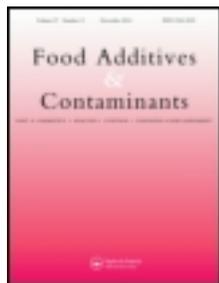


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### Risk ranking priority of carcinogenic and/or genotoxic environmental contaminants in food in Belgium

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## Risk ranking priority of carcinogenic and/or genotoxic environmental contaminants in food in Belgium

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This paper focuses on the risks of environmental carcinogenic and/or genotoxic contaminants in food. It describes, for each contaminant studied, the carcinogenicity and genotoxicity, the toxicological reference values, the exposure and the risk characterisation. The compounds studied were classified into 3 categories based on a risk assessment. Effects others than carcinogenicity and/or genotoxicity (e.g. endocrine disruption activity) were also taken into account for the classification. Given the low margin of exposure values for arsenic and lead, these two compounds are classified as priority 1 (high concern) for food safety and as a first priority to take actions to reduce exposure. Cadmium, methylmercury, dioxins and dioxin-like polychlorinated biphenyls (PCB), non-dioxin-like PCB and toxaphene are classified as priority 2 (medium concern). Polybrominated biphenyls, chlordane, heptachlor, dichlorodiphenyltrichloroethane (DDT) and metabolites, hexachlorobenzene, hexachlorocyclohexane (lindane included), polychlorophenols and their salts are classified as priority 3 (low concern).

**Keywords:** carcinogenic; genotoxic; contaminant; environment; food

### Introduction

The industrial revolution over the second half of the last century and its consequences in domains such as energy, transport, agriculture, food and health led to the synthesis, production and introduction into the environment millions of man-made chemicals or substances (Belpomme et al. 2007). As a result, according to the European Commission, about 100,000 chemicals have been so far marketed, since the Second World War, without sufficient toxicological control. Such products can act as persistent toxic pollutants and contaminate air, soil, water and food. Many of them are carcinogenic, mutagenic and/or reprotoxic molecules (Clapp et al. 2005) and can act as mutagens, promoters or both, or be co-carcinogenic (Newby & Howard 2006), meaning that they can contribute to the genesis of cancers and therefore account for their currently growing incidence in the population (Epstein 1994, 2004).

Persistent organic pollutants (POPs) are chemicals that accumulate in the food chain and are toxic to humans and wildlife (Colles et al. 2008). Due to their high stability and lipophilic properties, they accumulate in fat-containing foods and tissues. The most abundant POPs are chlorinated pesticides (like dichlorodiphenyltrichloroethane (DDT), dieldrin, chlordane, etc.) and industrial chemicals (such as polychlorinated biphenyls (PCBs)). Of particular

interest are also contaminants like polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans (PCDD/Fs). These POPs can cause acute as well as chronic health problems. A series of POPs were banned by the adoption of the Stockholm Convention in 2001 (Stockholm Convention 2008) such as the obsolete pesticides (OPs) like aldrin, dieldrin, heptachlor and chlordane. Compounds like DDT and hexachlorocyclohexane (HCH) have been widely used after the Second World War. They have seriously affected not only the environment, but also human health, e.g. by possessing endocrine disrupting effects (United Nations Environment Programme 2012).

Food may be the primary route of exposure to contaminants from different classes such as metals, POPs and OPs (Vogt et al. 2012). Contamination of food with toxic chemicals may originate from the environmental pollution with chemicals released from or formed during a wide number of industrial and anthropogenic activities (Larsen 2006). Dietary practices influence exposure to pesticides, metals, POPs and industrial pollutants through consumption patterns (Vogt et al. 2012).

Monograph programmes on the evaluation of carcinogenic risk to humans of the International Agency for Research on Cancer (IARC) have published carcinogenic risk assessments (Newby & Howard 2006).

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One of the most difficult issues in food safety is to advise on potential risks for human health when it is found that compounds that are both genotoxic and carcinogenic are present in food and their presence cannot be readily eliminated or avoided (Barlow et al. 2006).

JECFA noted that compounds that are both genotoxic and carcinogenic may show non-linear dose–response relationships, but the no observed effect level (NOEL) in a study of carcinogenicity represents the limit of detection in that bioassay, rather than an estimate of a possible threshold. Therefore, a health-based guidance value could not be established and previous advice had been to recommend that exposures should be reduced to as low as reasonably achievable (ALARA) (FAO/WHO 2005). JECFA referred to three main alternatives to the ALARA approach: first a calculation of a margin of exposure (MOE) between a point of departure (PoD) on the observed dose range for carcinogenicity and the estimated dietary exposure in humans; second a low-dose extrapolation to a dose associated with a defined estimate of risk; and third a linear extrapolation from a PoD on the observed dose range. EFSA concluded that the magnitude of an MOE could be used by risk managers for priority setting and was more informative than advising that exposures should be reduced to ALARA (EFSA 2005a).

The objective of this study was to establish priority for well-known carcinogenic and/or genotoxic environmental contaminants in food in order to formulate recommendations for risk managers.

## Materials and methods

### Contaminants

The relevant environmental contaminants in food that are studied are arsenic, cadmium, mercury and methylmercury (MeHg), lead, polybrominated biphenyls (PBBs), dioxins and dioxin-like polychlorinated biphenyls (DL-PCBs), non-dioxin-like polychlorinated biphenyls (NDL-PCBs), and forbidden pesticides (chlordane, heptachlor, dichlorodiphenyltrichloroethane (DDT) and metabolites, hexachlorobenzene (HCB), heptachlorohexane (HCH) (included lindane), polychlorophenols and their salts, toxaphene). The choice of these contaminants was made on the basis of an expert opinion.

### Ranking priority methodology

A risk assessment was realised for each contaminant according to the Codex Alimentarius Commission (CAC) (2003). The four steps involved in risk assessment are the same for all chemicals in food: hazard identification, hazard characterisation, exposure assessment and risk characterisation (Barlow, Dybing, et al. 2002; Barlow, Grieg, et al. 2002; Renwick et al. 2003).

The purpose of hazard identification in the present context is to identify whether or not the compound is deoxyribonucleic acid (DNA) reactive either as the parent compound or following bioactivation; in other words whether it is likely to be carcinogenic via a mechanism that theoretically may not show a threshold in the dose–response relationship. This knowledge has a major impact on the formulation of advice for risk management, and is therefore a crucial question in the overall risk assessment process. The decision on whether or not the compound is genotoxic via DNA reactivity is often the single most important criterion in selecting between a non-threshold or a threshold approach, respectively, for hazard characterisation (O'Brien et al. 2006).

For non-genotoxic substances, an NOAEL might be derived from the dose–response curve. A tolerable dose can be established by application of an uncertainty factor to the NOAEL.

For exposure assessment, the intake of the environmental contaminant from food is estimated by multiplying for each food in the diet the concentration of the contaminant in food by the consumption of this food and calculating the sum for all dietary intake. The average and high level of intake figures have been estimated or reported from literature studies for adults and children populations in Belgium and/or in Europe. The exposure assessment reported here is considered to be representative of the exposure assessment in industrialised countries.

Risk characterisation has been defined as “the quantitative or semi-quantitative estimate, including attendant uncertainties, of the probability of occurrence and severity of adverse effect(s)/event(s) in a given population under defined conditions based on hazard identification, hazard characterisation and exposure assessment” (EC 2000).

The EFSA Scientific Committee (2005a) recommends the use of the MOE approach for substances that are both carcinogenic and genotoxic. So for these substances, the MOE was calculated as the ratio of the benchmark dose lower confidence limit (BMDL) for the critical effect to the estimated exposure (WHO 2009).

The magnitude of the MOE gives an indication of the level of concern, but is not a precise quantification of risk: the larger the MOE, the smaller the potential risk posed by exposure to the compound under consideration. The EFSA Scientific Committee (2005a) considered that an MOE of 10,000 or more, based on animal cancer bioassay data, “would be of low concern from a public health point of view and might reasonably be considered as a low priority for risk management actions”.

For non-genotoxic substances, exposure has been compared with the tolerable dose.

The contaminants studied were classified into three classes of priority on the basis of risk (first class: high concern, second class: medium concern, and third class: low concern). The main criterion for the classification is

the value of the MOE or the percentage of the tolerable dose (e.g. TDI). Contaminants classified in the first class have an exposure exceeding the tolerable dose or a low MOE (<100). Contaminants classified in the third class have an exposure lower than 15% of tolerable dose or MOE > 10,000, and contaminants classified in the second class are contaminant for which the exposure is in between. Other effects than carcinogenicity and/or genotoxicity were also taken into account (e.g. endocrine disruption activity) for classification.

## Results and discussion

For each contaminant studied, carcinogenicity and genotoxicity, toxicological reference values, exposure and risk characterisation are described. A summary of the risk assessment is presented in Table 1, which gives for each contaminant three types of information: (1) toxicity – classification IARC, BMDL or TDI, genotoxic or not; (2) exposure – mean/P50 (50th percentile) and P95 (95th percentile) dietary exposure for a given population; and (3) risk characterisation – percentage TDI or MOE. Environmental contaminants are classified into one of the three priority classes.

### *(Inorganic) arsenic*

#### *Hazard identification and characterisation*

Arsenic occurs naturally in the Earth's crust and is present in soil, ground water and plants (Boyle & Jonasson 1973). Anthropogenic sources of arsenic include both industrial emissions, mainly non-ferrous metal smelting and the production of energy from fossil fuels (EFSA 2009a).

Arsenic toxicity depends on the chemical form and its solubility, and varies among animal species and with the route of administration. Generally, trivalent arsenic is more toxic than the pentavalent forms (FAO/WHO 2011). The main adverse effects reported to be associated with long-term ingestion of inorganic arsenic in humans are skin lesions, cancer, developmental toxicity, neurotoxicity, cardiovascular diseases, abnormal glucose metabolism and diabetes. Neurotoxicity is mainly reported with acute exposure from deliberate poisoning or suicide, or at high concentrations in drinking water. Inorganic arsenic has been classified by the IARC in Group 1 as a human carcinogen. The IARC (2012) concluded that arsenic in drinking water causes cancers of the urinary bladder, lung and skin and that the evidence was "limited" for cancer of the kidney, liver and prostate.

EFSA (2009a) concluded that the range of BMDL<sub>01</sub> values of 0.3–8 µg kg<sup>-1</sup> body weight (bw) day<sup>-1</sup> established for humans should be used instead of a single reference point in the risk characterisation for inorganic arsenic.

#### *Exposure assessment and risk characterisation*

In Belgium, intake of total arsenic for an adult of 70 kg was estimated as 1.04 µg kg<sup>-1</sup> bw day<sup>-1</sup> (SPECAS 2010). The largest part of the intake was due to intake of arsenobetaine. Mean intake of inorganic arsenic was 0.11 µg kg<sup>-1</sup> bw day<sup>-1</sup> for the adult population in Belgium (SPECAS 2010).

The MOE (i.e. the ratio between BMDL and the dietary intake) approach has been used for risk characterisation. The estimated mean dietary exposure to inorganic arsenic in Belgium (0.11 µg kg<sup>-1</sup> bw day<sup>-1</sup>) is in the range of BMDL<sub>01</sub> values for the general adult population. The estimated dietary exposures to inorganic arsenic for average (0.13–0.56 µg kg<sup>-1</sup> bw day<sup>-1</sup>) and high level adult consumers (0.37–1.22 µg kg<sup>-1</sup> bw day<sup>-1</sup>) in Europe are within the range of the BMDL<sub>01</sub> values (0.3–8 µg kg<sup>-1</sup> bw day<sup>-1</sup>) identified by the Panel on Contaminants in the Food Chain (CONTAM Panel) of EFSA (2009a) for lung and bladder cancer and for dermal lesions. The estimated dietary exposures of children (0.5–3.21 µg kg<sup>-1</sup> bw day<sup>-1</sup>) is below the range of BMDL<sub>01</sub>. Therefore there is little or no MOE and the possibility of a risk to some consumers cannot be excluded (EFSA 2009a).

### *Cadmium*

#### *Hazard identification and characterisation*

Cadmium is primarily an environmental contaminant that firstly occurs naturally and also may originate from industrial and agricultural sources.

Exposure to cadmium has been associated with nephrotoxicity, bone effects, neurotoxicity, carcinogenicity and genotoxicity, teratogenicity and respiratory effects, endocrine and reproductive effects (EFSA 2009b). The kidney is the critical target organ for chronic cadmium toxicity. Environmental exposure to cadmium is associated with renal tubular dysfunction (Koçak & Akçil 2006). Cadmium does not interact directly with DNA. It is genotoxic by induction of oxidative stress and inhibition of DNA repair. Cadmium can cause lung cancer in rats after inhalation (EFSA 2009b). The IARC (1993) has classified cadmium compounds in Group 1 as a human carcinogen. Data for human exposure to cadmium by the population have been associated with an increased risk of cancer such as lung cancer (Nawrot et al. 2006), endometrial cancer (Åkesson et al. 2008), bladder cancer (Kellen et al. 2007), prostate cancer (Verougstraete et al. 2003), and breast (McElroy et al. 2006) or liver cancer (Campbell et al. 1990).

Based on the meta-analysis, the CONTAM Panel established a tolerable weekly intake (TWI) of 2.5 µg kg<sup>-1</sup> bw (EFSA 2009b).

Table 1. Risk ranking priority of carcinogenic and/or genotoxic environmental contaminants.

Substance	Toxicity			Exposure ( $\mu\text{g kg}^{-1} \text{ bw day}^{-1}$ )			Risk characterisation		
	IARC classification	TDI ( $\mu\text{g kg}^{-1} \text{ bw day}^{-1}$ )	BMDL ( $\mu\text{g kg}^{-1} \text{ bw day}^{-1}$ )	Mean/P50	P95	Population	Reference point	MOE or %TDI	Remarks
<i>First priority ("high concern")</i>									
Arsenic (inorganic)	1		BMDL <sub>01</sub> = 0.3–8	0.11		Adults, Belgium	MOE	2.7–73	BMDL based on human data
Lead	2A		BMDL <sub>01</sub> = 1.50 for cardiovascular effects and BMDL <sub>10</sub> = 0.63 for renal effects BMDL <sub>01</sub> = 0.50 for developmental neurotoxicity	0.5	3.21	Children, European Union		0.1–16	
				0.13 (P50)	0.36	Adults, Belgium	MOE	1.8–11.5	BMDL based on human data; other effects considered than carcinogenicity
<i>Second priority ("medium concern")</i>									
Cadmium	1	0.36		0.14/0.12 0.58/0.42 0.0000072	0.29 1.04 0.0000137	Adults, Belgium Children, Belgium Adults, Belgium	TWI TWI TWI	34–81% 118–292% 36–68.5%	Endocrine disruptor
Dioxins and dioxin-like polychlorinated biphenyls (DL-PCB)	1	0.000002		0.043	0.073	Adults, Flanders, Belgium Adolescents, Flanders, Belgium	PTWI	23–68%	
Non-dioxin-like polychlorinated biphenyls (NDL PCB)	2A	0.01 (indicative)		0.0053–0.0061	0.0108–0.0122	Adults, Belgium	TWI	53–122%	Endocrine disruptor; indicative evaluation there is no health-based guidance value
Toxaphene	2B	0.1		0.005 0.025	0.062 0.07	Adults, Europa Infants, Europa	TDI	5–62% 25–70%	Endocrine disruptor

(continued)

Table 1. Continued.

Substance	Toxicity			Exposure ( $\mu\text{g kg}^{-1} \text{ bw day}^{-1}$ )			Risk characterisation			
	IARC classification	TDI ( $\mu\text{g kg}^{-1} \text{ bw day}^{-1}$ )	BMDL ( $\mu\text{g kg}^{-1} \text{ bw day}^{-1}$ )	Genotoxic	Mean/P50	P95	Population	Reference point	MOE or %TDI	Remarks
<i>Third priority ("low concern")</i>										
Chlordane	2B	0.5			0.0015 0.0025 0.0037	0.0032 0.0057 0.0084	Adults, Denmark Children, Denmark Adults, Denmark	PTDI TDI	0.3–0.64% 0.5–1.14% 0.037–0.084%	Endocrine disruptor
Dichlorodiphenyltri- chloroethane (DDT) and metabolites	2B	10			0.0067	0.0157	Children, Denmark		0.067–0.16%	
Heptachlor	2B	0.1			0.0002	0.0010	Adults, Belgium	TDI	0.21–1%	
Hexachlorobenzene	2B		TD <sub>5</sub> = 810	× little evidence	0.0013	0.0023	Adults, Denmark	MOE	1.7–6.2 × 10 <sup>5</sup>	TD <sub>5</sub> based on animal data
Hexachlorocyclohexane (HCH) and lindane	2B	5			0.0026 0.0008	0.0048 0.0014	Children, Denmark Adults, Denmark	TDI	0.02–0.03%	Lindane
Polybrominated biphenyls (PBB)	2B				0.0015	0.0027	Children, Denmark		0.03–0.05%	No concern
Polychlorophenols and their salts	2B	5	400 (slope factor)		0.015		Adults France	NOEL TDI	5–6 orders below NOEL 0–0.3%	Pentachlorophenol
					0.025		Children, France		0–0.5%	

Note: IARC, International Agency for Research on Cancer; BMDL, benchmark dose lower confidence limit; P, percentile; MOE, margin of exposure; TD<sub>5</sub>, tumorigenic dose 5; TWI, tolerable weekly intake; and NOEL, no observed effect level.

### Exposure assessment and risk characterisation

Based on consumption data from the Belgian food survey of 2004 (De Vriese et al. 2005) and cadmium concentration in food items from the control programme of the Belgian Federal Agency for the Safety of the Food Chain for 2006–2008, the mean, median and P95 dietary exposure of the Belgian adult population was estimated at 0.98, 0.85 and 2.02  $\mu\text{g kg}^{-1} \text{bw week}^{-1}$ , respectively (Vromman et al. 2010) and the mean, median and the P95 dietary exposure of the Belgian children population were estimated as 4.09, 2.96 and 7.3  $\mu\text{g kg}^{-1} \text{bw week}^{-1}$ , respectively (Sci Com 2009). A total of 2% of the Belgian adult population has a dietary exposure above the TWI of 2.5  $\mu\text{g kg}^{-1} \text{bw week}^{-1}$  established by EFSA in 2009 (Vromman et al. 2010).

The recent review of cadmium dietary exposure by EFSA (2012a) confirmed that children on average and adults at P95 dietary exposure could exceed health-based guidance values.

### Mercury and methylmercury (MeHg)

#### Hazard identification and characterisation

Mercury is found in various inorganic and organic forms and is persistent in the environment (WHO 2008). It is distributed throughout the environment by both natural and anthropogenic processes (WHO 2008).

The primary targets for the toxicity of mercury and mercury compounds are the nervous system, kidneys and cardiovascular system. It is generally accepted that developing organ systems (such as the foetal nervous system) are the most sensitive to toxic effects of mercury. MeHg is the most toxic form.

MeHg and mercury exert *in vitro* genotoxicity in mammalian cells, whereas data from laboratory animals and humans are inconsistent (EFSA 2012b). MeHg compounds are possibly carcinogenic to humans (Group 2B) whereas inorganic mercury is classified in Group 3 (not classifiable as to its carcinogenicity to humans).

EFSA (2012b) has established a TWI for inorganic mercury of 4  $\mu\text{g kg}^{-1} \text{bw}$  and for MeHg of 1.3  $\mu\text{g kg}^{-1} \text{bw}$ .

#### Exposure assessment and risk characterisation

Fish consumption is the main source of human dietary exposure to MeHg (Forsyth et al. 2004). The levels of contamination in fish vary among species. It tends to be higher in those who are at the top of the food chain (large predators).

Sioen (2007) has estimated the mean and P95 dietary exposure of the Flemish adolescent population in Belgium to MeHg through seafood at 0.12 and 0.51  $\mu\text{g kg}^{-1} \text{bw week}^{-1}$ . The mean and P95 dietary exposure of the adult population

to MeHg through seafood was estimated to be 0.30 and 0.88  $\mu\text{g kg}^{-1} \text{bw week}^{-1}$  (Sioen 2007).

The middle bound (MB) mean MeHg dietary exposure of the European population varied between 0.06  $\mu\text{g kg}^{-1} \text{bw week}^{-1}$  in the elderly and very elderly population to 1.57  $\mu\text{g kg}^{-1} \text{bw week}^{-1}$  in toddlers (EFSA 2012b). The MB P95 dietary exposure ranged from 0.14  $\mu\text{g kg}^{-1} \text{bw week}^{-1}$  in very elderly to 5.05  $\mu\text{g kg}^{-1} \text{bw week}^{-1}$  in adolescents.

The estimated dietary intake of MeHg through seafood by the Flemish population is below (9–68%) the PTWI of 1.3  $\mu\text{g kg}^{-1} \text{bw week}^{-1}$ . These intakes did not seem to be of toxicological concern. However, the P95 dietary exposure estimated by EFSA (2012b) is close or above the TWI for all age groups in Europe. High fish consumers may exceed the TWI by up to approximately six-fold, which is of concern. According to EFSA (2012b), the estimated dietary exposure for inorganic mercury in Europe does not exceed the TWI.

### Lead

#### Hazard identification and characterisation

Lead is an environmental contaminant that occurs naturally from the Earth's crust and mainly comes from anthropogenic activities such as mining, smelting and battery manufacturing. The historical use of lead in herbicides, gasoline, pipes, welds and paints has contributed to the contamination of the environment (Carlisle et al. 2009). Lead is a metal found in both organic and inorganic form, the latter being the predominant form in the environment (EFSA 2010a).

Lead exposure is associated with a wide series of effects, including many neurodevelopmental outcomes, mortality (mainly due to cardiovascular disease), decreased renal function, hypertension, impaired fertility and adverse consequences on pregnancies (WHO 2011).

Inorganic lead derivatives are classified as probable human carcinogen (in Group 2A) by the IARC (2006) based on animal data (renal tumours) and limited data in humans. Lead has a low mutagenic activity but promotes the genotoxicity of radiation and chemical agents ("co-carcinogenic effect") (Lauwerys et al. 2007). In humans an increased risk of lung cancer, gastric or bladder cancer has been suggested (Fu & Boffetta 1995; Steenland & Boffetta 2000). Even if they are partially metabolised to inorganic lead, organic lead compounds are not classifiable as carcinogenic to humans (Group 3).

The CONTAM Panel identified the following potential adverse effects of lead, developmental neurotoxicity in young children, cardiovascular effects and nephrotoxicity in adults, as the basis for the risk assessment (EFSA 2010a). The BMDL approach has been used by EFSA to characterise the dose–response relationship. The BMDL dietary intake values

derived from lead concentration in blood from an epidemiological study in humans were  $1.50 \mu\text{g kg}^{-1} \text{bw day}^{-1}$  for cardiovascular effects,  $0.63 \mu\text{g kg}^{-1} \text{bw day}^{-1}$  for renal effects and  $0.50 \mu\text{g kg}^{-1} \text{bw day}^{-1}$  for developmental neurotoxicity.

#### *Exposure assessment and risk characterisation*

According to EFSA (2010a), food is the major source of lead exposure, but it should be noted that for children ingestion of soil particles and dust may represent an important source of lead exposure. Among children aged 1–3 years old, it has been suggested that the activity “hand to mouth” accounts for 50% or more of the total intake of lead (LDAI 2008).

The P50 dietary lead exposure of the Belgian adult population was estimated by the probabilistic approach (MB scenario) to be  $0.13 \mu\text{g kg}^{-1} \text{bw day}^{-1}$  and the exposure at the P95 was estimated at  $0.36 \mu\text{g kg}^{-1} \text{bw day}^{-1}$  (Sci Com 2009). P50 and P95 lead dietary exposures of the children were estimated by the probabilistic approach to 0.42 and  $1.07 \mu\text{g kg}^{-1} \text{bw day}^{-1}$ , respectively (Sci Com 2009).

The MOE approach was used to characterise the risks of the Belgian population to lead. BMDL values determined by EFSA for the critical effects systolic blood pressure, chronic kidney disease and scores of intelligence quotient were divided by the dietary exposure estimates for the Belgian population (adult and children). Dietary exposures to lead are lower than the BMDL intake value for the effects on systolic blood pressure ( $1.50 \mu\text{g kg}^{-1} \text{bw day}^{-1}$ ) and for effects on the prevalence of chronic kidney disease ( $0.63 \mu\text{g kg}^{-1} \text{bw day}^{-1}$ ). MOEs ranged from 1.8 to 11.5.

Estimated exposure at P95 in children exceeds the BMDL of  $0.50 \mu\text{g kg}^{-1} \text{bw day}^{-1}$  for neurodevelopmental effects. MOEs ranged from 0.5 to 1.2. Therefore, the possibility of effects in some children cannot be excluded.

Moreover a daily intake of lead from the migration of metallic elements from traditional brass teapots of  $1.7$  to  $320 \mu\text{g kg}^{-1} \text{bw}$  was estimated in Belgium (Sci Com & CSS 2011) for a person weighing 60 kg, which corresponds to an MOE lower to much lower than 1, indicating serious potential risks for public health.

### ***Polybrominated biphenyls (PBBs)***

#### *Hazard identification and characterisation*

PBBs are additive flame retardants applied in synthetic fibres and polymers. As they are not chemically bound to the polymers they can leach into the environment.

The main targets of PBBs toxicity were the liver, thyroid hormone homeostasis and the reproductive, nervous and immune systems.

PBBs are carcinogenic in the liver of rodents, by a non-genotoxic mode of action, which is assumed to have a

threshold in the dose–response curve. A NOEL for hepatocarcinogenesis of  $150 \mu\text{g kg}^{-1} \text{bw}$  has been identified in a long-term National Toxicology Program (NTP) (1993) study with Firemaster FF-1, a flame retardant composed of PBBs. There is evidence that *ortho*-substituted congeners may cause cancer through interaction with nuclear receptors, such as the constitutive androstane receptor, whereas the non-*ortho*-congeners appear to cause tumours as a consequence of arylhydrocarbon receptor (AhR) activation and cytotoxicity, presumably via stimulation of regenerative proliferation (WHO 1994; ATSDR 2004; EFSA 2010b).

IARC (1986) has classified PBBs (FireMaster BP-6, 059536-65-1) in Group 2B (possibly carcinogenic to humans): there is sufficient evidence for the carcinogenicity of commercial mixtures of PBBs to experimental animals, but there is inadequate evidence for the carcinogenicity of PBBs to humans.

The CONTAM Panel of EFSA (2010b) concluded that it was inappropriate to use this NOEL to derive a health-based guidance value for PBBs.

#### *Exposure assessment and risk characterisation*

Environmental occurrence and human exposure in Europe are due to historical production and use of PBBs (EFSA 2010b). The highest exposure to PBBs is due to the consumption of fish and other seafood. The median estimated exposure for average consumers across countries of BB-153 (one of the most common congeners of PBB) is between  $2.4 \times 10^{-7}$  and  $5.5 \times 10^{-6} \mu\text{g kg}^{-1} \text{bw day}^{-1}$  for lower and upper bound, respectively.

The intake of PBBs by high and frequent consumers of fatty fish, the subgroup of the population with the highest dietary exposure, was approximately six orders of magnitude less than the NOEL of  $150 \mu\text{g kg}^{-1} \text{bw}$ . Exposure for high consuming breast-fed infants is five orders of magnitude less than this NOEL. The CONTAM Panel concluded that the risk to the European population from exposure to PBBs through the diet in Europe, even considering the difference in half-lives between rats and humans, is of no concern (EFSA 2010b).

### ***Dioxins and dioxin-like polychlorinated biphenyls (DL PCB)***

#### *Hazard identification and characterisation*

Dioxins, polychlorinated dibenzodioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) are by-products of combustion and of various industrial processes and are widely present in the environment (FAO/WHO 2002a).

Dioxins are generally not generated as single congeners but mostly as complex mixtures that are often

characteristic of the source. Due to the numerous sources, dioxins are ubiquitous. However, due to a number of regulatory measures since the 1980s the emission of dioxins into the environment has considerably decreased (EFSA 2011).

The most commonly reported pathologies related to exposure to PCDDs, PCDFs and PCBs are endometriosis, immunotoxic effects, cancer, birth defects, effects on the reproductive and neuroendocrine, immune systems, altered metabolism and specific organ dysfunction (EPA 2006).

Dioxins and among those especially 2,3,7,8-tetrachlorodibenzo-*p*-dioxine (TCDD) are so-called multiple-site multiple-species carcinogens. This means they cause cancer in different animal species in various organs.

In 2009, the IARC reviewed the carcinogenicity of TCDD as part of a systematic reassessment of all agents classified in Group 1 and classified the evidence of carcinogenicity in humans as sufficient, based on increased risk of all cancers combined (Baan et al. 2009).

Dioxins are not DNA-reactive, i.e. they do not bind covalently to nucleic acids. That is why other mechanisms have been proposed by which these substances cause tumours. A large number of studies have been conducted, most with the model compound TCDD (EFSA 2011).

On basis of the low observed adverse effect level (LOAEL) of 25,000 pg kg<sup>-1</sup> bw for decreased sperm production and altered sexual behaviour in male offspring, the Scientific Committee on Food of the European Commission (2001) has established a TWI of 14 pg TEQ kg<sup>-1</sup> bw.

#### *Exposure assessment and risk characterisation*

The mean dietary intake of PCDD/Fs and DL-PCBs in the Belgian adult population in 2008 was estimated to be 0.72 pg TEQ kg<sup>-1</sup> bw day<sup>-1</sup> (MB scenario, toxic equivalency factors (TEF) of 1998) based on occurrence data of 2008 and national food consumption data of 2004 (Windal et al. 2010). When using the 2005 TEF instead of the 1998 TEF, the mean dietary intake in the Belgian adult population was estimated to be 0.61 pg TEQ kg<sup>-1</sup> bw day<sup>-1</sup>. The P95 dietary intake of PCDD/Fs and DL-PCBs in the Belgian adult population was estimated at 1.37 pg TEQ kg<sup>-1</sup> bw day<sup>-1</sup>.

The Belgian dietary exposure of 0.72 pg TEQ kg<sup>-1</sup> bw day<sup>-1</sup> (or 5.04 pg TEQ kg<sup>-1</sup> bw week<sup>-1</sup> or 21.6 pg TEQ kg<sup>-1</sup> bw month<sup>-1</sup>) is clearly below the TWI of 14 pg TEQ kg<sup>-1</sup> bw set by the Scientific Committee on Food and below the provisional tolerable monthly intake of 70 pg TEQ kg<sup>-1</sup> bw set by JECFA. Considering the cumulative distribution, the intake was less than 1 pg TEQ kg<sup>-1</sup> bw day<sup>-1</sup> for more than 80% of the population and less than 2 pg TEQ kg<sup>-1</sup> bw day<sup>-1</sup> for the entire population (Windal et al. 2010).

#### *Non-dioxin-like polychlorinated biphenyls (PCBs)*

##### *Hazard identification and characterisation*

Due to their physicochemical properties, such as chemical stability, low heat conductivity and high dielectric constants, PCBs were widely used in a number of industrial and commercial applications such as hydraulic and heat transfer systems, cooling and insulating fluids in transformers and capacitors, pigments, dyes, repellents and carbonless copy paper or as plasticisers in paints, sealants, plastics and rubber products (EFSA 2010c). Their persistence in the environment corresponds to the degree of chlorination, and half-lives can vary from 10 days to 1.5 years (Stockholm Convention 2008).

PCBs have been shown to cause cancer in animals. PCBs have also been shown to cause a number of serious non-cancer health effects in animals, including effects on the immune system, reproductive system, nervous system, endocrine system and other health effects. Studies in humans provide supportive evidence for potential carcinogenic and non-carcinogenic effects of PCBs. The different health effects of PCBs may be interrelated, as alterations in one system may have significant implications for the other systems of the body (EPA 1996).

PCBs without distinction in dioxin-like or non-dioxin-like congeners were classified by IARC (1987) in Group 2A (probably carcinogenic to humans), based on limited evidence in humans and sufficient in animals.

The Rijksinstituut voor volksgezondheid en milieu (RIVM) has set a TDI at 10 ng kg<sup>-1</sup> bw day<sup>-1</sup> for the six indicator PCBs (PCB 28, 52, 101, 138, 153 and 180) considering that the six indicator PCBs account for almost 50% of all congeners present (209 PCBs). This value was also adopted by Agence Française de Sécurité Sanitaire des Aliments (2007) and the Vitenskapskomiteen for Mattrygghet (VKM) (Norwegian Scientific Committee for Food Safety) (2008). It is important to note that their opinion is focused on toxicological data coming from the exposure to mixture of PCBs, thus not on individual DL-PCBs. Therefore, some of the observed adverse effects are probably also related to the presence of DL-PCBs (Cimenci et al. 2013).

##### *Exposure assessment and risk characterisation*

The dietary intakes estimated by Cimenci et al. (2013) for the six indicator PCBs of the mean Belgian population are 5.33, 5.72 and 6.05 ng kg<sup>-1</sup> bw day<sup>-1</sup> for the lower-, medium- and upper-bound scenarios, respectively, and for the P95 of the population are 10.8, 11.6 and 12.2 for the lower-, medium- and upper-bound scenarios, respectively. The largest contribution to the mean intake comes from fishery products with 54.3%, followed by dairy products with 28.5%.

No health-based guidance value for humans can be established for NDL-PCBs because simultaneous exposure to NDL-PCBs and dioxin-like compounds hampers the interpretation of the results of the toxicological and epidemiological studies, and the database on effects of individual NDL-PCB congeners is rather limited. There are however indications that subtle developmental effects, being caused by NDL-PCBs, DL-PCBs or PCDD/Fs alone, or in combination, may occur at maternal body burdens that are only slightly higher than those expected from the average daily intake in European countries. Because some individuals and some European (sub)populations may be exposed to considerably higher average intakes, a continued effort to lower the levels of NDL-PCBs in food is warranted (EFSA 2005b).

Although no agreement has been reached on a “safe acceptable daily intake” for indicator PCBs, Cimenci et al. (2013) used the guidance value of  $10 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  for risk characterisation. The intake of the mean population is half this guidance value, contrary to the P99 that has an intake around 1.5 times higher than  $10 \text{ ng kg}^{-1} \text{ bw day}^{-1}$ .

## Chlordane

### Hazard identification and characterisation

Chlordane is a persistent chlorinated non-systemic, contact and ingested insecticide, which was extensively used from 1947 onward. It was mainly used as an agricultural insecticide but also for non-agricultural purposes (in veterinary preparations for the protection of livestock from different pests). In Europe it was mainly used for the protection of potatoes, small grains and sugar beets. The use of chlordane as a pesticide has been banned in the European Union since 1981 (EC 1978). Chlordane remains in the soil for a long time and has a reported half-life of 1 year.

Chlordane is likely to cause cancer and may cause liver cancer, can cause behavioural disorders in children if they were exposed before birth or while nursing, and harms the endocrine system, nervous system, digestive system and liver (EPA 2011a). Case reports of leukaemia and other blood dyscrasias have been associated with exposure to chlordane/heptachlor, primarily in domestic situations (WHO 2000). Chlordane is primarily metabolised to oxychlordane and to a minor extent may also be dehydrochlorinated to heptachlor. Oxychlordane and nonachlor are more toxic than *cis*- and *trans*-chlordane.

Chlordane has been classified by the IARC (2001) as possibly carcinogenic to humans (Group 2B). Chlordane is not mutagenic *in vivo* and not or only weakly mutagenic in a few tests *in vitro* (EFSA 2007a).

The Joint FAO/WHO Meeting on Pesticides Residues (JMPR) (FAO/WHO 1987) established an ADI of  $500 \text{ ng kg}^{-1} \text{ bw}$  by applying an uncertainty factor of 100

to an NOAEL of  $50,000 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  for liver toxicity in a long-term study in rats. In 1994, JMPR converted the ADI into a provisional tolerable daily intake (PTDI) with the same value (FAO/WHO 1995).

### Exposure assessment and risk characterisation

Food, particularly of animal origin, is the primary source of chlordane exposure in the general population (EFSA 2007a). Dietary exposure of the Belgian adult population to chlordane has been estimated as  $0.2 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  (mean) and  $1.13 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  (P97.5) on the basis on data from the Belgian control plan 2010 and 2011 (Sci Com 2013). Fromberg et al. (2011) have estimated the dietary intakes of chlordane for Danish adults as  $1.5 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  (mean),  $2.6 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  (P90) and  $3.2 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  (P95), which is the same level as the estimate made by Darnerud et al. (2006) for Sweden ( $1.6 \text{ ng kg}^{-1} \text{ bw day}^{-1}$ ). The calculated estimations for children were  $2.5 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  (mean),  $4.6 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  (P90) and  $5.7 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  (P95).

The current human dietary exposure to chlordane is in the low  $\text{ng kg}^{-1} \text{ bw day}^{-1}$  range, which is two to three orders of magnitude below the PTDI of  $500 \text{ ng kg}^{-1} \text{ bw}$ .

## Heptachlore

### Hazard identification and characterisation

Heptachlor was commercially introduced as a non-systemic contact insecticide in 1945. It was also a major constituent (about 10%) of technical chlordane. It was used for agricultural purposes, soil and seed treatment, wood protection and termite and household insect control. It has also been used in the control of malaria. It has been banned for use in the European Union since 1984 and in most other countries worldwide because of the persistency in the environment of the two breakdown products heptachlor epoxide and photoheptachlor (EFSA 2007b).

Heptachlor shows moderate acute toxicity and heptachlor epoxide and photoheptachlor are more toxic than heptachlor. In mammals, the main target organs are the nervous system and the liver, but also the reproductive and the immune systems are affected. Heptachlor and heptachlor epoxide cause liver tumours in mice, but are not genotoxic (EFSA 2007b). Heptachlor has been classified by IARC (2001) in Group 2B.

A TDI of  $100 \text{ ng kg}^{-1} \text{ bw}$  was derived based on histopathological changes in the liver in dog studies with an NOAEL of  $25,000 \text{ ng kg}^{-1} \text{ bw day}^{-1}$ . An uncertainty factor of 200 was used (10 for intra- and 10 for inter-species variation and an extra factor of 2 for inadequacy of the database) (WHO 2006).

*Exposure assessment and risk characterisation*

Dietary exposure of the Belgian adult population to heptachlor has been estimated as  $0.21 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  (mean) and  $0.97 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  (P95) on the basis of data from the Belgian control plan 2010 and 2011. Estimations of the dietary intake of total heptachlor in Poland during the period 1970–96 were less than  $10 \text{ ng kg}^{-1} \text{ bw}$  (Falandysz 2003). The main sources were thought to be meat, meat products and animal fats (WHO 2006). More recent data were not available. Concentrations of heptachlor were found under the LOQ of  $10 \text{ ng g}^{-1}$  in Belgian human milk collected in 2006 during the fourth WHO survey (Colles et al. 2008).

The available data indicate that the average daily intake of total heptachlor in the European Union is well below the TDI of  $100 \text{ ng kg}^{-1} \text{ bw}$ .

**Dichlorodiphenyltrichloroethane (DDT) and metabolites***Hazard identification and characterisation*

DDT was commercially introduced as an insecticide in the 1940s. It is a broad spectrum insecticide that was used during the Second World War to protect troops and civilians from the spread of malaria, typhus and other vector-borne diseases (EFSA 2006a). DDT has been broadly applied in agriculture to control insects on various kinds of crops and for the control of disease vectors. The use of DDT as a pesticide has been very restrictive since 1981 and banned since 1986 in the European Union. Although being banned in most countries worldwide, DDT is still used for vector control especially in areas with endemic malaria. Its stability, its persistence (as much as 50% can remain in the soil 10–15 years after application), and its widespread use has meant that DDT residues can be found everywhere; residual DDT has even been detected in the Arctic (Stockholm Convention 2008). DDT is included in the Stockholm convention on POPs.

The main target organs are the nervous system and the liver. DDT also affects hormonal tissues, reproduction, foetal development and the immune system (EFSA 2006a). DDT including *p,p'*-dichlorodiphenyldichloroethylene (DDE) and dichlorodiphenyldichloroethane (DDD) cause tumours mainly in the liver of experimental animals (mice, rats, monkeys) and are mostly negative in genotoxicity studies. In some studies, increased incidences of lung carcinomas and malignant lymphomas were observed. In hamsters, some increase in the incidence of adrenocortical adenomas was observed. Epidemiological studies in Colombia or Mexico City have found a moderately high risk of breast cancer in women with higher levels of DDE (Ibarluzea et al. 2004). DDT is classified by the IARC (1991) as possibly carcinogenic to humans (Group 2B).

The JMPR (FAO/WHO 2001) derived a PTDI for DDT of  $10,000 \text{ ng kg}^{-1} \text{ bw}$  on the basis of the NOAEL of  $1.10^6 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  for developmental toxicity in rats and an uncertainty factor of 100.

*Exposure assessment and risk characterisation*

Fromberg et al. (2011) have estimated the dietary intakes of DDT (sum) for Danish adults as  $3.7 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  (mean),  $6.5 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  (P90) and  $8.4 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  (P95). Calculated estimations for children were  $6.7 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  (mean),  $12.5 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  (P90) and  $15.7 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  (P95).

Mean, median and P95 intakes for *p,p'*-DDT and *p,p'*-DDE were found to be 2.8, 1.5 and 6.0 and 5.3, 3.8 and  $14.7 \text{ ng kg}^{-1} \text{ bw day}^{-1}$ , respectively, in a German study (EFSA 2006a).

Based on occurrence levels in food between 1999 and 2003 and data of the Czech national consumption data base for individuals, a median dietary intake (age 4–90 years, both genders) of  $29.1 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  was calculated for total DDT (sum of *p,p'*-DDT, *o,p'*-DDT, *p,p'*-DDE, *o,p'*-DDE, *p,p'*-DDD and *o,p'*-DDD) in the Czech Republic (EFSA 2006a).

*p,p'*-DDE was detected in all samples of Belgian human milk collected in 2006 during the fourth WHO Human biomonitoring campaigns (Colles et al. 2008). Mean concentration was  $121.6 \pm 93.3 \text{ ng g}^{-1} \text{ fat}$ . *p,p'*-DDT was detected just above the detection limit. Mean concentration was  $1.5 \pm 7.7 \text{ ng g}^{-1} \text{ fat}$ . The levels of exposure in Europe range between 5 and  $30 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  (EFSA 2006a). The percentage of the PTDI ranges between 0.037% and 0.3%.

**Hexachlorobenzene (HCB)***Hazard identification and characterisation*

HCB is a chlorinated aromatic hydrocarbon that has been used as both a pesticide and an industrial chemical. As a fungicide it was first introduced in 1945 for seed treatment, especially for control of bunt of wheat. The major agricultural application for HCB was as a seed dressing for crops such as wheat, barley, oats and rye to prevent the growth of fungi. The use of HCB in such applications was discontinued in many countries in the 1970s due to concerns about adverse effects on the environment and human health (EFSA 2006b).

The major target organ for HCB effects in experimental animals is the liver. Such effects include porphyria and disturbances in the metabolism of thyroid hormones. Other effects are immunotoxicity, reproductive toxicity, and induction of tumours in the liver, kidney and endocrine organs. HCB has been evaluated by the IARC (2001) as possibly carcinogenic to humans (Group 2B).

Studies on the evaluation of genotoxicity of HCB are limited, but in general they show a lack of evidence of mutagenicity, chromosomal damage or unscheduled DNA repair. Only in a small number of studies on bacteria and yeast HCB exhibited weak mutagenic activity (WHO 1997; IARC 2001). In one study HCB induced micronuclei in rat and human hepatocytes (EFSA 2006b).

In 1997, WHO suggested a health-based guidance value of  $170 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  for non-neoplastic effects based on an NOAEL for hepatic effects, ultrastructural changes in rats and increased urinary coproporphyrin and microsomal liver enzyme activity in pigs, and by incorporating an uncertainty factor of 300.

The approach for neoplastic effect is based on the tumorigenic dose 5 (TD<sub>5</sub>), i.e. the intake or exposure associated with a 5% excess incidence of tumours in experimental studies in animals. TD<sub>5</sub> values range from  $810,000 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  for neoplastic liver nodules in females of the two-generation carcinogenicity study in rats to  $2,010,000 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  for parathyroid adenomas in males (WHO 1997).

EFSA (2006b) does not derive health-based guidance values for compounds that are both carcinogenic and genotoxic, but uses an MOE approach comparing the BMDL with the actual exposure levels.

#### *Exposure assessment and risk characterisation*

Fromberg et al. (2011) have estimated the dietary intakes of HCB for Danish adults to  $1.3 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  (mean),  $1.9 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  (P90) and  $2.3 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  (P95). The calculated estimations for children were  $2.6 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  (mean),  $4.0 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  (P90) and  $4.8 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  (P95).

Mean daily intake for adults reported by Guatemala, Japan, the Netherlands, the UK and the United States were below  $25 \text{ ng kg}^{-1} \text{ bw}$  (Ahmed 1999).

The margin between the dose causing a 5% increase above background of liver tumours in rats ( $810,000 \text{ ng kg}^{-1} \text{ bw}$ ) and the human exposure range as given above is  $1.7\text{--}6.2 \times 10^5$ , which would indicate low concern from a public health point of view.

### **Hexachlorocyclohexane (HCH) and lindane**

#### *Hazard identification and characterisation*

Both technical HCH ( $\alpha$ -HCH,  $\beta$ -HCH,  $\delta$ -HCH) and  $\gamma$ -HCH (also known as lindane) have been globally used as insecticides. Lindane has also been used for medical treatment in humans and animals.

Because of the lipophilic properties and persistence in the environment,  $\beta$ -HCH followed by  $\alpha$ -HCH and to a less extent  $\gamma$ -HCH may give rise to bioaccumulation and biomagnification through the food chain (EFSA 2005c).

With respect to acute exposure,  $\gamma$ -HCH is the most toxic followed by  $\alpha$ -,  $\delta$ - and  $\beta$ -HCH. At chronic exposure, however,  $\beta$ -HCH is the most toxic followed by  $\alpha$ -,  $\gamma$ - and  $\delta$ -HCH. The increased toxicity of  $\beta$ -HCH following chronic exposures is probably due to its longer biological half-life in the body and its accumulation in the body over time (ATSDR 2005).  $\alpha$ - and  $\beta$ -HCH are tumour promoters in rat liver. HCHs were classified by the IARC in Group 2B (possibly carcinogenic) on the basis of inadequate evidence for carcinogenicity to humans, sufficient (for technical grade and the  $\alpha$ -isomer) and limited evidence for carcinogenicity to animals (for  $\beta$ - and  $\gamma$ -HCHs) (IARC 1987).

No ADI has been established by the JMPR for the technical-grade HCH. In 1992 Health Canada set a group TDI for all HCH isomers of  $300 \text{ ng kg}^{-1} \text{ bw}$  (EFSA 2005c). The JMPR (FAO/WHO 2002b) established an ADI of  $5000 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  for lindane on the basis of the NOAEL of  $470,000 \text{ ng kg}^{-1} \text{ bw day}^{-1}$ , in the long-term study of toxicity and carcinogenicity in rats using an uncertainty factor of 100.

#### *Exposure assessment and risk characterisation*

Fromberg et al. (2011) have estimated the dietary intakes of  $\alpha$ -HCH,  $\beta$ -HCH and lindane for Danish adults to 0.6, 0.6 and  $0.8 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  (mean), 0.9, 0.9 and  $1.2 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  (P90), and 1.0, 1.0 and  $1.4 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  (P95). Calculated estimations for children were 1.1, 1.1 and  $1.5 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  (mean), 1.8, 1.7 and  $2.4 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  (P90), and 2.1, 2.1 and  $2.7 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  (P95). Mean (range) dietary exposure of the adult population in France to lindane is estimated between 1 (0–7)  $\text{ng kg}^{-1} \text{ bw day}^{-1}$  (lower bound; LB) and 180 (170–190)  $\text{ng kg}^{-1} \text{ bw day}^{-1}$  (upper bound; UB). Mean exposure of children is estimated between 2 (0–8)  $\text{ng kg}^{-1} \text{ bw day}^{-1}$  (LB) and 240 (230–290)  $\text{ng kg}^{-1} \text{ bw day}^{-1}$  (UB) (Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail 2011). Mean (range) dietary exposure of other HCH for French adult is estimated to 210 (190–220)  $\text{ng kg}^{-1} \text{ bw day}^{-1}$  (UB) and for children is estimated to 240 (230–250)  $\text{ng kg}^{-1} \text{ bw day}^{-1}$  (UB).

Dietary exposure to lindane is in the low  $\text{ng kg}^{-1} \text{ bw day}^{-1}$  range, which is four orders of magnitude below the TDI of  $5000 \text{ ng kg}^{-1} \text{ bw day}^{-1}$ .

### **Polychlorophenols**

#### *Hazard identification and characterisation*

Chlorphenols are used as bactericides, insecticides, herbicides, fungicides, wood preservatives and as intermediates in the production of dyes and pharmaceuticals (ATSDR 2007; Olaniran & Igbinsosa 2011).

Chlorophenolic compounds are considered harmful for human health due to their potential carcinogenic and mutagenic activity, and toxicity (ATSDR 2007). Case-control studies have examined the association of chlorophenols with soft-tissue sarcoma (one study in New Zealand, four in Sweden and one in the United States), non-Hodgkin lymphoma (one study in New Zealand, one in Sweden and one in the United States), thyroid cancer (one study in Sweden), nasal and nasopharyngeal cancer (one study in Sweden), colon cancer (one study in Sweden), and liver cancer (one study in Sweden). These investigations have shown significant associations with several types of cancer, but the most consistent findings have been for soft-tissue sarcoma and non-Hodgkin lymphoma. It is not possible, however, to exclude a confounding effect of PCDDs which occur as contaminants in chlorophenols (Collins et al. 2006; McLean et al. 2009; Zheng et al. 2012).

There is limited evidence in humans for the carcinogenicity of combined exposures to polychlorophenols or to their sodium salts. There is evidence suggesting lack of carcinogenicity of 2,4-dichlorophenol in experimental animals. There is inadequate evidence in experimental animals for the carcinogenicity of 2,4,5-trichlorophenol. There is limited evidence in experimental animals for the carcinogenicity of 2,4,6-trichlorophenol. There is sufficient evidence in experimental animals for the carcinogenicity of pentachlorophenol. Combined exposures to polychlorophenols or to their sodium salts are possibly carcinogenic to humans (Group 2B) (IARC 1999).

The EPA (2010) has established a toxicological value for non-carcinogenic and for carcinogenic effects of pentachlorophenol.

For non-carcinogenic effects of pentachlorophenol, the EPA (2010) established a reference dose (RfD) of  $5 \mu\text{g kg}^{-1} \text{bw day}^{-1}$  on the basis of a LOAEL of  $1500 \mu\text{g kg}^{-1} \text{bw day}^{-1}$  for liver effects from the 1-year toxicity study in beagle dogs by application of a composite uncertainty factor of 300.

The RIVM suggest a TDI of  $3 \mu\text{g kg}^{-1} \text{bw day}^{-1}$  for chronic exposure to 2,4,6-trichlorophenol by the oral route (Baars et al. 2001). This value was established for 2,4-dichlorophenol and then applied it to all other chlorophenols (mono, di, tri and tetra) (INERIS 2005).

For carcinogenic effects, EPA (2010) selected the most sensitive cancer risk estimate, the slope factor of  $400 (\mu\text{g kg}^{-1} \text{bw day}^{-1})^{-1}$  derived for technical-grade pentachlorophenol, which is the higher cancer potency of the two formulations, to represent the cancer risk estimate for pentachlorophenol.

Levels of exposure associated with carcinogenic effects of chlorophenols have been reported by Demers et al. (2006) and Cooper & Jones (2008). Since cancer effects could occur at lower exposure levels, a system developed by EPA estimated excess risks, ranging from

a risk of 1 in 10,000 to 1 in 10,000,000. An oral minimal risk level of  $3 \mu\text{g kg}^{-1} \text{bw day}^{-1}$  would be applicable to trichlorophenol for intermediate exposure duration according to the updated toxicological profiles of chlorophenols of the Agency for Toxic Substances and Disease Registry of the US Department of Health and Human Services (ATSDR 2007).

#### *Exposure assessment and risk characterisation*

Estimates of total chlorophenol intake reviewed by WHO (1989) ranged from  $2.2 \mu\text{g/person day}^{-1}$  assuming contaminated water and fish were the main sources of exposure, to about  $10\text{--}40 \mu\text{g/person day}^{-1}$  assuming indoor rooms were treated with a chlorophenol preservative. Nougadère et al. (2011) have calculated an estimated daily intake (mean percentage of TDI) for pentachlorophenol between 0% and 0.5% for the French children and between 0% and 0.3% for the French adult on basis of a TDI from EPA.

### **Toxaphene**

#### *Hazard identification and characterisation*

Toxaphene is a complex mixture of chlorinated hydrocarbons produced by the chlorination of camphene. Toxaphene (camphechlor) was widely used from the late 1940s as an insecticide on crops and to control parasites on livestock (IARC 2001). Camphechlor has been the most heavily applied insecticide in the United States and in many parts of the world and replaced DDT as a major insecticide in the early 1970s (EFSA 2005d). Its production was banned in the European Union for all uses in 1984. The use of toxaphene is now phased out in most of the world.

Toxaphene belongs to those POPs that were initially chosen for elimination by the Stockholm Convention on POPs in May 2001 (EFSA 2005d).

Toxaphene can have the following harmful effects: injures to the kidney and liver, damage to the immune system, it harms the adrenal gland, causes changes in the development of unborn children, may cause cancer, damages the lungs as well as the nervous system (EPA 2011b). One case-control study in humans showed no significant increase in risk of non-Hodgkin lymphoma and leukaemia associated with exposure to toxaphene (IARC 2001). Toxaphene has been tested for carcinogenicity by oral administration in one study in mice and one study in rats. It increased the incidence of hepatocellular adenomas and carcinomas combined in male and female mice. In rats it produced thyroid follicular-cell adenomas and carcinomas in both males and females and pituitary adenomas in females (IARC 2001). Toxaphene has been classified by IARC (2001) in Group 2B.

Toxaphene was mutagenic in some *Salmonella* strains (TA98 and TA100, but not in TA1535 or TA1537) and is a weak inducer of sister chromatid exchanges *in vitro*. It induced micronuclei in the only assay for this endpoint performed in mammalian cells. Other *in vitro* tests of mutagenicity have been negative. A dominant lethal study in mice was negative and DNA adducts were not found in the livers of mice exposed to toxaphene using <sup>32</sup>P-post-labelling (Nordic Council of Ministers 1997; Hedli et al. 1998; Goodman et al. 2000). It also inhibited gap-junctional intercellular communication in cultured mammalian cells (IARC 2001).

Brüschweiler et al. (2004) derived a TDI of 100 ng kg<sup>-1</sup> bw day<sup>-1</sup> based on the NOAEL for immunotoxicity in a 33-week study in macaque using an uncertainty factor of 1000 because humans are exposed to a different mixture of toxaphene through food than the technical mixture used in experiment (EFSA 2005d).

#### Exposure assessment and risk characterisation

Based on fish consumption data (average fish consumption between 9 and 60 g day<sup>-1</sup>) and most recent concentrations of total of toxaphene (average of toxaphene concentration in fish of 20,000 ng kg<sup>-1</sup>) in European fishery products, an average daily intake between 3.5 and 20 ng kg<sup>-1</sup> bw was estimated for Norway, Germany, Ireland and the Netherlands. Similar results were obtained for the Netherlands by RIVM (2001). However, for high fish consumers from Norway (184 g day<sup>-1</sup>) the estimated daily average intake of toxaphene was 62 ng kg<sup>-1</sup> bw, respectively (EFSA 2005d). The daily intake of toxaphene by nursing infants is estimated between 25 and 70 ng kg<sup>-1</sup> bw (EFSA 2005d). Brüschweiler et al. (2004) estimated the daily intake of 25 ng total of toxaphene kg<sup>-1</sup> bw by linking toxaphene concentrations of medium-contaminated fish samples from Europe and Canada, milk and meat samples from Finland, and food samples of plant origin from the United States with a typical European diet according to the Global Environmental Monitoring System (GEMS/Food) by WHO. More than 65% of this intake was attributed to fish. Human dietary exposure is mainly from fatty fish, which is estimated to be between 1 and 25 ng kg<sup>-1</sup> bw day<sup>-1</sup>. High fish consumers may have intakes of about 60 ng kg<sup>-1</sup> bw day<sup>-1</sup>, which is still considered to remain without health effects.

#### Conclusions

The objective of this study was to establish priorities for well-known carcinogenic and/or genotoxic environmental contaminants in food in order to formulate recommendations to risk managers.

Given the low MOE values for arsenic and lead, these two compounds are considered to be of high concern for

food safety and as a first priority to take action in order to reduce exposure.

Cadmium, MeHg, dioxins and dioxin-like polychlorinated biphenyls (PCB), non-dioxin-like PCB and toxaphene are classified as priority 2 (medium concern). Polybrominated biphenyls, chlordane, heptachlor, dichlorodiphenyltrichloroethane (DDT) and metabolites, hexachlorobenzene, hexachlorocyclohexane (lindane included), polychlorophenols and their salts are classified as priority 3 (low concern). These substances are classified in Group 2B as possible carcinogenic by the IARC. Levels of exposure are weak (MOE above 10<sup>5</sup> or %TDI < 15%).

The prioritisation was not only based on carcinogenic and/or genotoxic effects but also on the most critical effect of the environmental contaminants studied.

Chronic dietary exposure assessments of the Belgian population and/or of other populations in Europe have been used in the risk assessment. It was assumed that the dietary exposure of the contaminants studied is representative of the exposure in industrialised countries. Other routes of exposure were not considered in this study (no aggregate exposure). Potential peaks of contamination were not taken into account in the risk assessment for prioritisation.

Regarding that most of these contaminants are POPs, it is highly recommended to maintain efforts to further reduce the exposure.

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