

Table 28

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

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

Compound	Nonylphenol				
	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/ ³ √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/ ³ √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

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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			
	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

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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			
	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 F1 live pups at birth

Compound	Nonylphenol		
Dose (mg/kg)	0 ^a	2	10
Number of live pups examined	412	276	343
<u>External abnormalities</u>			
Number of live pups	0	0	0

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

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

Morphological observations of F1 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
<u>External abnormalities</u>				
Number of pups	0	0	0	1
<u>Types and number</u>				
Subcutaneous hemorrhage in head	0	0	0	1
<u>Visceral abnormalities</u>				
Number of pups	0	0	0	0

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

b: including missing pups

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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
Number of pups examined	170	108	136
<u>External abnormalities</u>			
Number of pups	0	0	0
<u>Visceral abnormalities</u>			
Number of pups	0	0	0

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

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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
Number of weanlings examined	118	84	100
<u>External abnormalities</u>			
Number of weanlings	0	0	0

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

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

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

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

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

b: absolute weight

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

*: significant difference from control, p<0.05

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

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

Compound	Nonylphenol				
	0 ^a	2	10	50	
Dose (mg/kg)					
Terminal body weight (g)	57.9 \pm 4.8 (60)	57.8 \pm 4.5 (41)	57.9 \pm 4.5 (41)	57.1 \pm 4.0 (46)	
Ovaries (mg)	17.0 \pm 3.3 b (60) 2.9 \pm 0.6 c (60)	18.0 \pm 4.0 (41) 3.1 \pm 0.6 (41)	17.7 \pm 4.3 (41) 3.1 \pm 0.7 (41)	17.2 \pm 5.3 (46) 3.0 \pm 1.0 (46)	
Uterus (mg)	25.8 \pm 3.6 (60) 4.5 \pm 0.7 (60)	26.5 \pm 4.0 (41) 4.6 \pm 0.7 (41)	25.4 \pm 6.5 (41) 4.4 \pm 1.1 (41)	24.1 \pm 5.0 (46) 4.2 \pm 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
Number of F1 male weanlings examined	58	43	44
Number of F1 male weanlings showing abnormalities	0	0	4
Types and number			
Dilatation of renal pelvis	0	0	3
Reddish epididymis	0	0	1

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

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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)

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

Summary of histopathological findings in F1 male at weaning

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)		[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

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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

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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 F1 male weanlings; Mean \pm S.D. (N)

Compound	Nonylphenol				
	0 ^a	2	10	50	
Dose (mg/kg)					
Testosterone (ng/mL)	0.9 \pm 0.4 (28)	0.8 \pm 0.4 (20)	0.9 \pm 0.6 (22)	1.3 \pm 0.7 (23)	
LH (ng/mL)	5.9 \pm 1.9 (29)	5.2 \pm 0.9 (20)	6.6 \pm 2.1 (22)	5.8 \pm 2.6 (23)	
FSH (ng/mL)	147.5 \pm 84.2 (29)	123.8 \pm 27.3 (20)	211.9 \pm 148.5 (22)	183.5 \pm 105.5 * (23)	
TSH (ng/mL)	9.5 \pm 1.5 (29)	8.4 \pm 0.8 * (20)	9.9 \pm 2.4 (22)	9.6 \pm 1.9 (23)	
T3 (ng/mL)	1.4 \pm 0.2 (29)	1.5 \pm 0.2 (20)	1.3 \pm 0.2 (22)	1.2 \pm 0.2 ** (23)	
T4 (ng/mL)	52.9 \pm 8.6 (29)	45.4 \pm 8.4 * (20)	52.2 \pm 9.2 (22)	55.0 \pm 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

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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), triiodothyronine (T₃), thyroxine (T₄) estradiol in F₁ female weanlings; Mean±S.D. (N)

Compound	Nonylphenol				
	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)	
T ₃ (ng/mL)	1.5 ± 0.2 (30)	1.2 ± 0.2 * (19)	1.5 ± 0.4 (25)	2.0 ± 0.2 ** (23)	
T ₄ (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 F₁ 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 oral administration in rats

Clinical signs of F₁ males

Dose (mg/kg)	Clinical signs	No. of animals showing clinical signs											Total
		Weeks of treatment											
		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		

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

Clinical signs of F₁ females

Dose (mg/kg)	Clinical signs	No. of animals showing clinical signs																	
		Weeks of treatment		3		4		5		6		7		8		9		10	
		1	2	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	0/59	0/59	0/59	0/59	0/59	0/59	0/59	0/59	0/59	0/59
2	Hypothermia	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41
	Soiled perineal region	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41
	Morbidity	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41	0/41
10	Loss of teeth	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50
50	Salivation	0/46	7/46	18/46	30/46	35/46	39/46	41/46	38/46	19/23	20/23								

Table 45

Two generation reproductive toxicity study of NP by oral administration in rats
 Body weight of F₁ males after weaning; Mean±S.D. (N)

Compound	Nonylphenol				
	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)