Table 25

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

Serum concentrations of prolactin (PRL), luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid stimulating hormone (TSH), triiodthyronine (T_3), thyroxine (T_4), estradiol in F_0 females; Mean±S.D. (N)

Compound		Nonylphenol			
Dose (mg/kg)		0[a]	2	10	50
PRL	(ng/mL)	75.8 ± 67.7 (30)	124.8 ± 152.3 (21)	76.9 ± 144.4 (25)	79.3 ± 68.0 (23)
LH	(ng/mL)	10.7 ± 2.9 (30)	11.9 ± 3.9 (21)	12.0 ± 2.4 (25)	12.8 ± 2.6 (23)
FSH	(ng/mL)	268.9 ± 97.8 (30)	195.8 ± 52.3 ** (21)	305.8 ± 94.4 (25)	304.2 ± 92.3 (23)
TSH	(ng/mL)	17.2 ± 3.3 (30)	12.9 ± 2.4 ** (21)	17.9 ± 2.7 (25)	17.0 ± 2.5 (23)
T_3	(ng/mL)	1.2 ± 0.2 (30)	1.2 ± 0.3 (21)	1.1 ± 0.2 (25)	1.0 ± 0.2 ** (23)
T_4	(ng/mL)	66.3 ± 12.9 (30)	50.7 ± 10.4 ** (21)	68.6 ± 11.5 (25)	66.3 ± 11.9 (23)
Estradiol	(pg/mL)	15.3 ± 6.6 (5)	11.0 ± 2.9 (10)	19.9 ± 9.0 (4)	14.3 ± 6.7 (8)

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

Table 25 (continued)

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

Serum concentrations of prolactin (PRL), luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid stimulating hormone (TSH), triiodthyronine (T_3), thyroxine (T_4), estradiol in F_0 females; Mean±S.D. (N)

Compound		Nonylphenol	
Dose (mg/kg)		250	
PRL	(ng/mL)	254.5 ± 225.8	(19)
LH	(ng/mL)	17.6 ± 8.9	(19)
FSH	(ng/mL)	478.2 ± 319.8	(19)
TSH	(ng/mL)	27.2 ± 8.2	(19)
T_3	(ng/mL)	1.2 ± 0.2	(19)
T_4	(ng/mL)	67.8 ± 28.4	(19)
Estradiol	(pg/mL)	26.3 ± 14.7	(5)

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

Table 26

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

Development of F1 offspring up to weaning; Mean±S.D. (N)

Compound	Nonylphenol				
Dose (mg/kg)	0[a]	2	10	50	250[b]
Gestation period; days	22.1 ± 0.4 (30)	22.0 ± 0.4 (22)	21.8 ± 0.4 (25)	22.0 ± 0.4 (25)	
Implantations	15.3 ± 1.5 (30)	14.3 ± 2.4 (22)	14.7 ± 1.9 (25)	14.3 ± 2.2 (25)	
Delivery index; dams A)	100	100	100	100	
Day 0					
Fetuses ddelivered	13.9 ± 2.4 (30)	13.4 ± 2.6 (22)	14.0 ± 1.6 (25)	12.8 ± 2.7 (25)	
Delivery index; fetuses B)	90.9 ± 13.5 (30)	93.3 ± 6.5 (22)	95.2 ± 5.6 (25)	89.9 ± 13.6 (25)	
Live newborns	13.7 ± 2.3 (30)	12.9 ± 2.7 (22)	13.7 ± 1.8 (25)	12.3 ± 2.7 (25)	
Birth index C)	89.7 ± 13.4 (30)	90.3 ± 11.8 (22)	93.6 ± 7.8 (25)	86.3 ± 15.2 (25)	
Viability index D)	98.8 ± 3.4 (30)	96.8 ± 10.7 (22)	98.3 ± 5.9 (25)	96.1 ± 9.2 (25)	
Day 4					
Live offspring	13.5 ± 2.2 (30)	12.5 ± 3.7 (22)	13.4 ± 1.8 (25)	11.2 ± 4.2 (25)	
Viability index E)	98.7 ± 3.1 (30)	94.8 ± 21.4 (22)	98.1 ± 3.8 (25)	91.0 ± 27.5 (25)	
Offspring after culling	7.9 ± 0.7 (30)	7.9 ± 0.4 (21)	8.0 ± 0.0 (25)	8.0 ± 0.2 (23)	
Males	3.9 ± 0.6 (30)	4.0 ± 0.9 (21)	3.8 ± 0.8 (25)	4.0 ± 0.2 (23)	
Females	4.0 ± 0.3 (30)	3.9 ± 0.9 (21)	4.2 ± 0.8 (25)	4.0 ± 0.3 (23)	
Day 21					
Live offspring	7.9 ± 0.7 (30)	7.9 ± 0.4 (21)	8.0 ± 0.0 (25)	8.0 ± 0.2 (23)	
Males	3.9 ± 0.6 (30)	4.0 ± 0.9 (21)	3.8 ± 0.8 (25)	4.0 ± 0.2 (23)	
Females	4.0 ± 0.3 (30)	3.9 ± 0.9 (21)	4.2 ± 0.8 (25)	4.0 ± 0.3 (23)	
Weaning index F)	100 (30)	100 (21)	100 (25)	100 (23)	

A): Delivery index; dams = (no. of dams having live newborns / no. of pregnant females)
B): Delivery index; fetuses = (no. of fetuses delivered / no. of implantations) x 100
C): Birth bindex = (no. of live newborns / no. of implantations) x 100
D): Viability index; Day 0 = (no. of live newborns / no. of offspring delivered) x 100
E): Viability index; Day 4 = (no. of live offspring on day 4 / no. of live offspring on day 4) x 100
F): Weaning index = (no. of live offspring at weaning / no. of live offspring on day 4) x 100
a: vehicle control, corn oil (2 mL/kg)
b: animals were necropsied before mating

Table 27

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

Body weight of F1 offspring up to weaning; Mean±S.D. (N)

Compound	Nonylphenol			
Dose (mg/kg)	0[a]	2	10	50	250[b]
Day 0				
Male	6.6 ± 0.5 (30)	6.5 ± 0.6 (22)	6.6 ± 0.4 (25)	6.5 ± 0.6 (25)
Female	6.3 ± 0.6 (30)	6.2 ± 0.6 (22)	6.2 ± 0.4 (25)	6.2 ± 0.6 (25)
Day 4 (After culling)				
Male	10.3 ± 1.4 (30)	10.3 ± 1.2 (21)	10.2 ± 1.0 (25)	10.7 ± 1.6 (23)
Female	9.9 ± 1.3 (30)	9.7 ± 1.3 (21)	9.9 ± 1.0 (25)	10.3 ± 1.5 (23)
Day 7				
Male	16.9 ± 1.8 (30)	16.8 ± 1.5 (21)	17.0 ± 1.2 (25)	17.0 ± 1.8 (23)
Female	16.3 ± 1.7 (30)	16.0 ± 1.6 (21)	16.2 ± 1.2 (25)	16.4 ± 1.6 (23)
Day 14				
Male	34.1 ± 2.7 (30)	33.6 ± 2.7 (21)	34.4 ± 2.3 (25)	33.3 ± 2.5 (23)
Female	33.2 ± 2.7 (30)	32.4 ± 2.8 (21)	33.1 ± 2.5 (25)	32.5 ± 2.4 (23)
Day 21				
Male	56.0 ± 4.3 (30)	55.2 ± 4.0 (21)	55.3 ± 4.5 (25)	54.7 ± 4.1 (23)
Female	53.9 ± 4.3 (30)	53.2 ± 4.8 (21)	53.4 ± 4.1 (25)	52.7 ± 3.2 (23)

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

Table 28

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

Anogenital distance of F1 pups at birth; Mean±S.D. (N)

Compound	Nonylphenol			
Dose (mg/kg)	0[a]	2	10	50
Male				
Anogenital distance (mm)	2.7 ± 0.4 (198/30)[b]	2.6 ± 0.3 (148/22)	2.7 ± 0.3 (161/25)	2.9 ± 0.4 (154/25)
Body weight (g)	6.6 ± 0.5 (198/30)	6.5 ± 0.6 (148/22)	6.6 ± 0.4 (161/25)	6.6 ± 0.6 (154/25)
AGD/$\sqrt[3]{\text{BW}}$	1.46 ± 0.19 (198/30)	1.38 ± 0.16 (148/22)	1.43 ± 0.17 (161/25)	1.55 ± 0.19 (154/25)
Female				
Anogenital distance (mm)	1.3 ± 0.1 (214/30)	1.2 ± 0.1 (136/22)	1.2 ± 0.1 (182/25)	1.3 ± 0.1 (154/25)
Body weight (g)	6.3 ± 0.6 (214/30)	6.1 ± 0.6 (136/22)	6.2 ± 0.4 (182/25)	6.2 ± 0.6 (154/25)
AGD/$\sqrt[3]{\text{BW}}$	0.68 ± 0.08 (214/30)	0.67 ± 0.07 (136/22)	0.66 ± 0.04 (182/25)	0.71 ± 0.05 (154/25)

a: vehicle control, corn oil (2 mL/kg)
b: number of F1 pups examined / number of litters

Table 29

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

Behavioral and physical development of F1 male offspring; Mean±S.D. (N)

Compound	Nonylphenol							
Dose (mg/kg)	0[a]		2		10		50	
Behavioral development (days)								
Righting reflex	3.3 ± 0.9	(57/29)[b]	3.5 ± 1.4	(39/20)	3.3 ± 0.9	(41/22)	3.4 ± 1.1	(44/23)
Cliff drop aversion	6.8 ± 1.1	(57/29)	6.1 ± 0.9	(39/20)	6.8 ± 1.2	(41/22)	6.4 ± 1.2	(44/23)
Negative geotaxis	14.7 ± 1.6	(57/29)	12.6 ± 1.3 **	(39/20)	15.3 ± 1.3	(41/22)	14.9 ± 2.6	(44/23)
Physical development (days)								
Upper teeth eruption	9.7 ± 0.8	(57/29)	10.3 ± 0.9 *	(39/20)	10.3 ± 0.7 *	(41/22)	9.4 ± 0.6	(44/23)
Ear opening	12.4 ± 0.7	(57/29)	12.7 ± 0.5	(39/20)	12.8 ± 0.7	(41/22)	12.5 ± 0.6	(44/23)
Eyelid opening	14.8 ± 0.8	(57/29)	14.6 ± 0.8	(39/20)	14.8 ± 0.4	(41/22)	14.9 ± 0.7	(44/23)

a : vehicle control,corn oil (2 mL/kg)
b : no. of pups examined / no. of litters
* : significant difference from control, $p<0.05$
**: significant difference from control, $p<0.01$

Table 30

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

Behavioral and physical development of F1 female offspring; Mean±S.D. (N)

Compound	Nonylphenol							
Dose (mg/kg)	0[a]		2		10		50	
Behavioral development (days)								
Righting reflex	3.5 ± 1.1	(59/30)[b]	3.8 ± 1.5	(38/20)	4.3 ± 1.4	(48/25)	3.8 ± 1.2	(45/23)
Cliff drop aversion	6.7 ± 1.1	(59/30)	6.7 ± 1.0	(38/20)	7.7 ± 1.5 *	(48/25)	6.7 ± 1.6	(45/23)
Negative geotaxis	14.1 ± 1.4	(59/30)	12.5 ± 1.1 **	(38/20)	14.9 ± 1.7	(48/25)	15.2 ± 1.7 *	(45/23)
Physical development (days)								
Upper teeth eruption	9.7 ± 0.8	(59/30)	10.3 ± 0.8 *	(38/20)	10.0 ± 0.8	(48/25)	9.4 ± 0.6	(45/23)
Ear opening	12.2 ± 0.6	(59/30)	12.7 ± 0.7	(38/20)	12.7 ± 0.7 *	(48/25)	12.5 ± 0.6	(45/23)
Eyelid opening	14.6 ± 0.8	(59/30)	14.6 ± 0.6	(38/20)	14.7 ± 0.5	(48/25)	14.9 ± 0.7	(45/23)

a : vehicle control,corn oil (2 mL/kg)
b : no. of pups examined / no. of litters
* : significant difference from control, $p<0.05$
**: significant difference from control, $p<0.01$

Table 31

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

Morphological observations of F_1 live pups at birth

Compound	Nonylphenol			
Dose (mg/kg)	0[a]	2	10	50
Number of live pups examined	412	276	343	308
External abnormalities				
Number of live pups	0	0	0	0

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

Table 32

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

Morphological observations of F_1 dead pups during lactation period

Compound	Nonylphenol			
Dose (mg/kg)	0[a]	2	10	50
Number of dead pups[b]	12	22	13	40
Number of dead pups collected	7	12	9	25
Number of dead pups observed	7	1	6	11
External abnormalities				
Number of pups	0	0	0	1
Types and number				
Subcutaneous hemorrhage in head	0	0	0	1
Visceral abnormalities				
Number of pups	0	0	0	0

a: vehicle control, corn oil (2 mL/kg)
b: including missing pups

Table 33

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

Morphological observations of F1 pups culled on postnatal day 4

Compound	Nonylphenol			
Dose (mg/kg)	0[a]	2	10	50
Number of pups examined	170	108	136	98
External abnormalities				
Number of pups	0	0	0	0
Visceral abnormalities				
Number of pups	0	0	0	0

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

Table 34

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

External observations of F1 weanlings on postnatal day 22

Compound	Nonylphenol			
Dose (mg/kg)	0[a]	2	10	50
Number of weanlings examined	118	84	100	91
External abnormalities				
Number of weanlings	0	0	0	0

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

Table 35

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

Organ weight of F1 male weanlings; Mean ± S.D. (N)

Compound		Nonylphenol			
Dose (mg/kg)		0[a]	2	10	50
Terminal body weight	(g)	60.4 ± 4.4 (58)	59.5 ± 4.8 (43)	60.0 ± 5.3 (44)	59.8 ± 4.4 (45)
Testes	(mg)	271.6 ± 36.6 b (58)	267.4 ± 31.0 (43)	274.4 ± 27.5 (44)	275.9 ± 35.7 (45)
		45.0 ± 5.2 c	45.0 ± 4.6	45.9 ± 3.8	46.1 ± 4.7
Epididymides	(mg)	43.6 ± 7.2 (58)	43.6 ± 6.6 (43)	44.4 ± 5.0 (44)	45.1 ± 6.3 (45)
		7.2 ± 1.1	7.4 ± 1.1	7.4 ± 0.9	7.5 ± 0.9
Prostate + seminal vesicle	(mg)	68.4 ± 12.9 (57)	76.4 ± 13.6 * (43)	67.9 ± 18.5 (44)	74.0 ± 16.5 (45)
		11.4 ± 2.2	12.8 ± 2.0 *	11.4 ± 3.1	12.4 ± 2.7

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

Table 36

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

Organ weight of F1 female weanlings; Mean ± S.D. (N)

Compound		Nonylphenol			
Dose (mg/kg)		0[a]	2	10	50
Terminal body weight (g)		57.9 ± 4.8 (60)	57.8 ± 4.5 (41)	57.9 ± 4.5 (56)	57.1 ± 4.0 (46)
Ovaries	(mg)	17.0 ± 3.3 b (60)	18.0 ± 4.0 (41)	17.7 ± 4.3 (56)	17.2 ± 5.3 (46)
		2.9 ± 0.6 c (60)	3.1 ± 0.6 (41)	3.1 ± 0.7 (56)	3.0 ± 1.0 (46)
Uterus	(mg)	25.8 ± 3.6 (60)	26.5 ± 4.0 (41)	25.4 ± 6.5 (56)	24.1 ± 5.0 (46)
		4.5 ± 0.7 (60)	4.6 ± 0.7 (41)	4.4 ± 1.1 (56)	4.2 ± 0.9 (46)

a: vehicle control, corn oil (2 mL/kg)
b: absolute weight
c: relative weight (mg per 100g body weight)

Table 37

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

Macroscopic findings of F1 male weanlings on postnatal day 22

Compound	Nonylphenol			
Dose (mg/kg)	0[a]	2	10	50
Number of F1 male weanlings examined	58	43	44	45
Number of F1 male weanlings showing abnormalities	0	0	4	0
Types and number				
Dilatation of renal pelvis	0	0	3	0
Reddish epididymis	0	0	1	0

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

Table 38

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

Macroscopic findings of F1 female weanlings on postnatal day 22

Compound	Nonylphenol			
Dose (mg/kg)	0[a]	2	10	50
Number of F1 female weanlings examined	60	41	56	46
Number of F1 female weanlings showing abnormalities	0	0	0	0

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

Table 39

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

Summary of histopathological findings in F1 male at weaning

Group	0 mg/kg						2 mg/kg						10 mg/kg						50 mg/kg					
Grade	-	+/-	+	++	+++	Pos.	-	+/-	+	++	+++	Pos.	-	+/-	+	++	+++	Pos.	-	+/-	+	++	+++	Pos.
(Testis)	[10]						[0]						[0]						[10]					
No remarkable change																								
(Epididymis)	[10]						[0]						[0]						[10]					
No remarkable change																								
(Prostate: ventral lobe)	[9]						[0]						[0]						[10]					
No remarkable change																								
(Seminal vesicle & coagulating gland)	[9]						[0]						[0]						[10]					
No remarkable change																								

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

[ ], Number of animals examined

Table 40

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

Summary of histopathological findings in F1 female at weaning

Group	0 mg/kg						2 mg/kg						10 mg/kg						50 mg/kg					
Grade	-	+/-	+	++	+++	Pos.	-	+/-	+	++	+++	Pos.	-	+/-	+	++	+++	Pos.	-	+/-	+	++	+++	Pos.
(Ovary)	[10]						[0]						[0]						[10]					
No remarkable change																								
(Uterus)	[10]						[0]						[0]						[10]					
No remarkable change																								

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

[ ], Number of animals examined

Table 41

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_1 male weanlings; Mean±S.D. (N)

Compound	Nonylphenol			
Dose (mg/kg)	0[a]	2	10	50
Testosterone (ng/mL)	0.9 ± 0.4 (28)	0.8 ± 0.4 (20)	0.9 ± 0.6 (22)	1.3 ± 0.7 (23)
LH (ng/mL)	5.9 ± 1.9 (29)	5.2 ± 0.9 (20)	6.6 ± 2.1 (22)	5.8 ± 2.6 (23)
FSH (ng/mL)	147.5 ± 84.2 (29)	123.8 ± 27.3 (20)	211.9 ± 148.5 (22)	183.5 ± 105.5 * (23)
TSH (ng/mL)	9.5 ± 1.5 (29)	8.4 ± 0.8 * (20)	9.9 ± 2.4 (22)	9.6 ± 1.9 (23)
T_3 (ng/mL)	1.4 ± 0.2 (29)	1.5 ± 0.2 (20)	1.3 ± 0.2 (22)	1.2 ± 0.2 ** (23)
T_4 (ng/mL)	52.9 ± 8.6 (29)	45.4 ± 8.4 * (20)	52.2 ± 9.2 (22)	55.0 ± 9.2 (23)

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

Table 42

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

Serum concentrations of prolactin (PRL), luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid stimulating hormone (TSH), triiodthyronine (T_3), thyroxine (T_4) estradiol in F_1 female weanlings; Mean±S.D. (N)

Compound		Nonylphenol			
Dose (mg/kg)		0[a]	2	10	50
PRL	(ng/mL)	23.0 ± 10.3 (26)	18.4 ± 12.1 (18)	17.8 ± 7.2 (25)	17.6 ± 7.8 (23)
LH	(ng/mL)	7.2 ± 2.3 (30)	8.7 ± 3.3 (20)	7.3 ± 2.5 (25)	5.5 ± 1.7 * (23)
FSH	(ng/mL)	148.3 ± 91.4 (30)	181.8 ± 69.0 (20)	149.0 ± 90.3 (25)	156.0 ± 99.6 (23)
TSH	(ng/mL)	10.7 ± 2.6 (30)	8.4 ± 1.8 **(20)	10.2 ± 2.0 (25)	9.3 ± 1.7 * (23)
T3	(ng/mL)	1.5 ± 0.2 (30)	1.2 ± 0.2 * (19)	1.5 ± 0.4 (25)	2.0 ± 0.2 **(23)
T4	(ng/mL)	56.5 ± 8.8 (30)	47.5 ± 7.6 **(20)	55.0 ± 8.5 (25)	57.0 ± 10.1 (23)
Estradiol	(pg/mL)	20.1 ± 7.8 (28)	29.6 ± 16.4 (19)	21.5 ± 8.2 (24)	21.0 ± 11.1 (21)

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

Table 43

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

Clinical signs of F_1 males

Dose (mg/kg)	Clinical signs	No. of animals showing clinical signs									
	Weeks of treatment	1	2	3	4	5	6	7	8	9	10
	Days of treatment	1 – 7	8 – 14	15 – 21	22 – 28	29 – 35	36 – 42	43 – 49	50 – 56	57 – 63	64 – 70
0	Abnormality	0/59	0/59	0/59	0/59	0/59	0/59	0/59	0/59	0/30	0/30
2	Loss of teeth	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/21	2/21
10	Abnormality	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/25	0/25
50	Salivation	0/46	1/46	5/46	8/46	15/46	32/46	46/46	38/46	18/23	20/23

Table 43 (continued)

Two generation reproductive toxicity study of NP by oranl administration is rats

Clinical signs of F_1 males

Dose (mg/kg)	Clinical signs	No. of animals showing clinical signs									
	Weeks of treatmentt	11	12	13	14	15	16	17	18	19	Total
	Days of treatment	71 – 77	78 – 84	85 – 91	92 – 98	99 – 105	106 – 112	113 – 119	120 – 126	127 – 133	
0	Abnormality	0/30	0/30	0/30	0/30	0/30	0/28	0/ 8	0/ 8	0/ 4	0/59
2	Loss of teeth	2/21	1/21	1/21	1/21	1/21	1/21	1/21	1/20	1/ 6	2/41
10	Abnormality	0/25	0/25	0/25	0/25	0/25	0/23	0/ 1	–	–	0/50
50	Salivation	22/23	20/23	18/23	20/23	20/23	14/23	–	–	–	46/46

Table 44

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

Clinical signs of F_1 females

Dose (mg/kg)	Clinical signs	No. of animals showing clinical signs									
	Weeks of treatment	1	2	3	4	5	6	7	8	9	10
	Days of treatment	1 – 7	8 – 14	15 – 21	22 – 28	29 – 35	36 – 42	43 – 49	50 – 56	57 – 63	64 – 70
0	Abnormality	0/59	0/59	0/59	0/59	0/59	0/59	0/59	0/59	0/30	0/30
2	Hypothermia	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/21	0/21
	Soiled perineal region	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/21	0/21
	Moribundity	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/21	0/21
10	Loss of teeth	0/50	0/50	0/50	0/50	0/50	0/50	1/50	1/50	0/25	0/25
50	Salivation	0/46	7/46	18/46	30/46	35/46	39/46	41/46	38/46	19/23	20/23

Table 44 (Continued)

Two generation reproductive toxicity study of NP by oranl administration is rats

Clinical signs of F_1 females

Dose (mg/kg)	Clinical signs	Weeks of treatment	11	12	13	14	15	16	17	18	19	20	Total
		Days of treatment	71– 77	78– 84	85– 91	92– 98	99–105	106–112	113–119	120–126	127–133	134–140	
			No. of animals showing clinical signs										
0	Abnormality		0/30	0/30	0/30	0/30	0/30	0/26	0/24	0/13	0/ 2	0/1	0/59
2	Hypothermia		0/21	0/21	0/21	0/21	1/21	0/17	0/17	0/ 7	0/ 1	–	1/41
	Soiled perineal region		0/21	0/21	0/21	0/21	1/21	0/17	0/17	0/ 7	0/ 1	–	1/41
	Moribundity		0/21	0/21	0/21	0/21	1/21	0/17	0/17	0/ 7	0/ 1	–	1/41
10	Loss of teeth		0/25	0/25	0/25	0/25	0/25	0/21	0/19	0/ 9	–	–	1/50
50	Salivation		19/23	22/23	21/23	12/23	9/23	10/19	12/19	1/10	–	–	46/46

Table 45

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

Body weight of F_1 males after weaning; Mean±S.D. (N)

Compound	Nonylphenol			
Dose (mg/kg)	0[a]	2	10	50
Days of age				
21	55.6 ± 4.5 (117)	55.2 ± 4.3 (84)	55.4 ± 4.8 (94)	54.7 ± 4.6 (91)
28	96.2 ± 8.2 (59)	97.1 ± 7.0 (41)	97.2 ± 6.8 (50)	94.8 ± 10.2 (46)
35	152.8 ± 13.1 (59)	154.6 ± 12.4 (41)	153.5 ± 10.8 (50)	150.6 ± 15.2 (46)
42	211.9 ± 18.9 (59)	216.8 ± 18.1 (41)	213.6 ± 15.6 (50)	211.5 ± 20.2 (46)
49	272.3 ± 25.5 (59)	277.9 ± 23.3 (41)	274.5 ± 20.7 (50)	271.4 ± 25.9 (46)
56	322.4 ± 31.8 (59)	332.7 ± 26.0 (41)	328.7 ± 25.6 (50)	325.3 ± 31.4 (46)
63	368.0 ± 35.5 (59)	372.6 ± 29.1 (41)	375.5 ± 31.5 (50)	373.1 ± 34.7 (46)
70	403.3 ± 40.3 (59)	408.8 ± 31.5 (41)	414.0 ± 38.0 (50)	410.6 ± 38.8 (46)
77	436.7 ± 55.8 (30)	448.3 ± 37.6 (21)	447.2 ± 41.9 (25)	449.9 ± 41.3 (23)
84	466.4 ± 59.5 (30)	479.2 ± 40.5 (21)	478.1 ± 46.5 (25)	478.8 ± 43.8 (23)
91	491.3 ± 61.2 (30)	504.4 ± 41.4 (21)	505.1 ± 48.8 (25)	504.2 ± 46.6 (23)

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

Table 46

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

Body weight gain of F1 males after weaning; Mean±S.D. (N)

Compound	Nonylphenol			
Dose (mg/kg)	0[a]	2	10	50
Days of age				
21-28	40.2 ± 6.0 (59)	41.2 ± 4.0 (41)	41.5 ± 3.3 (50)	40.1 ± 8.1 (46)
21-35	96.8 ± 10.4 (59)	98.7 ± 9.8 (41)	97.8 ± 7.8 (50)	95.8 ± 13.0 (46)
21-42	155.9 ± 16.4 (59)	160.9 ± 15.6 (41)	157.9 ± 12.8 (50)	156.7 ± 17.9 (46)
21-49	216.3 ± 22.8 (59)	222.0 ± 21.0 (41)	218.8 ± 18.2 (50)	216.6 ± 23.8 (46)
21-56	266.4 ± 29.4 (59)	276.8 ± 24.0 (41)	273.0 ± 23.4 (50)	270.5 ± 29.2 (46)
21-63	312.0 ± 33.1 (59)	316.7 ± 27.5 (41)	319.7 ± 29.4 (50)	318.3 ± 32.3 (46)
21-70	347.3 ± 38.2 (59)	353.0 ± 29.9 (41)	358.3 ± 36.0 (50)	355.8 ± 36.6 (46)
21-77	380.4 ± 53.4 (30)	391.9 ± 35.4 (21)	391.5 ± 40.2 (25)	394.7 ± 39.8 (23)
21-84	410.1 ± 57.1 (30)	422.9 ± 38.2 (21)	422.5 ± 44.9 (25)	423.7 ± 42.3 (23)
21-91	435.0 ± 58.8 (30)	448.1 ± 39.2 (21)	449.5 ± 47.0 (25)	449.0 ± 45.2 (23)

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

Table 47

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

Body weight of F_1 females after weaning; Mean±S.D. (N)

Compound	Nonylphenol			
Dose (mg/kg)	0[a]	2	10	50
Days of age				
21	53.8 ± 4.5 (119)	53.4 ± 5.2 (82)	53.5 ± 4.5 (106)	52.7 ± 3.9 (92)
28	88.3 ± 6.3 (59)	88.5 ± 8.2 (41)	89.3 ± 6.2 (50)	88.5 ± 8.5 (46)
35	130.9 ± 10.0 (59)	131.6 ± 10.9 (41)	132.1 ± 9.6 (50)	130.5 ± 9.3 (46)
42	164.4 ± 13.9 (59)	166.1 ± 13.3 (41)	164.7 ± 11.5 (50)	164.4 ± 11.8 (46)
49	191.9 ± 16.9 (59)	191.1 ± 14.7 (41)	191.9 ± 13.4 (50)	191.2 ± 14.3 (46)
56	215.3 ± 20.2 (59)	213.5 ± 15.7 (41)	215.6 ± 16.5 (50)	214.2 ± 16.6 (46)
63	237.2 ± 23.5 (59)	233.5 ± 18.4 (41)	240.1 ± 17.6 (50)	234.7 ± 19.2 (46)
70	256.3 ± 26.3 (59)	250.3 ± 19.9 (41)	258.4 ± 21.2 (50)	250.3 ± 22.2 (46)
77	271.9 ± 32.6 (30)	261.0 ± 19.2 (21)	272.2 ± 20.6 (25)	258.2 ± 24.9 (23)
84	286.5 ± 35.7 (30)	273.9 ± 21.5 (21)	283.7 ± 23.7 (25)	269.9 ± 27.2 (23)
91	299.3 ± 36.2 (30)	282.1 ± 21.9 (21)	296.6 ± 24.6 (25)	278.3 ± 27.2 (23)

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

Table 48

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

Body weight gain of F_1 females after weaning; Mean±S.D. (N)

Compound	Nonylphenol			
Dose (mg/kg)	0[a]	2	10	50
Days of age				
21-28	34.0 ± 4.0 (59)	35.0 ± 4.1 (41)	35.6 ± 3.7 (50)	35.5 ± 7.1 (46)
21-35	76.6 ± 7.9 (59)	78.0 ± 7.1 (41)	78.4 ± 7.3 (50)	77.5 ± 7.1 (46)
21-42	110.1 ± 11.9 (59)	112.6 ± 9.7 (41)	111.0 ± 9.8 (50)	111.4 ± 9.8 (46)
21-49	137.6 ± 15.0 (59)	137.6 ± 11.5 (41)	138.2 ± 12.2 (50)	138.2 ± 12.9 (46)
21-56	161.0 ± 18.4 (59)	160.0 ± 12.9 (41)	161.9 ± 15.4 (50)	161.2 ± 15.6 (46)
21-63	182.9 ± 21.6 (59)	179.9 ± 16.4 (41)	186.4 ± 16.8 (50)	181.8 ± 18.2 (46)
21-70	202.1 ± 24.3 (59)	196.7 ± 18.3 (41)	204.6 ± 20.7 (50)	197.4 ± 21.1 (46)
21-77	217.9 ± 30.4 (30)	207.1 ± 17.1 (21)	218.2 ± 19.9 (25)	204.9 ± 23.6 (23)
21-84	232.5 ± 33.6 (30)	219.9 ± 19.7 (21)	229.7 ± 23.5 (25)	216.5 ± 26.0 (23)
21-91	245.2 ± 34.1 (30)	228.1 ± 20.1 (21)	242.6 ± 24.5 (25)	225.0 ± 25.9 * (23)

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

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

Table 49

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

Food consumption of F1 males after weaning; Mean±S.D. (N)

Compound	Nonylphenol			
Dose (mg/kg)	0[a]	2	10	50
Days of age				
23-24	9.9 ± 1.4 (59)	11.4 ± 5.0 (41)	10.0 ± 1.1 (50)	9.8 ± 1.4 (46)
30-31	15.7 ± 1.5 (59)	16.3 ± 1.7 (41)	15.7 ± 1.2 (50)	16.2 ± 1.3 (46)
37-38	21.3 ± 2.0 (59)	22.1 ± 1.7 (41)	21.3 ± 1.8 (50)	21.5 ± 2.8 (46)
44-45	24.4 ± 2.1 (59)	25.5 ± 1.8 (41)	24.5 ± 2.1 (50)	24.9 ± 2.5 (46)
51-52	26.6 ± 3.6 (59)	29.3 ± 1.7 ** (41)	27.2 ± 2.1 (50)	27.0 ± 2.4 (46)
58-59	28.3 ± 2.5 (59)	28.0 ± 6.2 (41)	28.5 ± 2.9 (50)	28.5 ± 1.7 (46)
65-66	27.1 ± 2.5 (59)	29.5 ± 2.3 ** (41)	28.4 ± 3.6 (50)	28.8 ± 3.8 (46)
72-73	27.5 ± 2.6 (59)	28.9 ± 2.1 (40)	28.2 ± 3.2 (50)	28.3 ± 3.1 (46)
79-80	29.2 ± 3.4 (30)	30.3 ± 3.1 (21)	29.5 ± 4.0 (25)	29.5 ± 3.4 (23)
86-87	29.6 ± 3.0 (30)	30.7 ± 3.8 (21)	30.3 ± 4.0 (25)	29.7 ± 3.7 (23)

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

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

Table 50

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

Food consumption of F1 females after weaning; Mean±S.D. (N)

Compound	Nonylphenol			
Dose (mg/kg)	0[a]	2	10	50
Days of age				
23-24	9.3 ± 1.9 (59)	9.7 ± 1.2 (41)	9.5 ± 0.9 (50)	9.1 ± 1.2 (46)
30-31	14.1 ± 1.2 (59)	14.8 ± 1.5 * (41)	15.2 ± 5.2 (50)	14.7 ± 1.2 * (46)
37-38	17.5 ± 1.9 (59)	17.5 ± 1.6 (41)	17.4 ± 1.4 (50)	17.7 ± 2.6 (46)
44-45	17.9 ± 1.9 (59)	17.9 ± 1.6 (41)	18.2 ± 1.6 (50)	18.8 ± 1.6 * (46)
51-52	18.8 ± 1.9 (59)	19.5 ± 1.7 (41)	18.2 ± 1.9 (50)	19.6 ± 2.1 (46)
58-59	19.9 ± 2.4 (59)	20.5 ± 2.1 (41)	19.3 ± 1.5 (50)	19.6 ± 2.4 (46)
65-66	19.5 ± 2.8 (59)	20.6 ± 1.7 (41)	19.4 ± 2.9 (50)	19.8 ± 3.9 (46)
72-73	20.0 ± 2.1 (59)	18.7 ± 4.2 (41)	19.6 ± 1.4 (50)	19.5 ± 2.6 (46)
79-80	20.9 ± 3.4 (30)	20.7 ± 3.4 (21)	20.1 ± 2.9 (25)	20.0 ± 3.6 (23)
86-87	21.9 ± 4.5 (30)	20.6 ± 2.3 (21)	21.4 ± 3.3 (25)	19.1 ± 2.7 * (23)

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

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

Table 51

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

Sexual maturation of F1 males ; Mean±S.D. (N)

Compound	Nonylphenol			
Dose (mg/kg)	0[a]	2	10	50
Age at preputial separation (day)	42.9 ± 2.1 (30)	42.3 ± 1.9 (21)	42.6 ± 1.9 (25)	42.9 ± 2.2 (23)
Body weight at preputial separation (g)	220.6 ± 19.9 (30)	219.6 ± 15.9 (21)	217.7 ± 13.2 (25)	219.5 ± 14.0 (23)

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

Table 52

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

Sexual maturation of F1 females ; Mean±S.D. (N)

Compound	Nonylphenol			
Dose (mg/kg)	0[a]	2	10	50
Age at vaginal opening (day)	33.4 ± 2.5 (30)	33.1 ± 2.0 (21)	33.4 ± 2.8 (25)	31.5 ± 1.8** (23)
Body weight at vaginal opening (g)	120.1 ± 13.0 (30)	121.8 ± 12.4 (21)	119.3 ± 12.1 (25)	110.2 ± 11.5 * (23)

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

Table 53

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

Open field test in F1 males; Mean±S.D. (N)

Compound	Nonylphenol			
Dose (mg/kg)	0[a]	2	10	50
The first day				
Latency (sec.)	16.9 ± 15.8 (29)	19.3 ± 22.2 (20)	21.4 ± 23.6 (25)	18.6 ± 21.3 (23)
Ambulation (cm)	932.1 ± 553.2 (29)	730.0 ± 283.8 (20)	734.0 ± 474.0 (25)	956.2 ± 445.7 (23)
Rearing (no.)	4.7 ± 3.6 (29)	2.6 ± 1.8 (20)	3.5 ± 2.6 (25)	4.7 ± 3.7 (23)
Grooming (no.)	0.1 ± 0.4 (29)	0.6 ± 0.7 * (20)	0.2 ± 0.4 (25)	0.5 ± 0.9 (23)
Defecation (no.)	2.0 ± 1.7 (29)	1.6 ± 1.9 (20)	2.1 ± 1.9 (25)	1.7 ± 1.5 (23)
Urination (no.)	0.4 ± 0.5 (29)	0.5 ± 0.7 (20)	0.4 ± 0.5 (25)	0.3 ± 0.5 (23)
The second day				
Latency (sec.)	10.6 ± 9.5 (29)	10.1 ± 7.8 (20)	10.2 ± 11.5 (25)	11.3 ± 16.1 (23)
Ambulation (cm)	1474.7 ± 860.3 (29)	1271.1 ± 698.9 (20)	1049.2 ± 636.3 (25)	1302.2 ± 661.7 (23)
Rearing (no.)	4.1 ± 3.3 (29)	3.1 ± 2.4 (20)	3.4 ± 2.7 (25)	4.4 ± 3.2 (23)
Grooming (no.)	0.6 ± 0.8 (29)	0.6 ± 0.6 (20)	0.4 ± 0.6 (25)	0.5 ± 0.7 (23)
Defecation (no.)	1.2 ± 1.6 (29)	1.4 ± 2.3 (20)	2.2 ± 2.1 (25)	1.7 ± 1.8 (23)
Urination (no.)	0.2 ± 0.4 (29)	0.1 ± 0.3 (20)	0.2 ± 0.4 (25)	0.2 ± 0.4 (23)
The third day				
Latency (sec.)	5.7 ± 6.6 (29)	5.1 ± 8.9 (20)	7.2 ± 15.9 (25)	4.1 ± 3.7 (23)
Ambulation (cm)	1631.6 ± 1099.0 (29)	1823.1 ± 868.6 (20)	1543.7 ± 788.4 (25)	1727.3 ± 821.9 (23)
Rearing (no.)	5.3 ± 5.2 (29)	4.4 ± 3.9 (20)	5.0 ± 4.1 (25)	4.7 ± 2.9 (23)
Grooming (no.)	0.3 ± 0.5 (29)	0.6 ± 0.7 (20)	0.4 ± 0.6 (25)	0.4 ± 0.8 (23)
Defecation (no.)	1.1 ± 1.4 (29)	1.2 ± 1.5 (20)	1.7 ± 2.0 (25)	1.2 ± 1.8 (23)
Urination (no.)	0.1 ± 0.3 (29)	0.1 ± 0.2 (20)	0.2 ± 0.4 (25)	0.1 ± 0.5 (23)

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

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

Table 54

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

Open field test in F1 females; Mean±S.D. (N)

Compound	Nonylphenol			
Dose (mg/kg)	0[a]	2	10	50
The first day				
Latency (sec.)	17.3 ± 17.5 (29)	9.7 ± 7.9 (20)	13.6 ± 10.9 (25)	18.0 ± 14.5 (23)
Ambulation (cm)	1518.8 ± 572.2 (29)	906.9 ± 456.9 ** (20)	1477.0 ± 593.4 (25)	1531.1 ± 657.1 (23)
Rearing (no.)	7.6 ± 5.5 (29)	4.6 ± 2.9 (20)	4.4 ± 2.4 (25)	6.7 ± 4.1 (23)
Grooming (no.)	0.3 ± 0.5 (29)	0.2 ± 0.4 (20)	0.3 ± 0.5 (25)	0.0 ± 0.2 (23)
Defecation (no.)	0.6 ± 1.2 (29)	0.9 ± 1.1 (20)	0.6 ± 0.9 (25)	0.7 ± 1.3 (23)
Urination (no.)	0.1 ± 0.3 (29)	0.1 ± 0.3 (20)	0.1 ± 0.3 (25)	0.3 ± 0.4 (23)
The second day				
Latency (sec.)	7.5 ± 9.3 (29)	8.1 ± 8.0 (20)	8.0 ± 6.3 (25)	6.5 ± 5.7 (23)
Ambulation (cm)	2189.9 ± 908.4 (29)	1331.2 ± 758.5 * (20)	1964.5 ± 1115.7 (25)	2232.7 ± 667.7 (23)
Rearing (no.)	8.2 ± 5.8 (29)	4.0 ± 2.8 * (20)	4.8 ± 3.3 (25)	7.1 ± 4.6 (23)
Grooming (no.)	1.0 ± 1.1 (29)	0.5 ± 0.6 (20)	0.5 ± 0.7 (25)	1.0 ± 0.9 (23)
Defecation (no.)	0.3 ± 0.9 (29)	1.2 ± 1.8 (20)	0.6 ± 1.6 (25)	0.3 ± 0.9 (23)
Urination (no.)	0.1 ± 0.3 (29)	0.2 ± 0.4 (20)	0.1 ± 0.3 (25)	0.0 ± 0.2 (23)
The third day				
Latency (sec.)	4.5 ± 6.5 (29)	5.1 ± 5.2 (20)	4.4 ± 6.1 (25)	3.1 ± 3.3 (23)
Ambulation (cm)	2508.8 ± 1122.9 (29)	1800.5 ± 893.2 (20)	2443.0 ± 1273.7 (25)	2711.8 ± 811.2 (23)
Rearing (no.)	9.0 ± 6.4 (29)	6.2 ± 4.2 (20)	6.1 ± 4.5 (25)	8.4 ± 6.8 (23)
Grooming (no.)	0.6 ± 0.7 (29)	0.5 ± 0.8 (20)	0.4 ± 0.7 (25)	0.4 ± 0.7 (23)
Defecation (no.)	0.3 ± 0.8 (29)	0.4 ± 0.8 (20)	0.4 ± 1.1 (25)	0.3 ± 1.1 (23)
Urination (no.)	0.0 ± 0.0 (29)	0.0 ± 0.0 (20)	0.0 ± 0.0 (25)	0.1 ± 0.3 (23)

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

Table 55

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

Water multiple T-maze test in F1 males; Mean±S.D. (N)

Compound		Nonylphenol							
Dose (mg/kg)		0[a]		2		10		50	
The first day									
1st trial	Time	51 ± 27	(29)	54 ± 29	(20)	51 ± 24	(25)	56 ± 28	(21)
	Error	12 ± 7		10 ± 5		12 ± 6		11 ± 7	
2nd trial	Time	38 ± 22	(29)	61 ± 41	(20)	40 ± 17	(24)	48 ± 33	(23)
	Error	10 ± 7		10 ± 7		9 ± 4		9 ± 8	
3rd trial	Time	31 ± 26	(29)	39 ± 34	(20)	43 ± 38	(24)	36 ± 25	(23)
	Error	5 ± 5		7 ± 5		7 ± 7		7 ± 7	
The second day									
1st trial	Time	35 ± 24	(29)	51 ± 25	* (19)	31 ± 14	(25)	34 ± 19	(23)
	Error	8 ± 7		9 ± 5		7 ± 5		6 ± 5	
2nd trial	Time	22 ± 19	(29)	26 ± 10	(19)	25 ± 21	(25)	17 ± 5	(23)
	Error	4 ± 4		5 ± 3		5 ± 6		2 ± 2	
3rd trial	Time	15 ± 5	(29)	21 ± 13	(20)	24 ± 26	(25)	15 ± 5	(23)
	Error	2 ± 2		4 ± 3		3 ± 4		2 ± 3	
The third day									
1st trial	Time	25 ± 20	(29)	35 ± 28	(20)	31 ± 22	(25)	22 ± 13	(23)
	Error	5 ± 6		5 ± 5		6 ± 6		4 ± 5	
2nd trial	Time	16 ± 7	(29)	17 ± 8	(20)	15 ± 8	(25)	14 ± 6	(23)
	Error	2 ± 2		2 ± 3		2 ± 3		1 ± 3	
3rd trial	Time	16 ± 8	(29)	16 ± 5	(20)	12 ± 4	(25)	13 ± 5	(23)
	Error	2 ± 3		1 ± 2		1 ± 1		1 ± 1	

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