

Table 6.
Serum levels of thyroid-related hormones of the offspring exposed to hexabromocyclododecane during the period from the mid-gestation to the end of lactation

	HBCD in diet (ppm)			
	0	100	1000	10,000
PND 21				
No. of offspring examined	10	10	10	10
T3 (ng/ml)	1.09 ± 0.11 ^a	1.13 ± 0.12	1.06 ± 0.08	0.93 ± 0.10 ^{**}
T4 (µg/dl)	4.39 ± 0.93	4.20 ± 0.77	4.78 ± 0.49	4.20 ± 0.52
TSH (ng/ml)	5.40 ± 0.62	6.66 ± 1.24	6.07 ± 1.41	7.00 ± 1.31 [*]
PNW 11				
No. of offspring examined	10	10	10	10
T3 (ng/ml)	0.96 ± 0.06	0.93 ± 0.07	0.88 ± 0.05 [*]	0.89 ± 0.06 ^{**}
T4 (µg/dl)	4.77 ± 0.70	4.84 ± 0.59	5.21 ± 0.65	5.20 ± 0.98
TSH (ng/ml)	4.74 ± 0.62	5.81 ± 1.72	5.36 ± 1.11	4.96 ± 0.80

^aMean±SD.

Abbreviations: HBCD, hexabromocyclododecane; PND, postnatal day; PNW, postnatal week.

,** Significantly different from the controls by Dunnett's test or Dunnett-type rank-sum test (* p<0.05, ** p<0.01).

Table 7.

Body and organ weights of the offspring exposed to hexabromocyclododecane during the period from the mid-gestation to the end of lactation examined at PNW 11.

	HBCD in diet (ppm)			
	0	100	1000	10,000
Relative organ weights, PNW 11				
Males				
No. of animals examined	10	10	10	10
BW (g)	454.3 ± 25.4 ^a	456.9 ± 24.8	450.8 ± 33.4	435.1 ± 24.6
Brain (g/100g BW)	0.46 ± 0.03	0.46 ± 0.02	0.47 ± 0.04	0.47 ± 0.02
Pituitary (mg/100g BW)	3.35 ± 0.19	3.43 ± 0.35	3.30 ± 0.21	3.24 ± 0.30
Spleen (g/100g BW)	0.18 ± 0.02	0.21 ± 0.03	0.19 ± 0.02	0.19 ± 0.02
Thymus (g/100g BW)	0.13 ± 0.03	0.14 ± 0.03	0.12 ± 0.04	0.12 ± 0.03
Liver (g/100g BW)	3.45 ± 0.27	3.81 ± 0.23**	3.58 ± 0.24	3.53 ± 0.22
Kidneys (g/100g BW)	0.66 ± 0.05	0.67 ± 0.05	0.67 ± 0.04	0.66 ± 0.05
Adrenals (mg/100g BW)	13.0 ± 1.5	12.4 ± 1.2	11.6 ± 1.8	12.3 ± 2.5
Testes (g/100 g BW)	0.77 ± 0.07	0.73 ± 0.04	0.78 ± 0.09	0.74 ± 0.05
Epididymides (g/100g BW)	0.23 ± 0.02	0.21 ± 0.01*	0.22 ± 0.02	0.21 ± 0.01
Prostate, ventral (mg/100g BW)	0.13 ± 0.02	0.13 ± 0.04	0.12 ± 0.03	0.12 ± 0.01
Prostate, dorso-lateral (mg/100g BW)	0.13 ± 0.03	0.13 ± 0.01	0.14 ± 0.03	0.13 ± 0.02
Seminal vesicles (mg/100g BW)	0.27 ± 0.05	0.26 ± 0.03	0.26 ± 0.05	0.26 ± 0.05
Thyroid (mg/100g BW)	4.85 ± 0.69	5.66 ± 0.67	5.78 ± 0.82*	6.20 ± 1.03**
Females				
No. of animals examined	10	10	10	10
BW (g)	286.2 ± 25.2	293.4 ± 21.5	289.2 ± 24.4	270.7 ± 19.6
Brain (g/100g BW)	0.68 ± 0.07	0.65 ± 0.05	0.68 ± 0.06	0.71 ± 0.04
Pituitary (mg/100g BW)	5.94 ± 1.00	5.63 ± 0.64	5.72 ± 1.31	5.71 ± 0.63
Spleen (g/100g BW)	0.19 ± 0.02	0.20 ± 0.03	0.21 ± 0.02	0.20 ± 0.03
Thymus (g/100g BW)	0.18 ± 0.03	0.19 ± 0.06	0.17 ± 0.04	0.16 ± 0.05
Liver (g/100g BW)	3.35 ± 0.20	3.59 ± 0.19	3.44 ± 0.25	3.30 ± 0.22
Kidneys (g/100g BW)	0.69 ± 0.03	0.65 ± 0.03	0.69 ± 0.06	0.65 ± 0.05
Adrenals (mg/100g BW)	21.1 ± 3.4	22.6 ± 2.0	23.7 ± 2.3	24.2 ± 4.7
Ovaries (mg/100 g BW)	31.8 ± 6.1	32.8 ± 2.6	32.2 ± 5.7	34.0 ± 4.8
Uterus (g/100g BW)	0.16 ± 0.04	0.15 ± 0.02	0.16 ± 0.02	0.17 ± 0.03
Thyroid (mg/100g BW)	8.20 ± 2.94	6.84 ± 0.81	7.35 ± 0.87	7.72 ± 0.83

^a Mean ± SD.

Abbreviations: HBCD, hexabromocyclododecane; PNW, postnatal week.

*, ** Significantly different from the controls by Dunnett's test or Dunnett-type rank-sum test (* p<0.05, ** p<0.01).

Table 8.
Brain morphometry of the white matter components of the offspring exposed to hexabromocyclododecane during the period from the mid-gestation to the end of lactation examined at PNW11.

	HBCD in diet (ppm)			
	0	100	1000	10,000
No. of offspring examined	10	10	10	10
CC region area (mm ²)	0.15 ± 0.02 ^a	0.15 ± 0.02	0.14 ± 0.01	0.14 ± 0.01
CNPase-positive cell count (count/mm ²)	181.6 ± 28.2	167.6 ± 23.2	160.3 ± 28.1	138.7 ± 23.7*

^aMean±SD.

Abbreviations: HBCD, hexabromocyclododecane; CC, corpus callosum; PNW, postnatal week

* Significantly different from the controls by Dunnett's test or Dunnett-type rank-sum test (* p <0.01).

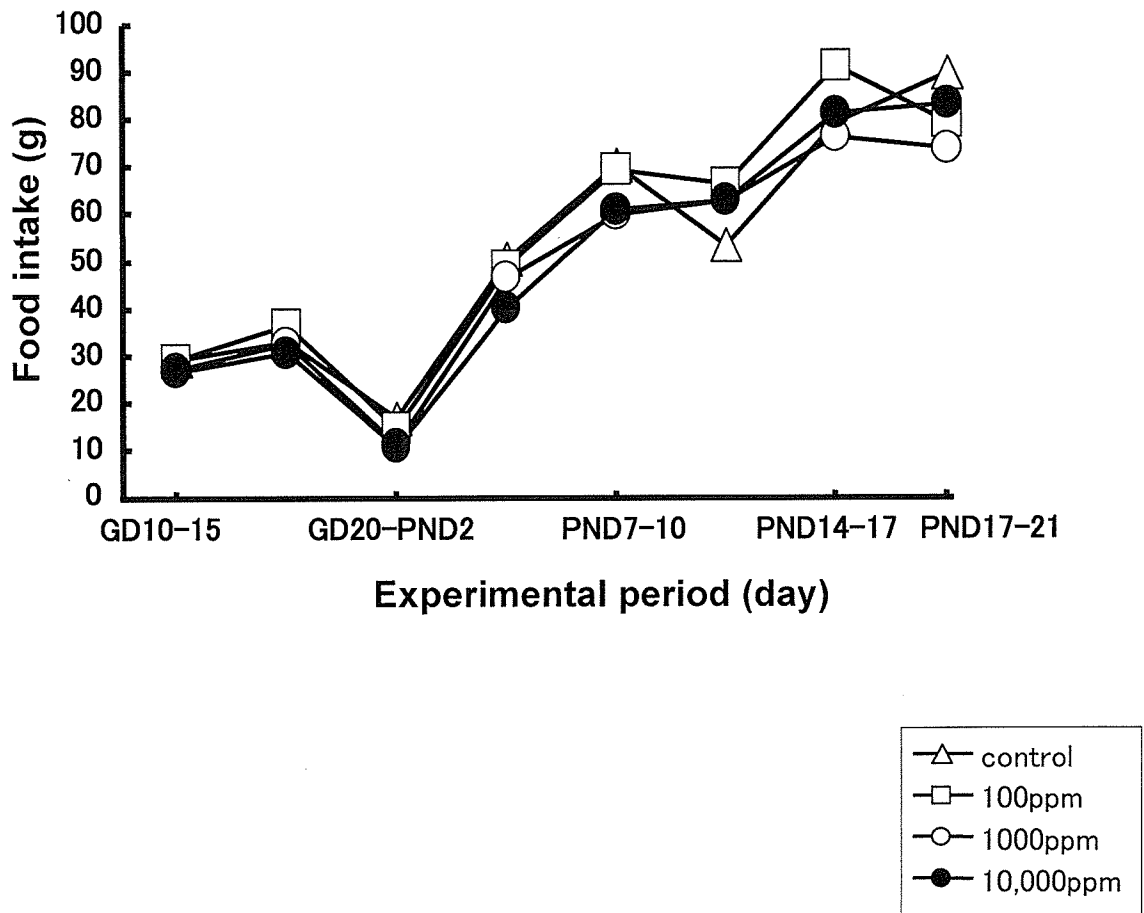


Fig. 12.
Food intake of dams exposed perinatally to tetrabromobisphenol A (TBBPA) during the period from the mid-gestation to the end of lactation.

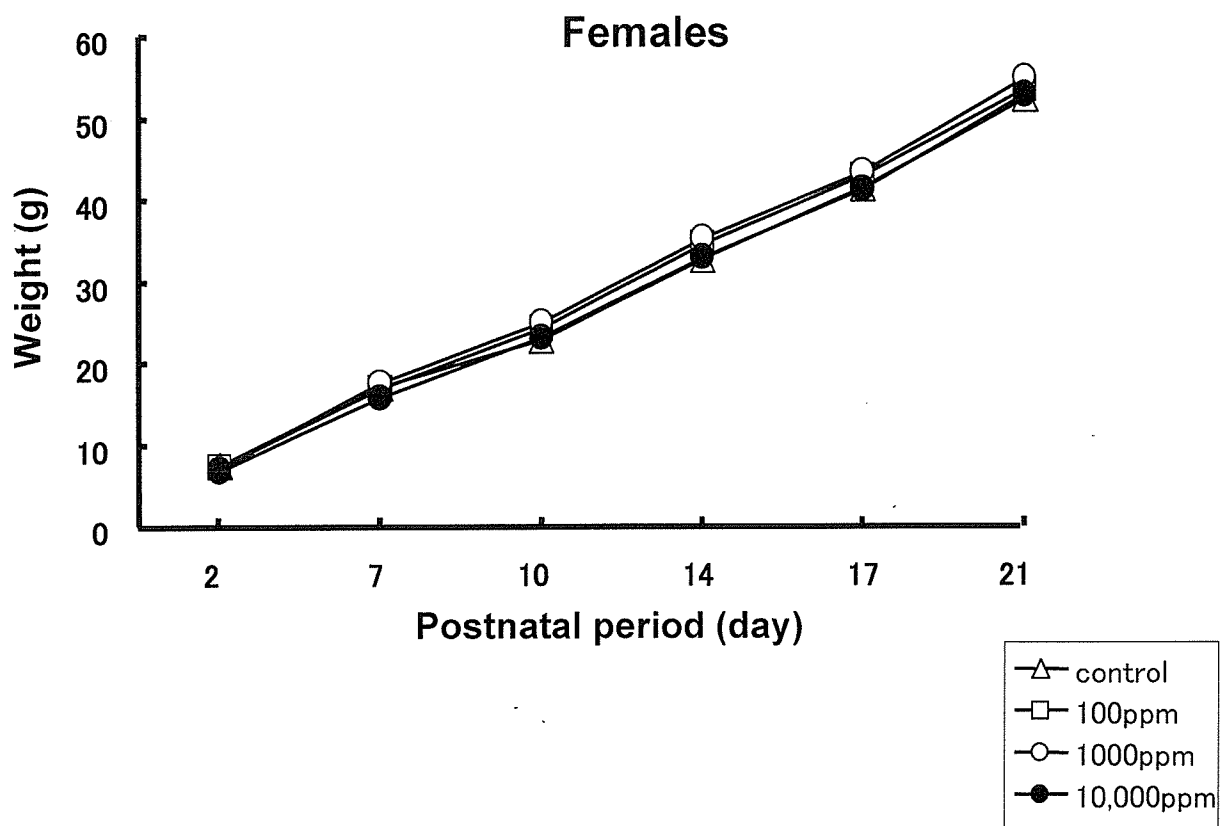
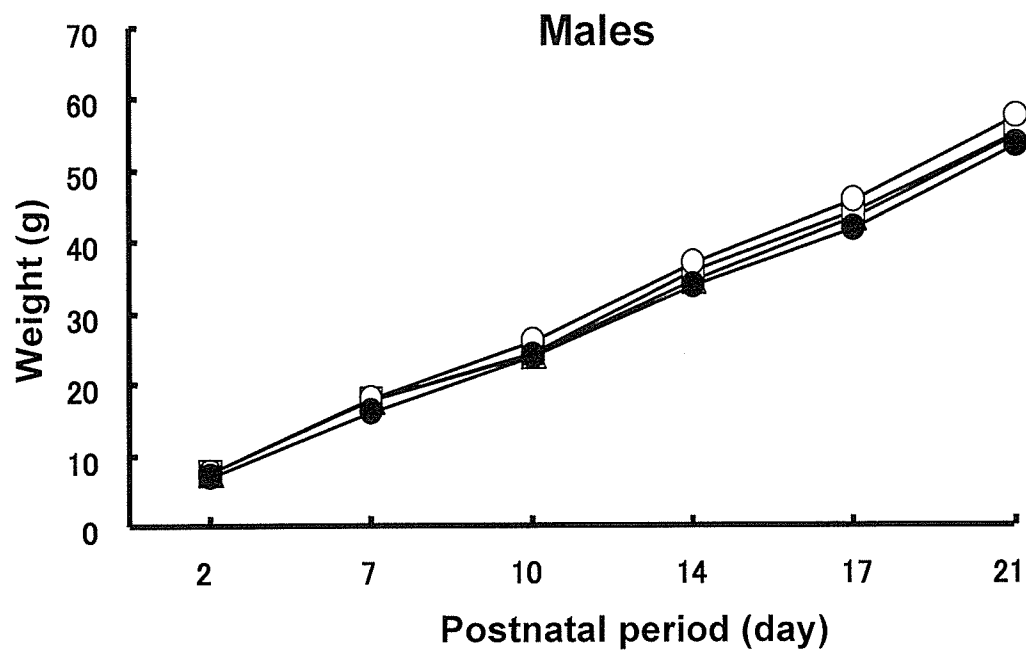


Fig. 13.
Growth curves during the lactation period of offspring exposed perinatally to tetrabromobisphenol A (TBBPA) during the period from the mid-gestation to the end of lactation.

Table 9.
Effects on dams and offspring until prepubertal necropsy with exposure study of tetrabromobisphenol A during the period from the mid-gestation to the end of lactation

	TBBPA in diet (ppm)			
	0	100	1000	10,000
No. of dams examined	8	8	8	8
Maternal parameter				
Body weight gain (g/day)				
GD 10-GD 20	11.33 ± 1.40 ^a	11.66 ± 1.50	11.39 ± 1.30	11.55 ± 0.90
PND 2-PND 10	6.58 ± 2.80	7.16 ± 1.96	6.30 ± 1.95	6.80 ± 1.68
PND 10-PND 21	0.31 ± 0.59	0.53 ± 0.73	0.46 ± 0.65	1.36 ± 0.70*
PND 21				
BW (g)	335.4 ± 25.0	334.0 ± 23.5	328.6 ± 26.3	338.4 ± 24.7
Thyroid weight (mg/100 g BW)	5.81 ± 1.24	6.41 ± 0.89	6.28 ± 0.67	6.67 ± 0.97
Offspring parameter				
No. of implantation sites	13.9 ± 1.9	13.5 ± 2.4	13.3 ± 3.2	14.0 ± 1.1
No. of live offspring	12.8 ± 2.6	12.8 ± 3.0	12.4 ± 3.1	13.1 ± 0.6
Male ratio (%)	51.9 ± 13.8	47.3 ± 14.2	47.8 ± 9.5	51.7 ± 15.6
BW, PND 2 (g)				
Males	7.59 ± 0.71	7.51 ± 1.04	7.49 ± 1.04	6.90 ± 0.35
Females	7.17 ± 0.80	7.06 ± 0.92	6.96 ± 0.94	6.60 ± 0.32
AGD, PND 2 (mm)				
Males	4.15 ± 0.22	4.01 ± 0.20	4.05 ± 0.24	4.00 ± 0.17
Females	2.03 ± 0.13	1.95 ± 0.12	2.03 ± 0.09	2.00 ± 0.08
Relative organ weights, PND 21				
No. of offspring examined	10	10	10	10
Males				
BW (g)	54.3 ± 4.4	53.0 ± 5.9	59.0 ± 7.0	52.6 ± 3.0
Liver (g/100g BW)	3.88 ± 0.25	3.60 ± 0.41	3.91 ± 0.25	3.76 ± 0.20
Kidneys (g/100g BW)	1.14 ± 0.06	1.12 ± 0.07	1.09 ± 0.08	1.11 ± 0.06
Brain (g/100g BW)	2.77 ± 0.18	2.88 ± 0.26	2.64 ± 0.32	2.82 ± 0.19
Spleen (g/100g BW)	0.39 ± 0.06	0.38 ± 0.09	0.37 ± 0.05	0.35 ± 0.06
Thymus (g/100g BW)	0.39 ± 0.06	0.37 ± 0.08	0.40 ± 0.03	0.37 ± 0.06
Adrenals (mg/100g BW)	26.3 ± 6.5	24.9 ± 4.2	29.0 ± 2.4	29.0 ± 2.8
Testes (g/100g BW)	0.42 ± 0.04	0.40 ± 0.04	0.41 ± 0.03	0.40 ± 0.05
Epididymides (g/100g BW)	0.065 ± 0.013	0.061 ± 0.007	0.065 ± 0.010	0.062 ± 0.007
Females				
BW (g)	50.4 ± 4.3	51.1 ± 5.1	53.3 ± 5.6	52.4 ± 2.7
Liver (g/100g BW)	3.86 ± 0.19	3.86 ± 0.14	3.94 ± 0.32	3.84 ± 0.20
Kidneys (g/100g BW)	1.17 ± 0.05	1.18 ± 0.06	1.13 ± 0.09	1.16 ± 0.10
Brain (g/100g BW)	2.90 ± 0.17	2.83 ± 0.20	2.75 ± 0.28	2.77 ± 0.15
Spleen (g/100g BW)	0.39 ± 0.06	0.42 ± 0.08	0.37 ± 0.02	0.38 ± 0.06
Thymus (g/100g BW)	0.40 ± 0.07	0.39 ± 0.06	0.44 ± 0.05	0.42 ± 0.08
Adrenals (mg/100g BW)	21.6 ± 5.3	24.3 ± 4.5	23.3 ± 4.9	22.0 ± 5.8
Ovaries (mg/100g BW)	24.9 ± 7.8	30.0 ± 5.6	25.3 ± 10.5	27.1 ± 8.5
Uterus (g/100g BW)	0.069 ± 0.008	0.074 ± 0.013	0.068 ± 0.011	0.074 ± 0.012

^a Mean ± SD.

Abbreviations: TBBPA, tetrabromobisphenol A; GD, gestational day; PND, postnatal day; BW, body weight; AGD, anogenital distance.

* Significantly different from the controls by Dunnett's test or Dunnett-type rank-sum test (* $p < 0.05$).

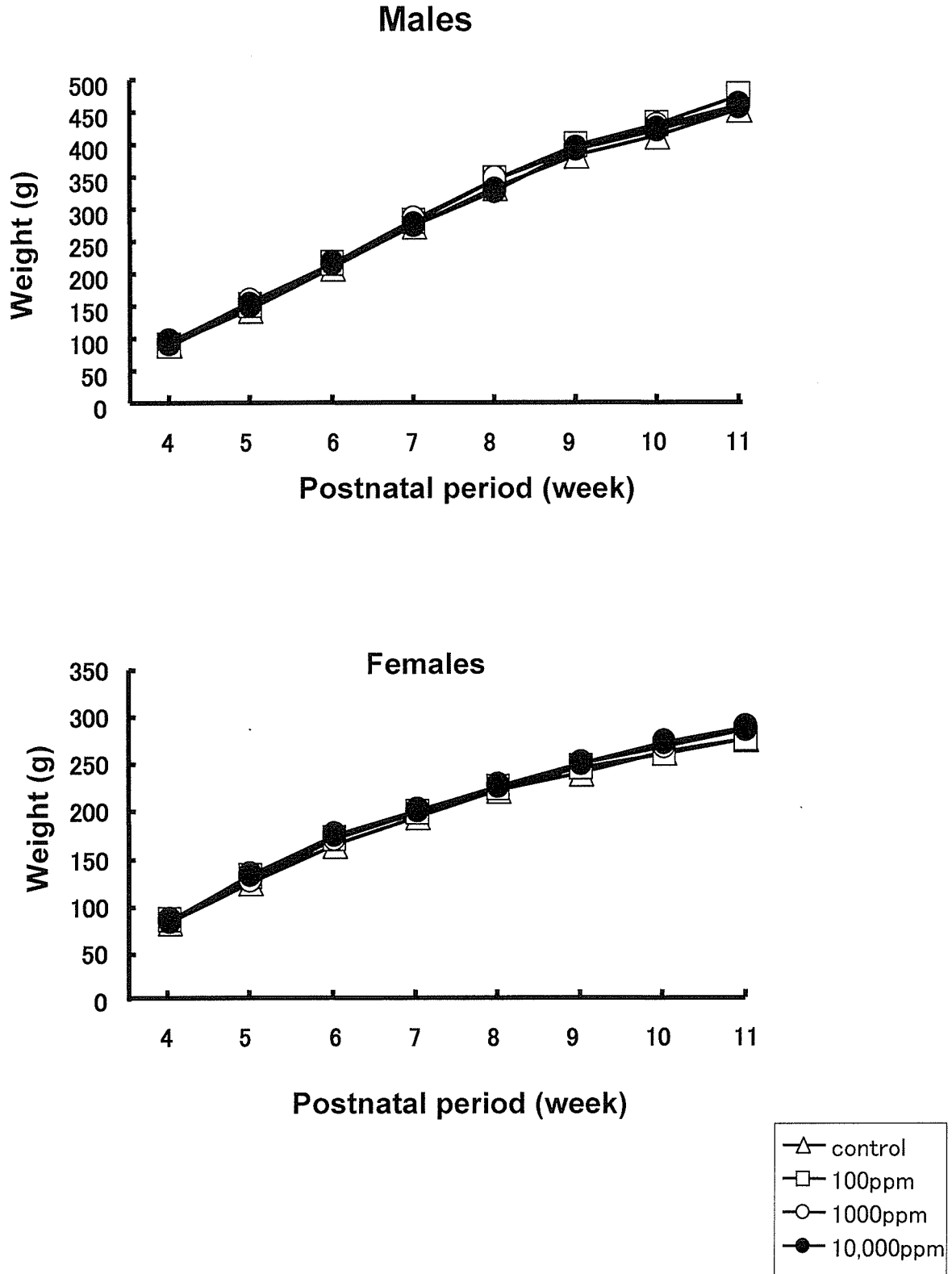


Fig. 14. Growth curves after weaning for offspring exposed perinatally to tetrabromobisphenol A (TBBPA) during the period from the mid-gestation to the end of lactation.

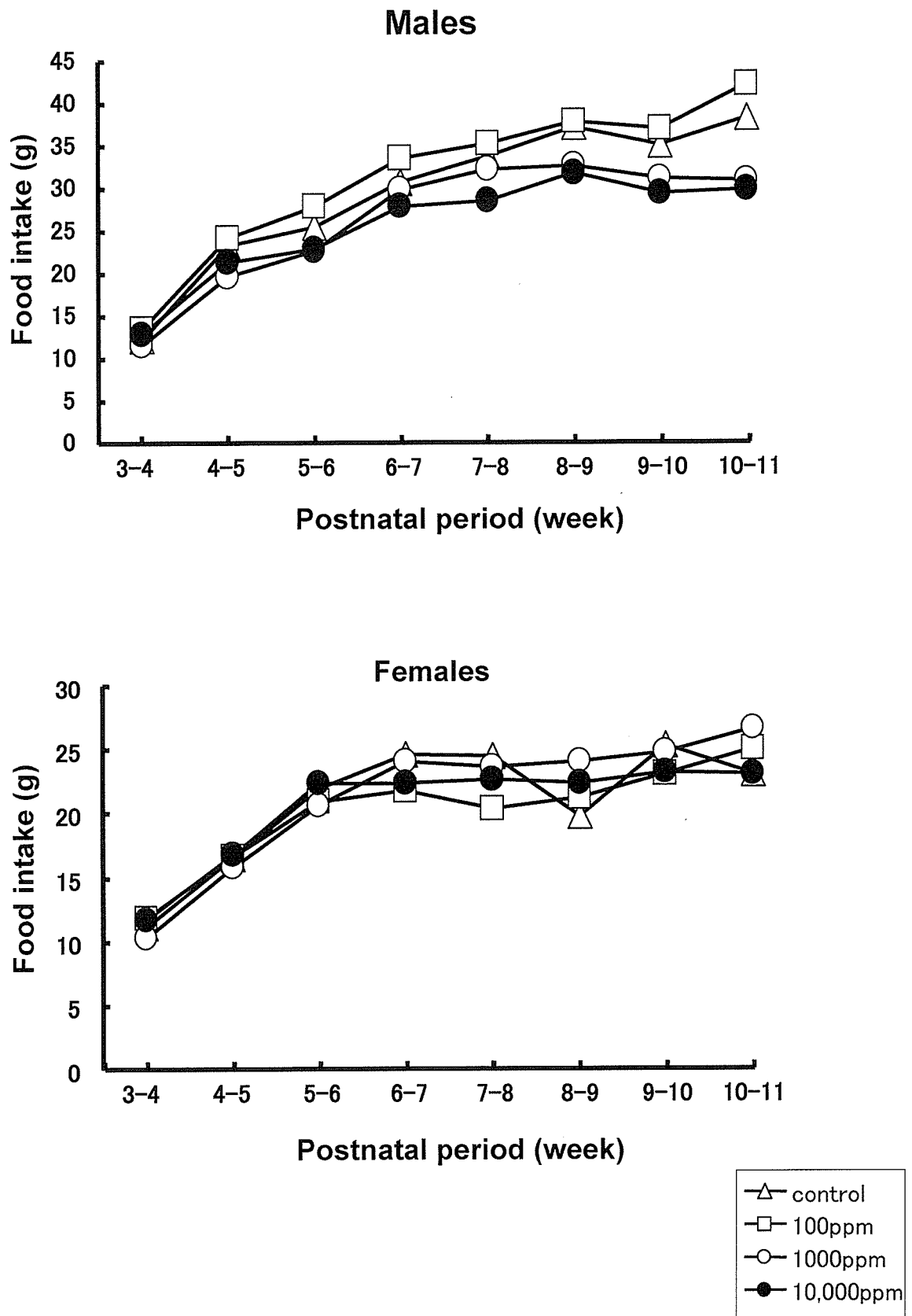


Fig. 15.
Food intake of offspring exposed perinatally to tetrabromobisphenol A (TBBPA) during the period from the mid-gestation to the end of lactation.

Table 10.
Onset of puberty and estrous cyclicity of the offspring exposed to tetrabromobisphenol A during the period from the mid-gestation to the end of lactation.

	TBBPA in diet (ppm)			
	0	100	1000	10,000
Onset of puberty				
Males				
No. of animals examined	12	12	12	12
Age by day	41.0 ± 1.0 ^a	41.8 ± 1.5	41.2 ± 1.1	42.7 ± 2.1
BW	204.9 ± 12.0	218.2 ± 12.3	209.0 ± 14.7	221.2 ± 17.6*
Females				
No. of animals examined	12	12	12	12
Age by day	34.9 ± 1.6	33.3 ± 1.4	33.5 ± 1.9	34.1 ± 2.4
BW	129.2 ± 11.2	123.9 ± 11.8	122.1 ± 8.5	128.7 ± 16.0
Estrous cyclicity during PNW 8–11				
No. of animals examined	10	10	10	10
Irregularity (Extended diestrus)	0	0	1	2

^a Mean ± SD.

Abbreviations: TBBPA, tetrabromobisphenol A; BW, body weight; PNW, postnatal week.

* Significantly different from the controls by Dunnett's test or Dunnett-type rank-sum test (* p<0.05).

Table 11.
Serum levels of thyroid-related hormones of the offspring exposed to tetrabromobisphenol A during the period from the mid-gestation to the end of lactation.

	TBBPA in diet (ppm)			
	0	100	1000	10,000
PND 21				
No. of offspring examined	10	10	10	10
T3 (ng/ml)	1.31 ± 0.12 ^a	1.13 ± 0.12*	1.15 ± 0.08*	1.20 ± 0.13
T4 (µg/dl)	4.86 ± 0.50	4.66 ± 0.64	4.85 ± 0.43	5.12 ± 0.52
TSH (ng/ml)	7.09 ± 1.32	6.68 ± 2.51	6.17 ± 1.78	5.45 ± 0.56
PNW 11				
No. of offspring examined	10	10	10	10
T3 (ng/ml)	0.89 ± 0.08	0.89 ± 0.05	0.92 ± 0.08	0.87 ± 0.04
T4 (µg/dl)	4.77 ± 0.53	5.11 ± 0.93	5.03 ± 0.40	4.49 ± 0.80
TSH (ng/ml)	7.12 ± 2.06	7.19 ± 2.23	6.72 ± 1.90	6.23 ± 1.62

^aMean±SD.

Abbreviations: TBBPA, tetrabromobisphenol A; PND, postnatal day; PNW, postnatal week.

* Significantly different from the controls by Dunnett's test or Dunnett-type rank-sum test (* p <0.01).

Table 12.

Body and organ weights of the offspring exposed to tetrabromobisphenol A during the period from the mid-gestation to the end of lactation examined at PNW 11.

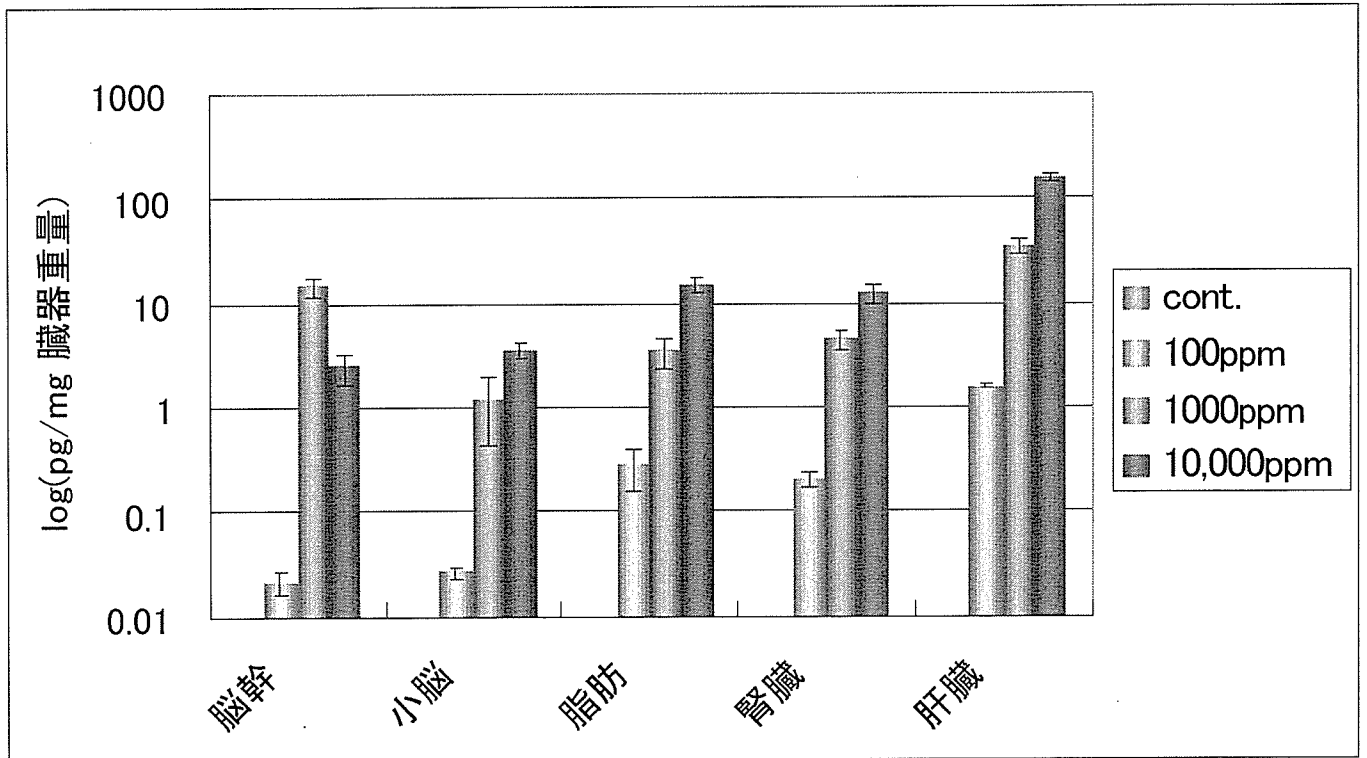
	TBBPA in diet (ppm)			
	0	100	1000	10,000
Relative organ weights, PNW 11				
Males				
No. of animals examined	10	10	10	10
BW (g)	456.1 ± 15.9 ^a	465.4 ± 29.1	452.6 ± 23.9	455.7 ± 33.3
Brain (g/100g BW)	0.48 ± 0.02	0.47 ± 0.02	0.47 ± 0.02	0.48 ± 0.04
Pituitary (mg/100g BW)	3.41 ± 0.38	3.32 ± 0.17	3.19 ± 0.21	3.37 ± 0.45
Spleen (g/100g BW)	0.19 ± 0.02	0.19 ± 0.03	0.19 ± 0.02	0.21 ± 0.04
Thymus (g/100g BW)	0.11 ± 0.03	0.13 ± 0.03	0.11 ± 0.02	0.14 ± 0.03
Liver (g/100g BW)	3.76 ± 0.18	3.68 ± 0.21	3.64 ± 0.28	3.53 ± 0.36
Kidneys (g/100g BW)	0.68 ± 0.04	0.69 ± 0.04	0.72 ± 0.05	0.69 ± 0.04
Adrenals (mg/100g BW)	12.4 ± 1.3	13.1 ± 1.7	12.6 ± 1.9	14.0 ± 2.3
Testes (g/100 g BW)	0.75 ± 0.08	0.72 ± 0.10	0.74 ± 0.11	0.76 ± 0.06
Epididymides (g/100g BW)	0.22 ± 0.02	0.21 ± 0.03	0.22 ± 0.03	0.23 ± 0.02
Prostate, ventral (mg/100g BW)	0.11 ± 0.02	0.12 ± 0.02	0.11 ± 0.02	0.12 ± 0.02
Prostate, dorso-lateral (mg/100g BW)	0.12 ± 0.01	0.12 ± 0.03	0.12 ± 0.02	0.12 ± 0.01
Seminal vesicles (mg/100g BW)	0.25 ± 0.03	0.24 ± 0.04	0.25 ± 0.02	0.25 ± 0.04
Thyroid (mg/100g BW)	4.72 ± 0.95	5.40 ± 0.96	5.09 ± 0.92	5.58 ± 0.86
Females				
No. of animals examined	10	10	10	10
BW (g)	285.4 ± 12.4	285.1 ± 20.7	289.7 ± 26.2	296.1 ± 25.0
Brain (g/100g BW)	0.70 ± 0.03	0.71 ± 0.6	0.68 ± 0.05	0.67 ± 0.06
Pituitary (mg/100g BW)	6.04 ± 0.58	6.16 ± 0.63	5.62 ± 0.93	5.82 ± 1.00
Spleen (g/100g BW)	0.22 ± 0.03	0.23 ± 0.05	0.19 ± 0.02	0.20 ± 0.02
Thymus (g/100g BW)	0.19 ± 0.04	0.16 ± 0.02	0.16 ± 0.03	0.20 ± 0.05
Liver (g/100g BW)	3.49 ± 0.25	3.47 ± 0.22	3.32 ± 0.20	3.51 ± 0.27
Kidneys (g/100g BW)	0.71 ± 0.04	0.70 ± 0.03	0.66 ± 0.05*	0.71 ± 0.04
Adrenals (mg/100g BW)	24.2 ± 3.5	25.4 ± 2.4	22.8 ± 2.5	24.3 ± 2.8
Ovaries (mg/100 g BW)	31.3 ± 3.8	34.9 ± 3.9	33.3 ± 3.2	34.6 ± 4.7
Uterus (g/100g BW)	0.18 ± 0.03	0.19 ± 0.03	0.18 ± 0.07	0.14 ± 0.02*
Thyroid (mg/100g BW)	7.19 ± 1.00	7.46 ± 1.78	6.60 ± 1.01	7.25 ± 1.09

^a Mean ± SD.

Abbreviations: TBBPA, tetrabromobisphenol A; PNW, postnatal week.

* Significantly different from the controls by Dunnett's test or Dunnett-type rank-sum test (* p<0.05).

3週目



11週目 : 検索した全ての臓器でいずれの用量でも測定限界以下
(0.02 pg/mg tissue以下)

Fig. 16. 各臓器におけるTBBPA蓄積量.

Table 13.**Brain morphometry of the white matter components of the offspring exposed to tetrabromobisphenol A during the period from the mid-gestation to the end of lactation examined at PNW11.**

	TBBPA in diet (ppm)			
	0	100	1000	10,000
No. of offspring examined	10	10	10	10
CC region area (mm ²)	0.14 ± 0.01 ^a	0.14 ± 0.01	0.14 ± 0.02	0.14 ± 0.01
CNPase-positive cell count (count/mm ²)	133.0 ± 16.7	120.8 ± 14.3	121.4 ± 15.4	127.1 ± 18.8

^aMean±SD.

Abbreviations: TBBPA, tetrabromobisphenol A; CC, corpus callosum; PNW, postnatal week

Up-regulated (≥ 2 -fold)

Down-regulated ($\geq 1/2$ -fold)

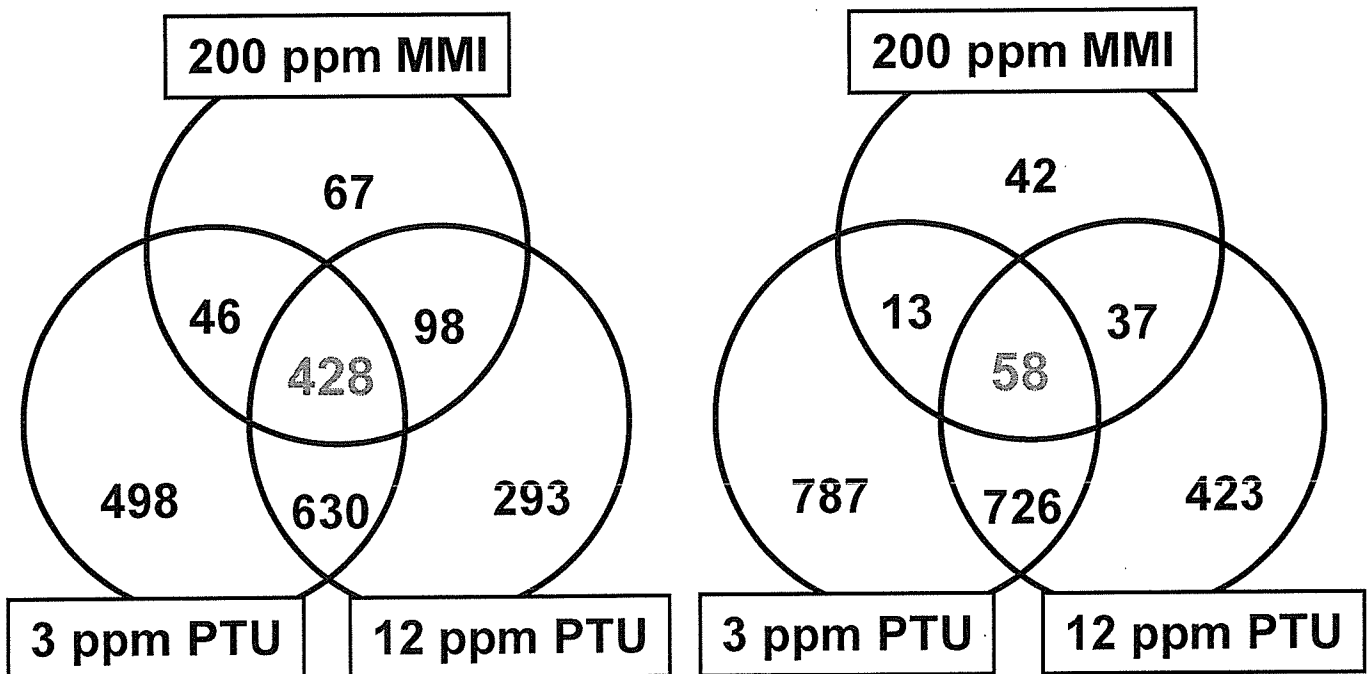


Fig. 17.

Venn diagram of genes showing altered expression in the white matter of rats at weaning exposed to anti-thyroid agents during the period from the mid-gestation to the end of lactation.

		example	
(central nervous system development)	neural	31	Nuclear receptor co-repressor 1
	cell migration	22)	Ephrin A4
	apoptosis	17	Follistatin-like 3
	proliferation	12	Ret proto-oncogene
	cell adhesion	6	Gastrulation brain homeobox 2
		8	SRY-box containing gene 6
			Vimentin
	others	174	Dynein-like protein 2
	EST	180	A kinase (PRKA) anchor protein 2
			Dynein light chain roadblock-type 2
		Kinesin 2	
		Neurotrophin receptor associated death domain	
total		428	

Fig. 18.
Ontology analysis of genes showing increased expression in the white matter of rats at weaning exposed to anti-thyroid agents during the period from the mid-gestation to the end of lactation.

neural	6	
(central nervous system		
development	5)	example
cell migration	0	GATA binding protein 3
apoptosis	0	Sine oculis homeobox homolog 1
proliferation	0	Zinc finger homeobox 1b
cell adhesion	2	Bone morphogenetic protein 6
others	24	
EST	26	
total	58	

Fig. 19.
Ontology analysis of genes showing decreased expression in the white matter of rats at weaning exposed to anti-thyroid agents during the period from the mid-gestation to the end of lactation.

Up-regulated (≥ 2 -fold)

Down-regulated ($\geq 1/2$ -fold)

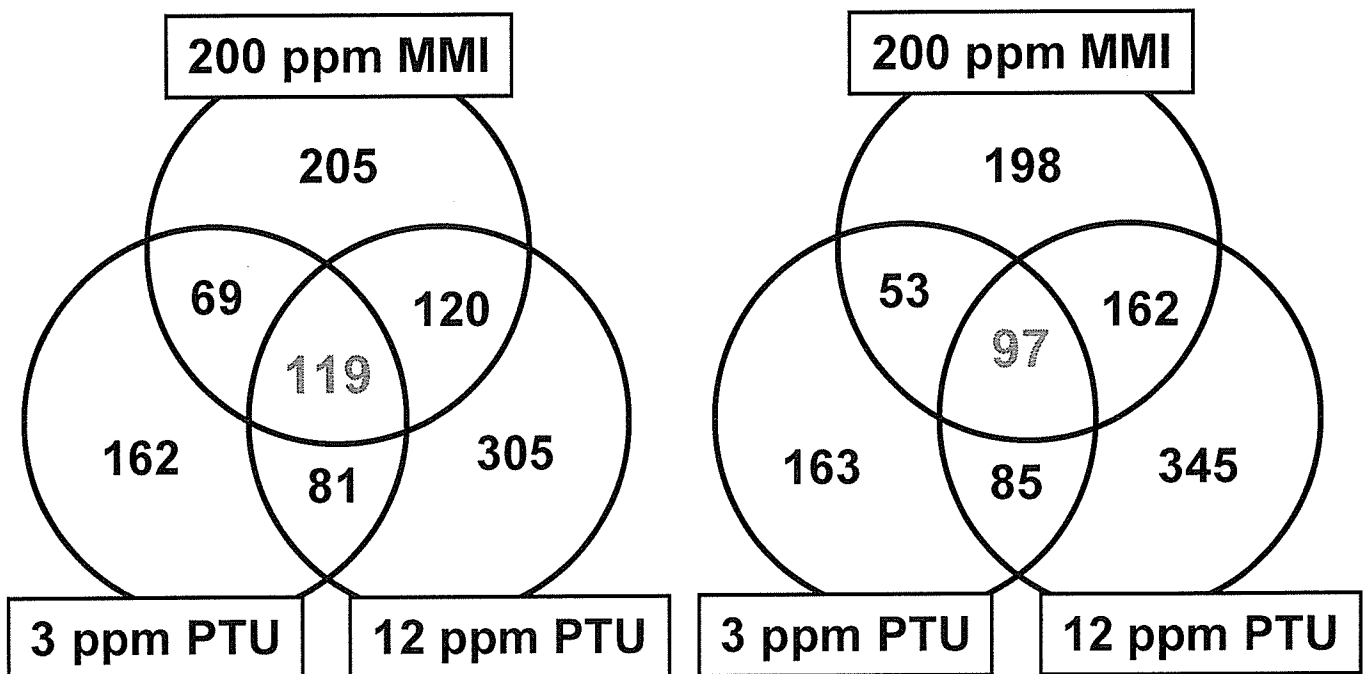


Fig. 20.

Venn diagram of genes showing altered expression in the hippocampal CA1 region of rats at weaning exposed to anti-thyroid agents during the period from the mid-gestation to the end of lactation.

neural	11	
(central nervous system		
development	7)	example
cell migration	1	Mindbomb homolog 1
apoptosis	4	Slit homolog 2
proliferation	1	Notch gene homolog 2
cell adhesion	2	Ephrin A5
others	49	Kinesin heavy chain family, member 2
EST	51	BH3 interacting domain
<hr/>		
total	119	

Fig. 21.
Ontology analysis of genes showing increased expression in the hippocampal CA1 region of rats at weaning exposed to anti-thyroid agents during the period from the mid-gestation to the end of lactation.

		example
neural (central nervous system development	16 15)	Endothelial differentiation, sphingolipid G-protein-coupled receptor, 8
cell migration	0	Eph receptor A7
apoptosis	4	Activating transcription factor 2
proliferation	0	Myelin-associated oligodendrocytic basic protein
cell adhesion	4	CCAAT/enhancer binding protein β
others	38	SRY-box containing gene 6
EST	35	Myelin oligodendrocyte glycoprotein
<hr/>		
total	97	

Fig. 22.

Ontology analysis of genes showing decreased expression in the hippocampal CA1 region of rats at weaning exposed to anti-thyroid agents during the period from the mid-gestation to the end of lactation.

Up-regulated (≥ 2 -fold)

Down-regulated ($\geq 1/2$ -fold)

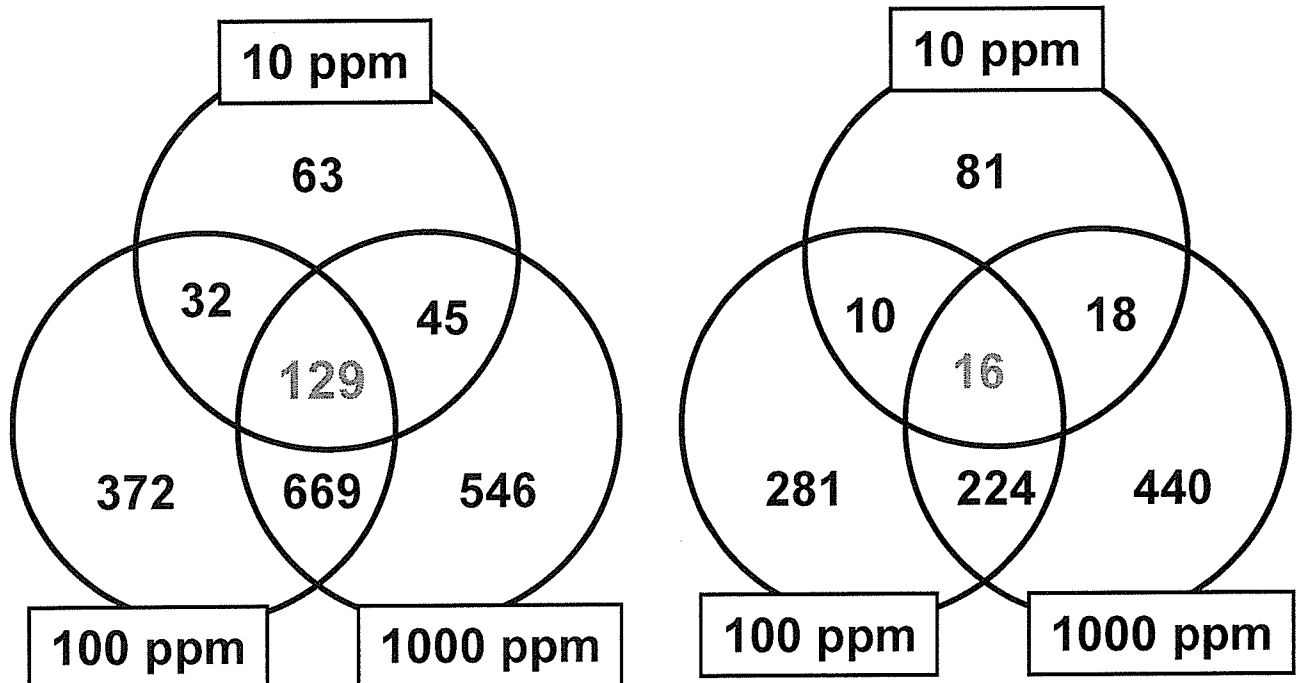


Fig. 23.

Venn diagram of genes showing altered expression in the white matter of rats at weaning exposed to decabromodiphenyl ether during the period from the mid-gestation to the end of lactation.