Supporting Information for: Exposure of the Irish Population to PBDEs in Food: Consideration of Parameter Uncertainty and Variability for Risk Assessment

David Trudel¹, Christina Tlustos², Natalie von Goetz*¹, Martin Scheringer¹, Peter Reichert³,
Konrad Hungerbühler¹

¹ Institute for Chemical and Bioengineering, ETH Zurich, Zurich, Switzerland

² Food Safety Authority of Ireland (FSAI), Dublin, Ireland

³ Eawag: Swiss Federal Institute of Aquatic Science and Technology, Dübendorf,
Switzerland

* Corresponding author address: Institute for Chemical and Bioengineering, ETH Zurich,
Wolfgang-Pauli-Str. 10, CH-8093 Zurich, Switzerland, natalie.von.goetz@chem.ethz.ch

1 Food consumption, composition, and concentration data

To assess the exposure to PBDEs via intake of contaminated foods a model with 47 food groups was implemented. The food groups with their according sample matrix composition and fat fractions, as well as their mean consumption for female and male adults are given in Table S1. Table S2 shows the total number of data points and the number of data points above the limit of detection (LOD), as well as the mean and standard deviation of the given datasets after treatment of nondetects (as described in section 2). The same datasets were used for the 1D-MCS study presented in Trudel et al. (2010).

26
27**Table S1. Modeled food groups (in total 47) with according sample matrix compositions, fat fractions, and mean food consumption for female and male adults (g/kg_{bw}/d).**

Food groups	Sample matrix 1	%	Sample matrix 2	%	Fat fraction	Food cons. female adults (g/kg _{bw} /d)	Food cons. male adults (g/kg _{bw} /d)
Black pudding	Porcine fat	100	-	-	0.10	0.008	0.021
Dairy - butter	Dairy fat	100	-	-	0.82	0.097	0.13
Dairy - cheese (hard)	Dairy fat	100	-	-	0.31	0.16	0.18
Dairy - cheese (soft and semisoft)	Dairy fat	100	-	-	0.23	0.053	0.032
Dairy - cream	Dairy fat	100	-	-	0.31	0.063	0.055
Dairy - custard	Dairy fat	100	-	-	0.04	0.034	0.032
Dairy - fat spreads <25% fat	Dairy fat	100	-	-	0.20		7E-05
Dairy - fat spreads 35-40% fat	Dairy fat	100	-	-	0.39	0.07	0.074
Dairy - fat spreads 60-65% fat	Dairy fat	100	-	-	0.65	0.12	0.16
Dairy - fat spreads 70-75% fat	Dairy fat	100	-	-	0.71	0.042	0.049
Dairy - fat spreads 80-85% fat	Dairy fat	100	-	-	0.82	0.017	0.016
Dairy - ice cream, vanilla	Dairy fat	100	-	-	0.10	0.1	0.082
Dairy - icecream, other	Dairy fat	100	-	-	0.09	0.012	0.0086
Dairy - other milk	Dairy fat	100	-	-	0.04		0.011
Dairy - semi skimmed milk	Dairy fat	100	-	-	0.02	0.89	0.49
Dairy - skimmed milk	Dairy fat	100	-	-	0.00	0.23	0.05
Dairy - whole milk	Dairy fat	100	-	-	0.04	2.4	3.1
Dairy - yoghurt	Dairy fat	100	-	-	0.02	0.26	0.16
Eggs	Egg fat	100	-	-	0.10	0.23	0.27
Fish - lean fish	Lean fish	100	-	-	-	0.11	0.13
Fish - oily fish	Oily fish	100	-	-	-	0.0077	0.016
Fish - oily fish, canned	Oily fish, canned	100	-	-	-	0.0014	0.008
Fish - salmon	Salmon	100	-	-	-	0.076	0.05
Fish - salmon, canned	Salmon, canned	100	-	-	-	0.01	0.015
Fish - shellfish	Shellfish	100	-	-	-	0.011	0.011
Fish - tuna, canned	Tuna, canned	100	-	-	-	0.036	0.022
Fish oil supplements	Fish oil	100	-	-	1.00	0.0014	0.0004
Mayonnaise	Vegetable oil	91	Egg fat	9	0.76	0.057	0.044
Mayonnaise light	Vegetable oil	88	Egg fat	12	0.28	0.0039	0.0022
Meat - bacon	Porcine fat	100	-	-	0.25	0.13	0.21
Meat - beef	Bovine fat	100	-	-	0.12	0.39	0.56
Meat - beef dripping	Bovine fat	100	-	-	0.99	0.0004	0.0005
Meat - beef fat cuts	Bovine fat	100	-	-	0.52	0.0015	0.0018
Meat - beef fat, suet	Bovine fat	100	-	-	0.87	0.00045	0.0008
Meat - ham&gammon	Porcine fat	100	-	-	0.05	0.19	0.28
Meat - lamb	Ovine fat	100	-	-	0.14	0.089	0.15
Meat - lambs offal	Ovine liver	100	-	-	0.13	0.0093	0.011
Meat - pig fat cuts	Porcine fat	100	-	-	0.52	0.00092	0.0034
Meat - pig lard	Porcine fat	100	-	-	0.99	0.0084	0.0094
Meat - pork liver	Porcine liver	100	-	-	0.08	0.0029	0.0015
Meat - pork Meat cuts	Porcine fat	100	-	-	0.11	0.14	0.18
Meat - salami and similar	Porcine fat	100	-	-	0.46	0.0022	0.0045
Meat - sausages	Porcine fat	100	-	-	0.23	0.1	0.17
Poultry	Poultry fat	100	-	-	0.04	0.46	0.44
Salad cream	Vegetable oil	80	Egg fat	20	0.30	0.0044	0.0036
Vegetable oils	Vegetable oil	100	-	-	0.99	0.053	0.053
White pudding	Porcine fat	100	-	-	0.30	0.015	0.02

28

29

30
31
32

Table S2. Measured sample matrices with number of observations (# obs), number of observations above LOD (>LOD), mean and standard deviation of concentrations in ng/g fresh weight for fish and ng/g fat weight for the other food groups. If only one observation was given no standard deviation has been calculated. Data are from Ireland and partially from England and taken from Fernandes et al. (2009) and UK Food Standards Agency (2006).

Sample matrix		Bovine fat	Dairy fat	Egg fat	Fish oil	Lean fish	Oily fish	Oily fish, canned	Ovine fat	Ovine liver	Porcine fat	Porcine liver	Poultry fat	Salmon	Salmon, canned	Shellfish	Tuna, canned	Vegetable oil
BDE-28	# obs	19	46	19	40	19	22	9	10	14	13	2	21	39	6	13	6	2
	>LOD	0	6	3	30	19	22	7	1	7	0	2	0	39	1	11	0	0
	mean	0.016	0.0037	0.007	0.12	0.032	0.043	0.025	0.0075	0.01	0.017	0.01	0.013	0.053	0.0058	0.015	0.0043	0.005
	sd	0.01	0.0084	0.0055	0.14	0.033	0.033	0.017	0.0079	0.0056	0.01	0.01	0.01	0.029	0.002	0.023	0.0018	
BDE-47	# obs	19	52	25	40	19	22	9	18	15	13	4	21	39	6	13	1	2
	>LOD	19	33	24	40	19	22	9	16	15	13	4	20	38	6	13	1	1
	mean	0.12	0.12	0.19	3.1	0.6	0.89	0.38	0.088	0.16	0.2	0.2	0.17	1.1	0.042	0.33	0.01	0.058
	sd	0.047	0.21	0.059	3.4	0.66	0.77	0.26	0.07	0.097	0.082	0.029	0.079	0.64	0.016	0.42		0.046
BDE-49	# obs	9	36	23	40	19	22	9	10	9	5	4	21	39	6	13	1	2
	>LOD	3	11	17	36	19	22	8	3	2	3	0	13	39	2	13	1	1
	mean	0.0067	0.0091	0.027	0.53	0.14	0.29	0.14	0.0081	0.0061	0.012	0.019	0.02	0.29	0.0067	0.07	0.001	0.0075
	sd	0.0025	0.0052	0.011	0.6	0.23	0.26	0.12	0.0068	0.0022	0.011	0.0063	0.012	0.19	0.0026	0.093		0.0035
BDE-99	# obs	19	52	23	40	19	22	9	18	15	13	4	21	39	6	12	1	2
	>LOD	19	31	23	40	19	22	8	18	15	13	4	21	39	1	11	1	1
	mean	0.13	0.1	0.25	0.57	0.068	0.16	0.12	0.12	0.24	0.28	0.21	0.22	0.37	0.012	0.13	0.01	0.078
	sd	0.077	0.19	0.099	0.61	0.1	0.12	0.12	0.03	0.33	0.16	0.09	0.11	0.34	0.0041	0.13		0.074
BDE-100	# obs	19	52	25	40	19	22	9	18	15	13	4	21	39	1	13	1	2
	>LOD	10	19	25	38	19	22	8	13	10	7	1	15	39	1	13	1	1
	mean	0.032	0.02	0.076	0.57	0.14	0.22	0.094	0.056	0.056	0.042	0.028	0.051	0.22	0.01	0.13	0.002	0.013
	sd	0.033	0.042	0.042	0.61	0.17	0.22	0.065	0.031	0.064	0.018	0.016	0.04	0.13		0.18		0.011
BDE-153	# obs	19	52	25	40	19	22	9	18	15	13	4	21	39	1	13	6	2
	>LOD	12	20	23	31	19	8	5	18	10	11	3	20	29	1	8	0	1
	mean	0.075	0.031	0.097	0.099	0.015	0.023	0.02	0.15	0.12	0.089	0.064	0.059	0.05	0.005	0.019	0.013	0.018
	sd	0.1	0.053	0.12	0.11	0.013	0.033	0.013	0.17	0.15	0.062	0.015	0.023	0.03		0.041	0.0059	0.018
BDE-154	# obs	19	52	25	40	4	21	9	18	15	13	2	21	39	6	13	6	2
	>LOD	9	7	14	34	2	14	4	11	4	6	1	11	36	0	7	0	0
	mean	0.024	0.0082	0.033	0.29	0.0029	0.056	0.033	0.035	0.028	0.039	0.013	0.027	0.11	0.013	0.054	0.013	0.005
	sd	0.016	0.02	0.036	0.35	0.00091	0.035	0.025	0.022	0.024	0.025	0.011	0.017	0.047	0.0041	0.071	0.0059	
BDE-183	# obs	8	43	19	39	19	1	9	10	3	5	2	13	39	6	13	6	2
	>LOD	4	8	19	2	10	1	0	10	3	5	2	7	0	0	0	0	1
	mean	0.016	0.015	0.029	0.01	0.0057	0.004	0.016	0.041	0.043	0.036	0.025	0.018	0.023	0.022	0.011	0.021	0.013
	sd	0.023	0.024	0.0097	0.0051	0.0069		0.011	0.028	0.023	0.029	0.0071	0.011	0.0057	0.0082	0.012	0.0098	0.011
BDE-209	# obs	4	30	19	40	19	8	4	10	3	1	2	13	3	1	8	1	1
	>LOD	4	0	19	0	14	8	1	4	3	1	1	3	3	1	5	0	0
	mean	0.21	0.11	0.75	0.3	0.075	0.084	0.053	0.25	0.95	0.17	0.29	0.24	0.17	0.07	0.071	0.02	0.31
	sd	0.1	0.066	0.82	0.012	0.056	0.061	0.045	0.17	0.6		0.3	0.2	0.21		0.058		

33
34

2 Data Preparation (Treatment of Nondetects)

This section describes in detail how nondetects in datasets were replaced: If at least two data points were above LOD the values below LOD were fitted using *robust regression on order statistics* (ROS) (Helsel, 2005). If only one data point above the LOD was given, then the values below LOD were set to one half of the LOD. On the basis of these adjusted datasets the lognormal distribution used for bootstrapping was derived (step 2 in Figure 2 of main text). For datasets that only consisted of values below LOD, each value was set to half of the LOD. The highest LOD was used as 99th quantile and the mean of the adjusted values as median of the lognormal distribution. We chose this procedure because the concentrations in food of animal origin are likely to be larger than zero (since PBDEs are persistent and ubiquitous in the environment) but below the LODs and can be assumed to be lognormally distributed. These distributions, however, were not used for bootstrapping but directly assigned as uncertainty distributions containing no variability but only uncertainty, i.e. in 2D-MCS random numbers from these distributions were only generated in the outer loop (step 6 in Figure 2 of the main text) and then used as constants in the inner loop. This procedure ensures that the dose estimates are conservative, because if datasets with all data points below LOD are influential, the distribution of dose D will contain a large uncertainty (and a large UVR). These datasets should be investigated more closely, eventually leading to additional measurements with improved analytical devices that have a lower LOD.

3 Uncertainty-to-Variability Ratio (UVR): Further Simulation Studies

To check the performance of the *UVR*, in addition to the study presented in the main text, we have conducted simulation studies with artificial data.

3.1 Selection of Parameters

The simulation study was performed with six random datasets for two distribution types (normal and lognormal) representing variability. The first three datasets were generated with a normal distribution as variable distribution and two normal distributions as parameters that parameterize the mean and standard deviation of the variable distribution. The values for the first parameter (the mean) are $\mu_{\text{mean}}=10$ and $\sigma_{\text{mean}} \in \{0.1, 0.5, 1\}$ and for the second (the standard deviation (sd)) $\mu_{\text{sd}}=0.5$ and $\sigma_{\text{sd}} \in 0.1$. The three datasets differ only in the value σ_{mean} . The values for the second three datasets were generated with a lognormal distribution as variable distribution and two normal distributions as its parameters. The first parameter (mean) has been parameterized with $\mu_{\text{mean}}=-2$ and $\sigma_{\text{mean}} \in \{0.1, 0.5, 1\}$ and the second (sd) with $\mu_{\text{sd}}=0.5$ and $\sigma_{\text{sd}} \in 0.1$. The three datasets differ only in the value σ_{mean} .

3.2 Results and Discussion

The graphical representation of the simulation results for the normal variable distribution is shown in Figure S1. We see increasing uncertainty from the lower (sd=0.1) to the upper panel (sd=1) as represented by the spread of the single distributions. The three-dimensional character of the results is shown in Figure S2 (for sd=0.5). This figure illustrates the dose D as consisting of a multitude of probability density functions (density) that together visualize uncertainty for all quantiles of the cumulative distribution functions (CDFs) representing the variability of the dose. The flatter the shape of the structure, the larger is the spread of the density and the larger the uncertainty. The according values for uncertainty, variability and UVR s are given in Table S3. We can see that the UVR decreases with decreasing uncertainty, assuming everything else is constant. This is supported by the visual inspection of the results presented in Figure S1.

The graphs showing the simulation results for the lognormal variable distribution are presented in Figure S3. For the normal distribution we can see increasing uncertainty from the lower (sd=0.1) to the upper panel (sd=1). This visual finding is in agreement with the calculated *UVRs* (Table S4) and, hence, gives support to the use of the *UVR* as a useful statistic in 2D-MCS. We again produced a three-dimensional graph (Figure S4) to better illustrate the structure of D (for sd=0.5). Other than shown in Figure S2 the shape of D changes from lower to upper quantiles of $D|p$ from spiky to flat.

3.3 Conclusions

To better understand the relation between uncertainty and population variability in 2D-MCS models and to better communicate the results, a statistic called uncertainty-to-variability ratio (*UVR*) was developed. The simulation studies reveal that the *UVR* performs as expected, i.e. if by visual interpretation of 2D-MCS generated doses dominance of uncertainty is derived, the *UVR* is larger than one and if the doses tend to be dominated by variability, the *UVR* is smaller than one – a finding that holds for normal as well as lognormal distributions. This is an encouraging result and supports the use of such a statistic to determine the relation between uncertainty and population variability in risk assessment studies. However, experience with the *UVR* is so far limited and further studies need to prove its usefulness.

Figure S1. Simulations with normal variable distributions to investigate the performance of the *UVR*. The uncertainty decreases from top to bottom panel, whereas the variability stays almost constant. CDF = cumulative distribution function.

Figure S2. Three-dimensional illustration of the simulation with normal variable distributions and $sd=0.5$. CDF = cumulative distribution function.

Figure S3. Simulations with lognormal variable distributions to investigate the performance of the *UVR*. The uncertainty and the variability decrease from top to bottom panel. CDF = cumulative distribution function.

Figure S4. Three-dimensional illustration of the simulation with lognormal variable distributions and $sd=0.5$. CDF = cumulative distribution function.

Table S3. Simulation results for uncertainty U , variability V and corresponding UVR s of normal variable distributions.

sd	U	V	UVR
0.1	0.01	0.27	0.039
0.5	0.3	0.26	1.2
1	1.14	0.26	4.4

Table S4. Simulation results for uncertainty U , variability V and corresponding UVR s of lognormal variable distributions.

sd	U	V	UVR
0.1	0.00023	0.0068	0.034
0.5	0.007	0.01	0.71
1	0.27	0.093	2.9

4 Risk Assessment – Selection of Toxicity Data and Method

In carrying out a risk assessment for the Irish adult population concerning PBDEs in food, we decided to compare exposure estimates with the reported threshold values (indicative of absence of adverse effects) for the various endpoints of liver toxicity, reproductive toxicity and neurodevelopmental effects (already used by other institutions) in a margin of safety (MOS) approach (for values see Table 4 in the main text). Below we provide the reasoning for the choice of the relevant toxicological studies and endpoints, respectively, and why we apply the MOS approach in our risk assessment.

The greatest concern for potential adverse health effects of PBDEs currently relates to their developmental neurotoxicity (Birnbaum et al., 2004; Branchi et al., 2003; McDonald, 2005). Animal studies in rodents have provided evidence that exposure to different PBDEs (e.g. BDE-47, BDE-99, BDE-153, BDE-209, or the penta mixture DE-71) during the pre-and/or post-natal periods, causes long-term behavioral abnormalities, particularly in the domains of motor activity and cognition (Branchi et al., 2002; Dufault et al., 2005; Gee et al., 2008; Johansson et al., 2008; Kuriyama et al., 2005; Rice et al., 2007; Viberg et al., 2003a; Viberg et al., 2003b; Viberg et al., 2007). Many toxicological studies have also focused on the effects of PBDE exposure on the components of the endocrine system, a system that plays a critical role in the regulation of bodily processes, development of the brain and nervous tissues, sexual maturation and function, metabolism and overall homeostasis (Vonderheide et al., 2008).

In carrying out an assessment of the health risk for human populations from exposure to food contaminants such as PBDEs, the traditional approach is to compare the estimated exposure with a Tolerable Daily Intake (TDI) established by an international risk assessment body such as the Joint FAO/WHO Expert Committee on Food Additives and Contaminants (JECFA) or

the European Food Safety Authority (EFSA). These expert bodies derive TDIs by considering the available toxicological database including animal studies and epidemiological studies. The TDI is derived by application of uncertainty factors to the No-Observed-Adverse-Effect-Level (NOAEL) of the chemical under consideration, or, in the absence of a NOAEL, a Lowest-Observed-Adverse-Effect-Level (LOAEL) from the pivotal study or studies available in the toxicological database. However, expert bodies such as JECFA or EFSA will only derive a TDI based on a reasonably robust toxicological database, including animal studies conducted according to current test guidelines and of extended duration (e.g. long-term chronic toxicity or carcinogenicity studies or, at a minimum, studies of at least 90-day duration). No TDIs for PBDEs have been derived by international bodies such as EFSA or JECFA as yet, due to the uncertainties and deficiencies in the toxicological databases for PBDEs. However, in 2005 JECFA stated that the limited toxicity data suggested that for the more toxic PBDE congeners, adverse effects would be unlikely to occur in rodents at doses of less than approximately 100 µg/kg_{bw}/day (JECFA, 2005).

In absence of TDIs for PBDEs that were established by international risk assessment bodies, assessment of risk can be assessed by comparing exposure to risk descriptors (points of departure (POD)) derived by bodies such as the European Commission (EC), the UK Committee on Toxicity (COT) and the US EPA. The EC evaluated Pentabromodiphenylether in 2000 and Octa- and Decabromodiphenylether in 2002 under the Existing Chemicals risk assessment program (Regulation 793/93; JRC, 2001; JRC, 2003). They identified liver toxicity as the pivotal toxicological parameter in the rat (Great Lakes Chemical Corporation, 1985; Great Lakes Chemical Corporation, 2001; National Toxicology Program (NTP), 1986) and effects on the reproductive system in rabbits (Breslin et al., 1989), in the absence of information on neurodevelopmental effects. They identified NOAELs for the liver and reproductive effects for penta- and octaBDE and a LOAEL for decaBDE. In

2003/2004 the UK COT adopted a Margin of Exposure (MOE) approach in which the estimated human exposures were compared with the relevant NOAEL or LOAEL identified in the EU risk assessments and from newer animal studies (Eriksson et al., 2002). The US EPA in 2008 published reference doses based on neurobehavioural effects for BDEs 47, 99, 153 and 209 in single dose gavage studies in neonate mice (Eriksson et al., 2001; Viberg et al., 2003a; Viberg et al., 2004).

Bakker et al. (2008) argued that gavage studies in neonate mice were not suitable to assess exposure in humans and derived an expected human NAEL for BDE-99, using a study based on intrauterine and lactational exposure to BDE-99 in mice (Branchi et al., 2002; Kuriyama et al., 2005). The expected human NAEL for neurodevelopmental toxicity was calculated at a range of 18.8 – 41.4 ng/kg bw/d for BDE-99. Another study (Kuriyama et al., 2005) used by the same authors was based on intrauterine prenatal exposure of BDE-99 leading to impaired spermatogenesis, with an expected human NAEL of between 0.23-0.30 ng BDE-99/kg bw/d. It is however uncertain whether the latter observed effect was due to cross-contamination with dioxins and furans and it remains uncertain if this effect is specific for BDE-99.

In 2009, Hardy et al (2009) published a health assessment of BDE-209 based on a critical review of available studies, and derived a reference dose (RfD) based on a precursor effect in the liver using the chronic NTP (1986) study on BDE-209 in rats. The latter study did not expose animals during the critical period of development and did not evaluate neurobehavioral toxicity. The authors argue that although studies are available that report effects at lower administered doses of BDE-209 (e.g., Viberg et al. (2003b; 2007); Johansson et al., (2008); Rice et al., (2007)), an evaluation of these studies using the Klimisch criteria followed by the US EPA's assessment factors revealed deficits in Viberg et al. (2003b; 2007); Johansson et al., (2008); Rice et al., (2007), which precluded their use as pivotal studies in a health assessment. Further, they supported their argument by citing the study by

193 Silberberg et al. (2009), which concludes that BDE-209 is not a developmental neurotoxicant
194 in rats at levels of up to 1000 mg/kg_{bw}/day.

195 **5 3D Illustration of Dose Distributions**

196 To better illustrate the shape of the dose distributions (D), we have generated three-
197 dimensional graphs. We show them for female adults' exposure to $\sum$ BDE in Figure S5, to
198 BDE-47 in Figure S6, to BDE-99 in Figure S7, and to BDE-209 in Figure S8. It is well
199 visible that the spread of D increases from BDE-47 to BDE-209. This is also reflected in the
200 UVR s for the doses of different congeners: 0.012 for BDE-47, 0.028 for BDE-99, and 0.13
201 for BDE-209 (see Table 2 in main text). The graphs for male adults are not presented here but
202 look similar. The graphs are slightly jagged for lower values of the CDF, which is an artifact
203 due to the limited resolution of the graphs.

204

205 **Figure S5. Three-dimensional plot of D for female adults' exposure to Σ BDE. CDF = cumulative distribution**
 206 **function.**

207

208 **Figure S6. Three-dimensional plot of D for female adults' exposure to BDE-47. CDF = cumulative distribution**
 209 **function.**

210

211 **Figure S7. Three-dimensional plot of D for female adults' exposure to BDE-99. CDF = cumulative distribution**
 212 **function.**

Figure S8. Three-dimensional plot of D for female adults' exposure to BDE-209. CDF = cumulative distribution function.

6 Uncertainty Range of Selected Dose Distributions

Figure S9 to Figure S11 show the density and CDF of $Q_{97.5}\{D|p\}$ for all values of p . All densities are slightly skewed to the right. It is also visible that for BDE-47 the highest dose is roughly two times larger and for BDE-99 roughly three times larger than the lowest dose whereas the highest dose for BDE-209 is about five times larger than the lowest dose.

Figure S9. Probability density (upper panels) and cumulative distribution function (lower panels) reflecting uncertainty for the 97.5th quantile of the variability dose distribution for BDE-47 ($Q_{97.5}\{D|p\}$ for all values of p). CDF = cumulative distribution function.

Figure S10. Probability density (upper panels) and cumulative distribution function (lower panels) reflecting uncertainty for the 97.5th quantile of the variability dose distribution for BDE-99 ($Q_{97.5}\{D|p\}$ for all values of p). CDF = cumulative distribution function.

Figure S11. Probability density (upper panels) and cumulative distribution function (lower panels) reflecting uncertainty for the 97.5th quantile of the variability dose distribution for BDE-209 ($Q_{97.5}\{D|p\}$ for all values of p). CDF = cumulative distribution function.

7 Uncertainty Analysis

To determine the most relevant input parameters (in this study these are model variables and their according distribution parameters) the contribution to variance (CtV) was calculated. The CtV for female adults is presented in Figure S12 and for male adults in Figure S13, respectively.

The most relevant food matrices for exposure to Σ BDE are dairy fat and lean fish, whereas the most relevant congeners are BDE-47, -99, and -209. The fat fraction of eggs has some influence on dose estimates for the exposure to BDE-99 (male adults only), -153 (male adults only), -209, and Σ BDE. This is due to the large spread of the fat fraction distribution for eggs (Q_{95}/Q_5 -ratio of the distribution is 27, whereas all other fat fraction distributions have a Q_{95}/Q_5 -ratio that is lower than 10 and more than 70% of the fat fraction distributions have a Q_{95}/Q_5 -ratio that is even below 2) and due to the comparably large BDE-209 concentrations measured in eggs. Generally, model variables are more influential than their distribution parameters, which is due to hierarchical structure of the model. A model variable is normally parameterized by two parameters and if one or two of these parameters are influential then the model variable becomes even more influential.

It has to be kept in mind, however, that due to the resampling method no CtVs can be calculated for the consumption of food. These input parameters are resampled directly from the dataset (and not represented by distributions like the other input parameters) and it is not possible to calculate correlations between the output and the different data points from the resampled dataset. Therefore, the CtVs need to be interpreted carefully, always considering that consumptions of different foods may also be important input parameters.

Figure S13. Contribution to variance (CtV) for male adults and high-var scenario (i.e. including variability for concentrations and fat fractions). Abbreviations: Conc. = concentration, par. = parameter, sd. = standard deviation. The distribution parameter representing the mean is denoted with “par.mean”, the distribution parameter representing the standard deviation is denoted with “par.sd”. The other input parameters are all model variables. “Cons.ind” represents the random number generated to choose one food consumption pattern per MCS run from the consumption patterns of the 468 investigated male adults. There is no reason why there should be any correlation between this random number and the dose of BDE-47. Therefore, we can conclude that BDE-47 has only three or maybe four influential input parameters and the CtV for “Cons.ind” has no meaning (as could be expected, the correlation between “Cons.ind” and the dose of BDE-47 is not statistically significant).

8 Dose Estimates and UVRs for Low-Var Scenario

The low-var scenario models only the uncertainty (standard error) in the arithmetic mean of the measured concentrations and treats the fat fractions as point estimates (arithmetic mean of the given fat fractions). The low-var scenario likely underestimates the variance in dose estimates, but provides a lower limit of dose levels.

8.1 Dose Estimates

All dose estimates of the upper quantiles calculated for the low-var scenario are lower when compared to dose estimates calculated for the high-var scenario (Table S5), which is due to

Table S5. $Q_{\alpha}[Q_{\beta}\{D|p\}]$ with $\alpha=\{2.5, 50, 97.5\}$ and $\beta=\{97.5, 99\}$ for low-var scenario for Irish female and male adults, respectively. Q stands for quantile and β selects the quantile of the distribution of dose D representing variability and α the quantile of D representing the uncertainty. All dose estimates in ng/kg_{bw}/d.

	$Q_{\alpha}[Q_{\beta}\{D p\}]$	$Q_{2.5}[Q_{97.5}\{D p\}]$	$Q_{50}[Q_{97.5}\{D p\}]$	$Q_{97.5}[Q_{97.5}\{D p\}]$	$Q_{2.5}[Q_{99}\{D p\}]$	$Q_{50}[Q_{99}\{D p\}]$	$Q_{97.5}[Q_{99}\{D p\}]$
Female adults	BDE-28	0.048	0.059	0.078	0.054	0.066	0.089
	BDE-47	0.98	1.2	1.5	1.1	1.4	1.7
	BDE-49	0.21	0.32	0.42	0.26	0.37	0.5
	BDE-99	0.36	0.44	0.53	0.41	0.51	0.63
	BDE-100	0.2	0.25	0.33	0.23	0.29	0.41
	BDE-153	0.077	0.088	0.11	0.082	0.095	0.12
	BDE-154	0.092	0.11	0.13	0.11	0.12	0.16
	BDE-183	0.035	0.04	0.051	0.037	0.043	0.055
	BDE-209	0.33	0.38	0.78	0.39	0.44	0.97
	Penta-mix ^{a)}	1.8	2.1	2.4	2	2.3	2.7
	Σ BDE ^{b)}	2.4	2.8	3.5	2.8	3.2	3.9
Male adults	BDE-28	0.048	0.059	0.078	0.054	0.066	0.089
	BDE-47	0.88	1.1	1.4	1.1	1.3	1.8
	BDE-49	0.2	0.28	0.4	0.25	0.36	0.5
	BDE-99	0.33	0.41	0.5	0.41	0.49	0.61
	BDE-100	0.18	0.24	0.32	0.22	0.28	0.4
	BDE-153	0.082	0.095	0.12	0.094	0.11	0.14
	BDE-154	0.075	0.088	0.11	0.093	0.11	0.15
	BDE-183	0.035	0.042	0.054	0.04	0.048	0.064
	BDE-209	0.36	0.4	0.67	0.42	0.46	0.77
	Penta-mix ^{a)}	1.6	1.8	2.1	1.9	2.2	2.6
	Σ BDE ^{b)}	2.2	2.5	3	2.7	3	3.5

^{a)} The penta-mix consists of BDE-47, -99, -100, -153, and -154 (note: this is not the sum of the single congeners due to nonlinearity of the model)

reduced variability in concentration and fat fraction data. The dose estimates for the low-var scenario are, however, generally still higher than those calculated with the 1D-MCS as presented in Trudel et al. (2010).

8.2 UVR

The *UVRs* in the low-var scenario for BDE-47, -99, and Σ BDE (Table S6) are slightly higher when compared to those of the high-var scenario (Table 2 in the main text). This is expected, as the variability in concentration data is no longer modeled. The *UVR* for BDE-209, however, is slightly lower than the *UVR* in the high-var scenario. This is because the concentration distribution for dairy fat (the most influential input parameter according to the CtV shown in Figure S12 and Figure S13) is based solely on data points below LOD and was assumed to contain only uncertainty in the high-var scenario (see also section 2 in this text). In the low-var scenario this distribution is replaced by a point estimate (the mean of the distribution) and, hence, the uncertainty is eliminated. Because the PBDE concentration in dairy fat is such an influential model variable for the total dose, the reduction of its uncertainty can overcompensate the reduction of variability in the other model variables and,

Table S6. Results for uncertainty, variability, and *UVRs* of the 2D-MCS model for doses of the low-var scenario of Σ BDE, BDE-47, BDE-99, and BDE-209 for Irish female and male adults.

Σ BDE	<i>U</i>	<i>V</i>	<i>UVR</i>
Female adults	0.0043	0.41	0.01
Male adults	0.0054	0.33	0.016
BDE-47			
Female adults	0.0018	0.09	0.020
Male adults	0.0024	0.07	0.032
BDE-99			
Female adults	0.00055	0.009	0.058
Male adults	0.00074	0.008	0.095
BDE-209			
Female adults	0.0004	0.01	0.04
Male adults	0.00024	0.0089	0.027

hence, the *UVR* decreases. Overall, we find that the *UVR*s for the low-var scenario are still clearly below one (Table S6), indicating that additional data points will not significantly improve the quality of dose estimates.

9 References

- Bakker M.I., De Winter-Sorkina R., De Mul A., Boon P.E., Van Donkersgoed G., Van Klaveren J.D., *et al.* Dietary intake and risk evaluation of polybrominated diphenyl ethers in The Netherlands. *Mol Nutr Food Res* 2008: 52(2): 204-216.
- Birnbaum L.S., Staskal D.F. Brominated flame retardants: Cause for concern? *Environ Health Perspect* 2004: 112(1): 9-17.
- Branchi I., Alleva E., Costa L.G. Effects of Perinatal Exposure to a Polybrominated Diphenyl Ether (PBDE 99) on Mouse Neurobehavioural Development. *Neurotoxicology* 2002: 23(3): 375-384.
- Branchi I., Capone F., Alleva E., Costa L.G. Polybrominated diphenyl ethers: Neurobehavioral effects following developmental exposure. *Neurotoxicology* 2003: 24(3): 449-462.
- Breslin W.J., Kirk H.D., Zimmer M.A. Teratogenic Evaluation of a Polybromodiphenyl Oxide Mixture in New-Zealand White-Rabbits Following Oral-Exposure. *Fundam Appl Toxicol* 1989: 12(1): 151-157.
- Dufault C., Poles G., Driscoll L.L. Brief postnatal PBDE exposure alters learning and the cholinergic modulation of attention in rats. *Toxicol Sci* 2005: 88(1): 172-180.
- Eriksson P., Jakobsson E., Fredriksson A. Brominated flame retardants: A novel class of developmental neurotoxicants in our environment? *Environ Health Perspect* 2001: 109(9): 903-908.
- Eriksson P., Viberg H., Jakobsson E., Orn U., Fredriksson A. 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. *Toxicol Sci* 2002: 67(1): 98-103.
- Fernandes A.R., Tlustos C., Smith F., Carr M., Petch R., Rose M. Polybrominated diphenylethers (PBDEs) and brominated dioxins (PBDD/Fs) in Irish food of animal origin. *Food Addit Contam Part B Surveill* 2009: 2(1): 86-94.

Gee J.R., Moser V.C. Acute postnatal exposure to brominated diphenylether 47 delays neuromotor ontogeny and alters motor activity in mice. *Neurotoxicol Teratol* 2008: 30(2): 79-87.

Great Lakes Chemical Corporation. 30 day dietary study in rats with pentabromodiphenyl oxide, including recover periods of 6, 12 and 24 weeks, Final report. Unpublished. WIL Research laboratories project no: WIL-12042. 1985.

Great Lakes Chemical Corporation. A 90 day inhalation toxicity study of octabromodiphenyl oxide in albino rats. Unpublished laboratory report, WIL Research Laboratories, Inc. 2001.

Hardy M.L., Banasik M., Stedeford T. Toxicology and human health assessment of decabromodiphenyl ether. *Crit Rev Toxicol* 2009: 39: 1-44.

Helsel D.R. *Nondetects and data analysis statistics for censored environmental data*. Wiley: Hoboken, N.J., 2005.

JECFA. Sixty-fourth meeting, Summary and Conclusions, Joint FAO/WHO Expert Committee on Food Additives. Rome, 2005.

Johansson N., Viberg H., Fredriksson A., Eriksson P. Neonatal exposure to deca-brominated diphenyl ether (PBDE 209) causes dose-response changes in spontaneous behaviour and cholinergic susceptibility in adult mice. *Neurotoxicology* 2008: 29(6): 911-919.

Kuriyama S.N., Talsness C.E., Grote K., Chahoud I. Developmental exposure to low-dose PBDE-99: Effects on male fertility and neurobehavior in rat offspring. *Environ Health Perspect* 2005: 113(2): 149-154.

McDonald T.A. Polybrominated diphenylether levels among United States residents: daily intake and risk of harm to the developing brain and reproductive organs. *Integr Environ Assess Manag* 2005: 1(4): 343-354.

National Toxicology Program (NTP). Toxicology and carcinogenesis studies of decabromodiphenyl oxide in F344N rats and B6C3F1 mice (feed studies). US Department of Health and Human Services: 1986.

NTP N.T.P. Toxicology and carcinogenesis studies of decabromodiphenyl oxide in F344N rats and B6C3F1 mice (feed studies). US Department of Health and Human Services: 1986.

Rice D.C., Reeve E.A., Herlihy A., Zoeller R.T., Thompson W.D., Markowski V.P. Developmental delays and locomotor activity in the C57BL6/J mouse following neonatal exposure to the fully-brominated PBDE, decabromodiphenyl ether. *Neurotoxicol Teratol* 2007: 29(4): 511-520.

Trudel D., Tlustos C., Goetz N.v., Scheringer M., Hungerbuehler K. PBDE Exposure from Food in Ireland: Optimizing Data Exploitation in Probabilistic Exposure Modelling. *J Expo Anal Environ Epidemiol* 2010.

UK FSA. Brominated chemicals in farmed and wild fish and shellfish and fish oil dietary supplements, 2006.

- Viberg H., Fredriksson A., Eriksson P. Neonatal exposure to polybrominated diphenyl ether (PBDE 153) disrupts spontaneous behaviour, impairs learning and memory, and decreases hippocampal cholinergic receptors in adult mice. *Toxicol Appl Pharmacol* 2003a: 192(2): 95-106.
- Viberg H., Fredriksson A., Jakobsson E., Orn U., Eriksson P. Neurobehavioral derangements in adult mice receiving decabrominated diphenyl ether (PBDE 209) during a defined period of neonatal brain development. *Toxicological Sciences: An Official Journal Of The Society Of Toxicology* 2003b: 76(1): 112-120.
- Viberg H., Fredriksson A., Eriksson P. 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. *Environ Toxicol Pharmacol* 2004: 17(2): 61-65.
- Viberg H., Fredriksson A., Eriksson P. Changes in spontaneous behaviour and altered response to nicotine in the adult rat, after neonatal exposure to the brominated flame retardant, decabrominated diphenyl ether (PBDE 209). *Neurotoxicology* 2007: 28(1): 136-142.
- Vonderheide A.P., Mueller K.E., Meija J., Welsh G.L. Polybrominated diphenyl ethers: Causes for concern and knowledge gaps regarding environmental distribution, fate and toxicity. *Sci Total Environ* 2008: 400(1-3): 425-436.