Table 12

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

Body weight gain of F_0 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 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	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 F_0 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.

Table 16

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

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

Compound	Nonylphenol				
Dose (mg/kg)	0[a]	2	10	50	250[b]
Days of lactation					
0～ 4	10.7 ± 16.4 (30)	10.1 ± 12.6 (21)	0.6 ± 12.3 * (25)	13.4 ± 14.8 (24)	
0～ 7	16.2 ± 15.1 (30)	15.9 ± 10.8 (21)	7.1 ± 14.7 * (25)	20.7 ± 14.3 (23)	
0～14	29.9 ± 15.3 (30)	31.9 ± 13.3 (21)	19.6 ± 13.9 * (25)	34.4 ± 17.3 (23)	
0～21	17.5 ± 18.6 (30)	19.3 ± 12.8 (21)	7.3 ± 17.7 (25)	22.2 ± 20.8 (23)	

a: vehicle control, corn oil (2 mL/kg)
b: animals were necropsied before mating.
*: significant difference from control, $p<0.05$

Table 17

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

Food consumption of F_0 females during pre-mating period; Mean±S.D. (N)

Compound	Nonylphenol				
Dose (mg/kg)	0[a]	2	10	50	250
Days of treatment					
1-2	17.9 ± 3.3 (35)	19.0 ± 2.5 (25)	17.0 ± 3.0 (25)	17.4 ± 2.9 (25)	15.6 ± 2.6 **(25)
4-5	17.2 ± 2.8 (35)	16.7 ± 2.7 (25)	16.8 ± 3.5 (25)	16.8 ± 2.6 (25)	6.4 ± 5.2 **(25)
8-9	18.3 ± 2.4 (35)	18.3 ± 2.4 (25)	17.5 ± 3.1 (25)	17.2 ± 2.6 (25)	11.7 ± 7.2 **(12)
11-12	17.7 ± 3.1 (35)	17.5 ± 3.0 (25)	17.0 ± 3.6 (25)	17.1 ± 2.3 (25)	16.5 ± 2.4 (9)

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

Table 18

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

Food consumption 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					
1～2	22.6 ± 2.2 (30)	22.8 ± 3.1 (22)	21.7 ± 2.6 (25)	21.0 ± 2.6 (25)	
7～8	23.4 ± 2.6 (30)	23.3 ± 3.3 (22)	24.0 ± 3.1 (25)	22.4 ± 2.7 (25)	
13～14	22.5 ± 2.8 (30)	23.2 ± 2.0 (22)	23.4 ± 2.6 (25)	24.0 ± 3.0 (25)	
19～20	22.4 ± 2.2 (30)	22.0 ± 3.0 (22)	22.8 ± 2.6 (25)	20.7 ± 3.1 (25)	

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

Table 19

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

Food consumption of F0 females during lactation period; Mean±S.D. (N)

Compound	Nonylphenol			
Dose (mg/kg)	0[a]	2	10	50	250[b]
Days of lactation					
3~4	36.2 ± 7.0 (30)	35.6 ± 5.4 (21)	35.7 ± 5.3 (25)	34.6 ± 6.6 (24)	
6~7	41.7 ± 5.2 (30)	41.9 ± 4.6 (21)	42.5 ± 4.3 (25)	41.2 ± 4.0 (23)	
9~10	49.2 ± 6.3 (30)	48.7 ± 5.0 (21)	49.5 ± 3.8 (25)	48.0 ± 5.6 (23)	

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

Table 20

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

Estrous cycle of F0 females

Compound	Nonylphenol				
Dose (mg/kg)	0[a]	2	10	50	250
Number of females examined	35	25	25	25	25
Mean length of estrous cycle in days					
Pre-treatment period; Mean±S.D.	4.0 ± 0.2	4.0 ± 0.0	4.0 ± 0.0	4.0 ± 0.0	4.0 ± 0.2
Treatment period; Mean±S.D.	4.0 ± 0.2	4.0 ± 0.2	4.0 ± 0.2	4.2 ± 0.8	5.0
Number of animals showing each type of cycle during pre-treatment period					
4-day cycle	34	25	25	25	24
5-day cycle	1	0	0	0	1
4/5-day cycle	0	0	0	0	0
Irregular	0	0	0	0	0
Changes of estrous cycle after treatment					
Number of animals whose estrous cycle was not changed	33	24	23	24	0
Number of animals whose estrous cycle was changed	2	1	2	1	25
[Pre-treatment] → [Treatment]					
4-day → 5-day	1	1	1	1	2
4-day → 4/5-day	0	0	0	0	0
4-day → irregular	0	0	1	0	0
5-day → 4-day	1	0	0	0	0
5-day → 4/5-day	0	0	0	0	0
5-day → irregular	0	0	0	0	0
4-day → monoestrus	0	0	0	0	19
4-day → anestrus	0	0	0	0	3
5-day → anestrus	0	0	0	0	1
Number of vaginal estrus during mating period Mean±S.D.	1.1 ± 0.3	1.2 ± 0.5	1.0 ± 0.2	1.0 ± 0.2	N.E.

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

Table 21

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

Reproductive performance of Fo animals

Compound	Nonylphenol			
mg/kg)	0[a]	2	10	50
Number of pairs examined (A)	35	25	25	25
Number of pairs successful copulation (B)	35	25	25	25
Copulation index [(B/A)×100,%]	100.0	100.0	100.0	100.0
Number of pregnant females (C)	33	22	25	25
Fertility index [(C/B)×100,%]	94.3	88.0	100.0	100.0
Pairing days until copulation Mean ± S.D.	2.7 ± 1.8	3.2 ± 3.0	2.3 ± 1.7	2.7 ± 2.4

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

Table 21 (continued)

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

Reproductive performance of F0 animals

Compound	Nonylphenol
mg/kg)	250[a]
Number of pairs examined (A)	23
Number of pairs successful copulation (B)	22
Copulation index [(B/A)×100,%]	95.7
Number of pregnant females (C)	21
Fertility index [(C/B)×100,%]	95.5
Pairing days until copulation Mean ± S.D.	2.9 ± 1.9

a: Animals were necropsied before mating. Males were mated with intact females.

Table 22

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

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

Compound		Nonylphenol							
Dose (mg/kg)		0[a]		2		10		50	250[d]
Terminal body weight	(g)	330.2 ± 17.3	(30)	332.0 ± 13.2	(21)	327.9 ± 22.5	(25)	330.8 ± 15.9	(23)
Brain	(g)	1.86 ± 0.08 b	(30)	1.86 ± 0.07	(21)	1.84 ± 0.06	(25)	1.86 ± 0.06	(23)
		0.56 ± 0.03 c	(30)	0.56 ± 0.02	(21)	0.56 ± 0.04	(25)	0.56 ± 0.03	(23)
Heart	(g)	1.09 ± 0.09	(30)	1.08 ± 0.07	(21)	1.07 ± 0.07	(25)	1.07 ± 0.08	(23)
		0.33 ± 0.02	(30)	0.33 ± 0.02	(21)	0.33 ± 0.03	(25)	0.32 ± 0.02	(23)
Lung	(g)	1.11 ± 0.08	(30)	1.08 ± 0.08	(21)	1.11 ± 0.06	(25)	1.10 ± 0.07	(23)
		0.34 ± 0.02	(30)	0.33 ± 0.02	(21)	0.34 ± 0.02	(25)	0.33 ± 0.02	(23)
Liver	(g)	14.18 ± 0.94	(30)	13.84 ± 1.32	(21)	14.29 ± 1.19	(25)	14.52 ± 1.46	(23)
		4.30 ± 0.29	(30)	4.17 ± 0.39	(21)	4.37 ± 0.43	(25)	4.39 ± 0.39	(23)
Spleen	(g)	0.66 ± 0.12	(30)	0.68 ± 0.12	(21)	0.64 ± 0.08	(25)	0.62 ± 0.07	(23)
		0.20 ± 0.03	(30)	0.20 ± 0.04	(21)	0.19 ± 0.03	(25)	0.19 ± 0.02	(23)
Kidneys	(g)	2.09 ± 0.13	(30)	2.20 ± 0.16	(21)	2.16 ± 0.21	(25)	2.08 ± 0.16	(23)
		0.64 ± 0.04	(30)	0.66 ± 0.05	(21)	0.66 ± 0.07	(25)	0.63 ± 0.05	(23)

a: vehicle control, corn oil (2 mL/kg)
b: absolute weight
c: relative weight (g per 100g body weight)
d: animals were necropsied before mating.

Table 22 (continued)

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

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

Compound		Nonylphenol			
Dose (mg/kg)		0[a]	2	10	50	250[d]
Terminal body weight	(g)	330.2 ± 17.3 (30)	332.0 ± 13.2 (21)	327.9 ± 22.5 (25)	330.8 ± 15.9 (23)	
Adrenal glands	(mg)	65.1 ± 10.3 b (30)	66.7 ± 8.4 (21)	63.3 ± 7.9 (25)	66.6 ± 11.4 (23)	
		19.8 ± 3.3 c (30)	20.1 ± 2.5 (21)	19.4 ± 2.5 (25)	20.1 ± 3.0 (23)	
Thymus	(mg)	183.2 ± 49.9 (30)	174.7 ± 56.6 (21)	161.7 ± 47.1 (25)	164.1 ± 57.2 (23)	
		55.5 ± 15.2 (30)	52.7 ± 17.4 (21)	49.7 ± 15.9 (25)	49.9 ± 18.0 (23)	
Ovaries	(mg)	89.8 ± 11.8 (30)	93.3 ± 11.5 (21)	88.2 ± 8.5 (25)	74.2 ± 10.1** (23)	
		27.2 ± 3.5 (30)	28.1 ± 3.6 (21)	27.0 ± 3.0 (25)	22.5 ± 3.4** (23)	
Uterus	(g)	0.36 ± 0.07 (30)	0.42 ± 0.09* (21)	0.36 ± 0.07 (25)	0.40 ± 0.10 (23)	
		0.11 ± 0.02 (30)	0.13 ± 0.03** (21)	0.11 ± 0.02 (25)	0.12 ± 0.03 (23)	
Thyroid gland	(mg)	14.0 ± 2.8 (30)	14.7 ± 4.2 (21)	14.4 ± 2.2 (25)	14.6 ± 2.9 (23)	
		4.3 ± 0.9 (30)	4.4 ± 1.3 (21)	4.4 ± 0.7 (25)	4.4 ± 0.9 (23)	
Pituitary gland	(mg)	13.5 ± 2.4 (30)	13.6 ± 2.0 (21)	13.1 ± 1.7 (25)	13.7 ± 1.7 (23)	
		4.1 ± 0.7 (30)	4.1 ± 0.6 (21)	4.0 ± 0.5 (25)	4.2 ± 0.6 (23)	

a: vehicle control, corn oil (2 mL/kg)
b: absolute weight
c: relative weight (g or mg per 100g body weight)
d: animals were necropsied before mating.
*: significant difference from control, $p<0.05$
**: significant difference from control, $p<0.01$

Table 23 - 1

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

Summary of macroscopic findings in Fo females at the end of the dosing period

Group	0 mg/kg		2 mg/kg		10 mg/kg		50 mg/kg	
Grade	-	+	-	+	-	+	-	+
(Uterus)	[35]		[25]		[25]		[25]	
Retention, fluid, lumen	34	1	25	0	25	0	25	0
(Kidney)	[35]		[25]		[25]		[25]	
Pale, cortex	35	0	25	0	25	0	22	3
Soft	35	0	25	0	25	0	24	1
Area, pale	35	0	25	0	25	0	24	1
Area, mottled, cortex	34	1	25	0	25	0	25	0
Cyst, left side	35	0	25	0	24	1	25	0
(Liver)	[35]		[25]		[25]		[25]	
Pale	35	0	25	0	25	0	24	1
(Stomach)	[35]		[25]		[25]		[25]	
Thickening, mucosa, glandular stomach	35	0	25	0	24	1	24	1
Area, dark, mucosa, glandular stomach	35	0	25	0	25	0	24	1
(Adrenal gland)	[35]		[25]		[25]		[25]	
Enlargement	35	0	25	0	24	1	23	2
(Thymus)	[35]		[25]		[25]		[25]	
Small	33	2	25	0	21	4	20	5

-, Negative; +, Positive

[ ], Number of animals examined

Table 23 - 2

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

Summary of macroscopic findings in Fo females

Group		250 mg/kg	
Grade		-	+
(Ovary)	[25]		
Small		23	2
(Uterus)	[25]		
Dilatation, lumen		22	3
Retention, requid		24	1
(Kidney)	[25]		
Rough surface		23	2
Enlargement		19	6
Pale		23	2
Area, pale/witish cloudy, cortex		13	12
Soft		23	2
Whitish cloudy, medulla		23	2
(Liver)	[25]		
Dark		23	2
Pale		24	1
Indistinct, lobular pattern		24	1
Congestion		21	4
(Spleen)	[25]		
Small		12	13
Indistinct, follicle		21	4
Elevated area		24	1
(Thymus)	[25]		
Small		9	16
(Lung)	[25]		
Dark		24	1
Area, dark		22	3
Emphysema		23	2
(Heart)	[25]		
Retention, blood		22	3
(Pancreas)	[25]		
Pale		21	4
(Adrenal gland)	[25]		
Enlargement		9	16
(Pituitary gland)	[25]		
Enlargement		24	1
(Thyroid gland)	[25]		
Small, left side		24	1
(Stomach)	[25]		
Whitish cloudy, mucosa, glandular stomach		24	1
Soft red/brown, mucosa, glandular stomach		22	3
Accumulation, gas		22	3
Decrease, content		21	4
(Urinary bladder)	[25]		
Retention, urine		24	1
(Born marrow)	[25]		
Pale		24	1
(Skin)	[25]		
Alopecia		19	6
Soiled fur		8	17

-, Negative; +, Positive

[ ], Number of animals examined

Table 24-1

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

Summary of histopathological findings in F0 female

Group	0 mg/kg						2 mg/kg						10 mg/kg						50 mg/kg					
Grade	-	+/-	+	++	+++	Pos.	-	+/-	+	++	+++	Pos.	-	+/-	+	++	+++	Pos.	-	+/-	+	++	+++	Pos.
(Ovary)	[9]						[0]						[0]						[9]					
Decrease, vesicular follicle	9	0	0	0	0	0													8	0	1	0	0	1
Increase, atresia, follicle	7	1	1	0	0	2													9	0	0	0	0	0
(Oviduct)	[9]						[0]						[0]						[9]					
No remarkable change																								
(Uterus: horn & cervix)	[9]						[0]						[0]						[9]					
No remarkable change																								
(Vagina)	[9]						[0]						[0]						[9]					
Mucification, epithelium	2	2	3	2	0	7													2	1	3	3	0	7
Cornification, epithelium	5	4	0	0	0	4													6	2	1	0	0	3
Cyst, lamina propria	8	0	0	1	0	1													9	0	0	0	0	0
(Mammary gland)	[9]						[0]						[0]						[9]					
Atrophy, focal	8	0	1	0	0	1													9	0	0	0	0	0
(Liver)	[9]						[9]						[10]						[9]					
Hepertrophy, hepatocyte, centrilobular	9	0	0	0	0	0	9	0	0	0	0	0	10	0	0	0	0	0	6	3	0	0	0	3
(Kidney)	[9]						[0]						[0]						[9]					
Basophilic tubule, cortex	6	3	0	0	0	3													8	1	0	0	0	1
Cast, cortex	8	1	0	0	0	1													9	0	0	0	0	0
(Spleen)	[9]						[0]						[0]						[9]					
Hematopoiesis, extramedullary	0	3	6	0	0	9													0	3	6	0	0	9
Deposit, pigment, brown	0	0	8	1	0	9													0	0	8	1	0	9

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

[ ], Number of animals examined

Table 24-1 (continued)

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

Summary of histopathological findings in F0 female

Group	0 mg/kg						2 mg/kg						10 mg/kg						50 mg/kg					
Grade	-	+/-	+	++	+++	Pos.	-	+/-	+	++	+++	Pos.	-	+/-	+	++	+++	Pos.	-	+/-	+	++	+++	Pos.
(Lung)	[9]						[0]						[0]						[9]					
Accumulation, foam cell	0	3	5	1	0	9													3	3	3	0	0	6
Hemorrhage, focal	6	2	1	0	0	3													7	2	0	0	0	2
Cellular infiltration, neutrophil, focal	7	2	0	0	0	2													7	2	0	0	0	2
Mineralization, artery	7	2	0	0	0	2													8	1	0	0	0	1
Metaplasia, osseous	6	3	0	0	0	3													9	0	0	0	0	0
(Thymus)	[9]						[0]						[0]						[9]					
Atrophy	8	1	0	0	0	1													8	1	0	0	0	1
(Urinary bladder)	[9]						[0]						[0]						[9]					
No remarkable change																								
(Thyroid gland)	[9]						[0]						[0]						[9]					
No remarkable change																								
(Parathyroid gland)	[9]						[0]						[0]						[9]					
No remarkable change																								
(Pituitary gland)	[9]						[0]						[0]						[9]					
No remarkable change																								
(Adrenal gland)	[9]						[0]						[0]						[9]					
No remarkable change																								
(Heart)	[9]						[0]						[0]						[9]					
No remarkable change																								

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

[ ], Number of animals examined

Table 24-2
Two generation reproductive toxicity study of NP by oral administration in rats
Summary of histopathological findings in F_0 female

Group	0 mg/kg						2 mg/kg						10 mg/kg						50 mg/kg					
Grade	-	+/-	+	++	+++	Pos.	-	+/-	+	++	+++	Pos.	-	+/-	+	++	+++	Pos.	-	+/-	+	++	+++	Pos.
(Uterus: horn & cervix)	[1]						[0]						[0]						[1]					
Hemorrhage, endmetrium	1	0	0	0	0	0													0	1	0	0	0	1
(Vagina)	[1]						[0]						[0]						[1]					
Mucification, epithelium	0	0	0	1	0	1													0	0	0	0	1	1
Cornification, epithelium	1	0	0	0	0	0													0	0	0	0	0	0
Cyst, lamina propria	1	0	0	0	0	0													0	0	0	0	0	0
(Liver)	[1]						[1]						[0]						[1]					
Hepertrophy, hepatocyte, centrilobular	1	0	0	0	0	0	1	0	0	0	0	0							1	0	0	0	0	0
Fatty change, periportal	1	0	0	0	0	0	1	0	0	0	0	0							0	0	0	0	1	1
(Kidney)	[1]						[0]						[0]						[1]					
Basophilic tubule, cortex	0	1	0	0	0	1													0	1	0	0	0	1
Degeneration, vacuolar, proximal tubule	1	0	0	0	0	0													0	1	0	0	0	1
Degeneration, fatty, proximal tubule	1	0	0	0	0	0													0	0	0	1	0	1
Cast, cortex	0	1	0	0	0	1													0	1	0	0	0	1
Mineralization, papilla & renal pelvis	0	1	0	0	0	1													1	0	0	0	0	0
(Spleen)	[1]						[0]						[0]						[1]					
Hematopoiesis, extramedullary	0	0	1	0	0	1													0	0	1	0	0	1
Deposit, pigment, brown	0	0	0	1	0	1													0	0	0	1	0	1
(Lung)	[1]						[0]						[0]						[1]					
Accumulation, foam cell	0	1	0	0	0	1													0	1	0	0	0	1
Hemorrhage, focal	1	0	0	0	0	0													1	0	0	0	0	0
Cellular infiltration, neutrophil, focal	1	0	0	0	0	0													1	0	0	0	0	0
Mineralization, artery	1	0	0	0	0	0													1	0	0	0	0	0
Metaplasia, osseous	1	0	0	0	0	0													1	0	0	0	0	0
(Thymus)	[1]						[0]						[0]						[1]					
Atrophy	1	0	0	0	0	0													0	0	0	0	1	1

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

Table 24 - 3
Two generation reproductive toxicity study of NP by oral administration in rats
Summary of histopathological findings in F0 female of 250 mg/kg

Group		250 mg/kg					
Grade		-	+/-	+	++	+++	Pos.
(Ovary)	[25]						
Decrease, corpus luteum		16	7	2	0	0	9
Increase, atrecia, follicle		18	7	0	0	0	7
Decease, vesicular follicle		21	3	1	0	0	4
Increase, interstitial gland		16	7	2	0	0	9
(Oviduct)	[25]						
No remarkable change							
(Uterus: horn & cervix)	[25]						
Hyperplasia, luminal epithelial cell		0	17	8	0	0	25
Metaplasia, squamous, luminal epithelium		24	1	0	0	0	1
Increase, endmetrium		9	4	12	0	0	16
Dilatation, lumen		18	4	1	2	0	7
(Vagina)	[25]						
Mucification, epithelium		14	1	5	5	0	11
Cornification, epithelium		8	15	2	0	0	17
(Adrenal gland)	[25]						
Hypertrophy, cortical cell		3	7	9	6	0	22
(Parathyroid gland)	[25]						
No remarkable change							
(Thyroid gland)	[22]						
Ectopic thymus		21	1	0	0	0	1
(Liver)	[25]						
Hypertrophy, hepatocyte, centrilobular		0	3	21	1	0	25
Degeneration, granular, eosinophilic, hepatocyte, centrilobular		23	2	0	0	0	2
Microgranuloma		24	0	1	0	0	1
Mitosis, hepatocyte		21	3	1	0	0	4
Fatty change, periportal		14	5	6	0	0	11
(Spleen)	[25]						
Atrophy		6	5	6	7	1	19
Hematopoiesis, extramedullary		7	13	5	0	0	18
Deposit, pigment, brown		0	0	4	21	0	25
(Thymus)	[23]						
Atrophy, with pyknosis/decrease of lymphocyte		6	4	3	5	5	17

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

Table 24 - 3 (continued)
Two generation reproductive toxicity study of NP by oral administration in rats
Summary of histopathological findings in F0 female of 250 mg/kg

Group		250 mg/kg					
Grade		-	+/-	+	++	+++	Pos.
(Kidney)	[25]						
Basophilic tubule, cortex		5	2	9	8	1	20
Basophilic tubule, medulla & papilla		3	8	9	5	0	22
Alteration, cytoplasmic, ralefaction & vacuolation, proximal & distal tubule, cortex		0	3	5	12	5	25
Dilatation, distal tubule, cortex & medulla		3	7	9	6	0	22
Dilatation, collecting tubule, medulla & papilla		12	6	4	3	0	13
Cell debris, lumen, distal & collecting tubule		5	8	11	1	0	20
Necrosis, epithelium, proximal tubule, cortex		4	12	2	3	4	21
Necrosis, epithelium, distal & collecting tubule		6	17	2	0	0	19
Mitosis, epithelium, collecting tubule, medulla & papilla		5	11	9	0	0	20
Cast, hyalin, cortex		22	1	2	0	0	3
Cellular infiltration, neutrophil, lumen, distal & collecting tubule		12	8	5	0	0	13
Cellular infiltration, neutrophil, epithelium & interstitium, cortex		22	2	1	0	0	3
Cellular infiltration, neutrophil, epithelium & interstitium, medulla/papilla		7	12	6	0	0	18
Hyperplasia, transitional epithelium, renal pelvis		16	9	0	0	0	9
Mineralization		6	14	4	1	0	19
(Urinary bladder)	[20]						
Hyperplasia, transitional, epithelium, diffuse		4	14	2	0	0	16
(Mammary gland)	[24]						
Hyperplasia		19	5	0	0	0	5
(Pancreas)	[4]						
No remarkable change							
(Heart)	[24]						
No remarkable change							
(Lung)	[25]						
No remarkable change							
(Pituitary gland)	[25]						
No remarkable change							
(Stomach)	[2]						
Erosion, mucosa, glandular stomach		1	1	0	0	0	1
Metaplasia, squamous, focal, mucosa, squamous hyperplasia, mucosa, forestomach		1	1	0	0	0	1
Squamous hyperplasia, mucosa, forestomach		0	0	2	0	0	2

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