AN ATTEMPT TO EVALUATE THE RISK OF THE PRESENT HUMAN EXPOSURE TO PCDD/F, PCB, PBDE AND HBCDD IN EUROPE

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Introduction
PCDD/Fs and PCBs have earlier been risk assessed and tolerable limit values were established by the Scientific Committee on Food (SCF) in 2001. The tolerable weekly intake (TWI) was set to 14 pg WHO-TEQ/kg bw.[1] The last years estimated average dietary intake by the European population of PCDD/Fs and non-*ortho* PCBs is 1-3 pg TEQ/kg bw and day,[2-6] which indicates that a large group of people exceeds the TWI. It has been estimated that about 1/10 of the general population, and in addition newborns and some fish consumers exceed the SCF TWI.[7]

United Kingdom followed up a risk assessment of the BDE-209 from 2002 [8] and in May 2004 a final draft was published, but still the human health risk assessment part is missing.[9] The Swedish Chemical Inspectorate has just finished their risk assessment of HBCDD as rapporteur to EU.[10] The human health risk characterisation urged for more information before decisions regarding management can be made.

Studies have shown that the placenta constitute an insufficient barrier for mother-foetus transfer of several POPs, such as PCB and PCB metabolites,[11-13] PBDEs (including DecaBDE) [11,13-15] and HBCDD.[13] Exposure to POPs is above all an issue considering foetuses, infants and young children, which have a high exposure and are in a particular susceptible stage of life. Significant intake of brominated flame retardants via dust have been reported in toddlers,[16,17] which means that the high exposure continues up to adulthood. It is not yet clear how this may affects the individual development.

The objectives of this paper are to report a summary of present human exposure levels of a few POPs reported in Europe, and to put these levels into a risk assessment perspective. An attempt to assess risk to newborns is presented.

Method
Recent reported human concentrations of PCDD/Fs, PCBs and PCB hydroxylated metabolites (OH-PCBs), PBDEs and HBCDD are summarised and representative levels together with their ranges are presented in Table 1. An estimated daily intake of POPs via milk was calculated based on the assumption that a 3 month infants consumes 800 ml milk/day and that the milk contains ~4% fat.

The attempt to perform a preliminary risk assessment of these substances was made according the final draft of the chapter regarding human health risk characterisation in the Technical Guidance Document, published by the European Chemicals Bureau [18]. A margin of safety ($MOS_{toxicant}$) is calculated between the no (or lowest) observed adverse effect level (N(L)OAEL) of the identified critical toxic effect, and the relevant exposure level of the toxicant, i.e. $MOS_{toxicant}$=N(L)OAEL/Exposure. The $MOS_{toxicant}$ is compared to a reference margin of safety ($MOS_{reference}$) which takes into account the uncertainties involved in the risk assessment and should be regarded as the minimum safety margin requested between toxicant exposure levels and threshold effects. If the $MOS_{reference}$>$MOS_{toxicant}$ the exposure level is considered "of concern" and $MOS_{reference}$<$MOS_{toxicant}$="of no concern".

The uncertainty factors used for establishing $MOS_{reference}$ were the following:
An extrapolation LOAEL → NOAEL (3x), interspecies extrapolation for rat (4x2.5), interspecies extrapolation for mouse (7x2.5), and inter-individual difference (10x).

Table 1 A summary of concentrations of POPs in human, serum/tissue, cord blood and milk reported in the European population between 1998-2004 (as cited in Weiss 2006 [15]). Estimated daily intake (ng/day) of POPs via milk of an infant is calculated, based on reported milk levels in the table

Median (Range)	**PCDD/Fs** (pg TEQ/g fat)	**CB-153** (ng/g fat)	**OH-PCBs** (pg/g fresh)	**PBDEs** (ng/g fat)	**BDE-209** (ng/g fat)	**HBCDD** (ng/g fat)
Serum/ tissue	24	240	340	3.3	1.5	0.65
	(7.7-55)	(20-1200)	(n.d.-5200)	(0.7-20)	(n.q.-9.7)	(n.q.-7.5)
Cord blood	n.r.	62	170	1.8	3	1.0
	n.r.	(20-250)	(n.d.-407)	(0.5-6.8)	n.r.	(n.d.-4.3)
Human milk	13	55	3	2.7	0.1	0.52
	(1.8-52)	(4.3-190)	(n.q.-5)	(0.3-70)	(n.d.-1.0)	(0.4-20)
EDI via milk[a]	0.42	1800	2.4	86	3	16
	(0.06-1.6)	(140-6000)	(n.d.-4)	(10-2200)	(n.d.-32)	(13-640)

[a]Estimated daily intake via milk (4% fat content, 800 ml milk/day) of infant (3 months of age), ng/day.
n.d.=not detected, n.q.=not quantified, n.r.=not reported

Risk evaluation

1. Dioxin

TCDD has been reported to decrease the daily sperm production in male offspring rats exposed daily prenatally and postnatally to 800 pg TCDD/kg bw and this may be considered a LOAEL.[19] This effect on the spermatogenesis is considered as a critical effect relevant to humans and several studies have been conducted to investigate the association between sperm quality and POP levels [20,21]. The reference margin of safety for TCDD in this study: $MOS_{reference}$=300.

The estimated dioxin intake by a 3 months old infant (~5.7 kg) via human milk is 420 pg $_{PCDD/F}$-TEQ /day with a maximum of 1600 pg $_{PCDD/F}$-TEQ/day (Table 1). To simplify the calculation it is assumed that concentrations of POPs in milk are constant during lactation. Thus, a newborn (3.6 kg) will daily be exposed to 120 or maximum 400 pg TEQ/kg bw, respectively. This is however an incorrect assumption since lipid content as well as POP levels fluctuate over lactation period [22]. MOS_{TEQ} (=LOAEL/Exposure)=800/120=7 (based on the median value) and 800/400=2 (based on the maximum value).

2. Brominated flame retardants

Reported NOAEL for developmental neurotoxic effects, with altered spontaneous behaviour in mice as the critical effect, are 0.7, 0.4 and 2 mg/kg bw for BDE-47, BDE-99 and BDE-209, respectively [23,24]. LOAEL for HBCDD exposure was reported at 0.9 mg/kg bw [25]. These are single dose exposures at postnatal day 10 and repeated dose exposure would have been more representative. The exposure concentrations used in the risk evaluation is based on estimated daily milk intake (0.8-610 ng/kg bw) by a newborn infant (3.6 kg bw). Reference margin of safety for PBDEs is $MOS_{reference}$=175, and margin of safety for HBCDD is $MOS_{reference}$=525. MOS_{PBDE} and MOS_{HBCDD} values vary between 660-$2.4^{x}10^{6}$ and 5100-$200^{x}10^{3}$, respectively[15].

Results and discussions

The $MOS_{reference}$ (300) clearly exceeds MOS_{TEQ} (2 and 7), which is an indication that present human $_{PCDD/F}$-TEQ exposure to infants via milk can be considered of concern regarding spermatogenesis. This attempt to estimate the risk of TEQ exposure includes only one toxicological effect. The human TEQ levels in Table 1 does not include TEQ contribution from PCBs. PCBs contributes to around 50% of the total TEQ in various matrices, e.g. human adipose tissue [26] and dairy products [27]. Even though dioxin in the majority of food products are below limit values, many fish products still contain levels of TEQ exceeding the limit values for products to be sold on

the EU market [4]. In February 2006 new revised limit values have been established including both PCDD/Fs and TEQ contributing PCBs. In general, the new values are doubled due to the PCB contribution to the TEQ value.[28]

The MOS_{PBDE} (660-2.4 ^{x} 10^{6}) and MOS_{HBCDD} (5100-200^{x} 10^{3}) clearly exceed the $MOS_{reference}$ (175 and 525, respectively) and the present concentrations of PBDEs and HBCDD reported in European humans are not considered to be of concern. However, for maximum PBDE exposure reported in human milk from Europe[29] are MOS values only factors of 2-10 times below potential critical toxic level. Since this is not a qualified estimation, inclusion of crucial uncertainty factors can have been missed, e.g. acute to chronic exposure extrapolation. The current margin of safety can be low for many individuals with elevated exposure circumstances. Additional to the estimated daily PBDE contribution via milk intake is the cord blood exposure levels of the infant ~2 ng/g fat (Table 1).

A similar estimation of the risk to a foetus in the U.S., based on daily milk intake concentrations of PBDE 1600-9600 ng/day [30], results in alarming MOS_{PBDE} of 150-1600 ($MOS_{reference}$=175). This indicates that infants in the U.S. can be exposed to PBDE levels of concern. Cord serum has been reported to contain mean 40 ng PBDE/g fat, maximum 460 ng/g fat [31]. Additionally, 5% of the U.S. population have PBDE tissue levels greater than 300 ng/g fat, that represents 15 million individuals [30].

In conclusion, the result of this attempt is indicating that the reported present human TEQ levels in Europe (i.e. PCDD/Fs exposure) are of concern. The ratio between threshold levels for adverse health effects and PCDD/F TEQ exposure levels is lower than margin of safety requested by the European Commission.[18]
Average levels of PBDE/HBCDD in the European population are estimated to be of no concern today, but for individuals with intakes at the 95th percentile are the current margins of safety small. A large group of the U.S. population is exceeding the MOS for PBDEs. HBCDD data are too weak for any assessment in the U.S.

This preliminary risk assessment does not take into consideration the so-called cocktail effects of different POPs with synergistic and antagonistic properties, which can decrease the margin of safety considerable.

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