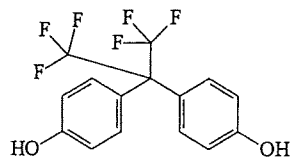
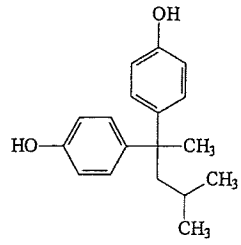
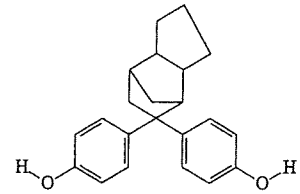


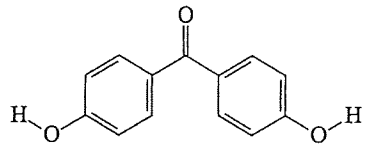
4,4'-(Hexafluoroispropylidene) diphenol



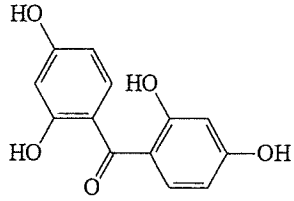
2,2-bis (4-Hydroxyphenyl)-4-methyl-n-pentane



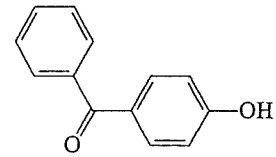
4,4'-(Octahydro-4,7-methano-5H-inden-5-ylidene) bisphenol



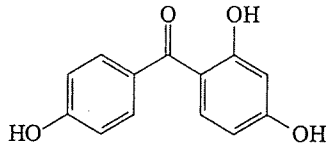
4,4'-Dihydroxybenzophenone



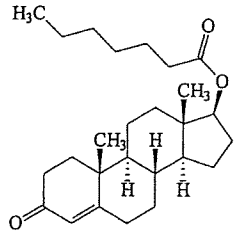
2,2',4,4'-Tetrahydroxybenzophenone



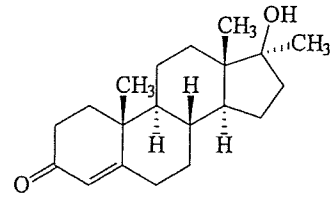
4-Hydroxybenzophenone



2,4,4'-Trihydroxybenzophenone



Testosterone enanthate

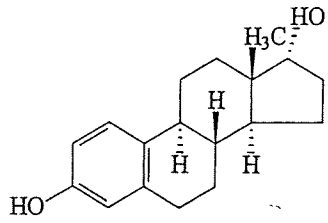


Methyltestosterone

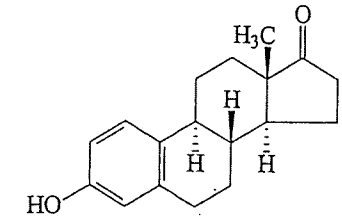
Fig. 1 (*Continued*)

adamantyl)phenol, 100 mg/kg 4,4′-(hexafluoroisopropylidene)diphenol, 10 and 40 mg/kg 2,2-bis (4-hydroxyphenyl)-4-methyl-n-pentane, 10 and 40 mg/kg 4,4′-(octahydro-4,7-methano-5H-inden-5-ylidene)bisphenol, 200 and 800 mg/kg 2,2′,4,4′-tetrahydroxybenzophenone, 40 mg/kg testosterone enanthate, and 40 mg/kg methyltestosterone.

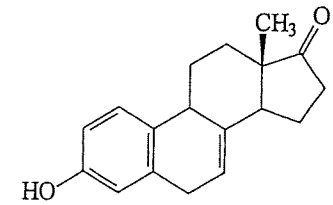
In this study, the uterine weight of rats given EE was higher than in rats given vehicle alone, and the uterine weight of rats given tamoxifen plus EE was lower than in rats given EE, confirming the reliability of this study. Uterine blotted weight increased significantly in rats given 2, 10, and 40 mg/kg 2,2-bis(4-hydroxyphenyl)-4-methyl-n-pentane, 4,4′-(octahydro-4,7-methano-5H-inden-5-ylidene)bisphenol and testosterone enanthate, 8, 40, and 100 mg/kg 4,4′-(hexafluoroisopropylidene)diphenol, 8, 40, and 200 mg/kg 4-(1-adamantyl)phenol, 10 and 40 mg/kg 4,4′-thiobis-phenol and methyltestosterone, 40 and 200 mg/kg p-dodecylphenol, 4-hydroxyazobenzene and 2,4,4′-trihydroxybenzophenone, 100, 400, and 800 mg/kg diphenyl-p-phenylenediamine, 200 and 800 mg/kg 2,2′,4,4′-tetrahydroxybenzophenone and 4-hydroxybenzophenone, 200 mg/kg p-(tert-pentyl)phenol, 4-cyclohexylphenol, 4-(phenylmethyl)phenol and 4,4′-dihydroxybenzophenone, and 800 mg/kg 4-n-amylphenol. Uterine blotted weight decreased significantly in rats given 2 and 10 mg/kg 2,2-bis(4-hydroxyphenyl)-4-methyl-n-pentane plus EE and 4,4′-(octahydro-4,7-methano-5H-inden-5-ylidene)bisphenol plus EE, 10 and 40 mg/kg 4,4′-thiobis-phenol plus EE, 40 and 200 mg/kg 2,2′,4,4′-tetrahydroxybenzophenone plus EE and 2,4,4′-trihydroxybenzophenone plus EE, 40 mg/kg 4,4′-(hexafluoroisopropylidene)diphenol plus EE, and 200 mg/kg p-(tert-pentyl)phenol plus EE, 4-(phenylmethyl)-phenol plus EE, 4,4′-dihydroxybenzophenone plus EE and 4-hydroxybenzophenone plus EE. With these chemicals, the wet absolute and relative weight changes were essentially the same as the blotted weight changes.



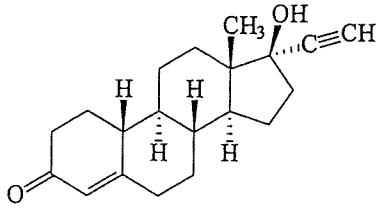
17 Alpha estradiol



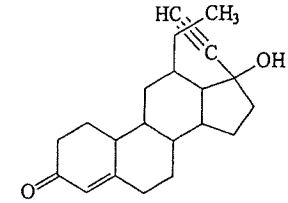
Estrone



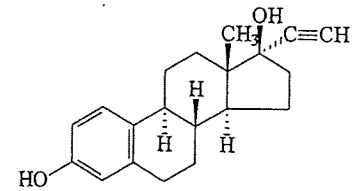
Equilin



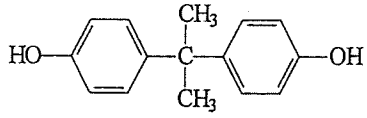
Norethindrone



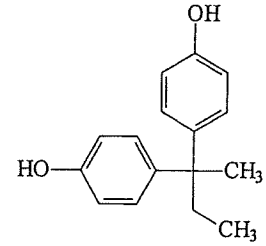
Norgestrel



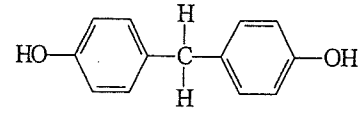
Ethynyl estradiol



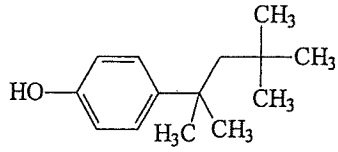
Bisphenol A



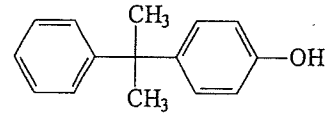
Bisphenol B



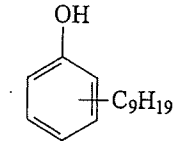
Bisphenol F



4-Tert-octylphenol



p-Cumyl phenol



Nonylphenol

Fig. 1 (*Continued*)

3.2. Hershberger assay

3.2.1. Clinical signs and body weights

Summary of general toxic signs in rats given chemicals and body weights are shown in Tables 3 and 5, respectively. Decreased spontaneous locomotion was seen in rats given 600 mg/kg 4-n-amylphenol, 200 and 600 mg/kg p-(tert-pentyl)phenol, 600 mg/kg 4-cyclohexylphenol, 200 and 600 mg/kg 4,4′-(hexafluoroisopropylidene)diphenol, 200 mg/kg 2,2-bis(4-hydroxyphenyl)-4-methyl-n-pentane, 600 mg/kg 2,2′,4,4′-tetrahydroxybenzophenone, 600 mg/kg 4-hydroxybenzophenone, 600 mg/kg bisphenol B, 1000 mg/kg bisphenol F, 200 and 600 mg/kg 4-tert-octylphenol, 200 and 600 mg/kg p-cumyl phenol, and 200 mg/kg nonylphenol. This sign was also detected in rats given the above chemicals plus TP. In addition, one rat given 600 mg/kg 4-n-amylphenol plus TP, two rats given 600 mg/kg 4,4′-(hexafluoroisopropylidene)diphenol plus TP, one rat given 600 mg/kg 2,2′,4,4′-tetrahydroxybenzophenone, and all rats given 600 mg/kg 4-tert-octylphenol and 600 mg/kg 4-tert-octylphenol plus TP died during the administration period. Significant decrease in body weight gain was observed in rats given 600

Table 2
Chemicals tested in the Hershberger assay

Chemicals	CAS no.	Source	Purity (%)
4-n-Amylphenol	14938-35-3	Tokyo Kasei Kogyo, Co.	99.2
p-Dodecyl-phenol	104-43-8	Kanto Chemical Co.	Unknown
p-(Tert-pentyl)phenol	80-46-6	Wako Pure Chemicals	100.0
4-Cyclohexylphenol	1131-60-8	Tokyo Kasei Kogyo Co.	99.7
4-(1-Adamantyl)phenol	29799-07-3	Aldrich Co.	97
4,4′-Thiobis-phenol	2664-63-3	Tokyo Kasei Kogyo Co.	99.8
diphenyl-p-phenylenediamine	74-31-7	Wako Pure Chemicals	97.2
4-Hydroxyazobenzene	1689-82-3	Wako Pure Chemicals	96
4-(Phenylmethyl)phenol	101-53-1	Tokyo Kasei Kogyo, Co.	99.8
4,4′-(Hexafluoroisopropylidene)diphenol	1478-61-1	Aldrich Co.	98.8
2,2-bis(4-Hydroxyphenyl)-4-methyl-n-pentane	6807-17-6	Wako Pure Chemicals	100.0
4,4′-(Octahydro-4,7-methano-5H-inden-5-ylidene)bisphenol	1943-97-1	Across Organics	99.5
4,4′-Dihydroxybenzophenone	611-99-4	Wako Pure Chemicals	98.5
2,2′,4,4′-Tetrahydroxybenzophenone	131-55-5	Wako Pure Chemicals	98.2
4-Hydroxybenzophenone	1137-42-4	Sigma Chemical Co.	98.0
2,4,4′-Trihydroxybenzophenone	1470-79-7	Aldrich Co.	95
Testosterone enanthate	315-37-7	Wako Pure Chemicals	99.6
Methyltestosterone	58-18-4	Wako Pure Chemicals	100.0
17 Alpha estradiol	57-91-0	Wako Pure Chemicals	100
Estrone	53-16-7	Wako Pure Chemicals	100
Equilin	474-86-2	Sigma Chemical Co.	99.5
Norethindrone	68-22-4	Wako Pure Chemicals	100.7
Norgestrel	797-63-7	Sigma Chemical Co.	99
Ethynyl estradiol	57-63-6	Sigma Chemical Co.	98
Bisphenol A	80-05-7	Kanto Chemical Co.	99.9
Bisphenol B	77-40-7	Tokyo Kasei Kogyo, Co.	99.8
Bisphenol F	620-92-8	Kanto Chemical Co.	99.9
4-Tert-octylphenol	140-66-9	Wako Pure Chemicals	98.5
p-Cumyl phenol	599-64-4	Wako Pure Chemicals	99.9
Nonylphenol	25154-52-3	Kanto Chemical Co.	96.7

mg/kg 4-n-amylphenol and 4-n-amylphenol plus TP, 600 mg/kg 4-cyclohexylphenol, 200 mg/kg 4-(1-adamantyl)phenol and 4-(1-adamantyl)phenol plus TP, 200 mg/kg 4,4′-thiobis-phenol, 600 mg/kg 4-(phenylmethyl)-phenol, 200 and 600 mg/kg 4,4′-(hexafluoroisopropylidene)diphenol and 4,4′-(hexafluoroisopropylidene)diphenol plus TP, 50 and 200 mg/kg 2,2-bis(4-hydroxyphenyl)-4-methyl-n-pentane and 200 mg/kg 2,2-bis(4-hydroxyphenyl)-4-methyl-n-pentane plus TP, 10 and 50 mg/kg 4,4′-(octahydro-4,7-methano-5H-inden-5-ylidene)bisphenol plus TP, 600 mg/kg 4,4′-dihydroxybenzophenone plus TP, 200 and 600 mg/kg 2,2′,4,4′-tetrahydroxybenzophenone and 600 mg/kg 2,2′,4,4′-tetrahydroxybenzophenone plus TP, 600 mg/kg 2,4,4′-trihydroxybenzophenone, 2 and 10 mg/kg 17alpha-estradiol plus TP, 2 and 10 mg/kg estrone and 10 mg/kg estroen plus TP, in all rats given equilin and equilin plus TP, in rats given 10 mg/kg norethindrone and norethindrone plus TP, 100 mg/kg norgestrel and norgestrel plus TP, 50 and 200 μg/kg EE and 200 μg/kg EE plus TP, 600 mg/kg bisphenol B and bisphenol B plus TP, 1000 mg/kg bisphenol F and 200 and 1000 mg/kg bisphenol F plus TP, 200 mg/day 4-tert-octylphenol, 600 mg/kg p-cumyl phenol and p-cumyl phenol plus TP, and 200 mg/kg nonylphenol.

3.2.2. Organ weights

Relative accessory sex organ weights are shown in Table 5. The accessory sex organ weights of rats given TP were higher than in rats given the vehicle alone, and the organ weights of rats given flutamide plus TP were lower than those of rats given

Table 3
General toxic signs in rats given each chemical without testosterone propionate in the Hershberger assay

Chemicals	Toxic signs
4-n-Amylphenol	Decreased body weight gain and decreased spontaneous locomotion in 600 mg/kg group
p-Dodecyl-phenol	No abnormalies detected
p-(Tert-pentyl)phenol	Decreased spontaneous locomotion in 200 and 600 mg/kg groups
4-Cyclohexylphenol	Decreased body weight gain and decreased spontaneous locomotion in 600 mg/kg group
4-(1-Adamantyl)phenol	Decreased body weight gain in 200 mg/kg group
4,4′-Thiobis-phenol	Decreased body weight gain in 200 mg/kg group
Diphenyl-p-phenylenediamine	No abnormalies detected
4-Hydroxyazobenzene	No abnormalies detected
4-(Phenylmethyl)phenol	Decreased body weight gain in 600 mg/kg group
4,4′-(Hexafluoroisopropylidene)diphenol	Decreased body weight gain and decreased spontaneous locomotion in 200 and 600 mg/kg groups
2,2-Bis(4-hydroxyphenyl)-4-methyl-n-pentane	Decreased body weight gain in 50 and 200 mg/kg groups and decreased spontaneous locomotion in 200 mg/kg group
4,4′-(Octahydro-4,7-methano-5H-inden-5-ylidene)bisphenol	No abnormalies detected
4,4′-Dihydroxybenzophenone	No abnormalies detected
2,2′,4,4′-Tetrahydroxybenzophenone	Decreased body weight gain in 200 and 600 mg/kg groups, and decreased spontaneous locomotion and a dead animal in 600 mg/kg group
4-Hydroxybenzophenone	Decreased spontaneous locomotion in 600 mg/kg group
2,4,4′-Trihydroxybenzophenone	Decreased body weight gain in 600 mg/kg group
Testosterone enanthate	No abnormalies detected
Methyltestosterone	No abnormalies detected
17 Alpha estradiol	No abnormalies detected
Estrone	Decreased body weight gain in 2 and 10 mg/kg groups
Equilin	Decreased body weight gain in 0.5, 2 and 10 mg/kg groups
Norethindrone	Decreased body weight gain in 10 mg/kg group
Norgestrel	Decreased body weight gain in 100 mg/kg group
Ethynyl estradiol	Decreased body weight gain in 50 and 200 mg/kg groups
Bisphenol A	No abnormalies detected
Bisphenol B	Decreased body weight gain and decreased spontaneous locomotion in 600 mg/kg group
Bisphenol F	Decreased body weight gain and decreased spontaneous locomotion in 1000 mg/kg group
4-Tert-octylphenol	Decreased body weight gain in 200 mg/kg group, decreased spontaneous locomotion in 200 and 600 mg/kg groups and dead animals in 600 mg/kg group
p-Cumyl phenol	Decreased body weight gain in 600 mg/kg group and decreased spontaneous locomotion in 200 and 600 mg/kg groups
Nonylphenol	Decreased body weight gain and decreased spontaneous locomotion in 200 mg/kg group

TP confirming the reliability of this study. Since body weight gain decreased in the high or middle and high dose groups of many chemicals in this study, we mainly used the relative organ weight changes to assess the effect of each chemical.

Relative accessory sex organ weights increased significantly in rats given testosterone enanthate and methyltestosterone. Relative ventral prostate, seminal vesicle, and glans penis weights increased significantly in rats given 2 and 10 mg/kg equilin. Relative ventral and seminal vesicle weights increased in rats given 30 and 100 mg/kg norgestrel, and relative glans penis weights increased in rats given 100 mg/kg norgestrel. The absolute weight changes with these chemicals were essentially the same, and some organ weights also increased in rats given each chemical plus TP. Relative ventral prostate weights increased significantly in rats given 10 mg/kg estrone and 50 μg/kg EE. In addition, relative ventral prostate weights decreased significantly in rats given 50 and 600 mg/kg 4-hydroxybenzophenone, and relative seminal vesicle weights increased significantly in rats given 800 mg/kg diphenyl-p-phenylenediamine, 10 mg/kg estrone, 50 μg/kg EE and 50 mg/kg 4-tert-

octylphenol. Relative BC/LA weights decreased in rats given 100 mg/kg p-dodecyl-phenol, 30 mg/kg 4-hydroxyazobenzene, 200 mg/kg 4,4′-(hexafluoroisopropylidene)diphenol, 200 mg/kg 4,4′-dihydroxybenzophenone and 200 and 600 mg/kg bisphenol B. Relative glans penis weight increased significantly in rats given 50 mg/kg diphenyl-p-phenylenediamine, 50 and 200 mg/kg 4-(phenylmethyl)phenol, 600 mg/kg 4,4′-(hexafluoroisopropylidene)diphenol, 50 and 200 μg/kg EE and 600 mg/kg bisphenol A. On the other hand, the relative ventral prostate weight increased significantly in rats given 10 and 200 mg/kg 4,4′-thiobis-phenol plus TP, 50 and 800 mg/kg diphenyl-p-phenylenediamine plus TP, 10 and 200 mg/kg 2,2-bis(4-hydroxyphenyl)-4-methyl-n-pentane plus TP and 200 and 600 mg/kg bisphenol B plus TP, whereas its weight decreased in rats given 200 mg/kg 4,4′-dihydroxybenzophenone plus TP. Relative seminal vesicle weight increased significantly in rats given 50 mg/kg p-(tert-pentyl)phenol plus TP, 200 mg/kg 4-(1-adamantyl)phenol plus TP, 10 and 200 mg/kg 4,4′-thiobis-phenol plus TP, 50 mg/kg 4-(phenylmethyl)phenol plus TP, 50 and 600 mg/kg 4,4′-(hexafluoroisopropylidene)diphenol plus TP, in all rats given estrone plus TP, in rats given 50 and 200 μg/kg EE plus TP, and 600 mg/kg bisphenol B plus TP, but its weight decreased in rats given 200 mg/kg nonylphenol plus TP. Relative BC/LA weight increased significantly in rats given 600 mg/kg bisphenol B plus TP, but it decreased in rats given 600 mg/kg 4-n-amylphenol plus TP and 200 mg/kg 4,4′-dihydroxybenzophenone plus TP. Relative glans penis weight increased significantly in rats given 10 mg/kg 4-hydroxyazobenzene plus TP, 50 and 600 mg/kg 4,4′-(hexafluoroisopropylidene)diphenol plus TP, 10 and 50 mg/kg 4,4′-(octahydro-4,7-methano-5H-inden-5-ylidene)bisphenol plus TP, 600 mg/kg 4,4′-dihydroxybenzophenone plus TP, 2 and 10 mg/kg estrone plus TP, 10 mg/kg norethindrone plus TP, 200 μg/kg EE plus TP, and 600 mg/kg bisphenol B plus TP. Relative Cowper's gland increased significantly in rats given 200 mg/kg 4-(1-adamantyl)phenol plus TP, 600 mg/kg 4,4′-(hexafluoroisopropylidene)diphenol plus TP, 600 mg/kg bisphenol B plus TP, 200 mg/kg bisphenol F plus TP, and 200 mg/kg 4-tert-octylphenol plus TP.

4. Discussion

The OECD proposed the rat uterotrophic assay and the Hershberger assay as screening methods to detect the estrogenic and androgenic properties of endocrine disrupting chemicals, and these assays have been reported to be useful in this regard (OECD, 2001). In the present study, we performed uterotrophic assays and Hershberger assays of 18 chemicals and Hershberger assays alone on 12 chemicals that showed an estrogen agonistic effect in our previous study (Yamasaki et al., 2002b).

All of the chemicals tested were positive in the uterotrophic assay, and thus they have estrogen agonistic properties. Androgen derivatives, such as testosterone enanthate and methyltestosterone, also tested positive in the uterotrophic assay. These androgen chemicals may be aromatized to estradiol. A decrease in uterine weight was observed in the high-dose group receiving p-(tert-pentyl)phenol plus EE, 4-(phenylmethyl)phenol plus EE, and 4,4′-dihydroxybenzophenone plus EE and also in the middle- and high-dose groups receiving 4,4′-thiobis-phenol plus EE and 2,4,4′-trihydroxybenzophenone plus EE. These findings clearly demonstrate that the above chemicals have partial agonistic properties and that they also reduce the agonistic effect of EE. In addition, a decrease in uterine weight was detected in the middle-dose groups receiving 4,4′-(hexafluoroisopropylidene)diphenol plus EE and 4-hydroxybenzophenone plus EE and also in the low- and middle-dose groups receiving 2,2-bis(4-hydroxyphenyl)-4-methyl-n-pentane plus EE, 4,4′-(octahydro-4,7-methano-5H-inden-5-ylidene)bisphenol and 2,2′,4,4′-tetrahydroxybenzophenone plus EE. These chemicals are also thought to reduce the agonistic effect of EE as well as the agonistic effects of the high dose. Interestingly, ten of the 18 chemicals examined in this study exhibited both estrogen agonistic properties and reduced the agonistic effect of EE. All of the (di and tri) phenyl methanes and benzophenone derivatives displayed both agonistic properties and reduced the agonistic effect of EE. In the benzophenone derivatives, the position of hydroxyl groups may be related to the uterotrophic affinity. Moreover, the observation that the agonistic effect of 4-(1-

Table 4
Body weight and uterine blotted weight in the uterotrophic assays of 18 chemicals with and without ethynyl estradiol (EE)

Chemicals	PC10 values for ER alpha	Groups (mg/kg per day)	Body weight (g)	Uterus blotted weight	
				Absolute (mg)	Relative (mg/100 g)
Para-alkylphenols					
4-n-Amylphenol	177 639	Vehicle control	57.8±4.8	29.7±3.8	51.2±4.7
		100	56.5±2.7	25.8±2.3	45.8±3.8
		400	56.4±2.6	37.2±9.5	65.9±16.1
		800	51.2±3.9	64.5±9.9**	126.1±18.0**
		Vehicle+EE	57.1±2.0	102.2±7.5	179.2±13.8
		100+EE	57.4±3.0	83.2±25.1	143.7±37.1
		400+EE	56.8±2.7	93.1±19.4	163.4±30.0
		800+EE	54.7±3.5	100.3±17.7	182.6±24.1
		Tamoxifen+EE	55.7±2.5	83.2±6.1**	149.3±7.0**
p-Dodecyl-phenol	23 645	Vehicle control	59.0±2.6	27.4±3.0	46.3±3.2
		8	57.7±1.7	28.9±2.9	50.0±4.9
		40	58.4±3.6	37.6±7.2*	64.5±11.8*
		200	56.7±3.4	97.3±15.1**	171.5±23.8**
		Vehicle+EE	56.3±2.6	100.3±25.6	177.1±37.9
		8+EE	56.0±2.8	99.6±10.8	177.7±15.4
		40+EE	57.2±1.6	100.6±11.5	175.6±17.6
		200+EE	58.2±3.3	116.1±11.7	199.5±15.9
		Tamoxifen+EE	55.6±2.6	76.0±4.7	137.1±12.7*
p-(Tert-pentyl)phenol	401 969	Vehicle control	57.4±3.1	29.4±3.6	51.2±4.9
		8	57.3±2.7	27.8±2.1	48.6±3.5
		40	57.9±1.9	33.8±7.8	58.4±13.6
		200	53.6±2.1	72.2±7.1**	134.5±9.7**
		Vehicle+EE	58.3±1.9	110.8±6.2	190.4±13.8
		8+EE	57.2±2.9	103.2±17.4	180.8±31.1
		40+EE	58.0±2.1	108.2±12.6	186.5±20.4
		200+EE	56.6±3.9	91.2±9.0**	161.0±10.9**
		Tamoxifen+EE	56.4±0.9	85.1±2.6**	151.1±4.9**
Phenol derivatives					
4-Cyclohexylphenol	64 256	Vehicle	56.6±2.4	27.9±1.1	49.5±2.6
		8	55.2±2.2	27.9±2.9	50.6±5.2
		40	55.6±1.5	29.7±4.5	53.4±8.6
		200	55.2±2.5	60.2±7.9**	108.9±11.8**
		Vehicle+EE	56.1±1.3	96.8±5.9	172.7±11.5
		8+EE	54.4±3.3	100.4±9.6	184.8±17.4
		40+EE	54.9±1.9	103.3±18.3	188.3±34.1
		200+EE	55.2±3.0	92.1±12.6	166.8±19.9
		Tamoxifen+EE	54.6±3.1	81.2±4.2**	149.4±14.1*
4-(1-Adamantyl)phenol	1248	Vehicle	59.0±3.7	31.4±3.3	53.1±4.0
		8	57.4±3.1	52.0±14.0*	90.5±23.7*
		40	57.5±2.9	102.3±15.5**	178.1±27.8**
		200	54.9±4.2	138.4±7.9**	252.8±17.0**
		Vehicle+EE	59.3±3.2	112.9±18.6	191.0±33.0
		8+EE	58.6±3.6	119.6±18.0	204.3±27.1
		40+EE	58.6±3.5	112.7±20.7	192.0±28.0
		200+EE	58.0±5.1	132.7±7.7*	230.6±26.7*
		Tamoxifen+EE	57.8±3.2	85.5±10.2*	148.4±19.4*
4,4′-Thiobis-phenol	20 087	Vehicle	55.2±2.0	28.6±1.5	51.8±2.9
		2	55.8±3.7	33.7±4.9	60.2±6.7*
		10	55.5±2.2	36.5±3.2**	66.0±6.6**

Table 4 (*Continued*)

Chemicals	PC10 values for ER alpha	Groups (mg/kg per day)	Body weight (g)	Uterus blotted weight	
				Absolute (mg)	Relative (mg/100 g)
		40	55.0±2.9	42.1±2.6**	76.5±4.7**
		Vehicle+EE	56.4±3.0	111.0±7.4	197.0±12.1
		2+EE	55.2±1.9	112.1±11.3	203.5±23.7
		10+EE	56.8±3.6	100.0±8.8*	176.3±17.9*
		40+EE	56.1±2.8	77.1±15.8**	136.8±23.8**
		Tamoxifen+EE	54.9±2.1	79.8±6.5**	145.4±11.5**
Non-condensed polycyclic compounds					
Diphenyl-p-phenylenediamine	2 300 407	Vehicle	52.8±3.4	24.6±2.8	46.6±5.5
		100	55.2±4.6	29.8±4.9*	53.9±7.6
		400	52.8±1.3	33.4±4.7**	63.4±9.3**
		800	52.0±2.9	48.9±6.9**	94.2±12.9**
		Vehicle+EE	54.2±3.0	98.2±7.5	181.8±18.4
		100+EE	54.3±1.3	113.6±13.7*	209.5±27.4
		400+EE	53.9±2.4	104.2±14.6	194.1±31.7
		800+EE	50.8±7.2	106.1±17.5	209.8±25.6
		Tamoxifen+EE	53.2±2.4	82.2±6.7**	154.5±12.7*
4-Hydroxyazobenzene	164 424	Vehicle	57.8±3.7	27.5±2.6	47.9±6.9
		8	57.0±4.0	29.5±4.2	51.8±7.0
		40	56.8±2.7	43.2±6.9**	76.1±11.9**
		200	56.4±2.4	56.2±6.0**	99.6±9.6**
		Vehicle+EE	57.8±2.6	104.2±13.5	180.8±26.7
		8+EE	58.0±3.1	112.5±19.1	194.4±32.8
		40+EE	57.6±3.5	108.8±4.3	189.3±7.2
		200+EE	57.0±2.1	93.4±3.7	164.4±11.8
		Tamoxifen+EE	56.1±4.3	81.1±7.1**	145.5±19.9*
(Di or tri) phenyl methanes					
4-(Phenylmethyl) phenol	1 198 024	Vehicle	61.1±4.8	33.2±8.1	54.1±10.7
		8	62.5±4.2	32.9±5.3	52.4±6.3
		40	60.9±3.2	36.0±4.9	59.1±7.9
		200	60.4±4.5	58.3±5.6**	96.8±9.2**
		Vehicle+EE	62.9±2.9	119.4±11.8	190.0±17.6
		8+EE	62.1±3.3	130.7±8.7	210.6±12.6*
		40+EE	62.8±3.5	120.6±9.1	192.3±13.6
		200+EE	62.3±3.3	101.2±14.0*	163.6±28.4*
		Tamoxifen+EE	60.3±3.3	81.6±8.0**	135.5±11.9**
(Di or tri) phenyl methanes					
4,4′-(Hexafluoro isopropylidene) diphenol	6906	Vehicle	56.1±4.3	28.6±4.9	50.9±7.4
		8	55.0±4.5	47.2±9.9**	85.1±11.9**
		40	56.6±4.0	65.9±9.8**	116.0±11.7**
		100	54.7±4.2	96.4±9.0**	177.2±22.2
		Vehicle+EE	56.5±3.8	110.3±15.7	195.4±25.0
		8+EE	56.7±3.8	95.1±6.1	168.0±9.4*
		40+EE	55.5±2.1	74.5±9.1**	134.2±15.4**
		100+EE	55.9±3.2	99.3±11.9	177.8±18.9
		Tamoxifen+EE	54.7±3.4	79.5±5.2**	145.9±14.4**
2,2-Bis (4-hydroxyphenyl)-4-methyl-n-pentane	1892	Vehicle	58.3±2.8	28.8±2.6	49.4±3.0
		2	58.0±2.7	58.4±8.8**	100.5±14.2**
		10	59.2±3.3	84.0±11.9**	141.6±15.3**

Table 4 (*Continued*)

Chemicals	PC10 values for ER alpha	Groups (mg/kg per day)	Body weight (g)	Uterus blotted weight	
				Absolute (mg)	Relative (mg/100 g)
		40	57.4±3.2	115.1±16.6**	200.3±25.3**
		Vehicle+EE	59.7±2.7	107.6±7.1	180.4±11.8
		2+EE	58.0±3.8	96.2±10.3*	165.7±13.3
		10+EE	59.0±3.0	92.5±7.9**	157.3±17.1*
		40+EE	57.9±3.1	112.3±15.9	193.8±23.9
		Tamoxifen+EE	58.1±2.4	87.5±5.5**	151.0±14.1**
4,4′-(Octahydro-4,7-methano-5H-inden-5-ylidene)bisphenol	37 162	Vehicle	54.9±3.2	28.3±4.4	51.6±7.1
		2	56.2±3.1	63.4±5.2**	112.9±7.8**
		10	53.2±3.8	86.2±6.5**	162.5±13.7**
		40	54.6±1.7	92.5±7.1**	169.3±10.3**
		Vehicle+EE	55.7±3.0	97.4±8.3	174.9±12.6
		2+EE	54.8±2.6	78.7±8.4**	143.9±16.7**
		10+EE	55.9±2.3	82.3±9.4*	147.4±15.3**
		40+EE	53.0±4.2	93.5±8.3	176.8±16.6
		Tamoxifen+EE	52.4±2.6	79.7±3.6**	152.2±4.7**
Benzophenone derivatives					
4,4′-Dihydroxybenzophenone	124 213	Vehicle	56.3±4.2	31.0±6.6	55.0±9.7
		8	54.3±6.1	28.9±3.9	53.8±8.9
		40	53.7±4.2	28.3±4.5	54.5±6.8
		200	56.1±3.9	45.0±5.0**	80.4±7.5**
		Vehicle+EE	54.9±2.9	95.0±5.4	173.1±9.2
		8+EE	55.8±5.2	110.1±17.4	197.8±30.1
		40+EE	55.7±5.1	106.9±17.8	192.3±29.0
		200+EE	54.4±4.4	69.8±14.8**	128.3±23.5**
		Tamoxifen+EE	54.2±4.5	84.7±7.8*	157.0±17.0
2,2′,4,4′-Tetrahydroxybenzophenone	106 427	Vehicle	58.1±3.3	34.2±4.2	58.9±6.8
		40	57.9±3.3	37.6±2.6	65.1±5.7
		200	57.4±1.5	77.2±10.4**	134.2±15.3**
		800	54.8±3.9	119.7±12.1**	218.9±20.2**
		Vehicle+EE	57.6±3.5	117.8±11.3	205.3±25.0
		40+EE	57.4±2.9	00.5±15.3*	175.1±27.6
		200+EE	56.8±3.4	67.0±10.3**	134.2±15.3**
		800+EE	53.0±2.4	124.3±9.2	218.9±20.2**
		Tamoxifen+EE	56.5±4.4	87.8±4.6**	156.1±12.6**
4-Hydroxybenzophenone	1 096 217	Vehicle	59.6±3.5	34.9±6.1	58.7±10.1
		40	57.6±2.8	39.6±3.7	68.8±5.3
		200	55.9±9.1	48.3±6.3**	88.7±19.2**
		800	55.9±2.5	86.1±12.7**	154.1±22.3**
		Vehicle+EE	57.5±2.5	108.3±11.5	188.4±19.6
		40+EE	59.5±2.4	115.1±12.2	194.2±26.9
		200+EE	57.2±2.9	84.7±15.1*	148.7±29.2*
		800+EE	57.4±2.2	95.5±12.1	166.4±20.0
		Tamoxifen+EE	57.7±3.3	85.2±8.9**	142.9±12.2**
Benzophenone derivatives					
2,4,4′-Trihydroxybenzophenone	43 765	Vehicle	59.2±4.5	34.9±2.1	59.1±4.5
		8	59.9±3.7	37.8±3.5	63.1±3.4
		40	58.2±4.3	45.1±4.2**	77.8±9.0**
		200	58.2±5.9	72.8±10.2**	125.1±12.0**

Table 4 (*Continued*)

Chemicals	PC10 values for ER alpha	Groups (mg/kg per day)	Body weight (g)	Uterus blotted weight	
				Absolute (mg)	Relative (mg/100 g)
		Vehicle+EE	58.2±3.5	116.5±12.6	199.7±12.1
		8+EE	58.2±3.2	109.5±15.0	187.5±17.8
		40+EE	58.1±2.8	94.5±10.4**	163.1±20.0**
		200+EE	55.2±3.3	67.7±11.6**	123.4±25.0**
		Tamoxifen+EE	58.8±3.3	84.2±3.8**	143.4±8.7**
Androgen derivatives					
Testosterone enanthate	17 140	Vehicle	59.7±3.0	36.6±3.0	61.3±4.2
		2	61.1±2.9	30.8±3.2**	50.5±6.3**
		10	61.9±2.3	60.5±9.6**	98.1±17.3**
		40	60.5±4.0	89.0±6.7**	147.3±10.0**
		Vehicle+EE	60.0±5.2	121.4±18.2	201.6±16.7
		2+EE	59.7±3.3	108.8±6.3	182.5±12.4*
		10+EE	60.9±3.0	121.7±12.6	199.9±19.0
		40+EE	61.0±2.4	129.6±16.8	211.9±20.4
		Tamoxifen+EE	58.1±2.8	86.7±6.3**	149.3±11.8**
Methyltestosterone	173 235	Vehicle	62.7±2.5	34.9±7.0	55.7±10.9
		2	63.1±4.3	35.5±3.1	56.4±4.4
		10	62.7±3.9	60.9±9.7**	97.6±18.0**
		40	63.3±3.2	96.1±17.4**	151.8±26.4**
		Vehicle+EE	61.9±2.2	115.8±16.1	187.2±25.8
		2+EE	63.6±3.4	103.3±7.7	162.4±7.0
		10+EE	64.4±2.9	118.3±7.1	184.0±11.8
		40+EE	62.2±1.1	129.6±7.8	208.5±13.3
		Tamoxifen+EE	61.6±3.3	86.8±9.6**	140.8±11.5**

* Significantly different from vehicle control or vehicle control plus EE at $P < 0.05$.
** Significantly different from vehicle control or vehicle control plus EE at $P < 0.01$.

adamantyl)phenol was enhanced by EE was quite interesting.

In the previous study, we performed a reporter gene assay for ER alpha-mediated transcriptional activation and an immature rat uterotrophic assay of 23 chemicals (Yamasaki et al., 2002b). In the reporter gene assay, the transcriptional activity of each chemical was tested over concentrations ranging from 10 pM to 10 μM. The EC50, PC50, and PC10 values were then calculated, and the results showed that the PC10 values were superior to the EC50 and PC50 values for predicting the estrogenic activity of chemicals. The PC50 and PC10 values defined as the test chemical concentrations estimated to show 50 and 10%, respectively, of the transcriptional activity of positive control wells treated with natural ligands (1 nM of 17β-estradiol) were calculated in our own made software. We selected all of the chemicals for the uterotrophic assay in this study based on their PC10 values in the reporter gene assay and found that all had estrogen agonistic effects. This demonstrates that the PC10 value is superior as a parameter for predicting estrogen agonistic activity of chemicals with a wide range of estrogenic potency and that the reporter gene assay is a potentially useful method for prioritizing chemicals to be tested in subsequent screening tests.

In the Hershberger assay, a clear androgen agonistic effect was detected in two androgen derivatives: testosterone enanthate and methyltestosterone. The weights of some accessory sex organs also increased in rats given estrogen equilin, norgestrel or estrone. However, whether these chemicals have an androgenic effect remains uncertain because these accessory sex organs may

Table 5
Body weight and relative accessory sex organ weight in rats given 30 chemicals with and without testosterone propionate (TP) for 10 days

Chemicals	Doses (mg/kg per day)	Body weight (g)	Ventral prostate (mg/100 g bw)	Seminal vesicle (mg/100 g bw)	BC/LA (mg/100 g bw)	Glans penis (mg/100 g bw)	Cowper's gland (mg/100 g bw)
Para-alkylphenols							
4-n-Amylphenol	Vehicle control	269.9±15.2	6.3±2.6	13.9±2.8	46.0±4.5	12.3±1.3	1.6±0.6
	50	266.0±13.0	5.5±0.5	13.3±2.1	50.3±8.4	12.6±1.9	1.2±0.4
	200	268.7±19.4	6.9±2.6	14.8±1.9	48.8±7.1	13.1±1.4	1.8±0.4
	600(400)[a]	248.8±15.5*	5.5±2.8	15.3±6.0	47.4±11.0	12.8±3.1	1.7±0.7
	Vehicle+TP	271.8±12.3	33.9±2.6	79.8±14.7	119.3±10.6	25.5±3.2	7.2±1.4
	50+TP	273.1±17.4	35.1±4.3	80.0±26.7	113.5±15.0	25.1±2.1	6.8±1.1
	200+TP	280.2±11.9	33.4±4.3	69.4±12.2	109.0±12.5	22.8±2.4	5.9±2.3
	600(400)+TP	254.2±11.9*	34.9±7.9	74.4±33.3	96.2±13.8*	25.6±0.6	7.0±1.2
	Flutamide+TP	276.0±12.9	5.8±1.2**	13.1±2.6**	52.8±8.2**	13.5±2.3**	1.6±0.6**
p-Dodecyl-phenol	Vehicle control	273.9±19.0	6.8±1.9	13.7±3.7	53.6±6.4	12.2±2.4	1.5±0.4
	10	264.6±21.4	6.7±2.9	16.2±6.1	48.0±8.0	12.5±3.7	1.5±0.4
	30	260.4±18.2	7.3±4.5	14.9±2.5	52.7±6.9	12.6±2.5	1.5±0.4
	100	249.7±21.3	6.6±2.0	16.5±1.9	46.1±3.8*	13.7±2.2	2.0±0.8
	Vehicle+TP	275.3±14.5	35.7±2.8	83.8±16.1	112.3±13.3	24.1±2.3	7.1±0.9
	10+TP	273.0±11.3	34.5±7.6	84.1±29.9	111.2±5.8	23.6±1.8	6.9±1.2
	30+TP	271.3±18.8	37.2±3.5	98.6±22.9	121.3±5.8	24.8±1.6	8.0±0.8
	100+TP	262.2±17.0	36.8±5.6	104.1±19.7	119.0±13.0	25.1±1.1	6.9±2.2
	Flutamide+TP	271.8±19.6	6.4±0.8**	14.0±3.6**	51.9±8.4**	13.2±1.8**	1.9±0.5**
p-(Tert-pentyl) phenol	Vehicle control	274.9±13.8	6.2±0.6	13.0±2.2	50.2±3.5	13.5±2.6	1.2±0.4
	50	267.6±6.9	6.6±1.2	15.0±2.5	53.2±7.0	14.0±2.0	1.7±0.7
	200	271.6±10.2	6.9±1.0	12.9±1.9	54.1±9.4	12.9±2.2	1.2±0.2
	600(400)	270.2±11.4	6.4±1.2	10.8±1.7	46.5±4.3	10.8±1.7	1.3±0.4
	Vehicle+TP	280.6±8.7	34.6±6.1	69.8±12.6	103.5±8.9	23.0±1.4	6.8±1.0
	50+TP	279.7±10.7	31.6±7.6	85.9±9.7*	107.0±21.6	23.7±2.1	6.0±1.4
	200+TP	279.9±13.4	39.2±3.2	79.8±13.9	108.6±15.5	22.7±2.8	7.7±1.6
	600(400)+TP	265.5±15.8	35.0±7.0	65.5±9.6	96.4±9.8	22.5±2.0	6.3±2.3
	Flutamide+TP	261.3±24.8	7.2±2.1**	13.7±3.1**	56.1±9.6**	12.2±2.3**	1.5±0.3**
Phenol derivatives							
4-Cyclohexylphenol	Vehicle control	280.7±12.3	5.7±0.6	13.1±1.4	50.4±8.3	12.5±2.5	1.5±0.3
	50	282.0±14.3	6.1±1.6	14.5±4.1	44.3±3.5	13.8±2.9	1.7±0.5
	200	281.7±10.4	6.4±0.7	14.3±3.8	50.9±9.7	12.2±2.9	1.7±0.4
	600(400)[a]	266.6±6.6*	6.3±0.7	12.8±1.2	42.1±8.7	12.2±1.8	1.8±0.6
	Vehicle+TP	283.2±10.3	38.9±6.6	99.8±34.1	110.9±12.3	23.1±3.7	7.9±2.2
	50+TP	287.3±16.4	39.5±11.0	79.8±26.2	110.4±12.1	23.1±2.5	7.1±0.8
	200+TP	287.4±12.0	39.7±7.6	76.5±25.5	113.7±12.4	22.6±1.3	7.4±1.0
	600(400)+TP	270.6±14.4	35.4±6.2	84.6±18.8	104.3±15.4	24.1±1.9	8.0±1.6
	Flutamide+TP	287.5±7.1	6.0±0.7**	11.5±2.3**	51.7±7.7**	11.1±2.3**	1.6±0.2**
4-(1-Adamantyl) phenol	Vehicle control	276.9±16.6	5.0±1.1	10.8±3.8	53.7±11.3	9.8±3.8	1.5±0.5

Table 5 (*Continued*)

Chemicals	Doses (mg/kg per day)	Body weight (g)	Ventral prostate (mg/100 g bw)	Seminal vesicle (mg/100 g bw)	BC/LA (mg/100 g bw)	Glans penis (mg/100 g bw)	Cowper's gland (mg/100 g bw)
	10	266.2±13.9	5.3±0.8	12.6±2.0	45.3±6.3	11.5±2.3	1.9±0.3
	50	266.0±12.8	5.7±1.2	12.5±3.4	48.0±5.9	11.5±2.7	1.8±0.7
	200	250.5±12.3*	6.1±1.3	13.7±2.4	53.6±6.1	12.9±2.8	2.0±0.9
	Vehicle+TP	282.1±15.8	38.2±5.5	78.1±14.7	123.3±12.5	23.9±1.3	7.4±0.8
	10+TP	278.7±8.7	37.6±5.7	75.2±9.8	110.3±10.7	22.3±1.5	7.4±1.7
	50+TP	279.4±14.2	35.1±4.9	73.8±17.4	118.6±6.6	22.9±1.3	6.8±1.6
	200+TP	259.3±13.5*	41.1±3.5	101.9±11.7*	126.5±17.6	26.8±3.0	9.2±1.1**
	Flutamide+TP	279.8±17.5	6.1±1.2**	11.4±2.4**	57.8±5.5**	11.3±3.3**	1.7±0.4**
4,4′-Thiobis-phenol	Vehicle control	269.6±9.7	5.6±0.7	12.3±2.1	45.5±11.2	11.3±1.5	1.5±0.4
	10	270.0±9.1	5.6±0.9	13.3±1.5	53.3±6.8	12.6±2.1	1.6±0.3
	50	271.8±17.6	5.5±0.8	12.0±1.9	51.1±7.1	10.7±2.3	1.7±0.4
	200	252.9±11.4*	5.6±0.5	13.0±1.6	47.4±6.8	13.1±1.3	1.4±0.4
	Vehicle+TP	277.7±10.8	31.9±4.3	79.3±8.8	117.6±6.0	23.2±2.7	7.4±0.9
	10+TP	277.8±17.6	43.7±6.8**	103.8±13.9**	119.3±10.8	23.7±1.4	8.0±1.1
	50+TP	274.8±13.9	37.9±6.5	95.3±35.2	125.3±21.3	25.0±1.8	7.3±2.5
	200+TP	267.2±15.2	38.5±5.3*	99.8±4.0**	119.4±13.5	24.7±1.4	7.5±0.9
	Flutamide+TP	271.1±15.5	7.0±1.0**	14.6±3.1**	53.0±4.8**	13.1±2.0**	1.4±0.3**
Non-condensed polycyclic compounds							
Diphenyl-p-phenylenediamine	Vehicle control	273.6±10.6	5.2±1.0	9.4±2.0	48.2±8.5	11.0±1.7	1.9±1.2
	50	259.1±16.4	5.6±1.1	11.9±2.7	50.8±5.8	13.8±1.1**	1.6±0.4
	200	258.1±13.5	5.9±0.7	10.6±2.6	51.8±7.0	10.4±1.3	1.4±0.4
	800	255.7±18.7	5.5±1.4	13.6±1.0**	51.8±5.4	12.7±2.8	1.5±0.5
	Vehicle+TP	269.0±15.8	27.8±3.6	63.1±14.0	111.0±11.5	21.3±4.5	6.4±1.8
	50+TP	275.1±17.6	33.4±4.8*	71.0±13.5	116.4±11.6	22.3±2.6	6.7±1.1
	200+TP	274.7±11.5	31.0±4.0	68.7±15.1	111.3±11.2	21.2±1.8	7.1±1.7
	800+TP	260.6±13.5	33.0±3.8*	68.9±7.9	110.4±14.9	23.5±2.6	6.8±1.3
	Flutamide+TP	268.3±16.5	6.5±0.8**	13.4±2.0**	48.7±6.3**	12.2±2.8**	1.5±0.3**
4-Hydroxy azobenzene	Vehicle control	280.2±18.7	5.9±0.8	13.8±0.8	53.0±6.2	11.9±1.7	2.0±0.5
	10	277.2±14.2	5.5±1.1	12.8±1.9	49.2±8.0	11.8±2.0	1.9±0.8
	30	275.5±11.1	5.7±2.1	12.5±2.5	43.6±5.4*	10.6±2.8	1.3±0.7
	100	271.5±12.4	6.3±1.1	12.5±1.9	49.4±7.7	12.4±2.1	2.0±0.9
	Vehicle+TP	282.4±11.6	33.0±5.9	70.6±14.4	105.1±10.6	21.2±1.7	6.8±1.2
	10+TP	283.0±17.7	34.4±2.8	74.1±12.4	104.3±12.4	24.1±1.6*	7.3±0.6
	30+TP	287.7±11.7	32.4±1.3	65.8±5.9	114.5±10.0	21.1±1.6	6.8±1.5
	100+TP	276.3±18.7	30.9±6.2	70.8±9.3	100.9±9.8	22.5±1.9	7.9±1.7
	Flutamide+TP	278.6±20.6	6.6±1.2**	13.4±3.6**	48.0±5.3**	11.2±2.6**	1.4±0.4**
(Di or Tri) phenyl methanes							
4-(Phenylmethyl) phenol	Vehicle control	279.4±14.3	5.7±0.6	12.8±2.1	51.1±4.1	10.0±2.0	1.7±0.4
	50	274.1±15.0	5.8±1.8	17.0±4.7	49.9±4.2	12.9±1.7*	1.9±0.4
	200	269.8±10.0	5.9±0.7	14.6±4.9	47.9±11.0	12.2±0.9*	1.5±0.4

Table 5 (*Continued*)

Chemicals	Doses (mg/kg per day)	Body weight (g)	Ventral prostate (mg/100 g bw)	Seminal vesicle (mg/100 g bw)	BC/LA (mg/100 g bw)	Glans penis (mg/100 g bw)	Cowper's gland (mg/100 g bw)
	600(400)[a]	261.1±13.4*	5.4±0.7	13.9±4.6	48.1±5.6	11.7±2.5	1.7±0.7
	Vehicle+TP	280.1±9.5	37.4±3.6	75.1±12.1	108.9±5.1	23.4±1.7	7.8±1.6
	50+TP	283.1±13.7	37.7±3.9	98.6±13.8*	114.9±13.0	23.5±2.4	7.7±1.6
	200+TP	282.8±8.8	35.4±3.5	78.3±15.6	111.6±8.7	22.9±1.5	7.4±0.9
	600(400)+TP	269.3±14.4	35.2±7.2	85.9±12.0	111.5±7.7	25.1±2.6	8.3±2.0
	Flutamide+TP	278.8±14.0	6.1±0.7**	12.5±1.2**	49.5±11.5**	11.4±2.7**	2.0±0.2**
(Di or tri) phenyl methanes							
4,4′-(Hexafluoroisoproylidene)diphenol	Vehicle control	275.1±9.7	5.8±0.9	11.3±2.1	53.2±6.3	12.6±1.0	1.5±0.5
	50	257.0±18.2	5.5±1.5	12.0±1.8	55.9±8.4	12.8±1.1	1.7±0.5
	200	259.9±12.8*	5.7±1.4	13.2±2.3	44.2±4.7*	12.2±2.0	1.3±0.4
	600(400)[a]	219.6±30.9*	6.2±1.6	13.6±1.2	48.9±3.5	15.1±1.8*	1.7±0.3
	Vehicle+TP	283.3±9.2	34.5±7.3	73.0±11.6	119.6±7.6	22.8±1.5	6.8±1.1
	50+TP	277.0±14.4	42.4±6.1	99.4±19.7*	120.2±13.4	25.5±1.7*	6.0±3.0
	200+TP	260.6±14.9*	39.3±10.2	109.0±37.8	118.7±20.1	25.3±2.6	8.4±1.6
	600(400)+TP	209.4±33.1*	37.1±2.5	126.7±27.7*	115.3±17.6	30.6±5.0*	8.5±0.8*
	Flutamide+TP	275.3±12.8	6.1±0.5**	13.2±1.0**	51.9±4.2**	13.0±1.4**	1.3±0.3**
2,2-Bis(4-hydroxyphenyl)-4-methyl-n-pentane	Vehicle control	275.7±12.7	5.8±1.2	12.9±2.7	54.0±5.7	13.1±1.3	1.7±0.2
	10	278.4±12.0	5.7±0.9	13.7±3.3	48.4±7.7	10.8±2.2	1.4±0.6
	50	254.7±10.6*	6.4±0.5	14.2±1.8	53.0±4.8	13.2±0.9	1.8±0.2
	200(100)	243.5±9.2**	6.1±0.3	13.8±1.7	54.5±11.0	13.8±1.7	2.0±1.0
	Vehicle+TP	275.6±11.1	32.2±6.2	78.9±25.3	108.7±14.9	22.2±3.7	7.0±1.2
	10+TP	280.9±19.8	39.5±4.8*	103.9±23.0	121.7±5.2	24.8±1.5	7.7±2.2
	50+TP	269.9±12.4	35.0±4.3	92.0±21.9	123.5±10.4	24.7±2.8	8.1±1.6
	200(100)+TP	253.6±16.3*	40.7±6.5*	101.5±20.3	122.8±11.5	26.2±2.6	8.8±2.3
	Flutamide+TP	276.7±11.1	7.1±1.0**	15.3±2.8**	53.5±7.2**	12.2±2.0**	1.5±0.6**
4,4′-(Octahydro-4,7-methano-5H-inden-5-ylidene)bisphenol	Vehicle control	276.2±13.9	5.5±0.9	12.5±3.3	52.7±9.9	13.6±1.0	1.6±0.2
	2	276.6±10.5	5.3±0.5	10.8±2.6	53.7±8.9	12.4±2.2	1.5±0.5
	10	267.5±11.4	5.5±0.6	12.8±1.0	56.8±8.0	12.2±1.5	1.6±0.3
	50	254.8±21.7	6.0±0.4	12.2±1.6	46.3±6.0	12.3±2.4	1.8±0.4
	Vehicle+TP	282.3±8.7	34.7±6.7	83.3±14.0	117.9±13.3	22.6±0.5	6.8±1.1
	2+TP	277.7±21.5	38.0±9.2	95.6±21.2	113.3±11.9	24.6±2.3	7.1±0.8
	10+TP	271.7±5.5*	36.3±3.8	92.5±20.4	119.9±10.8	25.2±1.3**	7.3±1.1
	50+TP	260.9±12.3**	36.7±5.5	94.3±12.5	115.9±17.7	25.8±2.1*	7.4±0.6
	Flutamide+TP	284.1±14.2	6.4±1.0**	11.5±1.7**	54.0±4.2**	12.3±2.0**	1.6±0.3**
Benzophenone derivatives							
4,4′-Dihydroxy benzophenone	Vehicle control	277.9±14.5	5.0±0.9	15.0±3.3	57.0±6.7	13.2±1.3	2.2±0.7
	50	280.0±12.8	6.4±0.7*	13.2±1.7	51.0±10.3	11.5±2.0	1.6±0.6
	200	264.4±15.5	6.3±1.0	14.2±2.9	43.7±5.7**	13.3±2.2	1.9±0.5

Table 5 (*Continued*)

Chemicals	Doses (mg/kg per day)	Body weight (g)	Ventral prostate (mg/100 g bw)	Seminal vesicle (mg/100 g bw)	BC/LA (mg/100 g bw)	Glans penis (mg/100 g bw)	Cowper's gland (mg/100 g bw)
	600	265.3±12.7	5.5±0.8	13.6±3.1	49.5±9.9	12.1±2.6	1.6±0.7
	Vehicle+TP	287.8±13.5	35.8±2.1	74.0±9.6	113.5±7.2	22.6±1.0	6.1±2.0
	50+TP	284.6±19.3	38.1±6.3	68.4±6.8	117.1±6.1	22.5±1.7	7.4±0.8
	200+TP	276.0±10.1	27.8±3.1**	72.7±16.9	98.3±10.3*	21.8±2.1	6.1±1.3
	600+TP	268.6±14.2*	32.2±4.8	77.7±18.3	116.3±12.6	24.7±0.6**	6.9±1.7
	Flutamide+TP	281.2±16.3	6.7±1.4**	13.4±1.9**	55.4±4.7**	12.0±1.6**	1.8±0.4**
2,2′,4,4′-Tetrahydroxy benzophenone	Vehicle control	283.5±15.0	5.2±0.9	15.0±1.5	55.2±10.6	10.9±2.5	1.7±0.2
	50	281.6±11.9	6.1±0.6	15.0±1.8	56.9±4.7	12.5±1.6	1.4±0.4
	200	255.7±19.2*	5.9±1.1	16.8±2.3	54.3±7.6	13.6±2.3	2.1±0.5
	600(400)[a]	258.6±6.4**	5.2±0.7	14.4±3.9	50.9±3.1	11.9±3.8	1.6±0.2
	Vehicle+TP	290.8±10.4	36.5±5.3	76.6±12.9	119.9±14.9	22.9±2.1	7.5±2.3
	50+TP	289.9±13.2	40.8±4.5	81.0±7.2	127.1±13.7	23.5±2.1	8.4±1.2
	200+TP	286.1±13.5	40.2±4.4	77.7±14.0	108.5±12.5	22.8±1.9	7.7±1.1
	600(400)+TP	272.7±11.9*	36.3±5.8	81.4±9.9	112.5±9.5	24.4±1.5	7.4±0.6
	Flutamide+TP	290.6±11.8	6.1±0.8**	15.1±1.8**	54.6±6.5**	11.8±1.8**	1.7±0.3**
4-Hydroxy benzophenone	Vehicle control	280.7±11.7	6.1±0.4	10.3±2.7	53.9±11.9	9.5±2.8	1.2±0.3
	50	280.5±15.0	5.3±0.8*	11.0±3.1	50.9±10.7	10.5±2.0	1.1±0.7
	200	278.6±13.9	6.1±0.9	13.1±3.4	51.6±5.7	11.6±1.4	1.4±0.4
	600	275.1±9.4	5.2±0.5**	12.3±2.8	45.4±6.8	10.3±2.3	1.6±0.8
	Vehicle+TP	281.7±15.2	31.8±5.9	70.7±13.0	116.9±14.3	22.4±1.4	7.0±1.3
	50+TP	288.7±9.8	33.9±4.6	75.9±9.0	112.6±11.8	22.1±1.9	6.1±1.2
	200+TP	284.5±16.1	34.1±4.6	77.0±17.0	117.1±11.9	23.1±1.6	6.1±1.5
	600+TP	282.3±13.7	36.1±7.3	77.5±22.4	117.2±7.5	23.3±0.6	8.0±2.2
	Flutamide+TP	282.1±12.2	6.7±0.7**	13.4±2.9**	52.1±10.6**	13.0±2.0**	1.1±0.4**
Benzophenone derivatives							
2,4,4′-Trihydroxy benzophenone	Vehicle control	279.2±8.1	5.9±0.8	12.2±1.9	52.3±6.7	12.6±1.1	1.4±0.3
	50	282.0±14.6	6.0±0.8	11.5±1.6	49.7±6.3	11.4±1.6	1.4±0.4
	200	264.4±17.5	5.8±0.8	12.0±2.7	51.0±6.4	12.9±1.3	1.5±0.4
	600	256.1±15.7**	6.0±0.9	13.7±2.4	48.5±7.5	13.2±2.0	1.5±0.6
	Vehicle+TP	288.5±21.1	34.5±6.0	84.4±16.7	119.0±15.0	23.6±1.8	7.3±1.6
	50+TP	284.3±11.3	35.6±5.7	84.9±10.9	116.1±10.6	22.9±2.5	6.6±1.4
	200+TP	274.7±13.0	36.3±5.5	90.7±19.6	121.1±13.3	24.6±1.9	7.0±0.8
	600+TP	273.7±11.1	32.0±6.8	75.2±18.0	119.0±12.8	23.0±1.7	7.0±1.6
	Flutamide+TP	287.1±16.2	6.4±0.8**	11.3±1.7**	51.8±10.2**	10.2±2.4**	1.5±0.6**
Androgen derivatives							
Testosterone enanthate	Vehicle control	275.7±7.4	6.4±1.1	13.9±3.0	49.2±6.4	12.0±1.1	1.6±0.3
	50	279.6±14.8	14.5±2.5**	23.9±6.7**	78.8±9.0**	15.5±2.6*	3.2±1.2*
	200	278.8±9.1	27.6±6.3**	48.3±7.8**	124.9±24.0**	22.6±2.8**	7.1±2.0**
	600	270.4±9.4	39.0±4.8**	131.9±34.9**	143.5±10.5**	25.5±1.2**	10.5±1.8**
	Vehicle+TP	285.6±14.7	35.2±4.0	73.9±10.0	111.1±19.5	23.4±1.3	6.6±1.4

Table 5 (*Continued*)

Chemicals	Doses (mg/kg per day)	Body weight (g)	Ventral prostate (mg/100 g bw)	Seminal vesicle (mg/100 g bw)	BC/LA (mg/100 g bw)	Glans penis (mg/100 g bw)	Cowper's gland (mg/100 g bw)
	50+TP	285.6±9.6	42.4±6.5*	98.2±15.7**	130.0±19.9	24.4±1.9	8.1±1.2
	200+TP	282.3±11.5	48.2±7.9**	125.3±24.4**	139.9±8.1*	24.6±1.9	9.4±1.8*
	600+TP	273.9±14.1	53.9±8.3**	176.3±35.1**	154.2±18.0**	27.9±1.4**	10.9±1.5**
	Flutamide+TP	274.5±6.0	6.5±0.9**	14.0±2.8**	50.9±6.7**	12.6±2.1**	2.2±0.7**
Methyltestosterone	Vehicle control	287.3±12.5	6.0±0.5	11.9±2.2	46.1±9.5	10.3±2.6	1.0±0.2
	0.5	283.2±7.4	8.0±0.9**	14.4±1.7*	53.9±5.1	11.8±2.3	2.0±0.2**
	5	284.4±7.9	15.7±3.1**	19.0±3.2**	54.4±7.3	13.8±1.8*	1.6±0.4**
	50	278.5±15.4	48.5±7.6**	100.0±25.4**	135.6±5.9**	25.3±2.2**	8.6±1.1**
	Vehicle+TP	294.1±9.0	37.0±4.8	78.7±5.1	111.0±13.6	23.5±1.5	7.7±0.5
	0.5+TP	293.7±12.0	38.9±3.5	86.2±16.9	117.3±9.0	24.0±1.8	6.9±1.5
	5+TP	292.3±13.0	42.8±6.0	100.5±23.2	125.4±15.0	24.4±2.7	9.4±2.0
	50+TP	287.8±9.5	59.7±10.3**	173.7±64.9*	150.3±14.4**	27.0±1.7**	11.4±1.4**
	Flutamide+TP	283.8±16.7	7.2±1.9**	13.1±2.1**	48.7±3.2**	11.9±0.6**	1.6±0.7**
Steroids							
17Alpha estradiol	Vehicle control	272.1±10.2	5.9±0.7	11.0±2.3	54.4±8.0	12.7±1.2	1.5±0.5
	0.5	265.1±18.1	5.7±1.0	11.1±1.5	56.0±4.3	13.1±2.2	1.6±0.6
	2	270.6±10.9	6.7±1.0	11.5±1.9	54.9±6.9	11.9±0.7	1.6±0.9
	10	254.0±28.3	5.7±0.7	11.1±2.4	52.3±5.3	12.5±3.4	1.4±0.6
	Vehicle+TP	286.2±11.7	38.9±5.2	77.6±8.9	126.4±5.7	24.5±2.5	7.6±1.4
	0.5+TP	287.8±21.2	40.6±5.0	78.9±20.8	125.4±16.9	23.6±2.8	7.7±1.0
	2+TP	267.7±11.0*	43.0±6.0	93.5±21.5	129.1±12.0	25.3±1.7	9.0±1.3
	10+TP	266.6±12.7*	38.7±3.8	90.0±14.7	123.4±10.0	25.3±1.2	8.1±1.3
	Flutamide+TP	280.6±20.3	7.1±1.3**	10.3±1.1**	56.4±6.4**	12.3±2.0**	1.3±0.4**
Estrone	Vehicle control	283.8±12.3	5.9±0.6	12.2±0.6	49.1±4.6	12.1±1.3	1.6±0.3
	0.5	271.4±13.2	6.7±1.0	13.3±2.1	55.8±10.6	13.2±1.9	1.8±0.7
	2	261.8±19.8*	6.0±0.8	13.6±1.9	50.5±2.1	13.0±1.5	1.5±0.6
	10(6)[a]	242.9±10.0**	6.6±0.4*	16.8±2.7**	48.5±7.3	13.6±3.6	2.1±0.6
	Vehicle+TP	285.7±15.3	30.0±5.9	62.0±9.2	109.0±14.7	22.1±1.5	6.3±1.3
	0.5+TP	283.1±9.3	33.3±5.3	76.0±9.7*	115.1±9.5	22.4±1.8	6.4±0.7
	2+TP	270.4±16.8	32.4±4.4	95.7±11.9**	121.6±3.2	25.1±1.3**	7.9±1.7
	10(6)+TP	243.4±13.3**	34.0±3.5	108.0±12.2**	113.7±7.5	26.8±2.6**	7.0±0.8
	Flutamide+TP	284.2±12.0	6.7±1.2**	12.0±2.4**	51.0±7.7**	12.4±2.6**	1.3±0.2**
Equilin	Vehicle control	286.2±12.3	5.4±0.8	12.1±1.6	51.6±9.8	11.8±1.7	1.4±0.4
	0.5	258.4±18.3*	5.8±0.5	13.5±2.5	51.5±7.0	13.6±1.8	1.3±0.5
	2	241.3±8.5**	6.6±0.8*	17.1±1.2**	50.9±3.3	14.2±1.2*	1.7±0.7
	10(6)	225.0±11.0*	6.5±0.5*	19.2±2.9**	50.3±7.8	14.6±0.6**	1.6±0.5
	Vehicle+TP	294.0±19.6	35.0±7.7	72.4±12.0	112.7±17.0	22.9±1.3	6.4±0.7
	0.5+TP	260.7±13.6**	33.6±8.1	96.5±20.1*	123.2±15.2	25.1±2.1	7.9±1.4*
	2+TP	251.4±9.5**	36.4±3.4	98.8±19.7*	123.7±14.6	24.8±2.3	8.2±0.9**
	10(6)+TP	237.8±12.4**	32.2±6.5	109.2±19.6**	117.8±8.7	26.5±2.0**	7.8±0.9*

Table 5 (*Continued*)

Chemicals	Doses (mg/kg per day)	Body weight (g)	Ventral prostate (mg/100 g bw)	Seminal vesicle (mg/100 g bw)	BC/LA (mg/100 g bw)	Glans penis (mg/100 g bw)	Cowper's gland (mg/100 g bw)
	Flutamide+TP	285.7±17.8	5.9±1.0**	12.9±2.7**	47.7±5.9**	12.2±1.1**	1.4±0.7**
Steroids							
Norethindrone	Vehicle control	280.8±6.6	5.2±1.1	9.9±0.6	48.2±5.8	10.3±1.0	1.3±0.4
	0.5	279.5±15.2	5.5±1.5	10.6±2.1	50.6±3.2	11.4±1.9	1.5±0.2
	2	278.7±7.1	5.2±0.9	10.8±2.3	50.3±7.5	10.4±2.1	1.4±0.2
	10	255.7±7.5**	5.3±0.9	10.4±1.7	47.9±3.2	11.1±1.3	1.4±0.4
	Vehicle+TP	293.2±10.9	29.6±4.0	56.9±13.1	105.3±14.9	22.7±2.0	5.8±1.4
	0.5+TP	287.3±10.0	31.0±3.6	57.1±5.3	113.8±10.2	22.4±1.4	5.8±0.9
	2+TP	284.3±11.1	33.2±2.9	71.9±15.7	110.8±6.8	23.9±1.6	5.8±1.3
	10+TP	263.8±11.1**	31.5±4.3	76.7±7.4	120.7±11.6	25.7±1.6*	7.6±1.6
	Flutamide+TP	283.1±8.2	7.1±1.2**	11.8±1.8**	57.6±8.6**	12.9±1.5**	1.3±0.3**
Norgestrel	Vehicle control	276.8±9.5	6.0±0.8	10.3±2.0	48.5±3.6	10.7±1.9	1.5±0.4
	10	275.6±12.5	6.8±1.9	11.2±1.3	56.4±8.2	12.3±1.3	1.4±0.4
	30	267.1±11.7	11.4±3.3**	14.9±2.5**	67.6±17.5*	13.7±3.2	1.7±0.4
	100	262.4±9.9*	20.9±9.9*	35.3±13.9**	94.3±22.3**	17.8±2.6**	2.7±1.8
	Vehicle+TP	286.3±17.0	33.9±3.8	85.9±16.5	121.9±15.8	23.5±0.9	6.9±1.3
	10+TP	285.0±6.2	33.8±5.8	76.2±18.6	112.3±13.9	22.1±2.4	7.0±1.3
	30+TP	279.5±18.7	32.0±3.8	83.9±27.3	133.6±20.4	24.8±3.4	7.6±1.5
	100+TP	259.6±13.7*	45.3±8.9*	117.4±28.5*	151.9±18.0*	26.5±1.9**	8.6±1.6
	Flutamide+TP	285.5±11.5	6.3±0.9**	10.3±1.3**	52.7±6.7**	11.5±1.9**	1.2±0.3**
Ethynyl estradiol	Vehicle control	278.0±18.1	4.9±1.2	10.7±1.2	48.7±6.5	10.5±0.9	1.5±0.7
	10	270.6±11.8	5.7±0.9	10.8±2.5	48.8±6.2	10.7±1.7	1.5±0.3
	50	255.4±14.0*	6.2±0.7*	12.6±1.7*	50.8±4.1	12.6±1.9*	1.5±0.2
	200	245.6±8.7**	5.7±0.7	12.7±1.9	44.0±3.0	12.6±1.1**	1.3±0.2
	Vehicle+TP	283.2±10.0	34.5±4.4	80.9±14.1	118.9±6.0	23.7±1.2	7.5±1.2
	10+TP	282.6±13.7	35.1±6.5	80.3±12.3	124.9±14.6	24.2±1.8	6.6±1.2
	50+TP	266.6±15.9	39.0±4.6	107.4±9.8**	129.1±10.0	25.4±1.7	7.5±1.4
	200+TP	259.8±14.7**	35.0±7.5	108.6±18.2*	125.2±11.8	26.2±2.2*	8.8±1.5
	Flutamide+TP	279.1±15.2	6.8±1.3**	10.2±0.9**	50.9±8.7**	10.5±1.9**	1.5±0.4**
Alkyl phenol							
Bisphenol A	Vehicle control	280.8±10.1	5.5±1.0	10.8±1.9	52.3±7.1	10.6±1.1	1.2±0.2
	50	280.2±13.5	5.4±1.0	12.0±2.6	46.1±6.1	11.6±2.0	1.1±0.4
	200	273.3±12.6	5.8±1.0	12.3±2.2	51.6±2.4	12.1±2.0	1.1±0.3
	600	272.8±13.9	5.9±1.0	12.8±1.6	53.0±9.1	13.1±1.1**	1.3±0.3
	Vehicle+TP	285.1±14.7	39.2±8.5	84.0±7.5	113.6±10.3	23.9±0.7	7.0±1.5
	50+TP	286.5±13.4	40.0±7.5	74.0±12.1	121.0±15.1	24.1±1.2	6.9±0.7
	200+TP	280.9±9.9	33.6±4.5	84.4±17.5	121.5±14.0	24.2±2.3	7.9±2.1
	600+TP	271.1±13.6	39.8±3.0	91.0±14.8	119.1±10.4	24.7±1.3	8.3±1.6
	Flutamide+TP	280.8±12.6	6.7±1.1**	12.6±2.6**	57.5±8.8**	11.9±1.9**	1.4±0.2**
Bisphenol B	Vehicle control	274.4±14.6	5.5±0.9	11.2±1.7	58.6±3.2	11.6±2.4	1.5±0.5

Table 5 (*Continued*)

Chemicals	Doses (mg/kg per day)	Body weight (g)	Ventral prostate (mg/100 g bw)	Seminal vesicle (mg/100 g bw)	BC/LA (mg/100 g bw)	Glans penis (mg/100 g bw)	Cowper's gland (mg/100 g bw)
	50	263.2±9.2	5.7±0.5	10.8±1.9	48.8±9.5	11.0±1.9	1.2±0.2
	200	260.1±9.4	6.1±0.8	12.9±1.3	47.8±8.0*	13.4±2.9	1.6±0.2
	600	251.6±7.6**	6.1±0.8	12.4±2.3	47.8±9.8*	12.5±2.1	1.3±0.3
	Vehicle+TP	281.1±12.7	29.2±3.7	72.2±20.3	112.1±11.1	23.3±2.2	6.8±0.9
	50+TP	273.8±12.8	30.4±5.6	68.8±19.8	109.6±9.0	22.5±2.4	6.9±1.1
	200+TP	270.5±10.4	35.3±3.8*	72.6±14.4	116.7±13.5	22.6±2.8	7.2±1.9
	600+TP	259.3±18.2*	45.6±5.6**	113.4±13.5**	142.8±17.0**	26.3±1.9*	8.7±1.4*
	Flutamide+TP	278.9±9.3	6.4±1.1**	13.7±4.8**	55.8±5.7**	12.5±2.3**	1.6±0.8**
Bisphenol F	Vehicle control	273.3±9.8	5.2±0.9	9.7±0.8	47.3±3.8	10.7±2.0	1.2±0.3
	50	268.5±10.1	5.2±1.3	10.9±1.1	47.7±7.9	11.8±1.5	1.2±0.3
	200	265.5±9.9	4.7±1.6	10.6±1.8	48.2±6.7	11.0±2.5	1.3±0.5
	1000	253.2±12.4*	5.7±0.4	10.7±1.3	47.9±4.6	10.9±2.4	1.4±0.3
	Vehicle+TP	282.1±13.1	31.3±6.4	75.9±21.1	115.3±19.6	23.2±1.8	5.8±1.4
	50+TP	276.9±8.2	33.6±4.7	76.7±22.4	105.3±19.2	23.6±1.1	6.9±0.9
	200+TP	266.0±11.2*	35.9±7.3	81.2±13.1	123.7±7.0	24.9±1.2	8.0±1.2*
	1000+TP	263.3±11.5*	34.9±4.8	85.9±23.1	114.6±14.5	23.2±2.8	7.6±2.3
	Flutamide+TP	282.2±7.9	6.4±0.9**	10.1±1.1**	51.4±9.8**	11.0±1.6**	1.1±0.3**
Alkyl phenol							
4-Tert-octylphenol	Vehicle control	281.9±7.9	5.2±0.7	10.2±1.2	50.0±5.4	11.6±1.3	1.2±0.4
	50	278.7±9.5	5.9±0.9	11.6±0.7*	50.8±6.7	12.8±1.4	2.1±1.1
	200	256.7±15.3**	5.8±0.9	10.4±1.9	49.4±7.8	12.3±2.1	1.7±0.4
	600(400)[a]	–	–	–	–	–	–
	Vehicle+TP	285.0±14.4	36.4±4.6	76.9±18.3	113.5±12.9	24.0±2.6	6.8±0.9
	50+TP	281.5±13.0	36.2±6.2	83.5±13.8	106.0±9.3	23.2±0.8	6.2±1.2
	200+TP	277.6±18.7	42.9±5.7	93.3±19.5	119.6±6.2	24.9±1.0	8.2±1.1*
	600(400)+TP	–	–	–	–	–	–
	Flutamide+TP	283.1±7.5	6.7±0.9**	10.8±1.7**	50.2±4.2**	11.3±2.6**	1.3±0.3**
p-Cumyl phenol	Vehicle control	279.9±17.4	5.7±1.2	10.5±2.8	56.3±6.8	11.1±2.3	1.5±0.7
	50	275.8±11.3	4.8±0.8	10.1±2.1	55.1±8.6	11.8±2.6	1.5±0.5
	200	274.8±14.3	6.0±0.4	10.5±2.1	51.8±6.5	12.0±2.4	1.5±0.4
	600	254.6±6.9*	5.7±1.2	12.4±2.6	51.6±4.8	12.9±3.0	1.4±0.4
	Vehicle+TP	287.1±7.9	33.9±7.2	71.7±12.0	116.6±12.4	23.1±1.5	6.9±0.9
	50+TP	289.0±14.6	36.6±7.9	67.6±16.8	109.8±8.4	22.5±0.4	6.5±1.0
	200+TP	286.5±11.7	35.7±2.2	79.7±15.9	122.0±13.6	23.6±2.2	5.7±1.5
	600+TP	271.5±13.8*	34.1±6.4	80.7±10.3	123.9±8.5	24.1±2.1	7.9±1.9
	Flutamide+TP	281.5±11.9	6.5±1.2**	10.2±1.9**	50.7±6.3**	11.4±2.4**	1.5±0.3**
Nonylphenol	Vehicle control	285.3±17.3	5.0±0.8	10.0±1.7	54.3±7.1	11.4±2.6	1.4±0.2
	10	279.8±16.8	5.4±0.3	10.3±1.0	49.0±6.2	10.8±1.2	1.1±0.4
	50	282.9±13.1	5.7±1.1	10.1±1.3	50.1±8.3	11.2±2.0	1.5±0.4
	200	251.4±23.6*	5.8±0.9	11.1±1.4	56.6±9.1	13.8±1.9	1.7±0.5

Table 5 (*Continued*)

Chemicals	Doses (mg/kg per day)	Body weight (g)	Ventral prostate (mg/100 g bw)	Seminal vesicle (mg/100 g bw)	BC/LA (mg/100 g bw)	Glans penis (mg/100 g bw)	Cowper's gland (mg/100 g bw)
	Vehicle+TP	288.8±18.4	35.9±3.2	91.2±12.5	117.2±8.2	23.5±1.1	7.0±1.0
	10+TP	290.1±7.3	34.1±7.2	78.1±19.8	119.9±14.1	23.8±0.7	6.9±1.0
	50+TP	287.9±14.4	40.0±6.0	85.6±19.9	123.4±16.4	24.7±2.2	7.1±1.6
	200+TP	270.9±22.5	37.4±5.6	76.6±9.4*	117.0±9.1	24.5±1.3	8.0±1.1
	Flutamide+TP	288.2±14.8	6.5±0.6**	10.2±1.2**	52.3±6.6**	11.7±1.8**	1.4±0.3**

[a] Numbers in parenthesis are reduced dose because toxic signs were observed during the study.
* Significantly different from vehicle control or vehicle plus TP at $P < 0.05$.
** Significantly different from vehicle control or vehicle plus TP at $P < 0.01$.
–, no data because animals died during the study.

contain estrogen receptors, which may mediate the weight changes observed in the rats given these chemicals. The seminal vesicle weight in rats given diphenyl-p-phenylenediamine and the glans penis weight in rats given 4,4′-(hexafluoroisopropylidene)diphenol, EE, and bisphenol A increased in the high-dose group and the middle- and high-dose groups, respectively. However, the control values for these organs in all of the studies varied considerably, and some of the accessory sex organ weight values for the groups tested with these chemicals are within the control ranges. Therefore, whether these chemicals exhibit an androgen agonistic property could not be determined. On the other hand, the seminal vesicle weight in rats given nonylphenol decreased in the high-dose plus TP group, but an apparent dose dependency was not observed. Furthermore, the seminal vesicle weight in this group was within the control ranges of other studies. Thus, nonylphenol was also not classified as an androgen antagonistic chemical. Further supportive data using in vitro assays are needed to determine the androgen agonistic or antagonistic effects of the chemicals examined in the Hershberger assay.

We did not classify chemicals as having an androgen agonistic effect or as inhibitors of the agonistic effect of TP if the organ weight of rats given the chemical increased without any clear dose-dependent relationship or if the organ weight of rats given the chemical decreased but did not decrease in rats given the chemical plus TP. On the other hand, the organ weights of rats given a particular chemical plus TP increased, but the same change was not clearly observed in rats given only chemical alone. This phenomenon is very interesting and suggests that the administration of these chemicals increases the availability or increases the action of TP.

Some chemicals have been found to have both estrogenic and androgenic effects in in vivo or in vitro assays (Cupp and Skinner, 2001; Re et al., 2001; Waters et al., 2002; Raun Andersen et al., 2002). Morphological testicular changes were detected in toxicological studies of estrogen agonistic compounds, such as EE or diethylstilbestrol (Atanassova et al., 1999; Yamasaki et al., 2002a), and the testicular changes and weight changes of

male accessory sex organs are thought to be attributable to increased secretion of FSH by the hypophysis following administration of estrogenic compounds for long periods (Atanassova et al., 1999). On the other hand, a decrease in ovary weight, increase in number of immature follicles in the ovaries, and increase in mammary gland secretion were detected in a repeated-dose oral toxicity study of the androgenic compound methyltestosterone (Okazaki et al., 2001). In the present study, uterotrophy by the androgen derivatives testosterone enanthate and methyltestosterone and increased accessory organ weights by estrogenic compounds equilin, norgestrel and estrone were detected. Estrogen and androgen receptors are said to be present in the accessory sex organs of male rats and mice (Re et al., 2001; Weihua et al., 2001; Williams et al., 2001), and specific androgen receptors have been demonstrated in the uterus of rats and mice (Beri et al., 1998). In our reporter gene assay, the PC10 values for ER-alpha of testosterone enanthate and methyltestosterone were 17 140 and 173 235, respectively, compared with values for EE and bisphenol A of <30 and 602 983 (Yamasaki et al., 2002b), respectively. Thus, the affinity for estrogen receptor alpha of testosterone enanthate and methyltestosterone in the reporter gene assay was higher than that of bisphenol A. The uterotrophy induced by androgen derivatives in the uterotrophic assay and increase in male accessory sex organ weights by estrogen compounds in the Hershberger assay may be receptor-mediated changes. Further studies using the receptor binding assays and reporter gene assays for androgen receptors as well as an aromatase assay are needed.

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