

Results of One-generation Tests in Evaluation of the Endocrine Disrupting Activities in Rodent

MOE, JAPAN

Aldrin

One-generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]				Dose [$\text{mg}/\text{kg}/\text{day}$]	Comments
0.1	0.5	2.5	12.5	1	
C	C	C	D	A*	Gavage for 42 days
F1 pups: High values of male sex ratio F2 pups: High values of male sex ratio	F0 dams: High values of food consumption F1 pups: Low values of viability F1 males: Low values of thymus (absolute/relative) weight F1 females: Low values of thymus (absolute/relative) weight F2 pups: High values of body weight, body weight gain	F0 dams: High values of food consumption F1 pups: High values of male sex ratio			

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

D: No statistically significant difference from the control was observed.

<Findings observed at A*> (The underlined findings have already been reported.)

F1 pups*: High values of liver relative weight. Low values of viability and air righting reflex rate in behavior test

F1 females*: High values of average section movement frequency, average grooming frequency and average rearing behavior frequency in open field test. Low values of body weight gain, body weight and thymus (absolute/relative) weight

Amitrole

One-Generation test

Concentration in drinking water [ppb]			Concentration in drinking water [ppm]		Comments
0.5	5	50	100	1,000	
Dose [$\mu\text{g}/\text{kg}/\text{day}$]			Dose [$\text{mg}/\text{kg}/\text{day}$]		
0.084-0.273	0.702-2.438	7.253-25.61	14.02-37.90	145.5-372.4	Drinking water for 42 days
D	D	C F1 females: Low values of body weight gain	A* ¹	A* ²	

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

D: No statistically significant difference from the control was observed.

<Findings observed at A*¹> (The underlined findings have already been reported.)

F0 dams*: High values of frequency of reddish or enlarged thyroid, thyroid (absolute/relative) weight, serum TSH level, frequency of follicular cell enlargement with colloid decrease or follicular capillary hyperemia or vascular degeneration of follicular cells in thyroid, serum T3 level, serum T4 level and frequency of chromophobic cell with enlargement or hyaline/vascular degeneration in pituitary gland. Low values of kidney (absolute/relative) weight, adrenal gland (absolute/relative) weight, food consumption and water intake.

F1 males*: High values of thyroid (absolute/relative) weight, follicular cell count in thyroid, frequency of enlarged/squamous follicular cell or follicular cell filled with lumen colloid or follicular capillary hyperemia in thyroid, frequency of chromophobic cell increase or acidophilic cell decrease in pituitary gland, frequency of depopulation or necrosis of reproductive cells in testis, frequency of outer cerebellar granular cell layer, serum T3 level and serum T4 level

F1 females*: High values of follicular cell number, frequency of enlarged follicular cell or capillary hyperemia in thyroid and frequency of chromophobic cell increase or acidophilic cell decrease or vascular/cystoid degeneration in pituitary gland. Low values of pituitary gland (absolute/relative) weight, serum T3 level, serum T4 level and rate of air righting reflex (delay).

<Findings observed at A*²> (The underlined findings have already been reported.)

F0 dams*: High values of frequency of reddish/enlarged thyroid, thyroid (absolute/relative) weight, serum TSH level, frequency of follicular cell enlargement/increase, capillary hyperemia in thyroid and frequency of chromophobic cell increase or hyaline/vascular degeneration of

chromophobic cells in pituitary gland. Low values of body weight gain, body weight, kidney (absolute/relative) weight, adrenal gland (absolute/relative) weight, food consumption, water intake, serum T3 level and serum T4 level

F1 males*: High values of frequency of enlarged or reddish thyroid, frequency of brain deformation, thyroid (absolute/relative) weight, follicular cell count in thyroid, frequency of enlarged follicular cell or squamous follicular cells or follicular cells filled with lumen colloid, and capillary hyperlemina in thyroid, frequency of chromophobic cell increase or acidophilic cell decrease in pituitary gland, frequency of depopulation or necrosis of reproductive cells in testis, frequency of outer cerebellar granular cell layer and frequency of partial cerebellum deficiency in brain. Low values of body weight, body weight gain, liver (absolute/relative) weight, serum T3 level, serum T4 level, brain size (absolute length), the rate of incisor eruption (delay), the rate of eyelid opening (delay), the rate of righting reflex (delay) and the rate of preputial separation (delay). High or Low values of testis (absolute/relative) weight

F1 females*: High values of thyroid (absolute/relative) weight, serum TSH level, frequency of enlarged/reddish thyroid, frequency of follicular cell increase or of enlarged follicular cell or squamous follicular cells or follicular cells filled with lumen colloid, and capillary hyperlemina in thyroid, frequency of brain deformation, body weight, frequency of chromophobic cell increase or acidophilic cell decrease in pituitary gland, frequency of outer cerebellar granular cell layer and the day of vaginal opening (delay). Low values of body weight, body weight gain, pituitary gland (absolute/relative) weight, the rate of incisor eruption (delay), the rate of eyelid opening (delay), the rate of air righting reflex (delay), serum T3 level, serum T4 level, ovary (absolute/relative) and weight, brain size (absolute length, length/width)

Benzophenone

One-generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]			Dose [$\text{mg}/\text{kg}/\text{day}$]		Comments
2	10	50	20	100	
C F0 dams: High values of food consumption	C F0 dams: High values of food consumption P F1 males: High values of serum LH level	C F1 males: Low values of dorsal prostate (absolute/ relative) weight P F1 males: Low values of spleen (absolute/relative) weight and serum FSH level F1 females: Low values of serum E2 level	A* ¹	A* ²	Gavage for 42 days

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

P: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. However, their biological/toxicological significance remains to be elucidated at present (pending).

<Findings observed at A*¹> (The underlined findings have already been reported.)

F0 dams*: High values of water intake

F1 males*: High values of kidney (absolute/relative) weight and serum LH level. Low values of serum E2 level and serum FSH level.

F1 females*: High values of adrenal (absolute/relative) weight and serum LH level. Low values of serum E2 level.

<Findings observed at A*²> (The underlined findings have already been reported.)

F0 dams*: High values of food consumption. Low values of number of delivered pups and gestation period.

F1 pups*: Low values of number of viable pups and viability of pups.

F1 males*: High values of AGD (absolute/relative) and serum LH level. Low values of residual nipples and serum FSH level. Degeneration of seminiferous tubule.

F1 females*: High values of kidney (absolute/relative) weight and serum LH level.

Bisphenol A

One-generation test

Concentration in drinking water [ppb]				Dose [mg/kg/day]	Comments
2	10	50	250		
Dose [$\mu\text{g}/\text{kg}/\text{day}$]					
0.473	2.24	11.8	53.8	500	
D	D	D	D	A*	2-250 ppb: Drinking water for 42 days 500 mg/kg/day: Gavage for 42 days

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

D: No statistically significant difference from the control was observed.

<Findings observed at A*> (The underlined findings have already been reported.)

F0 dams*: High values of number of individuals of muck on the meatal fur skin and kidney relative weight. Low values of food consumption and body weight. High or low values of body weight gain

F1 males*: High values of epididymis relative weight and testis relative weight

F1 females*: Low values of liver relative weight

Butylbenzyl phthalate

One-generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]				Dose [$\text{mg}/\text{kg}/\text{day}$]	Comments
2	12	60	300	500	
D	D	P F1 males: Low values of AR mRNA expression level in prostate and epididymis F1 females: Low values of AR mRNA expression level in ovary	P F1 females: High values of ER β mRNA expression level in uterus	A*	Gavage for 42 days

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

D: No statistically significant difference from the control was observed.

P: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. However, their biological/toxicological significance remains to be elucidated at present (pending).

<Findings observed at A*> (The underlined findings have already been reported.)

F0 dams*: Low values of food consumption

F1 pups*: Low values of number of viable pups

F1 males*: High values of serum levels of LH and FSH. Severity of necrotic seminiferous tubule atrophy. Low values of body weight, body weight gain, AGD (absolute/relative), epididymis size, vas deference size, testicular sperm cell count, epididymis sperm cell count, spermatic duct (absolute/relative) weight, testis (absolute/relative) weight, epididymis (absolute/relative) weight, seminal vesicle (absolute/relative) weight, prostate (absolute/relative) weight, conception rate after second mating with untreated female, ER β mRNA expression level in testis and AR mRNA expression level in prostate

F1 females*: High values of AGD (absolute/relative), Low values of body weight, body weight gain, conception rate, number of implantation, implantation rate, number of delivered pups, number of viable pups after second mating with untreated male and AR mRNA expression level in ovary

F2 pups* (from F1 female and untreated male): Low values of body weight gain.

cis-Chlordane

One-generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]				Dose [$\text{mg}/\text{kg}/\text{day}$]	Comments
0.1	0.5	2.5	12.5	10	
C	C	C	C	A*	Gavage for 42 days
F0 dams: Low values of kidney (absolute/relative) weight F1 females: High values of adrenal gland (absolute/relative) weight	F1 males: Low values of pituitary gland (absolute/relative) weight	F0 dams: Low values of food consumption, frequency of mineralization of the corticomedullary junction in the kidney F1 males: Low values of pituitary gland (absolute/relative) weight	F1 males: Low values of pituitary gland (absolute/relative) weight		

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

<Findings observed at A*> (The underlined findings have already been reported.)

F0 dams*: High values of food consumption. Low values of body weight gain and kidney relative weight

F1 pups*: Low values of viability

F1 males*: High values of frequency of vascular degeneration in liver cell. Low values of pituitary gland (absolute/relative) weight and kidney relative weight

F1 females*: High values of liver (absolute/relative) weight and frequency of vascular degeneration in liver cell

p,p'-DDD

One-generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]				Dose [$\text{mg}/\text{kg}/\text{day}$]	Comments
0.2	1	5	25	300	
D	D	D	D	A*	Gavage for 42 days

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

D: No statistically significant difference from the control was observed.

<Findings observed at A*> (The underlined findings have already been reported.)

F0 dams*: High values of liver relative weight. Low values of body weight and food consumption.
High or low values of body weight gain

F1 males*: High values of AGD relative, liver relative weight and frequency of vascular degeneration in cell around hepatic portal vein. Low values of body weight and pinna unfolding rate

F1 females*: High values of liver relative weight and spleen relative weight. Low values of body weight, pinna unfolding rate and brain absolute weight

p,p'-DDE

One-generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]				Dose [$\text{mg}/\text{kg}/\text{day}$]	Comments
0.03	0.30	3	30	50	
<p style="text-align: center;">C</p> <p>F1 pups: High values of male sex ratio</p> <p style="text-align: center;">P</p> <p>F1 males: Low values of C3mRNA expression level in prostates</p>	<p style="text-align: center;">C</p> <p>F1 pups: High values of male sex ratio</p> <p style="text-align: center;">P</p> <p>F1 males: Low values of C3mRNA expression level in prostates</p>	<p style="text-align: center;">C</p> <p>F1 pups: High values of male sex ratio</p> <p style="text-align: center;">P</p> <p>F1 males: Low values of C3mRNA expression level in prostates</p> <p style="text-align: center;">C</p> <p>F1 females: High values of the day of vaginal opening (delay), body weight and food consumption</p>	<p style="text-align: center;">P</p> <p>F1 males: Low values of C3mRNA expression level in prostates</p>	A*	Gavage for 42 days

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

P: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. However, their biological/toxicological significance remains to be elucidated at present (pending).

<Findings observed at A*> (The underlined findings have already been reported.)

F0 dams*: High values of liver (absolute/relative) weight and frequency of darkish hepatic color.

Low values of food consumption

F1 males*: High values of liver (absolute/relative) weight, frequency of centrilobular hypertrophy of the hepatocyte and food consumption. Low values of epididymis absolute weight, seminal vesicle absolute weight, C3mRNA expression level in prostates and thymus relative weight

F1 females*: High values of liver (absolute/relative) weight, frequency of centrilobular hypertrophy of the hepatocyte, rate of incisor eruption and food consumption

o,p'-DDT

One-generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]				Dose [$\text{mg}/\text{kg}/\text{day}$]	Comments
0.2	1	5	25	50	
D	D	P F0 dams: High values of frequency of thymic lymphatic tissue atrophy	P F0 dams: High values of frequency of thymic lymphatic tissue atrophy	A*	Gavage for 42 days

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

D: No statistically significant difference from the control was observed.

P: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. However, their biological/toxicological significance remains to be elucidated at present (pending).

<Findings observed at A*> (The underlined findings have already been reported.)

F0 dams*: Low values of conception rate (0%)

p,p'-DDT

One-generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]				Dose [$\text{mg}/\text{kg}/\text{day}$]	Comments
0.2	1	5	25	10	
D	C F0 dams: High values of food consumption	D	D	A*	Gavage for 42 days

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

D: No statistically significant difference from the control was observed.

<Findings observed at A*> (The underlined findings have already been reported.)

F0 dams*: High values of liver absolute weight

F1 males*: High values of liver (absolute/relative) weight, frequency of vascular degeneration in hepatocyte and rate of sperm head abnormality

F1 females*: High values of liver (absolute/relative) weight and frequency of vascular degeneration in hepatocyte

Di-*n*-butyl phthalate

One-generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]					Dose [$\text{mg}/\text{kg}/\text{day}$]	Comments
31	63	125	250	500	250	
C	D	D	D	D	A*	Gavage for 42 days
F1 males: High values of seminal vesicle (absolute/relative) weight						

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

D: No statistically significant difference from the control was observed.

<Findings observed at A*> (The underlined findings have already been reported.)

F1 males*: High values of spleen (absolute/relative) weight

2,4-Dichlorophenol

One-generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]				Dose [$\text{mg}/\text{kg}/\text{day}$]	Comments
0.8	4	20	100	400	
D	D	C F1 males: Low values of platelet count	D	A*	Gavage for 42 days

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

D: No statistically significant difference from the control was observed.

<Findings observed at A*> (The underlined findings of 1) and 2) have already been reported for F1 and F0, respectively.)

F0 dams*: High values of liver (absolute/relative) weight¹⁾ and body weight gain and percentage of monocyte. Low values of food consumption

F1 males*: Low values of body weight gain²⁾ and body weight.

F1 females*: Low values of body weight gain²⁾ and body weight.

Dicyclohexyl phthalate

One-generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]				Dose [mg/kg/day]	Comments
1.6	8	40	200	500	
C F1 males: Low values of pituitary gland (absolute/relative) weight F1 females: High values of fetal death rate	P F1 females: High values of ER α and AR mRNA expression level in uterus	P F1 females: High values of ER α and AR mRNA expression level in uterus	C F0 dams: Low values of implantation sites P F1 females: High values of ER α and AR mRNA expression level in uterus	A*	Gavage for 42 days

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

P: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. However, their biological/toxicological significance remains to be elucidated at present (pending).

<Findings observed at A*> (The underlined findings have already been reported.)

F0 dams*: High values of liver (absolute/relative) weight and adrenal (absolute/relative) weight. Hypertrophy of the centrilobular hepatocyte. Prolongation of gestation period. Low values of body weight, food consumption and number of delivered pups

F₁ males*: High values of mRNA expression level in AR in the prostate. Low values of body weight, testis (absolute/relative) weight, seminal vesicle (absolute/relative) weight, epididymides (absolute/relative) weight, kidney (absolute/relative) weight, prostate (absolute/relative) weight and levator ani muscle (absolute/relative) weight. Defects of the kidney, epididymis, ureter or seminal vesicle, small testis or epididymis, hypoplasia/agenesis of the epididymis, disappearance of the germ cell in the seminiferous tubule, hyperplasia/giant cell formation of Leydig cell, disappearance of the sperm in the lumen of the epididymis, cell debris in the lumen of the epididymis.

F₁ females*: Low values of body weight. Small uterus, hypoplasia/agenesis of the uterine horn, defects of the kidney, ureter, ovary, oviduct and uterine horn, and mineralization of the corticomedullary junction in the kidney.

Dieldrin

One-generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]				Dose [$\text{mg}/\text{kg}/\text{day}$]	Comments
0.1	0.5	2.5	12.5	1	
C F0 dams: Low values of food consumption F1 males: Low values of sperm head amplitude F1 females: Low values of body weight	C F1 females: Low values of body weight	D	C F0 dams: High values of body weight gain	A*	Gavage for 42 days

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

D: No statistically significant difference from the control was observed.

<Findings observed at A*> (The underlined findings have already been reported.)

F1 pups*: Low values of viability

F1 females*: High values of liver relative weight

Di-(2-ethylhexyl) adipate

One-generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]		Dose [$\text{mg}/\text{kg}/\text{day}$]			Comments
15	150	1.5	15	600	
D	C F0 dams: Low values of body weight gain	C F1 males: Low values of serum testosterone level	C F1 males: Low values of serum testosterone level	A*	Gavage for 42 days

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

D: No statistically significant difference from the control was observed.

<Findings observed at A*> (The underlined findings have already been reported.)

F0 dams*: High values of liver (absolute and relative) weight.

F1 pups*: High values of number of stillborns. Low values of weaning rate.

F1 males*: Low values of serum testosterone level.

F1 females*: Low values of ER α mRNA expression level in ovaries.

Di-(2-ethylhexyl) phthalate

One-generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]			Dose [$\text{mg}/\text{kg}/\text{day}$]		Comments
10	50	250	1.25	100	
D	C F1 females: High values of serum FSH level	D	D	A*	Gavage for 42 days

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

D: No statistically significant difference from the control was observed.

<Findings observed at A*> (The underlined findings have already been reported.)

F0 dams*: High values of liver (absolute/relative) weight and centrilobular hypertrophy of the hepatocyte. Increase of eosinophilic granule of the hepatocyte. Enlargement of liver.

Diethyl phthalate

One-generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]				Dose [$\text{mg}/\text{kg}/\text{day}$]	Comments
0.4	2	10	50	2,000	
C F0 dams: Low values of pituitary gland (absolute/relative) weight	C F0 dams: Low values of pituitary gland (absolute/relative) weight	C F0 dams: Low values of pituitary gland (absolute/relative) weight and thyroid (absolute/relative) weight	C F0 dams: Low values of pituitary gland (absolute/relative) weight and thyroid (absolute/relative) weight F1 females: delay of vaginal opening	A*	Gavage for 42 days

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

<Findings observed at A*> (The underlined findings have already been reported.)

F0 dams*: Low values of body weight, body weight gain, pituitary gland (absolute/relative) weight, food consumption, thyroid weight (absolute/relative) and Eosinophilic granular change of liver.

F1 pups*: Low values of viability rate and number of live offspring.

F1 males*: Low values of body weight, sperm motility (straight line velocity), body weight gain, thymus (absolute/relative) weight, testis (absolute/relative) weight; delays of behavioral development (negative geotaxis), physical development (pinna unfolding and eyelid opening) and preputial separation. Changed FSH level in serum (decreased; day 21 of lactation, increased; after mating), and histopathological changes in the testis (day 21 of lactation: decreased number of the germ cells and appearance of the elongated nuclear cells, after weaning: focal tubular atrophy).

F1 females*: High values of AGD (absolute and relative). Low values of body weight, body weight gain, thymus (absolute/relative) weight, kidney (absolute/relative) weight and motor activity (horizontal movement and rearing behavior). Delays of behavioral development (cliff aversion and negative geotaxis) and physical development (pinna unfolding, eyelid opening).

Dihexyl phthalate

One-generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]				Dose [$\text{mg}/\text{kg}/\text{day}$]	Comments
2	10	50	250	500	
P F1 males: Low values of average grooming frequency in open field test	D	D	C F1 males: High values of frequency of minor or moderate lymphocyte infiltration of prostate interstitial tissue	A*	Gavage for 42 days

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

D: No statistically significant difference from the control was observed.

P: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. However, their biological/toxicological significance remains to be elucidated at present (pending).

<Findings observed at A*> (The underlined findings have already been reported.)

F0 dams*: Low values of number of delivered pups and food consumption

F1 males*: Low values of body weight and AGD (absolute/relative)

F1 females*: Low values of implantation sites

Dipentyl phthalate

One-generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]				Dose [$\text{mg}/\text{kg}/\text{day}$]	Comments
2	10	50	250	1,000	
D	C F1 females: Low values of backing error frequency at the second trial on the first day of T-shaped water maize test	C F1 males: High values of select error frequency at the first and third trials on the first day of T-shaped water maize test	C F1 females: High values of spleen (absolute/relative) weight	A*	Gavage for 42 days

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

D: No statistically significant difference from the control was observed.

<Findings observed at A*> (The underlined findings have already been reported.)

F0 dams*: Low values of body weight, fertility rate, number of delivered pups (all dead), body weight gain and food consumption.

Dipropyl phthalate

One-generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]				Dose [$\text{mg}/\text{kg}/\text{day}$]	Comments
2	10	50	250	2,000	
C	C	D	C	A*	Gavage for 42 days
F1 females: Low values of body weight, body weight gain and food consumption	F0 dams: High values of body weight gain F1 males: Low values of the day of preputial separation (advance) F1 females: High values of brain absolute weight		F1 males: Low values of body weight and body weight gain F1 females: Low values of food consumption and body weight P F1 males: Low values of body weight and body weight gain		

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

D: No statistically significant difference from the control was observed.

P: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. However, their biological/toxicological significance remains to be elucidated at present (pending).

<Findings observed at A*> (The underlined findings have already been reported.)

F0 dams*: High values of liver (absolute/relative) weight and frequency of sialorrhea. Low values of food consumption

F1 pups*: Low values of viability

F1 males*: High values of mortality. Low values of body weight, body weight gain, brain absolute weight, spleen (absolute/relative) weight, food consumption and error frequency on the third day of learning test

F1 females*: High values of mortality, frequency of incisive malocclusion, the day of pinna unfolding and the day of vaginal opening. Low values of body weight, air righting reflex rate, spleen (absolute/relative) weight, body weight gain, food consumption and frequency of rearing behavior

Endrin

One-generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]				Dose [$\text{mg}/\text{kg}/\text{day}$]	Comments
0.1	1	5	25	0.4	
D	C F0 dams: Low values of food consumption	D	D	A*	Gavage for 42 days

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

D: No statistically significant difference from the control was observed.

<Findings observed at A*> (The underlined findings have already been reported.)

F0 dams*: High values of frequency of all newborns died. Low values of body weight gain, food consumption

F1 pups*: Low values of liver relative weight

F1 males*: High values of AGD relative

F1 females*: Low values of pituitary gland (absolute/ relative) weight

Heptachlor

One-generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]			Dose [$\text{mg}/\text{kg}/\text{day}$]		Comments
0.05	0.5	5	1	3	
D	D	C	A* ¹	A* ²	Gavage for 42 days
		F1 males : Low values of frequency of thyroid follicles epithelial edema			

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

D: No statistically significant difference from the control was observed.

<Findings observed at A*¹> (The underlined findings have already been reported.)

F1 pups*: High values of liver (absolute/relative) weight and frequency of hypertrophy of the centrilobular hepatocyte

F1 females*: High values of body weight at vaginal opening day. Delay of vaginal opening day

<Findings observed at A*²> (The underlined findings have already been reported.)

F0 dams*: High values of frequency of all newborns died

F1 pups*: High values of frequency of died, liver (absolute/relative) weight and frequency of hypertrophy of the centrilobular hepatocyte. Low values of viability

Hexachlorobenzene

One-generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]				Dose [$\text{mg}/\text{kg}/\text{day}$]	Comments
0.04	0.4	4	40	40	
C	C	C	C	A*	Gavage for 42 days
F1 males: Low values of sperm motility (path velocity, straight line velocity)	F1 males: Low values of sperm motility (path velocity, straight line velocity) F1 females: Low values of serum levels of triglyceride	F1 males: Low values of blood phospholipid level, serum levels of triglyceride and sperm motility (path velocity, straight line velocity, curvilinear velocity)	F1 males: Low values of blood phospholipid level, serum levels of triglyceride and sperm motility (path velocity, straight line velocity, curvilinear velocity) F1 females: Low values of serum levels of triglyceride		

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

<Findings observed at A*> (The underlined findings have already been reported.)

F0 dams*: High values of frequency of dysfunctional gestation (neglected pup, improper placental care, poor suckling behavior), frequency of tremor, frequency of autopsy finding (mammary gland developmental deficiency and defects of thymus), frequency of hypertrophy of the centrilobular hepatocyte, frequency of hepatic steatosis, frequency of hepatocellular necrosis, frequency of hepatocellular cell division, frequency of proximal tubular steatosis, frequency of defects of thymus, frequency of agalactosis and frequency of all pups died

F1 pups*: Low values of fertility rate, number of live offspring and viability

F1 males*: Low values of body weight and frequency of developed righting reflex

F1 females*: Low values of frequency of developed righting reflex

beta-Hexachlorocyclohexane

One-generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]				Dose [$\text{mg}/\text{kg}/\text{day}$]	Comments
0.1	0.5	2.5	12.5	5	
C	D	D	D	A*	Gavage for 42 days
F1 males: High values of endurance in swimming behavior test(first time) and liver (absolute/relative) weight					

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

D: No statistically significant difference from the control was observed.

<Findings observed at A*> (The underlined findings have already been reported.)

F0 dams*: Low values of body weight gain and food consumption

F1 pups*: Low values of number of live weaning pups and viability

F1 males*: High values of liver relative weight. Low values of testis absolute weight, brain absolute weight and prostate (absolute/relative) weight

F1 females*: High values of liver relative weight, pituitary gland relative weight, kidney relative weight, adrenal gland relative weight, frequency of reduction of corpora lutea in ovary, frequency of uterine squamous metaplasia, frequency of endometrial squamous metaplasia and frequency of vaginal cornification. Low values of thymus (absolute/relative) weight, body weight gain, brain absolute weight, ovary (absolute/relative) weight. Delay of vaginal opening day and first estrus. Persistent estrus. High or low values of uterus (absolute/relative) weight. High or low values of body weight

Malathion

One-generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]				Dose [$\text{mg}/\text{kg}/\text{day}$]	Comments
1	5	25	125		
D	C F0 dams: Low values of body weight gain and food consumption	C F0 dams: Low values of body weight gain and food consumption	C F0 dams: Low values of food consumption	A*	Gavage for 42 days

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

D: No statistically significant difference from the control was observed.

<Findings observed at A*> (The underlined findings have already been reported.)

F0 dams*: Low values of acetylcholine esterase activity in brain

Mirex

One-generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]				Dose [$\text{mg}/\text{kg}/\text{day}$]	Comments
0.02	0.2	2	20	2	
D	D	C F1 females: High values of body weight and body weight at autopsy	C F1 females: High values of body weight at autopsy	A*	Gavage for 42 days

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

D: No statistically significant difference from the control was observed.

<Findings observed at A*> (The underlined findings have already been reported.)

F0 dams*: High values of frequency of hypertrophy of the centrilobular hepatocyte and frequency of all newborns died. Low values of body weight gain and food consumption

F1 pups*: High values of frequency of cataract. Low values of viability, fertility rate number of live offspring and rate of developed righting reflex

F1 females*: Low values of rate of developed auditory canal and body weight gain. Delay of vaginal opening day

4-Nitrotoluene

One-generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]				Dose [$\text{mg}/\text{kg}/\text{day}$]	Comments
1	5	25	125	100	
C	C	C	C	A*	Gavage for 42 days
F0 dams: Low values of erythrocyte count and hematocrit	F0 dams: Low values of hematocrit	F0 dams: Low values of erythrocyte count, hemoglobin content and hematocrit P F1 males: Low values of reticulocyte count F1 females: High values of neutrophil percentage	F0 dams: Low values of hematocrit F1 male: Low values of body weight gain P F1 females: Low values of reticulocyte count		

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

P: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. However, their biological/toxicological significance remains to be elucidated at present (pending).

<Findings observed at A*> (The underlined findings have already been reported.)

F0 dams*: High values of body weight gain and average erythrocyte pigment level. Low values of erythrocyte count, hemoglobin content and hematocrit.

F1 males*: Low values of body weight gain, liver (absolute) weight and body weight and reticulocyte count.

F1 females*: High values of the day of incisor eruption (delay). Low values of body weight, hemoglobin content, reticulocyte count and leukocyte count

trans-Nonachlor

One-generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]				Dose [$\text{mg}/\text{kg}/\text{day}$]	Comments
0.05	0.5	5	50	10	
D	D	C F0 dams: Low values of body weight gain F1 males: High values of brain absolute weight F1 females: High values of brain absolute weight	C F1 males: High values of brain absolute weight	A*	Gavage for 42 days

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

D: No statistically significant difference from the control was observed.

<Findings observed at A*> (Underlined findings were only observed in preliminary tests.)

F0 dams*: High values of liver relative weight, frequency of hypertrophy of the centrilobular hepatocyte and frequency of hepatocellular ground glass appearance in central lobule. Low values of body weight gain

F1 males*: High values of brain absolute weight, liver (absolute/relative) weight, frequency of hypertrophy of the centrilobular hepatocyte and frequency of hepatocellular vacuolization in lobular intermediate zone

F1 females*: High values of brain absolute weight, liver (absolute/relative) weight, ovary relative weight, frequency of hypertrophy of the centrilobular hepatocyte and frequency of hepatocellular vacuolization in lobular intermediate zone

4-Nonylphenol(branched)

One-generation test

Concentration [ppb]				Dose of EE [µg/kg/day]	Comments
30	100	300	1,000		
Dose [µg/kg/day]				0.1	
6.9	23.2	70.9	234		
C F1 pups: Low values of male sex ratio F1 males: High values of body weight gain	C F0 dams: High values of food consumption	P F1 males: Low values of GAPDH mRNA expression level in prostate. High values of ERβ and AR mRNA expression levels in prostate	C F0 dams: High values of food consumption P F0 dams: High values of spleen (absolute/relative) weight F1 males: High values of ERβ and AR mRNA expression level in prostate F1 females: High values of GAPDH mRNA expression level in uterus	A*	Drinking water for 42 days EE: Subcutaneous injection for 42 days

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

P: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. However, their biological/toxicological significance remains to be elucidated at present (pending).

<Findings observed at A*> (Underlined findings were only observed in preliminary tests.)

F0 dams*: High values of food consumption

F1 males*: High values of body weight, body weight gain and water intake

F1 females*: High values of food consumption and water intake. Low value of the first estrus cycle period

Octachlorostyrene

One-generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]				Dose [$\text{mg}/\text{kg}/\text{day}$]	Comments
2.4	12	60	300	50	
C	D	C	C	A*	Gavage for 42 days
F1 females: High values of corpora lutea		F1 females: Low values of uterus (absolute/relative) weight	F1 males: High values of epididymis (absolute/relative) weight		
		P	P		
		F1 females: High values of ER β mRNA expression level in uterus	F1 females: High values of ER β mRNA expression level in uterus		

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

D: No statistically significant difference from the control was observed.

P: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. However, their biological/toxicological significance remains to be elucidated at present (pending).

<Findings observed at A*> (The underlined findings have already been reported.)

F0 dams*: Hypertrophy of the centrilobular hepatocyte. Slight proliferation of mammary gland lobule. Low values of food consumption and number of implantations.

F1 pups*: Low values of viability rate (all newborns died before Day 9 of lactation) and body weight.

4-*t*-Octylphenol

One-generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]				Dose of EE [$\mu\text{g}/\text{kg}/\text{day}$]	Comments
3	10	30	100	0.1	
D	C F1 females: Low values of spleen (absolute/relative) weight P F1 males: High values of GAPDH mRNA expression level in prostate	D	P F1 females: Low values of IGF-1 mRNA expression level in uterus	A*	Gavage for 42 days EE: subcutaneous injection for 42 days

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

D: No statistically significant difference from the control was observed.

P: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. However, their biological/toxicological significance remains to be elucidated at present (pending).

<Findings observed at A*> (Underlined findings were only observed in preliminary tests.)

F1 males*: High values of ER β and GAPDH mRNA expression level in prostate and testicular sperm count. Low values of AR mRNA expression level in prostate, body weight and spleen (absolute/relative) weight.

F1 females*: Low values of body weight spleen (absolute/relative) weight, IGF-1 mRNA expression level in uterus and the day of vaginal opening (advance).

Pentachlorophenol

One-Generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]				Dose [$\text{mg}/\text{kg}/\text{day}$]	Comments
0.5	5	50	500	30	
C	P	C	C	A*	Gavage for 42 days
F1 females: Low values of body weight gain. High values of error frequency at the first time of the third trial of T-shaped water maize tests	F1 females: High values of spleen (absolute/relative) weight	F1 males: Low values of seminal vesicle (absolute/relative) weight	F1 males: Low values of seminal vesicle (absolute/relative) weight. High values of error frequency at the third time of the first trial of T-shaped water maize tests and endurance in swimming behavior test F1 females: Low values of body weight gain		

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

P: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. However, their biological/toxicological significance remains to be elucidated at present (pending).

<Findings observed at A*> (The underlined findings have already been reported.)

F0 dams*: High values of liver (absolute/relative) weight. Low values of body weight, body weight gain and fertility rate

F1 pups*: High value of male sex ratio. Low values of number of delivered pups and number of viable pups

F1 males*: High values of testicular sperm cell count, the day of incisor eruption (delay) and the day of preputial separation (delay). Low values of body weight, body weight gain, pinna unfolding rate, testis (absolute/relative) weight, prostate (absolute/relative) weight and brain (absolute/relative) weight.

F1 females*: High values of ovary (absolute/relative) weight, thymus (absolute/relative) weight,

spleen (absolute/relative) weight and the day of incisor eruption (delay). Low values of body weight, body weight gain, pinna unfolding rate, endurance in swimming behavior test (at the first time of the first trial), error frequency in the T-shaped water maize test (at the first time of the third trial) and brain absolute weight.

F2 pups*: Low values of number of delivered pups and number of viable pups.

Permethrin (mixture)

(*cis*-Permethrin:*trans*-Permethrin=40:60)

One-generation test

Dose [$\mu\text{g}/\text{kg}/\text{day}$]				Dose [$\text{mg}/\text{kg}/\text{day}$]	Comments
0.5	5	50	500	100	
D	C F1 females: Low values of pituitary gland (absolute/ relative) weight	D	D	A*	Gavage for 42 days

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

D: No statistically significant difference from the control was observed.

<Findings observed at A*> (The underlined findings have already been reported.)

F0 dams*: High values of frequency of tremor or hypersensitivity

F1 females*: Low values of pituitary gland (absolute/ relative) weight

Tributyltin chloride

One-generation test

Concentration in diet [ppm]					Comments
0.15	0.45	1.5	4.5	30	
Dose [$\mu\text{g}/\text{kg}/\text{day}$]				Dose [$\text{mg}/\text{kg}/\text{day}$]	
10	30	100	300	2	
D	D	C F1 males: Low values of spleen (absolute/relative) weight	C F0 dams: High values of food consumption F1 males: Low values of spleen (absolute/relative) weight P F1 males: High values of neutrophil percentage	A*	Dietary for 42 days

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

D: No statistically significant difference from the control was observed.

P: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. However, their biological/toxicological significance remains to be elucidated at present (pending).

<Findings observed at A*> (The underlined findings have already been reported.)

F0 dams*: Low values of body weight, thymus (absolute/relative) weight, spleen (absolute/relative) weight, ovary (absolute/relative) weight and uterus (absolute/relative) weight.

F1 males*: Low values of spleen (absolute/relative) weight.

F1 females*: Low values of body weight and thymus (absolute/relative) weight.

Triphenyltin chloride

One-generation test

Concentration in diet [ppm]					Comments
0.015	0.15	1.5	5	15	
Dose [$\mu\text{g}/\text{kg}/\text{day}$]				Dose [$\text{mg}/\text{kg}/\text{day}$]	
1.1	11	107	370	1.117	
D	D	C F1 males: Low values of body weight	C F0 dams: High values of food efficiency P F1 females: Low values of serum levels of T3	A*	Dietary for 42 days

A: Substantial changes (statistically significant differences from the control) that have already been reported were observed around the LOEL or LOAEL.

C: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. In the present study, however, these changes are suggested to be within the range of biological/physiological deviation.

D: No statistically significant difference from the control was observed.

P: Statistically significant differences from the control were observed in certain endpoints below the LOEL or LOAEL at which some effects have already been reported. However, their biological/toxicological significance remains to be elucidated at present (pending).

<Findings observed at A*> (The underlined findings have already been reported.)

F0 dams*: Low values of food consumption.

F1 pups*: Low values of viability.