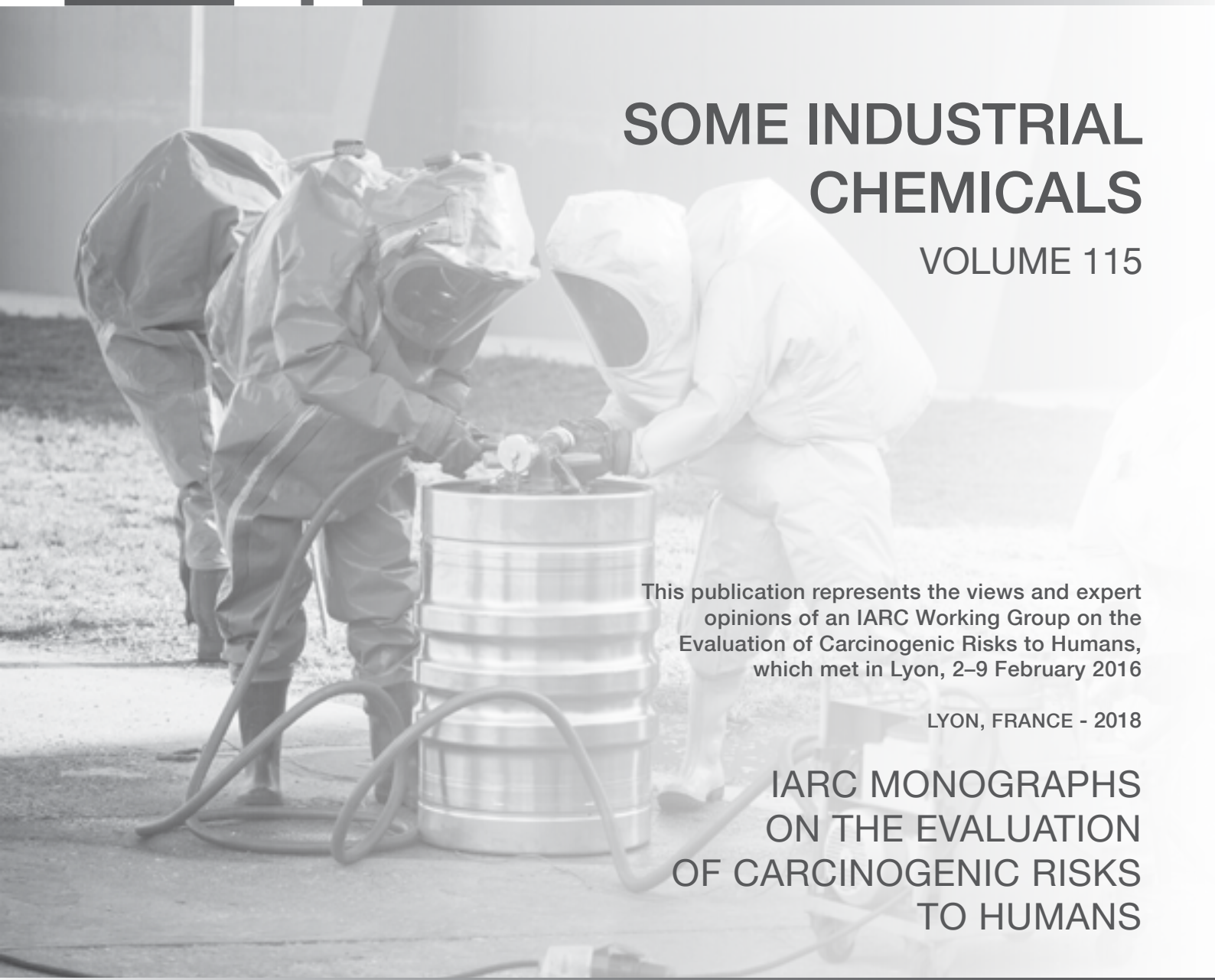
IARC MONOGRAPHS



SOME INDUSTRIAL CHEMICALS

VOLUME 115

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IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

TETRABROMOBISPHENOL A

1. Exposure Data

1.1. Identification of the agent

From NTP (2014), ECHA (2006)

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 79-94-7

Chem. Abstr. Serv. Name: Tetrabromobisphenol A

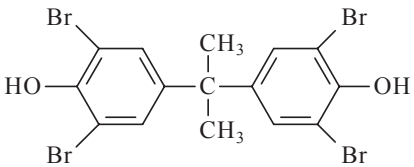
EINECS No.: 201-236-9

IUPAC Name: 2,2′,6,6′-Tetrabromo-4,4′-isopropylidenediphenol

Synonyms: 2,2-Bis(3,5-dibromo-4-hydroxyphenyl) propane; phenol, 4,4′–iso-propylidenebis, (dibromo-); 4,4′-isopropylidene-bis(2,6-dibromophenol); phenol, 4,4′-(1-methylethylidene)bis(2,6-dibromo-); 3,3′,5,5′-tetrabromobisphenol-A; tetrabromodihydroxy diphenylpropane

Acronyms: TBBP-A; TBBP; TBBPA

1.1.2 Structure and molecular formula, and relative molecular mass



Molecular formula: $C_{15}H_{12}Br_4O_2$

Relative molecular weight: 543.88

1.1.3 Physical and chemical properties of the pure substance

Description: White crystalline powder at 20 °C containing 58.4% bromine

Boiling point: ~316 °C (decomposes at 200–300 °C)

Melting point: 181–182 °C

Density: 2.12 g/cm^3

Volatility: Vapour pressure, 6.24 × 10^{-9} kPa at 25 °C

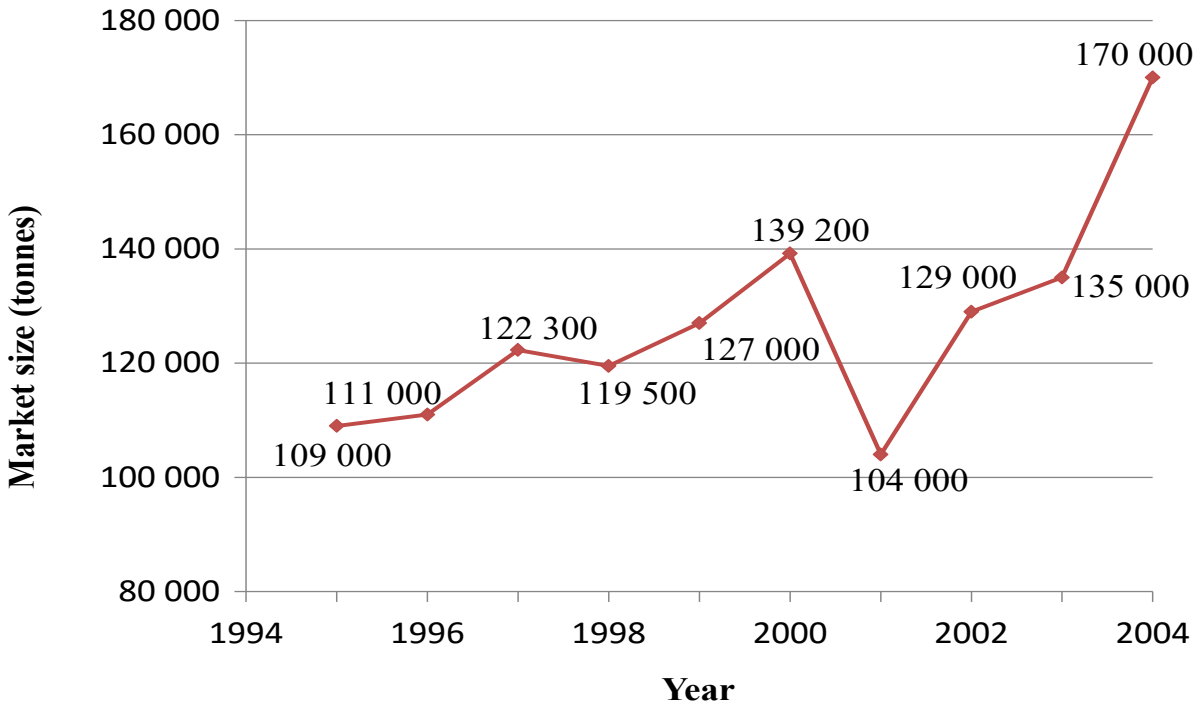
Water solubility: 1.26 mg/L at 25 °C

Octanol/water partition coefficient: log K_{ow}, 5.9

Decomposition: When heated to decomposition, emits bromine vapours

Conversion factor: 1 ppm = 22.6 mg/m^3 at 20 °C.

Fig. 1.1 Global market demand for tetrabromobisphenol A, 1995–2004



From Covaci et al. (2009); numbers were calculated from data published in ECHA (2008)

1.2 Production and use

1.2.1 Production

(a) Production methods

The production process for tetrabromobisphenol A involves the bromination of bisphenol A in the presence of a solvent, such as methanol, a halocarbon alone, or a halocarbon with water, or 50% hydrobromic acid, or aqueous alkyl monoethers (ECHA, 2006). Due to the nature of the process and the by-products (e.g. hydrobromic acid and methyl bromide) that can be formed, the production process is largely conducted in closed systems (Covaci et al., 2009).

(b) Production volume

Tetrabromobisphenol A is a compound with a high production volume that is currently produced in China, Israel, Japan, Jordan, and the USA, but no longer in the European Union. The total global production volume of tetrabromobisphenol A is estimated at > 100 000 tonnes per year (ECHA, 2008). Except for a minor reduction in production between 2000 and 2002, an overall increasing trend was observed in the estimated global market demand for tetrabromobisphenol A from 109 000 tonnes per year in 1975 to 170 000 tonnes per year in 2004 (Fig. 1.1).

1.2.2 Use

Approximately 58% of tetrabromobisphenol A is used as a reactive brominated flame retardant in epoxy, polycarbonate and phenolic resins in printed circuit boards, 18% is used for the production of tetrabromobisphenol A derivatives and oligomers, while 18% is used as additive flame retardant in the manufacture of acrylonitrile–butadiene–styrene resins or high impact polystyrene (Covaci et al., 2009).

(a) Reactive applications

Tetrabromobisphenol A is used primarily as an intermediate in the manufacture of polycarbonate unsaturated polyester and epoxy resins, in which it becomes covalently bound in the polymer. Polycarbonates are used in communication and electronic equipment, electronic appliances, transportation devices, sports and recreational equipment, and lighting fixtures and signs. Unsaturated polyesters are used in the manufacture of simulated marble floor tiles, bowling balls, furniture, coupling compounds for sewer pipes, buttons, and automotive patching compounds. Flame-retardant epoxy resins may be used mainly for the manufacture of printed circuit boards (Lassen et al., 1999). Moreover, epoxy resins containing tetrabromobisphenol A are used to encapsulate certain electronic components (e.g. plastic/paper capacitors, microprocessors, bipolar power transistors, "integrated gate bipolar transistor power modules" and "application specific integrated circuits" on printed circuit boards) (ECHA, 2008).

(b) Additive applications

Tetrabromobisphenol A is generally used with antimony oxide for optimum performance as an additive fire retardant (IPCS, 1995) that is applied in acrylonitrile–butadiene–styrene resins that are used in automotive parts, pipes and fittings, refrigerators, business machines and telephones (ECHA, 2008), and can also be applied to high-impact polystyrene resins used in casings of electrical and electronic equipment, furniture, building and construction materials (IPCS, 1995). The largest additive use of tetrabromobisphenol A is in television casings for which approximately 450 tonnes are used per year. Other uses include: personal computer monitor casings, components in printers, fax machines and photocopiers, vacuum cleaners, coffee machines and plugs/sockets (ECHA, 2008). As additive flame retardant, tetrabromobisphenol A does not react chemically with the other components of the polymer, and may therefore leach out of the polymer matrix after incorporation (Covaci et al., 2009).

1.3 Measurement and analysis

Several studies have reported on different methods for extraction of tetra-bromobisphenol A from different environmental and biological matrices (Table 1.1; Covaci et al., 2009). Solid-phase extraction on pre-packed C_{18} cartridges was the most commonly reported method for the extraction/clean-up of tetrabromobisphenol A from liquid samples, including water (Wang et al., 2015a), plasma (Chu & Letcher, 2013) and milk (Nakao et al., 2015). More aggressive extraction techniques such as Soxhlet extraction, pressurized liquid extraction, ultrasound-assisted extraction and microwave-assisted extraction were required for the efficient extraction of tetrabromobisphenol A from solid samples, including dust (Abdallah et al., 2008), soil (Tang et al., 2014), sediment (Labadie et al., 2010), sewage sludge (Guerra et al., 2010), polymers (Vilaplana et al., 2009), and frozen animal tissues (Tang et al., 2015). The inclusion of a relatively polar organic solvent (e.g. dichloromethane or acetone) was found to be necessary for the efficient extraction of tetrabromobisphenol A (Covaci et al., 2009). Hyphenated chromatographic methods coupled to mass spectrometric detection were commonly applied for the quantitative determination of tetrabromobisphenol A in various media (Table 1.1; Covaci et al., 2009). Other methods of analysis including enzyme-linked immunosorbent assay (Bu et al., 2014) and capillary electrophoresis (Blanco et al., 2005) were also reported for the determination of tetrabromobisphenol A in environmental samples.

Table 1.1 Overview of typical analytical procedures used for the determination of tetrabromobisphenol A in selected matrices

Matrix	Pretreatment	Extraction procedure (solvent)	Extract purification	Instrumental analysis	Recovery (%)	Limit of detection	References
River water, tap water, waste water	Filtration	HLB-SPE cartridge (2% ammonia in methanol)	SPE cartridge (2% formic acid in methanol)	LC-ESI-MS/MS	78–91	0.003 ng/mL	Yang et al. (2014)
Surface water	Filtration	SPE-cartridge (ethyl acetate)	–	UHPLC-UV	76	0.081 ng/mL	Kowalski & Mazur (2014)
Air samples	125-mm glass fibre filters and PUF disks	Soxhlet (DCM, 8 h)	SPE cartridge containing acidified silica (44% concentrated sulfuric acid)	LC-ESI-MS/MS	89	0.027 ng/m^3	Abdallah & Harrad (2010)
Dust	Sieving (250 µm)	Dispersive liquid–liquid microextraction	–	GC-MS	89	250 ng/g	Barrett et al. (2015)
Dust	Sieving (63 µm)	Ultrasonication (methanol:AcN:isopropanol (1:1:2), 60 °C, 30 min)	Filtration and online clean-up	LC-APCI-MS/MS	88	0.6 ng/g	Kopp et al. (2012)
Soil	Freeze-dried and sieved	PLE (DCM)	Activated silica gel column	LC-APCI-MS/MS	82–96	0.025 ng/g	Tang et al. (2014)
Soil	Mixed with sodium sulfate	Soxhlet (hexane:acetone (1:1), 24 h)	SPE cartridge	GC-MS	84–122	0.19 ng/g	Han et al. (2013)
Sediment	Sieved (230 mesh sieve)	PLE (hexane:DCM (1:3), activated copper)	Silica gel column	LC-ESI-MS/MS	70–110	0.05 ng/g	Lee et al. (2015)
Sediment	Mixed with sodium sulfate	Ultrasonication (hexane:acetone (1:1), 20 min)	Hydrochloric acid-activated copper strings and SPE cartridge	GC-NCI-MS	93	0.05 ng/g	Labadie et al. (2010)
Sewage sludge	–	Shaking with 5 mL methanol at 350 rpm, 60 min (3 cycles)	SPE cartridge	LC-ESI-MS/MS	106	–	Song et al. (2014)
Polymer fractions of WEEE	Powdered/granulated	MAE (isopropanol:hexane (1:1), 130 °C, 60 min)	0.45 mm Teflon filter	HPLC-UV	74–96	1630 ng/g	Vilaplana et al. (2009)
Human serum, human milk, dietary homogenate	Formic acid	LLE (hexane, ethanol then diethyl ether)	GPC with silica gel column	GC-NCI-MS	87–99	0.2 ng/g	Fujii et al. (2014b)

Table 1.1 (continued)

Matrix	Pretreatment	Extraction procedure (solvent)	Extract purification	Instrumental analysis	Recovery (%)	Limit of detection	References
Tissues of humans, dolphins and sharks	Mixed with sodium sulfate	Soxhlet (DCM:hexane (3:1), 16 h)	GPC and LLE with sulfuric acid and filtration	LC-ESI-MS/MS	93	0.0003 ng/g	Johnson-Restrepo et al. (2008)
Fish tissues	Freeze-dried, powdered	Soxhlet (hexane:acetone (1:1), 48 h)	Sulfuric acid and silica gel column	LC-ESI-MS/MS	84–99	0.025 ng/g	Tang et al. (2015)
Scallops, gills and digestive glands	Homogenization sodium sulfate	Soxhlet (hexane:DCM (4:1), 12 h)	SPE column	LC-ESI-MS/MS	79	5 ng/g	Hu et al. (2015b)
Egg	Homogenization sodium sulfate	Column extraction (acetone:cyclohexane (1:3), 1 h)	GPC and SPE column and derivatization	LC-TOF-MS GC-LRMS GC-HRMS	79 57	0.02 ng/g 0.01 ng/g 0.001 ng/g	Berger et al. (2004)
Birds muscle	Mixed with sodium sulfate, and ground	Soxhlet (hexane:acetone (1:1), 48 h)	GPC with silica gel column	LC-ESI-MS/MS	75	0.27 ng/g	He et al. (2010)

AcN, acetonitrile; DCM, dichloromethane; GC, gas chromatography; GC-MS, gas chromatography-mass spectrometry; GPC, gel permeation chromatography; HLB, hydrophilic lypophilic balanced; HPLC, high-performance liquid chromatography; HRMS, high-resolution mass spectrometry; LC-APCI-MS-MS/MS, liquid chromatography-atmospheric pressure chemical ionization tandem mass spectrometry; LC-ESI-MS/MS, liquid chromatography-electrospray tandem mass spectrometry; LLE, liquid-liquid extraction; LRMS, low-resolution mass spectrometry; MAE, microwave-assisted extraction; MS, mass spectrometry; NCI, negative chemical ionization; PLE, pressurized liquid extraction system; PUF, polyurethane foam; rpm, revolutions per min; SPE, solid-phase extraction; TOF, time-of-flight; UHPLC, reversed phase ultra high-performance liquid chromatography; UV, ultraviolet detection; WEEE, waste electrical and electronic equipment
Solvent mixtures: proportions as volume per volume (v/v)

1.4 Occurrence and exposure

1.4.1 Natural occurrence

Tetrabromobisphenol A does not occur naturally (ECHA, 2006).

1.4.2 Environmental occurrence

Tetrabromobisphenol A was first detected in the environment in 1983 at a level of 20 ng/g in sediment from the Neya River in Japan (Watanabe et al., 1983). Several studies have detected tetrabromobisphenol A in various biotic and abiotic matrices from different parts of the world over the past few years (Table 1.2 and Table 1.3). This chemical was detected in air, dust, water, soil, sediment, and sewage sludge from various areas across the globe (Covaci et al., 2009), including the Arctic, which indicates its ability to undergo long-range transport (Xie et al., 2007; de Wit et al., 2010). The frequent detection of tetrabromobisphenol A and the ubiquitous nature of this contaminant indicates that it is continuously released into the environment due to its reported half-life in the soil ($t_{0.5}$ = 48–84 days) (NTP, 2014). Moreover, tetrabromobisphenol A is frequently detected in biotic samples, including fish, birds, and human tissue (Covaci et al., 2009; Table 1.3).

A recent review reported that China was the region most affected by pollution with tetrabromobisphenol A. The most serious cases of tetrabromobisphenol A pollution were found in Guiyu, Guangdong (a primitive e-waste dismantling site), with concentrations reaching 66 010–95 040 pg/m^3 in the air (mean, 82 850 pg/m^3), in Shouguang, Shandong (a tetrabromobisphenol A-manufacturing site) with concentrations ranging from 1.64 to 7758 ng/g dry weight in the soil (mean, 672 ng/g) and in Chaohu Lake, Anhui (industrial concentration site), with concentrations reaching 850–4870 ng/L in water (Liu et al., 2016).

1.4.3 Occupational exposure

Occupational exposures to tetrabromobisphenol A have been measured in facilities manufacturing electronic products and, at higher concentrations, in recycling facilities.

Mean concentrations of tetrabromobisphenol A in the air were reported to be 30 ng/m^3 in the dismantling hall and 140 ng/m^3 in the shredder at an electronic products recycling plant, and to be several orders of magnitude higher than those found in the other indoor microenvironments investigated (e.g. 0.036 ng/m^3 in the offices) (Sjödin et al., 2001).

A low concentration of tetrabromobisphenol A (0.011 ng/m^3) was measured in the particulate matter collected from a medical equipment-manufacturing building (Batterman et al., 2010).

Occupational exposure of workers to tetrabromobisphenol A at a Chinese printed circuit-board plant via ingestion, dermal absorption, and inhalation of dust varied widely by process, with the greatest estimated exposures being 1930, 431, and 96.5 pg/kg body weight (bw) per day, respectively. Raw-material warehouse workers were the most highly exposed, with an average overall exposure of 2413 pg/kg bw per day. Dust ingestion was the predominant pathway of exposure (Zhou et al., 2014).

Low levels (< 0.09–63 ng/cm^2) of tetrabromobisphenol A were detected in patch samples attached to clothing of workers at an electronics dismantling facility and a circuit board factory in Finland. However, tetrabromobisphenol A was below the limit of quantification (< 2 ng/hand) in handwash samples (Mäkinen et al., 2009).

Tetrabromobisphenol A was also detected in the serum of workers at levels that are presented in Table 1.3.

Table 1.2 Concentrations of tetrabromobisphenol A in abiotic matrices

Matrix (number of samples)	Location	Concentration Mean[a] (range) or range	Reference
Air			
Particulate matter in office air (56)	China	949 [GM] (30–59 140) ng/g	Ni & Zeng (2013)
Homes (5)	United Kingdom	16 (9–22) pg/m³	Abdallah et al. (2008)
Offices (5)		16 (4–33) pg/m³	
Public microenvironments (4)		26 (17–32) pg/m³	
Outdoor air (5)		0.8 (0.7–0.9) pg/m³	
Cars (20)	United Kingdom	3 (0.2–5) pg/m³	Abdallah & Harrad (2010)
Homes (2)	Japan	8–20 pg/m³	Takigami et al. (2009)
Outdoor air (2)		7.0–9.5 pg/m³	
Indoor air microenvironments (4)	Japan	200 (< 100–600) pg/m³	Inoue et al. (2006)
Indoor air at an electronics recycling plant and other work environments	Sweden	200 (110–370) pg/m³	Sjödin et al. (2001)
Outdoor air rural site	Germany	< 0.04–0.85 pg/m³	Xie et al. (2007)
Outdoor air	Wadden Sea	0.31–0.69 pg/m³	
Outdoor air	North-eastern Atlantic	< 0.04–0.17 pg/m³	
E-waste recycling site	China	82 850 (66 010–95 040) pg/m³	Reported in Liu et al. (2016)
Dust			
House dust (34)	China	250 (< 1–2300) mg/g	Wang et al. (2015b)
House dust (42)	Colombia	21 (< 1–280) mg/g	
House dust (28)	Greece	36 (< 1–630) mg/g	
House dust (35)	India	45 (< 1–640) mg/g	
House dust (14)	Japan	360 (12–1400) mg/g	
House dust (16)	Republic of Korea	130 (43–370) mg/g	
House dust (17)	Kuwait	12 (< 1–36) mg/g	
House dust (22)	Pakistan	50 (< 1–800) mg/g	
House dust (23)	Romania	28 (< 1–380) mg/g	
House dust (19)	Saudi Arabia	61 (< 1–360) mg/g	
House dust (22)	USA	91 (< 1–650) mg/g	
House dust (12)	Viet Nam	99 (< 1–670) mg/g	
Houses (35)	United Kingdom	87 (0.5–382) mg/g	Abdallah et al. (2008)
Offices (28)		49 (0.5–140) mg/g	
Cars (20)		6.0 (0.5–25) mg/g	
Public microenvironments (4)		220 (52–350) mg/g	
Primary schools and daycare centres (43)	United Kingdom	200 (17–1400) mg/g	Harrad et al. (2010)
House dust (45)	Belgium	11.7 [median] mg/g	D'Hollander et al. (2010)
Office dust (10)		70.4 [median] mg/g	
House dust (20)	Germany	44 (3–233) mg/g	Fromme et al. (2014)
Gym dust (4)	USA	680 (200–900) mg/g	La Guardia & Hale (2015)
Water			
Lake water (9)	United Kingdom	0.14–3.20 mg/L	Harrad et al. (2009)
River and lake water (9)	Poland	260–490 mg/L	Kowalski & Mazur (2014)
River water (5)	France	< 0.035–0.064 mg/L	Labadie et al. (2010)
Surface water (14)	China	230 (ND–920) mg/L	Xiong et al. (2015)

Table 1.2 (continued)

Matrix (number of samples)	Location	Concentration Mean[a] (range) or range	Reference
Surface water in industry site	China	850–4870 mg/L	Reported in Liu et al. (2016)
Soil			
Soil from e-waste recycling site (5)	China	5–17 mg/g	Han et al. (2013)
Land-use soils (6)	China	< 0.3–144 mg/g	Huang et al. (2014)
Agricultural and industrial soils (11)	Spain	Agricultural, 0.3 mg/g; industrial, 3.4–32.2 mg/g	Sánchez-Brunete et al. (2009)
Agricultural soils (38)	China	107 [GM] (1.6–7758) mg/g	Zhu et al. (2014)
Soil from tetrabromobisphenol A manufacturing site	China	672 (1.64–7758) mg/g	Reported in Liu et al. (2016)
Sediment and sewage sludge			
Sediment (7) and sludge (7)	Spain	Sludge, < 10–1329 mg/g; sediment, < 9–15 mg/g	Guerra et al. (2010)
Lake sediment (9)	England	0.3–3.8 mg/g	Harrad et al. (2009)
Sediment (rivers and ponds) (31)	Czech Republic	3.8–17.7 mg/g	Hloušková et al. (2014)
River bed sediments (5)	France	0.07–0.3 mg/g	Labadie et al. (2010)
Nakdong river sediment	Republic of Korea	0.5–150 mg/g	Lee et al. (2015)
Dongjiang river sediment (17)	China	3.8–230 mg/g	Zhang et al. (2009)
Scheldt basin sediment (20)	Netherlands	5.4 (< 0.1–67) mg/g	Morris et al. (2004)
Skerne river sediment (22)	England	451 (< 2.4–9750) mg/g	Morris et al. (2004)
Lake Mjøsa sediment (3)	Norway	0.04–0.13 mg/g	Schlabach et al. (2004)
Marine sediment	Japan	5.5 mg/g	Suzuki & Hasegawa (2006)
Marine sediment	Singapore	0.05–0.06 mg/g	Zhang et al. (2015a)
Sewage sludge (Montreal water waste treatment plant)	Canada	300 mg/g	Saint-Louis & Pelletier (2004)
Municipal sewage sludge (52)	China	20.5 [GM] (1–259) mg/g	Song et al. (2014)
Municipal sewage sludge (57)	Sweden	2 [median] (< 0.3–220) mg/g	Oberg et al. (2002)
Municipal (4) and industrial (7) sludge	Republic of Korea	4–618 mg/g	Hwang et al. (2012)
Sewage sludge (17)	Spain	104 (< 10–472) mg/g	Gorga et al. (2013)
Sewage sludge (4)	Canada	2–28 mg/g	Chu et al. (2005)

[a] Arithmetic mean unless indicated otherwise in square brackets
GM, geometric mean; ND, not detected

Table 1.3 Concentrations of tetrabromobisphenol A reported in biological matrices or tissues

Species (No. of samples)	Matrix or tissue	Location	Concentration Mean (range) or range (ng/g lipid weight)[a]	Reference
Humans				
Occupational exposure:				
Electronics dismantling (4)	Serum	Sweden	< 1.1–4.0	Hagmar et al. (2000a)
Computer technicians (19)	Serum	Sweden	0.54–1.85	Jakobsson et al. (2002)
Electronics dismantling (5)	Serum	Norway	1.3 (0.64–1.8)	Thomsen et al. (2001)
Circuit board producers (5)	Serum		0.54 (< 0.1–0.80)	
Laboratory personnel (5)	Serum		0.34 (< 0.1–0.52)	
General population:				
General population (21)	Serum	Belgium	80 ng/L	Dirtu et al. (2008)
General population (93)	Serum	Norway	0.31–0.71	Thomsen et al. (2002)
General population (24)	Serum	Japan	0.001 (ND–3.7)	Nagayama et al. (2000)
General population (20)	Adipose tissue	New York, USA	0.048 (< 0.003–0.464)	Johnson-Restrepo et al. (2008)
Men (60)	Serum	Japan	0.05–0.95	Fujii et al. (2014a)
Women (91)	Milk Serum Cord serum	France	4.11 (0.06–37.3) mg/g fresh weight 19.8 (0.23–93.2) mg/g fresh weight 103 (2–649) mg/g fresh weight	Cariou et al. (2008)
Mothers (30)	Milk	Czech Republic	< 2–688	Lankova et al. (2013)
Mothers (19)	Milk	Japan	1.9 (< 0.02–8.7)	Nakao et al. (2015)
Mothers (110)	Milk	Ireland	0.33	Pratt et al. (2013)
Mothers (34)	Milk	England	0.06 (0.04–0.65)	Abdallah & Harrad (2011)
Mothers (43)	Milk	Boston, USA	0.03–0.55	Carignan et al. (2012)
Mothers (103)	Milk	China	0.41 (< LOD–12.5)	Shi et al. (2013)
Mothers and infants (78)	Serum	Republic of Korea	Mothers, 10.7 (< 0.05–74); infants, 83 (< 0.05–713)	Kim & Oh (2014)
Other species				
Common whelk (3)	Whole	North Sea	45 (5.0–96)	Morris et al. (2004)
Sea star (1)	Whole	Tees estuary, UK	205	
Hermit crab (9)	Whole	North Sea	11 (< 1–35)	
Mysid (2)	Whole	Scheldt estuary	0.8–0.9	Verslycke et al. (2005)
Snakehead fish (5)	Whole	China	0.04–1.3	Tang et al. (2015)
Mud carp (5)	Whole	China	0.03–2.85	Tang et al. (2015)
Fish (45)	Whole	Japan	0.01–0.11	Ashizuka et al. (2008)
Fresh water fish (30)	Muscle	England	< 0.3–1.7	Harrad et al. (2009)
Fish (59)	Muscle	Czech Republic	60.8 (5–203)	Svihlikova et al. (2015)
Whiting (3)	Muscle	North Sea	136 (< 97–245)	Morris et al. (2004)
Cod (2)	Liver	North Sea	< 0.3–0.8	
Hake (1)	Liver	Atlantic	< 0.2	
Eel (19)	Muscle	Scheldt estuary	1.6 (< 0.1–13)	
Eel (11)	Muscle	Dutch rivers	0.3 (< 0.1–1.3)	
Yellow eel (4)	Muscle	Scheldt basin	< 0.1–2.1	
Yellow eel (5)	Muscle	Dutch rivers	< 0.1–1.0	
Perch, pike, smelt, vendace, trout (12)	Muscle	Norway	1.0–13.7	Schlabach et al. (2004)

Table 1.3 (continued)

Species (No. of samples)	Matrix or tissue	Location	Concentration Mean (range) or range (ng/g lipid weight)[a]	Reference
Bull shark (13)	Muscle	Florida, USA	0.03–35.6	Johnson-Restrepo et al. (2008)
Atlantic sharpnose shark (3)	Muscle	Florida, USA	0.87 (0.5–1.4)	
African penguins (3)	Muscle	Gdansk zoo, Poland	2.7–8.9	Reindl & Falkowska (2015)
	Liver		4–9.3	
	Adipose		3–12	
	Brain		7–15	
	Egg		11.4 ± 2.6	
Cormorant (2)	Liver	Wales and England, UK	2.5–14	Morris et al. (2004)
Common tern (10)	Egg	Western Scheldt	< 2.9	
Predatory bird (62)	Egg	Norway	< 0.003–0.013	Herzke et al. (2005)
Harbour seal (2)	Blubber	Wadden Sea	< 14	Morris et al. (2004)
Harbour porpoise (9)	Blubber	North Sea	83 (0.1–418)	
Harbour porpoise (1)	Blubber	Tyne/Tees rivers, UK	0.31	
Harbour porpoise (82)	Blubber	UK	< 5–35	Law et al. (2006a)
Bottlenose dolphin (15)	Blubber	Florida, USA	0.05–8.48	Johnson-Restrepo et al. (2008)

[a] Unless otherwise indicated
LOD, limit of detection; ND, not detected

1.4.4 Exposure of the general population

As a reactive flame retardant, the only potential for exposure is from unreacted tetrabromobisphenol A, which may exist where an excess has been added during the production process. When used as an additive (up to 22% by weight), the potential for the migration of tetrabromobisphenol A out of the matrix is greater, due to abrasion, weathering and high temperatures (ECHA, 2006).

Exposure of the general population predominantly occurs through the diet and through ingestion of indoor dust. While intake by very young children is predominantly via ingestion of indoor dust, intake by adults occurs mainly via the diet. Very young children are estimated to have a higher daily intake than adults. Exposure may occur prenatally, and tetrabromobisphenol A has been measured in breast milk (see Table 1.3).

Average estimated exposures of the population in the United Kingdom to tetrabromobisphenol A via inhalation of outdoor and indoor air from different microenvironments were 100–300 pg per day (Abdallah et al., 2008). In Japan, adults were reported to inhale tetrabromobisphenol A at 67–210 pg per day, while the exposure of children was 37–114 pg per day (Takigami et al., 2009). The daily intake of tetrabromobisphenol A in a Chinese population via inhalation and ingestion of indoor dust particles of different particle sizes accumulated in air-conditioner filters was estimated. The results revealed that approximately 28.7 pg/kg bw per day particulate matter $(PM)_{2.5}$-bound tetrabromobisphenol A can be inhaled deep into the lungs, while 14.5 pg/kg bw per day PM_{10}-bound tetrabromobisphenol A tends to be

deposited in the upper parts of the respiratory system. The average adult intake of tetrabromobisphenol A was 17.6 pg/kg bw per day via dust inhalation and 966.2 pg/kg bw per day via dust ingestion (Ni & Zeng, 2013).

Several studies have highlighted the importance of the accidental ingestion of indoor dust as a pathway of human exposure to tetrabromobisphenol A. The significance of this pathway increases for toddlers who ingest more dust (due to increased hand-to-mouth behaviour) than adults, spend more time in close proximity to the floor and have lower personal hygiene standards. Moreover, the body weight of toddlers and children results in higher exposure to tetrabromobisphenol A when estimated on a per-kilogram of body weight basis (Harrad et al., 2010). Human exposure to tetrabromobisphenol A via the ingestion of indoor dust was estimated in 12 countries (Table 1.2). The highest estimated daily intake in dust was reported for infants and toddlers in Japan (median, 820 and 430 pg/kg bw per day, respectively), the Republic of Korea (median, 500 and 260 pg/kg bw per day, respectively) and China (median, 140 and 70 pg/kg bw per day, respectively). The estimated daily intake values for these three countries were several times higher than those found for other countries (Wang et al., 2015b).

In the United Kingdom, average estimated daily intakes of tetrabromobisphenol A from the ingestion of dust were 1600 and 4400 pg/day for adults and toddlers, respectively, contributing 34% and 90% of their overall daily intake of tetrabromobisphenol A from the air, dust and diet (Abdallah et al., 2008).

The average dietary intake of tetrabromobisphenol A by adults and toddlers in the United Kingdom was 1600 and 5400 pg/kg bw per day, respectively, from 19 food groups (FSA, 2006). [The Working Group noted that these estimates should be regarded with caution due to the large number of "non-detects" in the samples analysed. The concentration of tetrabromobisphenol A in the non-detects was assumed to be half the limit of detection, hence the estimates of overall dietary intake are largely dependent on the limit of detection of the method (0.36 µg/kg whole weight).]

In a smaller study on six food groups, the total average dietary intake of tetrabromobisphenol A by the Dutch population was 40 pg/kg bw per day (de Winter-Sorkina et al., 2003).

Tetrabromobisphenol A was measured in 48 Chinese total diet study samples collected in 2007. The medium bound estimated daily intake of tetrabromobisphenol A for an average adult from foods of animal origin was 256 pg/kg bw per day (Shi et al., 2009). In Japan, the daily adult intake of tetrabromobisphenol A ranged from 4 to 40 ng in 10 duplicate diet samples collected in 2004 from Okinawa. In 2009, the estimated intake of tetrabromobisphenol A from an analysis of another 10 duplicate diet studies from the same area decreased to 0.5–7.5 ng per day. The average estimated dietary intake of a Japanese adult was 185 pg/kg bw per day (Fujii et al., 2014b).

Dietary exposure to tetrabromobisphenol A among nursing infants via breast milk is well documented. The average estimated daily intake of tetrabromobisphenol A for a Japanese nursing infant was 3.4 ng/kg bw per day (Fujii et al., 2014b). The average intake of tetrabromobisphenol A of a baby aged 1 month in the United Kingdom via breast milk was estimated at 1000 pg/kg bw per day (Abdallah & Harrad, 2011). In China, the average estimated daily intake of tetrabromobisphenol A via human milk was 5094 pg/kg bw per day for nursing infants aged 1–6 months (Shi et al., 2009).

Tetrabromobisphenol A was also detected in all umbilical cord samples from 16 Japanese mothers (16 ± 5.5 pg/g wet weight), indicating potential prenatal exposure (Kawashiro et al., 2008).

[The Working Group noted that, in the above studies, the dust PM_{10} fraction, rather than the higher inhalable fraction, was reported.]

1.5 Regulations and guidelines

There are no current restrictions on the production of tetrabromobisphenol A or its derivatives in the European Union or worldwide. The only exposure limit value for tetrabromobisphenol A was provided by the United Kingdom Committee on Toxicology as a tolerable daily intake of 1 mg/kg bw per day (COT, 2004). According to the Global Harmonized System of Classification and Labelling of Chemicals, tetrabromobisphenol A is very toxic to aquatic life (H400), with long-lasting effects (H410) (ECHA, 2016).

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

See Table 3.1

3.1 Mouse

Groups of 50 male and 50 female B6C3F$_1$/N mice (age, 5–6 weeks) were given tetrabromobisphenol A (purity, > 99%) in corn oil by gavage at doses of 0 (control), 250, 500 or 1000 mg/kg bw on 5 days per week for up to 105 weeks (NTP, 2014). Survival of males and females at 1000 mg/kg bw was significantly lower than that of their respective vehicle-control group. Mean body weights of females at 1000 mg/kg bw were more than 10% lower than those of the vehicle controls after week 25. This decrease in survival at 1000 mg/kg bw was attributed to forestomach toxicity, which consisted of ulcers, inflammation, and/or hyperplasia. Because of the large decrease in survival of mice at 1000 mg/kg bw, this dose was not used in the statistical analysis for treatment-related tumour formation.

In male mice, increases in the incidence of hepatoblastoma were observed at both 250 and 500 mg/kg bw (2/50 controls, 11/50 at 250 mg/kg bw ($P = 0.006$), and 8/50 at 500 mg/kg bw [not significant]). The incidence of hepatoblastoma in the treated groups exceeded the upper bound of the range for historical controls for this tumour in studies with gavage in corn oil and for all routes. The historical incidence of hepatoblastoma in male mice for studies with gavage in corn oil was 9/250 (3.6% ± 2.6%; range, 0–6%) and for all routes was 40/949 (4.2% ± 3.5%; range, 0–12%). [Hepatoblastomas are uncommon spontaneous neoplasms that may occur after chemical administration, and have been seen after other chemical treatments (Bhusari et al., 2015).] An increased incidence of liver foci (clear cell and eosinophilic foci) and a significant increase in the incidence of hepatocellular adenoma (multiple) were seen in treated males (12/50 controls, 20/50 at 250 mg/kg bw, and 28/50 at 500 mg/kg bw ($P \leq 0.05$)). However, the incidence of hepatocellular adenoma (including multiple) was not increased in treated males (32/50 controls, 33/50 at 250 mg/kg bw, and 38/50 at 500 mg/kg bw). The historical incidence of hepatocellular adenoma (including multiple) in male mice in studies in which tetrabromobisphenol A was administered by gavage in corn oil was 145/250 (58.0% ± 5.1%; range, 52–64%), and for administration by all routes was 594/949 (62.6% ± 9.1%; range, 48–78%). The incidence of hepatocellular carcinoma was not significantly increased in male mice (11/50 controls, 15/50 at 250 mg/kg bw, and 17/50 at 500 mg/kg bw) and was within the historical ranges; the historical incidence of hepatocellular carcinoma in male mice in gavage studies (in corn oil) was 87/250 (34.8% ± 10.9%; range, 22–44%), and for administration by all routes was 348/949 (36.7% ± 11.4%; range, 22–56%). However, the incidence of hepatocellular carcinoma or hepatoblastoma (combined) was significantly increased at 250 mg/kg bw (12/50 controls, 24/50 at 250 mg/kg bw ($P = 0.008$), and 20/50

Table 3.1 Studies of carcinogenicity in experimental animals given tetrabromobisphenol A by oral gavage in corn oil

Species, strain (sex) Age at start Duration Reference	Purity Dose regimen No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Mouse, B6C3F$_1$/N (M) 5–6 wks 105 wks NTP (2014)	Purity, > 99% 0, 250, 500 mg/kg bw 5 days/wk for 105 wks 50/group 33, 26, 39	*Liver* Hepatoblastoma: 2/50, 11/50*, 8/50 Hepatocellular carcinoma: 11/50, 15/50, 17/50 Hepatocellular carcinoma or hepatoblastoma (combined): 12/50, 24/50*, 20/50 Hepatocellular adenoma: 32/50, 33/50, 38/50 *Large intestine (caecum or colon)* Adenoma or carcinoma (combined): 0/50, 0/50, 3/50 *All organs* Haemangioma: 2/50, 0/50, 1/50 Haemangiosarcoma: 1/50, 5/50, 8/50* Haemangioma or haemangiosarcoma (combined): 3/50, 5/50, 9/50	 *P = 0.006 NS *P = 0.008 NS Trend: P = 0.039 NS Trend: P = 0.014; *P = 0.019 Trend: P = 0.047	GLP study Due to the large decrease in survival of mice at 1000 mg/kg bw, this dose was not used in the statistical analysis for treatment-related tumour formation The historical incidence of hepatoblastoma in male mice was: corn oil gavage studies: 9/250 (3.6% ± 2.6%; range, 0–6%); all routes: 40/949 (4.2% ± 3.5%; range; 0–12%) The historical incidence of caecum or colon adenoma or carcinoma (combined) in male mice was: corn oil gavage studies: 0/250; all routes: 4/950 (0.4% ± 0.8%; range, 0–2%)
Mouse, B6C3F$_1$/N (F) 5–6 wks 105 wks NTP (2014)	Purity, > 99% 0, 250, 500 mg/kg bw 5 days/wk for 105 wks 50/group 40, 31, 36	*All sites* No treatment-related tumorigenic effects		GLP study Due to the large decrease in survival of mice at 1000 mg/kg bw, this dose was not used in the statistical analysis for treatment-related tumour formation
Rat, Wistar Han [Crl:WI(Han)] (M) 6–7 wks 104 wks NTP (2014)	Purity, > 99% 0, 250, 500, 1000 mg/kg bw 5 days/wk for 104 wks 50/group 33, 28, 38, 39	*Testis* Interstitial cell adenoma, bilateral: 0/50, 0/50, 1/50, 0/50 Interstitial cell adenoma (includes bilateral): 0/50, 0/50, 1/50, 3/50	 NS Trend: P = 0.023	GLP study Historical incidence of interstitial cell adenoma in male rats (all routes): 4/150 (2.7%)

Table 3.1 (continued)

Species, strain (sex) Age at start Duration Reference	Purity Dose regimen No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Rat, Wistar Han [Crl:WI(Han)] (F) 6–7 wks 105 wks NTP (2014)	Purity, > 99% 0, 250, 500, 1000 mg/kg bw 5 days/wk for 104 wks 50, 50, 50, 50 35, 34, 29, 33	*Uterus* (original transverse review)		GLP study Historical incidence of uterine adenocarcinoma (all routes): 7/150 (4.7%) in studies involving an original transverse examination; historical incidence of malignant mixed Müllerian tumour (all routes): 0/150 in studies involving an original transverse examination
		Adenoma: 0/50, 0/50, 3/50, 4/50	Trend: $P = 0.010$	
		Adenocarcinoma: 3/50, 3/50, 8/50, 9/50	Trend: $P = 0.016$	
		Malignant mixed Müllerian tumour: 0/50, 4/50, 0/50, 2/50	NS (rare tumour)	
		Adenoma, adenocarcinoma or malignant mixed Müllerian tumour (combined): 3/50, 7/50, 11/50*, 13/50**	Trend: $P = 0.003$; *$P = 0.013$; **$P = 0.005$	
		Uterus (residual longitudinal review)		
		Adenoma: 3/50, 2/50, 1/50, 3/50	NS	
		Adenocarcinoma: 4/50, 9/50, 15/50*, 15/50**	Trend: $P = 0.003$; *$P = 0.002$; **$P = 0.005$	
		Malignant mixed Müllerian tumour: 0/50, 0/50, 0/50, 1/50	NS (rare tumour)	
		Adenoma, adenocarcinoma or malignant mixed Müllerian tumour (combined): 6/50, 10/50, 16/50*, 16/50**	Trend: $P = 0.008$; *$P = 0.007$; **$P = 0.015$	
		Uterus (original transverse and residual longitudinal review combined)		
		Adenoma: 3/50, 2/50, 4/50, 6/50	NS	
		Adenocarcinoma: 4/50, 10/50, 15/50*, 16/50**	Trend: $P = 0.002$; *$P = 0.002$; **$P = 0.002$	
		Malignant mixed Müllerian tumour: 0/50, 4/50, 0/50, 2/50	NS	
		Adenoma, adenocarcinoma or malignant mixed Müllerian tumour: 6/50, 11/50, 16/50*, 19/50**	Trend: $P < 0.001$; *$P = 0.007$; **$P = 0.002$	

bw, body weight; F, female; GLP, good laboratory practice; M, male; NS, not significant; wk, week

at 500 mg/kg bw). The historical incidence of hepatocellular carcinoma or hepatoblastoma (combined) in male mice in gavage studies (in corn oil) was 93/250 (37.2% ± 10.0%; range, 24–48%) and for administration by all routes was 371/949 (39.1% ± 11.6%; range, 22–54%). The incidence of caecum or colon tumours (adenoma or carcinoma, combined) in male mice was 0/50 controls, 0/50 at 250 mg/kg bw, and 3/50 at 500 mg/kg bw, which was statistically significantly increased by the trend test ($P = 0.039$), but not by pairwise comparison. For the three male mice at 500 mg/kg bw with tumours of the large intestine, one had a caecum carcinoma, one had a colon carcinoma and one had a colon adenoma. The incidence of these tumours (3/50) exceeded the range for historical controls in gavage studies (in corn oil) and for administration by all routes. The historical incidence for caecum or colon adenoma or carcinoma (combined) in male mice in gavage studies (in corn oil) was 0/250 and for administration by all routes was 4/950 (0.4% ± 0.8%; range, 0–2%). A significant positive trend ($P = 0.014$) in the incidence of haemangiosarcoma (all organs) (1/50 controls, 5/50 at 250 mg/kg bw, and 8/50 at 500 mg/kg bw) was observed in males and the incidence at 500 mg/kg bw was also significantly increased ($P = 0.019$). The incidence of haemangiosarcoma (all organs) in historical controls in gavage studies (in corn oil) was 28/250 (11.2% ± 6.4%; range, 2–18%).

No significant increase in the incidence of tumours was observed in female mice treated with tetrabromobisphenol A. Treatment-related non-neoplastic lesions were found in the forestomach in male and female mice, and in the kidney in male mice (NTP, 2014).

[The strengths of this study, which complied with good laboratory practice, included the use of multiple doses, the large number of animals per group, and the treatment of males and females.]

3.2 Rat

Groups of 50 male and 50 female Wistar Han [Crl:WI(Han)] rats (age, 6–7 weeks) were given tetrabromobisphenol A (purity, > 99%) by gavage at doses of 0 (control), 250, 500, or 1000 mg/kg bw on 5 days per week for up to 104 (males) or 105 (females) weeks (NTP, 2014). Mean body weights of the males at 500 and 1000 mg/kg bw were at least 10% lower than those of the vehicle-control group after week 25. The mean body weights in the other groups of treated males and all groups of treated females were similar to those of the corresponding controls.

3.2.1 Original transverse examination of the uterus

In treated female rats, an increase in the incidence of uterine epithelial tumours was observed. The incidence of uterine adenoma was significantly increased according to trend statistics ($P = 0.010$), but not pairwise statistics (0/50 controls, 0/50 at 250 mg/kg bw, 3/50 at 500 mg/kg bw, and 4/50 at 1000 mg/kg bw), and the historical incidence in female rats was 0/150 (all routes). The incidence of uterine adenocarcinoma was also increased according to trend statistics ($P = 0.016$), but not pairwise statistics (3/50 controls, 3/50 at 250 mg/kg bw, 8/50 at 500 mg/kg bw, and 9/50 at 1000 mg/kg bw), and the historical incidence (all routes) in female rats was 7/150 (including one carcinoma of the endometrium). Malignant mixed Müllerian tumours were present in treated groups (0/50 controls, 4/50 at 250 mg/kg bw, 0/50 at 500 mg/kg bw, and 2/50 at 100 mg/kg bw), but were not seen in historical control data (all routes of exposure, 0/150). The incidence of uterine adenoma, adenocarcinoma, or malignant mixed Müllerian tumour (combined) was increased in treated groups (3/50 controls, 7/50 at 250 mg/kg bw, 11/50 at 500 mg/kg bw ($P = 0.013$), and 13/50 at 1000 mg/kg bw ($P = 0.005$)), with a statistically positive trend ($P = 0.003$), and the

historical incidence for these uterine tumours (combined) by all routes was 7/150 (4.7% ± 2.3%; range, 2–6%). In addition, cystic endometrial hyperplasia was reported in this initial evaluation (8/50 controls, 13/50 at 250 mg/kg bw, 11/50 at 500 mg/kg bw, and 18/50 at 1000 mg/kg bw ($P \leq 0.05$)). These findings were based on the traditional histopathology review of the uterus from the United States National Toxicology Program (NTP), with a transverse section through each uterine horn approximately 0.5 cm from the cervix of the uterus. The cervix and vagina were not investigated in most animals in this original review of uterine pathology.

3.2.2 Residual longitudinal examination of the uterus

While the initial (original) review of the uterus showed a treatment-related carcinogenic effect, an additional examination of the uterus called the "residual longitudinal" examination was conducted to examine all remaining parts of the uterus, cervix, and vagina more completely. This residual longitudinal examination consisted of trimming, embedding and sectioning the remaining uterine tissue, cervix, and vagina (remaining in the formalin-fixed samples) longitudinally. Additional non-neoplastic and neoplastic uterine lesions were found in this review that supported the original carcinogenic findings. The findings in Table 3.1 are presented as: the original carcinogenic findings; the carcinogenic findings of the residual longitudinal examination; and the combined carcinogenic findings of the original and residual longitudinal examinations. There were no historical control data for the residual or residual and original (combined) uterine tumour findings (NTP, 2014).

After the residual longitudinal examination of the uterus, the incidence of atypical endometrial hyperplasia was significantly increased in all treated groups (2/50 controls, 13/50 at 250 mg/kg bw ($P \leq 0.01$), 11/50 at 500 mg/kg bw ($P \leq 0.01$) and 13/50 at 1000 mg/kg bw ($P \leq 0.01$)). This lesion had not been identified in the original transverse review. [This lesion is considered to be preneoplastic (Bartels et al., 2012; van der Zee et al., 2013; NTP, 2014).] The incidence of uterine tumours in the residual longitudinal examination was: uterine adenoma – 3/50 controls, 2/50 at 250 mg/kg bw, 1/50 at 500 mg/kg bw, and 3/50 at 1000 mg/kg bw; uterine adenocarcinoma (P for trend, 0.003) – 4/50 controls, 9/50 at 250 mg/kg bw, 15/50 at 500 mg/kg bw ($P = 0.002$), and 15/50 at 1000 mg/kg bw ($P = 0.005$); malignant mixed Müllerian tumours – 0/50 controls; 0/50 at 250 mg/kg bw, 0/50 at 500 mg/kg bw, and 1/50 at 1000 mg/kg bw; and uterine adenoma, adenocarcinoma, or malignant mixed Müllerian tumour (combined) (P for trend, 0.008) – 6/50 controls, 10/50 at 250 mg/kg bw, 16/50 at 500 mg/kg bw ($P = 0.007$), and 16/50 at 1000 mg/kg bw ($P = 0.015$) (NTP, 2014).

3.2.3 Original transverse and residual longitudinal examinations of the uterus (combined)

The incidence of uterine tumours in the original and residual examinations (combined) was: uterine adenoma – 3/50 controls, 2/50 at 250 mg/kg bw, 4/50 at 500 mg/kg bw, and 6/50 at 1000 mg/kg bw; uterine adenocarcinoma (P for trend, 0.002) – 4/50 controls, 10/50 at 250 mg/kg bw, 15/50 at 500 mg/kg bw ($P = 0.002$), and 16/50 at 1000 mg/kg bw ($P = 0.002$); malignant mixed Müllerian tumours – 0/50 controls, 4/50 at 250 mg/kg bw, 0/50 at 500 mg/kg bw, and 2/50 at 1000 mg/kg bw; and uterine adenoma, adenocarcinoma or malignant mixed Müllerian tumours (combined) (P trend, < 0.001) – 6/50 controls, 11/50 at 250 mg/kg bw, 16/50 at 500 mg/kg bw ($P = 0.007$), and 19/50 at 1000 mg/kg bw ($P = 0.002$). The incidence of endometrium hyperplasia (atypical) was 2/50 controls, 13/50 at 250 mg/kg bw ($P \leq 0.01$), 11/50 at 500 mg/kg bw

($P \leq 0.01$), and 13/50 at 1000 mg/kg bw ($P \leq 0.01$). These uterine tumours were highly metastatic, with metastasis found in 24% (11/45) of the rats with uterine adenocarcinomas and 66% (4/6) of those with malignant mixed Müllerian tumours. Metastases of uterine tumours were found in the intestine, liver, mesentery, pancreas, glandular stomach, adrenal cortex, lymph nodes, spleen, thymus, skeletal muscle, lung, kidney and/or urinary bladder (NTP, 2014; Dunnick et al., 2015).

Based on current knowledge of the histogenesis of malignant mixed Müllerian tumours, the epithelial component is considered to be the primary component in these tumours, and the mesenchymal component is derived from the carcinoma. In the current study all the metastases were carcinomas, which supports this hypothesis. For this reason, the malignant mixed Müllerian tumours were combined with the epithelial tumours (NTP, 2014).

3.2.4 Other findings

The incidence of testicular (interstitial cell) adenoma in male rats occurred with a significant ($P = 0.023$) positive trend (0/50 controls, 0/50 at 250 mg/kg bw, 1/50 at 500 mg/kg bw, and 3/50 at 1000 mg/kg bw), and the incidence at the highest dose exceeded the incidence of this tumour in historical controls by all routes of administration (4/150). Treatment-related non-neoplastic lesions of the ovary (rete ovarii, cyst) were observed in female rats (NTP, 2014).

[The strengths of this study, which complied with good laboratory practice, included the use of multiple doses, large numbers of animals per group, and the use of males and females.]

3.3 Co-carcinogenicity

In one study (Imai et al., 2009), groups of six Fischer 344 rat dams [age not reported] received diets containing tetrabromobisphenol A [purity not reported, chemical grade at 0% (control), 0.01%, 0.1% or 1%, or drinking-water containing 0.01% of potassium perchlorate, for 3 weeks after parturition. Pups were selected randomly at 4 days after birth, to give approximately four males and four females in each litter, to maximize the uniformity of the growth rates of the offspring. The weaned offspring in each group were treated for 2 weeks in the same manner as their dams. All offspring (age, 6 weeks) received drinking-water containing *N*-bis(2-hydroxypropyl)nitrosamine (DHPN) (0.08% DHPN for males, and 0.2% DHPN for females) for 4 weeks. In addition, the female offspring (age, 7 weeks) received a single dose of 7,12-dimethylbenz[*a*]anthracene (50 mg/kg bw in 5 mL sesame oil) by gavage. All surviving male offspring were killed at age 39 weeks, and all surviving female offspring were killed at age 47 weeks. The liver, kidneys, lungs, oesophagus, thyroid, testes, epididymides, ovaries, urinary bladder, skin with mammary tissue, any subcutaneous nodules and other macroscopic abnormalities were fixed in formalin and routinely processed for histological examination. The incidence of thyroid follicular cell adenoma in female offspring treated with 1% tetrabromobisphenol A, and the incidence of transitional cell papilloma of the urinary bladder in female offspring treated with 0.01%, 0.1%, and 1% tetrabromobisphenol A, were increased compared with controls. The incidence of thyroid gland follicular cell adenoma in female offspring was 13/22 (59%) controls, 12/14 (86%) with potassium perchlorate, 9/13 (69%) with 0.01% tetrabromobisphenol A, 11/17 (65%) with 0.1% tetrabromobisphenol A, and 12/13 (92%; $P < 0.05$) with 1% tetrabromobisphenol A. The incidence of transitional cell papilloma of the urinary bladder in female offspring was: 0/23 (0%) in controls, 1/15 (7%) with potassium perchlorate, 3/13 (23%; $P < 0.05$) with 0.01% tetrabromobisphenol A, 4/17 (24%; $P < 0.05$) with 0.1% tetrabromobisphenol A, and 4/13 (31%; $P < 0.05$) with 1% tetrabromobisphenol

A. Treatment with tetrabromobisphenol A had no significant effect on tumour incidence in male offspring. [The Working Group noted the lack of control groups treated with tetrabromobisphenol A only. No historical data were available for this study, and no explanation was given as to why the group size varied. In addition, these data were not analysed to determine whether a litter effect occurred. The study was judged to be inadequate for the evaluation of the carcinogenicity of tetrabromobisphenol A.]

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism, excretion

4.1.1 Absorption, distribution, and excretion

(a) Humans

After administration of tetrabromobisphenol A as a single oral dose at 0.1 mg/kg bw in human subjects, conjugated metabolites were detected in the blood, with maximum concentrations observed between 2 and 6 hours. A small amount of the administered dose was excreted in the urine. The parent compound was below the limit of detection in all blood samples collected from 1 to 178 hours. The longest-lived conjugate reached its limit of detection in the blood at 124 hours (Schauer et al., 2006).

Tetrabromobisphenol A has been detected in the serum, tissues, and milk, as a result of environmental or occupational exposure. It has been detected in milk in surveys of the general population conducted in France, Japan, the United Kingdom, and the USA (Cariou et al., 2008; Abdallah & Harrad, 2011; Carignan et al., 2012; Akiyama et al., 2015), and in the serum of the general population in France, Japan, and Norway, as well as from exposed workers in Norway and Sweden (Hagmar et al., 2000b; Thomsen et al., 2001; Jakobsson et al., 2002; Thomsen et al., 2002; Hayama et al., 2004; Cariou et al., 2008). In many studies, mean concentrations of free tetrabromobisphenol A in tissues and fluids were < 1 ng/g of lipid, and were below the limit of detection in some subjects. In one study, adipose tissue obtained from cosmetic surgery contained about 0.05 ng/g of lipid (Johnson-Restrepo et al., 2008).

The half-life of tetrabromobisphenol A was estimated to be 2.2 days in a study of four occupationally exposed humans (Hagmar et al., 2000b).

In a study in vitro, human skin penetration was about 3.5% (of a total dose of 100 nmol/cm^2) within 24 hours of application (Knudsen et al., 2015).

(b) Experimental systems

Tetrabromobisphenol A was readily absorbed after oral administration of [^{14}C]-labelled doses in male or female rats (Hakk et al., 2000; Kuester et al., 2007; Knudsen et al., 2014). After dermal application in female rats, about 8% of the total dose (100 nmol/cm^2) reached the systemic circulation within 24 hours (Knudsen et al., 2015). The extent of absorption was calculated to be 3–11% of a total dose to male rats by dermal exposure (6 hours per day for 90 days) to up to 600 mg/kg bw (Yu et al., 2016).

Systemic bioavailability was <5% in female Wistar Han rats. The elimination half-life from plasma was 133 minutes following intravenous administration of 25 mg/kg bw, and about 290 minutes after oral administration of 250 mg/kg bw (Knudsen et al., 2014).

After intravenous administration of a 20 mg/kg bw dose in male Fischer 344 rats, tetrabromobisphenol A disappeared rapidly from the blood, with distribution and elimination half-lives of 5 and 82 minutes, respectively (Kuester et al., 2007). A similar dose administered by gavage resulted in a peak concentration in the blood at 30 minutes, with an elimination half-life similar to that after intravenous administration.

The level of tetrabromobisphenol A was below the limit of quantitation after 4 hours after either oral or intravenous administration. There was evidence of enterohepatic circulation, as also supported by Hakk et al. (2000) and Knudsen et al. (2014).

After oral administration of a dose of 250 mg/kg bw, tetrabromobisphenol A-derived radiolabel was detected in all assayed tissues 1 hour after treatment of female Wistar Han rats. Over 24 hours, the greatest amount of radiolabel was detected in the tissues and/or contents of the gastrointestinal tract. Of the other tissues assayed, the liver and pancreas contained the highest concentrations. No significant sex-specific differences in cumulative 72-hour oral disposition data were observed (Knudsen et al., 2014). In studies of repeated dosing in rats, accumulation of the administered dose was not observed in any of the tissues assayed after oral administration of up to 1000 mg/kg bw per day for 14 consecutive days (Kuester et al., 2007; Kang et al., 2009).

The major route of excretion of a dose of 20 mg/kg bw administered intravenously in male Fischer 344 rats was in the faeces, which contained about 75% of the total dose at 24 hours (Kuester et al., 2007). More than 90% of orally administered doses of 25, 250, or 1000 mg/kg bw in female Wistar Han rats was excreted in the faeces, up to 2% was excreted in the urine, and < 1% remained in tissues at 72 hours (Knudsen et al., 2014). After oral administration to male Sprague-Dawley rats, > 90% of a total dose of 2 mg/kg bw of tetrabromobisphenol A was excreted in the faeces within 72 hours, and about 3% of the total dose was recovered in the tissues and cumulative urine (Hakk et al., 2000). In male Fischer 344 rats that received tetrabromobisphenol A as a single gavage dose of 2, 20, or 200 mg/kg bw, reduced excretion of the highest dose in the faeces indicated the saturation of absorption and/or elimination processes; however, the cumulative data on faecal elimination were similar for the lowest and highest doses at 72 hours. The total dose remaining in tissues was < 1% (Kuester et al., 2007). In gavaged (2.0 mg/kg bw per day) bile duct-cannulated male Sprague-Dawley rats, > 70% of the total radioactivity was excreted in the bile, mostly within 24 hours (Hakk et al., 2000). About 50% of a dose of 20 mg/kg bw was excreted in the bile of male Sprague-Dawley rats within 2 hours after administration by gavage (Kuester et al., 2007).

The disposition of [^{14}C]-labelled tetrabromobisphenol A (250 or 1000 mg/kg bw) administered intraperitoneally to female rats differed from that of an oral dose. The total dose excreted in the faeces was lower and the tissue burdens and elimination half-lives were longer after intraperitoneal injection (Szymańska et al., 2001).

4.1.2 Metabolism

See Figure 4.1

(a) Humans

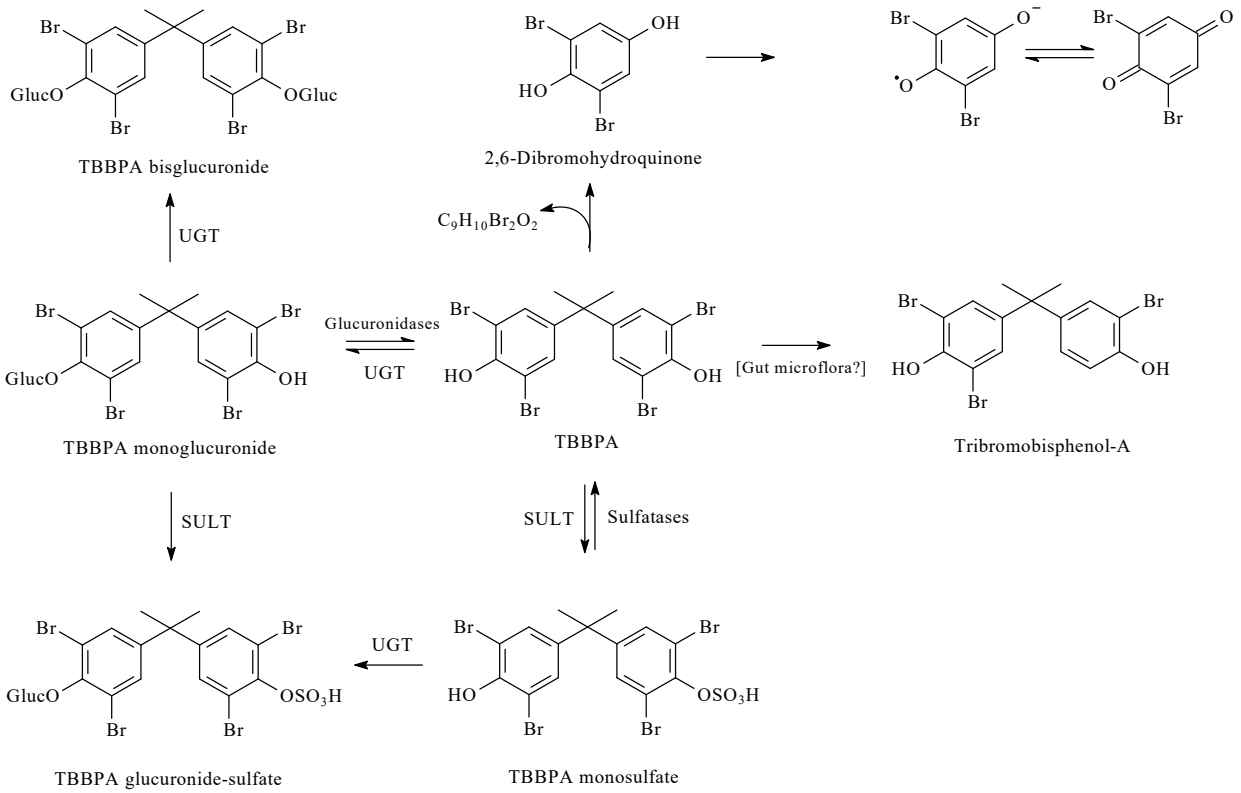
A monoglucuronide and/or monosulfate were detected in the blood and urine after oral administration of tetrabromobisphenol A in humans (Schauer et al., 2006).

The metabolism of tetrabromobisphenol A in human liver microsomes and metabolic activation preparations was described as being qualitatively similar to that observed in rat subcellular liver fractions. A glucuronide was formed in the metabolic activation system. Oxidative cleavage of the tetrabromobisphenol A molecule was a major pathway in microsomes (Zalko et al., 2006).

(b) Experimental systems

In male and female rats, tetrabromobisphenol A undergoes rapid metabolism catalysed by UDP glucuronosyltransferase and sulfotransferase isozymes to form glucuronide and sulfate conjugates (Hakk et al., 2000; Schauer et al., 2006; Kuester et al., 2007; Knudsen et al., 2014). The specific structures (mono, di/

Fig. 4.1 Metabolic scheme for tetrabromobisphenol A in rats



Gluc, $C_6H_9O_6$; SULT, sulfotransferase; TBBPA, tetrabromobisphenol A; UGT, uridine 5′-diphospho-glucuronosyltransferase
Adapted from NTP (2014)

bis, and mixed), presence and relative abundance of these conjugates in the blood, bile and/or excreta were sex- and strain-dependent and may also be dose- and species-dependent (Schauer et al., 2006; Dunnick et al., 2015). Tetrabromobisphenol A was identified in the plasma and faeces at low concentrations and its monoglucuronide was detected in the urine of Sprague-Dawley rats treated by gavage (Schauer et al., 2006). A glucuronide was formed in metabolic activation systems after incubation. Rat hepatocytes metabolized tetrabromobisphenol A to a monoglucuronide and monosulfate conjugate (Nakagawa et al., 2007). Glucuronide and sulfate conjugates were detected in *Xenopus laevis* tadpoles exposed to tetrabromobisphenol A in water (Fini et al., 2012). Oxidative cleavage of tetrabromobisphenol A is possible in vivo. The 2,6-dibromobenzenosemiquinone radical, derived from 2,6-dibromohydroquinone, was identified in the bile of male Sprague-Dawley rats that received tetrabromobisphenol A by intraperitoneal injection (Chignell et al., 2008). In rat microsomal preparations, the major metabolites of tetrabromobisphenol A were products of oxidative cleavage (Zalko et al., 2006).

4.2 Mechanisms of carcinogenesis

The evidence on the "key characteristics" of carcinogens (Smith et al., 2016) concerning whether tetrabromobisphenol A modulates receptor-mediated effects, induces oxidative stress, induces chronic inflammation, is immunosuppressive, alters cell proliferation, cell death, or nutrient supply, and is genotoxic, is summarized below.

4.2.1 Receptor-mediated effects

(a) Thyroid hormone pathway

(i) Exposed humans

Serum concentrations of tetrabromobisphenol A were positively correlated with serum concentrations of free thyroxine (T_4), but negatively correlated with serum triiodothyronine (T_3) in mothers of infants diagnosed with congenital hypothyroidism. No correlation was observed in the infants with congenital hypothyroidism, but they also had therapeutic T_4 supplementation (Kim & Oh, 2014).

Serum concentrations of tetrabromobisphenol A were not correlated with measures of thyroid function in another study of 515 adolescents (age, 13–17 years). These measurements included serum concentrations of free T_4, T_3 and thyroid-stimulating hormone (Kiciński et al., 2012).

To determine whether tetrabromobisphenol A interferes with measures of T_4 in human serum, McIver et al. (2013) tested several commercial immunoassays for serum total or free T_4 or T_3. The results indicated that high concentrations of tetrabromobisphenol A could displace tracer T_4 in an in-house serum total T_4 assay, but none of the other assays were disturbed. [This indicated that tetrabromobisphenol A may produce erroneously high T_4 readings in some assays.]

(ii) Human cells in vitro

Tetrabromobisphenol A exhibited a potent interaction with human transthyretin, and had greater avidity for binding than T_4 (displacing ^{125}I-T_4) (Meerts et al., 2000).

Tetrabromobisphenol A demonstrated both agonist and antagonist activity on thyroid hormone receptor activation in HepG2 cells, activating a transiently transfected thyroid hormone-responsive reporter at or above 10 µM and also inhibiting transactivation of the reporter by T_3 at 1 µM (Hofmann et al., 2009).

In contrast, tetrabromobisphenol A did not show agonist or antagonist activity on human thyroid hormone receptor TRα1 or TRβ1 in human embryonic kidney HEK293 cells. This assay was a transient transfection paradigm using a palindromic thyroid hormone-responsive element (TRE) to avoid the requirement for a TR:retinoid X receptor heterodimer formation on the TRE (Oka et al., 2013).

Tetrabromobisphenol A inhibited luciferase expression induced by T_3 in human embryonic kidney HEK293 cells stably transfected with a construct that would allow the detection of changes in intracellular free T_3 by one or more of several potential pathways. In a follow-up experiment using a murine cerebellar cell line expressing the TRα1 receptor, tetrabromobisphenol A significantly interfered with TRα1-mediated gene expression using a genome-wide RNa-Seq approach (Guyot et al., 2014).

In human liver microsomes, tetrabromobisphenol A inhibited the ativity of type 1 deiodinase, which converts T_4 to the more biologically active T_3, in the micromolar concentration range; 1 µM of tetrabromobisphenol A inhibited the activity by 20% and 10 µM inhibited the activity by 80% (Butt et al., 2011).

Tetrabromobisphenol A did not increase cell proliferation in human cervical cancer HeLa cells stably transfected with human TRα1, and did not appear to reduce the induction of luciferase activity by T_3 driven by a death receptor-4 promoter in a transient transfection paradigm (Yamada-Okabe et al., 2005). [The Working Group noted that the authors did not appear to correct for the efficiency of transfection of the HeLa-TR cells, which may have altered the outcome.]

(iii) Non-human mammalian systems in vivo

Tetrabromobisphenol A (100, 1000, or 10 000 ppm) given to pregnant rats throughout lactation did not affect serum T_4 or thyroid-stimulating hormone, but did slightly decrease levels of serum T_3 (Saegusa et al., 2009).

In a study of reproductive toxicity, tetrabromobisphenol A significantly reduced levels of serum T_4 in male and female rats exposed orally to various concentrations throughout fetal life, lactation, and the end of the experiment at age 12 weeks. Reduced levels of serum T_4 correlated with a cluster of measures related to thyroid function, including delayed onset of puberty and hearing deficits. However, in a short-term study, these effects were not observed in relation to the decrease in serum T_4 (Van der Ven et al., 2008).

Serum T_4 was significantly reduced in males and females exposed to tetrabromobisphenol A at 100 and 1000 mg/kg bw, and in both the parental and F_1 generations in a large multigeneration study of reproductive toxicity in Sprague-Dawley rats that complied with good laboratory practice. No effects were observed on serum T_3 or thyroid-stimulating hormone (Cope et al., 2015). [Because the units of serum T_4 were reported as ng/dL, the Working Group was unable to draw any conclusions on this study.]

No effect was seen on serum T_3 or thyroid-stimulating hormone in CD/SD rats (age, 8 weeks) administered 0, 100, 300, and 1000 mg/kg bw of tetrabromobisphenol A by gavage in corn oil daily. In contrast, mean serum T_4 concentrations (reported as ng/dL and ng/mL) were reduced at day 33 in males (4.96, 3.66, 3.42 and 3.39 at 0, 100, 300, and 1000 mg/kg bw, respectively) and females (4.27, 3.31, 3.24, and 3.33 at 0, 100, 300, and 1000 mg/kg bw, respectively) (Osimitz et al., 2016). [Because the units of serum T_4 were reported as both ng/dL and ng/mL, the Working Group was unable to draw any conclusions about this study.]

(iv) Non-human mammalian systems in vitro

Tetrabromobisphenol A (10^{-6} to 10^{-4} M) markedly inhibited the binding of T_3 to the TR in isolated nuclei from the rat pituitary MtT/E-2 cell line, and also stimulated proliferation and growth hormone production of rat pituitary GH3 cells. Tetrabromobisphenol A enhanced T_3-induced GH3 proliferation (at 10^{-4} M) and growth hormone production (at both 10^{-5} and 10^{-4} M). These data were interpreted to indicate that tetrabromobisphenol A could act on the TR as an agonist (Kitamura et al., 2002).

In contrast, tetrabromobisphenol A was antagonistic to the human TRα1 receptor in a transient transfection assay using CHO cells, and inhibited the effect of 10^{-8} M T_3 on luciferase activity in the 4–50 μM concentration range, at which it was not cytotoxic. However, tetrabromobisphenol A did not antagonize the TRβ1 receptor at concentrations that were not cytotoxic and did not exhibit agonistic action on TRα1 or TRβ1 (Kitamura et al., 2005a). This group later confirmed their original observation that tetrabromobisphenol A could stimulate growth hormone production in GH3 cells (Kitamura et al., 2005b).

Sun et al. (2009) reported that tetrabromobisphenol A did not exhibit TR agonist action, but suppressed transactivation by 10 nM T_3 at 10^{-4}M in CV-1 cells (African green monkey kidney cells). As CV-1 cells do not express TRs, this transient transfection system employed a GAL4/hTRβ1 fusion protein with a 4×UAS/luciferase construct.

Tetrabromobisphenol A inhibited T_3-induced luciferase expression at concentrations above 10 μM in rat pituitary GH3 cells stably transfected with a 2×DR4/luciferase construct, a system that is highly sensitive and can detect picomolar concentrations of T_3. Extensive validation was carried out and tetrabromobisphenol A did not induce an agonistic effect in this system (Freitas et al., 2011).

Tetrabromobisphenol A produced a TR agonist effect in the 10^{-5} to 10^{-4} M range in a yeast two-hybrid assay, an effect enhanced by prior incubation with a microsomal metabolic activation system. To detect chemical effects on the TR, this assay employed yeast cells transfected with human TRα and co-factor TIF2. The reporter gene was β-galactosidase (Terasaki et al., 2011).

Lévy-Bimbot et al. (2012) evaluated the effect of tetrabromobisphenol A on structural changes within the TRα receptor using a co-regulator recruitment assay. Tetrabromobisphenol A decreased the affinity of the TR ligand-binding domain for the NCoR-binding peptide, but did not simultaneously increase the affinity of the TR for the SRC2-binding peptide. The effective concentration of tetrabromobisphenol A was in the 1 μM range.

Grasselli et al. (2014) evaluated tetrabromobisphenol A in a rat hepatoma cell line (FaO) that does not express TRs but accumulates lipid droplets. Treatment with T_3 can cause a depletion of the lipids, which was mimicked by 10–6 M tetrabromobisphenol A. However, tetrabromobisphenol A induced the expression of genes related to lipid accumulation. [The Working Group noted that, in the absence of an antagonist to block T_3-dependent processes (that are also TR-independent), this study was difficult to interpret.]

(v) Non-mammalian experimental systems

Tetrabromobisphenol A inhibited T_3-induced tail resorption in *Rana rugosa* tadpoles at a concentration of 10^{-6} M, a similar range to that used in TR-binding studies, but exerted no effect on tail length in the absence of T_3 (Kitamura et al., 2005a). This observation was confirmed by Goto et al. (2006), who reported that both 10^{-7} and 10^{-6} M tetrabromobisphenol A inhibited T_3-induced tail resorption in *Rana rugosa* tadpoles, but again had no effect in the absence of T_3. During T_3-induced tail resorption, DNA becomes highly fragmented; Goto et al. (2006) also demonstrated that 10^{-6} M tetrabromobisphenol A could inhibit this fragmentation and block T_3-induced hind limb growth. Finally, they demonstrated in transgenic *Xenopus laevis* carrying a TRE-linked green fluorescent protein that T_3-induced fluorescence was blocked by tetrabromobisphenol A at 10^{-7} M. [The Working Group noted that, taken together, these data consistently demonstrated the antagonist action of tetrabromobisphenol A in amphibians and in the range of its binding to TR.]

In the tree frog, tetrabromobisphenol A was antagonistic to the TR. Veldhoen et al. (2006) reported that it was agonistic to metamorphic changes in *Pseudacris regilla*. At 10 nmol/L, tetrabromobisphenol A suppressed T_3-induced TRβ expression in the frog *Pelophylax nigromaculatu*, coincident with a suppression of several thyroid hormone-regulated genes (Zhang et al., 2015b).

(b) Other pathways

(i) Nuclear receptors and steroidogenesis

Several studies have addressed the possible agonistic or antagonistic properties of tetrabromobisphenol A on relevant nuclear receptors in various human cell lines, such as human mammary carcinoma MCF-7 and human cervical carcinoma HeLa cells. For the estrogen and progesterone receptors, no significant agonistic or antagonistic properties of tetrabromobisphenol A were detected (Samuelsen et al., 2001; Hamers et al., 2006; Molina-Molina et al., 2013). This lack of direct estrogenicity of tetrabromobisphenol A has also been shown in vivo in the mouse uterotrophic assay (Ohta et al., 2012). The androgen receptor antagonistic activity of tetrabromobisphenol A was detected at the lower micromolar levels in MDA-kb2 cells (Christen et al., 2010).

Tetrabromobisphenol A does not have any significant agonistic activity on the aryl hydrocarbon receptor (AhR), and several studies in vitro and in vivo showed that it does not induce AhR-mediated cytochrome P450 (CYP) A1 enzymes (Behnisch et al., 2003; Germer et al., 2006; Hamers et al., 2006). In addition to the data mentioned above, ToxCast identified interactions between tetrabromobisphenol A and the glucocorticoid receptor, the farnesyl X receptor, and the xenobiotic receptor PXR.

In stably transfected human HeLa cells and monkey Cos-7 kidney cells, significant agonistic activity for human peroxisome proliferator-activated receptor-γ1 and -γ2 was found below 1 μM (Christen et al., 2010; Watt & Schlezinger, 2015). In human choriocarcinoma JEG-3 cells, low nanomolar levels of tetrabromobisphenol A also increased peroxisome proliferator-activated receptor-γ, as well as increasing progesterone and β-human chorionic gonadotrophin (Honkisz & Wójtowicz, 2015). Furthermore, tetrabromobisphenol A (0.1 and 1 μM) induced aromatase (CYP19) in these JEG-3 cells (Honkisz & Wójtowicz, 2015), but not in human adenocarcinoma H295R cells (Song et al., 2008).

(ii) Neurotoxicity

The possible neurotoxic mechanisms of action of tetrabromobisphenol A were studied in SH-SY5Y human neuroblastoma cells in vitro. It was both neurotoxic and amyloidogenic, as demonstrated by increased intracellular calcium levels and a release of β-amyloid peptide (Aβ-42) at micromolar levels (Al-Mousa & Michelangeli, 2012). As further evidence of its potential neurotoxicity, tetrabromobisphenol A inhibited the plasma membrane uptake of the neurotransmitters dopamine, glutamate, and gamma-amino butyric acid in rat brain synaptosomes (Mariussen & Fonnum, 2003). However, in spite of the interactions of tetrabromobisphenol A in vitro with various neurotransmitters, neonatal exposure of mice did not induce any neurobehavioural changes (Eriksson et al., 2001; Viberg & Eriksson, 2011).

(iii) Other effects

Several studies in vitro have addressed the direct interaction of tetrabromobisphenol A with estrogen sulfotransferase (e.g. SULT1E1) and concluded that it strongly inhibits the estradiol binding process with half-maximal inhibitory concentrations between 12 and 33 nM (Kester et al., 2002; Hamers et al., 2006; Gosavi et al., 2013). In addition, many authors hypothesized that, at high concentrations, the conjugation of tetrabromobisphenol A to form tetrabromobisphenol A sulfate could possibly saturate the sulfation pathway (Kester et al., 2002; Hamers et al., 2006; Gosavi et al., 2013; Dunnick et al., 2015 Lai et al., 2015; Wikoff et al., 2016). [This competitive inhibition of estrogen sulfotransferases could lead to an increase in systemic and target tissue levels of estrogens.]

A follow-up 28-day study of tetrabromobisphenol A in rats was carried out by Borghoff et al. (2016) using the same dose levels as those in the 2-year NTP carcinogenicity bioassay (NTP, 2014). At the highest dose levels (250, 500, and 1000 mg/kg bw per day), a decrease in the ratio of tetrabromobisphenol A sulfates to tetrabromobisphenol A glucuronides occurred. These results demonstrated that the saturation of tetrabromobisphenol A sulfation also occurs in vivo at these dose levels, which were associated with uterine tumours in the 2-year NTP study. [The Working Group noted that neither the NTP (2014) nor Borghoff et al. (2016) studies took measurements that provided information on estrogen homeostasis.]

In addition, several other mechanistic explanations have been postulated to explain the uterine tumours in the 2-year NTP study (Dunnick et al., 2015; Lai et al., 2015), one of which is the interaction of tetrabromobisphenol A with dopamine and a subsequent decrease in prolactin levels that is considered to be a rat-specific mechanism (Neumann, 1991; Harleman et al., 2012). Tetrabromobisphenol A inhibited the cellular uptake of dopamine with a half-maximal inhibitory concentration of 9 μM (Mariussen & Fonnum, 2003). [At present, insufficient data were available to evaluate its relevance to the tetrabromobisphenol A-induced uterine tumours in the NTP (2014) study.]

4.2.2 Oxidative stress

(a) Humans

Treatment of isolated human neutrophil granulocytes with tetrabromobisphenol A at 1–12 µM for 60 minutes induced significant dose-dependent increases in the production of reactive oxygen species (ROS) and increased intracellular calcium concentrations (Reistad et al., 2005). ROS production was determined using the fluorescent probe 2,7-dichlorofluorescein diacetate or by lucigenin-amplified chemiluminescence. Production of ROS was inhibited by pretreatment with diphenyleneiodonium (a nicotinamide adenine dinucleotide phosphate oxidase inhibitor), U0126 (an inhibitor of mitogen-activated protein kinase kinases MEK1 and MEK2, i.e. MAPK/ERK kinase), bisindolylmaleimide (a protein kinase C inhibitor), erbstatin A (a tyrosine kinase inhibitor), or verapamil (a Ca^{2+} channel blocker), or by incubation in calcium-free media. A decrease in tetrabromobisphenol A-induced ROS by diethyldithiocarbamate, an inhibitor of superoxide dismutase (SOD), confirmed the involvement of the superoxide anion in the production of ROS by tetrabromobisphenol A (Reistad et al., 2005).

(b) Experimental systems

(i) Non-human mammalian systems in vivo

Chignell et al. (2008) administered tetrabromobisphenol A (100 or 600 mg/kg bw) to Sprague-Dawley rats together with the spin-trapping agent α-(4-pyridyl-1-oxide)-*N*-*t*-butylnitrone and detected the α-(4-pyridyl-1-oxide)-*N*-*t*-butylnitrone/•CH_3 spin adduct by electron paramagnetic resonance in the bile. Also measured in the bile was the 2,6-dibromobenzosemiquinone radical; reaction of the latter compound with oxygen could generate the superoxide anion.

Daily treatment of male Sprague-Dawley rats with tetrabromobisphenol A (500 mg/kg bw for 30 days, beginning on postnatal day 18), induced a significant increase in the levels of 8-hydroxy-2′-deoxyguanosine (a biomarker of oxidative DNA damage) in the testis and kidney. No increase in the levels of malondialdehyde was observed in the liver of exposed rats compared with controls (Choi et al., 2011).

Daily administration of tetrabromobisphenol A (750 or 1125 mg/kg bw) for 7 days to Wistar rats decreased the levels of reduced glutathione in females at both doses and increased the levels of malondialdehyde in male rats at the higher dose (Szymańska et al., 2000).

A single oral dose of tetrabromobisphenol A in Sprague-Dawley rats produced increases in kidney levels of thiobarbituric acid reactive substances (TBARS) at 1000 mg/kg bw and in SOD activity at 250–1000 mg/kg bw, but no significant changes in urine analysis parameters. These parameters were not increased in a 14-day repeated-dose experiment with the same doses of tetrabromobisphenol A (Kang et al., 2009).

(ii) Non-human mammalian systems in vitro

Exposure of hepatocytes isolated from Fischer 344/Jcl rats to tetrabromobisphenol A at 0.25–1.0 mM for up to 3 hours decreased the reduced glutathione content with concomitant increases in oxidized glutathione (GSSG), and increased malondialdehyde levels (TBARS). Treatment with tetrabromobisphenol A also reduced the mitochondrial membrane potential and had an uncoupling effect on mitochondrial oxidative phosphorylation (Nakagawa et al., 2007). [Based on the longer time needed to induce lipid peroxidation compared with the rapid reduction in cellular adenosine triphosphate levels, the results suggested that lipid peroxidation induced by tetrabromobisphenol A was due to impaired mitochondrial function.]

Incubation of primary cultures of cerebellar granule cells from Wistar rats with tetrabromobisphenol A at 2.5–7.5 µM produced significant increases in ROS production, with reductions in ^{45}Ca uptake, increases in

intracellular concentrations of ^{45}Ca, and a slight decrease in the mitochondrial membrane potential. The production of ROS was reduced by co-treatment with 0.1 mM ascorbic acid or 1 mM glutathione (Ziemińska et al., 2012). Reistad et al. (2007) also observed concentration-dependent increases in ROS, phosphorylation of ERK1/2 and intracellular calcium in primary cultures of rat cerebellar granule cells exposed to tetrabromobisphenol A. ROS formation was inhibited by pretreatment with the MAPK/ERK kinase inhibitor U0126, the tyrosine kinase inhibitor erbstatin A, the SOD inhibitor diethyldithiocarbamate or by eliminating calcium from the culture medium.

(iii) Fish and other species

In goldfish (*Carassius auratus*) given a single intraperitoneal injection of tetrabromobisphenol A (100 mg/kg bw), ROS were increased in the liver and bile, an effect inhibited by the hydroxyl radical scavenger mannitol. Lipid peroxidation products (TBARS) and protein carbonyl levels, indicators of oxidative damage, were significantly increased in the liver at 1–3 days after treatment with tetrabromobisphenol A (Shi et al., 2005). Tetrabromobisphenol A in aquarium water (3 mg/L for 7 days) significantly decreased reduced glutathione levels and antioxidant enzyme activites (SOD and catalase) in fish livers (He et al., 2015). In *Carassius auratus*, intraperitoneal injections of tetrabromobisphenol A (10 or 100 mg/kg bw for 14 days) decreased the activities of antioxidant enzymes (SOD, catalase, and glutathione peroxidase), decreased reduced glutathione levels and increased the levels of malondialdehyde (a marker of lipid peroxidation) in the liver (Feng et al., 2013).

In zebrafish embryos, tetrabromobisphenol A (0.05, 0.25, or 0.75 mg/mL for 96 hours) increased SOD activity, lipid peroxidation (TBARS), and the expression of heat-shock protein 70 (Hsp70) (Hu et al., 2009). Significant decreases in the activities of the antioxidant enzymes SOD, catalase, and glutathione peroxidase were observed in embryos and zebrafish larvae exposed to tetrabromobisphenol A at 0.4–1.0 mg/L in holding tanks for 3, 5, or 8 days post-fertilization (Wu et al., 2015). Similarly, increases in ROS production were observed in zebrafish embryos and larvae exposed to tetrabromobisphenol A at 0.1, 0.5, or 1.0 mg/L for 96 hours; the increases in ROS production were inhibited by co-incubation with puerarin (1 mg/L), an antioxidant free-radical scavenger. ROS production was measured with a fish ROS enzyme-linked immunosorbent assay kit using a horseradish peroxidase-labelled fish ROS antibody (Yang et al., 2015). Hepatic oxidative stress and general stress was induced in zebrafish exposed to tetrabromobisphenol A (0.75 or 1.5 μM) for 14 days and evaluated for hepatic changes in gene and protein expression (De Wit et al., 2008). [The Working Group noted that tetrabromobisphenol A induced oxidative stress, based on antioxidant-related responses, and general stress responses, based on stimulation of Hsp70 protein in the liver of zebrafish.]

Tetrabromobisphenol A also induced hydroxyl radical formation and oxidative stress in earthworms (*Eisenia fetida*). Lipid peroxidation was increased while the reduced glutathione/GSSG ratio was decreased (Xue et al., 2009). Exposure of earthworms to tetrabromobisphenol A at 50–400 mg/kg dry soil for 14 days resulted in an increased expression of genes encoding SOD and Hsp70 (Shi et al., 2015).

In scallops (*Chlamys farreri*), exposure to tetrabromobisphenol A in seawater tanks (0.2, 0.4, and 0.8 mg/L for up to 10 days) increased SOD activity, the reduced glutathione levels, and malondialdehyde levels in the gill and digestive gland (Hu et al., 2015a).

(iv) Plant systems

Tetrabromobisphenol A increased total free radical generation and enhanced lipid peroxidation in plants (*Ceratophyllum demersum L.*) exposed at 0.05–1.0 mg/L in growth solution.

In addition, levels of GSH were decreased (Sun et al., 2008). ROS were also induced in green alga (*Chlorella pyrenoidosa*) cultures exposed to tetrabromobisphenol A at 2.7–13.5 mg/L for 4–216 hours (Liu et al., 2008).

[The Working Group noted that the induction of oxidative stress by tetrabromobisphenol A has been well established on studies in human cells and in numerous experimental systems.]

4.2.3 Inflammation and immunosuppression

Studies in human cells and in several experimental systems have demonstrated immunosuppressive effects caused by exposures to tetrabromobisphenol A.

(a) Humans

No data in exposed humans were available to the Working Group.

The lytic and binding functions of isolated human natural killer (NK) cells were decreased when they were incubated with tetrabromobisphenol A at 0.1–5 µM for 1, 2, or 6 days. The effects of treatment with tetrabromobisphenol A on NK cells were dependent on both the concentration and duration of exposure. Exposure of NK cells to tetrabromobisphenol A at 1–10 µM for 1 hour resulted in a decrease in lytic function that persisted for at least 6 days. The loss of lytic function was more sensitive than the decrease in binding function to the treatment with tetrabromobisphenol A (Kibakaya et al., 2009).

Exposure of human NK cells to tetrabromobisphenol A (2.5 µM for 24 or 48 hours) caused significant decreases in the expression of cell surface proteins that are involved in NK cell binding and/or the lysis of target cells. The analysis was done by flow cytometry after reactions with anti-CD2, anti-CD11a, anti-CD16, anti-CD18, or anti-CD56 antibodies (Hurd & Whalen, 2011).

Phospho-p44/42 and phospho-p38 MAPKs were activated in isolated human NK cells exposed to tetrabromobisphenol A at 0.5–10 µM for 10 minutes, but not after exposures of 1 or 6 hours. Phosphorylation of MEK1/2 and MKK3/6, upstream activators of p44/42 and p38, respectively, was also increased in NK cells exposed to tetrabromobisphenol A at 5 or 10 µM for 10 minutes (Cato et al., 2014). This group had shown previously (Kibakaya et al., 2009) that tetrabromobisphenol A decreased the ability of human NK cells to lyse tumour cells, and that the activation of p44/42 can decrease the lytic function of NK cells. Thus, the aberrant activation of MAPKs by tetrabromobisphenol A may result in NK cells becoming unresponsive to subsequent encounters with tumour cells or virally infected cells.

Tetrabromobisphenol A also activates inflammatory pathways in the human first trimester placental cell line HTR-8/SVneo (Park et al., 2014). Trophoblast cells were cultured for 8, 16, or 24 hours in media containing tetrabromobisphenol A at 5, 10, 20, or 50 µM and analysed for cytokine release (interleukin-(IL)-6, IL-8 and tumour growth factor-β) and prostaglandin E2 (PGE2) production by enzyme-linked immunosorbent assay. Exposure to tetrabromobisphenol A increased the release of PGE2 and the proinflammatory cytokines IL-6 and IL-8, and reduced the release of the anti-inflammatory cytokine tumour growth factor-β. Treatment with NS-398, a cyclooxygenase-2 (COX-2)-specific inhibitor, suppressed the tetrabromobisphenol A-stimulated release of PGE2. Quantitative mRNA analyses by the reverse transcriptase polymerase chain reaction showed that exposure to tetrabromobisphenol A at 10 µM increased the expression of genes encoding prostaglandin-endo-peroxide synthase 2, COX-2, and IL-6 and IL-8. Thus, exposure to tetrabromobisphenol A activates inflammatory pathways in human placental cells (Park et al., 2014).

(b) Experimental systems

The pulmonary viral titer was significantly increased in BALB/c mice fed diets containing 1% tetrabromobisphenol A for 28 days and then intranasally infected with the A2 strain of respiratory syncytial virus. The viral titres were increased two- to threefold in tetrabromobisphenol A-treated mice compared with controls on day 5 after infection. Bronchoalveolar fluid from respiratory syncytial virus-infected mice treated with tetrabromobisphenol A showed enhanced production of tumour necrosis factor-α, IL-6 and interferon-γ, and reduced production of IL-4 and IL-10 (Watanabe et al., 2010).

In a study of immune/allergic responses in vitro to brominated flame retardants, exposure of splenocytes from NC/Nga mice to tetrabromobisphenol A at 1 or 10 μg/mL for 24 hours increased the expression of surface proteins on antigen presenting cells (major histocompatibility complex class II and CD86), and increased the expression of the T-cell receptor and the production of cytokine IL-4 in splenic T-cells. Exposure of isolated mouse bone marrow cells to tetrabromobisphenol A at 1 μM for 6 days did not affect bone marrow-derived dendritic cell activation or differentiation (Koike et al., 2013).

In splenocytes isolated from C57Bl/6 mice that had been incubated with tetrabromobisphenol A at 3 μM and concanavalin A (2 μg/mL) for 48 hours, the expression of the IL-2 receptor α chain (CD25), essential for proliferation of activated T-cells during the immune response, was suppressed (Pullen et al., 2003).

Exposure of the mouse macrophage cell line RAW 264.7 to tetrabromobisphenol A at 1–50 μM increased the mRNA expression and protein levels of COX-2, enhanced the production of PGE2 (a major metabolite of COX-2), and increased the mRNA expression and production of proinflammatory cytokines including tumour necrosis factor-α, IL-6 and IL-1β. Pretreatment of the cells with tetrabromobisphenol A and NS-398, a COX-2-specific inhibitor, inhibited the tetrabromobisphenol A-induced increase in PGE2 production, indicating that the effect of tetrabromobisphenol A is mediated by COX-2 activity. Thus, exposure to tetrabromobisphenol A may promote inflammation by transcriptionally activating the macrophage COX-2 gene and protein expression and increasing the expression and secretion of proinflammatory cytokines (Han et al., 2009).

Tetrabromobisphenol A activated MAPKs and protein kinase C in mussel haemocytes. The observed increase in extracellular superoxide production was reduced by pretreatment with kinase inhibitors specific for protein kinase C and MAPKs (Canesi et al., 2005).

4.2.4 Altered cell proliferation or death

The studies reviewed below indicated neither enhanced cell proliferation nor suppression of apoptosis after exposure to tetrabromobisphenol A, which was associated with an increase in apoptosis in several experimental systems.

(a) Humans

No data in exposed humans were available to the Working Group.

In human A549 epithelial alveolar lung cells and the human thyroid cell line Cal-62, tetrabromobisphenol A decreased the rates of DNA synthesis. A549 cells tended to arrest in the G1 phase, while Cal-62 cells tended to arrest in the G2 phase. MAPK cascades were also affected, but not in association with an increase in cell proliferation (Strack et al., 2007; see also Cagnol & Chambard, 2010).

(b) Experimental systems

(i) Non-human mammalian systems in vivo

Apoptosis was induced in the testes of CD-1 mice exposed to drinking-water containing tetrabromobisphenol A at a concentration of 200 μg/L during gestation, lactation, and up to

age 70 days. In addition, expression of the pro-apoptotic *Bax* gene was increased, while expression of the anti-apoptotic *Bcl-2* gene was decreased in tetrabromobisphenol A-exposed mice compared with controls (Zatecka et al., 2013).

Although increased incidences of atypical endometrial hyperplasia were observed in the uterus of female Wistar Han rats exposed to tetrabromobisphenol A (250 mg/kg bw per day) in a 2-year study of carcinogenicity (NTP, 2014; Dunnick et al., 2015), this effect was considered to be a preneoplastic lesion rather than an early event in the development of uterine cancer. [The Working Group noted that, in the 3-month study at doses (5 times per week) of up to 1000 mg/kg bw (NTP, 2014), no treatment-related lesions were observed in the uterus of Wistar Han rats, Fischer 344/NTac rats, or B6C3F$_1$/N mice treated with tetrabromobisphenol A.]

(ii) Non-human mammalian systems in vitro

In a non-transformed rat kidney (NRK) cell line, tetrabromobisphenol A decreased rates of DNA synthesis. NRK cells tended to arrest in the G1 phase. MAPK cascades were also affected, but not in association with an increase in cell proliferation (Strack et al., 2007; see also Cagnol & Chambard, 2010).

Tetrabromobisphenol A induced cell death in mouse TM4 cells, a cell line derived from mouse testicular Sertoli cells, via apoptosis involving mitochondrial depolarization due to increases in cytosolic Ca^{2+} levels. Intracellular levels of Ca^{2+} were elevated in TM4 cells within 1–3 minutes of incubation with tetrabromobisphenol A at 30 µM; after 18 hours, cell viability was < 50%. Tetrabromobisphenol A also caused rapid mitochondrial membrane depolarization. The loss of cell viability by tetrabromobisphenol A was suppressed by the caspase inhibitor Ac-DEVD-CMK, indicating that this loss was due in part to apoptosis. Tetrabromobisphenol A also inhibited Ca^{2+}-adenosine triphosphatase activity in rabbit muscle sarcoplasmic reticulum vesicles and in pig cerebellar microsomes at concentrations as low as 0.5 µM (Ogunbayo et al., 2008).

The treatment of primary cultured neurons from rat cerebellum with tetrabromobisphenol A at 5 µM for 24 hours induced apoptosis-like nuclear changes, characterized by condensed chromatin and DNA fragmentation; however, other hallmarks of apoptosis, including activation of caspase-3, were not observed. Tetrabromobisphenol A induced a concentration-dependent increase in the phosphorylation of ERK1/2 (Reistad et al., 2007).

(iii) Other experimental systems

Apoptotic cells were detected in the brain, heart, and tail of zebrafish embryos and larvae exposed to tetrabromobisphenol A at 1.0 mg/L in holding tanks for 96 hours (Wu et al., 2015); exposures to tetrabromobisphenol A at 0.1–1.0 mg/L induced the expression of three proapoptotic genes – *Tp53*, *Bax*, and caspase 9 – and decreased the expression of the anti-apoptotic gene *Bcl2* (Yang et al., 2015).

4.2.5 Genetic and related effects

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

(i) Non-human mammalian systems in vivo

See Table 4.1

No increase in DNA damage in the alkaline comet assay was observed in the testicular cells of CD-1 mice given tetrabromobisphenol A in corn oil twice (24 hours apart) at doses of 500, 1000, or 2000 mg/kg bw (Hansen et al., 2014). Tetrabromobisphenol A did not increase the frequency of micronucleated erythrocytes in the peripheral blood of male and female B6C3F$_1$ mice exposed by gavage (10–1000 mg/kg bw in corn oil on 5 days per week for 14 weeks) (NTP, 2014).

Table 4.1 Genetic and related effects of tetrabromobisphenol A in non-human mammals in vivo

Species, strain, sex	Tissue	End-point	Test	Results	Dose (LED/HID)	Route, duration, dosing regimen	Reference
Mouse, Swiss CD-1, M	Testis	DNA damage	DNA strand breaks (comet assay)	–	2000 mg/kg bw	Gavage; twice (24 h apart)	Hansen et al. (2014)
Mouse, B6C3F$_1$, M/F	Peripheral blood erythrocytes	Chromosomal damage	Micronucleus formation	–	1000 mg/kg bw	Gavage; 14 wk, 5 days/wk	NTP (2014)
Rat, Wistar Han, F	Uterine carcinoma	Mutation	*Tp53* mutation frequency	+	250 mg/kg bw	Gavage; 2 years, 5 days/wk	Harvey et al. (2015)

+, positive;–, negative; bw, body weight; F, female; HID, highest ineffective dose; LED, lowest effective dose; M, male; wk, week

Uterine carcinomas that were induced in female Wistar Han rats in a study of carcinogenicity (NTP, 2014) were examined for molecular alterations in genes relevant to human endometrial cancer (Harvey et al., 2015). This study identified a marked increase in the frequency of *Tp53* mutations and increased human growth factor receptor 2 gene expression in tetrabromobisphenol A-associated uterine carcinomas compared with spontaneous uterine carcinomas in vehicle controls. [The Working Group noted that it was not clear if the increased frequency of tumours with *Tp53* mutations was due to a genotoxic effect of tetrabromobisphenol A or to enhanced proliferation of cells with spontaneous mutations in the *Tp53* gene.]

(ii) Experimental systems in vitro

See Table 4.2

Tetrabromobisphenol A did not induce intragenic recombination in Sp5 or SPD8 cell lines (mutants isolated from V79 Chinese hamster cells) when tested at doses of 5–40 µg/mL. These cell lines have a partial duplication of the *Hprt* gene that results in a non-functional hypoxanthine-guanine phosphoribosyltransferase protein (Helleday et al., 1999).

In scallops (*Chlamys farreri*), tetrabromobisphenol A (0.2, 0.4 and 0.8 mg/L for up to 10 days) induced DNA damage in the gills and digestive gland tissues in a time- and dose-dependent manner (Hu et al., 2015b).

Studies on the genetic toxicology of tetrabromobisphenol A (up to 10 000 µg/plate) conducted by the NTP (2014) showed negative results for bacterial gene mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, in the presence or absence of metabolic activation by S9 from induced Syrian hamster or Sprague-Dawley rat liver, and in *Escherichia coli* strain WP2 *uvrA*/pKM101, in the presence or absence of metabolic activation by S9 mix from Sprague-Dawley rat liver.

(c) Acellular systems

The binding of tetrabromobisphenol A to calf thymus DNA was studied by ultraviolet-visible absorption, fluorometric competition with DNA-bound ethidium bromide, circular dichroism, and molecular modelling (Wang et al., 2014). Tetrabromobisphenol A intercalated into DNA [through an interaction involving hydrogen binding and hydrophobic interaction].

Table 4.2 Genetic and related effects of tetrabromobisphenol A in experimental systems in vitro

Phylogenetic class	End-point	Test	Results	Dose (LED or HID)	Reference
Chinese hamster Sp5 and SPD8 cell lines	DNA damage	Mutation	–	40 µg/mL; 24 h	Helleday et al. (1999)
Chlamys farreri (scallops)	DNA damage	DNA strand breaks (alkaline unwinding assay)	+	0.2 mg/L, 10 days	Hu et al. (2015b)
Salmonella typhimurium TA1535, TA1537, TA98, TA100	Mutation	Reverse mutation	–[a]	10 000 µg/plate	NTP (2014)
Escherichia coli WP2 *uvrA*	Mutation	Reverse mutation	–[a]	6000 µg/plate	NTP (2014)
Calf thymus DNA	DNA damage	DNA intercalation	+	100 µM	Wang et al. (2014)

[a] With and without metabolic activation
+, positive;–, negative; HID, highest ineffective dose; LED, lowest effective dose

4.3 Data relevant to comparisons across agents and end-points

For all compounds evaluated in the present volume of the *IARC Monographs*, including tetrabromobisphenol A, analyses of high-throughput screening data generated by the Tox21 and ToxCast research programmes of the government of the USA (Kavlock et al., 2012; Tice et al., 2013) are presented in the *Monograph* on 1-bromopropane, in the present volume.

4.4 Susceptibility to cancer

No data were available to the Working Group.

4.5 Other adverse effects

No other adverse effects were identified in exposed humans.

In a NTP 2-year bioassay in rats, the incidence of rete ovarii cyst was significantly increased in the group at the highest dose of tetrabromobisphenol A (1000 mg/kg bw) (NTP, 2014; Dunnick et al., 2015).

Brainstem auditory evoked potentials thresholds and latency were increased in females and latency was increased in males in a developmental study of rats (Lilienthal et al., 2008). [The Working Group noted that these findings may reflect an effect of tetrabromobisphenol A on thyroid hormone-regulated developmental events, including hearing and testis weight. However, no experimental group was available that would have tested this directly (e.g. tetrabromobisphenol A + T_4).] This group later published an additional study showing that tetrabromobisphenol A decreased serum total T_4 (Van der Ven et al., 2008) (see also Section 4.2.1).

Behl et al. (2015) reported that tetrabromobisphenol A was active in assays in vitro that were indicative of [potential] developmental toxicity and neurotoxicity in the low micromolar range. The assays used evaluated the effects of tetrabromobisphenol A on the differentiation of mouse embryonic stem cells, human neural stem cell proliferation and growth, and rat neuronal growth and network activity.

5. Summary of Data Reported

5.1 Exposure data

Tetrabromobisphenol A is a flame retardant with a high production volume that is applied in a wide variety of consumer products. The most common use is for printed circuit boards, whereby tetrabromobisphenol A is chemically bonded to the polymer matrix. Tetrabromobisphenol A is also applied as an additive compound in the manufacture of acrylonitrile–butadiene–styrene resins and high-impact polystyrene. It has been detected in almost all biotic and abiotic compartments worldwide. Occupational exposures to tetrabromobisphenol A have been measured in facilities manufacturing electronic products, and at higher concentrations in recycling facilities. Exposure of the general population predominantly occurs through the diet and through the ingestion of indoor dust. While intake by very young children is predominantly via the ingestion of indoor dust, intake by adults occurs mainly via the diet. Very young children are estimated to have a higher daily intake than adults. Exposure may occur prenatally, and tetrabromobisphenol A has been measured in breast milk.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3. Animal carcinogenicity data

Tetrabromobisphenol A was tested for carcinogenicity after oral administration by gavage in one study in male and female mice, and in one study in male and female rats. One co-carcinogenicity study of transplacental/perinatal exposure in rats was found to be inadequate for the evaluation of the carcinogenicity of tetrabromobisphenol A.

In the study in male mice, tetrabromobisphenol A caused significantly increases in the incidence of hepatoblastoma, of hepatocellular adenoma (multiple), and of hepatocellular carcinoma or hepatoblastoma (combined). Tetrabromobisphenol A significantly increased the incidence of haemangiosarcoma (all organs), with a significant positive trend. A significant positive trend in the incidence of adenoma or carcinoma (combined) of the large intestine (caecum or colon) was also observed; the incidence in mice receiving the highest dose exceeded the range for historical controls. Tetrabromobisphenol A did not cause any significant increases in tumour incidence in female mice.

In the study in male rats, tetrabromobisphenol A caused a significant positive trend in the incidence of interstitial cell adenoma of the testes. In female rats, tetrabromobisphenol A caused a significant increase in the incidence of adenocarcinoma of the uterus, with a significant positive trend. Several rats in the groups exposed to tetrabromobisphenol A were diagnosed with the rare uterine tumour, malignant mixed Müllerian tumour; this tumour was not reported in the data for historical controls. A significant increase was observed in the incidence of adenoma, adenocarcinoma, or malignant mixed Müllerian tumour (combined) of the uterus, with a significant positive trend.

5.4 Mechanistic and other relevant data

After oral administration in humans and rats, tetrabromobisphenol A is readily absorbed and widely distributed among tissues, is extensively metabolized to glucuronide and sulfate conjugates, and was shown to be excreted primarily in the faeces in rats. Tetrabromobisphenol A has been detected in human milk in surveys of the general population. In rats, tetrabromobisphenol A and its metabolites do not accumulate in the

tissues. A metabolic minor pathway involving radical formation has been demonstrated in vivo in rats. Quantitative species-, sex- and strain-dependent differences in conjugated metabolites have been observed.

With respect to the "key characteristics" of human carcinogens, there is *strong* evidence that tetrabromobisphenol A modulates receptor-mediated effects, induces oxidative stress and is immunosuppressive; there is *moderate* evidence that tetrabromobisphenol A induces chronic inflammation; and there is *weak* evidence that tetrabromobisphenol A is electrophilic, is genotoxic or alters cell proliferation, cell death or nutrient supply.

There is *strong* evidence that tetrabromobisphenol A can alter thyroid hormone receptor function both directly and indirectly. Studies in experimental animals demonstrated that tetrabromobisphenol A reduces serum levels of thyroxine. Cell-based assays that included the use of human cells, and biochemical studies showed that tetrabromobisphenol A can interact with thyroid hormone receptors directly, the outcome being dependent on several variables. Tetrabromobisphenol A is a potent inhibitor of sulfotransferases. ToxCast data supported the conclusion that tetrabromobisphenol A can interact with nuclear receptors, in particular peroxisome proliferator-activated receptor-γ, as well as inhibit aromatase and alter steroid biosynthesis in a human cell line.

There is *strong* evidence that tetrabromobisphenol A induces oxidative stress. No data were available in exposed humans. Oxidative stress was induced by tetrabromobisphenol A in vivo in rats (testis and kidney), goldfish, zebrafish, earthworms, and scallops. In vitro, tetrabromobisphenol A also induced oxidative stress in human neutrophils and granulocytes, and rat hepatocytes and cerebellar cells, with activation of the mitogen-activated protein kinase pathway. ToxCast data also supported the conclusion that tetrabromobisphenol A induces oxidative stress. Tetrabromobisphenol A activated inflammatory pathways in a human placental cell line.

There is *strong* evidence that tetrabromobisphenol A is immunosuppressive. Tetrabromobisphenol A decreased the lytic and binding functions of isolated human natural killer cells, and reduced the expression of cell-surface proteins needed for the attachment of human natural killer cells to target cells. The effects observed in vitro were supported by the observation in vivo of the reduced ability of mice exposed to tetrabromobisphenol A to suppress a respiratory virus.

In a mouse macrophage cell line, tetrabromobisphenol A increased the expression and production of proinflammatory cytokines. However, because of the absence of data on chronic effects in vivo, the evidence that tetrabromobisphenol A induces chronic inflammation is *moderate*.

There is *weak* evidence that tetrabromobisphenol A is genotoxic. Tetrabromobisphenol A interacted with calf thymus DNA by intercalation. An increased frequency of *Tp53* mutation was observed in uterine carcinomas induced by tetrabromobisphenol A in female rats.

There were few data on the other key characteristics of carcinogens (alters DNA repair or causes genomic instability, induces epigenetic alterations, or causes immortalization).

6. Evaluation

6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of tetrabromobisphenol A.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of tetrabromobisphenol A.

6.3 Overall evaluation

Tetrabromobisphenol A is *probably carcinogenic to humans* (*Group 2A*).

6.4 Rationale

In making its overall evaluation, a majority of the Working Group considered that the strong mechanistic evidence that tetrabromobisphenol A can operate through three key characteristics of carcinogens and that these can be operative in humans warranted an upgrade to *Group 2A*. Specifically, the evidence was strong for the modulation of receptor-mediated effects, for the induction of oxidative stress, and for the induction of immunosuppression:

- Tetrabromobisphenol A interacts directly with several human nuclear receptors relevant to human cancers, including thyroid hormone and peroxisome proliferator-activated receptor-γ. Tetrabromobisphenol A modulates enzymes relevant for the endocrine system, inhibits aromatase, and is a potent inhibitor of sulfotransferase.
- In multiple species in vivo and in human cells in vitro, tetrabromobisphenol A causes oxidative stress.
- Immunosuppressive effects were observed in mice exposed in vivo. Multiple experiments in human natural killer cells exposed in vitro also showed effects consistent with immunosuppression.

However, a minority of the Working Group judged that these data did not support a mechanistic upgrade.

References

Abdallah MA, Harrad S (2011). Tetrabromobisphenol-A, hexabromocyclododecane and its degradation products in UK human milk: relationship to external exposure. *Environ Int*, 37(2):443–8. doi:10.1016/j.envint.2010.11.008 PMID:21167604

Abdallah MA, Harrad S, Covaci A (2008). Hexabromocyclododecanes and tetrabromobisphenol-A in indoor air and dust in Birmingham, UK: implications for human exposure. *Environ Sci Technol*, 42(18):6855–61. doi:10.1021/es801110a PMID:18853800

Abdallah MAE, Harrad S (2010). Modification and calibration of a passive air sampler for monitoring vapor and particulate phase brominated flame retardants in indoor air: application to car interiors. *Environ Sci Technol*, 44(8):3059–65. doi:10.1021/es100146r PMID:20230020

Akiyama E, Kakutani H, Nakao T, Motomura Y, Takano Y, Sorakubo R et al. (2015). Facilitation of adipocyte differentiation of 3T3-L1 cells by debrominated tetrabromobisphenol A compounds detected in Japanese breast milk. *Environ Res*, 140:157–64. doi:10.1016/j.envres.2015.03.035 PMID:25863188

Al-Mousa F, Michelangeli F (2012). Some commonly used brominated flame retardants cause Ca2+-ATPase inhibition, beta-amyloid peptide release and apoptosis in SH-SY5Y neuronal cells. *PLoS ONE*, 7(4):e33059. doi:10.1371/journal.pone.0033059 PMID:22485137

Ashizuka Y, Nakagawa R, Hori T, Yasutake D, Tobiishi K, Sasaki K (2008). Determination of brominated flame retardants and brominated dioxins in fish collected from three regions of Japan. *Mol Nutr Food Res*, 52(2):273–83. doi:10.1002/mnfr.200700110 PMID:18246587

Barrett CA, Orban DA, Seebeck SE, Lowe LE, Owens JE (2015). Development of a low-density-solvent dispersive liquid-liquid microextraction with gas chromatography and mass spectrometry method for the quantitation of tetrabromobisphenol-A from dust. *J Sep Sci*, 38(14):2503–9. doi:10.1002/jssc.201500205 PMID:25931157

Bartels PH, Garcia FA, Trimble CL, Kauderer J, Curtin J, Lim PC et al. (2012). Karyometry in atypical endometrial hyperplasia: a Gynecologic Oncology Group study. *Gynecol Oncol*, 125(1):129–35. doi:10.1016/j.ygyno.2011.12.422 PMID:22155796

Batterman S, Godwin C, Chernyak S, Jia C, Charles S (2010). Brominated flame retardants in offices in Michigan, USA. *Environ Int*, 36(6):548–56. doi:10.1016/j.envint.2010.04.008 PMID:20483456

Behl M, Hsieh JH, Shafer TJ, Mundy WR, Rice JR, Boyd WA et al. (2015). Use of alternative assays to identify and prioritize organophosphorus flame retardants for potential developmental and neurotoxicity.

Neurotoxicol Teratol, 52:Pt B: 181–93. doi:10.1016/j.ntt.2015.09.003 PMID:26386178

Behnisch PA, Hosoe K, Sakai S (2003). Brominated dioxin-like compounds: in vitro assessment in comparison to classical dioxin-like compounds and other polyaromatic compounds. *Environ Int*, 29(6):861–77. doi:10.1016/S0160-4120(03)00105-3 PMID:12850102

Berger U, Herzke D, Sandanger TM (2004). Two trace analytical methods for determination of hydroxylated PCBs and other halogenated phenolic compounds in eggs from Norwegian birds of prey. *Anal Chem*, 76(2):441–52. doi:10.1021/ac0348672 PMID:14719895

Bhusari S, Pandiri AR, Nagai H, Wang Y, Foley J, Hong HL et al. (2015). Genomic profiling reveals unique molecular alterations in hepatoblastomas and adjacent hepatocellular carcinomas in B6C3F1 mice. *Toxicol Pathol*, 43(8):1114–26. doi:10.1177/0192623315599853 PMID:26289556

Blanco E, Casais MC, Mejuto MC, Cela R (2005). Analysis of tetrabromobisphenol A and other phenolic compounds in water samples by non-aqueous capillary electrophoresis coupled to photodiode array ultraviolet detection. *J Chromatogr A*, 1071(1-2):205–11. doi:10.1016/j.chroma.2004.10.075 PMID:15865195

Borghoff SJ, Wikoff D, Harvey S, Haws L (2016). Dose- and time-dependent changes in tissue levels of tetrabromobisphenol A (TBBPA) and its sulfate and glucuronide conjugates following repeated administration to female Wistar Han rats. *Toxicol Rep*, 3:190–201. doi:10.1016/j.toxrep.2016.01.007

Bu D, Zhuang H, Zhou X, Yang G (2014). Biotin-streptavidin enzyme-linked immunosorbent assay for detecting tetrabromobisphenol A in electronic waste. *Talanta*, 120:40–6. doi:10.1016/j.talanta.2013.11.080 PMID:24468340

Butt CM, Wang D, Stapleton HM (2011). Halogenated phenolic contaminants inhibit the in vitro activity of the thyroid-regulating deiodinases in human liver. *Toxicol Sci*, 124(2):339–47. PMID:21565810

Cagnol S, Chambard JC (2010). ERK and cell death: mechanisms of ERK-induced cell death–apoptosis, autophagy and senescence. *FEBS J*, 277(1):2–21. doi:10.1111/j.1742-4658.2009.07366.x PMID:19843174

Canesi L, Lorusso LC, Ciacci C, Betti M, Gallo G (2005). Effects of the brominated flame retardant tetrabromobisphenol-A (TBBPA) on cell signaling and function of Mytilus hemocytes: involvement of MAP kinases and protein kinase C. *Aquat Toxicol*, 75(3):277–87. doi:10.1016/j.aquatox.2005.08.010 PMID:16198432

Carignan CC, Abdallah MA, Wu N, Heiger-Bernays W, McClean MD, Harrad S et al. (2012). Predictors of tetrabromobisphenol-A (TBBP-A) and hexabromocyclododecanes (HBCD) in milk from Boston mothers. *Environ Sci Technol*, 46(21):12146–53. doi:10.1021/es302638d PMID:22998345

Cariou R, Antignac J-P, Zalko D, Berrebi A, Cravedi J-P, Maume D et al. (2008). Exposure assessment of French women and their newborns to tetrabromobisphenol-A: occurrence measurements in maternal adipose tissue, serum, breast milk and cord serum. *Chemosphere*, 73(7):1036–41. PMID:18790516

Cato A, Celada L, Kibakaya EC, Simmons N, Whalen MM (2014). Brominated flame retardants, tetrabromobisphenol A and hexabromocyclododecane, activate mitogen-activated protein kinases (MAPKs) in human natural killer cells. *Cell Biol Toxicol*, 30(6):345–60. doi:10.1007/s10565-014-9289-y

Chignell CF, Han S-K, Mouithys-Mickalad A, Sik RH, Stadler K, Kadiiska MB (2008). EPR studies of in vivo radical production by 3,3′,5,5′-tetrabromobisphenol A (TBBPA) in the Sprague-Dawley rat. *Toxicol Appl Pharmacol*, 230(1):17–22. doi:10.1016/j.taap.2008.01.035 PMID:18342900

Choi JS, Lee YJ, Kim TH, Lim HJ, Ahn MY, Kwack SJ et al. (2011). Molecular mechanism of tetrabromobisphenol A (TBBPA)-induced target organ toxicity in Sprague-Dawley male rats. *Toxicol Rev*, 27(2):61–70. doi:10.5487/TR.2011.27.2.061 PMID:24278553

Christen V, Crettaz P, Oberli-Schrämmli A, Fent K (2010). Some flame retardants and the antimicrobials triclosan and triclocarban enhance the androgenic activity in vitro. *Chemosphere*, 81(10):1245–52. doi:10.1016/j.chemosphere.2010.09.031 PMID:20943248

Chu S, Haffner GD, Letcher RJ (2005). Simultaneous determination of tetrabromobisphenol A, tetrachlorobisphenol A, bisphenol A and other halogenated analogues in sediment and sludge by high performance liquid chromatography-electrospray tandem mass spectrometry. *J Chromatogr A*, 1097(1-2):25–32. doi:10.1016/j.chroma.2005.08.007 PMID:16298182

Chu S, Letcher RJ (2013). Halogenated phenolic compound determination in plasma and serum by solid phase extraction, dansylation derivatization and liquid chromatography-positive electrospray ionization-tandem quadrupole mass spectrometry. *J Chromatogr A*, 1320:111–7. doi:10.1016/j.chroma.2013.10.068 PMID:24210890

Cope RB, Kacew S, Dourson M (2015). A reproductive, developmental and neurobehavioral study following oral exposure of tetrabromobisphenol A on Sprague-Dawley rats. *Toxicology*, 329:49–59. doi:10.1016/j.tox.2014.12.013 PMID:25523853

COT (2004). COT statement on tetrabromobisphenol A - review of toxicological data. London, England: Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment, Food Standards Agency. Available from: http://cot.food.gov.uk/sites/default/files/cot/cotstatements04tbbpa.pdf.

Covaci A, Voorspoels S, Abdallah MA, Geens T, Harrad S, Law RJ (2009). Analytical and environmental aspects of the flame retardant tetrabromobisphenol-A

and its derivatives. *J Chromatogr A*, 1216(3):346–63. doi:10.1016/j.chroma.2008.08.035 PMID:18760795

D'Hollander W, Roosens L, Covaci A, Cornelis C, Reynders H, Campenhout KV et al. (2010). Brominated flame retardants and perfluorinated compounds in indoor dust from homes and offices in Flanders, Belgium. *Chemosphere*, 81(4):478–87. doi:10.1016/j.chemosphere.2010.07.043 PMID:20709355

de Winter-Sorkina R., Bakker M, Van Donkersgoed G, Van Klaveren J (2003). Dietary intake of brominated flame retardants by the Dutch population. RIVM report 310305001/2003. Wageningen, The Netherlands: RIKILT Institute of Food Safety.

de Wit CA, Herzke D, Vorkamp K (2010). Brominated flame retardants in the Arctic environment – trends and new candidates. *Sci Total Environ*, 408(15):2885–918. doi:10.1016/j.scitotenv.2009.08.037 PMID:19815253

De Wit M, Keil D, Remmerie N, van der Ven K, van den Brandhof EJ, Knapen D et al. (2008). Molecular targets of TBBPA in zebrafish analysed through integration of genomic and proteomic approaches. *Chemosphere*, 74(1):96–105. doi:10.1016/j.chemosphere.2008.09.030 PMID:18976794

Dirtu AC, Roosens L, Geens T, Gheorghe A, Neels H, Covaci A (2008). Simultaneous determination of bisphenol A, triclosan, and tetrabromobisphenol A in human serum using solid-phase extraction and gas chromatography-electron capture negative-ionization mass spectrometry. *Anal Bioanal Chem*, 391(4):1175–81. doi:10.1007/s00216-007-1807-9 PMID:18193205

Dunnick JK, Sanders JM, Kissling GE, Johnson CL, Boyle MH, Elmore SA (2015). Environmental chemical exposure may contribute to uterine cancer development: studies with tetrabromobisphenol A. *Toxicol Pathol*, 43(4):464–73. doi:10.1177/0192623314557335 PMID:25476797

ECHA (2006). European Union risk assessment report on 2,2′,6,6′-tetrabromo-4,4'-isopropylidenediphenol(tetrabromobisphenol-A or TBBP-A). Part II, Human health. European Commission, Joint Research Centre *European Chemicals Bureau*, 63:EUR22161E

ECHA (2008). Risk assessment of 2,2′,6,6′-tetrabromo-4,4′-isopropylidene diphenol (tetrabromobisphenol-A). Final Environmental Rar of February 2008. Report No. R402_0802_env Part I, Environment, European Commission, Joint Research Centre, European Chemicals Bureau. Available from: http://echa.europa.eu/documents/10162/17c7379e-f47b-4a76-aa43-060da5830c07, accessed October 2017.

ECHA (2016). 2,2′,6,6′-Tetrabromo-4,4′-isopropylidenediphenol. Brief profile. Helsinki, Finland: European Chemicals Agency. Available from: https://echa.europa.eu/brief-profile/-/briefprofile/100.001.125.

Eriksson P, Jakobsson E, Fredriksson A (2001). Brominated flame retardants: a novel class of developmental neurotoxicants in our environment? *Environ Health Perspect*, 109(9):903–8. doi:10.1289/ehp.01109903 PMID:11673118

Feng M, Qu R, Wang C, Wang L, Wang Z (2013). Comparative antioxidant status in freshwater fish Carassius auratus exposed to six current-use brominated flame retardants: a combined experimental and theoretical study. *Aquat Toxicol*, 140-141:314–23. doi:10.1016/j.aquatox.2013.07.001 PMID:23880106

Fini J-B, Riu A, Debrauwer L, Hillenweck A, Le Mével S, Chevolleau S et al. (2012). Parallel biotransformation of tetrabromobisphenol A in Xenopus laevis and mammals: Xenopus as a model for endocrine perturbation studies. *Toxicol Sci*, 125(2):359–67. doi:10.1093/toxsci/kfr312 PMID:22086976

Freitas J, Cano P, Craig-Veit C, Goodson ML, Furlow JD, Murk AJ (2011). Detection of thyroid hormone receptor disruptors by a novel stable in vitro reporter gene assay. *Toxicol In Vitro*, 25(1):257–66. doi:10.1016/j.tiv.2010.08.013 PMID:20732405

Fromme H, Hilger B, Kopp E, Miserok M, Völkel W (2014). Polybrominated diphenyl ethers (PBDEs), hexabromocyclododecane (HBCD) and "novel" brominated flame retardants in house dust in Germany. *Environ Int*, 64:61–8. doi:10.1016/j.envint.2013.11.017 PMID:24368294

FSA (2006). Brominated chemicals: UK dietary intakes. London, England: Food Standards Agency. Available from: http://www.food.gov.uk/multimedia/pdfs/fsis1006.pdf, accessed 15 December 2016.

Fujii Y, Harada KH, Hitomi T, Kobayashi H, Koizumi A, Haraguchi K (2014a). Temporal trend and age-dependent serum concentration of phenolic organohalogen contaminants in Japanese men during 1989-2010. *Environ Pollut*, 185:228–33. doi:10.1016/j.envpol.2013.11.002 PMID:24291611

Fujii Y, Nishimura E, Kato Y, Harada KH, Koizumi A, Haraguchi K (2014b). Dietary exposure to phenolic and methoxylated organohalogen contaminants in relation to their concentrations in breast milk and serum in Japan. *Environ Int*, 63:19–25. doi:10.1016/j.envint.2013.10.016 PMID:24263137

Germer S, Piersma AH, van der Ven L, Kamyschnikow A, Fery Y, Schmitz HJ et al. (2006). Subacute effects of the brominated flame retardants hexabromocyclododecane and tetrabromobisphenol A on hepatic cytochrome P450 levels in rats. *Toxicology*, 218(2–3):229–36. doi:10.1016/j.tox.2005.10.019 PMID:16325980

Gorga M, Martínez E, Ginebreda A, Eljarrat E, Barceló D (2013). Determination of PBDEs, HBB, PBEB, DBDPE, HBCD, TBBPA and related compounds in sewage sludge from Catalonia (Spain). *Sci Total Environ*, 444:51–9. doi:10.1016/j.scitotenv.2012.11.066 PMID:23262324

Gosavi RA, Knudsen GA, Birnbaum LS, Pedersen LC (2013). Mimicking of estradiol binding by flame retardants and their metabolites: a crystallographic

analysis. *Environ Health Perspect*, 121(10):1194–9. PMID:23959441

Goto Y, Kitamura S, Kashiwagi K, Oofusa K, Tooi O, Yoshizato K et al. (2006). Suppression of amphibian metamorphosis by bisphenol A and related chemical substances. *J Health Sci*, 52(2):160–8. doi:10.1248/jhs.52.160

Grasselli E, Cortese K, Fabbri R, Smerilli A, Vergani L, Voci A et al. (2014). Thyromimetic actions of tetrabromobisphenol A (TBBPA) in steatotic FaO rat hepatoma cells. *Chemosphere*, 112:511–8. doi:10.1016/j.chemosphere.2014.03.114 PMID:25048947

Guerra P, Eljarrat E, Barceló D (2010). Simultaneous determination of hexabromocyclododecane, tetrabromobisphenol A, and related compounds in sewage sludge and sediment samples from Ebro River basin (Spain). *Anal Bioanal Chem*, 397(7):2817–24. doi:10.1007/s00216-010-3670-3 PMID:20383698

Guyot R, Chatonnet F, Gillet B, Hughes S, Flamant F (2014). Toxicogenomic analysis of the ability of brominated flame retardants TBBPA and BDE-209 to disrupt thyroid hormone signalling in neural cells. *Toxicology*, 325:125–32. doi:10.1016/j.tox.2014.08.007 PMID:25172293

Hagmar L, Jakobsson K, Thuresson K, Rylander L, Sjödin A, Bergman Å (2000a). Computer technicians are occupationally exposed to polybrominated diphenyl ethers and tetrabromobisphenol A. *Organohalogen Compd*, 47:202–5.

Hagmar L, Sjödin A, Höglund P, Thuresson K, Rylander L, Bergman Å (2000b). Biological half-lives of polybrominated diphenyl ethers and tetrabromobisphenol A in exposed workers. *Organohalogen Compd*, 47:198–201.

Hakk H, Larsen G, Bergman A, Örn U (2000). Metabolism, excretion and distribution of the flame retardant tetrabromobisphenol-A in conventional and bile-duct cannulated rats. *Xenobiotica*, 30(9):881–90. doi:10.1080/004982500433309 PMID:11055266

Hamers T, Kamstra JH, Sonneveld E, Murk AJ, Kester MH, Andersson PL et al. (2006). In vitro profiling of the endocrine-disrupting potency of brominated flame retardants. *Toxicol Sci*, 92(1):157–73. doi:10.1093/toxsci/kfj187 PMID:16601080

Han EH, Park JH, Kang KW, Jeong TC, Kim HS, Jeong HG (2009). Risk assessment of tetrabromobisphenol A on cyclooxygenase-2 expression via MAP kinase/NF-kappaB/AP-1 signaling pathways in murine macrophages. *J Toxicol Environ Health A*, 72(21-22):1431–8. doi:10.1080/15287390903212873 PMID:20077215

Han W, Wang S, Huang H, Luo L, Zhang S (2013). Simultaneous determination of brominated phenols in soils. *J Environ Sci (China)*, 25(11):2306–12. doi:10.1016/S1001-0742(12)60298-8 PMID:24552060

Hansen MK, Sharma AK, Dybdahl M, Boberg J, Kulahci M (2014). In vivo Comet assay–statistical analysis and power calculations of mice testicular cells. *Mutat Res Genet Toxicol Environ Mutagen*, 774:29–40. doi:10.1016/j.mrgentox.2014.08.006 PMID:25440908

Harleman JH, Hargreaves A, Andersson H, Kirk S (2012). A review of the incidence and coincidence of uterine and mammary tumors in Wistar and Sprague-Dawley rats based on the RITA database and the role of prolactin. *Toxicol Pathol*, 40(6):926–30. doi:10.1177/0192623312444621 PMID:22585942

Harrad S, Abdallah MAE, Rose NL, Turner SD, Davidson TA (2009). Current-use brominated flame retardants in water, sediment, and fish from English lakes. *Environ Sci Technol*, 43(24):9077–83. doi:10.1021/es902185u PMID:19921842

Harrad S, Goosey E, Desborough J, Abdallah MA, Roosens L, Covaci A (2010). Dust from U.K. primary school classrooms and daycare centers: the significance of dust as a pathway of exposure of young U.K. children to brominated flame retardants and polychlorinated biphenyls. *Environ Sci Technol*, 44(11):4198–202. doi:10.1021/es100750s PMID:20441148

Harvey JB, Osborne TS, Hong HL, Bhusari S, Ton TV, Pandiri AR et al. (2015). Uterine carcinomas in tetrabromobisphenol A-exposed Wistar Han rats harbor increased Tp53 mutations and mimic high-grade type I endometrial carcinomas in women. *Toxicol Pathol*, 43(8):1103–13. doi:10.1177/0192623315599256 PMID:26353976

Hayama T, Yoshida H, Onimaru S, Yonekura S, Kuroki H, Todoroki K et al. (2004). Determination of tetrabromobisphenol A in human serum by liquid chromatography-electrospray ionization tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed LifeSci*,809(1):131–6.doi:10.1016/j.jchromb.2004.06.013 PMID:15282103

He MJ, Luo XJ, Yu LH, Liu J, Zhang XL, Chen SJ et al. (2010). Tetrabromobisphenol-A and hexabromocyclododecane in birds from an e-waste region in South China: influence of diet on diastereoisomer- and enantiomer-specific distribution and trophodynamics. *Environ Sci Technol*, 44(15):5748–54. doi:10.1021/es101503r PMID:20666555

He Q, Wang X, Sun P, Wang Z, Wang L (2015). Acute and chronic toxicity of tetrabromobisphenol A to three aquatic species under different pH conditions. *Aquat Toxicol*, 164:145–54. doi:10.1016/j.aquatox.2015.05.005 PMID:25980965

Helleday T, Tuominen KL, Bergman A, Jenssen D (1999). Brominated flame retardants induce intragenic recombination in mammalian cells. *Mutat Res*, 439(2):137–47. doi:10.1016/S1383-5718(98)00186-7 PMID:10023042

Herzke D, Berger U, Kallenborn R, Nygård T, Vetter W (2005). Brominated flame retardants and other organobromines in Norwegian predatory bird eggs. *Chemosphere*, 61(3):441–9. doi:10.1016/j.chemosphere.2005.01.066 PMID:16182862

Hloušková V, Lanková D, Kalachová K, Hrádková P, Poustka J, Hajšlová J et al. (2014). Brominated flame retardants and perfluoroalkyl substances in sediments from the Czech aquatic ecosystem. *Sci Total Environ*, 470-471:407–16. doi:10.1016/j.scitotenv.2013.09.074 PMID:24140701

Hofmann PJ, Schomburg L, Köhrle J (2009). Interference of endocrine disrupters with thyroid hormone receptor-dependent transactivation. *Toxicol Sci*, 110(1):125–37. doi:10.1093/toxsci/kfp086 PMID:19403856

Honkisz E, Wójtowicz AK (2015). Modulation of estradiol synthesis and aromatase activity in human choriocarcinoma JEG-3 cells exposed to tetrabromobisphenol A. *Toxicol In Vitro*, 29(1):44–50. doi:10.1016/j.tiv.2014.09.003 PMID:25223798

Hu F, Pan L, Xiu M, Jin Q (2015b). Exposure of Chlamys farreri to tetrabromobisphenol A: accumulation and multibiomarker responses. *Environ Sci Pollut Res Int*, 22(16):12224–34. doi:10.1007/s11356-015-4487-6 PMID:25893623

Hu F, Pan L, Xiu M, Liu D (2015a). Dietary accumulation of tetrabromobisphenol A and its effects on the scallop Chlamys farreri. *Comp Biochem Physiol C Toxicol Pharmacol*, 167:7–14. doi:10.1016/j.cbpc.2014.08.002 PMID:25183548

Hu J, Liang Y, Chen M, Wang X (2009). Assessing the toxicity of TBBPA and HBCD by zebrafish embryo toxicity assay and biomarker analysis. *Environ Toxicol*, 24(4):334–42. doi:10.1002/tox.20436 PMID:18767142

Huang DY, Zhao HQ, Liu CP, Sun CX (2014). Characteristics, sources, and transport of tetrabromobisphenol A and bisphenol A in soils from a typical e-waste recycling area in South China. *Environ Sci Pollut Res Int*, 21(9):5818–26. doi:10.1007/s11356-014-2535-2 PMID:24443052

Hurd T, Whalen MM (2011). Tetrabromobisphenol A decreases cell-surface proteins involved in human natural killer (NK) cell-dependent target cell lysis. *J Immunotoxicol*, 8(3):219–27. doi:10.3109/1547691X.2011.580437 PMID:21623697

Hwang IK, Kang HH, Lee IS, Oh JE (2012). Assessment of characteristic distribution of PCDD/Fs and BFRs in sludge generated at municipal and industrial wastewater treatment plants. *Chemosphere*, 88(7):888–94. doi:10.1016/j.chemosphere.2012.03.098 PMID:22595527

Imai T, Takami S, Cho YM, Hirose M, Nishikawa A (2009). Modifying effects of prepubertal exposure to potassium perchlorate and tetrabromobisphenol A on susceptibility to N-bis(2-hydroxypropyl)nitrosamine- and 7,12-dimethylbenz(a)anthracene-induced carcinogenesis in rats. *Toxicol Lett*, 185(3):160–7. doi:10.1016/j.toxlet.2008.12.013 PMID:19152830

Inoue K, Yoshida S, Nakayama S, Ito R, Okanouchi N, Nakazawa H (2006). Development of stable isotope dilution quantification liquid chromatography-mass spectrometry method for estimation of exposure levels of bisphenol A, 4-tert-octylphenol, 4-nonylphenol, tetrabromobisphenol A, and pentachlorophenol in indoor air. *Arch Environ Contam Toxicol*, 51(4):503–8. doi:10.1007/s00244-005-0236-z PMID:16998634

IPCS (1995). Tetrabromobisphenol A and derivatives. Environmental Health Criteria No. 172. Geneva, Switzerland: International Programme on Chemical Safety, World Health Organization. Available from: http://www.inchem.org/documents/ehc/ehc/ehc172.htm, accessed October 2017.

Jakobsson K, Thuresson K, Rylander L, Sjödin A, Hagmar L, Bergman A (2002). Exposure to polybrominated diphenyl ethers and tetrabromobisphenol A among computer technicians. *Chemosphere*, 46(5):709–16. doi:10.1016/S0045-6535(01)00235-1 PMID:11999794

Johnson-Restrepo B, Adams DH, Kannan K (2008). Tetrabromobisphenol A (TBBPA) and hexabromocyclododecanes (HBCDs) in tissues of humans, dolphins, and sharks from the United States. *Chemosphere*, 70(11):1935–44. doi:10.1016/j.chemosphere.2007.10.002 PMID:18037156

Kang MJ, Kim JH, Shin S, Choi JH, Lee SK, Kim HS et al. (2009). Nephrotoxic potential and toxicokinetics of tetrabromobisphenol A in rat for risk assessment. *J Toxicol Environ Health A*, 72(21-22):1439–45. doi:10.1080/15287390903212907 PMID:20077216

Kavlock R, Chandler K, Houck K, Hunter S, Judson R, Kleinstreuer N et al. (2012). Update on EPA's ToxCast program: providing high throughput decision support tools for chemical risk management. *Chem Res Toxicol*, 25(7):1287–302. doi:10.1021/tx3000939 PMID:22519603

Kawashiro Y, Fukata H, Omori-Inoue M, Kubonoya K, Jotaki T, Takigami H et al. (2008). Perinatal exposure to brominated flame retardants and polychlorinated biphenyls in Japan. *Endocr J*, 55(6):1071–84. doi:10.1507/endocrj.K08E-155 PMID:18719292

Kester MH, Bulduk S, van Toor H, Tibboel D, Meinl W, Glatt H et al. (2002). Potent inhibition of estrogen sulfotransferase by hydroxylated metabolites of polyhalogenated aromatic hydrocarbons reveals alternative mechanism for estrogenic activity of endocrine disrupters. *J Clin Endocrinol Metab*, 87(3):1142–50. doi:10.1210/jcem.87.3.8311 PMID:11889178

Kibakaya EC, Stephen K, Whalen MM (2009). Tetrabromobisphenol A has immunosuppressive effects on human natural killer cells. *J Immunotoxicol*, 6(4):285–92. doi:10.3109/15476910903258260 PMID:19908946

Kiciński M, Viaene MK, Den Hond E, Schoeters G, Covaci A, Dirtu AC et al. (2012). Neurobehavioral function and low-level exposure to brominated flame retardants in adolescents: a cross-sectional study. *Environ Health*, 11(1):86. doi:10.1186/1476-069X-11-86 PMID:23151181

Kim UJ, Oh JE (2014). Tetrabromobisphenol A and hexabromocyclododecane flame retardants in infant-mother paired serum samples, and their relationships with thyroid hormones and environmental factors. *Environ Pollut*, 184:193–200. doi:10.1016/j.envpol.2013.08.034 PMID:24060738

Kitamura S, Jinno N, Ohta S, Kuroki H, Fujimoto N (2002). Thyroid hormonal activity of the flame retardants tetrabromobisphenol A and tetrachlorobisphenol A. *Biochem Biophys Res Commun*, 293(1):554–9. doi:10.1016/S0006-291X(02)00262-0 PMID:12054637

Kitamura S, Kato T, Iida M, Jinno N, Suzuki T, Ohta S et al. (2005a). Anti-thyroid hormonal activity of tetrabromobisphenol A, a flame retardant, and related compounds: affinity to the mammalian thyroid hormone receptor, and effect on tadpole metamorphosis. *Life Sci*, 76(14):1589–601. doi:10.1016/j.lfs.2004.08.030 PMID:15680168

Kitamura S, Suzuki T, Sanoh S, Kohta R, Jinno N, Sugihara K et al. (2005b). Comparative study of the endocrine-disrupting activity of bisphenol A and 19 related compounds. *Toxicol Sci*, 84(2):249–59. doi:10.1093/toxsci/kfi074 PMID:15635150

Knudsen GA, Hughes MF, McIntosh KL, Sanders JM, Birnbaum LS (2015). Estimation of tetrabromobisphenol A (TBBPA) percutaneous uptake in humans using the parallelogram method. *Toxicol Appl Pharmacol*, 289(2):323–9. doi:10.1016/j.taap.2015.09.012 PMID:26387765

Knudsen GA, Sanders JM, Sadik AM, Birnbaum LS (2014). Disposition and kinetics of tetrabromobisphenol A in female Wistar Han rats. *Toxicol Rev*, 1:214–23. doi:10.1016/j.toxrep.2014.03.005 PMID:24977115

Koike E, Yanagisawa R, Takigami H, Takano H (2013). Brominated flame retardants stimulate mouse immune cells in vitro. *J Appl Toxicol*, 33(12):1451–9. doi:10.1002/jat.2809 PMID:22972382

Kopp EK, Fromme H, Völkel W (2012). Analysis of common and emerging brominated flame retardants in house dust using ultrasonic assisted solvent extraction and on-line sample preparation via column switching with liquid chromatography-mass spectrometry. *J Chromatogr A*, 1241:28–36. doi:10.1016/j.chroma.2012.04.022 PMID:22546182

Kowalski B, Mazur M (2014). The simultaneous determination of six flame retardants in water samples using SPE pre-concentration and UHPLC-UV method. *Water Air Soil Pollut*, 225(3):1866. doi:10.1007/s11270-014-1866-4 PMID:24672141

Kuester RK, Sólyom AM, Rodriguez VP, Sipes IG (2007). The effects of dose, route, and repeated dosing on the disposition and kinetics of tetrabromobisphenol A in male F-344 rats. *Toxicol Sci*, 96(2):237–45. doi:10.1093/toxsci/kfm006 PMID:17234645

La Guardia MJ, Hale RC (2015). Halogenated flame-retardant concentrations in settled dust, respirable and inhalable particulates and polyurethane foam at gymnastic training facilities and residences. *Environ Int*, 79:106–14. doi:10.1016/j.envint.2015.02.014 PMID:25812808

Labadie P, Tlili K, Alliot F, Bourges C, Desportes A, Chevreuil M (2010). Development of analytical procedures for trace-level determination of polybrominated diphenyl ethers and tetrabromobisphenol A in river water and sediment. *Anal Bioanal Chem*, 396(2):865–75. doi:10.1007/s00216-009-3267-x PMID:19921511

Lai DY, Kacew S, Dekant W (2015). Tetrabromobisphenol A (TBBPA): possible modes of action of toxicity and carcinogenicity in rodents. *Food Chem Toxicol*, 80:206–14. doi:10.1016/j.fct.2015.03.023 PMID:25818463

Lankova D, Lacina O, Pulkrabova J, Hajslova J (2013). The determination of perfluoroalkyl substances, brominated flame retardants and their metabolites in human breast milk and infant formula. *Talanta*, 117:318–25. PMID:24209347

Lassen C, Løkke S, Andersen LI (1999). Brominated flame retardants- substance flow analysis and assessment of alternatives, Environmental Project 494. Copenhagen, Denmark: Danish Environmental Protection Agency; Available from https://www.indymedia.org/media/2009/07/926988.pdf.

Law RJ, Bersuder P, Allchin CR, Barry J (2006a). Levels of the flame retardants hexabromocyclododecane and tetrabromobisphenol A in the blubber of harbor porpoises (Phocoena phocoena) stranded or bycaught in the U.K., with evidence for an increase in HBCD concentrations in recent years. *Environ Sci Technol*, 40(7):2177–83. doi:10.1021/es052416o PMID:16646450

Lee IS, Kang HH, Kim UJ, Oh JE (2015). Brominated flame retardants in Korean river sediments, including changes in polybrominated diphenyl ether concentrations between 2006 and 2009. *Chemosphere*, 126:18–24. doi:10.1016/j.chemosphere.2015.01.004 PMID:25655576

Lévy-Bimbot M, Major G, Courilleau D, Blondeau JP, Lévi Y (2012). Tetrabromobisphenol-A disrupts thyroid hormone receptor alpha function in vitro: use of fluorescence polarization to assay corepressor and coactivator peptide binding. *Chemosphere*, 87(7):782–8. doi:10.1016/j.chemosphere.2011.12.080 PMID:22277881

Lilienthal H, Verwer CM, van der Ven LT, Piersma AH, Vos JG (2008). Exposure to tetrabromobisphenol A (TBBPA) in Wistar rats: neurobehavioral effects in offspring from a one-generation reproduction study. *Toxicology*, 246(1):45–54. doi:10.1016/j.tox.2008.01.007 PMID:18295390

Liu H, Yu Y, Kong F, He L, Yu H, Giesy JP et al. (2008). Effects of tetrabromobisphenol A on the green alga Chlorella pyrenoidosa. *J Environ Sci Health.*, 43(11):1271–8. doi:10.1080/10934520802177821

Liu K, Li J, Yan S, Zhang W, Li Y, Han D (2016). A review of status of tetrabromobisphenol A (TBBPA) in China. *Chemosphere*, 148:8–20. doi:10.1016/j.chemosphere.2016.01.023 PMID:26800486

Mäkinen MSE, Mäkinen MRA, Koistinen JTB, Pasanen A-L, Pasanen PO, Kalliokoski PJ et al. (2009). Respiratory and dermal exposure to organophosphorus flame retardants and tetrabromobisphenol A at five work environments. *Environ Sci Technol*, 43(3):941–7. doi:10.1021/es802593t PMID:19245040

Mariussen E, Fonnum F (2003). The effect of brominated flame retardants on neurotransmitter uptake into rat brain synaptosomes and vesicles. *Neurochem Int*, 43(4–5):533–42. doi:10.1016/S0197-0186(03)00044-5 PMID:12742101

McIver CR, Shaw IC, Gin S, Ellis MJ (2013). Can thyroid hormone mimics affect thyroid hormone measurement by immunoassay? *Clin Biochem*, 46(13–14):1302–4. PMID:23850848

Meerts IA, van Zanden JJ, Luijks EA, van Leeuwen-Bol I, Marsh G, Jakobsson E et al. (2000). Potent competitive interactions of some brominated flame retardants and related compounds with human transthyretin in vitro. *Toxicol Sci*, 56(1):95–104. doi:10.1093/toxsci/56.1.95 PMID:10869457

Molina-Molina JM, Amaya E, Grimaldi M, Sáenz JM, Real M, Fernández MF et al. (2013). In vitro study on the agonistic and antagonistic activities of bisphenol-S and other bisphenol-A congeners and derivatives via nuclear receptors. *Toxicol Appl Pharmacol*, 272(1):127–36. doi:10.1016/j.taap.2013.05.015 PMID:23714657

Morris S, Allchin CR, Zegers BN, Haftka JJ, Boon JP, Belpaire C et al. (2004). Distribution and fate of HBCD and TBBPA brominated flame retardants in North Sea estuaries and aquatic food webs. *Environ Sci Technol*, 38(21):5497–504. doi:10.1021/es049640i PMID:15575264

Nagayama J, Tsuji H, Takasuga T (2000). Comparison between brominated flame retardants and dioxins or organochlorine compounds in blood levels of Japanese adults. *Organohalogen Compd*, 48:27–30.

Nakagawa Y, Suzuki T, Ishii H, Ogata A (2007). Biotransformation and cytotoxicity of a brominated flame retardant, tetrabromobisphenol A, and its analogues in rat hepatocytes. *Xenobiotica*, 37(7):693–708. doi:10.1080/00498250701397697 PMID:17620216

Nakao T, Akiyama E, Kakutani H, Mizuno A, Aozasa O, Akai Y et al. (2015). Levels of tetrabromobisphenol A, tribromobisphenol A, dibromobisphenol A, monobromobisphenol A, and bisphenol a in Japanese breast milk. *Chem Res Toxicol*, 28(4):722–8. doi:10.1021/tx500495j PMID:25719948

Neumann F (1991). Early indicators for carcinogenesis in sex-hormone-sensitive organs. *Mutat Res*, 248(2):341–56. doi:10.1016/0027-5107(91)90067-X PMID:2046690

Ni HG, Zeng H (2013). HBCD and TBBPA in particulate phase of indoor air in Shenzhen, China. *Sci Total Environ*, 458-460:15–9. doi:10.1016/j.scitotenv.2013.04.003 PMID:23639907

NTP (2014). NTP technical report on the toxicology studies of tetrabromobisphenol A (CAS No. 79-94-7) in F344/NTac rats and B6C3F1/N mice and toxicology and carcinogenesis studies of tetrabromobisphenol A in Wistar Han [Crl:WI(Han)] rats and B6C3F1/N mice (gavage studies). NTP TR 587, NIH Publication No. 14-5929. Research Triangle Park (NC), USA: National Toxicology Program, United States Department of Health and Human Studies. Available from: http://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr587_508.pdf.

Oberg K, Warman K, Oberg T (2002). Distribution and levels of brominated flame retardants in sewage sludge. *Chemosphere*, 48(8):805–9. doi:10.1016/S0045-6535(02)00113-3 PMID:12222774

Ogunbayo OA, Lai PF, Connolly TJ, Michelangeli F (2008). Tetrabromobisphenol A (TBBPA), induces cell death in TM4 Sertoli cells by modulating Ca2+ transport proteins and causing dysregulation of Ca2+ homeostasis. *Toxicol In Vitro*, 22(4):943–52. doi:10.1016/j.tiv.2008.01.015 PMID:18329244

Ohta R, Takagi A, Ohmukai H, Marumo H, Ono A, Matsushima Y et al. (2012). Ovariectomized mouse uterotrophic assay of 36 chemicals. *J Toxicol Sci*, 37(5):879–89. doi:10.2131/jts.37.879 PMID:23037998

Oka T, Mitsui-Watanabe N, Tatarazako N, Onishi Y, Katsu Y, Miyagawa S et al. (2013). Establishment of transactivation assay systems using fish, amphibian, reptilian and human thyroid hormone receptors. *J Appl Toxicol*, 33(9):991–1000. doi:10.1002/jat.2825 PMID:23112079

Osimitz TG, Droege W, Hayes AW (2016). Subchronic toxicology of tetrabromobisphenol A in rats. *Hum Exp Toxicol*, 35(11):1214–26. doi:10.1177/0960327115627684 PMID:26860688

Park HR, Kamau PW, Korte C, Loch-Caruso R (2014). Tetrabromobisphenol A activates inflammatory pathways in human first trimester extravillous trophoblasts in vitro. *Reprod Toxicol*, 50:154–62. doi:10.1016/j.reprotox.2014.10.005 PMID:25461914

Pratt I, Anderson W, Crowley D, Daly S, Evans R, Fernandes A et al. (2013). Brominated and fluorinated organic pollutants in the breast milk of first-time Irish mothers: is there a relationship to levels in food? *Food Addit Contam Part A Chem Anal Control Expo Risk Assess*, 30(10):1788–98. doi:10.1080/19440049.2013.822569 PMID:23919530

Pullen S, Boecker R, Tiegs G (2003). The flame retardants tetrabromobisphenol A and tetrabromobisphenol A-bisallylether suppress the induction of interleukin-2 receptor alpha chain (CD25) in murine splenocytes. *Toxicology*, 184(1):11–22. doi:10.1016/S0300-483X(02)00442-0 PMID:12505372

Reindl AR, Falkowska L (2015). Flame retardants at the top of a simulated baltic marine food web–a case study concerning African penguins from the Gdansk Zoo. *Arch Environ Contam Toxicol*, 68(2):259–64. doi:10.1007/s00244-014-0081-z PMID:25224990

Reistad T, Mariussen E, Fonnum F (2005). The effect of a brominated flame retardant, tetrabromobisphenol-A, on free radical formation in human neutrophil granulocytes: the involvement of the MAP kinase pathway and protein kinase C. *Toxicol Sci*, 83(1):89–100. doi:10.1093/toxsci/kfh298 PMID:15456914

Reistad T, Mariussen E, Ring A, Fonnum F (2007). In vitro toxicity of tetrabromobisphenol-A on cerebellar granule cells: cell death, free radical formation, calcium influx and extracellular glutamate. *Toxicol Sci*, 96(2):268–78. doi:10.1093/toxsci/kfl198 PMID:17205976

Saegusa Y, Fujimoto H, Woo GH, Inoue K, Takahashi M, Mitsumori K et al. (2009). Developmental toxicity of brominated flame retardants, tetrabromobisphenol A and 1,2,5,6,9,10-hexabromocyclododecane, in rat offspring after maternal exposure from mid-gestation through lactation. *Reprod Toxicol*, 28(4):456–67. doi:10.1016/j.reprotox.2009.06.011 PMID:19577631

Saint-Louis R, Pelletier E (2004). LC-ESI-MS-MS method for the analysis of tetrabromobisphenol A in sediment and sewage sludge. *Analyst*, 129(8):724–30. doi:10.1039/b400743n PMID:15284916

Samuelsen M, Olsen C, Holme JA, Meussen-Elholm E, Bergmann A, Hongslo JK (2001). Estrogen-like properties of brominated analogs of bisphenol A in the MCF-7 human breast cancer cell line. *Cell Biol Toxicol*, 17(3):139–51. doi:10.1023/A:1011974012602 PMID:11693576

Sánchez-Brunete C, Miguel E, Tadeo JL (2009). Determination of tetrabromobisphenol-A, tetrachlorobisphenol-A and bisphenol-A in soil by ultrasonic assisted extraction and gas chromatography-mass spectrometry. *J Chromatogr A*, 1216(29):5497–503. doi:10.1016/j.chroma.2009.05.065 PMID:19524246

Schauer UMD, Völkel W, Dekant W (2006). Toxicokinetics of tetrabromobisphenol A in humans and rats after oral administration. *Toxicol Sci*, 91(1):49–58. doi:10.1093/toxsci/kfj132 PMID:16481339

Schlabach M, Fjeld E, Gundersen H, Mariussen E, Kjellberg G, Breivik E (2004). Pollution of Lake Mjøsa by brominated flame retardants. *Organohalogen Compd*, 66:3730–6.

Shi H, Wang X, Luo Y, Su Y (2005). Electron paramagnetic resonance evidence of hydroxyl radical generation and oxidative damage induced by tetrabromobisphenol A in Carassius auratus. *Aquat Toxicol*, 74(4):365–71. doi:10.1016/j.aquatox.2005.06.009 PMID:16054708

Shi YJ, Xu XB, Zheng XQ, Lu YL (2015). Responses of growth inhibition and antioxidant gene expression in earthworms (Eisenia fetida) exposed to tetrabromobisphenol A, hexabromocyclododecane and decabromodiphenyl ether. *Comp Biochem Physiol C Toxicol Pharmacol*, 174-175:32–8. doi:10.1016/j.cbpc.2015.06.005 PMID:26117064

Shi Z, Jiao Y, Hu Y, Sun Z, Zhou X, Feng J et al. (2013). Levels of tetrabromobisphenol A, hexabromocyclododecanes and polybrominated diphenyl ethers in human milk from the general population in Beijing, China. *Sci Total Environ*, 452-453:10–8. doi:10.1016/j.scitotenv.2013.02.038 PMID:23500394

Shi Z-X, Wu Y-N, Li J-G, Zhao Y-F, Feng J-F (2009). Dietary exposure assessment of Chinese adults and nursing infants to tetrabromobisphenol-A and hexabromocyclododecanes: occurrence measurements in foods and human milk. *Environ Sci Technol*, 43(12):4314–9. doi:10.1021/es8035626 PMID:19603640

Sjödin A, Carlsson H, Thuresson K, Sjölin S, Bergman A, Ostman C (2001). Flame retardants in indoor air at an electronics recycling plant and at other work environments. *Environ Sci Technol*, 35(3):448–54. doi:10.1021/es000077n PMID:11351713

Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I et al. (2016). Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environ Health Perspect*, 124(6):713–21. PMID:26600562

Song R, He Y, Murphy MB, Yeung LW, Yu RM, Lam MH et al. (2008). Effects of fifteen PBDE metabolites, DE71, DE79 and TBBPA on steroidogenesis in the H295R cell line. *Chemosphere*, 71(10):1888–94. doi:10.1016/j.chemosphere.2008.01.032 PMID:18313098

Song S, Song M, Zeng L, Wang T, Liu R, Ruan T et al. (2014). Occurrence and profiles of bisphenol analogues in municipal sewage sludge in China. *Environ Pollut*, 186:14–9. doi:10.1016/j.envpol.2013.11.023 PMID:24355443

Strack S, Detzel T, Wahl M, Kuch B, Krug HF (2007). Cytotoxicity of TBBPA and effects on proliferation, cell cycle and MAPK pathways in mammalian cells. *Chemosphere*, 67(9):S405–11. doi:10.1016/j.chemosphere.2006.05.136 PMID:17254629

Sun H, Shen OX, Wang XR, Zhou L, Zhen SQ, Chen XD (2009). Anti-thyroid hormone activity of bisphenol A, tetrabromobisphenol A and tetrachlorobisphenol A in an improved reporter gene assay. *Toxicol In Vitro*, 23(5):950–4. doi:10.1016/j.tiv.2009.05.004 PMID:19457453

Sun Y, Guo H, Yu H, Wang X, Wu J, Xue Y (2008). Bioaccumulation and physiological effects of tetrabromobisphenol A in coontail Ceratophyllum demersum L. *Chemosphere*, 70(10):1787–95. doi:10.1016/j.chemosphere.2007.08.033 PMID:17963815

Suzuki S, Hasegawa A (2006). Determination of hexabromocyclododecane diastereoisomers and tetrabromobisphenol A in water and sediment by liquid chromatography/mass spectrometry.

Anal Sci, 22(3):469–74. doi:10.2116/analsci.22.469 PMID:16733326

Svihlikova V, Lankova D, Poustka J, Tomaniova M, Hajslova J, Pulkrabova J (2015). Perfluoroalkyl substances (PFASs) and other halogenated compounds in fish from the upper Labe River basin. *Chemosphere*, 129:170–8. doi:10.1016/j.chemosphere.2014.09.096 PMID:25455680

Szymańska JA, Piotrowski JK, Frydrych B (2000). Hepatotoxicity of tetrabromobisphenol-A: effects of repeated dosage in rats. *Toxicology*, 142(2):87–95. doi:10.1016/S0300-483X(99)00108-0 PMID:10685508

Szymańska JA, Sapota A, Frydrych B (2001). The disposition and metabolism of tetrabromobisphenol-A after a single i.p. dose in the rat. *Chemosphere*, 45(4-5):693–700. doi:10.1016/S0045-6535(01)00015-7 PMID:11680765

Takigami H, Suzuki G, Hirai Y, Sakai S (2009). Brominated flame retardants and other polyhalogenated compounds in indoor air and dust from two houses in Japan. *Chemosphere*, 76(2):270–7. doi:10.1016/j.chemosphere.2009.03.006 PMID:19361833

Tang B, Zeng YH, Luo XJ, Zheng XB, Mai BX (2015). Bioaccumulative characteristics of tetrabromobisphenol A and hexabromocyclododecanes in multi-tissues of prey and predator fish from an e-waste site, South China. *Environ Sci Pollut Res Int*, 22(16):12011–7. doi:10.1007/s11356-015-4463-1 PMID:25874430

Tang J, Feng J, Li X, Li G (2014). Levels of flame retardants HBCD, TBBPA and TBC in surface soils from an industrialized region of East China. *Environ Sci Process Impacts*, 16(5):1015–21. doi:10.1039/c3em00656e PMID:24599331

Terasaki M, Kosaka K, Kunikane S, Makino M, Shiraishi F (2011). Assessment of thyroid hormone activity of halogenated bisphenol A using a yeast two-hybrid assay. *Chemosphere*, 84(10):1527–30. doi:10.1016/j.chemosphere.2011.04.045 PMID:21550628

Thomsen C, Lundanes E, Becher G (2001). Brominated flame retardants in plasma samples from three different occupational groups in Norway. *J Environ Monit*, 3(4):366–70. doi:10.1039/b104304h PMID:11523435

Thomsen C, Lundanes E, Becher G (2002). Brominated flame retardants in archived serum samples from Norway: a study on temporal trends and the role of age. *Environ Sci Technol*, 36(7):1414–8. doi:10.1021/es0102282 PMID:11999045

Tice RR, Austin CP, Kavlock RJ, Bucher JR (2013). Improving the human hazard characterization of chemicals: a Tox21 update. *Environ Health Perspect*, 121(7):756–65. doi:10.1289/ehp.1205784 PMID:23603828

Van der Ven LT, Van de Kuil T, Verhoef A, Verwer CM, Lilienthal H, Leonards PE et al. (2008). Endocrine effects of tetrabromobisphenol-A (TBBPA) in Wistar rats as tested in a one-generation reproduction study and a subacute toxicity study. *Toxicology*, 245(1–2):76–89. doi:10.1016/j.tox.2007.12.009 PMID:18255212

van der Zee M, Jia Y, Wang Y, Heijmans-Antonissen C, Ewing PC, Franken P et al. (2013). Alterations in Wnt-β-catenin and Pten signalling play distinct roles in endometrial cancer initiation and progression. *J Pathol*, 230(1):48–58. doi:10.1002/path.4160 PMID:23288720

Veldhoen N, Boggs A, Walzak K, Helbing CC (2006). Exposure to tetrabromobisphenol-A alters TH-associated gene expression and tadpole metamorphosis in the Pacific tree frog Pseudacris regilla. *Aquat Toxicol*, 78(3):292–302. doi:10.1016/j.aquatox.2006.04.002 PMID:16678281

Verslycke TA, Vethaak AD, Arijs K, Janssen CR (2005). Flame retardants, surfactants and organotins in sediment and mysid shrimp of the Scheldt estuary (The Netherlands). *Environ Pollut*, 136(1):19–31. doi:10.1016/j.envpol.2004.12.008 PMID:15809105

Viberg H, Eriksson P (2011). Differences in neonatal neurotoxicity of brominated flame retardants, PBDE 99 and TBBPA, in mice. *Toxicology*, 289(1):59–65. doi:10.1016/j.tox.2011.07.010 PMID:21820030

Vilaplana F, Ribes-Greus A, Karlsson S (2009). Microwave-assisted extraction for qualitative and quantitative determination of brominated flame retardants in styrenic plastic fractions from waste electrical and electronic equipment (WEEE). *Talanta*, 78(1):33–9. doi:10.1016/j.talanta.2008.10.038 PMID:19174199

Wang W, Abualnaja KO, Asimakopoulos AG, Covaci A, Gevao B, Johnson-Restrepo B et al. (2015b). A comparative assessment of human exposure to tetrabromobisphenol A and eight bisphenols including bisphenol A via indoor dust ingestion in twelve countries. *Environ Int*, 83:183–91. doi:10.1016/j.envint.2015.06.015 PMID:26177148

Wang X, Hu X, Zhang H, Chang F, Luo Y (2015a). Photolysis kinetics, mechanisms, and pathways of tetrabromobisphenol A in water under simulated solar light irradiation. *Environ Sci Technol*, 49(11):6683–90. doi:10.1021/acs.est.5b00382 PMID:25936366

Wang YQ, Zhang HM, Cao J (2014). Quest for the binding mode of tetrabromobisphenol A with calf thymus DNA. *Spectrochim Acta A Mol Biomol Spectrosc*, 131:109–13. doi:10.1016/j.saa.2014.04.077 PMID:24830628

Watanabe I, Kashimoto T, Tatsukawa R (1983). Identification of the flame retardant tetrabromobisphenol-A in the river sediment and the mussel collected in Osaka. *Bull Environ Contam Toxicol*, 31(1):48–52. doi:10.1007/BF01608765 PMID:6309291

Watanabe W, Shimizu T, Sawamura R, Hino A, Konno K, Hirose A et al. (2010). Effects of tetrabromobisphenol A, a brominated flame retardant, on the immune response to respiratory syncytial virus infection in mice. *Int Immunopharmacol*, 10(4):393–7. doi:10.1016/j.intimp.2009.12.014 PMID:20074668

Watt J, Schlezinger JJ (2015). Structurally-diverse, PPARγ-activating environmental toxicants induce adipogenesis and suppress osteogenesis in bone marrow mesenchymal stromal cells. *Toxicology*, 331:66–77. doi:10.1016/j.tox.2015.03.006 PMID:25777084

Wikoff DS, Rager JE, Haws LC, Borghoff SJ (2016). A high dose mode of action for tetrabromobisphenol A-induced uterine adenocarcinomas in Wistar Han rats: a critical evaluation of key events in an adverse outcome pathway framework. *Regul Toxicol Pharmacol*, 77:143–59. doi:10.1016/j.yrtph.2016.01.018 PMID:26828025

Wu S, Ji G, Liu J, Zhang S, Gong Y, Shi L (2015). TBBPA induces developmental toxicity, oxidative stress, and apoptosis in embryos and zebrafish larvae (Danio rerio). *Environ Toxicol*, (Apr):2 PMID:25846749

Xie Z, Ebinghaus R, Lohmann R, Heemken O, Caba A, Püttmann W (2007). Trace determination of the flame retardant tetrabromobisphenol A in the atmosphere by gas chromatography-mass spectrometry. *Anal Chim Acta*, 584(2):333–42. doi:10.1016/j.aca.2006.10.062 PMID:17386623

Xiong J, An T, Zhang C, Li G (2015). Pollution profiles and risk assessment of PBDEs and phenolic brominated flame retardants in water environments within a typical electronic waste dismantling region. *Environ Geochem Health*, 37(3):457–73. doi:10.1007/s10653-014-9658-8 PMID:25503846

Xue Y, Gu X, Wang X, Sun C, Xu X, Sun J et al. (2009). The hydroxyl radical generation and oxidative stress for the earthworm Eisenia fetida exposed to tetrabromobisphenol A. *Ecotoxicology*, 18(6):693–9. doi:10.1007/s10646-009-0333-2 PMID:19499334

Yamada-Okabe T, Sakai H, Kashima Y, Yamada-Okabe H (2005). Modulation at a cellular level of the thyroid hormone receptor-mediated gene expression by 1,2,5,6,9,10-hexabromocyclododecane (HBCD), 4,4′-diiodobiphenyl (DIB), and nitrofen (NIP). *Toxicol Lett*, 155(1):127–33. doi:10.1016/j.toxlet.2004.09.005 PMID:15585367

Yang S, Wang S, Sun F, Zhang M, Wu F, Xu F et al. (2015). Protective effects of puerarin against tetrabromobisphenol A-induced apoptosis and cardiac developmental toxicity in zebrafish embryo-larvae. *Environ Toxicol*, 30(9):1014–23. doi:10.1002/tox.21975 PMID:24596333

Yang Y, Lu L, Zhang J, Yang Y, Wu Y, Shao B (2014). Simultaneous determination of seven bisphenols in environmental water and solid samples by liquid chromatography-electrospray tandem mass spectrometry. *J Chromatogr A*, 1328:26–34. doi:10.1016/j.chroma.2013.12.074 PMID:24411090

Yu Y, Xiang M, Gao D, Ye H, Wang Q, Zhang Y et al. (2016). Absorption and excretion of tetrabromobisphenol A in male Wistar rats following subchronic dermal exposure. *Chemosphere*, 146:189–94. doi:10.1016/j.chemosphere.2015.12.027 PMID:26716882

Zalko D, Prouillac C, Riu A, Perdu E, Dolo L, Jouanin I et al. (2006). Biotransformation of the flame retardant tetrabromo-bisphenol A by human and rat sub-cellular liver fractions. *Chemosphere*, 64(2):318–27. doi:10.1016/j.chemosphere.2005.12.053 PMID:16473389

Zatecka E, Ded L, Elzeinova F, Kubatova A, Dorosh A, Margaryan H et al. (2013). Effect of tetrabrombisphenol A on induction of apoptosis in the testes and changes in expression of selected testicular genes in CD1 mice. *Reprod Toxicol*, 35:32–9. doi:10.1016/j.reprotox.2012.05.095 PMID:22677475

Zhang H, Bayen S, Kelly BC (2015a). Co-extraction and simultaneous determination of multi-class hydrophobic organic contaminants in marine sediments and biota using GC-EI-MS/MS and LC-ESI-MS/MS. *Talanta*, 143:7–18. doi:10.1016/j.talanta.2015.04.084 PMID:26078122

Zhang XL, Luo XJ, Chen SJ, Wu JP, Mai BX (2009). Spatial distribution and vertical profile of polybrominated diphenyl ethers, tetrabromobisphenol A, and decabromodiphenylethane in river sediment from an industrialized region of South China. *Environ Pollut*, 157(6):1917–23. doi:10.1016/j.envpol.2009.01.016 PMID:19232799

Zhang Y, Li Y, Qin Z, Wang H, Li J (2015b). A screening assay for thyroid hormone signalling disruption based on thyroid hormone-response gene expression analysis in the frog Pelophylax nigromaculatus. *J Environ Sci (China)*, 34:143–54. doi:10.1016/j.jes.2015.01.028 PMID:26257357

Zhou X, Guo J, Zhang W, Zhou P, Deng J, Lin K (2014). Tetrabromobisphenol A contamination and emission in printed circuit board production and implications for human exposure. *J Hazard Mater*, 273:27–35. doi:10.1016/j.jhazmat.2014.03.003 PMID:24709479

Zhu ZC, Chen SJ, Zheng J, Tian M, Feng AH, Luo XJ et al. (2014). Occurrence of brominated flame retardants (BFRs), organochlorine pesticides (OCPs), and polychlorinated biphenyls (PCBs) in agricultural soils in a BFR-manufacturing region of North China. *Sci Total Environ*, 481:47–54. doi:10.1016/j.scitotenv.2014.02.023 PMID:24576782

Ziemińska E, Stafiej A, Toczyłowska B, Lazarewicz JW (2012). Synergistic neurotoxicity of oxygen-glucose deprivation and tetrabromobisphenol A in vitro: role of oxidative stress. *Pharmacol Rep*, 64(5):1166–78. doi:10.1016/S1734-1140(12)70913-1 PMID:23238473