TOX/2020/43

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Review of the implications for risk management based on the EFSA opinion on "Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food"

Introduction

1. In November 2018, the European Food Safety Authority's (EFSA) Panel on Contaminants in the Food Chain (CONTAM) published a new scientific opinion on the "risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food", which is attached in Annex 1 of this review. This EFSA opinion has been previously discussed by the COT in September 2019[1], where it was decided "it was not reasonable to dismiss the conclusions of EFSA regarding acceptable intake".

2. The CONTAM panel established a Tolerable Weekly Intake (TWI) of 2 pg WHO-TEQ/kg bw, which is 7-fold lower than the previous Tolerable Daily intake (TDI) of 2 pg WHO-TEQ/kg bw. This has implications on the UK population where exposures for most of the population prior to the new TWI were below a level of concern exposure but could now at or above a level of concern. This suggests that current risk management measures for dioxin in food, which include regulatory limits and precautionary advice to consumers and are based on the previous TDI, may be inadequate.

3. It would be helpful to the FSA to understand whether the newly proposed TWI is relevant to all consumers and to place the various risks associated with exposure into perspective against other health risks, as well as nutritional benefits from food consumption. Furthermore, the food groups most implicated in exposure to dioxins are also the main dietary sources for a range of other environmental contaminants including several groups that are currently under consideration by EFSA (brominated flame retardants, perfluorinated alkyl substances, chlorinated paraffins).

[1] Minutes of the discussion paper presented in the September 2019 COT meeting can be accessed at: https://webarchive.nationalarchives.gov.uk/20200803163214/https://cot.food.gov.uk/sites/default/files/september2019minutes.pdf

Toxicity

4. Various toxicological endpoints from the animal and epidemiological studies presented in the EFSA opinion are shown in Table 1 and 2.

Table 1. Toxic endpoints of TCDD in animal studies with a reported NOAEL and/or LOAEL body burden (adapted from CONTAM, 2019.

Congener	Toxic endpoints	Dose/ Exposure Level/ POD	Species	Comments/ References
TCDD	**Systemic toxicity**			
			Rodent	
	Decreased **body weight** at 100 ng/kg bw per day. Hypertrophy, dose related toxic hepatic lesions at 46 ng/kg bw/day. Hepatopathy at 100 ng/kg bw/day	Doses (oral): 0, 3, 10, 22, 46, 100 ng/kg bw/day (5 days per week) 0, 2.1, 7.1, 15.7, 32.9 and 71.4 ng/kg bw/day (7 days per week) Duration: 105 weeks NOAEL: 3ng/kg bw/day	Rat (Sprague Dawley) (F)	NOAEL based hepatopathy at 105 weeks. NTP (2006)

		NOAEL body burden: 85 ng/kg bw		
TCDD	Inhibited **body weight gain** at 1,000 ng/kg bw/day. Dose-dependent **increase in liver-to-body weight %** and **thymus-to-body weight %** compared with control. Significant **decreased spleen-to-body weight %** observed at 1000ng/kg bw/day. **Dose dependent increases** in various serum **clinical chemistry** (ALP, AST, TBIL, TBA, TP GLOB, CHOL) and **haematological parameters** (i.e. RBC, haemoglobin and hematocrit). **Dose dependent decrease** in **clinical chemistry** (TRIG and GLUC) and **haematological parameters** (MCV, MCH and PLT). Histopathological changes were observed in liver at ≥ 22 ng/kg	Doses: 0, 3, 22, 100, 300, 1000 ng/kg bw per day Duration: 28 days NOAEL: 100 ng/kg bw per day NOAEL body burden: 789 ng/kg bw	Rat (Sprague Dawley) (F)	NOAEL based on bile duct hyperplasia and thymus atrophy. Harrill et al. (2016)

	bw/day, where dose-related increases in severity of **hepatocellular vacuolation** consistent with fatty change and inflammatory cell foci. Moderate **hepatocellular hypertrophy** at 1000 ng/kg bw/day and mild hepatocellular hypertrophy at 22-300 ng/kg bw/day. Histopathological changes were observed in the thymus at ≥300 ng/kg bw/day. Changes included a **loss of cellularity in the cortex of the thymus.**			
TCDD	**Immunotoxicity**			
			Rodent	
	Suppression of the percentage of LPS-induced IgM+ cells, yet an increment of (ex vivo LPS-induced) proliferation, indicating a dysregulation of the humoral immune response with an effect level in the wild type rats receiving 100 ng/kg. Also there was a **decrease percentage in natural killer cell** at 100 ng/kg.	Doses (oral): 0, 3, 22, 100, 300, 1000 ng/kg/day (5 days) Duration: 4 weeks NOAEL: 22 ng/kg bw/day NOAEL body burden: 250 ng/kg bw	Rat (Sprague Dawley) (M+F)	NOAEL based on distribution of lymphocytes and NK cells. Phadnis-Moghe et al. (2016).
	Reproductive Toxicity			
			Rodent	

TCDD	Reduced daily sperm production in male offspring on PND 70 and 170 and sperm number in epididymis was also reduced.	Doses (s.c): Initial loading dose: 25, 60, 300 ng kg/bw followed by a weekly maintenance dose of 5, 12 or 60 ng/kg bw NOAEL body burden: 25 ng/kg bw	Rat (Wistar) (M)	NOAEL based on decreased sperm production. Faqi et al. (1998)
	Decrease in the no. of alive pups on day 1 and **the number of pups surviving** between days 1-4 the 530 ng/kg diet dose group **Decreased body weight** in the F1 generation 93 and 530 ng/kg diet **Delayed balanopreputial separation** in F1 generation in all dose groups.	Doses (oral): 0, 28, 93, 530 ng/kg diet 0, 2.4, 8 or 46 ng/kg bw/ day (Average dose) Duration: Acute LOAEL: 2.4 ng/kg bw/day LOAEL body burden: 42 and 50 ng/kg bw on GD16 and GD21)	Rat (Wistar) (F)	Bell et al. (2007a) LOAEL based on delayed balanopreputial separation

TCDD	Significantly **lower litter size** (12% lower) in the 1000 ng/kg bw group compared to the control group during lactation (PND21) Reduced body weight gain in the F1 generation in the 1000 ng/kg bw dose group up to PND21. Slightly **reduced body weight** in F1 generation in the 200 ng/kg bw dose group up to PND7. In the 1000 ng/kg bw dose group there was a slight **decrease in testes weight** at PND70 and 120 and lower brain weight on PND120 nad liver to body weight ratios were increased across all dose groups.	Doses (oral): 0, 50, 200, 1000 ng/kg bw (single dose on GD15) Duration: 15 weeks LOAEL: 200 ng/kg bw NOAEL: 50 ng/kg bw NOAEL body burden (GD16): 56.2 ng/kg bw NOAEL body burden (GD21): 58.5 ng/kg bw	Rat (Han Wistar) (F)	Bell et al. (2007b) NOAEL/LOAEL based on decreased pup weight from PND1 to PND7
	Delayed puberty development of male F1 rats. F1 males at PND70 and PND120 had a proportion of **abnormal sperm** at the highest dose at PND70.	Doses: 0, 2.4, 8 or 46 ng TCDD/kg bw per day (diet) LOAEL: 2.4 ng/kg bw per day	Rat (Han Wistar) (M)	Bell et al. (2007c)

TCDD	~10% **decrease in testes weight** at PND70.	LOAEL body burden: 42 and 50 ng/kg bw on GD16 and GD21 respectively)		
	Embryo loss possibly sue to accumulation of TCDD in the uterus.	Doses: 0, 2, 50, 100 ng/kg bw (oral exposure) Duration 8 days NOAEL: 2ng/kg bw NOEL body burden: 9 ng/kg bw (GD1-3) NOAEL body burden: 25 ng/kg bw (GD 1-8)	Mouse (NIH) (F)	Li et al. (2006)
	Carcinogenicity			
			Rodent	
	Significant increase in hepatocellular adenomas and cholangiocarcinomas at 100 ng/kg bw/day.	Doses: 0, 3, 10, 22, 46,100 ng/kg bw/day (5 days per week)	Rat (Sprague-Dawley) (F)	NOAEL based on hepatopathy at 105 weeks. NTP (2006)

		0, 2.1, 7.1, 15.7, 32.9 and 71.4 ng/kg bw/day (7 days per week) Duration:105 weeks NOAEL: 3 ng/kg bw/day NOAEL body burden: 85 ng/kg bw		
TCDD	**Tooth and bone development**			
			Rodent	
	Decreased tibial length in LE rats at ≥17 µg/kg and in HW rats at 170 µg/kg. **Dose-dependent decrease in bone cross sectional size** in LE rats from 1.7 µg/kg. **Breaking forces of tibia and other bone parameters were reduced** by TCDD in HW rats at 170 µg/kg and 17µg/kg in LE rats.	Doses (s.c.): Cumulative doses: 0.17, 1.7, 17, 170 µg/kg via loading doses of 0.035, 0.35, 3.5 and 35 ng/kg bw/day. Followed by weekly maintenance doses:	Rat (Han wistar and long evans) (F)	NOAEL based on decreased tibia length, tibia geometry parameters, tibia ash weight and increased plasma ALP activity. Jämsä et al. (2001)

TCDD		0.007, 0.07, 0.7 and 7ng/kg bw/day. Calculated daily doses: 1, 10, 100, 1000 ng/kg bw/day Duration: 20 weeks NOAEL: 1ng/kg bw/day NOAEL body burden: 28 ng/kg bw		

Table 2. Toxic endpoints of dioxin congeners (TCDD, PCDDs, PCDFs, DL-PCBs) (Adapted from CONTAM, 2018)

Congener	Toxic endpoints	Dose/ Exposure Level/ POD	Species	Comments/ References
TCDD	**Immunotoxicity**			
			Human	
	A study in the Seveso area showed subjects from the zones contaminated by TCDD showed **lower plasma IgG levels** compared to subjects from the surrounding reference area. Plasma IgG decreased with increasing lipid-adjusted TCDD plasma concentration (r =-0.53; p=0.0002).	Exposure: 3.5 – 90 pg/g fat in blood (plasma) Duration: 20 years after exposure	Human (sex not specified)	Seveso study (Italy, Seveso) Baccarelli et al. (2004)
	Reproductive Toxicity			
			Rodent	
	Repeated dosing of TCDD resulted in **reduced ventral prostrate weight** in F1 rats and a **decreased male/female ratio** in their F2 offspring.	Doses Loading dose (administered to dams prior to mating): 400 ng/kg bw Weekly maintenance doses (administered during mating, pregnancy, lactation):	Rat (Holtzman rats) (F)	Ikeda et al. (2005)

		80 ng/kg bw NOAEL: not stated		
	Gestational TCDD exposure resulted in **abolished gender differences in the anteroventral periventricular nucleus expression of enzyme;** glutamic acid decarboxylase 67.	Doses: 1 µg/kg NOAEL: n/a	Rat (M +F)	Hays et al. (2002)
TCDD	A dose dependent **reduction in male/female ratio** was recorded when male mice were treated with TCDD prior to mating.	Initial loading dose: 2 or 2000 ng/kg Weekly maintenance dose: 0.4, 400 ng/kg NOAEL: not stated	Mouse (M)	Ishihara et al. (2007)
	At the two-cell embryo stage, the **proportion of male embryos was significantly lower** compared to the control group, suggesting a **diminished ability of Y-bearing sperm to conceive the ova**.	Initial loading dose: 2000 ng/kg Followed by a weekly maintenance dose: 400 ng/kg (TCDD2000/400 group). NOAEL: n/a	Mouse (M)	Ishihara et al. (2010)

			Human	
	Children (1-9 years) exposed to TCDD had negative associations with **sperm concentration** (53.6 vs 72.5 million/mL), **progressive motility** 33.2 vs 40.8%, **motile sperm count** 44.2 vs 77.5 x106.	Measurement of exposure: TCDD Median TCDD at time of explosion: 210 pg/g fat (blood) Median TCDD in control group: ≤15 pg/g fat. Duration: 22 years	Human (M)	Seveso Cohort (Italy, Seveso) Mocarelli et al. (2008)
TCDD	**Impaired semen quality** in men born and breastfed to mothers exposed in the Seveso incident. Sons who were breastfed by mothers who had TCDD levels of 19 pg/g after exposure had **lower sperm concentration** (36.3 vs 86.3 million/mL), **total sperm count** (116.9 vs 231.1 x 106), **progressive motility** (35.8 vs 44.2%) and **total motile count** (83.7 vs 98 million) compared to breastfed controls.	Measurement of exposure: TCDD Median TCDD (at conception calculated for 20-42 years of age using a TCDD half-life of 4 years) Mothers who breast-fed: 19 pg/g fat (maternal blood) Duration: 18-26 years	Human (M+F)	Seveso Cohort (Italy, Seveso) Mocarelli et al. (2011)

TCDD	Every 10-fold increase in serum TCDD resulted in a 25% **increase in time to pregnancy** and a doubling in odds of **infertility.**	Measurement of exposure: TCDD Median TCDD at time of exposure: 50 pg/g fat Extrapolated to time of conception: 13.4 pg/g fat Duration: >20 years	Human (M+F)	Seveso Women's Health Study (SWHS) Eskenazi et al. (2010)
	Increased probability of female births (**lower sex ratio**) with increasing serum TCDD concentrations from fathers (p=0.008).	Measurement of exposure: TCDD Median TCDD levels in blood – Fathers: 96.5 pg/g fat Median TCDD levels in blood - Mothers:		Seveso study (Italy, Seveso) Mocarelli et al. (2000)

		62.75 pg/g/fat Duration: n/a		
	Endocrine mediated activity			
			Rodent	
TCDD	Significant **Decreased T4 levels** by 14 weeks at 22 ng/kg bw/day.	Doses (oral): 0, 3, 10, 22, 46, 100 ng/kg bw/day (oral) 0, 2.1, 7.1, 15.7, 32.9 and 71.4 ng/kg bw/day (7 days per week) Duration: 105 weeks NOAEL: 3ng/kg bw/day NOAEL body burden: 85 ng/kg bw	Rat (F) (Sprague Dawley)	NOAEL based on hepatopathy at 105 weeks. NTP (2006)
			Human	
	Women who were premenarcheal at time of explosion, a 10-fold increase in serum TCDD level was associated with a **lengthening of the menstrual cycle** by 0.93 days and reduction of the odds of scanty menstrual flow.	Measurement of exposure: TCDD Median plasma TCDD levels: 67.5 pg/g fat Duration: 20-21 years		Seveso Women's Health Study (SWHS) (Italy, Seveso) Eskenazi et al. (2002)

TCDD	Higher proportion of children with **neonatal blood thyroid-stimulating hormone** (b-TSH) that was ≥5 µU/mL) who were born to mothers highly exposed in Seveso (Zone A). The proportion of children in Zone A with b-TSH levels ≥5 µU/mL was 16.1% compared to 4.9% in Zone B and 2.8% in the reference area (Zone R). TSH decreased with order of siblings in zone A and B, but not in Zone R. In a subgroup, neonatal blood TSH was significantly associated with TCDD levels.	Measurement of exposure: TCDD 17 PCDD/Fs 12 DL-PCBs Median TCDD levels in individuals 1-2 year after the accident (1977-1978): Zone A (very high contamination) = 447 pg/g fat (blood) Zone B (high contamination) = 94 pg/g fat (blood) Zone R (non-contaminated area) = 48 pg/g fat (blood) Mean TCCD levels in newborns with b-TSH ≥5 µU/mL: 39 pg/g fat (blood) Mean total TEQ levels in newborns with b-TSH ≥5 µU/mL:	Human (M+F)	Seveso Cohort (Seveso, Italy) Data on timing of TSH blood is missing, making quantitative association between TCDD and TSH uncertain in subgroup, as TSH can decrease by a factor of 5-10 in the first 2-3 days after birth. Baccarelli et al. (2008)

TCDD		84.5 pg/g fat (blood) Duration: 25 years		
	Increased levels of dioxin-like substances in adipose tissue in patients with **deep infiltrating endometriosis** (**DIE).**	Measurement of exposure: TCDD 17 PCDD/Fs 12 DL-PCBs Median TCDD (cases): 0.70 pg/g fat (adipose tissue) Median TCDD (controls): 0.40 pg/g fat (adipose tissue) Duration: n/a OR (TCDD): 1.41	Human (F)	Spain, Catalonia Martınez-Zamora et al. (2015)
	Carcinogenicity			
			Human	
	Increased SMR for **total cancer mortality; 1.41**	Measurement of exposure: TCDD Mean TCDD: 101.3 pg/g fat	Human (M)	Hamburg, Germany Becher et al. (1998)

TCDD	For workers exposed to TCDD dermally the SMR (all **cancers** combined) = 1.13. No marked specificity for any one cancer type was noted. Statistically significant positive linear trends in SMRs with increasing exposure for all cancer combined and **for lung cancer.** Regression analyses showed a significant trend for cancer with a 15-year lag time. The excess cancer was limited to the highest exposure group who were likely exposed to 100-1000 times the concentrations of the general population.	A cumulative exposure score of 20,000, which was the cut-off between septiles 6 and 7 would correspond to estimated exposure of: 38,000 pg/g-years (lipid adjusted) (e.g. mean serum TCDD level: 2,000 pg/g fat (over a 20-year period) *Cumulative exposure scores were calculated for each production plant exposure scores based on Job Exposure Matrix, calibrated against serum TCDD in subgroup. Duration/ Follow up: 15-57 years	Human (M)	USA Steenland et al. (1999)
	Mortality in men in Zones A and B increased for: **all cancers** (RR = 1.3), **rectal cancer** (RR = 2.4), **lung cancer** (RR = 1.3) RR increased after 15 years for lung and rectal cancer.	Measurement of TCDD: TCDD Median TCDD levels - (Zone A): 447 pg/g fat (1976-77)	Human (M+F)	Seveso study (Italy, Seveso) Bertazzi et al. (2001)

TCDD	Excess of **lymphohaematopoietic neoplasms** in both genders (RR=1.7) Risk of Hodgkin's disease elevated in the first 10 years observation period (RR=4.9), whereas the highest increase for **non-Hodgkin's lymphoma** (RR=2.8) and **myeloid leukaemia** (RR=3.8) occurred after 15 years.	73.7 pg/g fat (1993-94) Median TCDD levels (blood) - Zone B: 94 pg/g fat (1976-77) 12.4 pg/g fat (1993-94) Median TCDD levels (blood) -Zone R: 48 pg/g fat (1976-77) Median TCDD levels (blood) – Reference: 5.5 pg/g fat (1993-4)		
	A positive trend between increasing cumulative TCDD exposure and cancer mortality**.** Excess lifetime risk of dying of cancer at an intake of 1 pg/kg bw/day was 0.05-0.9% above a background lifetime risk of cancer death of 12.4%.	Measurement of exposure: TCDD Estimated mean cumulative serum TCDD levels at end of follow-up: 343 pg/g Estimated mean cumulative serum TCDD levels at end of exposure: 1,589 pg/g	Human (M)	USA Steenland et al. (2001)

TCDD	Individual serum TCDD levels in women aged 20 to ≥50 years correlated with **breast cancer incidence** at 20 years after the incident. Hazard ratio (HR) for breast cancer in women with a mean age of 50.8 years increased to 2.1 and was associated with a 10-fold increase in serum TCCD (Warner et al., 2002). The adjusted HR of 1.8 associated with a 10-fold increase in serum TCDD for **all cancers** combined significantly increased. For breast cancer, the adjusted HR of 1.44 was increased but not significantly and the increased risk for breast cancer seen in earlier studies not sustained.	Measurement of exposure: TCDD Warner et al. (2002): Median blood (serum) TCDD levels in breast cancer cases: 71.8 pg/g fat Median blood (serum) TCDD levels in non-cancer cases: 55.1 pg/g Warner et al. (2011): Mean blood TCDD levels in cancer cases: 95.3 pg/g fat. Mean blood TCDD levels in non-cancer cases: 67.9 pg/g fat	Human (F)	Seveso Women's Health Study Warner et al. (2002); Warner et al. (2011)
	Increased risk of **lymphatic** and **haematological cancer** in both TCDD exposed zones. Zone A (6 deaths): RR=2.23 Zone B (28 deaths): RR=1.59	Measurement of exposure: TCDD Median TCDD levels (blood) - Zone A:	Human (M+F)	Seveso Cohort (Italy, Seveso) Consonni et al. (2008)

TCDD		447 pg/g fat (1976-77) 73.3 pg/g fat (1992-96) Median TCDD levels (blood) – Zone B: 94.0 pg/g fat (1976–77) 12.4 pg/g fat (1992–96) Median TCDD levels (blood) – Zone R: 48 pg/g fat (1976-77) Median TCDD levels (blood) -Reference: 5.5 pg/g fat (1992-96) Duration/ follow up: 25 years	Human (M+F)	
	Increased risk of **lymphatic** and **haematological cancer** in both exposed zones: Zone A – RR=1.39 Zone B – RR=1.56 Increased risk of **breast cancer** in zone A after 15 years since the accident: RR=2.57	Measurement of exposure: TCDD Median TCDD levels (blood) - Zone A: 447 pg/g fat (1976-77) 73.3 pg/g fat (1992-96)		Seveso Cohort (Italy, Seveso) Pesatori et al. (2009)

TCDD		94 pg WHO_{2005}-TEQ/g fat (1993-94) Median TCDD levels (blood) – Zone B: 94 pg/g fat (1976–77) 12.4 pg/g fat (1992–96) 43.2 pg WHO_{2005}-TEQ/g fat (1993-94) Median TCDD levels (blood) – Zone R: 48 pg/g fat (1976-77) Median TCDD levels (blood) -Reference: 5.5 pg/g fat (1992-96) 38.8 pg WHO_{2005}-TEQ/g fat (1993-94) Duration/follow-up: 20 years		
	Greater number of death from **NHL** (SMR =1.3), **leukaemia** (SMR = 1.9) than expected and there were 4 deaths from **soft tissue sarcoma** (SMR= 4.1).	Measurement of exposure: TCDD TCDD levels (blood) - workers in trichlorophenol units: 15.9 pg/g fat	Human (sex not stated)	Michigan, US Collins et al. (2009a)

		TCDD levels (blood) in-worker referents =6.5 pg/g fat		
TCDD	There was an increase in the (SMR = 2.4) for **NHL**.	Measurement of exposure: TCDD TCDD levels (blood) - workers in trichlorophenol units: 15.9 pg/g fat TCDD levels (blood) in-worker referents: 6.5 pg/g fat	Human (sex not stated)	Michigan, US Collins et al. (2009b)
	Sufficient evidence in humans for **carcinogenicity** of TCDD (Group 1 carcinogen).		Human (M+F)	Based on data from experimental animals, epidemiological studies, and from the common mechanism of action. IARC, 2012
	Exposure to TCDD in a herbicide plant was associated with increased standardised mortality ratio (SMR) for **respiratory cancer** (SMR =1.64), **oesophageal cancer** (SMR = 2.56) and **rectum cancer** (SMR = 1.96) in men. In	Measurement of exposure: TCDD Median TCDD levels: 77 pg/g fat	Human (M+F)	Germany, Hamburg Manuwald et al. (2012)

	women, exposure was associated with an increased in breast cancer in women (SMR = 1.86).	Duration/ follow up: 23 year		
TCDD	**Neurotoxicity**			
			Human	
	Increased risk of children not being able to perform each milestone in mothers who had exposure >38 pg CALUX-TEQ/g lipid. Significant odds ratio identified between one **developmental milestone** (i.e. cannot crawl) at 6 months of age and dioxin -like activity >38 pg CALUX-TEQ/g lipid in plasma.	Measurement of exposure: CALUX determined bioanalytical equivalent (BEQ) levels 7, 19.6, 38.2, 56.6, 134.6pg CALUX-TEQ/g lipid (5th, 25th, 75th and 95th percentiles of plasma samples pg BEQs/g fat Duration: n/a	Human	Danish National Birth Cohort (Denmark) Authors stated that bioassay results may be confounded by PAHs Halldorsson et al. (2009) .
	Tooth and bone development			
			Rat	
	In utero exposure on GD15 or lactational exposure to TCDD, resulted in reduced size or prevented the development of	Doses (oral): 0.03, 0.1, 0.3, 1 µg/kg bw (single dose) NOAEL = not stated	Rat (Han Wistar) (F)	Kattainen et al. (2001)

	the third lower molars of rat pups.	Duration: 5-10 weeks		
TCDD	Administration of TCDD to lactating dams on day 1 after delivery resulted in half of pups **lacking one or more third molars** by day 22 and total lack of mineralisation in third molar cusps.	Doses (i.p injection): 50, 1000 µg/kg bw (single dose) NOAEL: not stated	Rat (Han Wistar) (F)	Lukinmaa et al. (2001)
	TCDD administered to dams resulted in **absence of third molars in pups** exposed in utero and via lactation. The frequency of missing molars was greater the earlier the dam was exposed: 100%, 88% and 50% of the offspring exposed on GD11, GD 13 and GD19 respectively.	Doses: 1 µg/kg bw NOAEL: n/a	Rat (Dioxin-sensitive line C rats) (F)	Miettinen et al. (2002)
	Cariogenic lesions were detectable in the enamel of pup molars who received 0.03 µg/kg.	Doses (oral): 0.03, 0.1, 0.3, 1 µg/kg (single dse) NOAEL: not stated	Rat (Dioxin-sensitive line C rats) (F	Miettinen et al. (2006)
			Monkey	

	Tooth abnormalities observed in the 300 ng/kg group when exposed during gestation (on GD20) and lactation.	Doses (s.c injection): 0, 30, 300 ng/kg Duration: 3-10 years NOAEL: not stated	Monkey (Rhesus macaque) (F)	Yasuda et al. (2005)
			Human	
TCDD	**Enamel defects:** 24% (27/113) of all subjects had enamel defects. 93% of subjects (25/27) with enamel defects were <5 years of aged at the time of the accident. Zone ABR subjects and zone non-ABR subjects had prevalence of tooth defects in those <5 years of age was 42% (15/36) and was 26% (10/39) respectively. Enamel defects in zone ABR correlated with TCDD levels: T1 = 1/10, T2 = 5/11, T3=9/15 (p=0.016). OR = 2.4 (for enamel defects in T2 and T3, with non-ABR children as referent population) **Hypodontia:**	TCDD concentration in zone ABR Median: 476 pg/g fat T1: 31-226 pg/g fat T2: 238-592 pg/g fat T3: 700-26,000 pg/g fat TCDD concentration in zone non-ABR Concentration was indicated by 2 pooled samples from children with 33.4 and 47.6 ng TCDD/g fat *T1-T3 = Tertile 1-3 Duration/ follow up: 25 years	Human (M+F)	Seveso Cohort (Italy, Seveso) Alaluusua et al. (2004)

TCDD	Lateral incisors or second premolars were missing in 12.5% (6/48) of subjects from zone ABR and in 4.6% (3/65) of non-ABR subjects. Frequency increased with serum TCDD level (p=0.005). *Zone A and B = contaminated areas. *Zone R = lightly contaminated areas.			
TCDD/ PCDD/Fs	**Carcinogenicity**			
			Human	
	The total **cancer** SMR was 1.41, with TCDD showing a significant trend in SMR and elevated risk of total cancer with increasing PCDD/F exposure.	Measurement of exposure: TCDD, PCDD/Fs Mean TCDD: Males: 108 ng/kg fat (blood) Females: 110.5 ng/kg fat (blood) Mean TEQO:	Human (M+F)	

TCDD/ PCDD/Fs		Males: 142 ng/kg fat (blood) Females: 62.7 ng/kg fat (blood) *PCDD/F calculated as TEQO		
PCDD/Fs/ DL-PBCs	**Genotoxicity**			
			Cow	
	Higher levels of dioxin in milk of exposed cows (Farm A) than both those permitted (i.e. 6 pg/g fat) and those reached in the control (Farm B). Increase in **chromosome aberrations** but no significant effect on sister chromatid exchange (SCE) in cows in Farm A	Measurement of exposure: 17 PCDD/Fs 12 DL-PCBs Doses - Sum of PCDDs, PCDFs and DL-PCBs in exposed (Farm A): 21.79 pg/g fat (milk) Doses - Sum of PCDDs, PCDFs and DL-PCBs in control (Farm B): 1.3 pg/g fat (milk) NOAEL: not stated	Ruminant (buffalo Cow)	Genualdo et al. (2012)

PCDD/Fs/ DL-PBCs	Increase in **chromosome aberrations** and slight increase in **SCE in lymphocytes** in cows from two farms with higher levels dioxin than those permitted (6.0 pg/g fat) and those in controls groups.	Measurement of exposure 17 PCDD/Fs 12 DL-PCBs Doses (Sum of PCDDs, PCDFs and DL-PCBs in Group B - control): 1.75 pg/g fat – Iannuzzi et al. (2009); Di Meo et al. (2011) Doses (Sum of PCDDs, PCDFs and DL-PCBs in Group A): 18.56 pg/g TEQ/g fat – Iannuzzi et al.(2009) Doses (Sum of PCDDs, PCDFs and DL-PCBs in Farm B: 8.56 pg/g TEQ/g fat (milk) – Di Meo et al. (2011)	Buffalo cows	Iannuzzi et al. (2009); Di Meo et al. (2011)
	Reproductive toxicity			
		Human		
	A prospective cohort study found an association of	Measurement of exposure:	Human (M+F)	

PCDD/Fs /DL-PCBs	maternal dietary exposure to dioxins and PCBs during pregnancy and increased risk of the **occurrence of wheeze** and **upper respiratory infection** in young children. A **reduced antibody response** to measles vaccination was also identified.	17 PCDD/Fs 12 DL-PCBs Median dietary intake of PCDD/Fs, and DL-PCBs: 0.58 pg WHO_{2005}-TEQ/kg bw/day Duration/follow up: 1 year Stolevik et al., (2011) Median dietary intake of PCDD/Fs, and DL-PCBs: 0.59 pg WHO_{2005}-TEQ/kg bw/day Duration/follow up: 3 years Stolevik et al., (2013)		BraMat (MoBa subcohort, Norway) Stolevik et al. (2011, 2013)
	Changes in time of **pubertal onset** (timing and growth) and **sexual maturity** and **altered**	Measurement of exposure: 17 PCDD/Fs	Human (M+F)	The Russian Children's Study. The CONTAM panel considered that there was

PCDD/Fs and/DL-PCBs	**semen parameter** in boys born to mothers exposed to dioxin. An association between sum of dioxins and PCBs in boys at the time of enrolment (aged 8-9 years) and earlier onset of **genitalia stage 2** in offspring at ages 11-12. PCDD was associated with decreased sperm parameters (sperm concentration, sperm count and motile sperm count) in men.	10 DL-PCBs (-77, -81, -126, -169, -105, -118, -156, -157, -167, -189) Median sum of PCDD/Fs and PCBs in blood of boys aged 8-9 years (pg WHO_{2005}-TEQ/g fat): Q1 = 4-14.5 Q2 = 14.6-21 Q3 = 21.1-33.2 Q4 = 33.3-174.7 Median = 21.1 – Burns et al. (2016) Mean total TEQ levels in boys at age of enrolment (8-9 years old) pg WHO_{2005}-TEQ/g fat (blood) Total TEQ=27.7 PCDD = 10.6 PCDF = 7.0 PCB = 8.1 – Korrick et al. (2011)		insufficient information to conclude on causal associations. (Korrick et al. (2011); Burns et al., 2016; Mınguez-Alarcón et al. (2017)

PCDD/Fs/ DL-PCBs		Median TEQ levels pg WHO^{2005}-TEQ/g fat in (blood) PCDD = 8.7 - Minguez-Alarcón et al. (2017)		
	Perinatal BEQ exposure associated with **increased growth** between 0 and 24 months.	Measurement of exposure: CALUX determined BEQ levels Mean (FLEHS I): 31.2 pg BEQ/g fat (cord serum) Mean (HUMIS): 7.9 pg BEQ/g fat (milk) Mean (Slovak PCB): 15.5 BEQ/g fat (milk)	Human (M+F)	Pooled analysis of 3 European birth cohorts: HUMIS (Norway) FLEHS I (Belgium) Slovak PCB (Slovakia) Iszatt et al. (2016)
	Significant inverse associations between **birth weight** for total PCDD-TEQ, PCDF-TEQ and PCB-TEQ levels in maternal blood from the Yusho cohort among male infants but not females.	Measurement of exposure: 17 PCDD/Fs 4 DL-PCB (-77, -81, -126, -169) Mean total TEQ:	Human (M+F)	Yusho Cohort (Japan, Western Japan) Tsukimori et al. (2012)

PCDD/Fs and/DL-PCBs		68.92 pg/g fat (maternal blood - Yusho) 23.36 pg/g fat (blood - general pop.) Mean total PCDDs TEQ: 16.01 pg/g fat (maternal blood - Yusho) 10.66 pg/g fat (blood - general pop.) Mean total PCDFs TEQ: 41.98 pg/g fat (maternal blood - Yusho) 4.09 pg/g fat (blood – general pop.) Mean total PCB TEQ: 10.93 pg/g fat (maternal blood – Yusho) 8.49 pg/g fat (blood - general pop.)		
	A negative trend reported with current exposure to PCDD/Fs and DL-PCBs for **age of first**	Measurement of exposure: 17 PCDD/Fs	Human (M)	Amsterdam/Zaandam Cohort (The Netherlands) Leijs et al. (2008)

PCDD/Fs and/DL-PCBs	**ejaculation** in boys aged 14-19 years.	3 DL-PCBs (-77, -126, -169) Median PCDD/F-TEQ: 28.6 pg I-TEQ/g fat (milk) Median current PCDD/F-TEQs exposure: 2.3 pg WHO_{2005}-TEQ/g fat (blood) Median current DL-PCB-TEQs exposure: 1.5 pg WHO_{2005}-TEQ/g fat (blood)		
	DL-PCBs were negatively correlated with **breast development** in girls (p=0.04, OR =0.56)	Measurement of exposure: CALUX determined BEQ levels Mean DL-PCBs: 32.1 pg BEQ/g fat (blood)	Human (F)	Flemish Environment and Health Study (FLEHS II) Croes et al. (2014)
	Immunotoxicity			
			Human	

PCDD/Fs/ DL-PBCs	PCDD/Fs and PCBs showed an inverse relationship with **atopic dermatitis** and **rhinitis**.	Measurement of exposure: 17 PCDD/Fs 12 DL-PCBs Percentiles (WHO_{2005}-TEQ/g fat): 5% = 4.8 25% = 9.7 50% = 16 75% 25 95% = 45 Duration: 8 years	Human (M+F)	(Japan) Nakamoto et al. (2013)
	Prenatal exposure of PCDFs were associated with a significantly increased risk of **otitis media**, especially among male infants (OR=2.5). Whereas exposure of PeCDF were associated with significantly increased risk of otitis media (OR=5.3). Weak association between dioxin-like compounds levels and allergic symptoms in infancy.	Measurement of exposure: 17 PCDD/Fs 4 DL-PCBs (-77, -81, -126, -169) Median total TEQs: 13.89 pg WHO_{2005}-TEQ/g fat Median PCDDs-TEQ: 6.92 pg WHO_{2005}-TEQ/g fat Median PCDFs-TEQ:	Human (M+F)	Hokkaido Study on Environment and Children's Health (Japan) The CONTAM panel considered that due to the extended number of outcomes measures, chance findings are likely. Miyashita et al. (2011)

		2.38 pg WHO_{2005}-TE/g fat Duration: 3 years		
	Endocrine mediated activity			
			Human	
PCDD/Fs/ DL-PCBs	Play behaviour in children in the Dutch cohort showed that higher PCDD/Fs in maternal milk was associated with higher scores on the feminine subscale scale of the Pre-School Activity Inventory (PSAI) in both sexes, indicating more **feminized play behaviour** in both sexes. Sum of PCBs in milk was associated with masculine play behaviour.	Measurement of exposure: 17 PCDD/Fs 6 DL-PCBs (-77, -126, -169, -105, -118, -156) Median PCDD/Fs Breast-fed boys: 36.6 WHO_{1998}-TEQ ng/kg fat Breast-fed girl: 36 WHO_{1998}-TEQ ng/kg fat Median DL-PCBs Breast-fed boys: 28.8 TEQ ng/kg fat Breast-fed girls: 28.8 TEQ ng/kg fat	Human (M+F)	Dutch PCB/dioxin cohort (Rotterdam, The Netherlands) Vreugdenhil et al. (2002)

PCDD/Fs/ DL-PCBs	Increased exposure to DL-compounds was associated with **endometriosis** in a case control women. Age adjusted OR = 2.44 for patients with low concentrations and group with high concentrations of DL-compounds OR (for moderate and severe endometriosis) =3.0	Measurement of exposure: CALUX determined BEQ levels Controls: 19.4 pg BEQs g/fat (in blood plasma) Endometriosis: 21.2 pg BEQ g/fat (in blood plasma) Duration: n/a	Human (F)	(Belgium, Leuven) Simsa et al. (2010)
	DL-PCB and PCDD/Fs were positively correlated with **free T4 hormone.**	Measurement of exposure: CALUX determined BEQ levels Mean PCDD/Fs: 108 pg BEQ/g fat (blood) Mean PCBs: 32.1 BEQ/g fat (blood)	Human (M+F)	Flemish Environment and Health Study (FLEHS II) Croes et al. (2014)
	ORs for **deep infiltrating endometriosis** (DIE) and ovarian endometrioma (OvE): DIE vs controls = 1.82	Measurement of exposure: 17 PCDD/Fs 12 DL-PCBs	Human (F)	France Ploteau et al. (2017)

PCDD/Fs and/or DL-PCBs	DIE + OvE vs controls = 2.86 DIE only vs controls = 1.39	(Median) Controls: 9.88 pg WHO_{2005}-TEQ/g fat (adipose tissue) Median (DIE): 8.94 pg WHO_{2005}-TEQ/g fat (adipose tissue) Median (DIE+OvE): 14.36 pg WHO_{2005}-TEQ/g fat (adipose tissue)		
	Significantly increased risk of **deep endometriotic (adenomyotic) nodules** (DEN) (OR= 3.3) for an increment of 10 pg in total TEQ levels/g fat. A marginal significant increased risk found for **peritoneal endometriosis** (PEND) (OR=1.9) for total TEQ levels and for PCDD/Fs alone (OR=3.2)	Measurement of exposure: 17 PCDD/Fs 12 DL-PCB PCDD/F-TEQs in blood: Controls: 15.5 pg WHO_{1998}-TEQ/g fat (blood) PEND: 20.9 pg WHO_{1998}-TEQ/g fat (blood)	Human (F)	Belgium Heilier et al. (2005)

PCDD/Fs /DL-PCBs		DEN: 26 pg WHO_{1998}-TEQ/g fat (blood) DL-PCBs-TEQs Control: 8.5 pg WHO_{1998}-TEQ/g fat (blood) PEND: 11 pg WHO_{1998}-TEQ/g fat (blood) DEN: 12.4 pg WHO_{1998}-TEQ/g fat		
	Placental dioxin levels were higher in women (age ≥ 19 years) with **irregular menstrual cycles** compared to women (≤ 18 years) with regular menstrual cycle at 18 years old. Placental DL-PCB-TEQ level was higher in women with menstrual cycles longer than 33 days vs. less than 33 days (p=0.006).	Measurement of exposure: 17 PCDD/Fs 12 DL-PCBs Mean PCDD/F-TEQ (placenta): 10.7 pg WHO-TEQ/g fat Mean DL-PCB-TEQs (placenta): 2.92 WHO-TEQ/g fat	Human (F)	Taiwan, Central Taiwan, Taichung Chao et al. (2007)

PCDD/Fs /DL-PCBs		Mean Total TEQs (placenta): 13.6 pg WHO-TEQ/g fat		
	Positive associations between total TEQs (PCDD/Fs and DL-PCBs) and **T3 and thyroxine binding globulin (TBG)** in female newborns who were exposed in utero.	Measurement of exposure: 17 PCDD/Fs 12 DL-PCBs Mean PCDD/Fs and DL-PCBs TEQs: 16.2 pg WHO_{1998}-TEQ/g fat (placenta)	Human (F)	Part of a prospective study of dioxins/PCBs for the general population (Taiwan) Wang et al. (2005)
	Significant interactions between sex and exposure, increased **feminine behaviour** was observed in boys (0= 3.24, whereas girls had decreased feminine behaviour (B=-3.59 when exposed to increases sum of PCDD/Fs and DL-PCB in maternal milk.	Measurement of exposure: 17 PCDD/Fs 12 DL-PCBs 21.5 pg WHO_{2005}-TEQ/g fat (maternal blood): 20.5 pg WHO_{2005}-TEQ/g fat (milk)	Human (M+F)	A follow up study of the Duisburg birth Cohort Winneke et al. (2014)
	Carcinogenicity			
			Human	

PCDD/Fs/ DL-PCBs	Total PCDFs were associated with a 3.5-fold increased risk for **NHL** in the highest quartile compared to lowest quartile and a significant trend across quartiles was observed (P=0.006). PCB congeners: PCB-156, PCB-180 and PCB-194 were also associated with increased risk of NHL ranging from 2.7 to 3.5-fold in the highest quartile compared to the lowest quartile.	Measurement of exposure: 17 PCDD/Fs 4 DL-PCBs (-77, -81, -126, -169) Levels divided into quartiles: Total PCDFs pg WHO_{1998}-TEQ/fat (blood): ≤2.94 >2.94-4.75 >4.75-6.89 >6.89 Total PCBs pg WHO_{1998}-TEQ/fat (blood): ≤6.40 >6.40-8.69 >8.69-13.17 >13.17	Human (M+F)	(USA - Iowa, Los Angeles County, metropolitan areas of Detroit and Seattle) De Roos et al. (2005)
	Immunotoxicity			
			Human	
	DL-PCBs were positively associated with the **development of animal allergy** (p=0.02, OR=1.46).	Measurement of exposure:	Human (M+F)	Flemish Environment and Health study (FLEHS II) Croes et al. (2014)

	Higher levels of PCDD/Fs were associated with a higher risk for **development of animal allergy** (p=0.03, OR=1.60) and **asthma** (p=0.004, OR = 1.42).	CALUX determined BEQ levels Mean PCDD/Fs: 108 pg BEQ/g fat (blood) Mean DL-PCBs: 32.1 pg BEQ/g fat (blood)		
PCDD/Fs/ DL-PCBs	Association found between exposure to PCDD/Fs and DL-PCBs in mothers breast milk and an **increased ratio of CD4/CD8 cells**, as well as an **increased percentage of CD3 cells** in children.	Measurement of exposure: 17 PCDD/Fs 3 DL-PCBs Median: 23 pg WHO_{1998}-TEQ/g fat (human milk)	Human (M+F)	The CONTAM panel concluded the clinical relevance of this finding to be unclear. Nagayama et al. (2007b)
	Negative effect on **polymorphic neutrophils** found in adolescents with higher current DL-PCB levels (p=0.021). In the neonatal period this negative effect was seen with prenatal PCDD/F exposure.	Measurement of exposure: 17 PCDD/Fs 3 DL-PCBs (-77, -126, -169) Mean prenatal exposure: 32.6 pg I-TEQ/g fat Mean current DL-PCB exposure:	Human (M+F)	Amsterdam/Zaandam Cohort (The Netherlands) Leijs et al. (2009)

		2.2 pg WHO_{2005}-TEQ/g fat (serum)		
	Neurotoxicity			
			Human	
PCDD/Fs/ DL-PCBs	Boys and girls aged 3 years who had mothers with high maternal dietary exposures of PCDD/Fs and DL-PCBs was associated with higher odds of **incomplete grammar** (OR =1.1) in boys and **severe language delay** (OR=2.9) in girls.	Measurement of exposure: 17 PCDD/Fs 12 DL-PCBs High maternal dietary exposure: >14 pg WHO_{2005}-TEQ/kg bw per week Low maternal dietary exposure: ≤14 pg WHO_{2005}-TEQ/kg bw per week	Human (M+F)	Norwegian Mother and Child Cohort study (MoBa) Cohort (Norway) Caspersen et al. (2016)
	Reproductive toxicity			
			Human	
PCDD/Fs, DL-PCBs and NDL-PCBs	Boys born to mothers exposed to TCDD had an association with maternal sum PCBs and **earlier onset of genitalia stage**	Measurement of exposure: 17 PCDD/Fs	Human (M+F)	The Russian Children's Study (Humblet et al. (2011)

PCDD/Fs, DL-PCBs and NDL-PCBs	**2** in offspring at age 11 to 12 years. Boys breast fed for >6 months there was a dose related **delay in pubertal onset** assessed by genital staging 2 and increasing quartiles of maternal total	10 DL-PCBs (-77, -81, -126, -169, -105, -118, -156, -157, -167, -189) NDL-PCBS Median Maternal Total TEQ: 25 (pg WHO_{2005}-TEQ/g fat (blood) Duration: 3 years		
PeCDF and HxCDF	**Tooth development**			
			Human	
	Parents reported **bearing teeth during the neonatal period** in 9.6% (7/73) of children in the exposed group and none in the control group. The percentages of children with **congenitally missing tooth germ** and **rotated teeth** were significantly increased in the exposed group (P=<0.05). The developmental defects combined (**fusion,**	Measurement of exposure: 2,3,4,7,8-PeCDF, 1,2,3,4,7,8-HxCDF Control: 12 pg TEQ/g fat (blood) Mean (PeCDFs and HxCDF) - low cases: 233 pg TEQ/g fat (blood) Mean (PeCDFs, HxCDF) - high cases:	Human (M+F)	Yucheng cohort (Taiwan, Qigu District, Yucheng) Wang et al. (2003)

PeCDF and HxCDF	**microdontia, pigmentation, enamel hypoplasia, and impaction**) increased with exposure (P=0.01).	1780 pg TEQ/g fat (blood)		
DL-PCBs	**Carcinogenicity**			
			Human	
	Sufficient evidence in humans for **carcinogenicity** of PCB-126 (Group 1 carcinogen).		Human	Based on data from experimental animals, epidemiological studies, and from the common mechanism of action. IARC, 2012

- (F) Female; (i.p) intraperitoneal; (LOAEL) lowest observed adverse effect level; (M) Male; (NOAEL) no observed adverse effect level; (POD) point of departure; (s.c.) subcutaneous.

5. In the EFSA opinion the term PCDD/Fs is used to refer to dioxins; PCDDs and PCDFs (EFSA, 2018).

6. Both animals and epidemiological studies reviewed by the CONTAM panel have reported dioxin to have adverse acute and chronic health effects in in males and females. For animal studies the CONTAM panel only considered studies that were not evaluated by the Scientific Committee on Food (SCF) in 2001 and that could potentially show effects at lower body burdens than that used to set the TWI (LOAEL of 40 ng/kg bw) in their assessment. With regards to human studies the CONTAM panel considered studies which analysed tissues (e.g. blood, human milk, adipose tissue) of subjects under study for TCDD or any other congener dominating the toxic equivalents (TEQ). For example due to a contamination incident, (ii) the 17 PCDD/Fs and 12 DL-PCBs, (iii) the 17 PCDD/Fs and 4 non-ortho DL-PCBs, (iv) the 17 PCDD/Fs and 3 non-ortho DL-PCBs (including PCB-126), or (v) the total TEQs (or BEQs analysed by, e.g. CALUX).

7. The toxicity and epidemiological data discussed below are derived from studies in the EFSA opinion that reported adverse health effects and were considered suitable for use in the risk assessment for human health (CONTAM, 2018). The epidemiological studies have been conducted in subjects/cohorts exposed to TCDD, PCDD/Fs and DL-PCBs at different life stages under different exposure conditions, e.g. from industrial accidents such as the Seveso Cohort or contamination incidents (Yusho or Yucheng Cohorts), from occupational exposure or from background levels mainly via the diet in the general population (Duisburg Cohort, Russian Children's study and others). More information on these cohorts is provided in Section 3.1.4 of the Opinion.

TCDD toxicity in humans

Reproductive toxicity

Environmental exposure (via industrial accident):

8. Adverse effects of females in the SWHS exposed to TCDD in an industrial accident (i.e. explosion) at a mean age of 17 years had median levels of 13.4 pg/g fat (blood), which were extrapolated from levels measured near to the explosion to the time of conception attempt. Each 10-fold increase in TCDD concentration was associated with a 25% increased time to pregnancy and a doubling in odds of infertility, defined as conception ≥12 months of trying (Eskenazi et al., 2010). In the Seveso study a lower male to female sex ratio in births occurred with mothers and fathers that were exposed to TCDD in an industrial accident between the ages of 3 and 45; mother and fathers had median levels of 62.75 and 96.5 pg/g fat (blood) respectively (Mocarelli et al., 2000).

9. TCDD exposure in males in the Seveso Cohort (aged 1-9 years at the time of explosion in 1976) with median TCDD levels of 210 pg/g fat (blood) was

associated with reduced sperm concentration, progressive motility and motile sperm count (Mocarelli et al., 2008). Other reproductive effects were observed in breastfed males who were born to and breastfed by mothers with median TCDD levels of 19 pg/g fat (blood) at the time of conception. These males had impaired semen quality consisting of lower sperm concentration, total sperm count, progressive motility and total motile count (Mocarelli et al., 2011).

Endocrine mediated effects

Environmental exposure (via industrial accident):

10. Additional adverse effects TCDD has been associated with in women in the SWHS, include endocrine mediated effects such as lengthening of the menstrual cycle and reduction in the odds of scanty menstrual flow. These effects occurred in those (aged ≤30 years of age at time of explosion) with median plasma levels of 67.5 pg/g fat (blood). It is important to note that in this study co-exposure to other dioxins and DL-PBCs were not accounted for (Eskenazi et al., 2002).

11. A recent case-control study in Spain reported higher concentrations of dioxins and PCBs in the adipose tissue of deep infiltrating endometriosis (DIE) cases than controls. The cases were aged 32 years on average and had median TCDD levels of 0.70 pg/g fat in adipose tissue. The source of exposure of the women was solely background. They had a mixed diet which included meat and fish and had no occupational exposure. In this study other congeners measured included PCDD/Fs and DL-PCBs (Martinez-Zamora et al. 2015).

12. Further to this, children (male and female) of mothers in the Seveso Cohort who were highly exposed to TCDD via an industrial accident had levels of neonatal blood- thyroid stimulating hormone (b-TSH) hormone of ≥5 μU/mL. The proportion of children with b-TSH ≥5 μU/mL was 16.1% in Zone A (very high contamination), 4.9% in Zone B (high contamination) and 2.8% in (Zone R). Additionally, the levels of TSH decreased with order of siblings in Zone A and B, but not in Zone R. Mothers in Zone A had median TCDD levels of 447 pg/g fat (blood), measured 1-2 years after the accident. Newborn infants with b-TSH ≥5 μU/mL had median TCDD levels of 39 pg/g fat (blood). Other exposures measured in this cohort were PCDD/Fs and DL-PCBs (Baccarelli et al., 2008).

Carcinogenicity

Occupational exposure:

13. Further effects of TCDD exposure in humans is carcinogenicity. As outlined in Annex 5 the committee on carcinogenicity (COC) reviewed TCDD in 1998, following the publication of the IARC monograph which concluded that TCDD

should be considered as a definite human carcinogen. The COC agreed that the information from the most heavily occupationally exposed cohorts suggested that there was, at most, only a weak carcinogenic effect in these individuals. It therefore concluded that there were insufficient epidemiological and toxicological data on TCDD to conclude a causal link with cancer in humans, but it would be prudent to consider TCDD as a "probable weak human carcinogen" (COT, 2001). IARC later classified TCDD as a group 1 carcinogen in 2012 (IARC, 2012).

14. Men in the USA occupationally exposed to TCDD had a positive trend between increasing cumulative TCDD exposure and risk of cancer mortality. Estimated serum TCDD levels at the end of the exposure period (1 year on average for Ranch Hand workers and a mean of 3 years for NIOSH workers) was 1,589 pg/g. Using a model based on the log of cumulative serum level lagged 15 years, lifetime excess risk (up to age 75 years), an excess lifetime risk of dying of cancer at an intake of 1 pg/g bw/day over 75 years was estimated to be 0.05-0.9%, above a background lifetime risk of cancer death of 12.4% (Steenland et al., 2001).

15. Males who were occupationally exposed and had mean TCDD levels of 101.3 pg/g fat (blood) had an increased SMR total cancer mortality of 1.41 (95% CI, 1.17-1.68) (Becher et al., 1998). The relative risk ratio (RR) for all cancers, rectal cancer, lung cancer in men part of the Seveso study were 1.3 (95% CI, 1.0-1.7), 2.4 (95% CI 1.2-4.6) and 1.3 (95%CI, 1.0-1.7) respectively in Zone A males with median TCDD levels of 447 pg/g fat (blood) between 1979-77 and 73.7 pg/g fat (blood) between 1993-94. As for Zone B males median TCDD levels were 94 pg/g fat (blood) between 1976-77 and 12.4 pg/g fat (blood) between 1993-94 (Bertazzi et al., 2001).

16. Additionally, male workers dermally exposed to TCDD had a SMR of 1.13 for all cancer. A cumulative exposure score of 20,000 (the cut-off between septiles 6 and 7) would correspond to estimated exposure of 38,000 pg/g-years (Steenland et al., 1999). Other cancers that occurred in male workers exposed to TCDD include the following: respiratory cancer, oesophageal cancer and rectum cancer with SMRs of 1.64 (95% CI 1.32-2.03), 2.56 (95% CI 1.27-4.57) and 1.96 (95% CI, 0.98-3.51) respectively. Median TCDD levels were 77 pg/g fat (Manuwald et al., 2012).

17. Both males and females in the Seveso study with occupational TCDD exposure had an RR of 1.7 (95% CI 1.2-2.5) for lymphohaematopoietic neoplasms, whereas other cancers observed were Hodgkin's disease, with a RR of 4.9 (95% CI, 1.5–16.4), in the first 10-year observation period. Non-myeloid leukaemia and myeloid leukaemia were observed after 15 years and had RR of 2.8 (95% CI, 1.1-7.0) and 3.8 (95% CI, 1.2-12.5). In this cohort median blood TCDD levels in residents in Zone A were 447 pg/g fat between 1979-77 and 73.7 pg/g fat between 1993-94. As for those in Zone B median

TCDD levels in blood were 94 pg/g fat between 1976-77 and 12.4 pg/g fat between 1993-94 (Bertazzi et al., 2001).

18. For non-hodgkin's lymphoma (NHL), leukaemia and soft tissue sarcoma the standardised mortality ratio (SMR) amongst workers with occupational TCDD exposure was reported to be 1.3 (95% CI, 0.6-2.5), 1.9 (95% CI, 1.1-3.2), 4.1 (95% CI, 1.1-10.5) respectively, although TCDD blood levels in exposed workers were 15.9 pg/g fat (Collins et al., 2009a).

Environmental exposure (via industrial accident):

19. Males and females (of various ages) apart of the Seveso Cohort accidentally exposed to TCDD also experienced an increased risk of lymphatic and haematological cancers in those exposed to TCDD. Relative risk ratios of those exposed in Zones A and B were reported to be 2.23 (95% CI, 1.00-4.97) and 1.59 (95% CI, 1.09-2.33) respectively by Consonni et al., 2008. However, Pesatori et al., 2009 reported RRs of those exposed in Zone A and B as 1.39 (95% CI, 0.52-3.71) and 1.56 (95% CI, 1.07-2.27) respectively. The median TCCD blood levels of those in Zone A were 447 pg/g fat between 1976-1977 and decreased to 73.3 pg/g fat between 1992-1996. In Zone B, median TCDD blood levels were 94 pg/g fat between 1976-1977 and 12.4 pg/g between 1992-1996.

20. Women exposed to TCDD in Zone A of Seveso had an increased risk of breast cancer 15 years after the incident, with a RR of 2.57 (95% CI, 1.07-6.20). The median blood TCDD levels between 1976-1977 and 1992-1996 were the same those mentioned above (Pesatori et al., 2009). Additionally, women in the SWHS aged between 20 and ≥50 years accidentally exposed to TCDD via explosion had median blood TCDD levels of 71.8 pg/g fat and an increased hazard ratio (HR) for breast cancer of 2.1 (95% CI, 1.0-4.6) (Warner et al., 2002). However, for all cancers combined the adjusted HR was 1.8 (95% CI 1.29–2.52) in women (Warner et al., 2011). Ultimately female workers exposed to dioxin in a chemical plant showed an increased risk of breast cancer, with an SMR of 1.86 (95% CI, 1.12-2.91) and median TCDD levels of 77 pg/g fat (Manuwald et al., 2012).

Immunotoxicity and neurotoxicity

Environmental exposure (via industrial accident):

21. Other possible adverse effects of TCDD exposure include immunotoxicity and neurotoxicity. In the Seveso study, subjects exposed to TCDD via an industrial accident had lower plasma IgG levels compared to subjects in the reference area when assessed 20 years after the accident. Blood levels of TCDD ranged between 3.5 and 90 pg/g fat (Baccarelli et al., 2004).

Background exposure (via diet):

22. As for neurotoxicity, this occurred in children born to mothers in the Danish National Birth Cohort study. Out of six infant developmental milestones, children experienced an two-fold increased risk of being unable to perform one developmental milestone ("cannot crawl"). Mothers of these children who were unable to perform this developmental milestone had CALUX determined bioanalytical equivalent (BEQ) maternal blood levels above the median (>38 pg CALUX-TEQ/g lipid), compared to children whose mother had exposure below the median. In this study the mid-pregnancy diet of mothers was assessed in order to identify dietary predictors of plasma dioxin-like activity. It was concluded that high fat intake may lead to increased plasma dioxin-like activity and thereby increased in utero exposure and the aforementioned effects relating to early infant development (Halldorsson et al., 2009).

Tooth development

Environmental exposure (via industrial accident:

23. Final chronic effects of accidental industrial TCDD exposure includes tooth development which occurred in both sexes in the Seveso Cohort, with median TCDD levels shortly after the accident of 476 pg/g fat (blood). When studied 25 years later, enamel defects were apparent in 24% of all subjects, with the majority of subjects (93%) being <5 years old at the time of the accident. Additionally, there was a higher prevalence of tooth defects in children <5 years old (OR = 2.4) (95% CI, 1.3-4.5) in contaminated areas compared to non-contaminated areas. Hypodontia (missing teeth) was also occurred where lateral incisors or second premolars were missing in 12.5% of subjects from zone ABR (Alaluusua et al., 2004).

TCDD and PCDD/F toxicity in humans

Carcinogenicity

Occupational exposure:

24. PCCD/Fs have been classed as Group 1 carcinogen (IARC, 2012). Males and females who were former herbicide and insecticide workers had an all cancer SMR of 1.41 (95% CI, 1.17-1.68), with TCDD showing a significant trend in SMR with increasing cumulative PCDD/Fs. Mean TCDD blood levels of 108 and 110.5 ng/kg fat were measured in males and females respectively. However, PCDF blood levels of 142 and 62.7 ng TEQO/kg fat were measured in males and females respectively (Flesch-Janys et al., 1998).

Dioxin and DL-PCB toxicity in humans

25. In order to assess and compare the toxicity of a mixture of congeners analysed in complex samples, the CONTAM Panel applied the concept of toxic equivalents (TEQs) based on different toxicity equivalency factors (TEFs) for the toxic congeners. It should be noted that the TEFs are order of magnitude estimates of the toxicity of TCDD, which adds uncertainty to the risk assessment.

26. In the European legislation, all regulatory levels for PCDD/Fs and DL-PCBs in food are presently expressed as TEQs using the WHO_{2005}-TEFs proposed by the World Health Organization (WHO) in 2005 (van den Berg et al., 2006). As for older data generated before 2005 are generally reported as WHO_{1998}-TEQs (van den Berg et al., 1998), I-TEQs (NATO/CCMS, 1988). EFSA (2010a) estimated a decrease by 14% following the switch from WHO_{1998}-TEFs to WHO_{2005}-TEFs, which is within the interval of 10–25%, estimated by van den Berg et al. (2006).

Reproductive toxicity

Background exposure (via diet):

27. Prenatal exposure to PCDD/Fs and DL-PCBs via maternal diet was associated with reproductive effects in male and female children in the birth cohort BraMat; a sub-cohort of the Norweigan Mother and Child Cohort Sutdy (MoBa). The children's mothers had an estimated median maternal dietary intake of 0.58 and 0.59 pg WHO_{2005}-TEQ/kg bw/day. Seafood was determined to be a major source of PCDD/Fs and DL-PCBs exposure. Additionally, cereals, eggs and milk also contributed to exposure. Children of these mothers who were aged between 1 and 4 years had increased risk of wheeze and upper respiratory infection as well reduced antibody response to measles vaccination (Stolevik et al., 2011, 2013).

Environmental exposure (via contamination):

28. Male children of the Russian Children's Study who were exposed to dioxins via environmental contamination from previous manufacture of chemical warfare agents, chlorine-containing industrial and agricultural chemicals, displayed further reproductive effects such as changes in time of pubertal onset and sexual maturity. These effects occurred between the ages of 8 and 18 years with median blood levels of 21.1 pg WHO_{2005}-TEQ/g fat (Burns et al., 2016).

29. Male children between the ages of 8 and 12 in the Russian Children's study also showed early pubertal onset (i.e. genitalia in stage 2 or higher or testicular volume >3mL on the puberty scale) with mean PCDD, PCDF and

PCB blood levels of 10.6, 7 and 8.1 pg WHO_{2005}-TEQ/g fat (Korrick et al., 2011). Alternatively, in the subgroup of male infants that were breast fed by their mothers for at least 6 months, with a median maternal blood sum of PCDD/Fs and DL-PCBs of 25 pg WHO_{2005}-TEQ/g fat had a delay in pubertal onset assessed by genital staging 2, compared those that were breast-fed less (Humblet et al., 2011).

30. Other reproductive effects observed in the Russian Children's Study was a reduction in semen parameters (sperm concentration, sperm count and motile sperm count) in men aged 18-19 years with median PCDD blood levels of 8.7 pg WHO_{2005}-TEQ/g fat respectively (Minguez-Alarcón et al., 2017). Further effects observed in males aged 14-19 years was a negative trend in current median PCDD/Fs and DL-PCBs exposure (2.3 and 1.5 pg WHO_{2005}-TEQ/g blood fat respectively) and occurrence of first ejaculation (Leijs et al., 2008).

31. A subset (n=355) of boys in the Russian Children's Study had high co-exposure indicated by high concentrations of organochlorine pesticides: hexachlorobenzene (HCB), beta-hexachlorocyclohexane (β-HCH) and dichlorodiphenyldichloroethylene (DDE). HCB was also associated with later pubertal onset whereas HCB and β-HCH was associated with later sexual maturity (Lam et al., 2014, 2015). The correlation between Spearman rank organochlorine pesticides and total TEQ was high (0.72, β-HCH) to moderate (0.51, DDE and 0.53, HCB). The correlations between serum PCBs and organochlorine pesticides were in similar range (0.71-0.49), making it difficult to create categories of high vs low co-exposure to multiple organochlorine compounds. However, as adjustment for these compounds was possible and these organochlorine pesticides were not strongly associated with semen quality, uncertainty due to such co-exposure is considered low, but if present it would lead to overestimation of the risk (CONTAM, 2018).

32. In the Flemish Environment and Health Study (FLEHS II) subjects were exposed to environmental pollution pressure in selected hotspot areas, signs of hindered sexual development was noted in females aged between 13 and 17 years who experienced negatively correlated breast development with estimated median DL-PCB levels of 32.1 pg BEQ/g fat (Croes et al., 2014).

33. Final reproductive effects occurring in both sexes were increases in birth weight. Perinatal environmental exposure to the bioanalytical equivalent of dioxin was associated with increased growth between the ages of 0 and 24 months across three different cohorts. Mean exposure via breast milk was 7.9 and 15.5 pg BEQ/g fat in the HUMIS and Slovak PCB cohorts, whereas mean exposure via cord blood was 31.2 pg BEQ/g fat in the FLEHS I cohort (Iszatt et al., 2016).

Accidental exposure (via diet):

34. Alternatively, an inverse association was identified between birth weight of male infants and PCDD/F and PCB exposure. Mothers of the Yusho Cohort

who were accidental exposed to rice oil contaminated with dioxins between the ages of 0-35 years had mean maternal blood exposures of PCDD, PCDF and PCB of 16.01, 41.98 and 10.93 pg TEQ/g fat respectively. These levels were higher than the general population evident in those with a lower birth weight (Tsukimori et al., 2012).

Endocrine mediated effects

Environmental exposure:

35. Additional adverse effects associated with environmental exposure to PCDD/Fs and DL-PCBs is endocrine mediated effects. Females exposed to dioxin-like compounds with blood levels of 21.2 pg BEQ/g fat displayed an increased risk of endometriosis compared to controls (Simsa et al., 2010). In a later study, females demonstrated increased risk for deep infiltrating endometriosis (DIE) and ovarian endometrioma (OvE) compared to controls. Individuals with increased risk of DIE had PCDD/F blood levels of 8.94 pg WHO_{2005}-TEQ/g fat, as for risk of DIE occurring concurrently with OvE PCDD/F blood levels were 14.36 pg WHO_{2005}-TEQ/g fat (Ploteau et al., 2017).

36. Females environmentally exposed to dioxin and DL-PCBs also had an increased risk of other types of endometriosis such as peritoneal endometriosis (PEND) and deep endometriotic nodules (DEN) when compared to controls. Those with increased risk of PEND has PCDD/F and DL-PCB blood levels of 20.9 and 11 pg WHO_{1998}-TEQ/g fat. Whereas those with increased risk of DEN had PCDDF and DL-PCBs blood levels of 26 and 12.4 pg WHO_{1998}-TEQ/g fat respectively (Heilier et al., 2005).

37. Additional endocrine effects affecting females ≥19 years of age with irregular menstrual cycles were found to have, higher placental dioxin levels compared to females with regular menstrual cycle at ≤18 years old. Women environmentally exposed to PCDD/F and DL-PCBs with irregular menstrual cycles had mean placental PCDD/F and DL-PCB_S levels of 10.7 and 2.92 pg WHO-TEQ/g fat respectively (Chao et al., 2007).

38. Endocrine mediated effects also occurred in male and female adolescents in FLEHS II, where subjects were environmentally exposed to dioxin and DL-PCBs via industrial hotspot areas. A positive correlation with PCDD/Fs and DL-PCBs with free T4 hormone was identified. Blood levels of PCDD/Fs and DL-PCBs were 108 and 32.1 pg BEQ/g fat respectively (Croes et al., 2014). In a further prospective study with pregnant mothers from the general population, positive associations between T3 and thyroxine binding globulin (TBG) were identified in female new-borns (<3 months of age) that had transplacental exposure to mean PCDD/Fs and DL-PCBs levels of 16.2 pg WHO_{1998}-TEQ/g fat (Wang et al., 2005).

39. In the Dutch PCB/dioxin cohort with mothers exposed to environmental levels of PCBs and dioxins, an association with higher exposure to PCDD/Fs in maternal milk and higher scores on the feminine subscale of the Pre-School Activity Inventory (PSAI) was identified. This indicated feminised play behaviour amongst male and female children. On the contrary, higher exposure to DL-PCBs was associated with masculine play behaviour. Estimated mean PCDD/F exposure levels in breast-fed boys and girls were 36.6 and 36 ng TEQ /kg fat respectively. Whereas the estimated median of the sum of planar and mono-PBC levels in breast-fed boys and girls was 28.8 ng WHO_{1998}-TEQ /kg fat (Vreugdenhil et al., 2002).

40. In the follow up study of Duisburg birth cohort findings of increased feminine behaviour in boys was also reported but decreased feminine behaviour in girls exposed to a mean sum of PCDD/Fs and DL-PLBs in breast milk at 21.5 pg WHO_{2005}-TEQ/g fat was apparent (Winneke et al., 2014). The CONTAM determined that there was insufficient information about co-exposure to determine confounding variables.

Carcinogenicity

Environmental exposure:

41. PCB-126 is classified as a group 1 carcinogen, with sufficient evidence in humans (IARC, 2012).

42. In a population-based case control study blood levels of PCDFs were also found to be associated with a 3.5-fold increased risk of NHL in those with the highest quartile (>6.89 pg WHO_{1998}-TEQ/fat) exposure compared to the lowest quartile. PCBs were also associated with an increased risk of NHL ranging between 2.7 to 3.5-fold in the highest quartile exposure group (>13.7 pg WHO_{1998}-TEQ/fat) (De Roos et al., 2005).

Immunotoxicity

Occupational exposure:

43. Other adverse effects of PCDD/Fs and PCBs in males and females include immunotoxicity. In a cross-sectional study with male and female subjects with background exposure to dioxin PCDD/Fs and PCBs had an inverse relationship with rhinitis and atopic dermatitis, with a 50^{th} percentile of 16 pg WHO_{2005}-TEQ/g fat in the blood (Nakamoto et al., 2013).

Environmental exposure:

44. Additionally, in the Hokkaido Study on Environment and Children's Health, prenatal exposure to environmental levels of PCDD/Fs increased risk of otis media in young male infants where PCDDs and PCDFs were present in blood at 6.92 and 2.38 pg WHO_{2005}-TEQ/g fat respectively. In this study the frequency of fish and meat consumption during pregnancy (the main sources

of exposure to dioxins in Japan) was found to not be related to total dioxin TEQs as adjustments made for the frequency of fish and meat intake did not change the relationships in this study (Miyashita et al., 2011).

Environmental exposure (via contamination):

45. Risk of development of animal allergies in male and female adolescents in the FLEHS II with environmental exposure from industrial hotspots were positively associated with DL-PBCs and PCDD/Fs with blood levels of 32.1 and 108 pg BEQ/g fat respectively (Croes et al., 2014). Further immune-related effects were identified amongst adolescents in the Amsterdam/Zaandam Cohort that were exposed to background levels of PCDD/Fs and DL-PCBs. These adolescents had higher current DL-PCBs blood levels of 2.2 pg WHO_{2005}-TEQ/g fat, and negative effects on polymorphic neutrophils were observed (Leijs et al., 2009).

46. Further associations were identified by Nagayama et al., 2007b, where median exposure to PCDD/Fs and DL-PCBs at 23 pg WHO_{1998}-TEQ/g fat (breast milk), increased ratio of CD4/CD8 cells and percentage of CD3 cells in male and female infants. Prenatal PCDD/F exposure of 32.6 pg I-TEQ/g fat (blood) was also associated with occurrence of this effect during the neonatal period (Leijs et al., 2009).

Neurotoxicity

Background exposure (via diet):

47. The CONTAM panel also addressed neurotoxicity associated with PCDD/F and DL-PCB exposure (CONTAM, 2018). Male and female children aged 3 years whose mothers in the MoBa cohort had high maternal dietary exposure to PCDD/Fs and DL-PCBs (i.e >14 pg WHO_{2005}-TEQ/kg bw) were associated with high odds of incomplete grammar in boys and language delay in girls which was assessed using grammar ratings and the Ages and Stages Questionnaire. In the majority of Norwegian pregnant women participating in this cohort oily fish was the main source of dioxin and PCB exposure (Caspersen et al., 2016a).

Tooth development

Accidental exposure (via diet):

48. Final adverse effects of dioxins in humans was on tooth development, which was observed in the Yucheng cohort, where ingestion of rice oil used for cooking was contaminated with dioxins. Parents reported that 9.6% of children (with a mean age of 9 years at the outcome assessment) had bearing teeth during the neonatal period. The exposed group also had higher percentages of congenitally missing tooth germ. Overall, developmental tooth defects increased with exposure compared to the control group. The exposure group had mean PeCDF and HxCDF levels of 233 and 1780 pg TEQ/g fat for

low and high cases respectively, whereas the control group had a level of 12 pg TEQ/g fat (Wang et al., 2003).

TCDD toxicity in animals

Systemic toxicity

49. Systemic effects of TCDD observed in animal studies consisted of body weight reductions observed in female Sprague Dawley rats orally administered with TCDD at 100 ng/kg per day although the NOAEL body burden of 85 ng/kg bw/day was based on hepatopathy (NTP, 2006). When calculating the NOAEL body burden, it was assumed the liver accounted for 4.5% of body weight and adipose tissue accounted for 8%, which gives an estimate of 681 + 0.045 + 505 + 0.08 = 71 ng/kg bw. A dose level of 2.1 ng/kg bw, the fraction residing in the liver and adipose tissue after repeated exposure in the rat is given by: fractional body burden = 1.934 9 ln(2.1) + 82.39, which gives 83.8%. The estimate of the body burden corresponding at the 105 week NOAEL of 2.1 ng/kg bw per day was therefore 71/0.84 = 85 ng/kg bw (CONTAM, 2018).

50. In a later study reduced body weight gain was observed in female Sprague Dawley rats receiving 100 ng/kg bw per/day, but the NOAEL body burden of 789 ng/kg bw was based on bile duct hyperplasia (Harrill et al., 2016). The NOAEL body burden was calculated by assuming the liver and adipose tissue account for 8 and 4.5% of the body weight which gives an estimate for the body burden of 3.2 x 0.008 +10.3 x 0.045 = 720 ng/kg bw. Accounting for the fraction residing in the liver and adipose tissues after repeated exposure at a dose level of 71 ng/kg bw gives a fractional burden of 1.934 9 ln(71) + 82.39, which gives 90.6%. The estimate of the body burden corresponding at the 4-week NOAEL of 71 ng/kg bw per day therefore is 720/0.91 = 789 ng/kg bw (CONTAM, 2018).

51. TCDD also dose-dependently increased organ-to-body weight % for liver and thymus from as low as 3 ng/kg bw, but decreased spleen-to body weight % at 1000 ng/kg bw/day. The NOAEL body burden of 789 ng/kg bw was based on bile duct hyperplasia and thymus atrophy (Harrill et al., 2016).

52. Other effects of TCDD were dose dependent changes to clinical chemistry and haematological parameters were also observed in female Sprague Dawley rats receiving TCDD between 3 and 100 ng/kg bw per day. The NOAEL body burden of 789 ng/kg bw established was based on bile duct hyperplasia and thymus atrophy (Harrill et al., 2016). Histopathological changes were also evident.

Reproductive toxicity

53. Male and female rats gestationally exposed to a single dose 1 µg/kg of TCDD had abolished gender differences in the anteroventral periventricular nucleus expression of enzyme; glutamic acid decarboxylase 67 (Hays et al., 2002).

54. Reproductive effects observed in male rat (Han Wistar) offspring were abnormal proportion of sperm and around a ~10% decrease in testes weight. Mothers were calculated to have LOAEL body burdens of 42 and 50 ng/kg bw on GD16 and GD21 (Bell et al. 2007c). LOAEL body burdens were calculated after correcting the experimentally determined LOAELS of 35.4 and 42.4 ng/kg bw per day on GD16 and GD21. These body burdens were corrected for the fraction of the body burden residing in the liver and adipose tissue (0.84, as calculated with y = 1.934ln(2.4) + 82.39), which gave subchronic body burdens of 35.4/0.84 = 42.1 ng/kg bw (GD16), and 42.4/0.84 = 50.4 ng/kg bw (GD21) (CONTAM, 2018).

55. Further to this, administration of a 400 ng/kg bw TCDD loading dose and weekly TCDD maintenance doses 80 ng/kg bw resulted in reduced ventral prostrate weight in F1 Holtzman rats and decreased male/female ratio in their F2 (Ikeda et al., 2005).

56. Pregnant female Han Wistar rats exposed to 530 ng/kg of TCDD via their diet had decreases in the number of pubs born alive on day 1 and the number of pubs surviving days 1-4, in addition to decreased body weight in the F1 generation which was also observed at 93 ng/kg/diet. Male rats in the F1 generation also showed delayed balanopreputial separation, LOAEL body burdens of 42 and 50 ng/kg bw on GD15 and GD21 respectively was based on this endpoint (Bell et al., 2007a). The LOAEL body burdens were calculated the same as Bell et al., 2007c).

57. Other effects reported in F1 male generations whose mothers were exposed to TCDD include reduced body weight gain and a 12% reduction in litter size and a slight decrease in testes weight at PND 70 and PND 21 in groups receiving 1000 ng/kg bw. Groups receiving 1000 ng/kg bw of TCDD also had decreases in testes weight at PND70 and PND120 and decreased brain weight at PND120. Whereas deceased liver to body weight ratios were increased across all doses. The NOAEL body burdens of 56.2 and 58.5 ng/kg bw on GD16 and GD12 were based on decreased pup weight from PND1 to PND7 (Bell et al. 2007b). The NOAEL body burden was experimentally determined as 18.8 and 19.6 ng/kg bw, which were based on summation of liver, adipose tissue and fetal deposition. Correcting these body burdens for the fraction of the body burden residing in the liver and adipose tissue ((0.87, as calculated from y = 0.7548ln0.05) + 88.77), then gives a GD16 body burden of 18.8/0.87 = 21.6, GD21 body burden of 19.6/0.87 = 22.5 ng TCDD/kg. Extrapolating the acute exposure to chronic exposure, applying a

factor 2.6 (SCF, 2001), then results in an estimated chronic GD16 body burden of 21.6 9 2.6 = 56.2 ng/kg bw, and GD21 body burden of 22.5 9 2.6 = 58.5 ng/kg bw (CONTAM, 2018).

58. Further discussion of the aforementioned Bell et al studies by the COT can be found in Annex 4 (COT, 2007).

59. Other reproductive toxicities were identified in other species such as ICR mice, male mice given an initial loading dose of 2000 ng/kg bw followed by a weekly maintenance dose of 400 ng/kg bw resulted a lower proportion of male embryos a the tow-cell embryo stage, suggesting a diminished ability of Y-bearing sperm to conceive the ova (Ishihara et al., 2010).

60. Pregnant mice encountered embryo loss and had a NOAEL body burden of 9 and 25 ng/kg bw in GD1-3 and GD1-8 respectively (Li et al., 2006). For calculations of the NOAEL body burden it was assumed that the body burden increased linearly with the exposure duration which as 3 days for GD1-3 and 8 days from GD1-8 and absorption fraction of 0.6 was assumed. Additionally, a factor of 2.6 was used to extrapolate a single acute dose to equivalent chronic fetal exposure. Hence, the corresponding chronic body burden ranged from 2 x 3 x 0.6 x 2.6 = 9.4 ng/kg bw to 2 x 8 x 0.6 x 2.6 = 25 ng/kg bw at the end of the GD1–3 and GD1–8 exposure period (CONTAM, 2018).

Endocrine mediated effects

61. Endocrine mediated effects observed in female Sprague Dawley rats included decreased T4 levels 14 weeks after receiving TCDD a 22 ng/kg bw/day. The NOAEL body burden for this study was 85 ng/kg bw, although this was based on hepatopathy (NTP, 2006). When calculating the NOAEL body burden, it was assumed the liver accounted for 4.5% of body weight and adipose tissue accounted for 8%, which gives an estimate of 681 + 0.045 + 505 + 0.08 = 71 ng/kg bw. A dose level of 2.1 ng/kg bw, the fraction residing in the liver and adipose tissue after repeated exposure in the rat is given by: fractional body burden = 1.934 9 ln(2.1) + 82.39, which gives 83.8%. The estimate of the body burden corresponding at the 105 week NOAEL of 2.1 ng/kg bw per day was therefore 71/0.84 = 85 ng/kg bw (CONTAM, 2018).

Carcinogenicity

62. Female Sprague Dawley rats exposed to TCDD showed a significant increase in hepatocellular adenoma and cholangiocarcinoma at 100 ng/kg bw day, the estimated NOAEL body burden (based on hepatopathy) was 85 ng/kg bw (NTP, 2006). The NOAEL body burden was calculated the same as in **paragraph 49.**

Immunotoxicity

63. Administration of TCDD to male and female wild-type rats showed suppression of the percentage of Lipopolysaccharide (LPS)-induced IgM+ cells compared to AhR knockout rats. An increment of (ex vivo LPS induced) proliferation was also observed, which indicated a dysregulation of the humoral immune response. A decrease in the percentage of natural killer cell (Phadnis-Moghe et al., 2016). The NOAEL body burden for this study was 250 ng/kg bw.

64. The study by Phadnis-Moghe et al. (2016) is based on the same animal study as Harrill et. al, 2016), but with a focus on immunological effects. The NOAEL body burden was calculated from the NOAEL of 22 ng/kg bw per day which corresponds to a daily exposure of 22 x 5/7 = 15.7 ng/kg bw per day. According to Harrill et al. (2016), this dose results in concentrations in adipose tissue and liver to around 1.5 and 2.2 ng/g tissue. Assuming the liver and adipose tissue to account for 8% and 4.5% of the body weight then gives an estimate for the body burden of 1.5 9 0.08 + 2.2 9 0.045 = 0.22 ng/g (220 ng/kg bw). At a dose level of 15.7 ng/kg bw, the fraction residing in the liver + adipose tissue after repeated exposure in the rat is given by: fractional body burden = 1.934 x ln(15.7) + 82.39, which gives 87.7%. The estimate body burden 220/0.88 = 250 ng/kg bw.

Tooth and bone development

65. Female Han Wistar rats exposed to single TCDD doses between 0.03 and 1 µg/kg bw in utero or via lactational exposure resulted in reduced size or prevented the development of their third lower molars (Kattainen et al., 2001).

66. Another study also demonstrated the effects of TCDD on tooth development, administration of single doses 50 and 1000 µg TCDD/kg bw to lactating rats on day 1 after delivery resulted in half of pups lacking one or more third molars by day 22 and total lack of mineralisation in third molar cusps (Lukinmaa et al., 2001).

67. Absence of third molars in pups was also evident in the Miettinen et al., 2002 study where pregnant Dioxin-sensitive line C rats received a single dose of TCDD at 1 µg/kg bw. Other effects observed in this study was a greater frequency of missing molars was greater the earlier exposure was. Frequency of missing molars were 100%, 88% and 50% of the offspring exposed on GD11 and GD13 and GD19 respectively. Further effects in observed in female Dioxin sensitive line C rats were cariogenic lesions in the enamel of pup molars who received 0.03 µg/kg (the lowest tested dose. A NOAEL for this study was not obtained (Miettinen et al., 2006).

68. Final effects include tooth abnormalities in the offspring of female Rhesus Macaque monkeys that were exposed to TCDD at 300 ng/kg during gestation and lactation. A NOAEL for this study was not obtained (Yasuda et al., 2005).

Dioxin and DL-PCB toxicity in animals

Genotoxicity

69. Genotoxic effects such as chromosome aberrations were evident in buffalo cows with summed PCDD/Fs and DL-PCBs milk levels of 21.79 pg/g fat compared to the controls, with summed levels of 1.3 pg/g fat (Genualdo et al., 2012). Increases in chromosome aberrations and slight increases in sister chromatid exchange (SCE) in lymphocytes were also observed in buffalo cows. The sum of PCDD/Fs and DL-PCBs milk levels was 18.56 pg/g fat and 8.56 pg/g in farm A and B cows respectively, whereas levels in the controls were 1.75 pg/g fat (Iannuzzi et al., 2009; Di Meo et al., 2011).

Summary

TCDD

Humans

70. In humans, reproductive effects occurred in females that had median blood TCDD levels in the range of 13.4 – 62.75 pg/g fat, and in males with median blood TCDD levels between 96.5 - 210 pg/g fat at the time of environmental exposure. However, some males experiencing reproductive effects were born to mothers with median TCDD levels of 19 pg/g fat.

71. Endocrine mediated effects were observed in females with median TCDD levels between 0.70 pg/g fat in adipose tissue to 447 pg/g fat in blood. Children that experienced endocrine mediated effects (i.e. elevated b-TSH levels) and were born to mothers exposed to TCDD had median blood TCDD levels of 39 pg/g fat.

72. Carcinogenicity has been reported in males and females with median blood TCDD levels between 12.4 and 447 pg/g fat.

73. Immunotoxicity was observed in individuals with TCDD blood levels ranging between 3.5 and 90 pg/g fat. An increased risk of neurotoxicity was identified in children born to mothers with maternal TCDD blood levels of >38 pg CALUX-TEQ/g lipid.

74. Tooth defects were evident in both sexes of children, ultimately, children (under the age of 5 years) with a higher prevalence of enamel defects and hypodontia had median TCDD blood levels of 476 pg/g fat.

Animals

75. In female Sprague Dawley rats with altered clinical chemistry and haematological parameters no NOAEL body burden was identified, but effects occurred between 3 and 100 ng/kg bw per day.

76. Pregnant mice had reproductive toxicities corresponding with NOAEL body burdens between 9 and 25 ng/kg bw. As for rats mothers of male rat offspring that encountered reproductive effects had LOAEL body burdens between 42 and 50 ng/kg bw and NOAEL body burdens between 56.2 and 58.5 ng/kg bw. Additional reproductive effects were seen in male mice receiving TCDD at 400 ng/kg bw per week after an initial loading dose of 2000 ng/kg bw. However,

77. Signs of carcinogenicity such as increases in hepatocellular adenomas and cholangiocarcinomas were seen in female rats with NOAEL body burdens of 100 ng/kg bw/day

TCDD and PCDFs

Humans

78. Cancer occurred in males and females with mean TCDD blood levels of 108 and 110.5 ng/kg fat in males and females respectively, whereas mean PCDD/F blood levels of 142 and 62.7 ng TEQ/kg fat occurred in males and females respectively.

Dioxin and DL-PCBs

Humans

79. In humans, reproductive effects occurred in females aged 13-17 years with estimated median DL-PCBs blood levels of 32.1 pg BEQ/g fat. However, mothers with reproductive effects evident in their male and female children, had median PCDD/Fs and DL-PCBs maternal dietary intakes of 0.58 to 0.59 pg WHO_{2005}-TEQ/kg bw/day respectively. Other reproductive effects were also evident in male and female children exposed to dioxins via breast milk in the mean range of 7.9 - 31.2 pg BEQ/g fat. Although, males exposed via

maternal blood had mean exposure levels between 10.93 and 41.98 pg TEQ/g fat. Furthermore, males aged 8 to 19 years had reproductive effects that were associated with mean and median blood levels between 1.5 and 21.1 pg WHO_{2005}-TEQ/g, whereas total dioxin levels were reported as 25 pg WHO_{2005}-TEQ/g.

80. Endocrine mediated effects in adult females were associated with mean and median PCDD/F and DL-PCB blood levels ranging between 2.92 – 26 pg WHO-TEQ/g fat. Whereas endocrine mediated effects occurring in both sexes of adolescents were associated with PCDD/F and DL-PCB blood levels between 32.1 and 108 pg BEQ/g fat. As for new-borns endocrine mediated effects were associated with mean transplacental levels of 16.2 pg WHO_{1998}-TEQ/g fat. Additional endocrine effects occurring in children associated with exposure via breast milk, had a mean sum of PCDD/F and DL-PCBs of 21.5 pg WHO_{2005}-TEQ/g fat levels and median PCDD/F and DL-PCB levels of 36.6 and 28.8 ng TEQ/kg fat respectively in girls. However, estimated median PCDD/F and DL-PCB levels in boys were 36 and 28.8 ng TEQ/kg fat respectively.

81. Increased risk of cancer in both sexes from PCDF and DL-PCB exposure has been reported alongside blood levels of >6.89 and 13.7 pg WHO_{1998}-TEQ/fat respectively. Additionally, males with mean blood levels of 142 ng TEQO/kg and 62.7 ng TEQO/kg in females showed increased of cancer.

82. Immunotoxicity was observed in adults (males and females) exposed to PCDD/F and DL-PCBs with median blood levels at 16 pg WHO_{2005}-TEQ/g fat. However, infants (male and female) displaying signs of immunotoxicity were exposed to median PCDD/F and DL-PCB levels in breast milk at 23 pg WHO_{1998}-TEQ/g fat and PCDD/Fs at 32.6 pg I-TEW/g fat. Young male infants with increased risk of immunotoxicity had PCDD and PCDF blood levels of 6.92 and 2.38 pg WHO_{2005}-TEQ/g fat respectively, whereas immunotoxicity in male and female adolescents was associated with DL-PCB levels of 2.2 pg WHO_{2005}-TEQ/g fat, and mean sum of PCDD/F and DL-PCB levels between 32.1 and 108 pg BEQ/g fat.

83. Neurotoxicity was identified in children (male and female) aged 3 years who were born to mothers with maternal dietary PCDD/F and DL-PCB levels of >14 pg WHO_{2005}-TEQ/kg bw. Other adverse effects include tooth development which was associated with mean PeCDF and HxCDF blood levels between 233 and 1780 pg TEQ/g fat.

Basis of the new TWI

Epidemiological data

84. The basis of EFSA's new TWI of 2 pg TEQ/kg bw/week was human epidemiological data on PCDD/T-TEQs and toxicokinetic modelling rather than animal data, which was used as supportive evidence.

85. Epidemiological data from the Russian children study that formed the basis of the TWI was the association between reduced sperm concentrations and blood PCDD/F-TEQ levels. Although, the association was no longer significant when taking into account the DL-PCB-TEQ blood levels, therefore EFSA considered it relevant to not only compare exposure to the total TEQ (i.e. sum of PCDD/Fs and DL-PCBs) with the TWI, but also PCDD/F-TEQ only.

86. Associations between exposure to TCDD during infancy/prepuberty and impaired semen quality were observed in three prospective studies (two after the Seveso incident and one from the Russian Children's Study). As described in section 3.1.8.1 of the EFSA opinion both studies had distinct differences but the Russian Children's study was selected over the Seveso study because it had more advantages such as the narrow age range (18–19 years) of participants, whereas the Seveso studies had broader age rangers, and adjusted for age. Semen samples were collected in a laboratory in the Russian Children's Study opposed to the Seveso studies in which the samples were collected at home. Additionally, not only TCDD was measured but other PCDD/Fs and DL-PCBs and the organochlorine pesticides; HCB, β-HCH and DDE were measured in the Russian Children's Study.

87. The Russian Children's Study showed effects at the lowest serum levels; EFSA considered the NOAEL to be 7 pg WHO_{2005}-TEQ/g fat for the sum of PCDD/F TEQ, which was the median in the lowest quartile. However, no significant association was observed when including also the Co-PCB-TEQ (PCB-77, PCB-8-81, PCB-126 and PCB-169) which the Panel considered may be related to a much lower potency of PCB-126 in humans than expressed by the current WHO_{2005}-TEF.

88. An additional possibility was effects of co-exposure to non-Dioxin Like PCBs, since the associations between TCDD or total TEQ and semen parameters became slightly stronger after adjustment for these, although there were no significant association between NDL-PCBs and semen parameters. Therefore, the CONTAM Panel only evaluated the association with PCDD/F-TEQ levels. For these levels, the median values in quartiles 2–4 were 10.9, 15.9 and 32.8 pg WHO_{2005}-TEQ/ g fat, respectively. The mean sperm concentration in the lowest quartile (quartile 1) of PCDD/F-TEQ was 64

million/mL and the mean levels in quartile 2–4 were about 40 million/mL. This difference was considered biologically relevant.

89. In the Seveso studies, sperm concentrations differed between exposed and control groups with much higher estimated TCDD, PCDD/F-TEQ, and total TEQ levels with an apparent NOAEL level higher than the LOAEL level in the Russian Children's Study.

90. The CONTAM Panel decided to use the NOAEL of the Russian Children's study of a median serum level of 7.0 pg WHO_{2005}-TEQ/g fat for the sum of PCDD/F TEQ in the lowest quartile as reference point for the HBGV and for derivation of the human exposure associated with this serum concentration at the age of 9 years.

91. Section 3.1.8.2 of the EFSA opinion discusses the toxicokinetic modelling used for human dietary exposure associated with the reference point for the HBGV. An age of 35 years for mothers was used in modelling, in order to cover a common age for having a first child. The first model for TCDD was the Edmond model developed by (Edmond et al., 2005) and evaluated by EFSA by transferring the ASLX codes into Berkeley-Madonna and then R. The adaptations for including a breastfeeding period were also evaluated but the model required further investigation. The CONTAM panel noted that there were several discrepancies between the calculations from the model and data reported on human levels.

92. The second toxicokinetic model developed for TCDD was the Concentration and Age-Dependent (CADM) model developed by (Carrier et al., 1995), optimised by (Aylward et al., 2005) and further adapted by (Ruiz et al., 2014) to include a growth curve and a breastfeeding period. The model estimates the TCDD levels in the fat compartment, liver and total body. However, blood levels were not predicted by the model but were assumed to be similar to those in adipose tissues when adjusted for lipid (CONTAM, 2018).

93. A number of issues were identified and the model was modified accordingly by the CONTAM Panel (Appendix E for model codes), regarding growth curves, adjustment of units for exposure after the breastfeeding period, milk intake when breastfeeding, absorption constant for infants, half-life in infants and body burden at birth.

94. Using the modified model and the NOAEL from the from the Russian Children's study, the CADM simulations indicated that following breastfeeding for 12 months, and a similar intake of sons after breastfeeding as for mothers, the intake should be below 0.3 pg TEQ/kg bw per day in order not to reach a serum concentration of 7.0 pg PCDD/F-WHO_{2005}-TEQ/g fat at 9 years of age.

95. When taking into account 12 months breastfeeding followed by two-fold higher intake by boys than by adults, the intake by the mothers should be below 0.25 pg PCDD/F-WHO_{2005}-TEQ/kg bw per day.

96. Considering the above, the Panel concluded that the data suggested that the long-term intake should remain below 0.25 pg WHO_{2005}-TEQ/kg bw per day or 1.75 pg WHO_{2005}-TEQ/kg bw per week to ensure that serum levels in boys remain below the NOAEL for effects on sperm concentrations of 7.0 pg WHO_{2005}-TEQ/g fat, also when breastfed for 12 months. The value of 1.75 was rounded to 2 considering the uncertainty in the estimation of the critical serum level and corresponding daily intake. The Panel decided not to apply additional UFs, since the HBGV was based on a NOAEL obtained in a study with a relatively large number of boys (n = 133) and repeated semen sampling. As a result, the TWI of 2pg WHO_{2005}-TEQ/kg bw per week was established.

97. It is important to note that the dietary exposure of breast infants should not be compared to the TWI. This is because the TWI was set to prevent a level in breast milk that would result in serum levels in children that have been associated with adverse effects. (CONTAM, 2018). In addition, the dietary exposures of toddlers and young children should not be directly compared to the TWI since an estimated two-fold higher exposure than mothers, to who the TWI applies, was already taken into account in the modelling used to establish the TWI.

Animal data

98. If the TWI were to be estimated based on LOAEL/NOAEL body burdens observed from animal data, EFSA estimated that it would have been 3 pg/kg bw per week, which is marginally higher than TWI of 2 pg TEQ/kg bw/week established by EFSA. The lowest body burden associated with adverse effects (LOAEL) was estimated to be 25 ng/kg bw estimated in the Faqi et al. (1998) study for effects on sperm concentration in male offspring. An uncertainty factor (UF) of 3.2 for extrapolating a LOAEL to NOAEL was applied and would have resulted in an estimated NOAEL body burden in the dams of 8.4 ng/kg bw. As a conservative approach, the default (UF) of 3.2 for interindividual toxicokinetic differences to account for interindividual toxicokinetic differences was applied on the NOAEL body burden, rather than the corresponding EDI leading to this body burden. CADM was used to estimate an EDI of 0.46 pg/kw bw per day which leads to this body burden in a pregnant woman after 35 years of exposure. The twofold higher exposure of a woman during childhood was not taken into account in these calculations, but this was shown to have a minor effect (CONTAM, 2018).

99. For effects on bone, the body burden at the lowest $BMDL_{05}$ was estimated to be 14 ng/kg bw, based on the study by Jämsä et al. (2001). Applying a UF of 3.2 to account for interindividual differences in toxicokinetics amongst humans

would give a body burden of 4.3 ng/kg bw for this second most sensitive endpoint, which is 1.7-fold higher than the 2.6 ng/kg bw derived for effects on semen quality in rats. As outlined in Annex 5 the COT, in 2001 set a TDI of 2 pg WHO-TEQ/kg bw to protect against effects on the developing male reproductive system resulting from the maternal body burden of dioxins (COT, 2001). This TDI was also considered protective against other possible effects of dioxins, such as cancer and cardiovascular effects. However, in 2004 a joint Scientific advisory committee on nutrition (SACN)/COT report giving advice on fish consumption established a higher guideline level of 8 pg TEQ/kg bw per day. This was to protect against non-developmental effects of dioxins and dioxin-like PCBs, which was applicable for males. This report is attached in Annex 6 of this review (COT/SACN, 2004).

Conclusion

100. The CONTAM panel concluded that based on the new TWI current exposure to PCDD/Fs and DL-PCBs are of concern as estimated intakes by the following consumer groups: Adolescents, Adults, Elderly and Very elderly exceed the new TWI (2 pg TEQ /kg bw per week) by up to a factor 15 .

101. However, the TWI is based on serum levels sampled from boys at the age of 8-9 years, and the critical window for the effects on sperm may actually be at younger age or during puberty. Furthermore, The TWI was considered protective for the general population and that it would prevent women from reaching a concentration in the blood that could lead to harmful pre- and postnatal effects. This could imply that a health-based guidance value higher than the TWI might be applicable to adult men and postmenopausal women.

Annexes to this paper

Annex 1: CONTAM opinion on the risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food.

Annex 2: Discussion paper on the EFSA Opinion on “Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food”

Annex 3: Item 5: Discussion paper on the EFSA Opinion on “Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food.”

Annex 4: COT statement on FSA funded study investigating the developmental effects of dioxin (TCDD) in rats.

Annex 5: COT statement on the tolerable daily intake for dioxins and dioxin-like polychlorinated biphenyls

Questions for the committee

102. Members are asked to consider the following questions:

i) Does the COT agree with the TWI of 2 pg WHO-TEQ/kg bw established by the CONTAM panel or should this be considered further?"

ii) Does the Committee agree that dietary exposures of infants and young children should not be compared to the new TWI since it applies to mothers and already takes into account the higher exposures of their breast-fed infants and young children?

iii) Are there any other population groups to which a health-based guidance value higher than the EFSA TWI might be applicable, e.g. men and postmenopausal women?

iv) If any higher health-based guidance value were to be set for such population groups, what would be the critical health endpoint and what data should be used?

Secretariat

September 2020

Abbreviations

b-TSH	b-Thyroid stimulating hormone
β-HCH	beta-hexachlorocyclohexane
BEQ	Bioanalytical equivalent
CALUX	Chemical activated luciferase gene expression
CI	Confidence interval
CONTAM	The Panel on Contaminants in the Food Chain
DDE	Dichlorodiphenyldichloroethylene
DEN	Deep endometriotic (adenomyotic) nodules
DIE	Deep infiltrating endometriosis
DL-PCBs	Dioxin like-polychlorinated bipehnyls
EFSA	European Food Safety Authority
F1	First filial generation
GD	Gestation day
HCB	Hexachlorobenzene
HR	Hazard ratio
HxCDDs	Hexachlorodibenzo-p-dioxin
IgG	Immunoglobulin G
i.p.	Intraperitoneal
i.m.	Intramuscular
I-TEQ	International Toxic Equivalent
LOAEL	Lowest observed adverse effect level
NOAEL	No observed adverse effect level
NHL	Non-Hodgkin’s lymphoma
OR	Odds ratio
OvE	Ovarian endometrioma
PCB	Polychlorinated biphenyl
PCDD	Polychlorinated dibenzo-p-dioxins
PCDF	Polychlorinated dibenzofurans
PeCDF	Pentachlorodibenzofuran

PEND	Peritoneal endometriosis
PND	Postnatal day
POD	Point of Departure
RR	Relative risk
s.c.	Subcutaneous
SCE	Sister chromatid exchange
SMR	Standardised mortality ratio
SWHS	Seveso Women's Health Study
T4	Thyroxine
TBG	Thyroxine binding globulin
TCDD	2,3,7,8-Tetrachlorodibenzodioxin
TCDF	2,3,7,8-tetrachlorodibenzofuran
TEQ	Toxic equivalents
TEQO	international toxic equivalencies without TCDD
WHO	World Health Organisation
WHO-TE	World Health Organisation- toxic equivalent

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COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

CONTAM opinion on the risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food.

This can be accessed at:

https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2018.5333

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Discussion paper on the EFSA Opinion on "Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food"

This can be accessed at:

https://cot.food.gov.uk/sites/default/files/tox201944furtherdiscussiononefsa.pdf

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Item 5: Discussion paper on the EFSA Opinion on "Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food."

This annex contains the minutes of the dioxins item that was discussed on the 17th September 2019.

This can be accessed at:

https://webarchive.nationalarchives.gov.uk/20200803163214/https://cot.food.gov.uk/cot-meetings/cotmeets/2019/cot-17-september-2019

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

COT statement on FSA funded study investigating the developmental effects of dioxin (TCDD) in rats.

This annex contains the COT's 2007 statement on FSA funded study investigating the developmental effects of dioxin (TCDD) in rats.

This can be accessed at:

https://webarchive.nationalarchives.gov.uk/20200803165015/https://cot.food.gov.uk/sites/default/files/cot/cotstatementdioxins200702.pdf

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

COT statement on the tolerable daily intake for dioxins and dioxin-like polychlorinated biphenyls

This Annex contains the COT's 2001 statement on the tolerable daily intake for dioxins and dioxin-like polychlorinated biphenyls.

This statement can be accessed at:

https://webarchive.nationalarchives.gov.uk/20200803134655/https://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2001/dioxinsstate

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

COT/SACN: Advice on fish consumption: risk and benefits

This annex contains the 2004 SACN/COT report on “Advice on fish consumption: benefits & risks”

This statement can be accessed at:

https://cot.food.gov.uk/sites/default/files/cot/fishreport200401.pdf