

Table 5

Two generation reproductive toxicity study of NP by oral administration in rats
 Organ weight of F0 males; Mean \pm S.D. (N)

Compound	Dose (mg/kg)	Nonylphenol					
		0 ^a	2	10	50	0 ^a	2
Terminal body weight (g)	586.9 \pm 60.4 (35)	620.1 \pm 56.6 (25)	574.7 \pm 64.6 (25)	551.0 \pm 68.5 (25)			
Brain (g)	2.03 \pm 0.08 b (35) 0.35 \pm 0.04 c (35)	2.01 \pm 0.07 (25) 0.33 \pm 0.03 * (25)	2.01 \pm 0.09 (25) 0.35 \pm 0.04 (25)	2.06 \pm 0.08 (25) 0.38 \pm 0.04 * (25)			
Heart (g)	1.43 \pm 0.16 (35) 0.25 \pm 0.02 (35)	1.53 \pm 0.11 * (25) 0.25 \pm 0.02 (25)	1.38 \pm 0.13 (25) 0.24 \pm 0.02 (25)	1.39 \pm 0.16 (25) 0.25 \pm 0.02 (25)			
Lung (g)	1.37 \pm 0.13 (35) 0.24 \pm 0.02 (35)	1.41 \pm 0.11 (25) 0.23 \pm 0.02 (25)	1.34 \pm 0.09 (25) 0.23 \pm 0.02 (25)	1.37 \pm 0.11 (25) 0.25 \pm 0.02 * (25)			
Liver (g)	18.45 \pm 2.64 (35) 3.13 \pm 0.20 (35)	19.86 \pm 2.53 (25) 3.20 \pm 0.23 (25)	18.77 \pm 2.85 (25) 3.26 \pm 0.22 (25)	19.13 \pm 2.80 (25) 3.47 \pm 0.19 ** (25)			
Spleen (g)	0.84 \pm 0.14 (35) 0.14 \pm 0.02 (35)	0.90 \pm 0.07 (25) 0.15 \pm 0.01 (25)	0.84 \pm 0.14 (25) 0.15 \pm 0.02 (25)	0.84 \pm 0.17 (25) 0.15 \pm 0.02 (25)			
Kidney (g)	3.17 \pm 0.32 (35) 0.54 \pm 0.04 (35)	3.30 \pm 0.29 (25) 0.53 \pm 0.04 (25)	3.21 \pm 0.32 (25) 0.56 \pm 0.04 (25)	3.57 \pm 0.35 ** (25) 0.65 \pm 0.05 ** (25)			
Adrenal glands (mg)	46.8 \pm 6.2 (35) 8.0 \pm 1.0 (35)	53.8 \pm 7.3 ** (25) 8.7 \pm 0.9 (25)	45.2 \pm 7.6 (25) 7.9 \pm 1.2 (25)	46.6 \pm 6.8 (24) 8.6 \pm 1.2 (24)			
Thymus (mg)	216.5 \pm 53.8 (35) 36.9 \pm 8.2 (35)	209.2 \pm 54.5 (25) 33.7 \pm 8.1 (25)	202.1 \pm 55.0 (25) 35.6 \pm 10.6 (25)	165.2 \pm 45.4 ** (25) 30.0 \pm 7.2 ** (25)			

a: vehicle control, corn oil (2 mL/kg)

b: absolute weight

c: relative weight (g or mg per 100g body weight)

*: significant difference from control, P<0.05

**: significant difference from control, P<0.01

Table 5 (continued)

Two generation reproductive toxicity study of NP by oral administration in rats
 Organ weight of F₀ males; Mean ± S.D. (N)

Compound	Dose (mg/kg)	Nonylphenol					
		0 ^a	2	10	50	50	(25)
Terminal body weight (g)	586.9 ± 60.4 (35)	620.1 ± 56.6 (25)	574.7 ± 64.6 (25)	551.0 ± 68.5 (25)			
Testes (g)	3.31 ± 0.47 b (35)	3.43 ± 0.30 (25)	3.33 ± 0.32 (25)	3.32 ± 0.35 (25)			
	0.57 ± 0.09 c (35)	0.60 ± 0.10 (25)	0.60 ± 0.10 (25)	0.60 ± 0.10 (25)			
Epididymides (g)	1.27 ± 0.17 (35)	1.36 ± 0.08 * (25)	1.29 ± 0.11 (25)	1.30 ± 0.13 (25)			
	0.22 ± 0.03 (35)	0.22 ± 0.02 (25)	0.23 ± 0.02 (25)	0.24 ± 0.03 (25)			
Ventral prostate (g)	0.61 ± 0.16 (35)	0.65 ± 0.16 (25)	0.63 ± 0.11 (25)	0.65 ± 0.12 (25)			
	0.11 ± 0.03 (35)	0.11 ± 0.03 (25)	0.11 ± 0.02 (25)	0.12 ± 0.03 (25)			
Seminal vesicle (g)	1.83 ± 0.34 (35)	1.92 ± 0.21 (25)	1.96 ± 0.31 (25)	1.89 ± 0.33 (24)			
	0.31 ± 0.06 (35)	0.31 ± 0.04 (25)	0.35 ± 0.07 (25)	0.35 ± 0.07 (24)			
Prostate + seminal vesicle (g)	2.94 ± 0.44 (35)	3.09 ± 0.36 (25)	3.07 ± 0.38 (25)	3.07 ± 0.38 (25)			
	0.50 ± 0.09 (35)	0.50 ± 0.08 (25)	0.54 ± 0.09 (25)	0.56 ± 0.11 ** (25)			
Thyroid gland (mg)	18.4 ± 3.3 (35)	21.6 ± 4.3 * (25)	17.0 ± 3.8 (25)	20.1 ± 5.5 (25)			
	3.1 ± 0.6 (35)	3.5 ± 0.7 (25)	3.0 ± 0.8 (25)	3.6 ± 0.8 * (25)			
Pituitary gland (mg)	10.6 ± 1.5 (35)	11.6 ± 1.6 (25)	11.3 ± 2.3 (25)	11.9 ± 1.7 (25)			
	1.8 ± 0.3 (35)	1.9 ± 0.3 (25)	2.0 ± 0.4 (25)	2.2 ± 0.3 ** (25)			

a: vehicle control, corn oil (2 mL/kg)

b: absolute weight

c: relative weight (g or mg per 100g body weight)

*: significant difference from control, p<0.05

**: significant difference from control, p<0.01

Table 6

Two generation reproductive toxicity study of NP by oral administration in rats
Epididymal sperm findings in F₀ males

Compound	Nonylphenol			
Dose (mg/kg)	0 ^a	2	10	50
Number of F ₀ males examined	34	25	25	25
% of motile (Mean ± S.D.)	94 ± 4	97 ± 3	94 ± 5	95 ± 4
% of progressive (Mean ± S.D.)	80 ± 6	85 ± 6	82 ± 7	82 ± 6
Sperm counts (Mean ± S.D.)	0.3022 ± 0.037	0.3331 ± 0.032	0.3034 ± 0.032	0.3058 ± 0.035
Caudal epididymis weight				
No. of sperm per caudal epididymis ($\times 10^6$)	681 ± 184	650 ± 192	746 ± 239	732 ± 168
No. of sperm per caudal epididymis weight ($\times 10^6/\text{g}$)	2270.9 ± 627.0	1957.9 ± 563.4	2483.8 ± 833.2	2416.2 ± 586.5

a: vehicle control, corn oil (2 mL/kg)

Table 6 (continued)

Two generation reproductive toxicity study of NP by oral administration in rats
Epididymal sperm findings in F₀ males

Compound	Nonylphenol
Dose (mg/kg)	250 ^a
Number of F ₀ males examined	18
% of motile (Mean ± S.D.)	91 ± 7
% of progressive (Mean ± S.D.)	74 ± 7
sperm counts (Mean ± S.D.)	0.1803 ± 0.038
Caudal epididymis weight	
No. of sperm per caudal epididymis ($\times 10^6$)	492 ± 127
No. of sperm per caudal epididymis weight ($\times 10^6/g$)	2802 ± 826

^a: necropsied on 13 or 14 weeks of age
Data in the 250 mg/kg group was excluded from statistical evaluation.

Table 7

Two generation reproductive toxicity study of NP by oral administration in rats

Serum concentrations of testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid stimulating hormone (TSH), triiodothyronine (T₃), thyroxine (T₄) in F₀ males; Mean±S.D. (N)

Compound	Nonylphenol				
	Dose (mg/kg)	0 ^a	2	10	50
Testosterone (ng/mL)	4.1 ± 2.3	(35)	6.3 ± 4.1 *	(25)	4.2 ± 2.5
LH (ng/mL)	12.6 ± 4.7	(35)	14.1 ± 3.0	(25)	12.5 ± 3.1
FSH (ng/mL)	186.9 ± 57.9	(35)	177.5 ± 66.5	(25)	198.1 ± 45.8
TSH (ng/mL)	11.8 ± 2.0	(35)	12.7 ± 2.0	(25)	13.0 ± 2.1
T ₃ (ng/mL)	1.0 ± 0.2	(35)	0.8 ± 0.1 **	(24)	1.0 ± 0.1
T ₄ (ng/mL)	75.1 ± 10.9	(35)	68.5 ± 9.1 *	(25)	72.4 ± 7.8

^a : vehicle control, corn oil (2 mL/kg)

* : significant difference from control, p<0.05

**: significant difference from control, p<0.01

(25) 4.0 ± 2.1 (25)

(25) 11.4 ± 3.8 (25)

(25) 201.3 ± 50.9 (25)

(25) 14.3 ± 2.3 ** (25)

Table 7 (continued)

Two generation reproductive toxicity study of NP by oral administration in rats
 serum concentrations of testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH),
 thyroid stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4) in F0 males; Mean \pm S.D. (N)

Compound	Nonylphenol		
Dose (mg/kg)	250		
Testosterone (ng/mL)	1.9 \pm 1.2	(23)	
LH (ng/mL)	17.2 \pm 7.3	(23)	
FSH (ng/mL)	306.3 \pm 91.5	(23)	
TSH (ng/mL)	21.3 \pm 4.6	(23)	
T3 (ng/mL)	1.4 \pm 0.2	(22)	
T4 (ng/mL)	72.9 \pm 24.0	(23)	

Data in the 250 mg/kg group was excluded from statistical evaluation.

Table 8 - 1
Two generation reproductive toxicity study of NP by oral administration in rats
Macroscopic findings in Fo males

Group	Grade	0 mg/kg		2 mg/kg		10 mg/kg		50 mg/kg	
		-	+	-	+	-	+	-	+
(Kidney)	Rough surface	[35]	35	0	[25]	25	0	[25]	25
	Enlargement		35	0		25	0		25
	Pale		35	0		25	0		25
	Dark		35	0		25	0		25
	Edematous/Soft		35	0		25	0		25
	Whitish cloudy, papilla		35	0		25	0		25
(Liver)	Cyst, cortex		35	0		25	0		25
	Dilatation, renal pelvis	[35]	34	1	[25]	25	0	[25]	25
	Dark		35	0		25	0		25
	Indistinct lobular pattern		35	0		25	0		25
(Thymus)	Diaphragmatic nodule	[35]	31	4	[25]	24	1	[25]	25
	Small	[35]	35	0	[25]	25	0	[25]	25
(Thyroid gland)	Enlargement	[35]	35	0	[25]	25	0	[25]	25
(Stomach)	Recessed area/nodule, mucosa, forestomach	[35]	34	1	[25]	24	1	[25]	25
(Testis)	Small	[35]	34	1	[25]	25	0	[25]	25
	(Epididymis)	[35]	34	1	[25]	25	0	[25]	25
(Prostate)	Small		35	0	[25]	25	0	[25]	25
	Nodule, yellowish white	[35]	34	1	[25]	25	0	[25]	25
	Small								

-, Negative; +, Positive

[], Number of animals examined

Table 8 - 2
Two generation reproductive toxicity study of NP by oral administration in rats
Macroscopic findings in F₀ males

Group	Grade	[25]	250 mg/kg	
			-	+
(Kidney)	Rough surface		1	24
	Enlargement		1	24
	Pale		6	19
	Dark		25	0
	Edematous/soft		22	3
	Whitish cloudy, papilla		18	7
	Cyst, cortex		24	1
	Dilatation, renal pelvis	[25]	25	0
(Liver)	Dark		21	4
	Indistinct lobular pattern		23	2
	Diaphragmatic nodule		25	0
		[25]	19	6
(Spleen)	Small		24	1
	Enlargement	[25]	2	23
		[25]	23	2
(Thymus)	Small			
(Adrenal gland)	Enlargement			
	Dark			
(Parathyroid gland)	Enlargement			
(Thyroid gland)	Enlargement			
(Stomach)	Pale/white, mucosa, forestomach	[25]	16	9
	Recessed area/nodule, mucosa, forestomac	[25]	25	0
(Ileum/Cecum)	Black content	[25]	21	4
(Testis)	Small	[25]	17	8
(Epididymis)	Small	[25]	18	7
	Nodule, yellowish white	[25]	25	0
(Prostate)	Small	[25]	15	10
	(Seminal vesicle & Coagulating gland)	[25]	10	15
	Small	[25]	23	2
(Urinary bladder)	Brown urine	[25]	22	3
(Bone marrow)	Pale	[25]	22	3
(Skin)	Alopecia	[25]	22	3
	Soiled fur	[24]	24	1

-, Negative; +, Positive

[] , Number of animals examined

Table 9 - 1

Two generation reproductive toxicity study of NP by oral administration in rats
Histopathological findings in F0 males

Group Grade	(Testis)	0 mg/kg		2 mg/kg		10 mg/kg		50 mg/kg								
		-	+/+	++	+++	Pos.	-	+/+	++	+++	Pos.	-	+/+	++	+++	Pos.
No remarkable change (Epididymis)	[10]			[0]			[0]				[0]					[10]
No remarkable change (Prostate: ventral lobe)	[10]			[0]			[0]				[0]					[10]
Cellular infiltration, lymphocyte, interstitium (Seminal vesicle and Coagulating gland)		5	3	2	0	0	5									
No remarkable change (Mammary gland)	[10]			[0]			[0]				[0]					[10]
No remarkable change (Liver)	[10]			[0]			[10]				[0]					[10]
Hypertrophy, hepatocyte, centrilobular Fatty change, periportal (Kidney)	10	0	0	0	0	0	10	0	0	0	0	10	0	0	0	2
Eosinophilic body Basophilic tubule, cortex Cast, hyaline, cortex/medulla Mineralization (Spleen)	3	2	4	1	0	7	4	2	4	0	0	6	4	0	0	4
4	5	1	0	0	0	6	7	3	0	0	0	3	5	4	1	5
10	0	0	0	0	0	0	9	1	0	0	0	1	9	1	0	1
10	0	0	0	0	0	0	9	1	0	0	0	1	10	0	0	0
Hematopoiesis, extramedullary Deposit, pigment, brown (Heart)	0	9	1	0	0	10					[0]					[10]
0	0	8	2	0	10					[0]					[10]	
Myocardial degeneration/fibrosis Hemorrhage, focal (Lung)	7	2	1	0	0	3					[0]					
9	1	0	0	0	1											
2	5	3	0	0	8											
6	4	0	0	0	4											

-, Negative; +/-, Very slight; +, Slight; ++, Moderate; +++, Severe; Pos., Total of positive grade

[], Number of animals examined

* , Significantly different from control p<0.05 (Two-tailed Mann-Whitney U test)

** , Significantly different from control p<0.01 (Two-tailed Mann-Whitney U test)

##, Significantly different from control p<0.01 (One-tailed Fisher exact test)

Table 9 - 1 (continued)

Two generation reproductive toxicity study of NP by oral administration in rats
Histopathological findings in F0 males

Group Grade	0 mg/kg			2 mg/kg			10 mg/kg			50 mg/kg		
	-	+/-	++	-	+/-	++	-	+/-	++	-	+/-	++
(Urinary bladder)	[10]			[0]			[0]			[0]		
No remarkable change												
(Thymus)	[10]			[0]			[0]			[0]		
No remarkable change												
(Adrenal gland)	[10]			[0]			[0]			[0]		
No remarkable change												
(Pituitary gland)	[10]			[0]			[0]			[0]		
No remarkable change												
(Parathyroid gland)	[4]			[0]			[0]			[0]		
No remarkable change												
(Thyroid gland)	[10]			[0]			[0]			[0]		
No remarkable change												
(Stomach)	[0]			[0]			[0]			[1]		
No remarkable change												

-, Negative; +/-, Very slight; +, Slight; ++, Moderate; +++, Severe; Pos., Total of positive grade
[], Number of animals examined

Table 9-2

Two generation reproductive toxicity study of NP by oral administration in rats
Summary of histopathological findings in F0 males of 250 mg/kg

Group Grade		250 mg/kg			
		-	+/-	+	++
(Testis)		[25]	21	2	0
	Atrophy, seminiferous tubule		2	0	2
	Degeneration, spermatocyte,			0	0
	in seminiferous tubule,		18	5	0
	Degeneration, spermaticid,			2	0
	in seminiferous tubule,		23	0	0
	Decrease, sperm,			2	0
	in seminiferous tubule,		23	0	0
	Decrease, spermatocyte & spermaticid,			0	0
	in seminiferous tubule,		23	0	1
	Multinucleated giant cell,			1	0
	in seminiferous tubule		21	4	0
	Vacuolization, germ cell layer,			0	0
	in seminiferous tubule		23	0	2
	Atrophy, Leydig cell, diffuse			0	0
		[25]	23	0	2
	Cell debris, lumen			0	0
	Decrease, sperm, lumen			0	0
(Prostate: ventral lobe)		[25]	23	0	0
	Atrophy			0	0
	Decrease, secretion			7	0
	Vacuolation, with cell debris,			9	7
	epithelium			1	1
	Cellular infiltration, lymphocyte,			11	10
	interstitium			2	2
(Seminal vesicle and Coagulating gland)		[25]	19	2	3
	Atrophy			1	1
	Decrease, secretion			0	0
	Vacuolation, with cell debris,			6	6
	epithelium			1	1
(Mammary gland)		[23]	18	3	2
	Atrophy			2	0
(Adrenal gland)		[25]	3	6	7
	Hypertrophy, cortical cell			5	5
(Liver)		[25]	0	11	10
	Hypertrophy, hepatocyte,			4	0
	centrilobular			0	25
			0	8	14
			3	3	0
			0	0	25

- , Negative; +/-, Very slight; +, Slight; ++, Moderate; +++, Severe; Pos., Total of positive grade

[], Number of animals examined

Table 9-2 (continued)

Two generation reproductive toxicity study of NP by oral administration in rats

Summary of histopathological findings in F0 males of 250 mg/kg

Group	Grade	250 mg/kg			Pos.
		-	+/-	++	
(Kidney)	[25]				
Eosinophilic body		11	6	7	0
Basophilic tubule, cortex		0	0	3	12
Basophilic tubule, medulla & papilla		0	2	10	5
Dilatation, distal tubule, cortex & medulla		0	1	8	6
Dilatation, collecting tubule, medulla & papilla		0	4	6	3
Necrosis, epithelium, proximal tubule, cortex		7	11	6	1
Degeneration, vacuolar, epithelium, proximal tubule		8	7	8	2
Necrosis, epithelium, distal & collecting tubule		6	7	11	1
Deposit, pigment, brown, proximal tubular epithelium		4	13	4	4
Cellular infiltration, neutrophil, lumen, distal & collecting tubule		2	11	4	6
Cellular infiltration, neutrophil, epithelium & interstitium, cortex		1	9	5	8
Cellular infiltration, neutrophil, epithelium & interstitium, medulla/papilla		2	6	6	9
Cell debris, lumen, distal & collecting tubule		3	8	4	6
Cast, hyalin, cortex/medulla		6	16	3	0
Mineralization		3	16	3	3
Metaplasia, transitional epithelium, collecting tubule, papilla		19	1	4	1
Hyperplasia, transitional epithelium, renal pelvis		7	5	10	3
Edema, interstitium, medulla & papilla		2	7	3	9
Fibrosis, interstitium, interstitium, cortex		12	11	1	1
Cellular infiltration, neutrophil & lymphocyte, transitional epithelium		25	0	0	0

-, Negative; +/-, Very slight; +, Slight; ++, Moderate; +++, Severe; Pos., Total of positive grade

[], Number of animals examined

Table 10

Two generation reproductive toxicity study of NP by oral administration in rats

Clinical signs of F₀ females

Table 11

Two generation reproductive toxicity study of NP by oral administration in rats
Body weight of F₀ females during pre-mating period; Means±S.D. (N)

Compound	Dose (mg/kg)	Nonylphenol					
		0 ^a	2	10	50	250	
Days of treatment							
1	258.3 ± 12.1 (35)	255.6 ± 7.7 (25)	259.7 ± 13.0 (25)	259.4 ± 13.5 (25)	259.6 ± 12.3 (25)		
4	259.3 ± 14.3 (35)	255.6 ± 10.3 (25)	260.8 ± 14.4 (25)	261.1 ± 14.2 (25)	249.2 ± 13.0 * (25)		
8	264.3 ± 14.6 (35)	261.8 ± 10.8 (25)	266.4 ± 14.9 (25)	265.5 ± 13.8 (25)	240.5 ± 20.2 ** (14)		
11	268.1 ± 15.0 (35)	264.5 ± 11.3 (25)	268.8 ± 15.0 (25)	267.8 ± 13.7 (25)	257.5 ± 12.2 (9)		
15	273.2 ± 16.3 (35)	271.1 ± 11.0 (25)	275.5 ± 16.6 (25)	272.9 ± 14.2 (25)	253.1 ± 21.4 ** (9)		
18	277.6 ± 15.7 (12)	279.7 ± 11.2 (7)	302.1 (2)	289.2 ± 15.8 (4)			
22	308.8 ± 22.4 (3)	290.8 (2)	325.9 (1)	297.7 (1)			
25	318.1 ± 17.8 (3)	297.9 (2)		297.7 (1)			
29	336.1 ± 21.3 (3)						

a: vehicle control, corn oil (2 mL/kg)

*: significant difference from control, P<0.05

**: significant difference from control, P<0.01