Table 4 (continued)

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

Food consumption of Fo males during treatment period; Mean±S.D. (N)

Compound	Nonylphenol				
Dose (mg/kg)	0[a]	2	10	50	250
Days of treatment					
60-61	24.5 ± 3.2 (35)	27.0 ± 3.0 * (25)	23.7 ± 2.9 (25)	25.7 ± 3.8 (25)	22.8 ± 5.7 (24)
64-65	24.1 ± 3.0 (35)	25.9 ± 2.6 (25)	23.4 ± 6.0 (25)	24.8 ± 3.2 (25)	24.8 ± 4.3 (23)
67-68	24.4 ± 3.5 (35)	26.9 ± 2.8 * (25)	23.2 ± 3.2 (25)	23.9 ± 3.7 (25)	26.4 ± 8.1 (23)
71-72	23.1 ± 3.3 (35)	24.3 ± 2.6 (25)	23.4 ± 3.2 (25)	24.1 ± 3.7 (25)	22.4 ± 4.3 (23)
74-75	23.7 ± 3.3 (35)	26.0 ± 2.4 * (25)	23.6 ± 3.1 (25)	23.1 ± 4.0 (25)	27.5 ± 9.0 (23)
78-79	23.6 ± 2.9 (35)	26.4 ± 2.9 * (25)	23.8 ± 3.1 (25)	23.5 ± 4.5 (25)	22.7 ± 8.3 (22)
81-82	23.6 ± 3.7 (35)	26.0 ± 3.7 (25)	23.7 ± 3.2 (25)	23.5 ± 4.0 (25)	23.7 ± 5.1 (21)
99-100	24.3 ± 5.1 (35)	25.6 ± 3.2 (25)	23.7 ± 2.3 (25)	23.3 ± 3.4 (25)	
102-103	24.1 ± 4.0 (35)	25.2 ± 2.8 (25)	23.8 ± 2.8 (25)	23.4 ± 3.8 (25)	
106-107	23.2 ± 3.4 (35)	24.2 ± 2.7 (25)	23.5 ± 3.0 (25)	23.6 ± 4.0 (25)	
109-110	23.6 ± 2.9 (35)	26.0 ± 3.2 ** (25)	23.8 ± 2.8 (25)	24.0 ± 3.3 (25)	
113-114	24.2 ± 3.1 (35)	25.2 ± 2.3 (25)	23.5 ± 2.4 (25)	22.7 ± 2.9 (25)	
116-117	24.5 ± 3.1 (35)	26.0 ± 2.7 (25)	24.1 ± 2.8 (25)	24.1 ± 3.6 (25)	

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

*: Significant difference from control, $p<0.05$

**: Significant difference from control, $p<0.01$

Table 5

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

Organ weight of F0 males; Mean ± S.D. (N)

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

a: vehicle control, corn oil (2 mL/kg)
b: absolute weight
c: relative weight (g or mg per 100g body weight)
*: signifiant difference from control, $p<0.05$
**: signifiant difference from control, $p<0.01$

Table 5 (continued)

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

Organ weight of Fo males; Mean ± S.D. (N)

Compound		Nonylphenol							
Dose (mg/kg)		0[a]		2		10		50	
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)
*: signifiant difference from control, $p<0.05$
**: signifiant 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 F0 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.)				
Caudal epididymis weight	0.3022 ± 0.037	0.3331 ± 0.032	0.3034 ± 0.032	0.3058 ± 0.035
No. of sperm per caudal epididymis (x 10^6)	681 ± 184	650 ± 192	746 ± 239	732 ± 168
No. of sperm per caudal epididymis weight (x 10^6/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 F0 males examined	18
% of motile (Mean ± S.D.)	91 ± 7
% of progressive (Mean ± S.D.)	74 ± 7
Sperm counts (Mean ± S.D.)	
Caudal epididymis weight	0.1803 ± 0.038
No. of sperm per caudal epididymis (x 10^6)	492 ± 127
No. of sperm per caudal epididymis weight (x 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), triiodthyronine (T_3), thyroxine (T_4) in F_0 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 (25)	4.0 ± 2.1 (25)
LH	(ng/mL)	12.6 ± 4.7 (35)	14.1 ± 3.0 (25)	12.5 ± 3.1 (25)	11.4 ± 3.8 (25)
FSH	(ng/mL)	186.9 ± 57.9 (35)	177.5 ± 66.5 (25)	198.1 ± 45.8 (25)	201.3 ± 50.9 (25)
TSH	(ng/mL)	11.8 ± 2.0 (35)	12.7 ± 2.0 (25)	13.0 ± 2.1 (25)	14.3 ± 2.3 ** (25)
T_3	(ng/mL)	1.0 ± 0.2 (35)	0.8 ± 0.1 ** (24)	1.0 ± 0.1 (25)	0.9 ± 0.1 (25)
T_4	(ng/mL)	75.1 ± 10.9 (35)	68.5 ± 9.1 * (25)	72.4 ± 7.8 (25)	75.4 ± 10.5 (25)

a : vehicle control, corn oil (2 mL/kg)
* : significant difference from control, $p<0.05$
**: significant difference from control, $p<0.01$

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), triiodthyronine (T_3), thyroxine (T_4) in F_0 males; Mean±S.D. (N)

Compound		Nonylphenol	
Dose (mg/kg)		250	
Testosterone	(ng/mL)	1.9 ± 1.2	(23)
LH	(ng/mL)	17.2 ± 7.3	(23)
FSH	(ng/mL)	306.3 ± 91.5	(23)
TSH	(ng/mL)	21.3 ± 4.6	(23)
T_3	(ng/mL)	1.4 ± 0.2	(22)
T_4	(ng/mL)	72.9 ± 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	0 mg/kg		2 mg/kg		10 mg/kg		50 mg/kg	
Grade	−	+	−	+	−	+	−	+
(Kidney) [35]			[25]		[25]		[25]	
Rough surface	35	0	25	0	25	0	25	0
Enlargement	35	0	25	0	25	0	25	0
Pale	35	0	25	0	25	0	25	0
Dark	35	0	25	0	25	0	23	2
Edematous/Soft	35	0	25	0	25	0	25	0
Whitish cloudy, papilla	35	0	25	0	25	0	25	0
Cyst, cortex	35	0	25	0	25	0	25	0
Dilatation, renal pelvis	34	1	25	0	25	0	25	0
(Liver) [35]			[25]		[25]		[25]	
Dark	35	0	25	0	25	0	25	0
Indistinct lobular pattern	35	0	25	0	25	0	25	0
Diaphragmatic nodule	35	0	24	1	25	0	25	0
(Thymus) [35]			[25]		[25]		[25]	
Small	31	4	25	0	22	3	20	5
(Thyroid gland) [35]			[25]		[25]		[25]	
Enlargement	35	0	25	0	25	0	24	1
(Stomach) [35]			[25]		[25]		[25]	
Recessed area/nodule, mucosa, forestomach	34	1	24	1	25	0	25	0
(Testis) [35]			[25]		[25]		[25]	
Small	34	1	25	0	25	0	25	0
(Epididymis) [35]			[25]		[25]		[25]	
Small	34	1	25	0	25	0	25	0
Nodule, yellowish white	35	0	25	0	25	0	24	1
(Prostate) [35]			[25]		[25]		[25]	
Small	34	1	25	0	25	0	25	0

−, Negative; +, Positive
[ ], Number of animals examined

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

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

-, Negative; +, Positive

Table 9 - 1

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						
	-	+/-	+	++	+++	Pos.	-	+/-	+	++	+++	Pos.	-	+/-	+	++	+++	Pos.	-	+/-	+	++	+++	Pos.	
(Testis)	[10]						[0]						[0]						[10]						
No remarkable change																									
(Epididymis)	[10]						[0]						[0]						[10]						
No remarkable change																									
(Prostate: ventral lobe)	[10]						[0]						[0]						[10]						
Cellular infiltration, lymphocyte, interstitium	5	3	2	0	0	5													6	3	1	0	0	4	
(Seminal vesicle and Coagulating gland)	[10]						[0]						[0]						[10]						
No remarkable change																									
(Mammary gland)	[10]						[0]						[0]						[10]						
No remarkable change																									
(Liver)	[10]						[10]						[10]						[10]						
Hypertrophy, hepatocyte, centrilobular	10	0	0	0	0	0	10	0	0	0	0	0	10	0	0	0	0	0	2	8	0	0	0	** 8	##
Fatty change, periportal	10	0	0	0	0	0	7	0	0	3	0	3	10	0	0	0	0	0	10	0	0	0	0	0	
(Kidney)	[10]						[10]						[10]						[10]						
Eosinophilic body	3	2	4	1	0	7	4	2	4	0	0	6	6	4	0	0	0	4	7	3	0	0	0	* 3	
Basophilic tubule, cortex	4	5	1	0	0	6	7	3	0	0	0	3	5	4	1	0	0	5	2	8	0	0	0	8	
Cast, hyalin, cortex/medulla	10	0	0	0	0	0	9	1	0	0	0	1	9	1	0	0	0	1	9	1	0	0	0	1	
Mineralization	10	0	0	0	0	0	9	1	0	0	0	1	10	0	0	0	0	0	9	1	0	0	0	1	
(Spleen)	[10]						[0]						[0]						[10]						
Hematopoiesis, extramedullary	0	9	1	0	0	10													0	4	6	0	0	10	
Deposit, pigment, brown	0	0	8	2	0	10													0	0	8	2	0	10	
(Heart)	[10]						[0]						[0]						[10]						
Myocardial degeneration/fibrosis	7	2	1	0	0	3													7	2	1	0	0	3	
Hemorrhage, focal	9	1	0	0	0	1													10	0	0	0	0	0	
(Lung)	[10]						[0]						[0]						[10]						
Accumulation, foam cell	2	5	3	0	0	8													0	8	1	1	0	10	
Mineralization, artery	6	4	0	0	0	4													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					
	-	+/-	+	++	+++	Pos.	-	+/-	+	++	+++	Pos.	-	+/-	+	++	+++	Pos.	-	+/-	+	++	+++	Pos.
(Urinary bladder)	[10]						[0]						[0]						[10]					
No remarkable change																								
(Thymus)	[10]						[0]						[0]						[10]					
No remarkable change																								
(Adrenal gland)	[10]						[0]						[0]						[10]					
No remarkable change																								
(Pituitary gland)	[10]						[0]						[0]						[10]					
No remarkable change																								
(Parathyroid gland)	[4]						[0]						[0]						[6]					
No remarkable change																								
(Thyroid gland)	[10]						[0]						[0]						[10]					
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 adoministrationin in rats
Summary of histopathological findings in F0 males of 250 mg/kg

Group	250 mg/kg					
Grade	-	+/-	+	++	+++	Pos.
(Testis) [25]						
Atrophy, seminiferous tubule	21	2	0	2	0	4
Degeneration, spermatocyte, in seminiferous tubule,	18	5	0	2	0	7
Degeneration, spermatid, in seminiferous tubule,	23	0	0	2	0	2
Decrease, sperm, in seminiferous tubule,	23	0	0	0	2	2
Decrease, spermatocyte & spermatid, in seminiferous tubule,	23	0	1	1	0	2
Multinucleated giant cell, in seminiferous tubule	21	4	0	0	0	4
Vacuolization, germ cell layer, in seminiferous tubule	23	0	2	0	0	2
Atrophy, Leydig cell, diffuse	23	0	0	2	0	2
(Epididymis) [25]						
Cell debris, lumen	23	0	2	0	0	2
Decrease, sperm, lumen	23	0	0	0	2	2
(Prostate: ventral lobe) [25]						
Atrophy	0	7	11	7	0	25
Decrease, secretion	0	8	9	7	1	25
Vacuolation, with cell debris, epithelium	11	10	2	2	0	14
Cellular infiltration, lymphocyte, interstitium	19	2	3	1	0	6
(Seminal vesicle and Coagulating gland) [25]						
Atrophy	2	10	9	3	1	23
Decrease, secretion	2	10	9	1	3	23
Vacuolation, with cell debris, epithelium	18	3	2	2	0	7
(Mammary gland) [23]						
Atrophy	3	6	7	5	2	20
(Adrenal gland) [25]						
Hypertrophy, cortical cell	0	11	10	4	0	25
(Liver) [25]						
Hypertrophy, hepatocyte, centrilobular	0	8	14	3	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 adoministrationin ın rats
Summary of histopathological findings in F0 males of 250 mg/kg

Group	250 mg/kg					
Grade	-	+/-	+	++	+++	Pos.
(Kidney) [25]						
Eosinophilic body	11	6	7	1	0	14
Basophilic tubule, cortex	0	0	3	12	10	25
Basophilic tubule, medulla & papilla	0	2	10	5	8	25
Dilatation, distal tubule, cortex & medulla	0	1	8	6	10	25
Dilatation, collecting tubule, medulla & papilla	0	4	6	3	12	25
Necrosis, epithelium, proximal tubule, cortex	7	11	6	1	0	18
Degeneration, vacuolar, epithelium, proximal tubule	8	7	8	2	0	17
Necrosis, epithelium, distal & collecting tubule	6	7	11	1	0	19
Deposit, pigment, brown, proximal tubular epithelium	4	13	4	4	0	21
Cellular infiltratıon, neutrophil, lumen, distal & collecting tubule	2	11	4	6	2	23
Cellular infiltration, neutrophil, epithelium & interstitium, cortex	1	9	5	8	2	24
Cellular infiltration, neutrophil, epithelium & interstitium, medulla/papilla	2	6	6	9	2	23
Cell debris, lumen, distal & collecting tubule	3	8	4	6	4	22
Cast, hyalin, cortex/medulla	6	16	3	0	0	19
Mineralization	3	16	3	3	0	22
Metaplasia, transitional epithelium, collecting tubule, papilla	19	1	4	1	0	6
Hyperplasia, transitional epithelium, renal pelvis	7	5	10	3	0	18
Edema, interstitium, medulla & papilla	2	7	3	9	4	23
Fibrosis, interstitium, interstitium, cortex	12	11	1	1	0	13
Cellular infiltration, neutrophil & lymphocyte, transitional epithelium	25	0	0	0	0	0

-, 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 adoministrationin in rats
Summary of histopathological findings in F0 males of 250 mg/kg

Group	250 mg/kg					
Grade	-	+/-	+	++	+++	Pos.
(Urinary bladder) [24]						
Hyperplasia, transitional epithelium, diffuse	0	10	14	0	0	24
(Spleen) [25]						
Atrophy	10	5	4	6	0	15
Hematopoiesis, extramedullary	0	14	11	0	0	25
Deposit, pigment, brown	0	0	6	15	4	25
(Thymus) [25]						
Atrophy, with pyknosis/decrease of lymphocyte	10	6	2	3	4	15
(Heart) [25]						
Myocardial degeneration/fibrosis	20	5	0	0	0	5
Necrosis, myocardium, focal, left papillary muscle	24	0	1	0	0	1
Cellular infiltration, neutrophil, left papillary muscle	24	0	1	0	0	1
Hemorrhage, focal, left papillary muscle	24	0	1	0	0	1
(Lung) [25]						
Accumulation, foam cell	7	16	2	0	0	18
Mineralization, artery	21	4	0	0	0	4
Metaplasia, osseous	24	1	0	0	0	1
Congestion	22	0	3	0	0	3
(Pituitary gland) [22]						
No remarkable change						
(Parathyroid gland) [20]						
No remarkable change						
(Thyroid gland) [22]						
No remarkable change						
(Stomach) [9]						
Squamous hyperplasia, forestomach	0	5	4	0	0	9
(Bone marrow of femur) [2]						
Increase, fat tissue	0	0	1	1	0	2
Decrease, hematopoiesis	0	0	1	1	0	2

-, 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 F_0 females

Dose (mg/kg)	Clinical signs	No. of animals showing clinical signs											Total
	Weeks of treatment	1	2	3	4	5	6	7	8	9	10	11	
	Days of treatment	1–7	8–14	15–21	22–28	29–35	36–42	43–49	50–56	57–63	64–70	71–77	
0	Abnormality	0/35	0/35	0/35	0/35	0/35	0/35	0/31	0/30	0/30	0/6	–	0/35
2	Abnormality	0/25	0/25	0/25	0/25	0/25	0/25	0/23	0/22	0/21	0/ 4	0/1	0/25
10	Salivation	0/25	0/25	0/25	0/25	0/25	0/25	0/25	0/25	0/25	0/2	–	0/25
	Loss of hair (chest)	0/25	0/25	0/25	0/25	0/25	1/25	1/25	2/25	2/25	0/2	–	2/25
	Loss of hair (abdomen)	0/25	0/25	0/25	0/25	0/25	0/25	0/25	1/25	1/25	0/2	–	1/25
50	Salivation	1/25	12/25	22/25	17/25	17/25	5/25	14/23	17/23	18/23	0/ 1	0/1	23/25
	Loss of hair (chest)	0/25	0/25	0/25	0/25	0/25	0/25	0/23	1/23	0/23	0/25	0/1	1/25
	Poor development of nipple	0/25	0/25	0/25	0/25	0/25	1/25	0/23	0/23	0/23	0/25	0/1	1/25
	Soiled hair (perioral)	0/25	0/25	0/25	0/25	0/25	1/25	0/23	0/23	0/23	0/25	0/1	1/25
	(abdomen)	0/25	0/25	0/25	0/25	0/25	1/25	0/23	0/23	0/23	0/25	0/1	1/25
250	Salivation	25/25	12/14	5/9	–	–	–	–	–	–	–	–	25/25
	Soiled hair (perioral smudge)	7/25	0/14	0/9	–	–	–	–	–	–	–	–	7/25
	(perineal)	5/25	6/14	2/9	–	–	–	–	–	–	–	–	12/25
	(vulva)	4/25	0/14	0/9	–	–	–	–	–	–	–	–	4/25
	Loose stool	11/25	1/14	1/9	–	–	–	–	–	–	–	–	11/25
	Loss of hair (abdomen)	0/25	2/14	2/9	–	–	–	–	–	–	–	–	2/25
	(femur)	0/25	2/14	2/9	–	–	–	–	–	–	–	–	2/25
	(lumbar)	1/25	0/14	0/9	–	–	–	–	–	–	–	–	1/25
	(perineal)	2/25	0/14	0/9	–	–	–	–	–	–	–	–	2/25
	Decrease in stool	7/25	3/14	0/9	–	–	–	–	–	–	–	–	10/25
	Emaciation	6/25	4/14	0/9	–	–	–	–	–	–	–	–	10/25
	Incomplete eyelid	6/25	0/14	0/9	–	–	–	–	–	–	–	–	6/25
	Moribundity	7/25	5/14	0/9	–	–	–	–	–	–	–	–	12/25
	Death	4/25	0/14	0/9	–	–	–	–	–	–	–	–	4/25
	Listless	8/25	4/14	0/9	–	–	–	–	–	–	–	–	12/25
	Hypothermia	3/25	1/14	0/9	–	–	–	–	–	–	–	–	4/25

Table 11

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

Body weight of F0 females during pre-mating period; Mean±S.D. (N)

Compound	Nonylphenol									
Dose (mg/kg)	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, $p<0.01$

Table 12

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

Body weight gain of Fo females during pre-mating period; Mean±S.D. (N)

Compound	Nonylphenol				
Dose (mg/kg)	0[a]	2	10	50	250
Days of treatment					
1- 4	1.0 ± 5.1 (35)	0.0 ± 6.4 (25)	1.1 ± 5.6 (25)	1.7 ± 4.9 (25)	-10.4 ± 10.5 **(25)
1- 8	6.0 ± 6.0 (35)	6.2 ± 6.7 (25)	6.7 ± 5.9 (25)	6.1 ± 5.8 (25)	-14.6 ± 17.6 **(14)
1-11	9.8 ± 6.2 (35)	8.9 ± 7.3 (25)	9.1 ± 5.7 (25)	8.3 ± 6.8 (25)	0.6 ± 8.4 **(9)
1-15	14.9 ± 7.1 (35)	15.5 ± 7.7 (25)	15.8 ± 7.6 (25)	13.4 ± 7.1 (25)	-3.8 ± 19.9 **(9)
1-18	21.6 ± 8.3 (12)	22.0 ± 10.9 (7)	34.7 (2)	17.4 ± 13.0 (4)	
1-22	47.0 ± 7.6 (3)	38.4 (2)	62.6 (1)	46.8 (1)	
1-25	56.3 ± 2.4 (3)	45.5 (2)		46.8 (1)	
1-29	74.4 ± 5.5 (3)				

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

**: significant difference from control, $p<0.01$

Table 13

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

Body weight of F0 females during gestation period; Mean±S.D. (N)

Compound	Nonylphenol				
Dose (mg/kg)	0[a]	2	10	50	250[b]
Days of gestation					
0	278.2 ± 14.7 (30)	275.1 ± 11.0 (22)	277.9 ± 18.6 (25)	275.4 ± 15.2 (25)	
4	299.1 ± 17.1 (30)	296.8 ± 12.4 (22)	297.8 ± 20.5 (25)	294.6 ± 15.1 (25)	
7	308.4 ± 16.7 (30)	307.4 ± 12.6 (22)	308.0 ± 22.1 (25)	303.4 ± 15.4 (25)	
14	339.6 ± 18.1 (30)	337.2 ± 11.0 (22)	338.5 ± 23.8 (25)	333.2 ± 18.2 (25)	
20	412.9 ± 20.8 (30)	409.3 ± 15.6 (22)	410.1 ± 29.9 (25)	400.1 ± 23.4 (25)	

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

b: animals were necropsied before mating.

Table 14

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

Body weight gain of Fo females during gestation period; Mean±S.D. (N)

Compound	Nonylphenol				
Dose (mg/kg)	0[a]	2	10	50	250[b]
Days of gestation					
0~ 4	20.8 ± 5.5 (30)	21.7 ± 5.1 (22)	19.9 ± 7.2 (25)	19.2 ± 5.2 (25)	
0~ 7	30.2 ± 5.6 (30)	32.2 ± 5.8 (22)	30.1 ± 8.4 (25)	28.0 ± 7.1 (25)	
0~14	61.4 ± 8.4 (30)	62.0 ± 7.7 (22)	60.6 ± 10.4 (25)	57.8 ± 9.0 (25)	
0~20	134.7 ± 13.7 (30)	134.1 ± 16.4 (22)	132.2 ± 16.3 (25)	124.7 ± 16.8 (25)	

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

b: animals were necropsied before mating.

Table 15

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

Body weight of F_0 females during lactation period; Mean±S.D. (N)

Compound	Nonylphenol				
Dose (mg/kg)	0[a]	2	10	50	250[b]
Days of lactation					
0	312.7 ± 22.6 (30)	310.0 ± 22.6 (22)	320.6 ± 26.7 (25)	305.3 ± 29.2 (25)	
4	323.4 ± 18.1 (30)	322.8 ± 13.6 (21)	321.2 ± 21.7 (25)	320.8 ± 21.3 (24)	
7	328.9 ± 18.3 (30)	328.6 ± 12.8 (21)	327.7 ± 18.8 (25)	329.2 ± 19.6 (23)	
14	342.6 ± 17.2 (30)	344.6 ± 12.9 (21)	340.2 ± 18.9 (25)	343.0 ± 18.8 (23)	
21	330.2 ± 17.3 (30)	332.0 ± 13.2 (21)	327.9 ± 22.5 (25)	330.8 ± 15.9 (23)	

a: vehicle control, corn oil (2 mL/kg)
b: animals were necropsied before mating.