria as for soil was applied. The initial focus was on recent studies performed in Belgium but if no such data exist the recent data from other studies performed in Europe were reviewed.

### 6.2.1 Outdoor air

Data on the presence of BDE-99 outdoor air in Belgium during the last 10 years were not found.

Wong et al. (Wong *et al.*, 2018) reported on PBDEs and other BFRs in outdoor air collected in an urban area in Sweden (Stockholm) as well as from background locations (>70km distance from Stockholm) during 2014-2015 (total of 26 locations). BDE-99 concentrations (sum of gas and particle phase) in the two background sites (0.028-0.043 pg/m$^3$ were within the range of the concentration reported in the samples taken from the urban site (range <0.009 – 0.15 pg/m$^3$). Therefore, median concentration based on all samples is 0.038 pg/m$^3$.

Degrendele et al (Degrendele *et al.*, 2018) reported on temporal trends of PBDEs in air in central Europe. Weekly samples were collected at a background site in the Czech Republic between 2011 and 2014. Average concentrations on BDE-99 in the gas phase and the particle phase were both 0.071 pg/m$^3$. The total average concentration is 0.134 pg/m$^3$, with a minimum concentration of 0.025 and maximum concentration of 0.65 pg/m$^3$.

**Selected value for background concentration**
Both studies showed average BDE-99 concentrations in outdoor air. Wong et al. (Wong *et al.*, 2018) reported for multiple sites, whereas Degrendele et al. (Degrendele *et al.*, 2018) reported on weekly samples during a 3-year period for one location. As Degrendele et al. (Degrendele *et al.*, 2018) has the larger data set (including seasonal variation of the air concentration), the average concentration of 0.134 pg/m$^3$ was selected as the background outdoor air concentration.

### 6.2.2 Indoor air

Data on indoor air concentrations of BDE-99 in Belgium were not found in samples taken within the last ~10 years, below follows a summary of air concentrations in indoor air sampled in Europe.

Wemken et al. (Wemken *et al.*, 2019) reported on BDE-99 concentrations in indoor collected in homes (n = 28), offices (n=31) and schools (n=31) in samples collected in 2016/2017 in Ireland using passive samplers. Median concentrations of BDE-99 were 6.1 pg/m$^3$ in homes (range <0.43−330 pg/m$^3$), 4.2 pg/m$^3$ in offices (range <0.43−880 pg/m$^3$), and 3.1 pg/m$^3$ in schools (range <0.43−99 pg/m$^3$).

Tao et al. (Tao *et al.*, 2019) reported on BDE-99 concentrations in offices (n=10) in Stockholm, Sweden during 2016/2017. The samples were taken during a 24-hour period during the winter. In eight of the 10 samples, BDE-99 concentrations were <MLOQ of 0.89 pg/m$^3$ while concentrations in the two remaining offices were 2.2 and 6.3 pg/m$^3$.

Wong et al. (Wong *et al.*, 2018) reported on PBDEs and other BFRs in indoor air collected in offices during 2014-2015 in Stockholm, Sweden. Samples were taken over a 48–72-hour period. BDE-99 was detected in 91% of the indoor air samples with a median BDE-99 concentration of 4.2 pg/m$^3$ and a range of <1.3 to 8.4 pg/m$^3$.

**Selected value for background concentration**

The above studies reported on BDE-99 concentrations in indoor air collected in homes, offices, and schools. Concentrations in indoor air from homes would represent the background concentrations best. Therefore, data from Wemken et al (Wemken *et al.*, 2019) on air collected in homes in Ireland during 2016/2017 were selected. A median concentration of 6.1 pg/m$^3$ was used as background indoor air concentration.

## 6.3 Drinking water

No data were found on BDE-99 in drinking water in Belgium.

In drinking water sampled in Austria during 2017/2018, BDE-99 concentrations were >LOQ in only 10% of the tested samples (2/20), with reported concentrations of 0.15 and 0.20 ng/L for the two samples (LOQ was 0.14 ng/L) (Brueller *et al.*, 2018).

Studies performing human exposure assessment to BDE-99 from multiple pathways didn't include drinking water as a relevant exposure route due to the lipophilic character of the substances and thus expecting concentrations in drinking water to be negligible (Roosens *et al.*, 2010; EFSA, 2011b).

**Selected value for background concentration**
Concentrations in drinking water are expected to be low due to their hydrophobic character, which is supported by the study performed in Austria where concentrations >LOQ were only found in 10% of the tested samples. As a worst case, the highest value measured was selected as the background concentration in drinking water, i.e. 0.20 ng/L

## 6.4 Concentrations in foodstuffs and intake via food

For determining the BDE-99 exposure to humans via food, it is also important to use recent data as concentrations in food have been shown to decline over time. Gebbink et al. (Gebbink *et al.*, 2019) showed significantly declining concentrations of BDE-99 in bovine meat and milk, meat from pigs and broilers and hen eggs collected in the Netherlands between 2009 and 2014. More recently, Ma et al. (Ma *et al.*, 2023) showed declining BDE-99 concentrations in beef, lamb, pork, chicken, salmon, mackerel, tuna, trout, and cheese collected in the UK from 2015 to 2020/2021, with declines in meat and fish of 90% from 2015 to 2020/2021.

Studies investigating the presence of BDE-99 in food from Belgian supermarkets in recent years are very limited. However, Poma et al. (Poma *et al.*, 2018) performed an extensive survey on the presence of PBDEs in various foods collected from Belgian supermarkets in 2015/2016. A total of 183 samples were collected in the following food groups: Milk and dairy products (n=38), food for infants and children (n=18), animal and vegetable fat (n=9), fish and fish products (n=61), eggs and egg products (n=4), grains and grain products (n=7), potatoes and derived products (n=4), other foods (n=7; including spinach and zucchini) and meat and meat products (n=35). Concentrations of BDE-99 in all the samples were below the limit of quantification (LOQ) of 5 pg/g ww. Other studies have reported on comparable LOQ values for BDE99 ((Gebbink *et al.*, 2019; Ma *et al.*, 2023) supporting the data from Poma et al (Poma *et al.*, 2018) that BDE-99 concentrations were below the LOQ.

Recent data on BDE-99 in food from Latvia collected during 2016-2019 showed similar results as for the Belgian results (i.e. concentration smaller or similar to 5 pg/g ww): concentration in milk and dairy products was 1.8 pg/g ww (n=38), 3.8 pg/g ww in eggs (n=13), 6.3 pg/g ww in meat and meat products (n=25) (Zacs *et al.*, 2021), while BDE-99 concentrations in fish and fish products (n=43), vegetable oils (n=9) and grains and grain

products (n=10) were generally higher compared to the Belgian results, with average concentrations at 41 pg/g ww, 9 pg/g ww and 8 pg/g ww, respectively.

EFSA published an updated report on the risk assessment of PBDEs in food early 2024 (Chain *et al.*, 2024). The report includes occurrence data of PBDEs in food collected between 2010 and 2019 submitted by 13 European countries. More than 10.000 results were included in the report for BDE-99 with 56% of the data having quantified concentrations and the remaining 44% were either below the LOD or LOQ. Mean concentrations of BDE-99 were 0.025 (LB) and 0,088 (UB) µg/kg ww in fish meat, 0.009 (LB) and 0.037 (UB) µg/kg ww in mammal meat, 0.018 (LB) and 0.038 (UB) µg/kg ww in eggs and egg products, 0.093 (LB) and 0.213 (UB) µg/kg ww in animal and vegetable fats and oils, and 0.002 (LB) and 0.038 (UB) µg/kg ww in milk and dairy products. The number of samples analysed within the vegetable and vegetable products group was limited (n=125) and specific concentrations of PBDE congeners were not included in the report.

Information on recent dietary intake of PBDEs has only been published by EFSA (Chain *et al.*, 2024), the other above-mentioned studies reported only on concentrations in food but didn't link food consumption intake data to the concentrations (Poma *et al.*, 2018) or only reported dietary intake for sum-PBDEs and not individual congeners (Zacs *et al.*, 2021).

Table 9 provides an overview of the lower bound and upper bound dietary intakes of BDE-99 for various age groups based on the 2011-2019 input data. It can be seen that the LB dietary intakes are generally lower based on the 2011-2019 data compared to the LB dietary intakes based on the 2001-2009 data. Meat and meat products were the major food group responsible for the BDE-99 exposure and contributed 68% of the total dietary intake (based on median value), followed by fish and seafood (13.7% of the total dietary intake) and milk and dairy products (8%). Egg and egg products, animal and vegetable fats, sugars, and composite dishes contributed between 0.3% and 4.1% to the total dietary intake of BDE-99.

Table 9: Dietary intakes (ng/kg bw/day) of BDE-99 for various age group reported by EFSA

| | **2011 – 2019 input data (all countries)** | | **Dietary intake Belgium** | | **2001 – 2009 input data (all countries)** | |
|---|---|---|---|---|---|---|
| | **Dietary intake LB** | **Dietary intake UB** | **Dietary intake LB** | **Dietary intake UB** | **Dietary intake LB** | **Dietary intake UB** |
| Infant (<1 year) | 0.01 | 0.29 | NA[##] | NA | NA | NA |
| Toddler (1-3 years) | 0.23 | 1.09 | 0.16 | 1.09 | 0.58 | 1.24 |
| Other children (3-10 years) | 0.22 | 0.86 | 0.21 | 0.76 | 0.42*/0.35** | 0.94*/0.81** |
| Adolescents (10-18 years) | 0.11 | 0.42 | 0.1 | 0.36 | 0.22 | 0.40 |
| Adults (18-65 years) | 0.09 | 0.3 | 0.07 | 0.29 | 0.18[#] | 0.32[#] |
| Elderly (65-75 years) | 0.07 | 0.3 | 0.06 | 0.34 | NA | NA |
| Very elderly (>75 years) | 0.,7 | 0.31 | 0.05 | 0.34 | NA | NA |

* dietary intake reported for age group 3-6 years
** dietary intake reported for age group 6-10 years
[#] dietary intake reported for age group >18 years
[##] not available

Although preferably data on BDE-99 concentrations and dietary intakes are taken from the same study to determine background concentrations and intake as input into S-RISK, however, the above-mentioned studies all have their limitations. All these studies have focused on food groups with high occurrence and likelihood for PBDEs to be detected such

as fish, meat, eggs and other fatty related products. Data on the presence of PBDEs in fruits, different types of vegetables and potatoes is extremely limited. Poma et al. (Poma *et al.*, 2018) only analysed several individual vegetable samples investigating the presence of BDE99 in potatoes, leafy vegetables and fruit vegetables. Also, the EFSA dataset covers a period of 10 years in which it is likely that concentrations would have declined as other studies have shown, so using their data might overestimate current human exposure via the diet.

**Selected value for background concentration**

In order to determine the background exposure via the diet, data from Poma et al. (2018) on BDE99 concentrations in food were combined with food consumption data for Belgium (values taken from S-RISK and from the food consumption survey held in Belgium in 2014-2015). Poma et al. (Poma *et al.*, 2018) contains data that could be used for the following food groups that are included in S-RISK:

- Potatoes
- Leafy vegetables
- Fruit vegetables
- Beef
- Offal
- Milk and dairy products
- Eggs
- Butter
- Grains and grain products
- Fish and fish products

Root vegetables, bulbous vegetables, cabbages and leguminous vegetables are food groups included in S-RISK but Poma et al. (Poma *et al.*, 2018) didn't include any of these foods in their study. Since no other data on BDE99 concentrations for these food groups were found for Belgium or other European countries it was decided to make the assumption that concentrations potatoes could be used as read-across for root vegetables and bulbous vegetables, and that concentrations leafy and fruit vegetables could be used as read-across for cabbages and leguminous vegetables. **As BDE-99 concentrations in all analysed food samples were below the LOQ of 5 pg/g ww, an Upper Bound (UB) intake scenario (using the LOQ as concentrations) and Medium Bound (MB) intake scenario (using half of the LOQ as concentration) were estimated.**

The daily dietary intakes were estimated using the concentration of 2.5 pg/g ww (MB) and 5 pg/g ww (UB) and food consumption data used in S-RISK and are shown in Table 10 below for all the food groups and different age groups.

The UB estimated total dietary intakes (on a pg/kg bw/d basis) are generally comparable to the EFSA intake and fall between the EFSA LB and UB intakes based on 2011-2019 input data. The estimated MB intakes are below the LB intakes reported by EFSA. Reasons why the estimated dietary intakes could be generally lower than the EFSA estimated intakes could be due to several factors. For example, variation in LOQ values could have that the time period from which data was used by EFSA spans 10 years. Concentrations in food could have decreased during this period.

Table 10: Daily dietary intakes of BDE-99 (pg/d) via various food groups

| Food group | Age group (years) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1-<3 | 3-<6 | 6-<10 | 10-<15 | 15-<21 | 21-<31 | 31-<41 | 41-<51 | 51-<61 | ≥61 |
| **Medium Bound intake** | | | | | | | | | | |
| Potatoes | 91 | 213 | 252 | 302 | 351 | 325 | 311 | 323 | 336 | 343 |
| Root and tuberous plant | *25* | *39* | *42* | *46* | *60* | *67* | *67* | *67* | *67* | *67* |
| Bulbous plants | *15* | *23* | *27* | *33* | *42* | *48* | *48* | *48* | *48* | *48* |
| Fruit vegetables | 22 | 35 | 54 | 78 | 124 | 198 | 198 | 198 | 198 | 198 |
| Cabbages | *18* | *29* | *28* | *28* | *34* | *46* | *46* | *46* | *46* | *46* |
| Leafy vegetables | 20 | 31 | 41 | 55 | 68 | 82 | 82 | 82 | 82 | 82 |
| Leguminous vegetables | *14* | *22* | *25* | *29* | *35* | *39* | *39* | *39* | *39* | *39* |
| Beef | 25 | 25 | 45 | 75 | 93 | 80 | 90 | 93 | 95 | 88 |
| Organ meat | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 |
| Milk | 988 | 968 | 850 | 700 | 573 | 538 | 453 | 465 | 478 | 528 |
| Butter | 1 | 1 | 2 | 4 | 7 | 8 | 9 | 12 | 15 | 19 |
| Eggs | 38 | 73 | 75 | 75 | 83 | 103 | 108 | 113 | 118 | 110 |
| Bread/cereal | 253 | 253 | 303 | 335 | 353 | 375 | 375 | 350 | 350 | 350 |
| Fish | 35 | 35 | 38 | 35 | 40 | 53 | 53 | 73 | 73 | 73 |
| **Total (pg/d)** | **1542** | **1746** | **1782** | **1795** | **1860** | **1961** | **1878** | **1908** | **1944** | **1990** |
| **Total (pg/kg bw/d)*** | **125** | **99** | **67** | **40** | **30** | **29** | **27** | **27** | **26** | **27** |
| **Total (ng/kg bw/d)** | **0.13** | **0.099** | **0.067** | **0.040** | **0.030** | **0.029** | **0.027** | **0.027** | **0.026** | **0.027** |
| **Upper Bound intake** | | | | | | | | | | |
| Potatoes | 182 | 427 | 504 | 603 | 701 | 650 | 623 | 646 | 672 | 686 |
| Root and tuberous plant | *49* | *78* | *84* | *91* | *119* | *135* | *135* | *135* | *135* | *135* |
| Bulbous plants | *29* | *46* | *55* | *66* | *84* | *96* | *96* | *96* | *96* | *96* |
| Fruit vegetables | 44 | 70 | 108 | 157 | 249 | 396 | 396 | 396 | 396 | 396 |
| Cabbages | *36* | *57* | *56* | *55* | *68* | *93* | *93* | *93* | *93* | *93* |
| Leafy vegetables | 39 | 62 | 82 | 109 | 136 | 164 | 164 | 164 | 164 | 164 |
| Leguminous vegetables | *27* | *43* | *50* | *58* | *69* | *78* | *78* | *78* | *78* | *78* |
| Beef | 50 | 50 | 90 | 150 | 185 | 160 | 180 | 185 | 190 | 175 |
| Organ meat | 0 | 0 | 1 | 2 | 2 | 1 | 1 | 1 | 1 | 1 |
| Milk | 1975 | 1935 | 1700 | 1400 | 1145 | 1075 | 905 | 930 | 955 | 1055 |
| Butter | 2 | 2 | 5 | 8 | 13 | 16 | 17 | 24 | 30 | 38 |
| Eggs | 75 | 145 | 150 | 150 | 165 | 205 | 215 | 225 | 235 | 220 |
| Bread/cereal | 505 | 505 | 605 | 670 | 705 | 750 | 750 | 700 | 700 | 700 |
| Fish | 70 | 70 | 75 | 70 | 80 | 105 | 105 | 145 | 145 | 145 |
| **Total (pg/d)** | **3084** | **3491** | **3565** | **3589** | **3720** | **3921** | **3756** | **3817** | **3888** | **3980** |
| **Total (pg/kg bw/d)*** | **251** | **198** | **133** | **81** | **60** | **57** | **53** | **54** | **53** | **55** |
| **Total (ng/kg bw/d)** | **0.25** | **0.20** | **0.13** | **0.081** | **0.060** | **0.057** | **0.053** | **0.054** | **0.053** | **0.055** |

Note: Dietary intakes reported in Italics are assumptions as no monitoring data for these vegetables existed. Read-across from other vegetables is made (see text).

* body weight information was taken from the S-RISK model.

# 7 TRANSFER TO PLANTS

Data on the uptake of PBDEs in plants has recently been summarized in two review papers ((Dobslaw *et al.*, 2021; Zhang *et al.*, 2021). PBDEs cover diphenyl ethers with a wide range of 2–10 bromo substituents. Hence, PBDEs reveal a large range of molar masses, heterogeneous lipophilicity and volatility. Therefore, BDE congener specific transport and plant uptake mechanisms (soil–air–plant vs. soil–soil moisture–root–plant) strongly differ and depend on compound physical parameters. Plant uptake by the soil–soil moisture–root–plant pathway is of higher relevance for low and medium brominated PBDEs (including BDE-99) compared higher brominated PBDEs (Dobslaw *et al.*, 2021). **On the other hand, atmospheric uptake is the dominant pathway for high brominated PBDEs compared to low and medium brominated PBDEs.**

Bioconcentration factors for BDE-99 from soil to plant were calculated using the soil concentrations (in mg/kg dw) and the BDE-99 concentration in the plant (in mg/kg dw) (data was taken from the two review papers and/or the original studies; see Table 11). Concentrations in the edible parts of the plant were used to estimate the BCF, if these data were not available then concentrations in the roots or stem were used to estimate the BCF. Table 11 provides an overview of the calculated BCFs in the variable plants. If no data was available for a given plant type, read-across from another plant of the same type was used to generate a BCF value.

The study design from the various studies used to calculate BCF values varied from using naturally contaminated soil and growing the plants in a controlled environment (Yang *et al.*, 2018), amended soil (with e.g. sludge or spiked) and growing the plants in a controlled environment (Bizkarguenaga *et al.*, 2016; Navarro *et al.*, 2017) to field-based studies where soil and plants were directly sampled from the studied location (Wang *et al.*, 2011b; Parolini *et al.*, 2012; Wang *et al.*, 2016). All BCF values were based on coupled soil/vegetable concentrations from the same studies.

Table 11: Overview of calculated BCF values for various foods from soil to plant.

| Plant | Type | BCF | Comment | Reference |
|---|---|---|---|---|
| Potato | Tuber | 7.15 | Read-across sweet potato | (Wang *et al.*, 2016) |
| Carrot | Root | 0.57 | | (Wang *et al.*, 2011b) |
| Radish | Root | 0.43 | | (Wang *et al.*, 2011b) |
| Scorzonera | Root | 0.50 | Read-across carrot/radish (average value) | |
| Onion | Foliar | 7.1 | Average value multiple studies (range 0.6 – 13) | (Wang *et al.*, 2011b; Wang *et al.*, 2016) |
| Leek | Foliar | 7.1 | Read-across onion | |
| Tomatoes | Above ground non-foliar | 2.5 | Estimated value, data taken from a graph. | (Navarro *et al.*, 2017) |
| Cucumber | Above ground non-foliar | 2.5 | Read-across tomato | |
| Paprika | Above ground non-foliar | 2.5 | Read-across tomato | |
| Cabbage | Above ground non-foliar | 1.1 | Based on Chinese kale | (Wang *et al.*, 2011b) |
| Cauliflower | Above ground non-foliar | 0.57 | Based on Pak-choi | (Wang *et al.*, 2011b) |
| Sprout | Above ground non-foliar | 0.86 | Read-across average cabbage/cauliflower | |
| Lettuce | Foliar | 0.94 | Average value multiple studies (range 0.11-1.7) | (Wang *et al.*, 2011b; Bizkarguenaga *et al.*, 2016) |

| Plant | Type | BCF | Comment | Reference |
|---|---|---|---|---|
| Lamb's lettuce | Foliar | 0.78 | Read-across average lettuce/spinach | |
| Endive | Foliar | 0.78 | Read-across average lettuce/spinach | |
| Spinach | Foliar | 0.61 | Average value multiple studies (range 0.35-0.87) | (Navarro *et al.*, 2017; Wu *et al.*, 2018) |
| Chicory | Foliar | 0.78 | Read-across average lettuce/spinach | |
| Celery | Foliar | 0.78 | Read-across average lettuce/spinach | |
| Beans | Above ground non-foliar | 1 | Read-across peas | |
| Peas | Above ground non-foliar | 1 | | (Wang *et al.*, 2011b) |
| Grass | Foliar | 9.2 | | (Parolini *et al.*, 2012) |
| Maize | Above ground non-foliar | 0,0038 | | (Huang *et al.*, 2011) |

For carrots, radish, onion, tomatoes, lettuce, spinach, peas, grass and maize the BCF values are based on data of the crops themselves. For several vegetables, a read-across was made to vegetables for which BCF data existed but are not mentioned in S-Risk, these were sweet potato for potato, Chinese kale for cabbage and pak-choi for cauliflower. For the remaining vegetables, a read-across to other vegetables within the same plant type were made.

# 8 TRANSFER TO ANIMAL PRODUCTS

Literature on the transfer of PBDEs from feed to animal products is limited. Several studies reported on the presence of BDE-99 in cows' milk and/or meat (Grümping *et al.*, 2006; Kierkegaard *et al.*, 2009; Parolini *et al.*, 2012; Oloruntoba *et al.*, 2019), milk from goats (Ounnas *et al.*, 2010) or chicken eggs, liver and/or fat (Pirard & Pauw, 2007; Covaci *et al.*, 2009; Oloruntoba *et al.*, 2019).

In order to calculate the BioTransfer Factor (BTF) information on the daily intake via food as well as concentration in milk, eggs or meat (on wet weight basis, not on a lipid-basis) is needed. Most of the studies mentioned above included concentrations in milk, eggs or meat, but data on the daily intake was not provided (Grümping *et al.*, 2006; Oloruntoba *et al.*, 2019).

Kierkegaard et al. (Kierkegaard *et al.*, 2009) studied the mass balance of tri-hexaBDEs in lactating cows and reported on BDE-99 concentrations in feed, cow's milk and liver. The study reported on carry-over rates (COR) of PBDE congeners from feed to milk whereby the chemical flux in milk (in mg/day) is divided by the daily intake (in mg/day). The COR of BDE-99 in the two studied cows were 0.17 and 0.24. BTFs for PBDEs were not included in the study. PBDE concentrations in the milk and liver were only reported on a lipid weight basis, not on a wet weight basis. In order to calculate the BTF, wet weight concentrations are divided by the daily intake, not lipid weight concentrations. To convert the milk and liver lipid weight concentrations to wet weight concentrations, a generic percent lipid in milk and liver in cows was used, 4.6% for milk[5] and 3.6% for liver[6]. Based on the wet weight concentrations, BTF values for milk and liver were 0.0099 for milk (average value for the two cows) and 0.012 for liver.

BTF values have in the past also been estimating using various models. Travis and Arms (Travis & Arms, 1988) used hydrophobicity (Kow) as input to estimate BTF values, however, Hendriks et al. (Hendriks *et al.*, 2007) showed no correlation between Kow and BTF for persistent chemicals and showed that metabolism of chemicals in cattle to be an important parameter in estimating BTF values. Takaki et al. (Takaki *et al.*, 2015) reviewed existing methods to estimate transfer of chemicals from feed to milk and tissues and further developed a model by including metabolism. The model was used to estimate BTF values for a range of dioxin, PCB and PBDE congeners. For BDE-99 the BTF for milk was estimated to be 0.0083 and for meat the BTF value was 0.013. These values were comparable to the values estimated by using the data from Kierkegaard et al. (2009).

Table 12 provides an overview of the BTF values for the various tissues, milk and eggs. For milk, an average BTF value of 0.009 was selected. Estimated BTF values based on Travis and Arms (Travis & Arms, 1988) are used as default values in S-Risk and are listed in Table 12 as well.

[5] FoodData Central (usda.gov)
[6] FoodData Central (usda.gov)

Table 12: Overview of BTF values.

| | Travis and Arms (S-Risk) | BTF value literature | Reference |
|---|---|---|---|
| Beef | 0.1 | 0.013 | (Takaki *et al.*, 2015) |
| Sheepsmeat | 0.1 | No data | |
| Liver | 0.1 | 0.012 | (Kierkegaard *et al.*, 2009) |
| Kidney | 0.1 | No data | |
| Milk | 0.0158 | 0.0099<br>0.0083 | (Kierkegaard *et al.*, 2009)<br>(Takaki *et al.*, 2015) |
| Soil - eggs | 0 | No data | |
| Food - eggs | 0 | No data | |

The model by Travis and Arms (Travis & Arms, 1988) estimating the BTF has an applicability domain for chemicals with log Kow values ranging between 3 and 7, although Takaki et al. (Takaki *et al.*, 2015) noted that the Travis and Arms model predict increasing BTF values for chemicals with log Kow >6.5 whereas this is contradictory to experimental data. The Travis and Arms model therefore includes a cut-off value for the log Kow of 6.5. The Log Kow value for BDE-99 is 7.4.

Travis and Arms (Travis & Arms, 1988) only use hydrophobicity (log Kow) as the only parameter predicting BTF values. Hendriks et al. (Hendriks *et al.*, 2007) reported on a weak correlation between the Kow and BTF values for persistent chemicals ($r^2$ = 0.02), and metabolism was found to be an important factor impacting the BTF rather than hydrophobicity (Staples *et al.*, 1997; Hendriks *et al.*, 2007). Takaki et al. (Takaki *et al.*, 2015), included metabolism in their model predicting BTF values (to milk and beef) and the model was validated for chemicals such as PCBs, PCDD/F and PBDEs.

In order to estimate the impact of using BTF values from Travis and Arms (Travis & Arms, 1988) and Takaki et al. (Takaki *et al.*, 2015), Application I SRV for the agricultural scenario were estimated using both sets of BTF (see Table 13).

Table 13: Estimated SRV II -Agriculture using BTF values from Takaki et al. (2015) and Travis and Arms (1988).

| | Takaki *et al.* (2015) | Travis and Arms (1988) |
|---|---|---|
| SRV II -Agriculture (mg/kg ds) | **$3.973 \times 10^{-3}$** | **$2.407 \times 10^{-3}$** |
| BTF beef | 0.013 | 0.10 |
| BTF milk | 0.009 | 0.0158 |

The estimated SRV for the agriculture scenario using both sets of BTF values are similar and only vary by a factor of 1.6. Therefore, as the Takaki et al. (2015) data is based on a model including metabolism and their data is comparable to experimental data (BTF milk from Kirkegaard et al. (Kierkegaard *et al.*, 2009)), the BTF values based on Takaki et al. (Takaki *et al.*, 2015) and Kirkegaard et al. (Kierkegaard *et al.*, 2009) are used to estimate the SRV.

# 9 TOXICOLOGY

## 9.1 Introduction

The toxicology overview of BDE-99 is mainly based on the EFSA (2011), US-EPA (2008), ECB (2000) and ATSDR (2017) reports and on publications from scientific journals. The main toxicological targets in oral exposure are the liver, hormone homeostasis, reproduction and neurodevelopment. Studies involving inhalation exposure were not found.

Hazard classifications that are legally binding in the European Union (EU) are listed in Annex VI of CLP legislation (MichiganDepartmentofEnvironmentalQuality, 2008) and are called harmonised classifications. BDE-99 does not have a harmonized classification, pentaBDE does. PentaBDE is classified as Lact. (H362: May cause harm to breast-fed children), STOT RE 2 (H373: May cause damage to organs through prolonged or repeated exposure), Aquatic Acute 1 (H400: Very toxic to aquatic life), Aquatic Chronic 1 (H410: Very toxic to aquatic life with long lasting effects)[7].
US-EPA reports that there is inadequate information to assess the carcinogenic potential of BDE-99 (US-EPA, 2008).

BDE-99 nor pentaBDEs are included in the 15th Report on Carcinogens (NTP, 2021).

## 9.2 Toxicokinetics

Toxicokinetics include the absorption, distribution, metabolization, and excretion of substances after exposure. The key elements that determine the kinetics, and consequently the half-life of a substance, are the storage in adipose tissues, the binding affinity for certain liver enzymes, and finally, the metabolization and excretion rate (OVAM, 2007).
Data on toxicokinetics of BDE-99 in humans are very limited. Data on the toxicokinetics of the pentaBDEs in humans are limited to findings on levels in adipose tissues, blood, liver, and maternal milk, which demonstrate that they are absorbed from the environment and distributed to tissues (US-EPA, 2008). Several studies evaluating toxicokinetics in laboratory animals have been published. These studies are discussed below.

### 9.2.1 Absorption after oral intake

There are no studies available examining specifically the oral absorption of BDE-99 in humans. The data that demonstrate human absorption come from measurements of BDE-99 in human biological media after anthropogenic exposures (adipose tissues, blood, liver, and maternal milk), but do not permit estimation of route-specific uptake parameters (US-EPA, 2008). Data on absorption of BDE-99 in several strains of rats and mice are available.

In the study by Hakk *et al.* (2002), $^{14}$C-labelled BDE-99 was given as a single oral dose of 8 mg/kg to groups of conventional and bile-duct-cannulated male rats. Radioactivity in 24-hour faeces accounted for 22.3 ± 15.8 % and 52.5 ± 26.9 % of administered radioactivity in conventional and bile-cannulated rats. Thence, absorption efficiencies for BDE-99 were estimated to be of at least 78 and 48% respectively. The higher faecal excretion on day 1 in the bile-duct-cannulated rats indicates that gastrointestinal emulsion by bile is a major factor governing absorption.

[7] C&L Inventory (europa.eu)

Chen *et al.* (2006) compared radioactivity profiles in 24-hour excreta and tissues of male rats after gavage of 0.6 mg/kg $^{14}$C-BDE-99. The percent of the dose in the faeces 24 hours after oral exposure was 43.1 ± 4.7%. Chen et al. (2006) conducted the same study in male mice and found that the absorption of 0.6 mg/kg $^{14}$C-BDE-99 in mice was comparable to that in rats, based on the comparison of faecal loss after oral (27.1 ± 5.3%) exposures. The estimated oral absorption efficiency was determined to be of approximately 85% in both male rats and male mice. The dose used by Chen et al. (2006) was lower than that used by Hakk et al. (2002) and is therefore consistent with the higher average estimate of absorption.

In addition, Eriksson *et al.* (2002) demonstrated that $^{14}$C-labelled BDE-99 can be taken up and retained in the neonatal mouse brain. Neonatal male mice were administered 0 or 8 mg/kg of $^{14}$C-BDE-99 in a fat emulsion on postnatal day (PND) 3, 10, or 19, and the animals were sacrificed 24 hours or 7 days after administration. The amount of radioactivity in the brain was between 0.4 and 0.5% of the administered dose in all mice, 24 hours after administration. $^{14}$C-BDE-99 or its metabolites could still be detected in the brain 7 days after administration. These data prove the uptake of BDE-99 from the gastrointestinal tract and transport across the blood-brain barrier in mice.

EFSA (2011a) uses an oral absorption of 50-80% for its risk assessment of a group of congeners that includes BDE-99. In the discussion about absorption, EFSA refers to studies from Hakk *et al.* (2002) and Chen *et al.* (2006), who investigated the fate of $^{14}$C-radiolabelled BDE-99 in rats after a single oral dose. In addition, ATSDR (2017a) also reported a range for estimates of oral absorption efficiencies of 70–85% for tetraBDE (BDE 47), pentaBDE (BDE-99, BDE-100), and hexaBDE (BDE-153, BDE-154).

**An oral absorption of 85% is used for the calculation of soil remediation values.** The value of 85% was measured in a comparative study with male rats and mice that were administered BDE-99 by gavage. Furthermore, EFSA uses an oral absorption range for various pentaBDE congeners of 50-80% and ATSDR (2017) reported a range of 70–85%. The available animal studies show that the oral absorption of BDE-99 via the gastrointestinal tract is high (with 85% as the highest value for absorption). Since there is evidence that BDE-99 can cross the blood-brain barrier, the most conservative approach is used, and the highest derived experimental absorption value of 85% is selected.

### 9.2.2 Oral relative bioavailability from soil/dust

Bioaccessibility determines the amount of substance that becomes available in the gastrointestinal tract and does not take into account absorption through the intestinal wall (which bioavailability does).
Bioaccessibility from dust in indoor and outdoor air was measured with an *in vitro* system that simulates a fasting stomach by Yu *et al.* (2012); the air was collected in 4 different seasons in Shanghai (China). Total PBDE concentrations were lowest in autumn in both indoor and outdoor air. This is in line with some (but not all) other studies showing that PBDE concentrations are generally higher in warm months than in cold months. Temperature (indoor air) and wet deposition (outdoor air) may be the most important parameters that can explain the seasonal variation. A lower temperature in autumn leads to a lower rate of emissions from household products (in winter the effect of lower emissions is offset by lower ventilation than in autumn when windows are opened to ventilate). Autumn in Shanghai is usually windy and dry; the absence of wet deposition and the blowing away of small air particles (small particles absorb more PBDEs than large ones) could explain the lower PBDE concentrations in autumn. The average measured bioaccessibility was:

- for dust in indoor air: 18.5% (autumn) – 23.4% (spring)

- for dust in outdoor air: 14.2% (summer and autumn) – 21.1% (spring)

Yu *et al.* (2012) did not discuss whether the seasonal variation of the PBDE concentration can explain the difference in bioaccessibility between the seasons. The presence of food during substance intake increases bioaccessibility. If the dust were ingested together with food, which is usually the case in reality, the bioaccessibility would probably be higher than that measured in the empty stomach simulation (Yu *et al.*, 2012).

Bioaccessibility of BDEs in 13 types of food, including fish, meat, rice, flour and vegetables, was measured using an *in vitro* digestion model. Bioaccessibility was found to be 2.6–41.3% (Yu *et al.*, 2010); there was a positive correlation with fat and carbohydrates and a negative correlation with the protein and fiber content of the food. In a similar study, the bioaccessibility of PBDEs in 299 vegetables and animal food products collected in China was measured using a human gastrointestinal digestion model (Yu *et al.*, 2011). Bioaccessibility ranged from 2.6 – 39.9% in vegetables and from 5.2 – 105.3% in animal food products.

The measured bioaccessibility via substance ingestion of PBDEs by Yu *et al.* (2012) would underestimate the actual bioavailability if diet had a major impact or overestimate it if absorption through the gastrointestinal tract was very low; in the latter case, only a small fraction of the bioaccessible substance would be effectively absorbed into the bloodstream and thus become bioavailable.

In order to derive the soil remediation value, not the absolute but the relative bioavailability (RBA) from soil is used as a parameter. RBA is the ratio of bioavailability in one medium (soil and dust in the case of soil remediation) compared to bioavailability in another medium.

In a review paper on a uniform approach for determining bioavailability, Collins *et al.* (2015) report results from published measured bioavailability values of BDEs, including that of BDE-99 from dust. The most abundant PBDE congeners present in dust are BDE 47, BDE-99, BDE 183 and BDE 209. The less brominated congeners of which BDE-99 is a part had a value between 40 and 60%.
Relative bioavailability of BDE-99 from house dust and corn oil solution was measured in rats fed 1 or 6 µg/kg bw via diet for 21 days (Huwe *et al.*, 2008). In the high-dose groups, retention in tissues was 43.7±5.2% for dust and 53.7±6.4% for corn oil; the RBA was 81.4% (43.7/53.7). Intake via house dust or corn oil made no difference to the absorption.

The study by Huwe *et al.* (2008) showed that the bioavailability of BDE-99 in dust is slightly lower than that in corn oil. The highest measured RBA is 81.4%.

**An oral RBA from soil of 0.81 is selected for the calculation of soil remediation values.**

### 9.2.3 Absorption after inhalation

There are no data available on absorption following exposure via inhalation.

### 9.2.4 Absorption after dermal contact

No human data are available but based on the physicochemical properties of BDE-99 and the analogy with PCBs, a maximum absorption of 1% is assumed (ATSDR, 2017a).

### 9.2.5 Dermal absorption from water

There are no literature data on dermal absorption from water. The calculated dermal permeability coefficient from water (Kp) is 0.0373 cm/h (DermWin v2.02)[8].
**A dermal absorption from water of 0.0373 cm/h is selected for the calculation of soil remediation values.**

### 9.2.6 Dermal absorption from soil/dust

There are no literature data on dermal absorption (ABSd) from soil or dust. The default value for the dermal absorption fraction from soil for semi-volatile organic compounds (SVOC) in the US-EPA Superfund Risk Assessment Guidance for dermal exposure is 0.1 (EPA, 2004). This value is an average of measured values of SVOCs.

**For the calculation of soil remediation values, a fraction for dermal absorption from soil/dust of 0.1 is selected.**

### 9.2.7 Distribution

BDE-99 has a high Kow, which suggests a strong potential for accumulation in lipid-rich tissues *(US-EPA, 2008)*. Studies performed in rats and mice with BDE-99 confirmed a body distribution with a preference for lipid-rich tissues such as adipose tissue, and to a lesser extent gastrointestinal tract, muscle tissue, skin, adrenals and liver.
Human biomonitoring studies are available for adipose tissue, liver, milk and blood samples and indicate that PBDEs tend to spread through these media. No quantitative data are available on the extent of distribution to and accumulation in tissues. Therefore, it is unknown whether BDE-99 also distributes to other tissues as well. However, the number of samples examined across studies and countries is rather small.

#### 9.2.7.1 Human data

***Adipose Tissue***
Breast adipose samples were collected between 1996 and 1998 from 23 San Francisco Bay area women as part of a case-control study on organochlorine compounds and breast cancer. Breast adipose samples were analyzed for BDE-47 (tetraBDE), BDE-99 and -100 (pentaBDEs), and BDE-153 and -154 (hexaBDEs). The highest concentrations found were for BDE-47, followed by hexaBDEs and pentaBDEs (She *et al.*, 2002).

In a study in New York City, 52 adipose fat tissue samples were collected in 2003 and 2004 from patients undergoing liposuction procedures. BDE-47 was the major congener detected, followed by BDE-100 and -99 (Johnson-Restrepo *et al.*, 2005).

In a study in Japan, 10 human adipose samples taken from the general Tokyo population in 2000 were analyzed for BDE-28, -47, -99, -100, -153, -154, and -183. Median concentrations (in ng/g lipid weight (lw) of the PBDE congeners were, in decreasing order, BDE-47 (0.5), BDE-153 (0.4), BDE-100 (0.3), BDE-99 (0.1), BDE-154 (0.06), and BDE-183 (0.05) (Choi *et al.*, 2003).

Tetra-, penta-, and hexaBDEs were analyzed in the adipose tissues from 3 women and 10 men between the ages of 28 and 83 and living in Spain for at least 10 years. The average concentrations of BDE-47, BDE-99, and BDE-153 were 1.4, 0.4, and 1.8 ng/g lw, respectively (Meneses *et al.*, 1999).

[8] (EPI Suite™-Estimation Program Interface | US EPA)

***Liver***
In a Swedish study, paired samples of human liver and adipose tissue obtained at autopsy from one woman (age 47) and four men (ages 66–83) were analyzed for 9 tri- to hexaBDE congeners. PBDEs were found in all samples. BDE-47, -99, and -153 were the predominant PBDE congeners in both liver and adipose tissue. For the pentaBDEs, BDE-99 was the predominant congener in both liver and adipose tissue, followed by BDE-100 and -85. The mean total concentrations of these three pentaBDEs were higher in liver than in adipose tissue and amounted to 4.3 and 1.7 ng/g lw, respectively (Guvenius *et al.*, 2001) (Meironyte Guvenius *et al.*, 2001).

***Human Milk***
In a study conducted in 2002 of levels of PBDEs in human milk in the U.S., 47 samples from Caucasian, African American, and Hispanic nursing mothers of 20–41 years of age and living in Texas were analyzed for 13 PBDE congeners. The maximum and mean concentrations of BDE-99 were 111 and 14 ng/g lw, respectively (Schecter *et al.*, 2003).

Milk samples were collected in 2003 from 40 first-time mothers with 2- to 8-week-old infants and residing in urban areas in the Pacific Northwest of the U.S. and Canada. BDE-47 was found at the highest level with median concentration of 28 ng/g lw, followed by BDE-99 (5.4 ng/g lw), BDE-100 (5.3 ng/g lw), and BDE-153 (4.8 ng/g lw) (She *et al.*, 2007).

Breast milk was collected from 12 primiparous 24- to 33-year-old nursing women in Japan, at one month after delivery. The most abundant PBDE congeners in human milk were BDE-47 and BDE-153, followed by BDE-99 and -100 and triBDEs (Ohta *et al.*, 2002). In another study in Japan, PBDEs were detected in eight pooled human milk samples collected in 2000, BDE-47 was the predominant congener (0.5 ng/g lw), followed by hexaBDEs (0.4 ng/g lw), pentaBDEs (0.3 ng/g lw), triBDEs (0.1 ng/g lw), and heptaBDEs (0.04 ng/g lw). BDE-100 was the most abundant (0.17 ng/g lw) of the pentaBDEs, followed by BDE-99 (0.15 ng/g lw) and BDE-85 (0.01 ng/g lw) (Akutsu *et al.*, 2003).

Breast milk concentrations of BDE-47, BDE-99 and -100, and BDE-153 and -154 were determined in samples from 93 primiparous women, collected from 1996–1999 in Uppsala County, Sweden. The women ranged in age from 20–35 years. BDE-47 was the major congener (mean value 2.4 ng/g lw) and constituted 60% of the mean concentration of PBDEs of 4.0 ng/g lw, followed by BDE-99 and -153 (0.6 ng/g lw each), BDE-100 (0.4 ng/g lw), and BDE-154 (0.07 ng/g lw) (Lind *et al.*, 2003).

***Blood***
In 2000–2002, the sum of the median concentrations of 6 tetra- to hexaBDEs in serum pools collected in the U.S. was 61 ng/g lw. PBDEs included in this study were BDE-47, BDE-85, -99, and -100, and BDE-153 and -154 (Sjödin *et al.*, 2004).

Serum samples from 24 pregnant Mexican immigrant women living in an agricultural community in California were collected during 1999 and 2001. Tetra-, penta-, hexa-, and hepta-BDE congeners were measured in the serum samples. The median concentration of the sum of all BDE congeners was 21 ng/g lw with a median concentration for BDE-47, -99, -100, and -153 of 11, 2.9, 1.8, and 1.5 ng/g lw, respectively (Bradman *et al.*, 2007).

Concentrations of five lower brominated congeners BDE-47, -99, -100, -153, and -154 were measured in serum samples collected during 2004 from a family residing in Berkeley, California (35- and 36-year-old father and mother, respectively, 5-year-old daughter, and 18-month-old son). The 18-month-old son was exclusively breast-fed for 0-6 months and was breast-fed during the study period. The sum of the PBDE levels was much higher in the infant (418 ng/g lw) and the child (247 ng/g lw) than in their parents (mother 106 ng/g lw; father 64

ng/g lw). BDE-47 was the predominant congener for all ages, followed by hexaBDE-153, -100, and -99 (Fischer *et al.*, 2006).

In Norway, pooled serum samples collected in 1998 from eight population groups of different ages (0 to >60 years) and genders were analyzed for tri- to hexaBDEs. Total concentration of these PBDEs in men older than 60 years was 5.3 ng/g lw, with BDE-47 being the most abundant congener (3.4 ng/g lw), followed by BDE-153 (0.6 ng/g lw); BDE-100, BDE-99, and BDE-154 (all at approximately 0.4 ng/g lw each); and BDE-28 (0.1 ng/g lw). The sum of the concentration of these PBDEs in serum was highest for the 0- to 4-year-old children (12 ng/g lw) but was about one-third lower and relatively constant for the different age groups above 4 years. Except for the 0- to 4-year-olds who seemed to experience elevated exposure, there was a lack of an age-related trend of PBDE body burdens. This may be explained by the fact that PBDEs were relatively new contaminants in the environment in 1998; the time period for human exposure was therefore relatively short, and different age groups (except the 0- to 4-year-old group) may thus have experienced a similar exposure period. The high level of PBDEs in the serum of the 0- to 4-year-olds could be due to higher exposure from human milk and/or certain behavioural activity, such as crawling or sucking on flame-retardant materials (Thomsen *et al.*, 2002).

***Placental Transport***

Twelve paired samples of maternal and cord blood collected in 2001 from women in Indiana were analyzed for tetra- to heptaBDE congeners. BDE-47 (tetra-congener) was the most abundant congener, followed by BDE-99 and BDE-100. PBDE concentrations were highly correlated between mother and fetal sera, indicating that PBDEs cross the placenta into the fetal circulation. There was a decreasing trend in the concentration of PBDE congeners in maternal and fetal sera with increasing degree of bromination (Mazdai *et al.*, 2003). Samples of maternal and cord blood plasma were collected during 2000–2001 from 15 Swedish mothers. BDE-47 was the most abundant of all the congeners, and comparable median concentrations were found in maternal and cord blood plasma. Levels of BDE-99 to -183 were higher in maternal blood than in cord blood, indicating that the higher brominated PBDEs do not pass through the placenta to the same extent as the lower brominated congener BDE-47. This was not reported in the Mazdai *et al.* (2003) study, where comparable levels were found in maternal and fetal sera for all PBDE congeners studied. The concentrations of PBDEs found in maternal and fetal blood samples in Indiana women (Mazdai *et al.*, 2003) were substantially higher than those found in Swedish women Guvenius *et al.* (2003).

In summary, the predominant congener found in adipose tissue, human milk, and blood samples is tetraBDE-47, followed by pentaBDE-99 and -100, respectively. The concentration profiles of PBDEs in different regions of the U.S. in adipose tissue, serum, and human milk are similar. However, median concentrations of the sum of PBDEs measured in human biological media in the U.S. are substantially higher than the levels found in human populations in Europe or Japan.

#### *9.2.7.1.1 Animal data*

The animal data on BDE-99 distribution are limited but more quantitative than the human data because they represent the distribution after deliberate dosing studies.

In a study by Hakk *et al.* (2002), tissue distribution of radiolabeled BDE-99 was assessed in young adult male rats (conventional and bile-duct-cannulated) after a single oral dose (8 mg/kg). In the conventional rat, BDE-99 was preferentially found in lipophilic tissues, with 39% of the administered dose being found in the carcass, 6% in the gastrointestinal tract, and 4% in adipose tissue. The tissue data support the hypothesis that bile salts are necessary for the

intestinal absorption of BDE-99, since tissue levels of $^{14}$C-BDE-99 for the bile-duct-cannulated rats were much lower when compared to those of conventional rats (2% in the carcass, 1.5% in the gastrointestinal tract, and 0.8% in adipose tissue). The most lipophilic tissues (adipose, adrenal, gastrointestinal tract, and skin) had the highest amounts of BDE-99 when the tissue distribution statistics were represented on a concentration basis. The highest lipid content and BDE-99 concentrations were found in adipose tissue. However, the concentrations of BDE-99 in the kidney and lung, which have larger lipid contents than the liver, were lower than those in the liver.

Chen *et al.* (2006) compared tissue levels of 14C-labeled BDE-99 in male rats and mice at 24 hours after a single exposure to 0.6 or 6 mg/kg with the tissue levels at 24 hours after 10 days of daily exposure to 0.6 mg/kg (a total of 6 mg/kg). The tissues that contained the largest portion of the radiolabel from a 0.6 mg/kg-day oral dose in both rats and mice were the adipose deposits, muscle, skin, and liver. Adipose tissue contained the highest percentage of the dose in rats and mice. In rats, the next-to-the-highest percentage was in the skin, while in mice it was the muscle tissue. All other tissues evaluated contained less than 1% of the dose. For all tissues except adipose tissue, the single 6 mg/kg dose resulted in a higher tissue concentration than the 10 single 0.6 mg/kg-day doses. In adipose tissues, the level of label 24 hours after the last of the ten 0.6 mg/kg-day single doses was higher than that after the single 6 mg/kg dose, illustrating the potential for accumulation of BDE-99 in body lipids.

Darnerud and Risberg (2006) studied the overall qualitative distribution of 14C-labeled BDE-99 in male and female mice, administered by intravenous (i.v.) injection or by gavage at 20 µmol/kg (~11 mg/kg). They observed that the distribution of radioactivity in mice after i.v. administration was characterized by a high initial uptake of radioactivity in fatty tissues. Accumulation of 14C-BDE-99 was especially seen in the liver, adrenal cortex, lung, ovaries, and nasal epithelium accumulated radioactivity. In addition, intermediate radioactivity levels were found also in the brain tissue. No radioactivity was observed in the thyroid gland. At 16 days post-injection, labeling was still visible in the fat tissues, liver, lung, and adrenal cortex, and elimination from the lungs seemed to be slower than from the liver. Some faint labeling remained in the brain. The distribution pattern after oral administration of BDE-99 was similar to what was found after i.v. injection, which showed that the gastrointestinal uptake is effective.

Eriksson *et al.* (2002) demonstrated that BDE-99 can be distributed and retained in the neonatal mouse brain after oral administration of 8 mg/kg of $^{14}$C-BDE-99 in a fat emulsion on PND 3, 10, or 19. The neonatal mice were sacrificed 24 hours or 7 days after administration. The amount of radioactivity in the brain was between 0.4 and 0.5% of the administered dose, 24 hours after administration. Seven days after the administration, 14C-BDE-99 (or its metabolites) could still be detected in the brain, with a concentration of 0.1 to 0.3% of the administered dose in mice exposed on PND 3, 10, or 19.

In the study of Branchi *et al.* (2005), BDE-99 at 0 or 18 mg/kg bw/d was administered to mice from gestation day (GD) 6 to PND 21 by gavage or by letting the mice drink BDE-99 dissolved in corn oil from a syringe. The brains collected from treated male pups on PND 22 showed significantly elevated BDE-99 concentration: 640 µg/kg compared to <5 µg/kg for controls. There was no difference between the concentrations of BDE-99 in the two administration groups.

Ceccatelli *et al.* (2006) studied the distribution of BDE-99 in adult male and female offspring of pregnant rats exposed to BDE-99 by subcutaneous injections (1 or 10 mg/kg-day) on GDs 10–18. The offspring had BDE-99 present in the brain, plasma, and adipose tissues 120 days after birth. For the 1 mg/kg-day dose, the level in the adipose tissue was about 400 times greater than that in plasma. For the 10 mg/kg dose, the level in adipose tissue was about

1,500 times greater than that in plasma. There was considerable variability in the levels found in the adipose tissue among the individual samples analyzed.

In summary, the highest levels of radiolabeled BDE-99 following oral exposure are predominantly found in adipose tissues, liver, muscle, skin, gastrointestinal tract, and the adrenals. The observed distribution pattern for BDE-99 did not consistently correlate with tissue lipid content and there is an indication that distribution is slightly different in mice and rats. In addition, BDE-99 was found to be distributed in fetal brain after oral administration in several animal studies, which is an indication that BDE-99 can pass the blood-brain barrier and can accumulate in brain tissue. BDE-99 was also found to be transferred to offspring during lactation, following maternal exposure. However, neonatal excretion seemed to prevent accumulation and high levels in offspring compared with maternal levels.

### 9.2.8 Metabolisation

BDE-99 appears to be one of the most extensively metabolized PBDE congeners (Hakk *et al.*, 2002).
The excretion of BDE-99 was investigated in normal and bile-duct cannulated male rats that were administered a single dose of 8 mg/kg by gavage (Hakk *et al.*, 2002). Parent BDE-99 compound and metabolites were analyzed in urine, faeces, and bile collected at daily intervals for 3 days. Approximately 20–30% of the extractable faecal radiolabel was unmetabolized in the conventional and bile-duct-cannulated rats. This result is confirmed by Staskal *et al.* (2006) who estimated that about 70% of the BDE-99 in urine and 80% in faecal matter were present as metabolites in mice, following i.v. injection of a 1 mg/kg bw dose.
Studies of Hakk *et al.* (2002, 2006), Staskal *et al.* (2006), and Chen *et al.* (2006) in mice and rats support a metabolic pathway that involves epoxidation as the initial reaction for BDE-99, transforming BDE-99 into hydroxylated (OH-) metabolites via the activity of liver enzymes, such as cytochrome P450 (CYP). This process can be followed by debromination and possibly by conjugation of the hydroxylated derivatives with GSH, glucuronate, and/or sulfate. Hydrolysis of the ether linkage between the two phenyl rings may also occur, producing brominated phenols. There is consistency among these studies of metabolites with regard to the production of mono- and dihydroxylated metabolites as well as hydroxylated and debrominated metabolites.

A study of (Stapleton *et al.*, 2009) on human hepatocytes is consistent with the available data on metabolites in faeces and urine of rats and mice. Stapleton et al. (2009) exposed human hepatocytes to solutions containing 10 µM BDE-99 for periods of 24-72 hr. These incubations resulted in the formation of 2,4,5-tribromophenol, two monohydroxylated pentabrominated diphenylether metabolites and an unidentified tetrabrominated metabolite.

### 9.2.9 Excretion

BDE-99 is mainly excreted via faeces, whereas urine represents a minor route of elimination. Urinary excretion appears to be more substantial in mice than rats (Staskal *et al.*, 2006), (Darnerud & Risberg, 2006). Both parent compound and metabolites are identified in the excreta, and bile is an important contributor to the radiolabel in faecal matter (US-EPA, 2008).

The excretion of BDE-99 was investigated in normal and bile-duct-cannulated male Sprague-Dawley rats that were administered a single dose of 8 mg/kg by gavage (Hakk *et al.*, 2002). Parent BDE-99 compound, and metabolites were analyzed in urine, faeces, and bile collected at daily intervals for 3 days. Excretion in urine was low and amounted to 0.9% of the dose in the conventional rat and 0.4% in the bile-duct-cannulated rat. Biliary elimination was only 4% over the same period of time. Faeces were the major route of elimination of BDE-99.

Approximately 43% of the dose in conventional rats and 87% in bile-duct-cannulated rats was found in the faeces within 3 days. In order to explain the difference between the conventional and bile-duct-cannulated rats, it is suggested that bile salts are needed for the intestinal uptake of BDE-99.
Chen *et al.* (2006) observed in their 10-day study similar results. In male F344 rats receiving a single oral dose of 0.6 mg/kg BDE-99, 43% of the dose was present in the faeces on day 1. The cumulative amount excreted in faeces was 56% by day 10 after exposure. Urinary excretion was 1.6% on day 1 and 2.9% by day 10. Over the 10-day period, about half of the single dose had been excreted, the remainder was retained by the tissues.

### 9.2.10 Half-life Determinations

Hakk *et al.* (2002) estimated, based on the disposition and excretion results obtained in their study, that the whole-body half-life of BDE-99 in male rats was about 6 days. Their results also indicated that BDE-99 has bioaccumulation potential. Von Meyerinck *et al.* (1990) determined the terminal half-life of pentaBDEs in perirenal fat of the rat after oral exposure to a single dose (300 mg/kg bw) of the commercial mixture Bromkal 70. The results of this study, which indicate half-lives varying from 19.1 (for tetraBDE) to 119 days, are indicative for the potential for bioaccumulation of PBDEs in the rat.

Data suggests that PBDEs half-life tends to increase at decreasing bromination of the PBDE congener in humans (EFSA, 2011a). Geyer *et al.* (2004) estimated the whole body half-live of BDE-99 in humans according to a linear one compartment open pharmacokinetic model, from the daily intake and the total body burden under steady conditions in non-occupationally adult humans in Sweden. The analysis of Geyer *et al.* (2004) was extended by Bakker *et al.* (2008) to the situation in The Netherlands, resulting in similar half-live estimates (see table 14). Trudel *et al.* (2011) used estimated PBDE uptake values (including oral exposure from food, dust, and soil; inhalation of air; dermal uptake) in combination with PBDE biomonitoring data as input for a pharmacokinetic model to derive the elimination half-live for BDE-99. In their model, they used the concentration of BDE-99 measured in human adipose tissue. The median half-life estimate for BDE-99 was 510 days, respectively.

*Table 14: Estimated elimination half-lives in days of BDE-99 in humans.*

| Estimated half-life (days) of BDE-99 in humans | Publication |
|---|---|
| 1040 (663 – 1442) | Geyer et al. (2004) |
| 694 – 876 | Bakker et al. (2008) |
| 510 (median) | Trudel et al. (2011) |

## 9.3 Effects on test animals

### 9.3.1 Acute toxicity

No acute toxicity studies are available for BDE-99. However, ECB (2001) reported results based on studies in which different commercial pentaBDE formulations were gavage-fed to groups of male and female rats at dosages up to 10000 mg/kg bw Mortality occurred between days 2 and 9 post-dosing, with LD50 values ranging from 2640 to 6200 mg/kg bw. These results are in line with IPCS (1994) who reports that the acute oral toxicity of commercial pentaBDE is low in rats.
The dermal toxicity in rabbits is also low. Short-term inhalation exposure in rats and the application of pentaBDE to the conjunctival sac in rabbits caused only mild, transient effects IPCS (1994).

Table 15: Overview of acute toxicity data

| Species | Route | Dosis (mg/kg bw/d) | Effects | LD50 | Reference |
|---|---|---|---|---|---|
| Rat | Oral (gavage) | Up to 10000 (pentaBDE formulations) | Mortality occurred between days 2 and 9 post-dosing. | From 2640 to 6200 mg/kg bw | ECB, 2001 |

### 9.3.2 Carcinogenicity

Animal chronic toxicity/carcinogenicity studies have not been conducted for BDE-99.

### 9.3.3 Developmental and reproductive toxicity

Kuriyama *et al.* (2005) investigated in rats the effect of in utero exposure to BDE-99 on locomotor activity and male reproductive health in offspring. Rats were given single doses of 0, 0.06, or 0.3 mg/kg of BDE-99 by gavage on GD 6. Since PBDEs may interfere with thyroid hormone homeostasis, a reference group for thyroid-mediated effects was included in which dams were treated from GDs 7–21 with 5 mg/l of the goitrogen 6-n-propyl-2-thiouracil (PTU) in drinking water (approximate dose: 0.9 mg/kg-day).
Developmental parameters (eruption of incisors, fur development, eye opening, and testes descent) and postnatal reflexes (development of spontaneous cliff-drop aversion reflex starting on PND 3 and ability to stay on a rotating rod for 3 minutes at seven revolutions/minute starting on PND 18) were evaluated in male and female pups. The eruption of incisors was significantly delayed in the PTU-treated group and in the 0.3 mg/kg BDE-99-treated group. The development of spontaneous cliff-drop aversion reflex was significantly delayed in the PTU-treated male and female offspring and in male offspring exposed to 0.3 mg/kg BDE-99. No other effects on developmental landmarks or spontaneous reflexes were seen.
On PNDs 36 and 71, the circadian locomotor activity of one male and one female per litter per group, was evaluated over 24-hour periods. There was no difference between the sexes for all groups, and therefore the data for males and females were pooled. On PND 36, the total activity (light beam interruption (LBI) count) was significantly increased in the offspring of dams treated with 0.3 mg/kg BDE-99 and in the PTU-treated group. The number of active hours per day was also higher in the 0.3 mg/kg group, an effect not seen in the PTU group. LBI counts/active phase and duration of activity/active phase were also significantly increased in the BDE-99 group at 0.3 mg/kg and in the PTU-treated group. PTU-treated animals, while temporarily hyperactive on PND 36, restored to normal levels on PND 71. On PND 71, both total activity and duration of activity per day were significantly increased at 0.06 and 0.3 mg/kg BDE-99 but not in the PTU-treated groups.
Twelve males per treatment group were sacrificed on PND 140, and thymus, liver, spleen, testis, epididymis, ventral prostate, and seminal vesicle weights were recorded. Spermatids and sperms were counted, sperm morphology was examined, and testosterone and luteinizing hormone (LH) levels were measured. No effects were seen on body weight or absolute and relative liver, thymus, seminal vesicle, or prostate weights in BDE-99-treated animals. Sperm morphology, LH, and testosterone were unaffected. Absolute and relative spleen weights were increased but not in a dose-dependent manner. Relative testis weight was significantly decreased at 0.3 mg/kg BDE-99 and in the PTU group, and relative epididymis weight was significantly decreased at 0.06 and 0.3 mg/kg BDE-99 and in the PTU-treated group. Sperm numbers were significantly decreased compared to those in controls at both BDE-99 doses but not in a dose-dependent manner. Daily sperm production and spermatid count were

significantly decreased at both doses in a dose-dependent manner. The percentage of abnormal sperm was within normal limits in all groups.
Reproductive effects were also examined in this study. Adult male offspring from the BDE-99- and PTU-treated groups were mated with untreated females to determine whether the males were fertile and could produce normal offspring. The dams were sacrificed on GD 21. Uterine and fetal weights, number of implantations, implantations per litter, viable fetuses per litter, percent total resorptions, and male/female sex ratio were all within the normal range of control in all treatment groups. Sexual behaviour in male offspring were also normal in all treatment groups compared to controls. The only effect seen was a significant decrease in the 0.3 mg/kg BDE-99 group in the number of animals that had two or more ejaculations during 20 minutes of mating. Approximately 50% of controls had a second ejaculation, while 70% of the PTU-treated animals achieved a second ejaculation. In the 0.06 and 0.3 mg/kg BDE-99 groups, only 39 and 21%, respectively, of the males achieved a second ejaculation. Therefore, PTU treatment improved the sexual performance of mice, while BDE-99 decreased it. The biological significance of this effect is uncertain.
The LOAEL in this study was 0.06 mg/kg, based on increases in certain locomotor activity parameters on PND 71. A NOAEL for absence of hyperactivity was not identified in this study. The LOAEL for decreased sperm production, spermatid count, and relative epididymis weight on PND 140 was 0.06 mg/kg, the lowest dose tested.

Talsness *et al.* (2005) investigated the effect of BDE-99 on the reproductive system of female rats. A single dose of 0.06 or 0.3 mg/kg BDE-99 was administered by gavage on GD 6.
A reference control group was treated with PTU at a concentration of 5 mg/l in drinking water on GDs 7 through 21, since PBDEs may interfere with thyroid hormone homeostasis. 20 virgin female F1 offspring from each group were mated with untreated males to evaluate fertility. Pregnancy rate, total implantation sites, mean implantation sites per gravid dam, total live fetuses per dam, resorption rate, and percentage of dams with resorptions in the F1 females were not statistically different from controls at both doses of BDE-99. The only statistically significant effect noted was an increase in mean fetal weights at 0.06 mg/kg BDE-99, but not at 0.3 mg/kg BDE-99, and in the PTU-treated group. Pregnancy rate in the PTU-treated group was also significantly lower than in controls. Histologic evaluation by electron or light microscopy of the ovary, uterus, and vagina was performed in the F1 female offspring on PND 90. Electron micrographs and photomicrographs revealed qualitative ultrastructural changes in the ovaries and hyperplastic vacuolar degeneration of the vaginal epithelium in the F1 offspring from the 0.06 and 0.3 mg/kg BDE-99 and PTU-exposed groups. No significant changes were observed in the different ovarian follicle types following exposure to either BDE-99 or PTU, indicating that follicle numbers and maturation of follicles were unaffected. Skeletal anomalies were observed in two animals from the F2 generation from two different litters, following exposure of the F0 dams to 0.3 mg/kg BDE-99 on GD 99. The possible causes for these anomalies remain unknown, they may be either spontaneous or substance related.

In a study of Blanco *et al.* (2012), female Sprague-Dawley rats were exposed to BDE-99 at doses of 0, 0.5, 1, or 2 mg/kg bw/day via gavage from GD 6 to 19 or GD 20. Fetuses showed significantly increased skeletal variations including delayed ossification of parietal and occipital bones, caudal vertebrae, and floating ribs at 2 mg/kg/day. A significant increase in the size of the ventricles of the heart and liver enlargement were also observed. No significant changes were observed in the number of live fetuses, the sex ratio, the average fetal body weight/litter or external malformations (ATSDR, 2017a).

(Blanco *et al.*, 2012), found a dose-dependent increase in the level of all evaluated oxidative stress markers (superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) activity, glucocorticoid receptor (GR) and the total level of thiobarbituric acid reactive substances (TBARS) in the fetal rat liver), indicating that the production of reactive oxygen species (ROS) in fetal rat liver was proportional to the level of BDE-99 exposure in pregnant

dams. Dams were exposed to 0.5, 1 and 2 mg/kg bw BDE-99 per day from GD 6 to 19 in this study. Activation of nuclear hormone receptors AhR (aryl hydrocarbon), PXR (pregnane X) and primarily CAR (constitutive active receptor) induced the upregulation of CYP1A1, CYP1A2, CYP2B1, and CYP3A2 isoforms in the fetal liver. These isoforms were correlated with the activity level of the enzyme catalase and the levels of thiobarbituric acid reactive substances. These findings indicate that the large increase in the CYP system and the production of ROS in fetal liver due to possible hormonal changes can be at the cause of embryo/fetal toxicity.

A study with the congener BDE-47 conducted by Zhang *et al.* (2013) is also available. In this study, groups of 20 male rats were exposed to BDE-47 at 0, 0.001, 0.03, or 1 mg/kg/day by gavage 6 days/week for a period of 8 weeks. The testes showed a significant increase in the number of multinucleated giant cells starting from a dosage of 0.03 mg/kg/day and abundant vacuolar spaces in the seminiferous epithelium at 1 mg/kg/day. Apoptotic cells were significantly increased by 1.9-and 3-fold in the testes of rats from the 0.03 and 1 mg/kg/day groups, and the mRNA levels of several apoptosis genes were elevated in a dose-related manner. Daily sperm production decreased by 23% in the 1 mg/kg/day group, compared to controls. Serum testosterone was significantly decreased by 34, 53, and 62% in the 0.001, 0.03, and 1 mg/kg/day groups, respectively. No exposure-related changes were observed. Based on these results, a minimal LOAEL of 0.001 mg/kg/day was established, with the reduction in serum testosterone as most critical effect.

### 9.3.4 Genotoxic effects

BDE-99 did not induce gene mutations in the Ames test neither chromosomal aberration in the Allium test (Evandri *et al.*, 2003). Several congeners (including BDE-99) induced micronuclei in human mammary carcinoma cells (Barber *et al.*, 2006).
A study with healthy Korean subjects from the general population reported that serum concentrations (not provided) of BDE-99 were not associated with DNA-telomere length in peripheral lymphocytes; *in vitro* and animal experiments with exposure to low-doses of carcinogenic chemicals suggest that elongated telomere may function as a tumour promoter at the very early stage of carcinogenesis in humans (Shin *et al.*, 2010).
The available information is insufficient to draw conclusions on the genotoxicity potential of BDE-99.

### 9.3.5 Endocrine disruption

Hakk *et al.* (2002) examined the effect of BDE-99 on total thyroxine (T4) plasma levels in young adult male rats. A single dose of 8 mg/kg bw of 14C-BDE-99 was administered orally to groups of conventional and bile-duct-cannulated rats. Average total plasma T4 concentration (bound and free) was 1.7 µg/dl in the control rats. In the treated conventional rats, the average total T4 levels increased approximately twofold to 3.2 µg/dL at 3 days after exposure, remained elevated at 3.0 µg/dL at 6 days after exposure, but by day 12 returned to control levels at 1.9 µg/dl.

Kuriyama *et al.* (2007) evaluated thyroid hormone concentrations, hepatic enzyme activities and tissue concentrations of BDE-99 in rats after treatment by gavage on GD 6 with a single dose of 0, 0.06 or 0.3 mg BDE-99/kg bw. The dose of 0.06 mg/kg bw reduced T4 concentration in dams at the first day of lactation, and caused a slight reduction in T4 on PND22, although not statistically significant. In offspring, reduced T4 was observed on PND22 at 0.3 mg/kg bw, probably due to cumulative effects of BDE-99 during lactation. Based on these results a LOEL of 0.06 mg/kg bw was determined.

Alonso *et al.* (2010) administered a single dose of 0.6 or 1.2 mg/kg bw BDE-99 to adult rats. No changes in serum T3 and T4 were observed, however testosterone and progesterone levels decreased. Based on the decreasing testosterone and progesterone levels a LOEL of 0.6 mg/kg bw was determined.

Skarman *et al.* (2005) aimed to determine the effects on plasma T4 in juvenile mice following maternal gestational and lactational exposure to BDE-99. NMRI mice were exposed to either BDE-99 or Bromkal 70-5DE (main constituents of 37% BDE-99 and 35% tetraBDE-47) at 452 and 262 mg/kg bw/day, from GD4 to PND17. Dam and offspring body weights were not affected by BDE-99 or Bromkal treatment. Significantly increased liver-to-body-weight ratio was seen in dams treated with BDE-99 but not in their offspring. Pregnancy rate, gestation length, and litter size were not statistically different from controls. Plasma total and free T4 in the pregnant dams, in the postweaning dams, and in the offspring were unaffected by BDE-99 treatment. On the other hand, plasma total and free T4 were significantly reduced in the offspring of the Bromkal groups but returned to control levels by PND 18. This suggests that other components in Bromkal are responsible for the hypothyroxinemia. One of the components of Bromkal is tetraBDE-47, which has been shown to cause a decrease in T4 levels in mice and rats and may be the component responsible for the reduction of T4 levels seen with commercial pentaBDE mixtures (US-EPA, 2008).

Also, Branchi *et al.* (2005) found a non-significant decrease of serum T4 on PND22, following daily exposure to 18 mg/kg bw BDE-99 from GD 6 to PND 21 in mice (CD-1 Swiss strain).

### 9.3.6 Neurotoxicity

***Neurodevelopmental studies based on single exposures***

Eriksson *et al.* (2001) examined whether exposure to BDE-99 during the period of rapid brain growth in neonatal mice could lead to disruption of the adult brain function. Single doses of 0, 0.8, or 12 mg/kg BDE-99 were administered by gavage to male mice on PND 10. Spontaneous motor behaviour tests (locomotion, rearing, and total activity) and habituation capability were measured and evaluated in 2- and 4-month-old mice. At the age of 5 months, Swim maze performance, a measure of learning and memory ability, was examined in mice given the high dose of BDE-99 (12 mg/kg).
There were no clinical signs of dysfunction throughout the experimental period nor any significant deviations in body-weight gain in the BDE-99-treated mice compared to the control mice. The spontaneous motor behaviour data for locomotion, rearing, and total activity showed a dose-related disruption in mice treated with BDE-99, and the aberrations were more pronounced in 4-month-old mice than in 2-month-old mice, indicating worsening with increasing age. Mice receiving 0.8 and 12 mg/kg of BDE-99 displayed significantly less activity (hypoactive) during the first 20-minute period (0–20 minutes), while during the third 20-minute period (40–60 minutes) they were significantly more active (hyperactive) in relation to control animals, for all three behavioural variables. The habituation capability significantly decreased with age in mice exposed to BDE-99 at 0.8 and 12 mg/kg.
Performance of 5-month-old mice in the swim maze learning/memory test was significantly worse in mice exposed to 12 mg/kg BDE-99 than in control mice. The lowest-observed-adverse-effect level (LOAEL) in this study was 0.8 mg/kg for effects on spontaneous motor behaviour and decreased habituation capability.

Eriksson *et al.* (2002) also investigated whether behavioural disturbances observed in adult mice following neonatal exposure to BDE-99 are induced during a defined neonatal brain developmental window of unique biological susceptibility. On PND 3, 10, or 19, male and

female NMRI mice were given a single oral dose of 0 or 8 mg/kg BDE-99 by gavage. There were no effects on body weight or body-weight gain nor clinical signs of dysfunction in the BDE-99-treated mice at any time during the experimental period. Spontaneous motor behaviour tests (locomotion, rearing, and total activity) were measured over three 20-minute periods in 4-month-old male mice. Mice exposed to BDE-99 on PND 3 or 10 showed decreased activity during the first 20-minute interval of the 60-minute period for all three behavioural variables compared to the control groups. During the last 20-minute period, a significantly increased activity was seen for all three behavioural variables. In mice exposed to BDE-99 on PND 19, there were no changes in the three behavioural variables compared to controls. In conclusion, the behavioural disturbances observed in adult mice, following neonatal exposure to BDE-99, are induced during a defined critical period of neonatal brain development, and mice exposed on PND 10 are most susceptible to the neurotoxic effects of BDE-99.

Viberg *et al.* (2002) determined whether changes in spontaneous behaviour in adult mice that were neonatally exposed to BDE-99 would include effects on the cholinergic system, changing the response in the adult animals to the cholinergic agent nicotine. On PND 10, male NMRI mice received 0 or 8 mg/kg BDE-99 by gavage. Mice of 2 months old were subjected to spontaneous motor behaviour testing (locomotion, rearing, and total activity) for a 60-minute period, divided into three 20-minute periods. Directly after the spontaneous behaviour test, the mice were given a single subcutaneous injection of saline solution (control) or 0.08 mg/kg nicotine base and were immediately tested a second time for spontaneous motor behaviour. This amount of nicotine is known to cause an increased activity level in normal adult NMRI mice. BDE-99-treated mice displayed significantly less activity (hypoactivity) for all three variables during the first 20-minute period and significantly increased activity (hyperactivity) during the last 20-minute period. A significant increase in response to nicotine in the neonatally vehicle treated mice was observed during the first 20-minute period (60-80 minutes) for all three variables (locomotion, rearing and total activity). In contrast, animals treated with BDE-99 on PND 10 and injected with nicotine at the age of 2 months showed significantly decreased activity during the first 20-minute period compared to BDE-99-treated animals injected with saline. Based on these results, it can be concluded that neonatal exposure to BDE-99 on PND 10 can affect the cholinergic system. This translates to changes in the adult mouse response to the cholinergic agent nicotine.

Another similar study in rats was conducted by Viberg *et al.* (2002). Single oral doses of 0, 0.8, 8.0, or 16 mg/kg BDE-99 were given to male Sprague-Dawley rats on PND 10. The spontaneous motor behaviour tests described in Viberg *et al.* (2002) were carried out in 2-month-old mice. Rats exposed on PND 10 to 8.0 and 16 mg/kg bw BDE-99 displayed significantly less activity for locomotion, rearing, and total activity during the first 20-minute period, while during the third 20-minute period they were significantly more active than the control animals for all three behavioural variables. Rats receiving BDE-99 at 0.8 mg/kg did not show any difference from controls in locomotion or rearing activities over the 60-minute test period. A slight decrease in the total activity variable was seen only during the first 20-minute period but returned to control levels during the second and third 20-minute periods. The NOAEL in this study was determined to be 0.8 mg/kg and the LOAEL was 8.0 mg/kg due to the observed significant changes in spontaneous motor behaviour. The NOAEL/LOAEL values in this study indicate that rats are equally or perhaps less sensitive than mice to the spontaneous motor behaviour effects of BDE-99.

Viberg *et al.* (2004a) also conducted a study to determine whether exposure to BDE-99 during a period of rapid brain growth in neonatal mice could lead to disruption of the adult brain function. Single oral doses of BDE-99 of 0, 0.4, 0.8, 4.0, 8.0, or 16 mg/kg were administered by gavage to male and female mice on PND 10. Spontaneous motor behaviour was tested for each dose at ages 2, 5, and 8 months. Spontaneous motor behaviour tests used measured

locomotion (horizontal movement), rearing (vertical movement), and total activity. The habituation ratio was used to analyze alteration in habituation between 2-month-old and 8-month-old mice, within each treatment group, in comparison with their respective controls. There were no clinical signs of toxicity or effects on body weight gain or body weight at any of the dose groups. There were significant dose-related changes in spontaneous motor behaviour (locomotion, rearing, and total activity) at 0.8 mg/kg and above in male and female mice at ages 2, 5, and 8 months. These disturbances were also worse with increasing age. Male and female mice receiving doses of 0.8 mg/kg and higher showed significantly decreased activity during the first 20-minute period (hypoactive) and significantly increased activity during the last 20-minute period (hyperactive) compared to control animals. Male and female mice exposed to the lowest dose (0.4 mg/kg) did not significantly differ in activity in any of the three behavioural variables during any of the three 20-minute periods. The habituation capability for the locomotion and rearing variables was significantly decreased in the 2- and 8-month-old male and female mice at 0.8 mg/kg and above, as evidenced by dose-related increases in the habituation ratio. The decline in habituation capability (i.e., the increase in the habituation ratio) was more pronounced in the 8-month-old mice than in the 2-month-old mice. This indicated that the capability of the animals to habituate to a new environment decreased with increasing BDE-99 dose and with age. No major gender differences in spontaneous motor behaviour responses or habituation capability were seen in this study. The NOAEL for spontaneous motor behaviour effects in this study was 0.4 mg/kg. The LOAEL was 0.8 mg/kg due to significant changes in spontaneous motor behaviour and decreases in the rearing and locomotion habituation capability in both male and female mice, worsening with increasing age.

Viberg *et al.* (2004b) conducted another study to determine effects on spontaneous behaviour in adult male mice neonatally exposed to BDE-99 and whether these effects would include changes in the density of cholinergic nicotinic receptors in the hippocampus of the adult animal. Such changes have been proposed to affect learning and memory functions. Single oral doses of 0, 0.2, 0.4, or 12 mg/kg of BDE-99 were given by gavage to male mice on PND 10. Spontaneous motor behaviour was measured at the age of 4 months. Ten mice were tested, randomly picked from three to five different litters in each treatment group. Spontaneous motor tests evaluated locomotion, rearing, and total activity behaviours.
There were no clinical signs of toxicity or significant differences in body weight gain or adult weight between controls and mice treated with BDE-99 at any time during the experimental period. Mice exposed neonatally to 12 mg/kg of BDE-99 displayed significantly less activity (hypoactive) for all three behavioural variables during the first 20-minute period (0–20 minutes) compared to the controls, while during the third 20-minute period (40–60 minutes), they were significantly more active (hyperactive) than the control animals in relation to all three behavioural variables. Mice receiving 0.2 or 0.4 mg/kg BDE-99 showed no significant differences in activity for any of the three behavioural variables compared to the control animals at any of the 20-minute periods. The NOAEL in this study was 0.4 mg/kg and the LOAEL 12 mg/kg for effects on spontaneous motor behaviour.

Ankarberg (2003) studied whether neonatal exposure to nicotine could affect the susceptibility of adult mice to BDE-99. Starting on PND 10, NMRI mice received subcutaneous injections of saline or nicotine base at 0.033 mg/kg twice daily for 5 consecutive days. At the age of 5 months, the animals received by gavage 0 (control) or 8 mg/kg BDE-99. 24 hours after exposure to BDE-99, the mice were tested for spontaneous motor activity (locomotion, rearing, and total activity) for three 20-minute periods. Control animals and animals that only received 8 mg/kg BDE-99 as adults showed a normal decrease in activity over the 60- minute test period, indicating a normal habituation pattern. Animals that received nicotine on PND 10 and BDE-99 as adults showed a lack of habituation. These animals displayed hypoactive behaviour in the first 20 minutes of the spontaneous behaviour test but became hyperactive in the last 20 minutes of the test period, indicating that the neonatal nicotine exposure affected

the susceptibility to BDE-99 in the adult animals. At the age of 7 months, the animals were again tested for spontaneous motor behaviour. The lack of habituation in the nicotine BDE-99-treated mice was even more pronounced, indicating a disturbance that worsens with age. Overall, this study indicates that neonatal nicotine exposure enhances the susceptibility to BDE-99 in the adult animal.

In a study of Alm *et al.* (2006), BDE-99 was shown to alter expression of proteins involved in neuroplasticity and maturation in the striatum (GAP43, stathmin and synclein) and proteins of metabolism and energy production in the hippocampus (e.g. ATP-synthase, α- and γ-enolase) of mice after administration of 12 mg/kg bw BDE-99 on PND 10 by gavage.

In addition, Hallgren *et al.* (2015) administered a single oral dose of 12 mg/kg bw of BDE-99 on PND 10 to neonatal mice. Changes in transcription of several cholinergic genes in the hippocampus and cortex of mice were reported. Changes in the hippocampus were already seen 24 h after dosing. The changes in cortex were seen when the mice were 2 months old, together with significant changes in the spontaneous locomotor activity.

***Neurodevelopmental studies based on repeated exposures***

Branchi *et al.* (2005), assessed the effects of BDE-99 on pregnancy and somatic and neurobehavioural development of pups after parental exposure in female mice. BDE-99 was administered by gavage at 0, 0.6, 6, or 30 mg/kg-day from GD 6 through PND 21, at which time the pups were weaned.
Body weight gain of pregnant females, pregnancy duration, proportion of successful deliveries, pup sex ratio, and body weight gain of pups from birth to weaning were not affected by treatment with BDE-99. Six to eight male and female pups from each litter of each treatment group were used in a series of tests to assess somatic and neurobehavioural development from PNDs 2 to 20. BDE-99 treatment did not affect somatic development (hair growth and day of eyelid and ear opening and incisor eruption). There was a statistically significant 2-day delayed appearance of screen-climbing response in the high-dose group (30 mg/kg-day); all other responses based on neuromotor coordination from PNDs 2 to 20 were not affected by BDE-99 treatment. Ultrasonic vocalization on PNDs 4, 8, and 12 and homing tests on PND 11 were carried out on one male and one female not previously handled or tested from each litter of each treatment group. No effects were seen in any of the treatment groups on ultrasonic vocalization or homing performance assessed on PND 11 both for distance travelled and latency to reach the scent area. In addition, an open-field apparatus was used to test locomotion (horizontal movement), rearing (vertical movement), and thigmotaxis (time and distance travelled close to the walls) in one male and one female from each litter of each treatment group for 30-minute sessions on PNDs 22 and 34 and for 60-minute sessions on PNDs 60 and 120. There was no statistically significant difference in activity between controls and treatment groups on PND 22. However, BDE-99 exposure affected several behavioural and activity parameters in the open-field arena on PNDs 34, 60, and 120, indicating that behavioural alterations due to perinatal BDE-99 exposure seem to worsen with increasing age. On PND 34, mice were hyperactive in the 0.6 and 6 mg/kg-day dose groups but not in the high-dose group. Mice exhibited a statistically significant increase in rearing frequency, with mice in the 0.6 mg/kg-day dose group being more hyperactive than mice in the 6 mg/kg-day dose group. The mice in the 6 mg/kg-day dose group also exhibited signs of increased locomotion as evidenced by increases in distance travelled, although this was not apparent in the low- and high-dose groups. Thigmotactic response, considered as index of anxiety, was not affected at any dose. On PND 60, mice in the 0.6 mg/kg-day group, but not in the 6 and 30 mg/kg-day groups, displayed significantly more locomotion compared to controls. Thigmotactic behaviour on PND 60, measured as percent of time spent near the walls, was significantly lower at the medium dose only (6 mg/kg-day) in comparison with control mice, indicating a less marked fearful response in this treated group. On PND 120 (adulthood), the

0.6 and 6.0 mg/kg-day groups displayed significantly lower levels of locomotion than controls during the last part of the 60-minute test session. At this age, rearing and thigmotaxis were not affected at any BDE-99 dose. The lack of a clear dose-response relationship in the behaviour and activity changes in this study did not permit clear identification of the NOAEL/LOAEL for alteration in behavioural or activity parameters.

Branchi *et al.* (2005) conducted another study to investigate the effects of BDE-99 on neurobehavioural development in offspring. BDE-99 was administered at 0 or 18 mg/kg-day to mice from GD 6 to PND 21, except for PND 0 (day of birth). Two modes of administration were used in this study, by gavage or by self-administration through a modified syringe. Pregnancy duration, body weight gain of dams, proportion of successful deliveries, litter size, pup weight, and sex ratio were not affected by treatment with BDE-99 or by the method of administration in comparison with the respective control groups. On PNDs 34, 60, 90, and 120, male mice were tested for locomotion (horizontal movement), rearing (vertical movement), and thigmotaxis (time and distance travelled close to the walls) in an open-field apparatus. Testing sessions were 30 minutes (three 10-minute blocks) on PND 34 and 60 minutes (six 10-minute blocks) on PNDs 60, 90, and 120. Distance travelled and frequency of rearing were not affected by the exposure methods. On PND 34, offspring of dams treated with BDE-99 showed hyperactivity for distance travelled and frequency of rearing during the third 10-minute testing period. On PNDs 60, 90, and 120, behavioural parameters (distance travelled and frequency of rearing) in treated mice were not different from those of controls at any time point during the 60-minute testing period. With regard to thigmotactic behaviour, an index of anxiety, mice administered BDE-99 by gavage spent more time near the wall than self-administered BDE-99 mice. however, the difference in thigmotactic behaviour was minor, suggesting that the effect of the gavage route of administration was temporary. On PND 22, two male mice of each group were sacrificed and BDE-99 levels were determined in the brain. No effect of the administration route was found on the level of BDE-99 in the brain. The mean BDE-99 level in the brain of treated mice was 640 µg/kg compared to 5 µg/kg for the controls. Serum total and free T4 levels were also measured in BDE-99-treated male mice on PND 22 and were not found to be statistically different from control levels. No effect of the method of administration was found on T4 levels.

Cheng *et al.* (2009) tested the memory of rats exposed via gavage to 2 mg/kg bw BDE-99 from GD 6 to PND 21 in a Morris water maze. The rats displayed poor short-term memory when tested at PND 34-36, and lower antioxidant enzyme activity in the brain at PND 37 was observed. Another study of Zhao *et al.* (2014), also reported a small significant increase in lipid peroxidation in the brain of offspring of rats dosed with BDE-99 at 0.2 mg/kg bw per day from GD1 to PND21. However, no effects on other measures of oxidative stress were reported, neither did that dose result in adverse neurobehavioural effects.

In a 90-day oral repeated dose study conducted by Daubié *et al.* (2011), adult rats were administered a daily dose 0, 0.15, 1.5 or 15 µg/kg bw BDE-99 by gavage. Before and after the 90 days of exposure, behavioural tests including the open-field, the elevated plus-maze test for locomotor activity and anxiety, and the Morris water maze for spatial learning were conducted. No effects on behavioural parameters were found in any of the dose groups.

In an oral repeated dose study conducted by Blanco *et al.* (2013) in rats, BDE-99 was administered by gavage at a dose of 0, 1 or 2 mg/kg bw per day from GD 6 to PND 21. The offspring was tested for neurobehavioural effects early after weaning at PND 21. A reduction in the level of anxiety (with the potential to adversely affect adaptation to stressful situations) was reported in rat offspring at PND 22 at the highest dose (2 mg/kg bw/d). No effects on learning, memory performances, and locomotor activity were observed. Hippocampal and cortical tissues were also evaluated for gene expression levels of TRα1, TRα2, TRβ1, and brain-derived-neurotrophic factor (BDNF) in PND 21 offspring. The only exposure-related

change observed was a significant decrease in BDNF expression in the hippocampus at 2 mg/kg bw/d. Based on these effects, a LOAEL of 2 mg/kg bw/d and a NOAEL of 1 mg/kg bw/d were determined.

Lichtensteiger *et al.* (2004) exposed pregnant Long-Evans rats from GD 10 to GD 18 to 1 or 10 mg/kg of BDE-99 by subcutaneous administration. This resulted in induced feminization in male mice, an increased sweet preference, and a decreased sexual behaviour in females in rats exposed to 10 mg/kg of BDE-99. The LOEL was therefore determined to be 10 mg/kg.

### 9.3.7 Liver toxicity

Skarman *et al.* (2005) also aimed to determine the hepatic enzyme activities in juvenile mice following maternal gestational and lactational exposure to BDE-99 in their study. NMRI mice were exposed to either BDE-99 or Bromkal 70-5DE (main constituents of 37% BDE-99 and 35% tetraBDE-47) at 452 and 262 mg/kg bw/d, from GD4 to PND17. Hepatic microsomal CYP-450 enzyme activity was measured in the maternal and juvenile mice by means of the EROD activity assay, a marker of CYP-1A1 activity. Hepatic EROD activity in pregnant dams sampled on GD 17 and in postweaning dams sampled on PND 20 was unaffected by treatment with BDE-99. Induced EROD activity was seen in the Bromkal group in dams on GD 17 but returned to control levels on PND 20. Offspring sampled on PNDs 11 and 18 showed increased hepatic EROD activity in the treatment groups relative to controls but returned to control levels by PND 37. The increase in EROD activity was similar for the Bromkal and BDE-99 groups. Hepatic uridine diphosphoglucuronosyl transferase (UDPGT) activity was studied in offspring on PNDs 11 and 18. UDPGT activity was not different from that in controls in the BDE-99 group at both time points. The Bromkal group showed an increase in UDPGT enzyme activity of borderline significance on PND 18 only.
van der Ven *et al.* (2008) administered a purified commercial pentaBDE mixture (containing approximately 45 % pentaBDE congeners), orally (gavage) to rats over 28 days. This resulted in increased liver weight, centrilobular hepatocellular hypertrophy, decrease in apolar hepatic retinoids, and induction of hepatic CYP1A and CYP2B enzymes. The $BMDL_{10}$ were 7.6 mg/kg bw/d for liver enlargement, 1.1 (males) and 1.8 (females) mg/kg bw/d for decreased plasma T4, 0.5 (males) and 2.3 (females) mg/kg bw/d for decreased apolar liver retinoids, and 0.07 (males) and 0.8 (females) mg/kg bw/d for increased CYP2B1 mRNA. Increased serum alanine aminotransferase activities in treated males only ($BMDL_{10}$ 15.5 mg/kg bw per day) were also noted. Most effects seen in the liver were mediated by activation of the nuclear receptor CAR which regulates, among others, the expression of CYP2B1. CAR activation was reported to be more sensitive in male than in female rats.

Albina *et al.* (2010) treated adult male rats with a single dose of 0, 0.6 or 1.2 mg/kg bw of BDE-99 by gavage to examine oxidative stress (OS) in the liver. After 45 days, they found significant increases in hepatic SOD activity and oxidized glutathione (GSSG) levels while the reduced glutathione (GSH) levels were decreased. Catalase activity was reduced at the highest dose. Based on these results it was concluded that BDE-99 can lead to oxidative stress in rat liver at a dose level of 0.6 mg/kg bw and above.

In a 13-week study, Dunnick and Nyska (2009) administered DE-71[18] orally to rats and mice. Rats receiving 50 mg/kg bw or more per day and mice receiving 100 mg/kg bw or more per day both had hepatocellular hypertrophy and vacuolization. At exposure doses of 50 mg/kg bw per day and higher, liver CYP1A1, 1A2, and 2B levels were elevated in both species. The most sensitive indicator was liver enlargement, which was shown in rats and mice at 5 mg/kg bw per day and higher, respectively. According to the scientists, these alterations in the rodent liver may be a sign that the commercial PentaBDE combination has the potential to promote tumor growth.

According to Szabo *et al.* (2009), DE-71 administered by gavage to pregnant Long-Evans rats between GD6 and PND21 lowered serum T4 and induced a variety of hepatic CYPs and UGTs in the male pups. Additionally, the expression of SULT1b1 was increased together with a number of hepatic export pumps, including Mdr1, Mrp2, and Mrp3, as well as the import transporter Oatp1A4. The expression of deiodinase I and transthyretin decreased. The authors came to the conclusion that a number of hepatic processes might account for the observed decrease in serum T4 levels.

However, the up-regulation of CYPs observed in the Dunnick and Nyska (2009) and Szabo et al. (2009) studies with DE-71 might be due to planar contaminants such as polybrominated dibenzofurans present in DE-71; these contaminants are known to exert the dioxin-like effect of up-regulation of CYPs through an AhR dependent mechanism. Oral dosing of technical DE-71 or single PBDEs, including BDE-99, to adult male rats on three consecutive days resulted in weak up-regulation of hepatic CYP1A1 mRNA. Furthermore, a marked induction of the constitutive active receptor (CAR-) and Pregnane X Receptor (PXR, NR1I2/Nr1i2) regulated CYP2B and CYP3A transcripts in the liver was observed. DE-71 was contaminated with polybrominated dibenzofurans. PBDEs appear capable of up-regulating CYP2B and CYP3A in rats at doses similar to that for non-dioxin-like PCB153 via an AhR independent mechanism (Sanders *et al.*, 2006).

Bruchajzer *et al.* (2010) treated female rats for 7, 14, 21, or 28 days with 0, 2, 8, 40 or 200 mg/kg bw/d pentaBDE by gavage. After 28 days of treatment, an increase in hepatic GSH at 2 mg/kg bw/d (lowest dose) of pentaBDE was reported. PentaBDE led to an increase in hepatic malondialdehyde levels, Furthermore, at 2 mg/kg bw/d penta BDE markedly induced hepatic ethoxyresorufin O-dealkylase (CYP 1A, EROD) and pentoxyresorufin O-dealkylase (CYP 2B, PROD) activities, At the highest dose of pentaBDE hepatic steatosis and increased serum alanine transaminase (ALT) and aspartate transaminase (AST) activity levels were also observed.

Öberg *et al.* (2010) treated male and female rats over 28 days with 0, 2.5, 25 and 250 mg Bromkal 70-5DE/kg bw/d by gavage. In treated animals increased hepatic EROD and PROD activities, enhanced liver weight and depletion of hepatic retinoids were observed. Furthermore, treatment led to histopathological changes (hepatocellular hypertrophy, fatty degeneration). Chemical analysis of the PBDE mixture by GC-MS showed impurities of polybrominated dibenzofurans and to a lesser extent dibenzodioxins, in total levels of about 7.0 µg/g of Bromkal 70-5DE. The animals were thereby exposed to an estimated dose of dioxin-like equivalents corresponding to 1.3-131 ng TEQ/kg bw The authors did not rule out that TEQ contaminations had contributed to these effects.

### 9.3.8 Summary toxicity studies in animals

Table 16: Overview of toxicity studies on BDE-99 in animals

| Species | Route | Administration time | Dosis (mg/kg bw/d) | Effects | Test substance | NOAEL (mg/kg) | LOAEL (mg/kg) | Reference |
|---|---|---|---|---|---|---|---|---|
| Rat (Wistar) | Oral | Single dose (GD 6) | 0.06 or 0.3 | Impaired spermatogenesis in terms of decrease in sperm and spermatic counts (PND 140). Hyperactivity (PND 36 and PND 71). | BDE-99 | - | 0.3 (PND 36) 0.06 (PND 71) | Kuriyama et al., 2005 |
| Rat (Wistar) | Oral (gavage) | Single dose (GD 6) | 0.06 or 0.3 | Female reproductive tract changes in the F1 generation, which were apparent at adulthood. increased resorption rates in the PBDE groups of F1 females mated with untreated males. | BDE-99 | - | 0.06 | Talsness et al., 2005 |
| Rat (Sprague-Dawley) | Oral (gavage) | 14 days (Gd 6-19) | 0, 0.5, 1, or 2 | Delayed ossification,liver and hearthypertrophy, increase in the level of all evaluated oxidative stress markers (SOD, CAT, GPx, and GR and the total level of TBARS in the fetal rat liver). | BDE-99 | 1 | 2 | Blanco et al., 2012 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Rat | Oral (gavage) | 6 days/week for a period of 8 weeks | 0, 0.001, 0.03, or 1 | The testes showed a significant increase in the number of multinucleated giant cells starting from a dosage of 0.03 mg/kg/day and abundant vacuolar spaces in the seminiferous epithelium at 1 mg/kg/day. Apoptotic cells were significantly increased by 1.9-and 3-fold in the testes of rats from the 0.03 and 1 mg/kg/day groups, and the mRNA levels of several apoptosis genes were elevated in a dose-related manner. Daily sperm production decreased by 23% in the 1 mg/kg/day group, compared to controls. Serum testosterone was significantly decreased by 34, 53, and 62% in the 0.001, 0.03, and 1 mg/kg/day groups. | BDE-47 | - | 0.001 | Zhang et al. 2013 |
| Rat (Sprague-Dawley) | Oral (gavage) | Single dose | 8 | Average total plasma T4 concentration was 1.7 µg/dL in the control rats. In the treated conventional rats, the average total T4 levels increased approximately twofold to 3.2 µg/dL at 3 days after exposure, remained elevated at 3.0 µg/dL at 6 days after exposure, but by day 12 returned to control levels at 1.9 µg/dL. | BDE-99 | - | - | Hakk et al., 2002 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Rat (Wistar) | Oral | Single dose (GD 6) | 0.06 or 0.3 | In dams reduced T4 at PND 1 at 0.06 mg/kg bw; In offspring reduced T4 at PND 22 at 0.3 mg/kg bw | BDE-99 | - | 0.06 | Kuriyama et al., 2007 |
| Rat (Sprague-Dawley) | Oral (gavage) | Single dose | 0.6 or 1.2 | No effect changes in serum T3, T4 and free T4. Decrease in testosterone and progesterone levels. | BDE-99 | - | 0.6 (testosterone and progesterone) | Alonso et al., 2010 |
| Mouse (NMRI) | Oral | GD 4 - PND 17 every 3 days | BDE-99: 452, Bromkal70-5DE: 262 | Decrease of T4 in offspring on PND11 in Bromkal 70-5DE group; recovery by PND37. No changes in serum T4 in dams. No changes in serum T4 in offspring in BDE-99 group. | BDE-99 or Bromkal 70-5DE (main constituents of 37% BDE-99 and 35% tetraBDE-47) | (BDE-99): 452 | (Bromkal70-5DE): 262 | Skarman et al., 2005 |
| Mouse (CD-1 Swiss) | Oral | GD 6 - PND 21 | 18 | Non-significant decrease of T4 on PND22. | BDE-99 | 18 | - | Branchi et al., 2005 |
| Mouse (NMRI) | Oral | Single dose (PND 10) | 0.8 or 12.0 | Alterations in spontaneous behaviour (2 and 4 months old). Decreased habituation. Decreased performance in Morris swim maze (12.0 mg/kg; 5 months old) which points to deficits in learning and memory function. | BDE-99 | - | 0.8 | Eriksson et al., 2001 |
| Mouse (NMRI) | Oral | PND 3 or 10 or 19 | 8 | Alterations in spontaneous behaviour. Decreased habituation. | BDE-99 | - | 8 | Eriksson et al., 2002 |
| Mouse (NMRI) | Oral | Single dose (PND 10) | 0 or 8 | hypoactivity during the first 20-minute period and hyperactivity during the last 20 minute period. | BDE-99 | - | - | Viberg et al., 2002 |
| Rat (Sprague-Dawley) | Oral | Single dose (PND10) | 0.8, 8.0, or 16 | Neurobehavioural developmental effects; significant dose-related changes in spontaneous motor behaviour. | BDE-99 | 0.8 | 8.0 (changes in spontaneous motor behaviour) | Viberg et al., 2005 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Mouse (C57/BI) | Oral | Single dose (PND 10) | 0.4, 0.8, 4.0, 8.0 or 16.0 | Alterations in spontaneous behaviour (2, 5 and 8 months old). Decreased habituation (2 and 8 months old). | BDE-99 | 0.4 (spontaneous motor behaviour effects) | 0.8 (significant changes in spontaneous motor behaviour and decreases in the rearing and locomotion habituation capability) | Viberg et al., 2004a |
| Mouse (NMRI) | Oral | Single dose (PND 10) | 0.2, 0.4 or 12.0 | Decreased habituation. | BDE-99 | 0.4 | 12.0 | Viberg et al., 2004b |
| Mouse (NMRI) | Nicotine: subcutaneous injections<br><br>BDE-99: oral | Nicotine: PND 10 – PND 15 (twice daily for 5 consecutive days)<br>BDE-99: single dose as adults | 0.033 nicotine, 0 (control) or 8 mg/kg BDE-99 | A lack of habituation. Hypoactive behaviour in the first 20 minutes of the spontaneous behaviour test, hyperactive in the last 20 minutes of the test period.<br>At the age of 7 months: The lack of habituation in the nicotine BDE-99-treated mice was even more pronounced. | Nicotine, BDE-99 | - | - | Ankarberg, 2003 |
| Mouse (NMRI) | Oral (gavage) | Single dose (PND 10) | 12 | Altered expression of proteins involved in neuroplasticity and maturation in the striatum (GAP43, stathmin and synclein) and proteins of metabolism and energy production in the hippocampus (e.g. ATP synthase, α- and γ-enolase). | BDE-99 | - | - | Alm et al., 2006 |
| Mouse (NMRI) | Oral (gavage) | Single dose (PND 10) | 12 | Decreased spontaneous activity and impaired habituation at 2 months. | BDE-99 | - | 12 | Hallgren et al., 2015 |
| Mouse (CD-1 Swiss) | Oral | GD 6 - PND 21 | 0.6, 6.0 and 30.0 | Hyperactivity at PND 22, 34 and 60, and hypoactivity at PND 120. Decreased | BDE-99 | - | 0.6-6.0 | Branchi et al., 2002 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | thigmotaxis indicating reduced anxiety-like behaviour (PND 60). | | | | |
| Mouse (CD-1 Swiss) | Oral | GD 6 - PND 21 | 18 | Hyperactivity and decreased habituation at PND 34 (assessed at PND 34, 69, 90 and 120). | BDE-99 | - | 18 | Branchi et al., 2005 |
| Rat (Sprague-Dawley) | Oral | GD 6 - PND 21 | 2 | Impaired short-term memory (PND 34-36). Lower antioxidant enzyme activity in the brain (PND 37). | BDE-99 | - | 2 | Cheng et al., 2009 |
| Rat (Sprague-Dawley) | Oral | GD 1 - PND 21 | 0 or 0.2 | No exposure-related changes in reflex maturation, motor coordination, or spatial learning of PND 3-36 offspring; no offspring body weight effects. | BDE-99 | 0.2 | - | Zhao et al., 2014 |
| Rat (Sprague-Dawley) | Oral | 90 days | 0.15, 1.5, 15 µg/kg bw per day | No effect on behaviour, locomotor activity, spatial learning, anxiety. | BDE-99 | - | - | Daubié et al., 2011 |
| Rat (Sprague-Dawley) | Oral | GD6-PND21 | 0, 1 or 2 | Altered neurobehaviour, decreased hippocampal BDNF, and decreased serum T3, T4, and freeT4 in offspring at PND 21-23 | BDE-99 | 1 | 2 | Blanco et al., 2013 |
| Rat (Long-Evans) | daily sub-cutaneous injection | GD10-18 | 1 or 10 | Induced feminization in male mice, an increased sweet preference, and a decreased sexual behaviour in females | BDE-99 | - | 10 | Lichtensteiger et al., 2004 |
| Rat (F344) (male) | Oral | 3 days | 0.57, 5.7, 57 | CYP1A induction, CYP2B induction, CYP3A induction. | DE-71 (commercial mixture) and BDE-47, -99 and -153 | CYP1A induction: 5.7 CYP2B induction: 0.57 CYP3A induction:5.7 | CYP1A induction: 57 CYP2B induction: 5.7 CYP3A induction: 57 | Sanders et al., 2005 |
| Rat (Wistar) | Oral (gavage) | 28 days | 0.27, 0.82, 2.47, 7.4, 22.2, 66.7, 200 | Increased liver weight, Centrilobular hepatocellular Hypertrophy, BMDL10: 7.6 (females). | pentaBDE mixture (containing approximately 45 | - | - | Van der Ven et al., 2008a |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Decrease in apolar hepatic retinoids, BMDL10: 0.5 (males) and 2.3 (females). Induction of CYP2B1, BMDL10: 0.07 (males) and 0.8 (females) Increased serum alanine Aminotransferase, BMDL10: 15.5 (males) | % pentaBDE congeners) | | | |
| Rat (Sprague-Dawley) | Oral (gavage) | Single dose | 0, 0.6, 1.2 | Increased GSSG, GSSG/GSH, SOD activity, decrease in liver GSH. | BDE-99 | - | Liver GSSG/GSH, GSSG, GSH, SOD: 0.6 | Albina et al., 2010 |
| Rat (F344/N) and Mouse (B6C3F1) | Oral (gavage) | 13 weeks, 5 days a week | 0.01, 5, 50, 100, 500 | Hepatocellular hypertrophy, Vacuolization, increased CYP 1A1, 1A2, 2B, UGT levels, and liver enlargement. | DE-71 (commercial mixture) and BDE-47, -99 and -153 | 0.01 (males) 50 (females): hepatocellular hypertrophy, vacuolization<br><br>5: CYP 1A1, 1A2, 2B, UGT levels Increased<br><br>0.01 (rats), 5 (male mice), 50 (female mice): Liver enlargement | 5 (males), 100 (females): hepatocellular hypertrophy, vacuolization<br><br>50: CYP 1A1, 1A2, 2B, UGT levels Increased<br><br>5 (rats), 50 (male mice), 100 (female mice): Liver enlargement | Dunnick and Nyska, 2009 |
| Rat (Long-Evans) | Oral (gavage) | GD6 to PND21 | 1.7, 10.2, 30.6 (Bromkal 70-5DE) | Male pups: CYPs, UGTs, SULT1b1, Mdr1, Mrp2, Mrp3, Oatp1A4 increased; transthyretin, deiodinase I decreased. | DE-71 (commercial mixture) and BDE-47, -99 and -153 | - | At PND4 (21): CYP1A1, EROD CYP2B1, 2B2, PROD: 1.7 (1.7) CYP3A1: 30.6 (10.2) BROD: 10.2 (1.7) | Szabo et al., 2009 |
| Rat (Wistar) | Oral (gavage) | 7, 14, 21, or 28 days | 0, 2, 8, 40, 200 | Increased activity liver GSH, EROD,PROD, Malondialdehyde, ALT and AST | PentaBDE | - | Liver GSH:2 Malondialdehyde:8 Steatosis, increased ALT, AST: 200 EROD, PROD: 2 | Bruchajzer et al., 2010 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Rat (Sprague-Dawley) | Oral (gavage) | 28 days | 0, 2.5, 25, 250 (Bromkal 70-5DE) | Induction EROD, PROD. Histopathological changes Decreased relative liver weight. Decrease in hepatic retinoids | Bromkal 70-5DE | Males: histop. changes:2.5, PROD: 2.5, hepat. retinoids:25,<br><br>Females: rel. liver weight: 2.5, Relative liver weight: 25, Histop. Changes: 2.5, Hepatic Retinoids: 2.5 PROD: 2.5 | Males: EROD: 2.5, histop. changes:25, PROD:25, hepat. retinoids:250, Rel. liver weight: 25<br><br>Females: Liver weight: 250, Histop. changes: 25, Hepat. retinoids: 25, EROD:2.5, PROD: 2.5 | Öberg et al., 2010 |

## 9.4 Effects on humans

### 9.4.1 Carcinogenicity

Epidemiological studies of exposure to BDE-99 and cancer occurrence in humans are not available.

### 9.4.2 Developmental and reproductive toxicity

Harley *et al.* (2010) studied the association of maternal concentrations of PBDEs in serum during pregnancy with time to pregnancy (TTP) and menstrual cycle. Increasing levels of BDE-99 were associated with longer TTP (decreased odds of pregnancy each month). PBDEs were not associated with menstrual cycle characteristics.

Akutsu *et al.* (2008) studied the relationship between human serum PBDEs and sperm quality and testis size. Blood serum and sperm samples were collected monthly from 10 young Japanese males. Four congeners (BDE-47, -99, -100 and -153) were mainly detected in human serum samples. No significant relationships were observed between the serum concentrations of BDE-99 and the sperm concentration or testis size. However, The EFSA Panel on Contaminants in the Food Chain (CONTAM) noted that the reliability of these results is low because of the small size of the study group and the limitations of the analysis (EFSA, 2011).

A prospective Danish-Finnish study conducted by Main *et al.* (2007) investigated whether exposure to PBDEs was associated with cryptorchidism[9]. The study analysed whole placentas (for 95 cryptorchid and 185 healthy boys) and individual human milk samples for 14 PBDEs, including BDE-99. In 86 placenta-milk pairs, placenta PBDE concentrations in fat were lower than in human milk, and a larger number of congeners were not detectable. There was no significant difference between boys with and without cryptorchidism for all congeners. The concentration of PBDEs in human milk was significantly higher in mothers of boys with cryptorchidism than in controls. In addition, a positive correlation between the sum of PBDEs and serum luteinizing hormone was reported. In conclusion, PBDE levels in human milk, but not in placenta, showed an association with congenital cryptorchidism.

### 9.4.3 Immunotoxicity

Gascon *et al.* (2011), examined the association between pre- and postnatal PBDE exposure and thyroid hormones levels in children in a prospective birth cohort in Spain. PBDE concentrations were measured in cord blood and in serum of 4 years olds. Among all congeners analysed (BDE-12/13, -17, -32, -28/33, -47, -66, -71, -85, -99, -100, -116, -119, -126, -138, -153, -154, -155, -183 and -190) only BDE-47 was quantified in a reasonable number of samples. Levels of thyroid stimulating hormone (TSH), total T3 and free T4 were not associated with PBDE exposure.

In a study performed by Abdelouahab *et al.* (2011), serum thyroid hormones and the concentration of BDE-47, -99, -100 and -153 were measured from fifty Canadian men that were recruited in a fertility clinic. In a multiple regression analysis, T4 levels were negatively associated with serum BDE-47, BDE-99, sum of PBDEs, controlling for age and other covariates. No relations were observed between T3, TSH and any of the chemicals measured.

[9] A condition when one or more testes has not moved to its proper position before birth

Chevrier *et al.* (2010) also reported a negative association between the sum of PBDEs and BDE-99 and TSH serum concentrations in pregnant women around the 27th week of gestation. No association was found between PBDEs and free and total T4.

However, Roze *et al.* (2009) reported that BDE-47, -99 and -100 correlated with higher concentrations of T3, when investigating the influence of prenatal exposure to organohalogen compounds (OHCs), including brominated flame retardants (BFRs), on motor, cognitive and behavioural outcome in healthy children of school age.

Herbstman *et al.* (2010) conducted a longitudinal cohort study in 329 pregnant women in New York. Cord blood PBDE measurements of their children were assessed at the age of 1, 2, 3, 4 and 6 years, respectively. Cord blood total mercury and lead concentrations were also measured to exclude the possibility that these covariates affected the relationship between PBDE concentrations and developmental indicators. Children with the higher prenatal concentrations of BDE-47, -99, and -100 scored lower than the rest of the population on nearly all neurodevelopmental indices at all time points (1-4 and 6 years). There are also indications that children who had a higher cord blood concentration of BDE-47, -99 and -100 scored lower in some tests for mental and physical development.

## 9.5 Overview of the available toxicological reference values

A summary of toxicological reference values derived by different authorities is given in Table 21. The derivation of these values and the underlying studies are discussed below.

**EFSA (2011)**
According to the EFSA expert panel (CONTAM), most toxicological studies were conducted with different experimental design, with single or repeated doses during pregnancy, postnatal or during adulthood. In addition, most studies have a limited number of doses and have not been conducted according to standard guidelines, meaning that they do not provide results that are suitable for risk assessment purposes. However, the CONTAM Panel noted, despite the limitations and the concerns regarding the single administration protocol, that there are also arguments supporting the use of the results from these studies.

- They provide the lowest doses leading to neurobehavioural effects, and therefore need particular consideration. Due to the fact that effects are observed, these studies apparently cover a relevant neurodevelopmental period in experimental animals.
- The half-lives and the lipophilic nature of a number of PBDE congeners are such that even a single dose would maintain exposure for an appreciable period of time.

Therefore, the CONTAM Panel concluded that in this case, single-dose studies should be considered for the assessments of risk to human health.

Main targets for BDE-99 toxicity were the liver, thyroid hormone homeostasis, and the reproductive and the nervous system. The CONTAM Panel noted that the observed effects on thyroid hormone levels were not always consistent. For BDE-99, three studies showed no effects on thyroid hormones (T4) after prenatal exposure (Branchi et al., 2005; Skarman et al., 2005) or in adults (single exposure) (Alonso et al., 2010), one study (Hakk et al., 2002) with single exposure showed, a two-fold increase of average total T4 levels in treated rats 3 days after exposure, but T4 levels returned to normal 12 days after exposure. In the last study, single exposure on GD 6 resulted in a decrease of T4 with a LOEL of 0.06 mg/kg bw (Kuriyama et al., 2007). The CONTAM Panel was not able to identify an explanation for these contradictory results, which makes it difficult to draw a clear conclusion on the effects of PBDE on thyroid hormone homeostasis. Therefore, these studies were not considered for human

health risk assessment. Studies revealing adverse effects on the liver were also not included in the assessment because the LOAELs/NOAELs were based on induction of microsomal liver enzymes (CYPs). The expert panel considered that these early indicators, which are not adverse, could not form the basis for the human risk assessment of PBDEs, BDE-99 included.

Based on the information from animal experiments on neurodevelopmental behavioural changes and effects on sperm quality and reproductive performance, the CONTAM Panel derived benchmark doses (BMDs) with a benchmark response rate of 10% ($BMD_{10}$), and their corresponding $BMDL_{10}$ values (the lower confidence limit for the benchmark dose of a 10 % response) for the most critical endpoints for BDE-99. These values and the studies on which they are based are listed in Table 17.

*Table 17: $BMD_{10}$ and $BMDL_{10}$ values for critical effects of BDE-99.*

| **Critical endpoint** | **$BMD_{10}$ µg/kg bw** | **$BMDL_{10}$ µg/kg bw** | **Body burden at $BMDL_{10}$ µg/kg bw** | **References** |
|---|---|---|---|---|
| Mice, total activity | 22 | 12 | 9 | Eriksson et al., 2001[10] |
| Rat, locomotion | 116 | 82 | Not used | Kuriyama et al., 2005 |

Elimination kinetics between experimental animals and humans differ considerably for most PBDE congeners. The consequence of this difference is that exposure to similar doses for BDE-99 will result in higher concentrations in the human body than in rodents. Therefore, the CONTAM Panel converted the lowest derived $BMDL_{10}$ into estimated human intake associated with the body burden at the $BMDL_{10}$ (Table 17), as basis for the risk assessment. The body burden provides a more appropriate dose metric for a direct comparison of internal effect doses in animals and in humans. Because the $BMDL_{10}$ values for BDE-99 were derived from studies applying a single oral dose, the body burden at $BMDL_{10}$ can directly be calculated by multiplication of the $BMDL_{10}$ with the absorbed fraction. The CONTAM Panel used an oral absorption for BDE-99 in rodents of 75% for their calculation. This resulted in a body burden at the $BMDL_{10}$ of 9 µg/kg bw (table 17). However, the CONTAM Panel concluded that due to the limitations and uncertainties in experimental data on BDE-99 today, the derivation of a health-based guidance value directly from the body burden at the $BMDL_{10}$ was not appropriate. Instead, the Panel used a margin of exposure (MOE) approach for the risk characterization of BDE-99. Based on the body burden of 9 µg/kg bw and the longest human half-life of 1442 days reported by Geyer et al. (2004), an estimated chronic human dietary intake ($D_{r,h}$) of 4.2 ng/kg bw per day associated with the steady state body burden at the $BMDL_{10}$ for BDE-99 could be calculated. MOEs for different European general population groups, derived by dividing $D_{r,h}$ by the estimated daily intake, are listed in table 18.

[10] wrongly cited as Viberg et al. (2004b) in Table 40 of EFSA (2011) (EFSA 2023)

*Table 18: Overview of the margins of exposure (MOEs) for BDE-99 for different population groups, based on the minimum lower bound (LB) and maximum upper bound (UB) of the dietary intake (ng/kg bw).*

| Exposed population | Estimated intake (ng/kg bw/d) | | $D_{r,h}$ (ng/kg bw/d) | MOE | |
|---|---|---|---|---|---|
| | LB (min) | UB (max) | | at LB (min) | at UB (max) |
| Children (1-3 years), average consumers | 0.58 | 2.99 | 4.2 | 7 | 1.4 |
| Children (1-3 years), high consumers | 1.36 | 6.16 | 4.2 | 3 | 0.7 |
| Adults, average consumers | 0.11 | 0.65 | 4.2 | 38 | 6.5 |
| Adults, high consumers | 0.30 | 1.07 | 4.2 | 14 | 3.9 |
| Adults, high fish consumers | 0.60 | 1.40 | 4.2 | 7 | 3 |

bw: body weight; LB: lower bound; UB: upper bound; MOE: margin of exposure

The Panel considered that a MOE larger than 2.5 might indicate that there is no health concern. The UB MOEs for BDE-99 for young children (1-3 years) with average and high exposure are 1.4 and 0.7, respectively. These MOEs indicate a potential health concern for dietary exposure to BDE-99 for this population group.

**RIVM (2016)**

In 2016, the Dutch National Institute for Public Health and the Environment (RIVM) published its update of the dietary exposure of the Dutch population to five PBDE congeners, including BDE-99 (Lijzen *et al.*, 2018). The RIVM translated these EFSA $BMDL_{10}$ values into Guidance Values (GVs) for long-term intake to assess whether long-term exposures to PBDE congeners poses a health concern. This was done by dividing the $D_{r,h}$ by EFSA (2011) for BDE-99 (4.2 ng/kg bw/d) by the value of 2.5 corresponding to the minimum MOE that would indicate no health concern. This reasoning resulted in the derivation of a GV for long-term intake for BDE-99 of 1.7 ng/kg bw/d. An additional guidance value of 0.23 ng/kg bw/d was established for BDE-99 based on reproductive toxicity (Bakker *et al.*, 2008).

**EFSA (2024)[11]**

The European Commission asked EFSA to update its 2011 risk assessment on PBDEs in food (Chain *et al.*, 2024).. In this report, the new approach regarding benchmark dose (BMD) modelling, as described in the 2023 EFSA Guidance on the use of the BMD approach in risk assessment (Committee *et al.*, 2022), is applied; this approach derives endpoint specific benchmark responses, resulting in a combined MOE (MOE Total or MOET). Also, new studies have been published since 2011 and have provided additional data in relation to effects on the liver, thyroid hormones, and the reproductive, nervous and immune systems. The CONTAM Panel concluded that the neurodevelopmental effects on behaviour and reproductive/developmental effects are still the critical effects for the hazard characterisation. The studies on which the risk assessment is based are therefore different from those of EFSA 2011 (see table 19). $BMDL_{10}$ values for were derived for both neurodevelopmental effects and effects on reproduction. For BDE-99, the lowest $BMDL_{10}$ is **0.05 mg/kg bw/d** for developmental effects (increased resorption rates in dams following single dose administration on GD 6) based on the study by Talsness et al., (2005). A $BMDL_{10}$ of **0.43 mg/kg bw/d** is obtained for neurodevelopmental effects (reduction in the level of anxiety, with the potential to

[11] At the time of the literature review, S-RISK modelling to determine the SRV and writing of the first draft of this document, the EFSA opinion was published as draft report. The results stated in the draft report were not seen as final and therefore not used in this report.

adversely affect adaptation to stressful situations, after repeated exposure) based on the study of Blanco et al., (2013).
The CONTAM Panel used in EFSA (2011) the 1-compartment approach for the calculation of the body burden at the BMDL. In the EFSA 2023 draft, another approach is used to calculate the body burden at the BMDL, namely the tissue level approach. The tissue concentrations measured by Chen et al. (2006) in adult rats dosed with BDE-99 are used for the estimation of the body burden at the BMDL. This resulted in a body burden of

- **1.443 mg/kg bw** (for the Blanco (2013) study on neurodevelopmental effects) and
- **0.0155 mg/kg bw** (for the Talsness (2005) study on reproductive/developmental effects).

Considering these values, the Reference Points expressed as a chronic human dietary intake corresponding to the calculated body burden at the BMDL, were calculated based on the the median half-life in humans of 280 days reported by Trudel et al. (2011) instead of the worst-case maximum half-life estimated in humans (based on Geyer et al., 2004) used in EFSA 2011. A Reference Point for BDE-99 is calculated to be **3575 ng/kg bw per day** for neurodevelopmental effects and **38.4 ng/kg bw per day** for developmental effects.

*Table 19: Comparison of the Reference Points in the EFSA 2011 Opinion and the EFSA 2024 Opinion.*

| EFSA CONTAM Panel, 2011 | | | | EFSA CONTAM Panel, 2024 | | | |
|---|---|---|---|---|---|---|---|
| $BMDL_{10}$ (mg/kg bw) | Body Burden at the $BMDL_{10}$ (mg/kg bw) | Estimated chronic human dietary intake at the $BMDL_{10}$ body burden (ng/kg bw/day) | Study | $BMDL_{10}$ (mg/kg bw/day) | Body Burden at the $BMDL_{10}$ (mg/kg bw) | Estimated chronic human dietary intake at the $BMDL_{10}$ body burden (ng/kg bw/day) | Study |
| 0.012 | 0.009 | 4.2 | Eriksson et al., 2001 (neuro single exposure) | 0.43 | 1.443 | 3575 | Blanco et al., 2013 (neuro repeated exposure) |
| - | - | - | - | 0.05 | 0.0155 | 38.4 | Talsness et al., 2005 (develop. single exposure) |

The CONTAM Panel concluded in EFSA 2024 that the MOET approach was the most appropriate risk metric instead of only the individual MOE for each congener and applied a tiered approach to the risk characterisation. A MOET smaller than 25 (2.5 (interspecies differences in toxicodynamics) × 3.2 (individual differences in kinetics) × 3.2 (individual differences in toxicodynamics)) would raise a health concern.

To conclude, there is a difference in the risk characterisation method used in EFSA 2024 compared to EFSA 2011..

**ECB (2001)**
The EU Risk Assessment Report (RAR) estimated the total daily human intake (TDHI) of commercial pentaBDE through the environment to be 0.048 mg/kg/d via local sources and $7.9x10^{-4}$ mg/kg/day via regional sources. Margin of Safety values (MOS) have been calculated by comparing TDHI from both regional and local sources with the NOAEL for liver effects derived from a 30-day oral rat study (Assessment, 2002).

In this 30-day repeated dose study, male and female rats were administered 0, 0.01, 0.05, 0.1, 0.5, or 1.0 mg/kg/d of DE-71 daily in the diet. No adverse effects were observed in this study. Therefore, the NOAEL was determined to be 1 mg/kg/day. However, as this NOAEL is derived for a commercial product of pentaBDE, which contains 50-62% pentaBDE and considering a maximum oral absorption of 90%, a NOAEL of 0.45 mg/kg bw/day was derived by the ECB.
The risk to the general population from the consumption of cow's milk is largely contributing to the risk for total exposure via the environment. PentaBDEs have been shown to be also present in human breast milk. Therefore, the ECB found it appropriate to assess whether this presents a risk to breast-feeding babies. The assessment for human breast milk is applying for both regional and local sources of exposure. The average daily uptake of the breast-feeding infant was first estimated by the EBC and then compared to the NOAEL for liver effects and with the LOEL for behavioural differences. The studies on which the ECB relied for the LOEL were those of Eriksson et al. (1998, 1999). Eriksson et al. (1998, 1999), reported differences in behaviour of mice treated with pentaBDE as neonates after one single oral dosing (0.8 and 12 mg/kg bw). The LOEL was concluded to be 0.8 mg/kg/d.

*Table 20: Margin of safety (MOS) values for risk assessment following environmental exposure to pentaBPEs (ECB 2000)*

| Exposure scenario | Daily intake (mg/kg/day) | MOS based on liver effects (NOAEL 0.45 mg/kg/d) | MOS based on Behavioural differences (LOEL 0.8 mg/kg/day) |
|---|---|---|---|
| Regional sources | $7.9x10^{-4}$ | 570 | - |
| Local sources | 0.048 | 9.37 | - |
| Human breast milk | $0.95x10^{-5}$ | 47368 | 84111 |

The low body burden via regional sources together with its relatively high MOS suggests a low concern for the risks of effects on the liver. In contrast, the relatively high body burden via local sources and its MOS would indicate a cause for concern. The high MOS values for human breast milk would also lead to little cause for concern. However, The ECB stated that there are too many uncertainties with respect to this risk assessment and that there is too little information available to derive a reliable conclusion.

**ATSDR (2017)**
ATSDR has derived an **MRL** (minimal risk level) of **0.00006 mg/kg/d** ($6x10^{-5}$ mg/kg/d) for acute-duration oral exposure (14 days or less) to lower-brominated diphenyl ethers, including BDE-99. This value was based on the studies revealing endocrine effects in rat dams and reproductive and neurobehavioural effects in F1 offspring exposed to BDE 99 on GD 6 via gavage (Kuriyama et al. 2005, 2007; Talsness et al. 2005). The MRL was estimated by dividing the 0.06 mg/kg LOAEL by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for animal to human extrapolation, and 10 for human variability).
Additionally, ATSDR also derived an **MRL** of **0.000003 mg/kg/day** ($3x10^{-6}$ mg/kg/d) for intermediate-duration oral exposure (15 – 364 days) to those same lower-brominated BDEs. The intermediate oral MRL is based on a study with the congener BDE-47 conducted by Zhang *et al.* (2013). The MRL was estimated by dividing the 0.001 mg/kg/d minimal LOAEL by an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for animal to human extrapolation, and 10 for human variability).
A chronic-duration oral MRL was not derived for lower-brominated PBDEs due to insufficient data.

**US-EPA (2008)**

US-EPA (2008) derived an RfD (reference dose) of 0.1 µg/kg/d from the lower bound on the BMD ($BMDL_{1SD}$)[12] of 0.29 mg/kg/day, based on the effects of BDE-99 on spontaneous motor behaviour observed in the study of Viberg et al., (2004a). To calculate the RfD, a total UF (uncertainty factor) of 3000 was applied to this $BMDL_{1SD.}$ This total UF of 3000 was calculated by multiplying assessment factor values for interspecies variability (10), intrahuman variability (10), extrapolation from a single dose to a chronic exposure (3), and for database deficiencies (10). The available experimental data for BDE-99 are currently very scarce. Chronic studies investigating BDE-99 toxicity have not yet been performed in experimental animals and there is also a lack of developmental and reproductive toxicity and neurotoxicity studies, and standard subchronic studies of systemic toxicity. In addition, there is no data available regarding the potential toxicity of BDE-99 in humans exposed via the oral route, and no suitable toxicokinetic models have been developed to reduce uncertainty in extrapolating from mice to humans.

The study of Viberg et al. (2004a) was selected as the main study for deriving the RfD, and neurobehavioural developmental effects were identified as the critical effect. The primary reasons for selecting this study were:

- several different dose levels of BDE-99 were employed,
- quantitative dose-response data were available for benchmark dose (BMD) modeling,
- good model fits were obtained in subsequent BMD modeling,
- a clear NOAEL was identified,
- the results of this study are supported by several other studies in mice and rats.

However, several concerns regarding the experimental design of the Viberg et al. (2004a) study used in deriving the RfD have been raised. Confidence in the principal study is low because the study protocol was unique and did not conform to health effects test guidelines for neurotoxicity, the dosing regimen did not include gestation and lactation exposure, several pups per litter were used for the behavioural testing, and only single doses were given. Therefore is the overall confidence in the RfD low.

[12] One standard deviation

*Table 21: Toxicological reference values for BDE-99*

| Institution/author | Value type | Value (mg/kg bw/d) | Effect | Study | Uncertainty factor | Reference |
|---|---|---|---|---|---|---|
| **Oral (mg/kg bw/d)** | | | | | | |
| EFSA | *Chronic human intake (4.2 ng/kg bw/d) derived from the body burden at $BMDL_{10}$ (9 µg/kg bw) and the longest human half-life (1442 days) and a MOE* | *$1.7x10^{-6}$ (4.2 (ng/kg bw/d)/2.5, see RIVM)* | *Neurodevelopmental behavioural changes* | *Eriksson et al., 2001* | *MOE: >2.5* | EFSA (2011a) |
| EU-RAR | *NOAEL (0.45 mg/kg/day) and a MOS* | - | *No adverse effects were observed* | *Great Lakes Chemical corporation, 1985* | *MOS* | ECB (2001) |
| US-EPA | *RfD from a $BMDL_{1SD}$ (0.29 mg/kg bw/d) and an uncertainty factor* | *$1x10^{-4}$* | *Neurodevelopmental behavioural changes and decreased habituation* | *Viberg et al., 2004* | *3000 (interspecies variability (10) x intrahuman variability (10) x extrapolation from a single dose to a chronic exposure (3) x database deficiencies (10))* | US-EPA (2008) |
| ATSDR | *MRL acute from a LOAEL (0.06 mg/kg and an uncertainty factor* | *$6x10^{-5}$* | *Endocrine effects in rat dams and reproductive and neurobehavioural effects in F1 offspring* | *Kuriyama et al. 2005, 2007; Talsness et al. 2005* | *1000 (use of a LOAEL (10) x animal to human extrapolation (10) x human variability (10))* | ATSDR (2017a) |
| | *MRL intermediate from a LOAEL* | *$3x10^{-6}$* | *Reduction in serum testosterone* | *Zhang et al. 2013b* | *300 (use of a minimal LOAEL (3) x animal to human* | ATSDR (2017a) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | *(0.01 mg/kg and an uncertainty factor* | | | | *extrapolation (10) x human variability (10))* | |
| RIVM | *Chronic human intake estimated by EFSA (2011) (4.2 ng/kg bw/d) and a MOE* | *$1.7x10^{-6}$ (4.2 (ng/kg bw/d)/2.5)* | *Neurodevelopmental behavioural changes* | *EFSA 2011* | *MOE: 2.5* | Lijzen *et al.* (2018) |
| | | *$2.3x10^{-7}$* | *Impaired spermatogenesis* | *Bakker et al., 2008* | | Bakker *et al.* (2008) |

## 9.6 Proposal for toxicological reference values to be used

An overview of the reference values that were selected for the calculation of soil remediation values is given in **Error! Reference source not found.** 22.

*Table 22: Toxicological reference values for soil standards*

| Effect | Non Carcinogenic | | | Carcinogenic | | |
|---|---|---|---|---|---|---|
| Route | Oral | Inhalation | Dermal | Oral | Inhalation | Dermal |
| Value | $1x10^{-4}$ mg/kg bw/d | $3,5\ x10^{-4}$ mg/m³ | $8,5\ x10^{-5}$ mg/kg bw/d | - | - | - |
| Reference | US-EPA (2008) | Derived from oral guidance value (Cornelis & Touchant, 2016a) | Derived from oral guidance value (Cornelis & Touchant, 2016a) | - | - | - |

References values for carcinogenic effects are not available.

The arguments for selection are discussed below.

### 9.6.1 Oral

The toxicological reference values for non-carcinogenic toxicity come from primary sources (EFSA, EU-RAR, US-EPA and ATSDR) and a tertiary source (RIVM). Preference is given to a primary source.
The EU-RAR worked with a NOAEL & MOS respectively, however they did not derive a toxicological reference value. They concluded there were many uncertainties regarding the available experimental data at that time and the methods used to calculate the MOS.
US-EPA derived a RfD of $1x10^{-4}$ mg/kg bw/d based on the lower bound on the BMD ($BMDL_{1SD}$ of 0.29 mg/kg) and an UF of 3000. ATSDR was only able to derive a toxicological reference value for acute -and intermediate oral exposure to BDE-99. MRLs of $6x10^{-5}$ mg/kg bw/d for acute and $3x10^{-6}$ mg/kg bw/d for intermediate exposure were determined based on a LOAEL and an UF.
EFSA estimated the chronic human dietary intake (4.2 ng/kg bw/day) associated with the body burden at the $BMDL_{10}$ (9 µg/kg bw) for BDE-99 and used an MOE approach for risk characterization. Due to the limitations and uncertainties in the experimental data, the derivation of a health-based guidance value directly from the body burden at the $BMDL_{10}$ was not appropriate according to EFSA. However, the RIVM calculated a guidance value using the chronic human dietary intake that EFSA estimated and the MOE of 2.5. EFSA considered that a MOE larger than 2.5 might indicate that there is no health concern. Dividing the chronic human dietary intake (4.2 ng/kg bw/day) by the upper bound MOE of 2.5, a guidance value of $1.7x10^{-6}$ mg/kg bw/day was determined for chronic exposure.

The discussion is therefore mainly about the choice between the RfD of US-EPA and the guidance value derived from EFSA 2011 by RIVM. Arguments for and against are listed in Table 23.

The RfD from US-EPA is derived by using a BMD approach by fitting the continuous models available in BMD software (BMDS) to the neurobehavioral data in mice coming from the Viberg et al. (2004a) study. Neurobehavioural developmental effects were identified as the critical

effect by US-EPA and the study of Viberg et al. (2004a) was selected as the principal study by the arguments below:

- several different dose levels of BDE-99 were employed,
- a clear NOAEL was identified,
- the results of this study are supported by several other studies in mice and rats,
- good model fits were obtained in subsequent BMD modeling and quantitative dose-response data were available for benchmark dose (BMD) modeling.

In contrast to US-EPA, EFSA selected the study by Eriksson et al. (2011) as the main study. However, all BMDS models used by US-EPA (i.e., linear, polynomial, and power models) showed a significant lack of fit ($p < 0.1$) for all endpoints analyzed from Eriksson et al. (2001). The Hill model was not applied to these data due to its requirement for at least five dose groups, whereas the Eriksson et al. (2001) study used only three. Due to the lack of adequately fitting models, no BMD or BMDL estimates could be derived for Eriksson et al. (2001).

However, several concerns regarding the experimental design of the Viberg et al. (2004a) study used in deriving the RfD have been raised. Confidence in the principal study is low. The study protocol was not conform to test guidelines for neurotoxicity, the dosing regimen did not include gestation and lactation exposure, several pups per litter were used for the behavioural testing, and only single doses were given. Therefore, overall confidence of US-EPA in the RfD is low.

As already mentioned above, EFSA 2011 did select the Eriksson et al. (2001) study for risk assessment. The CONTAM Panel also considered neurodevelopment and effects on sperm quality and reproductive performance as the critical endpoint. They derived BMDs and their corresponding lower 95 % confidence limit, the BMDLs, of the most critical endpoints. For BDE-99, the lowest reference point to be used in the hazard characterization used was obtained from the Eriksson et al. (2001) study and not the Viberg et al. (2004a) study. Due to the limitations and uncertainties in the, at that time available database, the Panel concluded that it was inappropriate to use the BMDL to establish guidance values. They used an MOE approach for the health risk assessment instead.

However, the RIVM used the $BMDL_{10}$ value derived by the CONTAM Panel to calculate a guidance value for long-term intake. According to the CONTAM panel, an MOE of 2.5 (or higher) between the estimated human intake value and its corresponding actual intake does not indicate a potential health concern. Dividing the derived intake value by this factor results therefore in GVs for long-term intake that, when exceeded, are indicative for a potential health concern. While EFSA has not derived a guideline value, the RIVM has done so based on the data collected and calculated by the CONTAM Panel. Therefore, it can be considered that this guidance value is reliable.

Both EFSA and US-EPA cite the limitations and uncertainties of the data available at the time. In addition, the European Commission asked EFSA to update its 2011 risk assessment on PBDEs in food. EFSA 2022 concluded that the MOET approach was the most appropriate risk metric instead of the MOE used in EFSA 2011. When EFSA's draft report becomes a final report, EFSA 2011 will become outdated.

Based on this advancing scientific insight and the following methodological arguments, the RfD guidance value derived by US-EPA ($1x10^{-4}$ mg/kg bw/day) is selected as the toxicological reference value for the calculation of soil remediation values:

- Guidance value derived from data of a primary source

- Effect (neurobehaviour) is also described by other studies
- Chronic exposure
- Male and female mice
- Neonatal exposure

*Table 23: Arguments pro and contra for the choice between RfD (US-EPA 2008) and RIVM (2016)*

| Reference value | Pro | Contra |
|---|---|---|
| RfD (US-EPA) based on Viberg 2004 | Primary source | Confidence in the RfD is low |
| | Chronic exposure | Single dose exposure |
| | All institutes base their derivations on neurobehavioral studies | Only one endpoint was assessed |
| | Male and female mice | Experimental design, no standard protocol |
| | Neonatal mice (critical phase for neurological development) | |
| | Subsequent studies with the same or a different design and with repeated administration confirm neurobehavioral effects | |
| | In line with the selection of the RfD for BDE-209 for soil remediation value derivation; both RfDs are based on the same study. | |
| Guidance value for oral chronic exposure (RIVM based on EFSA 2011) based on Eriksson 2001 | Derived value based directly on information from a primary source | Tertiary source; EFSA did not derive a health-based guidance value due to the limitations and uncertainties in experimental data |
| | Chronic exposure | Single dose exposure |
| | All institutes base their derivations on neurobehavioural studies | Only male mice |
| | Neonatal mice (critical phase for neurological development) | Only one endpoint was assessed |
| | Most recent derivation | Experimental design, no standard protocol |
| | Most conservative value | All BMDS models used by US-EPA showed a significant lack of fit ($p < 0.1$) for all endpoints analyzed from Eriksson et al. (2001). |
| | Subsequent studies with the same or a different design and with repeated administration confirm neurobehavioral effects | The European Commission asked EFSA to update its 2011 risk assessment on PBDEs in food. EFSA 2022 concluded in that the MOET approach was the most appropriate risk metric instead of the MOE used in EFSA 2011. When EFSA's draft report becomes a final report, |

| | | |
|---|---|---|
| | | EFSA 2011 will become outdated |
| | | Guidance value derived because a value was needed for comparison with Dutch intake data |

### 9.6.2 Inhalation

A toxicological reference value for inhalation is not available, therefore it is calculated from the RfD, with a tidal volume of 20 m³/d and a body weight of 70 kg, according to the REACH guidelines for human dose-response evaluation (ECHA, 2012).

$$RWihl = RWorl * (\frac{BW}{tidal\ volume})$$

With:

- RWihl: toxicological reference value for inhalation (mg/m³)
- RWorl: oral reference value (mg/kg bw/d)
- BW: bodyweight of 70 kg
- Tidal volume: 20 $m^3$/day (adult)

The result is 3,5 $x10^{-4}$ mg/m³; it is assumed that absorption via inhalation is equal to that for oral exposure (85%, section 9.2).

A unit risk is not available. No inhalation carcinogenic studies are available. Reference values for carcinogenic effects are not available and therefore no unit risk could be calculated.

### 9.6.3 Dermal

A dermal reference value is not available in literature. Therefore, the dermal TDI (tolerable daily intake) and slope factor are derived from the oral TDI and slope factor, respectively, according to the guidelines of Cornelis and Touchant (2016a). The reference values for the dermal route refer to absorbed dose, the oral reference value is an external dose; therefore, oral absorption (85% for BDE-99) must be taken into account when calculating the dermal reference values.

TDIdermal = TDIoral*ABSoral = $1x10^{-4}$ mg/kg bw/d * 0,85 = $8,5x10^{-5}$ mg/kg bw/d

No reference values for carcinogenic effects available and therefore no Slope factor dermal could be calculated.

## 9.7 Proposal for toxicological reference values according to EFSA 2023 draft report

Because both the US-EPA RfD (2008) and the estimated chronic daily intake from EFSA (2011) were not considered very reliable, the toxicological reference values have also been calculated based on the estimated chronic daily intake from the EFSA 2024 report for comparison.

At the time when the literature search for toxicological reference values, SRV estimation and writing of the draft report, the EFSA Opinion was still in a draft form, and the results were not seen as final. In this chapter, a comparison was made between the Toxicological Reference Values stated by the US EPA and the values stated in the EFSA Opinion. Table 25 shows that the TRV for oral exposure were comparable with the US EPA values being slightly lower. At an advanced stage of this report the EFSA report was published, however, it was agreed with OVAM that although a preference would be given to the new EFSA TRVs, the report would not be updated using these values in the SRV estimation. For clarity, Annex C contains an overview of the SRV estimating using the TRV from the US EPA and EFSA.

Since 2011, new studies have been published which provided additional data in relation to effects on the liver, thyroid hormones, and the reproductive, nervous, and immune systems. The CONTAM Panel concluded that the neurodevelopmental effects on behaviour and reproductive/developmental effects are still the critical effects for the hazard characterisation. A new approach regarding benchmark dose (BMD) modelling (Guidance on the use of the BMD approach in risk assessment, (Committee *et al.*, 2022)), is also applied in the draft report. This approach derives endpoint specific benchmark responses, resulting in a combined MOE, the MOET. A MOET smaller than 25 would raise a health concern. To calculate an oral TDI, the same method was applied as the one used by RIVM in 2016 ($D_{r,h}$ (ng/kg bw/d) / MOE(T)). An overview of the reference values that were calculated based on the EFSA 2024 report is given in **Error! Reference source not found.** 25.

*Table 24: Toxicological reference values for soil standards*

| **Effect** | **Non Carcinogenic** | | |
|---|---|---|---|
| **Route** | **Oral** | **Inhalation** | **Dermal** |
| Value | 1,43x10$^{-4}$ mg/kg bw/d | 5x10$^{-4}$ mg/m³ | 7x10$^{-5}$ mg/kg bw/d |
| Reference | Based on EFSA (2023), value calculated according to the method by RIVM | Derived from oral guidance value (Cornelis & Touchant, 2016a) | Derived from oral guidance value (Cornelis & Touchant, 2016a) |

*Table 25:Comparison of the Reference Points derived from US EPA 2008 and the EFSA 2024 Opinion.*

| **US EPA, 2008** | | **EFSA CONTAM Panel, 2024** |
|---|---|---|
| **Effect** | **Non Carcinogenic** | **Non Carcinogenic** |

| Route | Oral | Inhalation | Dermal | Oral | Inhalation | Dermal |
|---|---|---|---|---|---|---|
| Value | $1x10^{-4}$ mg/kg bw/d | $3,5\ x10^{-4}$ mg/m³ | $8,5x10^{-5}$ mg/kg bw/d | $1,43x10^{-4}$ mg/kg bw/d | $5x10^{-4}$ mg/kg bw/d | $7x10^{-5}$ mg/kg bw/d |
| Reference | US-EPA (2008) | Derived from Rfd value US-EPA (Cornelis & Touchant, 2016a) | Derived from Rfd value US-EPA (Cornelis & Touchant, 2016a) | Based on EFSA (2024) | Derived from oral guidance value (Cornelis & Touchant, 2016a) | Derived from oral guidance value (Cornelis & Touchant, 2016a) |

### 9.7.1 Oral

The studies selected for risk assessment in EFSA 2024 are different from those of EFSA 2011 (see Table 26). In addition, $BMDL_{10}$ values were derived for both neurodevelopmental effects and effects on reproduction (see table 17). For comparison with the US-EPA RfD, the $BMDL_{10}$ body burden of neurodevelopmental effects is selected for derivation of the oral reference value. EFSA (2023) calculated a reference point of 3575 ng/kg bw per day expressed as the chronic human dietary intake which was based on the median human half-life of 280 days (Trudel et al., 2011) instead of the estimated worst-case maximum half-life (based on Geyer et al., 2004) used in EFSA 2011.

*Table 26: Comparison of the Reference Points in the EFSA 2011 Opinion and the EFSA 2024 Opinion.*

| ***EFSA CONTAM Panel, 2011*** | | | | ***EFSA CONTAM Panel, 2024*** | | | |
|---|---|---|---|---|---|---|---|
| *$BMDL_{10}$ (mg/kg bw/day)* | *Body Burden at the $BMDL_{10}$ (mg/kg bw)* | *Estimated chronic human dietary intake at the $BMDL_{10}$ body burden (ng/kg bw/day) ($D_{r,h}$)* | *Study* | *$BMDL_{10}$ (mg/kg bw/day)* | *Body Burden at the $BMDL_{10}$ (mg/kg bw)* | *Estimated chronic human dietary intake at the $BMDL_{10}$ body burden (ng/kg bw/day) ($D_{r,h}$)* | *Study* |
| *0.012* | *0.009* | *4.2* | *Eriksson et al., 2001 (neuro single exposure)* | *0.43* | *1.443* | *3575* | *Blanco et al., 2013 (neuro repeated exposure)* |

In 2016 RIVM translated the EFSA 2011 $BMDL_{10}$ values into Guidance Values (GVs) for long-term intake. This was done by dividing the $D_{r,h}$ of EFSA (2011) by the value of 2.5 corresponding to the minimum MOE that would indicate no health concern. The same approach was used to derive the oral toxicological reference value from the EFSA 2024 $D_{r,h}$. However, The CONTAM Panel concluded in EFSA 2024 that the MOET approach was the most appropriate risk metric instead of the individual MOE for each congener and applied a tiered approach to the risk characterisation. A MOET smaller than 25 (2.5 (interspecies differences in toxicodynamics) × 3.2 (individual differences in kinetics) × 3.2 (individual differences in toxicodynamics)) would raise a health concern.
A toxicological reference value can be calculated form the estimated chronic human dietary intake at the BMDL10 body burden (3575 ng/kg bw/day) and the MOET (25):

Oral TDI = 3575/25 = 143 ng/kg bw/d = 0,000143 mg/kg bw/d

### 9.7.2 Inhalation

A toxicological reference value for inhalation is not available, therefore it is calculated from the oral reference value, with a tidal volume of 20 m³/d and a body weight of 70 kg, according to the REACH guidelines for human dose-response evaluation (ECHA, 2012).

$$RWihl = RWorl * (\frac{BW}{tidal\ volume})$$

With:

- RWihl: toxicological reference value for inhalation (mg/m³)
- RWorl: oral reference value (mg/kg bw/d)
- BW: bodyweight of 70 kg
- Tidal volume: 20 $m^3$/day (adult)

The result is 5 x$10^{-4}$ mg/m³; it is assumed that absorption via inhalation is equal to that for oral exposure (50% for BDE-99 according to EFSA 2024 report).

A unit risk is not available. No inhalation carcinogenic studies are available. Reference values for carcinogenic effects are not available and therefore no unit risk could be calculated.

### 9.7.3 Dermal

A dermal reference value is not available in literature. Therefore, the dermal TDI (tolerable daily intake) and slope factor are derived from the oral TDI and slope factor, respectively, according to the guidelines of Cornelis and Touchant (2016a). The reference values for the dermal route refer to absorbed dose, the oral reference value is an external dose; therefore, oral absorption (50% for BDE-99) must be taken into account when calculating the dermal reference values.

TDIdermal = TDIoral*ABSoral = 1,43x$10^{-4}$ mg/kg bw/d * 0,5 = 7x$10^{-5}$ mg/kg bw/d

No reference values for carcinogenic effects available and therefore no Slopefactordermal could be calculated.

# 10 ECOTOXICOLOGY

In accordance with the guidelines for establishing soil remediation standards outlined by Cornelis and Touchant (Cornelis & Touchant, 2016b), an examination was conducted to determine whether other organizations had recently derived ecotoxicologically substantiated values. The following sources were referenced:

• US EPA: http://www.epa.gov/ecotox/ecossl/index.html
• CCME Canada:
http://www.ccme.ca/en/resources/canadian_environmental_quality_guidelines/index.html
• RIVM Nederland (interventiewaarden, landelijke referentiewaarden):
http://www.rivm.nl/rvs/Normen/Milieu/Bodeminterventiewaarden ,
http://www.rwsleefomgeving.nl/onderwerpen/bodem-ondergrond/bbk/instrumenten/nobo
• ECHA-database: http://echa.europa.eu/information-on-chemicals

No derived ecotoxicological standards were found for BDE-99. The next step is to review ecotoxicological data on soil invertebrates and plants to derive a reference value, based on the method described by Bierkens[13] (2001). Our search encompassed ecotoxicological data derived from primary sources, databases, as well as supplementary secondary sources. Ultimately, we have chosen to use a Predicted No Effect Concentration (PNEC) for soil derived from pentabromodiphenyl ether derivatives (CAS nr. 32534-81-9) as the ecotoxicological reference value. The results of this inventory are summarized in section 12.3, Ecotoxicological reference value.

[13] The report of Bierkens (2001) is not published. Extracts, relevant for BDE-99 are shown in addendum: Annex B.

# 11 LEGAL LIMITS

### 11.1.1 Outdoor and indoor air

No legal EU standards or guideline values have been found for BDE-99 in air. Consequently, the toxicological reference value for inhalation (section 9.7.2) is selected for the calculation of soil remediation value; the reference value for inhaled air is 3.5 $x10^{-4}$ mg/m³ (Annex A).

### 11.1.2 Drinking water

No legal EU standards or guideline values have been found for BDE-99 in drinking water. However, a calculated value of 1.61 x $10^{-2}$ ng/l for a pentaBDE mixture, of which BDE-99 is a component, is proposed by the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) for drinking water (Scientific Committee on Health, 2023).
This value was calculated using the threshold level of 0.23 ng kg bw/day for reproductive toxicity from a study with BDE99 (Bakker et al, 2008). The SCHEER endorses the selection of this value especially because BDE99 appeared to be the most toxic congener from three BDEs evaluated by EFSA (2011).
The drinking water standards and guideline values of various countries and institutions were searched, only a regional screening level (USA) of 2 µg/l for BDE-99 in tap water was found (EPA. 2017) [14].

The soil remediation value for groundwater was calculated to be 0.6 µg/l (Section 12.2). As the soil remediation value for groundwater is lower than the value set by the US EPA, this value is set as the concentration limit.

### 11.1.3 Diet and fodder

BDE-99 has no limit values in EU legislation on chemicals in food and livestock fodder.

### 11.1.4 Regulation (EU) 2019/1021 on persistent organic pollutants

The EU regulation (EU) 2019/1021 (EU, 2019) regulation persistent organic pollutants (POPs). POPs are not only persistent but also accumulate in the environment and biota and can therefore be subjected to long-range transport. They can also pose a risk to the environment as well as human. The POP regulation aims to protect the environment and humans.

Within the regulation on POPs there is an obligation to proper waste management for waste containing POPs. Annex IV within the regulation states the POPs which fall under the waste management and the limit value for waste to be considered POP-containing waste. These limit values are defined as Lower POP Concentration Limit (LPCL). Waste containing higher concentrations of POP than the LPCL needs to be processed according to methods described in Annex I of the POPs Regulation. These processing methods should result that the waste doesn't contain POPs.
Exceptions can be made when it is shown that the removal of POPs from the waste is not possible. The conditions when the exceptions can be made are stated in article 7(4)(b).

The POP regulation covers five PBDE homologues:

- Tetrabromodiphenylether (tetraBDE)
- Pentabromodiphenylether (pentaBDE)

[14] *Regional Screening Level (RSL) Summary Table:* http://www.epa.gov/risk/regional-screening-levels-rsls-generic-tables-may-2016)

- Hexabromodiphenylether (hexaBDE)
- Heptabromodiphenylether (heptaBDE)
- Decabromodiphenylether (decaBDE)

The LPCL mentioned in Annex IV of the Regulation covers the sum of the five PBDE homologues. The LPCL is currently 500 mg/kg but will be reduced to 350 mg/kg by December 2025 and finally to 200 mg/kg by December 2027.

The target value for Unintentional Trace Contaminant as stated in Annex I in the Regulation is 500 mg/kg for the sum of the five PBDE homologues in mixtures and articles.

Table 27: UTC, LPCL and UPCL started in the POP Regulation for PBDEs

| UTC (Annex I) | LPCL (Annex IV) | UPCL (Annex V) |
|---|---|---|
| 500 mg/kg | 500 mg/kg | 10.000 mg/kg |
| | 350 mg/kg as of December 2025 | |
| | 200 mg/kg as of December 2027 | |

It is unclear which part of the POP Regulation covers soil, therefore, an expert judgement is made that soil is covered by UTC.

The limit values stated in the POPs Regulation are expressed on a fresh weight (fw) basis, while the soil remediation values are expressed on a dry weight (dw) basis. In order to convert the fw concentrations to dw concentrations, a default value for the moisture content in a standard soil is used (i.e., 0,2 $cm^3/cm^3$) and a bulk density of 1500 $kg/m^3$ resulting in a moisture content of 0,13 kg water/kg fw. The UTC value of 500 mg/kg can therefore be converted by dividing by 0,87 kg dm/kg fw, resulting in 577 mg/kd dw (=580 mg/kg dw based on two significant figures.

# 12 CALCULATION OF THE SOIL REMEDIATION VALUE

## 12.1 Groundwater

The soil remediation value (SRV) for groundwater was calculated using the following formula (Cornelis & Touchant, 2016):

$$SRV = \frac{TDIoral\ x\ 1000\ x\ RF\ x\ BW}{Q}$$

With:

- SRV soil remediation value groundwater (µg/l)
- TDI tolerable daily intake (mg/kg lg/d)
- 1000 conversion factor mg to µg
- RF reduction factor (default 0,2)
- BW bodyweight (60 kg)
- Q drinking water consumption (2l)

The values for RF, BW and Q are taken from the WHO drinking water quality guidelines (WHO, 2017). The oral TDI is $1x10^{-4}$ mg/kg bw/d (Annex A). As a result, the proposed SRV for groundwater is **0.6 µg/l.**

The detection limit in groundwater is 0.01 µg/l, well below the proposed SRV. The background value is equal to the detection limit of 0.01 µg/l.

## 12.2 Soil

The soil remediation value (SRV) for BDE-99 is being estimated using Application I of the S-Risk model (v 3.4.4) and Application II with adjusted bufferspace (to 0.75 m) for the interpretation of the different exposure pathways. Transfer from soil to plants is estimated by using BCF values based on soil concentrations on dry weight, normally BCFs for organic chemicals are based on pore water concentrations. Therefore, an adjustment was made in S-Risk. The input data used to estimate the SRV are listed in the Substance data sheet in Annex A.

The SRV are estimated for several scenarios:

- SRV II – Agriculture
- SRV III – Residential with vegetable garden
- SRV IVa – Day recreation, outdoor sports
- SRV IVb – Holiday resort, mainly indoor
- SRV Va – Light industry
- SRV Vb – Heavy industry

The limit of detection (LOD) for BDE-99 in soil is 0.55 µg/kg dw[15], well below the proposed SRV.

[15] Personal communication Hendrik Van De Weghe (VITO).

The background value for anthropogenic chemicals is being set at the LOD for both soil and groundwater.

The estimated SRV for BDE-99 for the different scenarios are listed in Table 28.

*Table 28: Estimated Soil Remediation Value (SRV) (based on human toxicology) for BDE-99 (mg/kg dw).*

| | **Scenario** | | | |
|---|---|---|---|---|
| | **II** | **III** | **IV** | **V** |
| SRV | 0.004 | 0.038 | IVa 54 | Va 920 |
| | | | IVb 51 | Vb 420 |

An overview of the contribution of the various exposure pathways for the different scenarios is given in Figure 1, scenarios II, III and IV show the results from children ages 1-<6 years and scenario V shows the results for adults aged 15-<71 years old. The relative contributions are estimated for each scenario with the risk index being equal to 1. For almost all scenarios, oral exposure is the predominant exposure pathway (highlighted in green in Figure 1). For scenario II (agriculture), more than 85% of the total exposure results from intake via meat and milk, while the remaining exposure results from locally grown vegetables. For scenario III (residence with vegetable garden), >99% of the exposure results from the intake of locally grown vegetables. For scenario IV (day recreation, outdoor sports and holiday resort, mainly indoor), the exposure results from both ingestion and dermal uptake of soil and dust. For scenario V (light and heavy industry), oral exposure of soil and dust are the predominant exposure pathway for BDE-99 (>80%) with dermal uptake via soil and dust being the second important pathway (8 – 18%), exposure via inhalation of indoor or outdoor air resulted in < 2.6% of the total exposure.

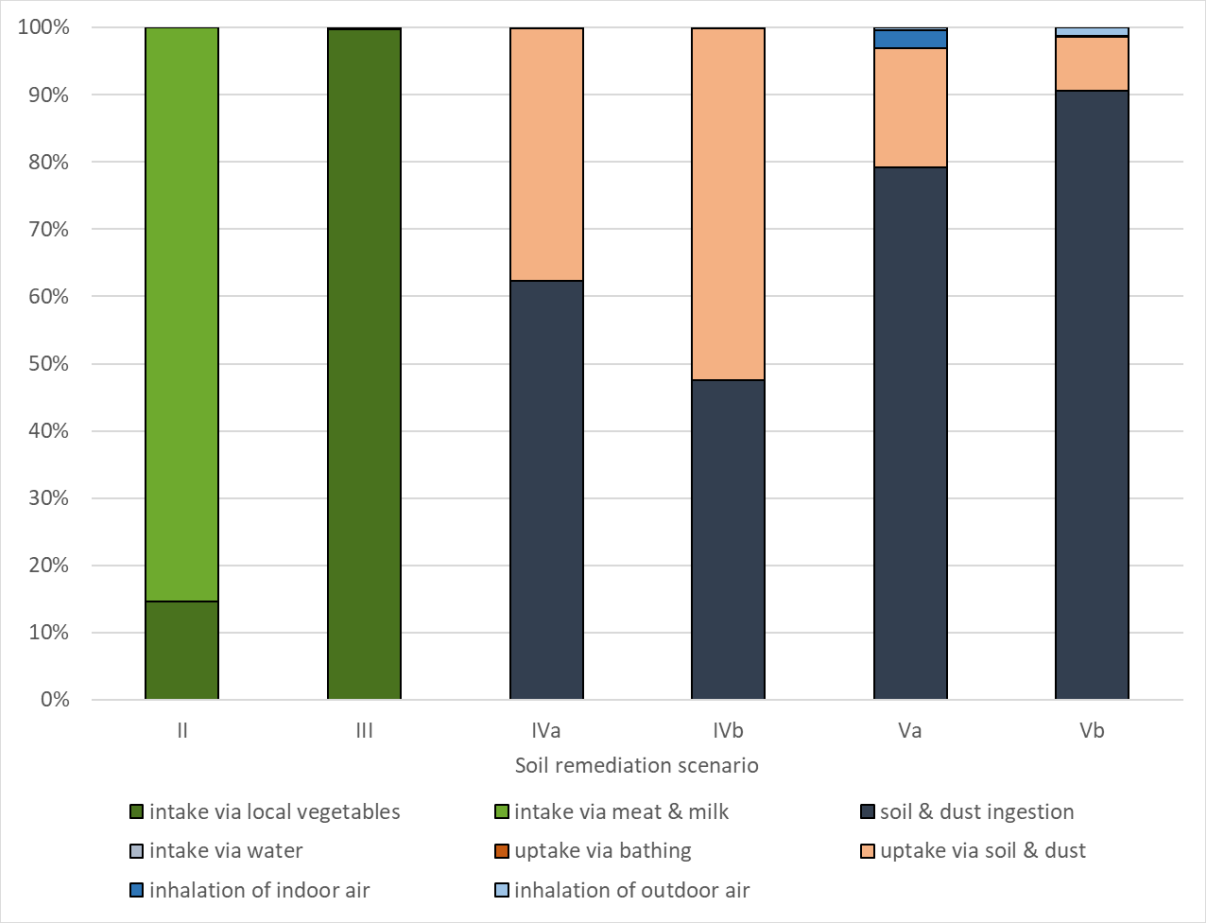



*Figure 1: Relative contribution of oral, dermal and inhalation exposure pathways to the total BDE-99 exposure for children aged 1-<6 years (scenarios II, III, IVa, and IVb) and adults aged 15-<71 years (scenarios Va and Vb).*

## 12.3 Ecotoxicological reference value

No derived ecotoxicological standards were found for BDE-99 in the agencies (see chapter 10) and there is no REACH-dossier available on the ECHA website.
However, **the EU Risk Assessment report (RAR)** (ECB, 2000) for pentabromodiphenylether derivatives calculated a Predicted No Effect Concentration for soil ($PNEC_{soil}$). PentaBDE (CAS number 32534-81-9) refers to the group of different isomers with PBDE congener numbers 82-127. Data in the RAR, and the derived values, are mostly based on commercial mixtures of pentaBDE. These mixtures contain a significant fraction of BDE-99. We consider these data representative for BDE-99. However, as a precautionary measure, we will compare them with other available sources for BDE-99 to ensure their similarity.

The $PNEC_{soil}$, proposed in the RAR is **0.38 mg/kg** dry weight (dw). This value is based on ecotoxicity data for the terrestrial compartment consisting of 1 study on microorganisms, 1 study on earthworms and a study on six plant species. The No Observed Effect Concentrations (NOECs) are given in **Error! Reference source not found.**29.

The lowest NOEC is obtained from the test on soil microorganisms (> 1 mg/kg dw), but the test concentrations used in this study were very low. In the RAR, this NOEC is therefore not considered valuable because the tested concentrations are lower than the $PNEC_{soil}$, derived using the equilibrium partitioning method (EPM) based on the $PNEC_{surface\ water}$ -value (**$PNEC_{soil}$**

**= 5.91 mg/kg dw**). The $PNEC_{surface\ water}$ of 0.53 µg/l is based on the lowest NOEC of 5.3 µg/l for Daphnia and an assessment factor (AF) of 10.
The NOEC obtained from a plant study, specifically on corn, at 16 mg/kg dw, was selected to derive the $PNEC_{Soil}$. This NOEC was normalized to the standard organic matter content of soil as used in the Technical Guidance Document (TGD[16]) and resulted in a $NOEC_{standard}$ of 18.8 mg/ kg dry weight.
To derive the $PNEC_{soil}$, an AF of 50 was applied based on the available ecotoxicological data, which resulted in a **$PNEC_{Soil}$ of 0.38 mg/kg dw.**

For comparison between the $PNEC_{soil}$ of 5.91 mg/ kg dw, derived using the equilibrium partitioning method and the $PNEC_{soil}$ of 0.38 mg/ kg dw, derived using ecotoxicological data, both PNECs need to be based on the same assessment factor. The assessment factors used for the $PNEC_{soil}$ calculations are 10 and 50 respectively. Using an assessment factor of 10 for both PNECs would give a $PNEC_{soil}$ of 5.91 mg/ kg dw and a $PNEC_{soil}$ of 1.9 mg/ kg dw (0.38*50/10). This comparison shows both methods deriving a $PNEC_{soil}$ in the same range. The RAR-report indicates a preference for using the $PNEC_{soil}$ of 0.38 mg/kg dw as the preferred value.

*Table 29: Ecotoxicity data (NOECs) for PentaBDE extracted from the RAR CAS nr. 32534-81-9 (ECB, 2000)*

| Contaminant | Ecotox Endpoint | Unit | Value | Test type | Source |
|---|---|---|---|---|---|
| PentaBDE (CAS 32534-81-9 and commercial pentaBDE mixtures) | ***Microorganisms*** | | | | |
| | NOEC Soil Microorganisms | mg/kg dw | >1 | OECD216 | ECB (2000) |
| | ***Plants*** | | | | |
| | NOEC Corn *Zea Mays* | mg/kg dw | 16 | OECD 208 | ECB (2000) |
| | NOEC Onion *Allium cepa* | | >=1000 | | |
| | NOEC Rye grass *Lolium perenne* | | >=1000 | | |
| | NOEC Cucumber *Cucumis sativa* | | >=1000 | | |
| | NOEC Soybean *Glycine max* | | >=1000 | | |
| | NOEC Tomato *L. esculentum* | | 125 | | |
| | ***Soil Invertebrates*** | | | | |
| | NOEC Earthworm *Eisenia fetida* | mg/kg dw | >500 | OECD 207 | ECB (2000) |

In the NORMAN Database, a $PNEC_{surface\ water}$ is given for BDE-99 (CAS 60348-60-9) equal to 0.5 µg/l. This value is based on (equal to) the PNEC derived in the RAR. The source referred to in the NORMAN Database is the INERIS database. INERIS shows 2 $PNEC_{soil}$, both based on the values in the RAR (ECB, 2000): a PNECsoil of 0.38 mg/kg dw and a PNECsoil of 5.21 mg/kg dw. The latter is done by the EPM with a slightly different result than the value in the RAR-report.

[16] TGD preceeding REACH guidance R10 with the following reference: Commission of the European Communities, 1996. Technical Guidance Documents in Support of the Commission Directive 93/67/EEC on risk assessment for new substances and the Commission Regulation (EC) No 1488/94 on risk assessment of existing substances. Commission of the European Communities, Brussels, Belgium. ISBN 92-827-801[1234]

The next step involves deriving ecotoxicological soil standards based on available ecotoxicity data for soil organisms, following a method described in Bierkens (Bierkens, 2001).

The EcoTox DataBase[17] refers to a study from Behl et al (Behl *et al.*, 2016) in which they tested the effects of pure BDE-99 as well as the DE-71[18] commercial mixture (38.7% BDE-99) on the nematode *C. elegans*, using 3 biological endpoints (feeding, larval development and reproduction). The Lowest Effective Concentration (LEC) was estimated and is given in **Error! Reference source not found.**30. The LEC for the endpoint larval development (0.16 µM) was lower compared to the other two endpoints. According to the authors, this was explained by the mitochondrial toxicity of BDE-99, as there is an association between *C. elegans* larval development and mitochondrial dysfunction.

*Table 30: Ecotoxicity data on C. elegans by Behl et al (2016), exposed to BDE-99 (100%) and to a mixture with BDE-99 (38.7%)*

| Endpoint criterium | LEC with 100% BDE-99 | LEC with DE-71 (38.7% BDE-99) |
|---|---|---|
| Larval Development (48h) | 0.16 µM | 0.16 µM |
| Reproduction (48h) | 13 µM | 1.6 µM |
| Feeding behaviour (24h) | 7.90 µM | 5 µM |

Even though this nematode is a soil dwelling species, comparison with NOECs from **Error! Reference source not found.**29 is not possible because the nematodes were tested on agar plates and not in soil medium. Because the RAR calculated a $PNEC_{Soil}$ based on the derived $PNEC_{surface\ water}$, we decided to convert de LECs in Table 31 to the unit mg/l to check if these values are in the same range as the NOECs based on aquatic species in the RAR. Convergence gives the following results:

*Table 31: Converted values of **Error! Reference source not found.**, by using 564.7 g/mol as t he molar mass for BDE-99*

| Endpoint | LEC with 100% BDE-99 |
|---|---|
| Larval Development (48h) | 0.09 mg/l |
| Reproduction (48h) | 7.34 mg/l |
| Feeding behaviour (24h) | 4.46 mg/l |

In the RAR, long-term NOECs are available for fish, water fleas and algae. Ultimately, the $PNEC_{surface\ water}$ (with an AF = 10) is 0.53 µg/l, based on the lowest NOEC of 5.3 µg/l for *Daphnia*. Both the NOEC for *Daphnia* and the LEC for *C. elegans* (90 µg/ l) are situated in the 1-100 µg/l range. **This analogy is an argument to consider the $PNEC_{Soil}$ based on pentaBDE as representative for BDE-99**.

Another study testing the ecotoxicity of BDE-99 on *C. elegans* evaluated the effects on feeding activity (Čadková *et al.*, 2020). The exposure took place in Eppendorf tubes in a liquid medium simulating the soil solution composition and concentrations. BDE-99 ranged between 0 and 1 mg/l. There was no significant observed effect of BDE-99 on the feeding behaviour of *C. elegans.* This is in line with the study of Behl et al (2006): an effect on feeding behaviour was only registered at a concentration above 1 mg/l (4.46 mg/l).

[17] https://cfpub.epa.gov/ecotox/search.cfm

[18] The following PBDEs were observed in DE-71 by Behl et al (2016) using gas chromatography: BDE-47 (42.27%), BDE-99 (38.72%), BDE-100 (8.32%), BDE-85 (2.19%), BDE-154 (2.26%), and BDE-153 (2.61%) for a total purity of 96.37%. BDE-47 is a tetraBDE, BDE-153 and BDE-154 are hexaBDEs and BDE-85, -99 and -100 are pentaBDE.

No additional ecotoxicological data were found from pure BDE-99 tests on soil invertebrates, plants or microorganisms. No additional ecotoxicological data is found for pentaBDE (CAS number 32534-81-9) in the ECOTOX DATABASE (data for the terrestrial compartment are based on mammalian test organisms only). There is no REACH-file either. Therefore, we cannot derive new ecotoxicological soil standards.

The $PNEC_{soil}$ is currently not included in the guidelines for soil standards derivation (Cornelis & Touchant, 2016). However, in the European guidelines for surface water standards derivation, $PNEC_{surface\ water}$ is considered an important parameter to consider in the derivation. Therefore, and because no other information on the ecotoxicity of BDE-99 is available, this report will use the $PNEC_{soil}$ as the base for derivation of a soil standard. The same approach was used for BDE-209 and this approach is also described and applied by RIVM (RIVM, 2004; 2009).

The derivation of $PNEC_{soil}$ does not take into account the land use type. $PNEC_{soil}$ is solely based on adverse effects on invertebrate soil organisms (e.g., earthworms), microorganisms, and plants through direct soil contact (ECHA, 2008a), without considering uptake through crops by grazers. The CCME method does take grazer's uptake into account for agricultural areas. Similar to the CCME approach where a certain degree of tolerance is allowed for less sensitive forms of land use, such as industrial and commercial zones, it is not recommended to use $PNEC_{soil}$ as the Environmental Soil Quality Standard ($EQS_{Soil}$), *in casu* soil remediation value (SRV) for the industrial land use type.

Based on the discussion above, and similar to the choices made for deriving an ecotoxicological reference value for BDE-209, **the $PNEC_{soil}$ of 0.38 mg/kg dw is selected** as the SRV for land use types agriculture (II), residential (III), and recreational stay (IV). For the industrial land use type, $PNEC_{soil}$ as $SRV_I$ for BDE-99 is not applicable. In **Error! Reference source not found.**32 the $PNEC_{soil}$ is compared to other reference values from different sources and countries. A detailed explanation of these values is written in the following paragraphs.

*Table 32: Comparison of proposed Ecotoxicological Reference Values or EQS for BDE-99, PentaBDE and mixtures, for the compartments Soil, Sediment and for Secondary Poisoning*

| Contaminant | Ecotox Reference value | Unit | Value | Source |
|---|---|---|---|---|
| ***Proposed EQS for Soil*** | | | | |
| PentaBDE CAS-nr. 32534-81-9 | $PNEC_{Soil}$ | mg/kg dw | 0.38 | ECB(2000) |
| PentaBDE mixture | $ENEV_{Soil}$ | mg/kg dw | 0.27 | (Canada, 2006) |
| ***Proposed EQS for Sediment*** | | | | |
| BDE-99 | $FSeQG_{Sediment}$ | mg/kg dw | 0,0004 | (Canada, 2013) |
| 6 indicators PBDEs (including BDE-99) | $SQG_{Sediment}$ | mg/kg dw | 0,052 | Ecotoxcenter Switzerland |
| ***Proposed EQS for Secondary Poisoning*** | | | | |
| 6 indicators PBDEs (including BDE-99) | $SQG_{Sec\ Pois}$ | mg/kg dw | 0,0009 | Ecotoxcenter Switzerland |

**The Ecological Screening Assessment report on PBDEs from the Canadian Environmental Protection Act (Canada, 2006)** calculated a risk quotient (Q) analysis for

PeBDE commercial mixture. This mixture predominantly consists of pentaBDE, tetraBDE and hexaBDE congeners, but may also contain trace levels of heptaBDE and tribromodiphenyl ether (triBDE) congeners. Although BDE-99 is a pentaBDE, it is not considered in this assay, nor present in the commercial PeBDE mixture regarded in the Canadian report. The Q value for PeBDE is **0.13 – 0.26 mg/ kg dw for soil**. The Q includes background exposure, based on data of a Swedish study. Because our own method does not take background exposure into consideration, the calculated Estimated No-Effect Value (ENEV) is more representative for comparison. The ENEV, based on soil organisms for PeBDE is **0.27 mg/ kg dw soil**. The derivation of this ENEV is based on chronic ecotoxicity data, including data on corn and earthworms. Corn was more sensitive to PeBDE exposure than earthworms and a NOEC of corn was used for the calculation, applying an AF of 100 (extrapolation of laboratory results to the field and taking into account intraspecies and interspecies variation as the high potential of bioaccumulation and persistency). The value was adapted to soils containing 2% organic carbon. Although this assessment does not consider BDE-99, it is worth mentioning that the risk quotient, and more specifically the ENEV derivation, indicates **secondary poisoning of wildlife as the greatest potential environmental risk from PBDEs** (and PeBDEs in particular).

**In 2013, Federal Environmental Quality Guidelines (FSeQG) from Environment Canada** for PBDEs were proposed, but these guidelines are only based on ecotoxicity data from aquatic species and avian and mammalian predators. Moreover, this report does not provide guidelines for soil. A **sediment** quality guideline for BDE-99 is given**: 0.4 ng/g dw (or 0.4 µg/kg dw)**, for the protection of sediment dwelling animals as well as pelagic animals. Data on plants are not used in the calculation.

**The Ecotoxcenter[19] (Switzerland)** has given a **sediment** quality criterium value**,** but this value represents a sum of 6 indicators PBDEs (including BDE-99): **52.0 µg/kg dw soil,** based on 1% organic carbon. Because of the potential bioaccumulation and -magnification, a SQG for **secondary poisoning** is also calculated: **0.90 µg/kg dw soil,** this is a preliminary value because of insufficient effect data. The Swiss derivation procedure[20] for sediment quality criteria is largely based on the EU Technical Guidance for Deriving Environmental Quality Standards (European Commission: Directorate-General for & Food, 2017).

**The Danish Environmental Protection Agency (DEPA)** published a report in 2012 about the risk evaluation of persistent organic contaminants in sewage sludge (DEPA, 2012) Considering ecotoxicity of PBDE to soil dwelling organisms, little information is available. However, a few studies indicate a very low toxicity by the higher brominated flame retardants like BDE-209, most likely due to their size and strong adsorption to the soil matrix. Darnerud et al. (2002) states that the lower brominated PBDEs, such as BDE-99, accumulate in biota. The very low toxicity of BDE-209 to soil dwelling organisms should therefore not be equated with the potential toxicity of BDE-99 to these organisms. Kuiper et al. (2007) asserts that the lower brominated PBDEs are considered the most potent and hazardous PBDEs when compared to the higher brominated PBDEs, in aquatic environments. Additionally, the EU-RAR (2001) mentions the high toxicity of pentaBDE to aquatic organisms and the potential long-term adverse effects in the aquatic environment. This is based on ecotoxicity data, the lack of biodegradation and the high bioconcentration factors. No ecotoxicity data of BDE-99 is mentioned in the report of DEPA, but based on the information in this report, we could assume **a higher ecotoxicological effect than for BDE-209**. This can also be demonstrated by comparing the $PNEC_{soil}$ of BDE-209 derived in the EU-RAR (ECB, 2002) and the $PNEC_{soil}$ for BDE-99, 98 mg/kg ds and 0.38 mg/kg ds respectively.

[19] https://www.ecotoxcentre.ch/expert-service/quality-criteria/sediment-quality-criteria
[20] https://www.ecotoxcentre.ch/media/195577/fact-sheet-sqk-derivation-method_en.pdf

**Conclusion: an ecotoxicological reference value ($SRV_{eco}$) for BDE-99 is proposed:**
**- For agricultural and residential land use types: 0.38 mg/kg ds**
**- For the industrial use land type, this value is deemed overly cautious and hence no $SRV_{eco}$ was proposed.**

## 12.4 Target values and values for the re-use of excavated soil

Target values or values for free re-use of excavated soil are derived by calculating the impact by spreading into soil or groundwater in 3 application scenarios (more details in Broos et al., 2015):

- An application of excavated soil sensitive to leaching directly into groundwater
- An application of excavated soil sensitive to leaching (Kd, Q10) on top of a soil layer
- An application of excavated soil moderately sensitive to leaching (Kd, Q50) on top of a soil layer

For the groundwater compartment the maximum calculated groundwater concentration at the point of compliance must at no point in time exceed the safe value in groundwater. The safe value in groundwater is set equal to the proposed groundwater criterion of 0,6 µg/l. For the soil compartment the calculated average concentration over the top layer (0-30 cm) after 100 years must not exceed the safe value in soil. The safe value in soil is set equal to 60% of the lowest soil remediation value and is 0,0024 mg/kg ds.

The risk-based limit values are calculated as the maximum allowable concentration in each of the 3 application scenarios that will not lead to an exceedance of the safe values in groundwater and in soil. The physico-chemical properties used in the calculations are the same as in the S-Risk calculations.

In Table 33 the results for the risk-based limit values for the 3 application scenarios are given. Given the limited mobility of BDE-99 in soil and groundwater, accumulation in the top layer of the soil underneath the application is the most critical process. The calculations show that with a concentration of 0.068 mg/kg dw in an application with a material sensitive to leaching, the calculated average concentration in the top layer after 100 year equals the safe value in soil (of 0,0024 mg/kg ds). With this concentration of 0,068 mg/kg dw in an application sensitive to leaching, concentrations in groundwater stay beneath the safe value for groundwater (of 0,6 µg/l) with a groundwater concentration of 0,03 µg/l for an application directly into the groundwater and a groundwater concentration of 0,006 µg/l for an application onto soil. Therefore, the value of 0,068 mg/kg dw is selected as the lowest risk-based value applicable for the application scenarios with an application sensitive to leaching (GW1 and GW2).

Similarly, calculations are done for a material moderately sensitive to leaching. The calculations show that with a concentration of 0,54 mg/kg dm in the application with a material sensitive to leaching, the calculated average concentration in the top layer after 100 year equals the safe value in soil (of 0,0024 mg/kg ds). With this concentration of 0,54 mg/kg dm in an application sensitive to leaching, concentrations in groundwater stay beneath the safe value for groundwater (of 0,6 µg/l) with a calculated groundwater concentration of 0,05 µg/l for an application onto soil. The value of 0,54 mg/kg dm is therefore selected as the risk-based value GW3.

*Table 33: Calculated risk-based limit values for BDE-99 for an application into groundwater (GW1), an application onto soil with material sensitive to leaching (GW2) and an application onto soil with material moderately sensitive to leaching (GW3)*

| | GW1 (mg/kg ds) | GW2 (mg/kg ds) | GW3 (mg/kg ds) |
|---|---|---|---|

| | | | |
|---|---|---|---|
| **BDE-99** | >0,068 | 0,068 | 0,540 |

## 12.5 Integration and evaluation

### 12.5.1 Soil

The calculations performed for the soil remediation values for BDE-99 were done in S-Risk, where small adjustments were made to the model, i.e., the transfer from soil to plants (BCF values) were calculated based on the concentrations in the soil and not using the porewater concentrations (which is normally done). All input parameters to the S-Risk model for the estimation of the soil remediation values based on human health toxicity data are summarized in the Substance data sheet in Annex A. Data on the transfer of BDE-99 from soil to plants and animals was limited, resulting in increased uncertainty in the estimated SRV.

There is limited data on the occurrence of BDE-99 in soil in Belgium in order to determine a background value. The background value for man-made chemicals is therefore set as the detection limit. Subsequently, the SRV needs to be five times higher than the background value (Cornelis & Touchant, 2016b). The limit of detection for BDE-99 in soil is 0.55 µg/kg dw, and the lowest SRV is more than five times higher than the LOD.

An overview of the SRV based on human health toxicity and ecotoxicity data are given in Table 34. The SRV based on human health toxicity data are lowest for Scenarios II, III and V, while for Scenario IV the lowest SRV is based on ecotoxicity data.

*Table 34: The proposed SRV (mg/kg ds) for BDE-99 with the preferred value in bold.*

| | II | III | IV | V |
|---|---|---|---|---|
| **Flemish legislation on soil (Vlarebo)** | | | | |
| Proposal human health based tox | **0.004** | **0.038** | 51 | **420** |
| Proposal ecotox | 0.38 | 0.38 | **0.38** | |
| POPs Regulation | | | | 580 |
| Background value (LOD) | 0.00055 | 0.00055 | 0.00055 | 0.00055 |

The impact of the organic matter (OM) and clay content in soil on the proposed soil remediation values was investigated. In S-Risk, the percentage of OM and clay was varied to match the soil types used in S-Risk. As seen in Figure 2, the SRV for the various scenarios were not impacted by a change in percentage OM or clay.

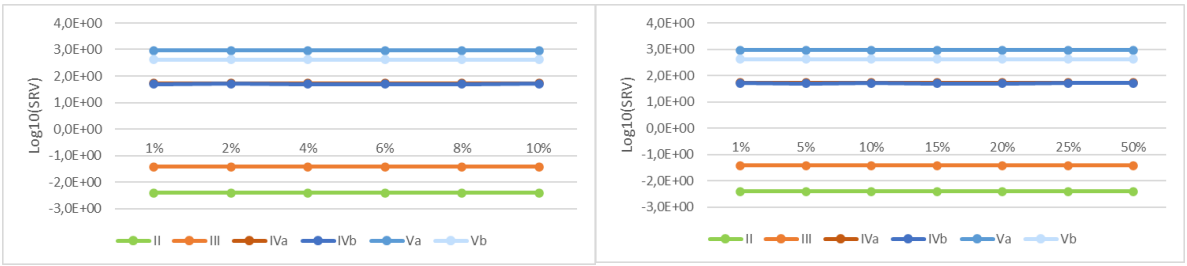



*Figure 2:* Impact of variation of percentage organic matter (left plot) and clay (right plot) on the soil remediation values for the various scenarios. Default values for organic matter and clay in S-Risk are 2% and 10%, respectively.

### 12.5.2 Groundwater

The SRV value for groundwater is based on human health toxicology data and the methodology stated by Cornelis and Touchant (2016). The proposed SRV for groundwater is 0.6 µg/L. The detection limit of BDE-99 in water is 0.01 µg/L.

### 12.5.3 Target value/value for free re-use of excavated soil

To derive a target value for an organic parameter with a background value determined by the LOQ, the following boundary conditions apply:

- The target value is at least 3 times the background value
- The target value is not higher than 80% of the soil remediation value for type I/II

Since the lowest risk-based value of 0.068 mg/kg dw is higher than the soil remediation value type II, the second boundary condition applies and the target value is set to **0.0032 mg/kg dw**, equal to 80% of soil remediation value type II.

### 12.5.4 Value for the use of excavated soil for building sites or in a fixed form product

The value for the use of excavated soil for building sites is derived based on the calculated risk-based value and topped off by the highest soil remediation value.

The highest calculated risk-based value is **0.54 mg/kg dw**. This is considerably lower than the highest soil remediation value of 420 mg/kg dw and is therefore selected as the value for the use of excavated soil for building sites or in a fixed form product.

### 12.5.5 Comparison with foreign soil remediation values

Foreign standards have been consulted in order to be able to compare them with the proposed soil remediation values.

US EPA proposes Regional Screening Levels (RSL) as the source of environmental screening levels for Superfund sites in all the EPA regions, as well as Regional Removal Management Levels (RMLs).
US EPA has calculated screening levels for BDE-99, i.e. 6.3 mg/kg for residential soil, 82 mg/kg for industrial soil and 2.0 µg/l for tap water (Abe *et al.*, 2017)[21]. These levels are based on non-cancer effects. In the case of BDE-99, the RSL and RMLs are equal. No consideration is given to ecological effects in the values, as they are entirely based on human toxicity.
The proposed concentrations for both soil types are higher than the previous mentioned $PNEC_{soil}$ (6.30 mg/kg for resident soil; 82.0 mg/kg for industrial soil).

[21] Screening level tables available at 404331.xlsx (live.com)

# 13 CONCLUSION

The present report includes a proposition for soil remediation values for 2,2',4,4',5-Pentabromodiphenyl ether (BDE-99).

The report covers the detailed approach for the proposed values. All the data is summarized in the Substance Data sheet (Annex A), which was used as input for the S-Risk model. The S-Risk model (www.s-risk.be) was used to estimate the soil remediation values. Data collection follows the guidelines stated by Cornelis and Touchant (2016).

Table 35 lists the proposed soil remediation values for the various scenarios

*Table 35: The proposed SRV (mg/kg ds) for BDE-99 with the preferred value in bold.*

| | II | III | IV | V |
|---|---|---|---|---|
| **Flemish legislation on soil (Vlarebo)** | | | | |
| Proposal human health based tox | **0.004** | **0.038** | 51 | **420** |
| Proposal ecotox | 0.38 | 0.38 | **0.38** | |
| POPs Regulation | | | | 580 |
| Background value (limit of detection) | 0.00055 | 0.00055 | 0.00055 | 0.00055 |

All SRVs are at least a factor of 5 higher than the background value (LOD) for BDE-99 in soil. The impact of organic matter in soil had little impact on the estimated SRVs.

For scenario II (agriculture), more than 85% of the total exposure results from intake via meat and milk, while the remaining exposure results from locally grown vegetables. For scenario III (residence with vegetable garden), >99% of the exposure results from the intake of locally grown vegetables. For scenario IV (day recreation, outdoor sports and holiday resort, mainly indoor), the exposure results from both ingestion and dermal uptake of soil and dust. For scenario V (light and heavy industry), oral exposure of soil and dust are the predominant exposure pathway for BDE-99 (>80%) with dermal uptake via soil and dust being the second important pathway (8 – 18%), exposure via inhalation of indoor or outdoor air resulted in < 2.6% of the total exposure.

The SRV for groundwater is based on a human health toxicity evaluation and matches the drinking water standard (Cornelis & Touchant, 2016b). The proposed SRV for groundwater is 0.6 µg/L, while the background value for groundwater is based on the limit of detection and is 0.01 µg/L.

The proposed target value for soil is 0.0032 mg/kg dm which equals 80% of the SRV Type II. The proposed SRV value for the use of excavated soil for building sites is determined at 0.54 mg/kg dm.

# REFERENCES

(2002) Besluit van de Vlaamse Regering van 12/10/2001 tot wijziging van het Besluit van de Vlaamse Regering van 05/03/1996 houdende vaststelling van het Vlaams Reglement betreffende de bodemsanering (Vlarebo bis).

Abbasi, G., Li, L. & Breivik, K. (2019) Global Historical Stocks and Emissions of PBDEs. *Environmental Science & Technology*, **53**, 6330-6340.

Abdelouahab, N., Ainmelk, Y. & Takser, L. (2011) Polybrominated diphenyl ethers and sperm quality. *Reproductive toxicology*, **31**, 546-550.

Abe, T., Takahashi, M., Kano, M., Amaike, Y., Ishii, C., Maeda, K., Kudoh, Y., Morishita, T., Hosaka, T., Sasaki, T., Kodama, S., Matsuzawa, A., Kojima, H. & Yoshinari, K. (2017) Activation of nuclear receptor CAR by an environmental pollutant perfluorooctanoic acid. *Arch Toxicol*, **91**, 2365-2374.

Akutsu, K., Kitagawa, M., Nakazawa, H., Makino, T., Iwazaki, K., Oda, H. & Hori, S. (2003) Time-trend (1973–2000) of polybrominated diphenyl ethers in Japanese mother's milk. *Chemosphere*, **53**, 645-654.

Akutsu, K., Takatori, S., Nozawa, S., Yoshiike, M., Nakazawa, H., Hayakawa, K., Makino, T. & Iwamoto, T. (2008) Polybrominated diphenyl ethers in human serum and sperm quality. *Bulletin of environmental contamination and toxicology*, **80**, 345-350.

Albina, M.L., Alonso, V., Linares, V., Bellés, M., Sirvent, J.J., Domingo, J.L. & Sánchez, D.J. (2010) Effects of exposure to BDE-99 on oxidative status of liver and kidney in adult rats. *Toxicology*, **271**, 51-56.

Alm, H., Scholz, B., Fischer, C., Kultima, K., Viberg, H., Eriksson, P., Dencker, L. & Stigson, M. (2006) Proteomic evaluation of neonatal exposure to 2, 2′, 4, 4′, 5-pentabromodiphenyl ether. *Environmental health perspectives*, **114**, 254-259.

Alonso, V., Linares, V., Bellés, M., Albina, M.L., Pujol, A., Domingo, J.L. & Sánchez, D.J. (2010) Effects of BDE-99 on hormone homeostasis and biochemical parameters in adult male rats. *Food and Chemical Toxicology*, **48**, 2206-2211.

Ankarberg, E. (2003) Neurotoxic effects of nicotine during neonatal brain development: critical period and adult susceptibility. Acta Universitatis Upsaliensis.

Assessment, R.B. (2002) NORTH AMERICA REGIONAL REPORT.

ATSDR (2017a) Toxicological profile for polybrominated diphenyl ethers (PBDEs). In services, U.S.D.o.h.a.h., Service, P.H. (eds). Agency for Toxic Substances and Disease Registry.

ATSDR (2017b) Toxicological Profile for polybrominated diphenyl ethers (PBDEs). Agency for Toxic Substances and Disease Registry, pp. 592.

Bakker, M.I., de Winter-Sorkina, R., de Mul, A., Boon, P.E., van Donkersgoed, G., van Klaveren, J.D., Baumann, B.A., Hijman, W.C., van Leeuwen, S.P. & de Boer, J. (2008)

Dietary intake and risk evaluation of polybrominated diphenyl ethers in The Netherlands. *Molecular nutrition & food research*, **52**, 204-216.

Barber, J.L., Walsh, M.J., Hewitt, R., Jones, K.C. & Martin, F.L. (2006) Low-dose treatment with polybrominated diphenyl ethers (PBDEs) induce altered characteristics in MCF-7 cells. *Mutagenesis*, **21**, 351-360.

Behl, M., Rice, J.R., Smith, M.V., Co, C.A., Bridge, M.F., Hsieh, J.H., Freedman, J.H. & Boyd, W.A. (2016) Editor's Highlight: Comparative Toxicity of Organophosphate Flame Retardants and Polybrominated Diphenyl Ethers to Caenorhabditis elegans. *Toxicol Sci*, **154**, 241-252.

Bierkens, J. (2001) Methodiek voor het afleiden van ecologische bodemnormen in Vlaanderen, VITO, Mol. TOX/2001/R/011.

Bizkarguenaga, E., Zabaleta, I., Mijangos, L., Iparraguirre, A., Fernandez, L.A., Prieto, A. & Zuloaga, O. (2016) Uptake of perfluorooctanoic acid, perfluorooctane sulfonate and perfluorooctane sulfonamide by carrot and lettuce from compost amended soil. *The Science of the total environment*, **571**, 444-451.

Blanco, J., Mulero, M., Domingo, J.L. & Sánchez, D.J. (2012) Gestational exposure to BDE-99 produces toxicity through upregulation of CYP isoforms and ROS production in the fetal rat liver. *Toxicological Sciences*, **127**, 296-302.

Blanco, J., Mulero, M., Heredia, L., Pujol, A., Domingo, J.L. & Sánchez, D.J. (2013) Perinatal exposure to BDE-99 causes learning disorders and decreases serum thyroid hormone levels and BDNF gene expression in hippocampus in rat offspring. *Toxicology*, **308**, 122-128.

Bradman, A., Fenster, L., Sjödin, A., Jones, R.S., Patterson Jr, D.G. & Eskenazi, B. (2007) Polybrominated diphenyl ether levels in the blood of pregnant women living in an agricultural community in California. *Environmental health perspectives*, **115**, 71-74.

Braekevelt, E., Tittlemier, S.A. & Tomy, G.T. (2003) Direct measurement of octanol–water partition coefficients of some environmentally relevant brominated diphenyl ether congeners. *Chemosphere*, **51**, 563-567.

Branchi, I., Capone, F., Vitalone, A., Madia, F., Santucci, D., Alleva, E. & Costa, L.G. (2005) Early developmental exposure to BDE 99 or Aroclor 1254 affects neurobehavioural profile: interference from the administration route. *Neurotoxicology*, **26**, 183-192.

Bruchajzer, E., Frydrych, B., Sporny, S. & Szymańska, J.A. (2010) Toxicity of penta-and decabromodiphenyl ethers after repeated administration to rats: a comparative study. *Archives of toxicology*, **84**, 287-299.

Brueller, W., Inreiter, N., Boegl, T., Rubasch, M., Saner, S., Humer, F., Moche, W., Schuhmann, A., Hartl, W., Brezinka, C., Wildt, L. & Allerberger, F. (2018) Occurrence of chemicals with known or suspected endocrine disrupting activity in drinking water, groundwater and surface water, Austria 2017/2018. *Die Bodenkultur: Journal of Land Management, Food and Environment*, **69**, 155-173.

Čadková, Z., Száková, J., Mukhtorova, D., Hlava, J., Pulkrabová, J., Balík, J., Tlustoš, P. & Vadlejch, J. (2020) The response of soil nematode Caenorhabditis elegans on the sewage sludge-derived micropollutants. *Journal of Hazardous Materials*, **384**, 121468.

Canada, E. (2006) Ecological Screening Assessment Report on Polybrominated Diphenyl Ethers (PBDEs).

Canada, E. (2013) Federal Environmental Quality Guidelines Polybrominated Diphenyl Ethers (PBDEs).

Ceccatelli, R., Faass, O., Schlumpf, M. & Lichtensteiger, W. (2006) Gene expression and estrogen sensitivity in rat uterus after developmental exposure to the polybrominated diphenylether PBDE 99 and PCB. *Toxicology*, **220**, 104-116.

Cetin, B. & Odabasi, M. (2005) Measurement of Henry's law constants of seven polybrominated diphenyl ether (PBDE) congeners as a function of temperature. *Atmospheric Environment*, **39**, 5273-5280.

Chain, E.P.o.C.i.t.F., Schrenk, D., Bignami, M., Bodin, L., Chipman, J.K., del Mazo, J., Grasl-Kraupp, B., Hogstrand, C., Hoogenboom, L., Leblanc, J.-C., Nebbia, C.S., Nielsen, E., Ntzani, E., Petersen, A., Sand, S., Schwerdtle, T., Wallace, H., Benford, D., Fürst, P., Hart, A., Rose, M., Schroeder, H., Vrijheid, M., Ioannidou, S., Nikolič, M., Bordajandi, L.R. & Vleminckx, C. (2024) Update of the risk assessment of polybrominated diphenyl ethers (PBDEs) in food. *EFSA Journal*, **22**, e8497.

Chen, L.-J., Lebetkin, E., Sanders, J. & Burka, L. (2006) Metabolism and disposition of 2, 2′, 4, 4′, 5-pentabromodiphenyl ether (BDE99) following a single or repeated administration to rats or mice. *Xenobiotica*, **36**, 515-534.

Cheng, J., Gu, J., Ma, J., Chen, X., Zhang, M. & Wang, W. (2009) Neurobehavioural effects, redox responses and tissue distribution in rat offspring developmental exposure to BDE-99. *Chemosphere*, **75**, 963-968.

Chevrier, J., Harley, K.G., Bradman, A., Gharbi, M., Sjödin, A. & Eskenazi, B. (2010) Polybrominated diphenyl ether (PBDE) flame retardants and thyroid hormone during pregnancy. *Environmental health perspectives*, **118**, 1444-1449.

Choi, J.-w., Fujimaki, S., Kitamura, K., Hashimoto, S., Ito, H., Suzuki, N., Sakai, S.-i. & Morita, M. (2003) Polybrominated dibenzo-p-dioxins, dibenzofurans, and diphenyl ethers in Japanese human adipose tissue. *Environmental Science & Technology*, **37**, 817-821.

Collins, C.D., Craggs, M., Garcia-Alcega, S., Kademoglou, K. & Lowe, S. (2015) Towards a unified approach for the determination of the bioaccessibility of organic pollutants. *Environment international*, **78**, 24-31.

Committee, E.S., More, S.J., Bampidis, V., Benford, D., Bragard, C., Halldorsson, T.I., Hernández-Jerez, A.F., Bennekou, S.H., Koutsoumanis, K. & Lambré, C. (2022) Guidance on the use of the benchmark dose approach in risk assessment. *Efsa Journal*, **20**, e07584.

Cornelis, C., De Brouwere, K., De Fré, R., Goyvaerts, M.P., Schoeters, G., Swaans, W. & Van Holderbeke, M. (2007) Voorstel voor milieukwaliteitsnormen voor depositie van dioxines en PCB's, Mol, België.

Cornelis, C., Standaert, A. & Willems, H. (2017) S-Risk Technical guidance document (version March 2017. Study accomplished under the authority of OVAM. https://s-risk.be/sites/s-risk.be/files/SRisk%20model%20equations.pdf, pp. 174.

Cornelis, C., Standaert, A. & Willems, H. (2022) S-Risk Technical guidance document (revision). Study accomplished under the authority of OVAM. https://s-risk.be/documents/technical-guidance-FL.pdf, pp. 174.

Cornelis, C. & Touchant, K. (2016a) Basisinformatie voor risico-evaluaties: werkwijze voor het opstellen van bodemsaneringsnormen en toetsingswaarden, richtwaarden en streefwaarden. VITO, Mol.

Cornelis, C. & Touchant, K. (2016b) Basisinformatie voor risico-evaluaties: werkwijze voor het opstellen van bodemsaneringsnormen en toetsingswaarden, richtwaarden en streefwaarden. VITO, Mol, pp. 73.

Covaci, A., Roosens, L., Dirtu, A.C., Waegeneers, N., Van Overmeire, I., Neels, H. & Goeyens, L. (2009) Brominated flame retardants in Belgian home-produced eggs: Levels and contamination sources. *Science of the Total Environment*, **407**, 4387-4396.

Cumming, H. & Rücker, C. (2017) Octanol-Water Partition Coefficient Measurement by a Simple (1)H NMR Method. *ACS Omega*, **2**, 6244-6249.

Darnerud, P.O. & Risberg, S. (2006) Tissue localisation of tetra-and pentabromodiphenyl ether congeners (BDE-47,-85 and-99) in perinatal and adult C57BL mice. *Chemosphere*, **62**, 485-493.

Daubié, S., Bisson, J.-F., Lalonde, R., Schroeder, H. & Rychen, G. (2011) Neurobehavioral and physiological effects of low doses of polybrominated diphenyl ether (PBDE)-99 in male adult rats. *Toxicology letters*, **204**, 57-63.

de Boer, J., de Boer, K. & Boon, J.P. (2000) Polybrominated Biphenyls and Diphenylethers. In Hutzinger, O., Paasivirta, J. (eds) *Volume 3 Anthropogenic Compounds Part K*. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 61-96.

Degrendele, C., Wilson, J., Kukučka, P., Klánová, J. & Lammel, G. (2018) Are atmospheric PBDE levels declining in central Europe? Examination of the seasonal and semi-long-term variations, gas–particle partitioning and implications for long-range atmospheric transport. *Atmos. Chem. Phys.*, **18**, 12877-12890.

DEPA (2012) Risk evaluation of five groups of persistent organic contaminants in sewage sludge. Environmental Project No. 1406 2012. Danish Environmental Protection Agency.

Ding, C., Chow Wai, L. & He, J. (2013) Isolation of Acetobacterium sp. Strain AG, Which Reductively Debrominates Octa- and Pentabrominated Diphenyl Ether Technical Mixtures. *Applied and Environmental Microbiology*, **79**, 1110-1117.

Dobslaw, D., Woiski, C., Kiel, M., Kuch, B. & Breuer, J. (2021) Plant uptake, translocation and metabolism of PBDEs in plants of food and feed industry: A review. *Reviews in Environmental Science and Bio/Technology*, **20**, 75-142.

Drage, D.S., Newton, S., de Wit, C.A. & Harrad, S. (2016) Concentrations of legacy and emerging flame retardants in air and soil on a transect in the UK West Midlands. *Chemosphere*, **148**, 195-203.

Dunnick, J.K. & Nyska, A. (2009) Characterization of liver toxicity in F344/N rats and B6C3F1 mice after exposure to a flame retardant containing lower molecular weight polybrominated diphenyl ethers. *Experimental and Toxicologic Pathology*, **61**, 1-12.

EC-JRC (2002) European Union Risk Assessment Report - Bis(pentabromophenyl)ether. In Bureau, E.C. (ed).

EC (2008) Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures. In Commission, E. (ed), O.J. L 353.

ECB (2000) Risk assessment Methyl tertiary-Butyl Ether (MTBE) - draft, Ispra, Italië.

ECB (2001) European Union Risk Assessment Report. Diphenyl ether, pentabromo derivative. CAS No: 32534-81-9. Office for Official Publications of the European Communities.

ECHA (2012) Guidance on information requirements and chemical safety assessment. Chapter R. 8: Characterisation of dose [concentration]-response for human health. Version 2.1, November 2012. ECHA-2010-G-19-EN.

EFSA (2011a) Scientific opinion on polybrominated diphenyl ethers (PBDEs) in food. *EFSA journal*, **9**, 2156.

EFSA (2011b) Scientific opinion on Polybrominated Diphenyl Ethers (PBDEs) in Food. *The EFSA Journal*, **9**, 2156.

EFSA (2023) Update of the risk assessment of PBDEs in food.

EnvironmentCanada (2004) Environmental Screening Assessment Report on Polybrominated Diphenyl Ethers (PBDEs). In Canada, E. (ed).

EPA (2008) Toxicological review of 2,2',4,4',5-pentabromodiphenyl ether (BDE-99). In EPA, U. (ed).

EPA, A. (2004) Risk assessment guidance for superfund. Volume I: human health evaluation manual (Part E, supplemental guidance for dermal risk assessment). EPA/540/R/99.

Eriksson, P., Jakobsson, E. & Fredriksson, A. (2001) Brominated flame retardants: a novel class of developmental neurotoxicants in our environment? *Environmental health perspectives*, **109**, 903-908.

Eriksson, P., Viberg, H., Jakobsson, E., Örn, U. & Fredriksson, A. (2002) A brominated flame retardant, 2, 2, 4, 4, 5-pentabromodiphenyl ether: uptake, retention, and induction of neurobehavioral alterations in mice during a critical phase of neonatal brain development. *Toxicological sciences*, **67**, 98-103.

EU-RAR (2001) European Union risk assessment report on diphenyl ether, pentabromo deriv., https://www.echa.europa.eu/information-on-chemicals/information-from-existing-substances-regulation, pp. 293.

European Commission: Directorate-General for, H. & Food, S. (2017) *Technical guidance for deriving environmental quality standards*. European Commission.

Evandri, M.G., Mastrangelo, S., Costa, L.G. & Bolle, P. (2003) In vitro assessment of mutagenicity and clastogenicity of BDE-99, a pentabrominated diphenyl ether flame retardant. *Environmental and molecular mutagenesis*, **42**, 85-90.

Fang, L., Huang, J., Yu, G. & Wang, L. (2008) Photochemical degradation of six polybrominated diphenyl ether congeners under ultraviolet irradiation in hexane. *Chemosphere*, **71**, 258-267.

Fischer, D., Hooper, K., Athanasiadou, M., Athanassiadis, I. & Bergman, Å. (2006) Children show highest levels of polybrominated diphenyl ethers in a California family of four: a case study. *Environmental Health Perspectives*, **114**, 1581-1584.

Gascon, M., Vrijheid, M., Martínez, D., Forns, J., Grimalt, J.O., Torrent, M. & Sunyer, J. (2011) Effects of pre and postnatal exposure to low levels of polybromodiphenyl ethers on neurodevelopment and thyroid hormone levels at 4 years of age. *Environment international*, **37**, 605-611.

Gebbink, W.A., van der Lee, M.K., Peters, R.J.B., Traag, W.A., Dam, G.t., Hoogenboom, R.L.A.P. & van Leeuwen, S.P.J. (2019) Brominated flame retardants in animal derived foods in the Netherlands between 2009 and 2014. *Chemosphere*, **234**, 171-178.

Geyer, H.J., Schramm, K.-W., Feicht, E., Fried, K., Henkelmann, B., Lenoir, D., Darnerud, P., Aune, M., Schmid, P. & McDonald, T.A. (2004) Terminal elimination half-lives of the brominated flame retardants TBBPA, HBCD, and lower brominated PBDEs in humans.

Grümping, R., Petersen, M., Kuchen, A. & Tlustos, C. (2006) Levels of polybrominated diphenyl ethers in Swiss and Irish cow's milk. *Organohalogen compounds*, **68**, 2147-2150.

Guvenius, D.M., Aronsson, A., Ekman-Ordeberg, G., Bergman, A. & Norén, K. (2003) Human prenatal and postnatal exposure to polybrominated diphenyl ethers, polychlorinated biphenyls, polychlorobiphenylols, and pentachlorophenol. *Environmental health perspectives*, **111**, 1235-1241.

Hakk, H., Larsen, G. & Klasson-Wehler, E. (2002) Tissue disposition, excretion and metabolism of 2, 2′, 4, 4′, 5-pentabromodiphenyl ether (BDE-99) in the male Sprague-Dawley rat. *Xenobiotica*, **32**, 369-382.

Hallgren, S., Fredriksson, A. & Viberg, H. (2015) More signs of neurotoxicity of surfactants and flame retardants–Neonatal PFOS and PBDE 99 cause transcriptional alterations in cholinergic genes in the mouse CNS. *Environmental toxicology and pharmacology*, **40**, 409-416.

Harley, K.G., Marks, A.R., Chevrier, J., Bradman, A., Sjödin, A. & Eskenazi, B. (2010) PBDE concentrations in women's serum and fecundability. *Environmental health perspectives*, **118**, 699-704.

Harner, T. & Shoeib, M. (2002) Measurements of Octanol−Air Partition Coefficients (KOA) for Polybrominated Diphenyl Ethers (PBDEs): Predicting Partitioning in the Environment. *Journal of Chemical & Engineering Data*, **47**, 228-232.

Hendriks, A.J., Smítková, H. & Huijbregts, M.A. (2007) A new twist on an old regression: transfer of chemicals to beef and milk in human and ecological risk assessment. *Chemosphere*, **70**, 46-56.

Herbstman, J.B., Sjödin, A., Kurzon, M., Lederman, S.A., Jones, R.S., Rauh, V., Needham, L.L., Tang, D., Niedzwiecki, M. & Wang, R.Y. (2010) Prenatal exposure to PBDEs and neurodevelopment. *Environmental health perspectives*, **118**, 712-719.

Huang, H., Zhang, S. & Christie, P. (2011) Plant uptake and dissipation of PBDEs in the soils of electronic waste recycling sites. *Environ Pollut*, **159**, 238-243.

Huwe, J.K., Hakk, H., Smith, D.J., Diliberto, J.J., Richardson, V., Stapleton, H.M. & Birnbaum, L.S. (2008) Comparative absorption and bioaccumulation of polybrominated diphenyl ethers following ingestion via dust and oil in male rats. *Environmental science & technology*, **42**, 2694-2700.

IPCS (1994) Environmental health criteria series, No 162 Brominated Diphenyl Ethers - https://inchem.org/documents/ehc/ehc/ehc162.htm *International Programme on Chemical Safety*, Geneva.

Jinhui, L., Yuan, C. & Wenjing, X. (2017) Polybrominated diphenyl ethers in articles: a review of its applications and legislation. *Environmental Science and Pollution Research*, **24**, 4312-4321.

Johnson-Restrepo, B., Kannan, K., Rapaport, D.P. & Rodan, B.D. (2005) Polybrominated diphenyl ethers and polychlorinated biphenyls in human adipose tissue from New York. *Environmental science & technology*, **39**, 5177-5182.

Kierkegaard, A., Wit, C.A.d., Asplund, L., McLachlan, M.S., Thomas, G.O., Sweetman, A.J. & Jones, K.C. (2009) A Mass Balance of Tri-Hexabrominated Diphenyl Ethers in Lactating Cows. *Environmental Science & Technology*, **43**, 2602-2607.

Kuiper, R.V., van den Brandhof, E.J., Leonards, P.E., van der Ven, L.T., Wester, P.W. & Vos, J.G. (2007) Toxicity of tetrabromobisphenol A (TBBPA) in zebrafish (Danio rerio) in a partial life-cycle test. *Arch Toxicol*, **81**, 1-9.

Kuivikko, M., Sorsa, K., Kukkonen, J.V.K., Akkanen, J., Kotiaho, T. & Vähätalo, A.V. (2010) Partitioning of tetra- and pentabromo diphenyl ether and benzo[a]pyrene among water and dissolved and particulate organic carbon along a salinity gradient in coastal waters. *Environmental Toxicology and Chemistry*, **29**, 2443-2449.

Kuramochi, H., Maeda, K. & Kawamoto, K. (2007) Physicochemical properties of selected polybrominated diphenyl ethers and extension of the UNIFAC model to brominated aromatic compounds. *Chemosphere*, **67**, 1858-1865.

Kuriyama, S.N., Talsness, C.E., Grote, K. & Chahoud, I. (2005) Developmental Exposure to Low-Dose PBDE-99: Effects on Male Fertility and Neurobehavior in Rat Offspring. *Environmental Health Perspectives*, **113**, 149-154.

Kuriyama, S.N., Wanner, A., Fidalgo-Neto, A.A., Talsness, C.E., Koerner, W. & Chahoud, I. (2007) Developmental exposure to low-dose PBDE-99: tissue distribution and thyroid hormone levels. *Toxicology*, **242**, 80-90.

Lee Lip, K. & He, J. (2010) Reductive Debromination of Polybrominated Diphenyl Ethers by Anaerobic Bacteria from Soils and Sediments. *Applied and Environmental Microbiology*, **76**, 794-802.

Lichtensteiger, W., Faass, O., Ceccatelli, R. & Schlumpf, M. (2004) Developmental exposure to PBDE 99 and PCB affects estrogen sensitivity of target genes in rat brain regions and female sexual behavior.

Lijzen, J.P.A., Wassenaar, P.N.H., Smit, C.E., Posthuma, C.J.A.M., Brand, E., Swartjes, F., Verbruggen, E.M.J. & Versteegh, J.F.M. (2018) Risicogrenzen PFOA voor grond en grondwater. Uitwerking ten behoeve van generiek en gebiedsspecifiek beleid (herziene versie). RIVM, Bilthoven, Netherlands, pp. 96.

Lind, Y., Darnerud, P.O., Atuma, S., Aune, M., Becker, W., Bjerselius, R., Cnattingius, S. & Glynn, A. (2003) Polybrominated diphenyl ethers in breast milk from Uppsala County, Sweden. *Environmental research*, **93**, 186-194.

Ma, Y., Stubbings, W.A., Abdallah, M.A., Cline-Cole, R. & Harrad, S. (2023) Temporal trends in concentrations of brominated flame retardants in UK foodstuffs suggest active impacts of global phase-out of PBDEs and HBCDD. *The Science of the total environment*, **863**, 160956.

Mackay, D., Arnot, J.A., Gobas, F.A. & Powell, D.E. (2013) Mathematical relationships between metrics of chemical bioaccumulation in fish. *Environ Toxicol Chem*, **32**, 1459-1466.

Main, K.M., Kiviranta, H., Virtanen, H.E., Sundqvist, E., Tuomisto, J.T., Tuomisto, J., Vartiainen, T., Skakkebæk, N.E. & Toppari, J. (2007) Flame retardants in placenta and breast milk and cryptorchidism in newborn boys. *Environmental health perspectives*, **115**, 1519-1526.

Mazdai, A., Dodder, N.G., Abernathy, M.P., Hites, R.A. & Bigsby, R.M. (2003) Polybrominated diphenyl ethers in maternal and fetal blood samples. *Environmental health perspectives*, **111**, 1249-1252.

Meironyte Guvenius, D., Bergman, Å. & Noren, K. (2001) Polybrominated diphenyl ethers in Swedish human liver and adipose tissue. *Archives of environmental contamination and toxicology*, **40**, 564-570.

Meneses, M., Wingfors, H., Schuhmacher, M., Domingo, J., Lindström, G. & Bavel, B. (1999) Polybrominated diphenyl ethers detected in human adipose tissue from Spain. *Chemosphere*, **39**, 2271-2278.

Meylan, W.M. & Howard, P.H. (2005) Estimating octanol-air partition coefficients with octanol-water partition coefficients and Henry's law constants. *Chemosphere*, **61**, 640-644.

MichiganDepartmentofEnvironmentalQuality (2008) Polybrominated diphenyl ethers: A scientific review with risk characterization and recommendations. In Quality, M.D.o.E. (ed).

Navarro, I., de la Torre, A., Sanz, P., Porcel, M.Á., Pro, J., Carbonell, G. & Martínez, M.d.l.Á. (2017) Uptake of perfluoroalkyl substances and halogenated flame retardants by crop plants grown in biosolids-amended soils. *Environmental Research*, **152**, 199-206.

Newton, S., Sellström, U. & De Wit, C.A. (2015) Emerging Flame Retardants, PBDEs, and HBCDDs in Indoor and Outdoor Media in Stockholm, Sweden. *Environmental Science & Technology*, **49**, 2912-2920.

NICNAS (2020) Pentabromodiphenyl Ether - Priority Existing Chemical Assessment Report Assessment No. 43. In Scheme, N.I.C.N.a.A. (ed).

NTP (2021) 15th Report on carcnogens (RoC) - National Toxicology Program.Report on carcinogens, 1U.S. Department of Health and Human Services, Public Health Service, at https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/roc#toc1. National Toxicology Program.

O'Sullivan, G. & Megson, D. (2014) Environmenal Forensics for Persistent Organic Pollutants. Chapter 1 - Brief Overview: Discovery, Regulation, Properties, and Fate of POPs, pp. 1-20.

Öberg, M., Westerholm, E., Fattore, E., Stern, N., Hanberg, A., Haglund, P., Wiberg, K., Bergendorff, A. & Håkansson, H. (2010) Toxicity of Bromkal 70-5DE, a technical mixture of polybrominated diphenyl ethers, following 28 d of oral exposure in rats and impact of analysed impurities. *Chemosphere*, **80**, 137-143.

Ohta, S., Ishizuka, D., Nishimura, H., Nakao, T., Aozasa, O., Shimidzu, Y., Ochiai, F., Kida, T., Nishi, M. & Miyata, H. (2002) Comparison of polybrominated diphenyl ethers in fish, vegetables, and meats and levels in human milk of nursing women in Japan. *Chemosphere*, **46**, 689-696.

Oloruntoba, K., Sindiku, O., Osibanjo, O., Balan, S. & Weber, R. (2019) Polybrominated diphenyl ethers (PBDEs) in chicken eggs and cow milk around municipal dumpsites in Abuja, Nigeria. *Ecotoxicology and Environmental Safety*, **179**, 282-289.

Olsen, E.N., F. (2001) Predicting Vapour Pressures of Organic Compounds from Their Chemical Structure for Classification According to the VOCDirective and Risk Assessment in General. *Molecules*, **6**, 370-389.

Ounnas, F., Feidt, C., Toussaint, H., Marchand, P., Bizec, B.L., Rychen, G. & Jurjanz, S. (2010) Polychlorinated Biphenyl and Low Polybrominated Diphenyl Ether Transfer to Milk in Lactating Goats Chronically Exposed to Contaminated Soil. *Environmental Science & Technology*, **44**, 2682-2688.

OVAM (2007) Voorstel voor normering van PCB's en PCDD/F's, pp. 166.

OVAM (2020) Afleiden van streefwaarden voor perfluorverbindingen en enkele andere 'emerging contaminants' – DEEL 3: Beleidsadviezen ‘emerging contaminants’.

Pan, Y., Tsang, D.C.W., Wang, Y., Li, Y. & Yang, X. (2016) The photodegradation of polybrominated diphenyl ethers (PBDEs) in various environmental matrices: Kinetics and mechanisms. *Chemical Engineering Journal*, **297**, 74-96.

Parolini, M., Guazzoni, N., Binelli, A. & Tremolada, P. (2012) Polybrominated Diphenyl Ether Contamination in Soil, Vegetation, and Cow Milk From a High-Mountain Pasture in the Italian Alps. *Archives of Environmental Contamination and Toxicology*, **63**, 29-44.

Pirard, C. & Pauw, E.D. (2007) Absorption, disposition and excretion of polybrominated diphenyl ethers (PBDEs) in chicken. *Chemosphere*, **66**, 320-325.

Poma, G., Malysheva, S.V., Goscinny, S., Malarvannan, G., Voorspoels, S., Covaci, A. & Van Loco, J. (2018) Occurrence of selected halogenated flame retardants in Belgian foodstuff. *Chemosphere*, **194**, 256-265.

RIVM (2004) Guidance for deriving Dutch Environmental Risk Limits from EU-Risk Assessment Reports of existing substances. In M.P.M. Janssen, T.P.T., J-P. Rila, van Vlaardingen, P.L.A. (ed).

RIVM (2009) Handreiking voor de afleiding van indicatieve milieurisicogrenzen (interimversie). In Poorter, R.v.H.P.J.C.M.J.T.H.A.H.L.R.M.d. (ed).

Roberts, S.C., Noyes, P.D., Gallagher, E.P. & Stapleton, H.M. (2011) Species-Specific Differences and Structure−Activity Relationships in the Debromination of PBDE Congeners in Three Fish Species. *Environmental Science & Technology*, **45**, 1999-2005.

Robrock, K.R., Korytár, P. & Alvarez-Cohen, L. (2008) Pathways for the Anaerobic Microbial Debromination of Polybrominated Diphenyl Ethers. *Environmental Science & Technology*, **42**, 2845-2852.

Roosens, L., Cornelis, C., D'Hollander, W., Bervoets, L., Reynders, H., Van Campenhout, K., Van Den Heuvel, R., Neels, H. & Covaci, A. (2010) Exposure of the Flemish population to brominated flame retardants: Model and risk assessment. *Environment International*, **36**, 368-376.

Roze, E., Meijer, L., Bakker, A., Van Braeckel, K.N., Sauer, P.J. & Bos, A.F. (2009) Prenatal exposure to organohalogens, including brominated flame retardants, influences motor, cognitive, and behavioral performance at school age. *Environmental health perspectives*, **117**, 1953-1958.

Salih Al-Omran, L. (2019) Physiochemical Properties and Environmental Levels of Legacy and Novel Brominated Flame Retardants. In Zafar, F. (ed) *Flame Retardants*.

Sanders, J., Lebetkin, E., Chen, L.-J. & Burka, L. (2006) Disposition of 2, 2′, 4, 4′, 5, 5′-hexabromodiphenyl ether (BDE153) and its interaction with other polybrominated diphenyl ethers (PBDEs) in rodents. *Xenobiotica*, **36**, 824-837.

Schecter, A., Pavuk, M., Päpke, O., Ryan, J.J., Birnbaum, L. & Rosen, R. (2003) Polybrominated diphenyl ethers (PBDEs) in US mothers' milk. *Environmental health perspectives*, **111**, 1723-1729.

Scientific Committee on Health, E.a.E.R.S. (2023) Final Opinion on Draft Environmental Quality Standards for Priority Substances under the Water
Framework Directive - PBDEs.

She, J., Holden, A., Sharp, M., Tanner, M., Williams-Derry, C. & Hooper, K. (2007) Polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) in breast milk from the Pacific Northwest. *Chemosphere*, **67**, S307-S317.

She, J., Petreas, M., Winkler, J., Visita, P., McKinney, M. & Kopec, D. (2002) PBDEs in the San Francisco Bay Area: measurements in harbor seal blubber and human breast adipose tissue. *Chemosphere*, **46**, 697-707.

Shin, J.-Y., Choi, Y.Y., Jeon, H.-S., Hwang, J.-H., Kim, S.-A., Kang, J.-H., Chang, Y.-S., Jacobs Jr, D.R., Park, J.Y. & Lee, D.-H. (2010) Low-dose persistent organic pollutants increased telomere length in peripheral leukocytes of healthy Koreans. *Mutagenesis*, **25**, 511-516.

Sjödin, A., Jones, R.S., Focant, J.-F., Lapeza, C., Wang, R.Y., McGahee 3rd, E.E., Zhang, Y., Turner, W.E., Slazyk, B. & Needham, L.L. (2004) Retrospective time-trend study of polybrominated diphenyl ether and polybrominated and polychlorinated biphenyl levels in human serum from the United States. *Environmental health perspectives*, **112**, 654-658.

Skarman, E., Darnerud, P.O., Öhrvik, H. & Oskarsson, A. (2005) Reduced thyroxine levels in mice perinatally exposed to polybrominated diphenyl ethers. *Environmental Toxicology and Pharmacology*, **19**, 273-281.

Söderström, G., Sellström, U., de Wit, C.A. & Tysklind, M. (2004) Photolytic Debromination of Decabromodiphenyl Ether (BDE 209). *Environmental Science & Technology*, **38**, 127-132.

Staples, C.A., Peterson, D.R., Parkerton, T.F. & Adams, W.J. (1997) The environmental fate of phthalate esters: A literature review. *Chemosphere*, **35**, 667-749.

Stapleton, H.M., Kelly, S.M., Pei, R., Letcher, R.J. & Gunsch, C. (2009) Metabolism of polybrominated diphenyl ethers (PBDEs) by human hepatocytes in vitro. *Environ Health Perspect*, **117**, 197-202.

Staskal, D.F., Hakk, H., Bauer, D., Diliberto, J.J. & Birnbaum, L.S. (2006) Toxicokinetics of polybrominated diphenyl ether congeners 47, 99, 100, and 153 in mice. *Toxicological sciences*, **94**, 28-37.

Stenzel, J.I.M., B.J. (1997) Pentabromodiphenyl oxide: Determination of the water solubility *Wildlife International Ltd*.

Streets, S.S., Henderson, S.A., Stoner, A.D., Carlson, D.L., Simcik, M.F. & Swackhamer, D.L. (2006) Partitioning and Bioaccumulation of PBDEs and PCBs in Lake Michigan. *Environmental Science & Technology*, **40**, 7263-7269.

Szabo, D.T., Richardson, V.M., Ross, D.G., Diliberto, J.J., Kodavanti, P.R. & Birnbaum, L.S. (2009) Effects of perinatal PBDE exposure on hepatic phase I, phase II, phase III, and deiodinase 1 gene expression involved in thyroid hormone metabolism in male rat pups. *Toxicological sciences*, **107**, 27-39.

Takaki, K., Wade, A.J. & Collins, C.D. (2015) Assessment and improvement of biotransfer models to cow's milk and beef used in exposure assessment tools for organic pollutants. *Chemosphere*, **138**, 390-397.

Talsness, C.E., Shakibaei, M., Kuriyama, S.N., Grande, S.W., Sterner-Kock, A., Schnitker, P., De Souza, C., Grote, K. & Chahoud, I. (2005) Ultrastructural changes observed in rat ovaries following in utero and lactational exposure to low doses of a polybrominated flame retardant. *Toxicology letters*, **157**, 189-202.

Tao, F., Sellström, U. & de Wit, C.A. (2019) Organohalogenated Flame Retardants and Organophosphate Esters in Office Air and Dust from Sweden. *Environmental Science & Technology*, **53**, 2124-2133.

Thomsen, C., Lundanes, E. & Becher, G. (2002) Brominated flame retardants in archived serum samples from Norway: a study on temporal trends and the role of age. *Environmental science & technology*, **36**, 1414-1418.

Tittlemier, S.A., Halldorson, T., Stern, G.A. & Tomy, G.T. (2002) Vapor pressures, aqueous solubilities, and Henry's law constants of some brominated flame retardants. *Environmental Toxicology and Chemistry*, **21**, 1804-1810.

Travis, C. & Arms, A. (1988) Bioconcentration of organics in beef, milk and vegetation. *Environmental Science & Technology*, **22**, 271-274.

Trudel, D., Scheringer, M., von Goetz, N. & Hungerbühler, K. (2011) Total consumer exposure to polybrominated diphenyl ethers in North America and Europe. *Environmental science & technology*, **45**, 2391-2397.

US-EPA (2008) Toxicological review of 2,2',4,4',5-pentabromodiphenyl ether (BDE-99). U.S. Environmental Protection Agency Washington, DC, http://www.epa.gov/iris.

US-EPA (2012a) Estimating Physical / Chemical and Environmental Fate Properties with EPI Suite™ *Sustainable Futures / P2 Framework Manual*. US-EPA Office of Chemical Safety and Pollution Prevention, Washington, DC, pp. 22.

US-EPA (2012b) Sustainable Futures / P2 Framework Manual 2012 EPA-748-12-0015. Estimating Physical / Chemical and Environmental Fate Properties with EPI Suite™ https://www.epa.gov/sites/default/files/2015-05/documents/05.pdf, pp. 22.

van den Berg, R. (1997) Verantwoording van gegevens en procedures voor de 1e tranche interventiewaarden: van RIVM-rapporten naar de Notitie Interventiewaarden bodemsanering, Bilthoven, Nederland.

van der Ven, L.T., van de Kuil, T., Verhoef, A., Leonards, P.E., Slob, W., Cantón, R.F., Germer, S., Hamers, T., Visser, T.J. & Litens, S. (2008) A 28-day oral dose toxicity study enhanced to detect endocrine effects of a purified technical pentabromodiphenyl ether (pentaBDE) mixture in Wistar rats. *Toxicology*, **245**, 109-122.

Vermeulen, F., Covaci, A., D'Have, H., Van den Brink, N.W., Blust, R., De Coen, W. & Bervoets, L. (2010) Accumulation of background levels of persistent organochlorine and organobromine pollutants through the soil-earthworm-hedgehog food chain. *Environ Int*, **36**, 721-727.

Viberg, H., Fredriksson, A. & Eriksson, P. (2002) Neonatal exposure to the brominated flame retardant 2, 2, 4, 4, 5-pentabromodiphenyl ether causes altered susceptibility in the cholinergic transmitter system in the adult mouse. *Toxicological Sciences*, **67**, 104-107.

Viberg, H., Fredriksson, A. & Eriksson, P. (2004a) Investigations of strain and/or gender differences in developmental neurotoxic effects of polybrominated diphenyl ethers in mice. *Toxicological Sciences*, **81**, 344-353.

Viberg, H., Fredriksson, A. & Eriksson, P. (2004b) Neonatal exposure to the brominated flame-retardant, 2, 2′, 4, 4′, 5-pentabromodiphenyl ether, decreases cholinergic nicotinic receptors in hippocampus and affects spontaneous behaviour in the adult mouse. *Environmental Toxicology and Pharmacology*, **17**, 61-65.

Von Meyerinck, L., Hufnagel, B., Schmoldt, A. & Benthe, H. (1990) Induction of rat liver microsomal cytochrome P-450 by the pentabromo diphenyl ether Bromkal 70 and half-lives of its components in the adipose tissue. *Toxicology*, **61**, 259-274.

Vonk, M.W. (1985) Permeatie van organische verbindingen door leidingmaterialen. KIWA, pp. 529-538.

Wang, S., Wang, Y., Luo, C., Li, J., Yin, H. & Zhang, G. (2016) Plant selective uptake of halogenated flame retardants at an e-waste recycling site in southern China. *Environmental Pollution*, **214**, 705-712.

Wang, W., Delgado-Moreno, L., Ye, Q. & Gan, J. (2011a) Improved Measurements of Partition Coefficients for Polybrominated Diphenyl Ethers. *Environmental Science & Technology*, **45**, 1521-1527.

Wang, Y., Luo, C., Li, J., Yin, H., Li, X. & Zhang, G. (2011b) Characterization of PBDEs in soils and vegetations near an e-waste recycling site in South China. *Environmental Pollution*, **159**, 2443-2448.

Wania, F. & Dugani, C.B. (2003) Assessing the long-range transport potential of polybrominated diphenyl ethers: A comparison of four multimedia models. *Environmental Toxicology and Chemistry*, **22**, 1252-1261.

Wemken, N., Drage, D.S., Abdallah, M.A.-E., Harrad, S. & Coggins, M.A. (2019) Concentrations of Brominated Flame Retardants in Indoor Air and Dust from Ireland Reveal Elevated Exposure to Decabromodiphenyl Ethane. *Environmental Science & Technology*, **53**, 9826-9836.

Wong, A., Lei, Y.D., Alaee, M. & Wania, F. (2001) Vapor Pressures of the Polybrominated Diphenyl Ethers. *Journal of Chemical & Engineering Data*, **46**, 239-242.

Wong, F., de Wit, C.A. & Newton, S.R. (2018) Concentrations and variability of organophosphate esters, halogenated flame retardants, and polybrominated diphenyl ethers in indoor and outdoor air in Stockholm, Sweden. *Environmental Pollution*, **240**, 514-522.

Wu, X., Wang, W. & Zhu, L. (2018) Enhanced organic contaminants accumulation in crops: Mechanisms, interactions with engineered nanomaterials in soil. *Environmental Pollution*, **240**, 51-59.

Yang, C.Y., Wu, S.C., Lee, C.C. & Shih, Y.H. (2018) Translocation of polybrominated diphenyl ethers from field-contaminated soils to an edible plant. *J Hazard Mater*, **351**, 215-223.

Yu, Y.-X., Huang, N.-B., Zhang, X.-Y., Li, J.-L., Yu, Z.-Q., Han, S.-Y., Lu, M., Van de Wiele, T., Wu, M.-H. & Sheng, G.-Y. (2011) Polybrominated diphenyl ethers in food and associated human daily intake assessment considering bioaccessibility measured by simulated gastrointestinal digestion. *Chemosphere*, **83**, 152-160.

Yu, Y.-X., Li, J.-L., Zhang, X.-Y., Yu, Z.-Q., Van de Wiele, T., Han, S.-Y., Wu, M.-H., Sheng, G.-Y. & Fu, J.-M. (2010) Assessment of the bioaccessibility of polybrominated diphenyl ethers in foods and the correlations of the bioaccessibility with nutrient contents. *Journal of agricultural and food chemistry*, **58**, 301-308.

Yu, Y.-X., Pang, Y.-P., Li, C., Li, J.-L., Zhang, X.-Y., Yu, Z.-Q., Feng, J.-L., Wu, M.-H., Sheng, G.-Y. & Fu, J.-M. (2012) Concentrations and seasonal variations of polybrominated diphenyl ethers (PBDEs) in in-and out-house dust and human daily intake via dust

ingestion corrected with bioaccessibility of PBDEs. *Environment international*, **42**, 124-131.

Yue, C. & Li, L.Y. (2013) Filling the gap: Estimating physicochemical properties of the full array of polybrominated diphenyl ethers (PBDEs). *Environmental Pollution*, **180**, 312-323.

Zacs, D., Perkons, I., Abdulajeva, E., Pasecnaja, E., Bartkiene, E. & Bartkevics, V. (2021) Polybrominated diphenyl ethers (PBDEs), hexabromocyclododecanes (HBCDD), dechlorane-related compounds (DRCs), and emerging brominated flame retardants (EBFRs) in foods: The levels, profiles, and dietary intake in Latvia. *The Science of the total environment*, **752**, 141996.

Zhang, Q., Yao, Y., Wang, Y., Zhang, Q., Cheng, Z., Li, Y., Yang, X., Wang, L. & Sun, H. (2021) Plant accumulation and transformation of brominated and organophosphate flame retardants: A review. *Environmental Pollution*, **288**, 117742.

Zhang, Z., Zhang, X., Sun, Z., Dong, H., Qiu, L., Gu, J., Zhou, J., Wang, X. & Wang, S.-L. (2013) Cytochrome P450 3A1 mediates 2, 2′, 4, 4′-tetrabromodiphenyl ether-induced reduction of spermatogenesis in adult rats. *PloS one*, **8**, e66301.

Zhao, S., Rogers, M.J., Ding, C. & He, J. (2018) Reductive Debromination of Polybrominated Diphenyl Ethers - Microbes, Processes and Dehalogenases. *Frontiers in Microbiology*, **9**.

Zhao, W., Cheng, J., Gu, J., Liu, Y., Fujimura, M. & Wang, W. (2014) Assessment of neurotoxic effects and brain region distribution in rat offspring prenatally co-exposed to low doses of BDE-99 and methylmercury. *Chemosphere*, **112**, 170-176.

# ANNEX A – SUBSTANCE DATA SHEET

| Parameter | Unit | Value | Source |
|---|---|---|---|
| Name | | 2,2',4,4',5-Pentabromodiphenyl ether | |
| CAS number<br>EC number | | 60348-60-9 | |
| Type | | | |
| Dissociative | | | |
| Acid constant (pKa) | | - | BDE-99 does not ionize under environmental conditions (AICIS, 2020) |
| Molar mass | g/mol | 564.7 | |
| Water solubility | mg/l | 0.0054 (at 25˚C) | Average value experimental data (Tittlemier et al., 2002; Kuramochi et al., 2007; Stenzel and Markley, 1997) |
| Vapour pressure | Pa | 4.3e-5 (at 25˚C) | Average value experimental data (Tittlemier et al., 2002; Kuramochi et al., 2007; Wong et al., 2001; EC, 2002) |
| Henry coefficient | Pa m³/mol | 1.07 (at 25˚C) | |
| Log $K_{ow}$<br>$K_{ow}$ | g/g | 7.36<br>$2.29x10^{+7}$ | |
| Log $K_{oc}$<br>$K_{oc}$ | dm³/kg | 6,4<br>$2.51x10^{+6}$ | Average value experimental data |
| Log $K_{oa}$ | g/g | | Estimated in S-Risk |
| BCF | (mg/kg dm)/(mg/m³) | see table below | |
| Dpe | m²/d | $1x10^{-7}$ | Lijzen et al. (2018) |
| Dpvc | m²/d | $1x10^{-10}$ | Cornelis et al (2017) |
| Diffusion for organic substance in air (Da) | m²/d | 0.308 | Cornelis et al (2022) |
| Diffusion for organic substance in water (Dw) | m²/d | $3.17x10^{-5}$ | Cornelis et al (2022) |
| Kp | [cm/h] | 0.0373 | DermWin |
| Fraction absorbed water (FA) | - | 1 | ATSDR, 2017 |
| ABS dermal soil/dust | | 0.1 | EPA, 2004 |
| RBA soil/dust | | 0.81 | Huwe et al. (2008) |
| BTF beef | d/kg | $1.3x10^{-2}$ | Takaki et al. (2015) |
| BTF sheepmeat | d/kg | | Estimated in S-Risk |
| BTF liver | d/kg | $1.2x10^{-2}$ | Kierkegaard et al. (2009) |
| BTF kidney | d/kg | | Estimated in S-Risk |
| BTF milk | d/kg | $9x10^{-3}$ | Kierkegaard et al. (2009); Takaki et al. (2015) |
| BTF soil – egg | d/kg | | |
| BTF food - egg | d/kg | | |
| Carcinogenicity | No data available | | |
| Systemic effects threshold | | | |
| TDI oral | mg/kg.d | $1x10^{-4}$ | US EPA (2008) |
| TCA inhalatory | [mg/m³] | 3.5-4 | US EPA (2008) |
| TDI dermal | mg/kg.d | $8.5x10^{-5}$ | US EPA (2008) |

| | | | |
|---|---|---|---|
| smoothing - ages | | | |
| Systemic effects non threshold | | | |
| Slope factor oral | (mg/kg/d) | Not available | |
| Unit risk inhalation | (mg/m³) | Not available | |
| Slope factor dermal | (mg/kg/d) | Not available | |
| Limit in air | mg/m³ | $3.5x10^{-4}$ | toxicological reference value |
| Limit in drinking water | mg/m³ | 0.6 | SRV for groundwater |
| Crop standard | mg/kg fw | - | |
| Meat and edible offal standard | | - | |
| Beef | mg/kg fw | - | |
| Sheepmeat | mg/kg fw | - | |
| Liver | mg/kg fw | - | |
| Kidney | mg/kg fw | - | |
| Milk | mg/kg fw | - | |
| Butter | mg/kg fw | - | |
| Egg | mg/kg fw | - | |
| Dietary background all age groups including children | mg/kg/d | $1.25x10^{-7}$ (1 - < 3 y) | Based on concentrations from Poma et al (2018) and food consumption data from S-RISK |
| | mg/kg/d | $9.92x10^{-8}$ (3 - < 6 y) | |
| | mg/kg/d | $6.65x10^{-8}$ (6 - < 10 y) | |
| | mg/kg/d | $4.04x10^{-8}$ (10 - < 15 y) | |
| | mg/kg/d | $2.98 x10^{-8}$ (15 - < 21 y) | |
| | mg/kg/d | $2.86 x10^{-8}$ (21 - < 31 y) | |
| | mg/kg/d | $2.66 x10^{-8}$ (31 - < 41 y) | |
| | mg/kg/d | $2.69 x10^{-8}$ (41 - < 51 y) | |
| | mg/kg/d | $2.63 x10^{-8}$ (51 - < 61 y) | |
| | mg/kg/d | $2.75 x10^{-8}$ (≥ 61 y) | |
| Background potato | mg/kg fw | $2.5 x10^{-6}$ | Poma et al. (2018) |
| Background root vegetables | mg/kg fw | $2.5 x10^{-6}$ | Poma et al. (2018) |
| Background bulbous vegetables (onion, etc.) | mg/kg fw | $2.5 x10^{-6}$ | Poma et al. (2018) |
| Background fruiting vegetables | mg/kg fw | $2.5 x10^{-6}$ | Poma et al. (2018) |
| Background cabbage | mg/kg fw | $2.5 x10^{-6}$ | Poma et al. (2018) |
| Background leafy vegetables | mg/kg fw | $2.5 x10^{-6}$ | Poma et al. (2018) |
| Background legumes | mg/kg fw | $2.5 x10^{-6}$ | Poma et al. (2018) |
| Background beef | mg/kg fw | $2.5 x10^{-6}$ | Poma et al. (2018) |
| Background offal | mg/kg fw | $2.5 x10^{-6}$ | Poma et al. (2018) |
| Background milk | mg/kg fw | $2.5 x10^{-6}$ | Poma et al. (2018) |
| Background butter | mg/kg fw | $2.5 x10^{-6}$ | Poma et al. (2018) |
| Background eggs | mg/kg fw | $2.5 x10^{-6}$ | Poma et al. (2018) |
| Background outdoor air | mg/m³ | $1.34x10^{-10}$ | Degrendele et al. (2018) |
| Background indoor air | mg/m³ | $6.1x10^{-9}$ | Wemken et al (2019) |
| Background drinking water | mg/m³ | $2x10^{-4}$ | Brueller et al. (2018) |

| Plant | BCF or BCF model | Source |
|---|---|---|
| **potatoes** | | |
| potatoes | 7.15 | Wang et al. (2016) |
| **root and tuber vegetables** | | |
| carrots | 0.57 | Wang et al. (2011) |
| salsify | 0.50 | Read-across average carrot/radish |
| other root vegetables (such as radish) | 0.43 | Wang et al. (2011) |
| **bulbous vegetables** | | |
| bulbous vegetables (such as onion) | 7.1 | Wang et al. (2011, 2016) |
| leek | 7.1 | Read-across onion |
| **fruiting vegetables** | | |
| tomato | 2.5 | Navarro et al. (2017) |
| cucumber | 2.5 | Read-across tomato |
| other fruiting vegetables (such as peppers) | 2.5 | Read-across tomato |
| **cabbages** | | |
| cabbage | 1.1 | Wang et al. (2011) |
| cauliflower and broccoli | 0.57 | Wang et al. (2011) |
| sprouts | 0.86 | Read-across average cabbage/cauliflower |
| **leafy vegetables** | | |
| lettuce | 0.94 | Bizkarguenaga et al. (2016), Wang et al. (2011) |
| lamb's lettuce | 0.78 | Read-across average lettuce/spinach |
| endive | 0.78 | Read-across average lettuce/spinach |
| spinach | 0.61 | Navarro et al. (2017), Wu et al. (2018) |
| chicory | 0.78 | Read-across average lettuce/spinach |
| celery | 0.78 | Read-across average lettuce/spinach |
| **legumes** | | |
| beans | 1 | Read-across peas |
| peas | 1 | Wang et al. (2011) |
| **grasses** | | |
| grass | 9.2 | Parolini et al. (2012) |
| **cereals** | | |
| maize | 0.0038 | Huang et al (2011) |

# ANNEX B – METHODOLOGY FOR THE DERIVATION OF ECOTOXICOLOGICAL STANDARDS

For the calculation of soil standards, the method for deriving ecotoxicological standards prescribes, depending on the number and nature of the available literature data, one of the following three methods:

1. If there is sufficient chronic data, the Weight of Evidence method is applied. To do this, the 25th percentile of the NOEC and LOEC frequency distribution is taken and divided by an uncertainty factor to derive a Threshold Effect Concentration (TEC).
2. In case of insufficient data, the lowest chronic LOEC is divided by an uncertainty factor to obtain a TEC value, this is the LOEC method.
3. When only acute toxicity data are available, the Median Effect method is applied and the lowest reported EC50 or LC50 is divided by an uncertainty factor to derive the TEC value.

Depending on the number of data, 1 of the three methods is applied.

*Deriving from $TEC_{soil}$*

For BDE-99, only 2 NOEC values are available for deriving the $TEC_{soil}$. Consequently, methods 1 (many data) and 3 (only acute data) are not applicable. The following conditions apply to method 2 (the LOEC method):

- at least 3 studies in which a NOEC and LOEC are included as an endpoint; whose
- at least 1 test for terrestrial invertebrates; and
- at least 1 test on terrestrial plants.

There are only 2 reliable studies available, so the LOEC method cannot be applied.

*Deriving from $NECC_{soil}$*

For BDE-99 there are no data available for deriving the $NECC_{soil}$. Consequently, methods 1 (a lot of data) and 3 (only acute data) do not apply. The following conditions apply to method 2 (the LOEC method):

- at least 3 studies in which a NOEC and LOEC are included as an endpoint;
- the LOEC values from the C cycle and N mineralization never exceed a response rate of 40%;
- LOEC values for N-fixation or nitrification studies at single dose are > $EC_{15}$ and <EC40;
- LOEC values for single-dose C-cycle and N-mineralization studies are > $EC_{15}$ and <EC25.

There are no studies available, so the LOEC method cannot be applied.

# ANNEX C – COMPARISON OF SRV BASED OF TOXICOLOGICAL REFERENCE VALUES FROM US EPA OR EFSA

As described in Chapter 9.7, the EFSA report (2024) was not finalized at the time of writing this report, therefore the TRV for oral exposure was not used. The Table below provides an overview of the SRV estimated using the TRV from US EPA as well as from EFSA. Also, target values for free re-use of excavated soil and target value for the use of excavated soil for building sites were estimated using the TRV from both the US EPA and EFSA.

| | SRV (mg/kg dw) based on US EPA TRV | SRV (mg/kg dw) based on EFSA TRV |
|---|---|---|
| SRV Scenario 2 | 0.004 | 0.0057 |
| SRV Scenario 3 | 0.038 | 0.054 |
| SRV Scenario 4a | 54 | 59 |
| SRV Scenario 4b | 51 | 52 |
| SRV Scenario 5a | 918 | 1140 |
| SRV Scenario 5b | 420 | 560 |
| Value for free re-use of excavated soil | 0.0032 | 0.0045 |
| Value for the use of excavated soil for building sites | 0.54 | 0.77 |

vision on technology
for a better world