

反復投与毒性・生殖発生毒性併合試験

Table 1 Hematological examinations of rats treated orally with *O,O'*-diethyl dithiophosphate in the combined repeated dose and reproductive/developmental toxicity screening test

Dose level		0 mg/kg	30 mg/kg	100 mg/kg	300 mg/kg	0 mg/kg ^{a)}	300 mg/kg ^{a)}
Male							
No. of animals examined		5	5	5	5	5	5
WBC	($\times 10^3/\text{mm}^3$)	10.29 \pm 4.24	12.85 \pm 0.62	9.87 \pm 1.12	10.85 \pm 2.88	10.16 \pm 1.01	13.70 \pm 2.66*
RBC	($\times 10^6/\text{mm}^3$)	8.89 \pm 0.27	8.87 \pm 0.14	8.50 \pm 0.20	8.47 \pm 0.32*	8.58 \pm 0.25	8.92 \pm 0.55
HGB	(g/dL)	15.7 \pm 0.7	15.6 \pm 0.6	14.9 \pm 0.4	14.6 \pm 0.5*	15.4 \pm 0.3	15.2 \pm 0.7
HCT	(%)	44.3 \pm 2.0	44.5 \pm 1.7	42.0 \pm 1.2	42.0 \pm 0.9	43.3 \pm 1.3	42.2 \pm 1.1
MCV	(μm^3)	49.8 \pm 1.1	50.2 \pm 1.9	49.4 \pm 1.2	49.7 \pm 1.3	50.5 \pm 0.4	47.5 \pm 2.8
MCH	(pg)	17.6 \pm 0.4	17.6 \pm 0.7	17.5 \pm 0.4	17.3 \pm 0.8	18.0 \pm 0.4	17.1 \pm 1.5
MCHC	(%)	35.3 \pm 0.2	35.1 \pm 0.4	35.5 \pm 0.6	34.8 \pm 0.8	35.6 \pm 0.8	36.0 \pm 1.3
PLT	($\times 10^3/\text{mm}^3$)	1068 \pm 110	1012 \pm 60	957 \pm 44	1112 \pm 138	1067 \pm 82	1121 \pm 114
Differential leukocyte counts							
NEUT	($\times 10^3/\text{mm}^3$)	1.86 \pm 0.54	1.55 \pm 0.40	1.56 \pm 0.26	2.27 \pm 0.48	1.31 \pm 0.54	2.45 \pm 0.76*
	(%)	19.0 \pm 4.1	12.0 \pm 2.6*	16.1 \pm 4.0	21.4 \pm 3.7	13.2 \pm 6.0	17.8 \pm 3.3
LYMPH	($\times 10^3/\text{mm}^3$)	7.87 \pm 3.50	10.74 \pm 0.32	7.75 \pm 1.21	8.10 \pm 2.46	8.52 \pm 1.44	10.75 \pm 2.00
	(%)	75.7 \pm 3.0	83.7 \pm 2.7**	78.2 \pm 3.8	74.0 \pm 3.9	83.5 \pm 6.2	78.6 \pm 2.8
MONO	($\times 10^3/\text{mm}^3$)	0.29 \pm 0.16	0.25 \pm 0.06	0.25 \pm 0.04	0.24 \pm 0.06	0.17 \pm 0.03	0.23 \pm 0.07
	(%)	2.7 \pm 0.5	1.9 \pm 0.5	2.6 \pm 0.4	2.3 \pm 0.6	1.7 \pm 0.3	1.7 \pm 0.3
EOSN	($\times 10^3/\text{mm}^3$)	0.11 \pm 0.06	0.13 \pm 0.05	0.16 \pm 0.03	0.12 \pm 0.03	0.07 \pm 0.02	0.15 \pm 0.06*
	(%)	1.0 \pm 0.4	1.0 \pm 0.3	1.6 \pm 0.4	1.2 \pm 0.5	0.7 \pm 0.2	1.1 \pm 0.4
BASO	($\times 10^3/\text{mm}^3$)	0.01 \pm 0.01	0.02 \pm 0.01	0.01 \pm 0.00	0.01 \pm 0.01	0.01 \pm 0.01	0.02 \pm 0.01
	(%)	0.1 \pm 0.1	0.2 \pm 0.1	0.1 \pm 0.0	0.1 \pm 0.1	0.1 \pm 0.1	0.1 \pm 0.1
LUC	($\times 10^3/\text{mm}^3$)	0.15 \pm 0.08	0.16 \pm 0.08	0.14 \pm 0.08	0.11 \pm 0.04	0.09 \pm 0.02	0.11 \pm 0.02
	(%)	1.5 \pm 0.7	1.3 \pm 0.6	1.4 \pm 0.7	1.0 \pm 0.2	0.9 \pm 0.2	0.8 \pm 0.2
Reticulocyte	(%)	2.2 \pm 0.2	2.0 \pm 0.4	1.9 \pm 0.4	2.7 \pm 0.6	2.0 \pm 0.4	2.1 \pm 0.6
Coagulation							
PT	(sec.)	19.3 \pm 1.5	19.3 \pm 0.7	20.7 \pm 2.6	23.8 \pm 3.9	18.8 \pm 3.5	20.1 \pm 2.8
APTT	(sec.)	22.0 \pm 1.8	22.9 \pm 1.8	21.4 \pm 2.9	22.6 \pm 1.9	23.0 \pm 1.8	23.5 \pm 2.5
Female							
No. of animals examined		5	5	5	5	5	4
WBC	($\times 10^3/\text{mm}^3$)	12.30 \pm 2.13	11.83 \pm 2.68	15.72 \pm 3.80	10.58 \pm 4.13	5.43 \pm 1.99	4.67 \pm 1.45
RBC	($\times 10^6/\text{mm}^3$)	7.10 \pm 0.48	7.12 \pm 0.32	7.00 \pm 0.39	6.62 \pm 0.40	8.16 \pm 0.44	8.70 \pm 0.14
HGB	(g/dL)	13.6 \pm 0.4	13.6 \pm 0.7	13.6 \pm 0.6	12.9 \pm 0.7	15.0 \pm 0.7	16.1 \pm 0.3*
HCT	(%)	39.0 \pm 1.2	39.1 \pm 1.1	38.1 \pm 1.9	37.1 \pm 1.3	41.6 \pm 2.2	44.2 \pm 1.0
MCV	(μm^3)	55.0 \pm 2.3	54.9 \pm 1.6	54.5 \pm 2.0	56.2 \pm 2.4	51.0 \pm 0.5	50.8 \pm 0.7
MCH	(pg)	19.2 \pm 0.8	19.1 \pm 0.8	19.5 \pm 0.7	19.5 \pm 0.6	18.4 \pm 0.2	18.5 \pm 0.2
MCHC	(%)	34.9 \pm 0.8	34.8 \pm 1.2	35.8 \pm 0.7	34.6 \pm 0.8	36.1 \pm 0.3	36.5 \pm 0.6
PLT	($\times 10^3/\text{mm}^3$)	1304 \pm 60	1129 \pm 109	1286 \pm 256	1017 \pm 89*	1061 \pm 146	1115 \pm 150
Differential leukocyte counts							
NEUT	($\times 10^3/\text{mm}^3$)	4.24 \pm 1.12	4.73 \pm 1.36	5.28 \pm 1.70	3.01 \pm 2.15	1.21 \pm 0.75	0.95 \pm 0.75
	(%)	34.2 \pm 6.5	39.7 \pm 4.7	33.9 \pm 7.0	27.2 \pm 11.2	21.6 \pm 7.0	19.0 \pm 9.8
LYMPH	($\times 10^3/\text{mm}^3$)	7.55 \pm 1.33	6.59 \pm 1.48	9.67 \pm 2.62	7.06 \pm 2.79	3.95 \pm 1.38	3.51 \pm 0.91
	(%)	61.6 \pm 6.5	55.8 \pm 4.2	61.2 \pm 6.3	67.5 \pm 10.5	73.5 \pm 6.8	76.4 \pm 10.5
MONO	($\times 10^3/\text{mm}^3$)	0.34 \pm 0.13	0.33 \pm 0.11	0.50 \pm 0.08	0.27 \pm 0.09	0.12 \pm 0.06	0.10 \pm 0.05
	(%)	2.7 \pm 0.7	2.8 \pm 0.9	3.3 \pm 0.6	2.7 \pm 0.8	2.2 \pm 0.6	2.1 \pm 0.7
EOSN	($\times 10^3/\text{mm}^3$)	0.08 \pm 0.04	0.06 \pm 0.03	0.08 \pm 0.04	0.08 \pm 0.05	0.11 \pm 0.07	0.08 \pm 0.03
	(%)	0.6 \pm 0.3	0.6 \pm 0.2	0.5 \pm 0.2	0.9 \pm 0.4	2.0 \pm 1.0	1.8 \pm 0.6
BASO	($\times 10^3/\text{mm}^3$)	0.01 \pm 0.01	0.01 \pm 0.00	0.01 \pm 0.01	0.01 \pm 0.01	0.00 \pm 0.01	0.00 \pm 0.01
	(%)	0.1 \pm 0.0	0.1 \pm 0.0	0.1 \pm 0.0	0.1 \pm 0.0	0.1 \pm 0.0	0.1 \pm 0.1
LUC	($\times 10^3/\text{mm}^3$)	0.09 \pm 0.03	0.11 \pm 0.03	0.17 \pm 0.14	0.15 \pm 0.05	0.03 \pm 0.02	0.03 \pm 0.01
	(%)	0.8 \pm 0.2	1.0 \pm 0.3	1.0 \pm 0.7	1.7 \pm 0.9	0.6 \pm 0.2	0.7 \pm 0.1
Reticulocyte	(%)	6.0 \pm 2.1	6.9 \pm 1.2	7.1 \pm 2.3	7.5 \pm 2.8	2.0 \pm 0.3	1.6 \pm 0.3
Coagulation							
PT	(sec.)	18.2 \pm 0.5	17.7 \pm 0.7	18.4 \pm 1.0	18.5 \pm 1.3	15.8 \pm 1.0	15.6 \pm 0.4
APTT	(sec.)	16.7 \pm 1.7	16.1 \pm 2.4	17.0 \pm 2.0	15.0 \pm 1.3	18.6 \pm 1.0	18.7 \pm 1.2

NEUT: Neutrophil LYMPH: Lymphocyte MONO: Monocyte EOSN: Eosinophil BASO: Basophil LUC: Large unstained cells

Values are expressed as Mean \pm S.D.

Significant difference from control group; * $p \leq 0.05$, ** $p \leq 0.01$.

a) Recovery group

Table 2 Blood chemical examinations of rats treated orally with O,O'-diethyl dithiophosphate in the combined repeated dose and reproductive/developmental toxicity screening test

Dose level		0 mg/kg	30 mg/kg	100 mg/kg	300 mg/kg	0 mg/kg ^{a)}	300 mg/kg ^{a)}
Male							
No. of animals examined		5	5	5	5	5	5
T.protein	(g/dL)	6.28 ± 0.24	6.31 ± 0.12	6.21 ± 0.31	5.85 ± 0.33	6.08 ± 0.09 (4)	6.16 ± 0.46
Albumin	(g/dL)	3.18 ± 0.16	3.21 ± 0.16	3.10 ± 0.20	3.10 ± 0.16	3.15 ± 0.11 (4)	3.13 ± 0.15
A/G		1.03 ± 0.08	1.04 ± 0.09	1.00 ± 0.11	1.13 ± 0.05	1.08 ± 0.11 (4)	1.04 ± 0.10
Glucose	(mg/dL)	150 ± 4	157 ± 4	156 ± 20	140 ± 21	146 ± 5 (4)	147 ± 5
Triglyceride	(mg/dL)	41.5 ± 7.4	54.1 ± 30.3	46.2 ± 36.5	64.0 ± 44.4	34.7 ± 12.5 (4)	46.6 ± 17.7
T.cholesterol	(mg/dL)	70 ± 6	63 ± 15	56 ± 15	70 ± 18	64 ± 4 (4)	59 ± 9
BUN	(mg/dL)	13.0 ± 1.8	12.8 ± 1.2	13.8 ± 1.7	13.7 ± 1.4	12.1 ± 1.1 (4)	12.3 ± 2.6
Creatinine	(mg/dL)	0.31 ± 0.02	0.28 ± 0.03	0.28 ± 0.03	0.27 ± 0.04	0.28 ± 0.01 (4)	0.28 ± 0.02
T.bilirubin	(mg/dL)	0.06 ± 0.02	0.06 ± 0.01	0.06 ± 0.01	0.06 ± 0.01	0.06 ± 0.02 (4)	0.04 ± 0.01
AST	(U/L)	78 ± 17	90 ± 18	110 ± 34	85 ± 15	86 ± 9 (4)	87 ± 9
ALT	(U/L)	31 ± 7	30 ± 4	36 ± 10	37 ± 9	29 ± 2 (4)	34 ± 5
ALP	(U/L)	385 ± 52	399 ± 48	476 ± 105	426 ± 79	365 ± 79 (4)	387 ± 90
Gamma-GTP	(U/L)	0.9 ± 0.2	1.1 ± 0.2	0.9 ± 0.1	0.9 ± 0.2	0.8 ± 0.2 (4)	0.9 ± 0.2
ChE	(U/L)	49 ± 33	48 ± 14	36 ± 9	26 ± 2	41 ± 13 (4)	43 ± 13
Calcium	(mg/dL)	9.58 ± 0.17	9.64 ± 0.22	9.63 ± 0.40	9.74 ± 0.32	9.53 ± 0.11 (4)	9.53 ± 0.23
I.phosphorus	(mg/dL)	6.67 ± 0.23	6.25 ± 0.24	6.07 ± 0.66	6.78 ± 0.39	6.36 ± 0.24 (4)	6.06 ± 0.29
Sodium	(mmol/L)	141.9 ± 0.7	142.1 ± 0.7	141.4 ± 1.2	141.6 ± 0.6	145.3 ± 1.5 (4)	144.2 ± 1.4
Potassium	(mmol/L)	4.67 ± 0.26	4.45 ± 0.36	4.65 ± 0.33	4.70 ± 0.23	4.31 ± 0.23 (4)	4.37 ± 0.32
Chloride	(mmol/L)	106.9 ± 0.8	108.1 ± 0.9	108.6 ± 1.2	108.0 ± 1.7	108.4 ± 0.3 (4)	108.8 ± 1.4
Total bile acid	(μmol/L)	9.9 ± 6.7	12.3 ± 6.5	16.1 ± 6.9	20.2 ± 12.2	18.5 ± 16.5 (4)	10.2 ± 3.7
Female							
No. of animals examined		5	5	5	5	5	4
T.protein	(g/dL)	6.43 ± 0.35	6.18 ± 0.33	6.30 ± 0.31	5.95 ± 0.35	7.15 ± 0.48	6.50 ± 0.46
Albumin	(g/dL)	3.37 ± 0.16	3.30 ± 0.12	3.35 ± 0.20	3.14 ± 0.26	3.91 ± 0.30	3.68 ± 0.15
A/G		1.11 ± 0.10	1.16 ± 0.13	1.13 ± 0.07	1.13 ± 0.14	1.21 ± 0.06	1.31 ± 0.09
Glucose	(mg/dL)	150 ± 12	138 ± 16	146 ± 7	143 ± 18	133 ± 9	129 ± 10
Triglyceride	(mg/dL)	71.5 ± 25.5	44.6 ± 19.0	53.6 ± 25.0	58.9 ± 31.1	39.3 ± 20.1	23.1 ± 15.9
T.cholesterol	(mg/dL)	68 ± 19	76 ± 11	72 ± 19	81 ± 16	87 ± 23	74 ± 10
BUN	(mg/dL)	15.4 ± 1.5	15.0 ± 1.7	15.2 ± 2.5	15.4 ± 2.3	15.7 ± 1.8	14.0 ± 2.2
Creatinine	(mg/dL)	0.37 ± 0.01	0.32 ± 0.03*	0.35 ± 0.06	0.30 ± 0.04*	0.35 ± 0.04	0.34 ± 0.04
T.bilirubin	(mg/dL)	0.05 ± 0.01	0.06 ± 0.02	0.06 ± 0.01	0.06 ± 0.02	0.05 ± 0.02	0.05 ± 0.01
AST	(U/L)	131 ± 56	105 ± 12	97 ± 5	103 ± 12	133 ± 122	74 ± 7
ALT	(U/L)	64 ± 29	46 ± 9	52 ± 4	46 ± 8	61 ± 64	24 ± 3
ALP	(U/L)	276 ± 51	278 ± 81	298 ± 94	282 ± 77	147 ± 22	237 ± 31**
Gamma-GTP	(U/L)	1.1 ± 0.8	0.7 ± 0.3	0.6 ± 0.2	1.1 ± 0.2	1.0 ± 0.3	1.1 ± 0.1
ChE	(U/L)	375 ± 46	210 ± 75*	135 ± 63*	80 ± 7*	557 ± 152	514 ± 207
Calcium	(mg/dL)	9.92 ± 0.12	10.07 ± 0.23	10.18 ± 0.28	10.19 ± 0.43	10.21 ± 0.33	9.75 ± 0.29
I.phosphorus	(mg/dL)	8.62 ± 1.09	8.29 ± 1.17	7.53 ± 0.86	7.22 ± 0.47	4.59 ± 0.73	4.62 ± 0.92
Sodium	(mmol/L)	141.7 ± 0.9	141.1 ± 0.7	141.6 ± 0.8	141.1 ± 0.7	142.7 ± 1.3	144.1 ± 0.4
Potassium	(mmol/L)	4.02 ± 0.46	4.43 ± 0.30	4.12 ± 0.25	4.65 ± 0.43*	4.13 ± 0.09	4.15 ± 0.34
Chlorid	(mmol/L)	105.8 ± 1.5	106.4 ± 1.6	106.6 ± 1.0	106.5 ± 3.0	109.0 ± 1.3	110.2 ± 0.6
Total bile acid	(μmol/L)	14.4 ± 10.0	15.8 ± 7.2	28.6 ± 26.2	24.1 ± 15.6	19.2 ± 7.1	14.9 ± 5.4

Values are expressed as Mean ± S.D.

Values in parentheses are expressed no. of animals examined

Significant difference from control group; * $p \leq 0.05$. ** $p \leq 0.01$.

a) Recovery group

Table 3 Absolute and relative organ weights of rats treated orally with *O,O'*-diethyl dithiophosphate in the combined repeated dose and reproductive/developmental toxicity screening test

Dose level	0 mg/kg	30 mg/kg	100 mg/kg	300 mg/kg	0 mg/kg ^{a)}	300 mg/kg ^{a)}
Male						
No. of animals examined	7	12	11	7	5	5
Body weight (g)	431 ± 34	424 ± 36	428 ± 42	410 ± 23	427 ± 37	415 ± 22
Absolute organ weight						
Brain (g)	2.10 ± 0.07	2.17 ± 0.08	2.26 ± 0.09**	2.20 ± 0.11	2.14 ± 0.09	2.13 ± 0.08
Salivary gland (mg)	717 ± 57	681 ± 43	700 ± 84	618 ± 79*	700 ± 79	637 ± 52
Thyroid gland (mg)	23 ± 7	23 ± 6	26 ± 8	26 ± 7	23 ± 6	24 ± 3
Thymus (mg)	262 ± 48	312 ± 57	340 ± 84*	355 ± 35*	292 ± 129	306 ± 94
Heart (g)	1.34 ± 0.12	1.36 ± 0.10	1.35 ± 0.12	1.28 ± 0.06	1.27 ± 0.05	1.47 ± 0.21
Liver (g)	11.05 ± 1.47	10.76 ± 1.25	11.46 ± 1.74	11.63 ± 1.08	10.75 ± 1.77	10.95 ± 1.11
Spleen (g)	0.64 ± 0.10	0.67 ± 0.10	0.70 ± 0.06	0.71 ± 0.11	0.62 ± 0.08	0.75 ± 0.15
Kidneys (g)	2.91 ± 0.34	2.90 ± 0.26	3.12 ± 0.42	3.06 ± 0.21	2.90 ± 0.38	3.00 ± 0.24
Adrenals (mg)	59 ± 13	55 ± 11	54 ± 7	53 ± 11	54 ± 9	51 ± 2
Testes (g)	3.10 ± 0.18	3.29 ± 0.23	3.19 ± 0.22	2.61 ± 0.60	3.23 ± 0.34	1.55 ± 0.32**
Epididymides (mg)	1172 ± 93	1248 ± 76	1217 ± 85	944 ± 108**	1321 ± 91	854 ± 71**
Relative organ weight						
Brain (g%)	0.489 ± 0.037	0.516 ± 0.057	0.533 ± 0.050	0.536 ± 0.017	0.503 ± 0.048	0.514 ± 0.040
Salivary gland (mg%)	166.641 ± 6.976	161.508 ± 16.691	164.012 ± 18.054	150.646 ± 17.835	164.442 ± 19.646	154.034 ± 17.206
Thyroid gland (mg%)	5.281 ± 1.389	5.465 ± 1.582	6.041 ± 1.647	6.211 ± 1.671	5.379 ± 1.444	5.717 ± 0.974
Thymus (mg%)	60.551 ± 8.153	73.525 ± 12.011	80.526 ± 23.539	86.719 ± 9.318**	69.166 ± 30.351	74.137 ± 23.972
Heart (g%)	0.312 ± 0.019	0.322 ± 0.025	0.315 ± 0.021	0.314 ± 0.023	0.299 ± 0.019	0.355 ± 0.051*
Liver (g%)	2.558 ± 0.169	2.535 ± 0.139	2.666 ± 0.157	2.834 ± 0.187**	2.508 ± 0.254	2.635 ± 0.190
Spleen (g%)	0.148 ± 0.019	0.159 ± 0.018	0.165 ± 0.013	0.174 ± 0.026*	0.145 ± 0.010	0.183 ± 0.040
Kidneys (g%)	0.675 ± 0.047	0.684 ± 0.042	0.729 ± 0.061	0.748 ± 0.058*	0.678 ± 0.055	0.723 ± 0.064
Adrenals (mg%)	13.762 ± 2.552	13.071 ± 2.357	12.708 ± 2.022	13.082 ± 3.197	12.646 ± 1.740	12.276 ± 1.085
Testes (g%)	0.725 ± 0.094	0.779 ± 0.075	0.749 ± 0.074	0.642 ± 0.167	0.758 ± 0.050	0.374 ± 0.073**
Epididymides (mg%)	274.114 ± 37.841	296.404 ± 31.391	286.335 ± 30.898	231.012 ± 34.904	310.335 ± 21.985	205.984 ± 16.992**
Female						
No. of animals examined	12	11	12	5	5	4
Body weight (g)	290 ± 18	292 ± 24	281 ± 16	286 ± 12	270 ± 15	262 ± 28
Absolute organ weight						
Brain (g)	2.05 ± 0.12 (11)	1.99 ± 0.04	2.07 ± 0.07	2.09 ± 0.12	1.97 ± 0.12	1.98 ± 0.03
Salivary gland (mg)	534 ± 30	501 ± 58	518 ± 38	506 ± 37	429 ± 20	403 ± 34
Thyroid gland (mg)	20 ± 4	18 ± 4	18 ± 4	18 ± 3	15 ± 4	19 ± 7
Thymus (mg)	253 ± 65	226 ± 29	202 ± 82	224 ± 42	263 ± 38	266 ± 59
Heart (g)	0.97 ± 0.07	0.96 ± 0.06	0.98 ± 0.09	1.05 ± 0.11	0.92 ± 0.12	0.88 ± 0.02
Liver (g)	9.52 ± 0.84	9.69 ± 0.87	9.73 ± 0.59	10.44 ± 1.37	6.93 ± 0.59	6.46 ± 0.44
Spleen (g)	0.57 ± 0.08	0.61 ± 0.08	0.59 ± 0.06	0.58 ± 0.10	0.46 ± 0.04	0.44 ± 0.01
Kidneys (g)	2.01 ± 0.25	1.99 ± 0.21	2.02 ± 0.19	2.39 ± 0.39*	1.83 ± 0.14	1.84 ± 0.17
Adrenals (mg)	72 ± 9	67 ± 10	68 ± 8	72 ± 7	70 ± 6	66 ± 5
Ovaries (mg)	93 ± 11	91 ± 17	91 ± 20	92 ± 7	76 ± 10	84 ± 8
Relative organ weight						
Brain (g%)	0.709 ± 0.045(11)	0.684 ± 0.052	0.740 ± 0.053	0.732 ± 0.037	0.731 ± 0.028	0.761 ± 0.083
Salivary gland (mg%)	184.646 ± 14.805	171.664 ± 17.397	184.596 ± 10.829	177.202 ± 13.015	159.329 ± 10.415	154.524 ± 12.990
Thyroid gland (mg%)	6.780 ± 1.371	6.256 ± 1.229	6.230 ± 1.298	6.287 ± 1.003	5.724 ± 1.455	7.432 ± 2.969
Thymus (mg%)	87.074 ± 20.569	77.436 ± 8.683	71.426 ± 27.988	78.682 ± 16.277	97.765 ± 15.371	101.983 ± 23.926
Heart (g%)	0.334 ± 0.026	0.329 ± 0.019	0.347 ± 0.022	0.369 ± 0.042*	0.340 ± 0.032	0.336 ± 0.033
Liver (g%)	3.282 ± 0.266	3.317 ± 0.167	3.468 ± 0.118	3.648 ± 0.313	2.571 ± 0.174	2.476 ± 0.163
Spleen (g%)	0.196 ± 0.022	0.208 ± 0.021	0.212 ± 0.021	0.205 ± 0.038	0.172 ± 0.012	0.168 ± 0.017
Kidneys (g%)	0.690 ± 0.065	0.682 ± 0.063	0.722 ± 0.066	0.838 ± 0.142**	0.679 ± 0.045	0.708 ± 0.103
Adrenals (mg%)	25.039 ± 3.605	23.007 ± 4.351	24.427 ± 3.143	25.158 ± 2.476	26.207 ± 3.223	25.466 ± 2.909
Ovaries (mg%)	32.176 ± 3.894	31.426 ± 6.199	32.486 ± 7.512	32.457 ± 3.435	28.307 ± 3.860	32.238 ± 2.329

Values are expressed as Mean ± S.D.

(%) (Organ weight / body weight) × 100

Values in parentheses are expressed no. of animals examined

Significant difference from control group; **p* ≤ 0.05, ***p* ≤ 0.01.

a) Recovery group

Table 4 Summary of histological findings with statistical analysis treated orally with O,O'-diethyl dithiophosphate in the combined repeated dose and reproductive/developmental toxicity screening test (ReproTox study)

Dose level (mg/kg)	Sacrificed												Non-pregnancy												
	0				30				100				300				30				300				
Organ Findings	1	2	3	T	1	2	3	T	1	2	3	T	1	2	3	T	1	2	3	T	1	2	3	T	
Male																									
No. of animals necropsied	7				11				11				5				1				2				
CARDIOVASCULAR SYSTEM																									
heart	(5)				(0)				(1)				(3)				(0)				(0)				
cardiomyopathy	1	0	0	1	-	-	-	-	1	0	0	1	1	1	0	0	1	-	-	-	-	-	-	-	-
myocarditis	0	0	0	0	-	-	-	-	0	0	0	0	1	0	0	1	1	-	-	-	-	-	-	-	-
DIGESTIVE SYSTEM																									
glandular stomach	(5)				(5)				(5)				(3)				(0)				(0)				
erosion	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	2	-	-	-	-	-	-	-	-
exocrine pancreas	(5)				(0)				(0)				(3)				(0)				(0)				
edema	0	0	0	0	-	-	-	-	-	-	-	-	1	0	0	1	1	-	-	-	-	-	-	-	-
atrophy, acinus	0	0	0	0	-	-	-	-	-	-	-	-	1	0	0	1	1	-	-	-	-	-	-	-	-
decrease, zymogen granules, acinar cell	0	0	0	0	-	-	-	-	-	-	-	-	1	0	0	1	1	-	-	-	-	-	-	-	-
cellular infiltration, mixed cell	0	0	0	0	-	-	-	-	-	-	-	-	1	0	0	1	1	-	-	-	-	-	-	-	-
ileum	(5)				(0)				(1)				(3)				(0)				(0)				
diverticula	0	0	0	0	-	-	-	-	1	0	0	1	0	0	0	0	0	-	-	-	-	-	-	-	-
liver	(5)				(1)				(0)				(3)				(0)				(0)				
atrophy, hepatocyte	0	0	0	0	1	0	0	1	-	-	-	-	0	0	0	0	0	-	-	-	-	-	-	-	-
vacuolation, hepatocyte	5	0	0	5	0	0	0	0	-	-	-	-	3	0	0	3	3	-	-	-	-	-	-	-	-
microgranuloma	5	0	0	5	0	0	0	0	-	-	-	-	1	0	0	1	1	-	-	-	-	-	-	-	-
URINARY SYSTEM																									
kidney	(5)				(1)				(0)				(3)				(0)				(0)				
basophilic tubules	2	0	0	2	0	0	0	0	-	-	-	-	0	0	0	0	0	-	-	-	-	-	-	-	-
dilatation	0	0	0	0	1	0	0	1	-	-	-	-	0	0	0	0	0	-	-	-	-	-	-	-	-
hyaline droplet	0	0	0	0	0	0	0	0	-	-	-	-	2	0	0	2	2	-	-	-	-	-	-	-	-
REPRODUCTIVE SYSTEM																									
testis	(5)				(5)				(5)				(3)				(1)				(2)				
Sertoli only syndrome	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1	-	-	-	-	-	-	-	-
atrophy, seminiferous tubule	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	1	0	0	1
vacuolation, Sertoli cell	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	3	3	3*	0	0	0	0	2	0	2
epididymis	(5)				(5)				(5)				(3)				(1)				(2)				
cell debris, lumen	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	2	2	0	0	0	0	2	0	0	2
decrease, sperm	0	0	0	0	0	0	0	0	0	0	0	0	2	0	1	3	3	3*	0	0	0	0	2	0	2
prostate	(5)				(0)				(0)				(3)				(0)				(0)				
cellular infiltration, lymphocyte	1	0	0	1	-	-	-	-	-	-	-	-	3	0	0	3	3	-	-	-	-	-	-	-	-
ENDOCRINE SYSTEM																									
thyroid gland	(5)				(0)				(0)				(3)				(0)				(0)				
ultimobranchial remnant	3	0	0	3	-	-	-	-	-	-	-	-	0	0	0	0	0	-	-	-	-	-	-	-	-
SPECIAL SENSE SYSTEM																									
Harderian gland	(5)				(0)				(0)				(3)				(0)				(0)				
cellular infiltration, lymphocyte	1	0	0	1	-	-	-	-	-	-	-	-	0	0	0	0	0	-	-	-	-	-	-	-	-

Grade of histopathological finding; 1:slight, 2:moderate, 3:marked T:Total - :Not examined
 Numbers in parentheses indicate no. of animals examined microscopically at this site
 Significant difference from control group; Fisher: * $p \leq 0.05$, Mann-Whitney: # $p \leq 0.05$.

Table 5 Summary of histological findings with statistical analysis treated orally with O,O'-diethyl dithiophosphate in the combined repeated dose and reproductive/developmental toxicity screening test (Recovery study)

Dose level (mg/kg)	Sacrificed							
	0				300			
Organ Findings	1	2	3	T	1	2	3	T
Male								
No. of animals necropsied	5				5			
CARDIOVASCULAR SYSTEM								
heart	(5)				(5)			
cardiomyopathy	2	0	0	2	2	0	0	2
RESPIRATORY SYSTEM								
lung	(5)				(5)			
hemorrhage	0	0	0	0	1	0	0	1
accumulation of foamy cells	1	0	0	1	1	0	0	1
hypertrophy, alveolar cell	0	0	0	0	1	0	0	1
osseous metaplasia	1	0	0	1	0	0	0	0
DIGESTIVE SYSTEM								
exocrine pancreas	(5)				(5)			
decrease, zymogea granules, acinar cell	0	0	0	0	0	1	0	1
colon	(5)				(5)			
hemorrhage	1	0	0	1	0	0	0	0
liver	(5)				(5)			
fatty change, hepatocyte	0	0	0	0	2	0	0	2
vacuolation, hepatocyte	5	0	0	5	5	0	0	5
microgranuloma	3	0	0	3	3	0	0	3
URINARY SYSTEM								
kidney	(5)				(5)			
basophilic tubules	3	0	0	3	3	0	0	3
hyaline droplet	3	0	0	3	2	0	0	2
REPRODUCTIVE SYSTEM								
testis	(5)				(5)			
atrophy, seminiferous tubule	0	0	0	0	1	1	3	5***
decrease, germ cell	0	0	0	0	1	2	2	5***
vacuolation, Sertoli cell	0	0	0	0	1	1	3	5***
interstitial cell hyperplasia	0	0	0	0	3	1	0	4*#
epididymis	(5)				(5)			
cell debris, lumen	0	0	0	0	2	1	0	3
decrease, sperm	0	0	0	0	0	0	5	5***
prostate	(5)				(5)			
cellular infiltration, lymphocyte	3	0	0	3	4	0	0	4
SPECIAL SENSE SYSTEM								
Harderian gland	(5)				(5)			
cellular infiltration, lymphocyte	1	0	0	1	0	0	0	0

Grade of histopathological finding; 1:sligh, 2:moderate, 3:marked T:Total

Numbers in parentheses indicate no. of animals examined microscopically at this site

Significant difference from control group; Fisher: * $p \leq 0.05$, ** $p \leq 0.01$, Mann-Whitney: # $p \leq 0.05$, ## $p \leq 0.01$.

Table 5 (Continued)

Dose level (mg/kg)	Dead				Sacrificed							
	300				0				300			
	1	2	3	T	1	2	3	T	1	2	3	T
Organ Findings												
Female												
No. of animals necropsied			1				5				4	
CARDIOVASCULAR SYSTEM												
heart	(0)				(5)				(4)			
cardiomyopathy	-	-	-	-	0	0	0	0	1	0	0	1
HEMATOPOIETIC SYSTEM												
bone marrow	(1)				(0)				(0)			
hemorrhage	1	0	0	1	-	-	-	-	-	-	-	-
lymph node	(1)				(0)				(0)			
congestion	1	0	0	1	-	-	-	-	-	-	-	-
thymus	(0)				(5)				(4)			
Kuersteiner's duct/cyst	-	-	-	-	1	0	0	1	0	0	0	0
RESPIRATORY SYSTEM												
lung	(1)				(5)				(4)			
congestion	1	0	0	1	-	-	-	-	-	-	-	-
edema	1	0	0	1	-	-	-	-	-	-	-	-
thickening, alveolar wall	-	-	-	-	1	0	0	1	0	0	0	0
cellular infiltration, lymphocyte	-	-	-	-	1	0	0	1	0	0	0	0
trachea	(1)				(0)				(0)			
desquamation epithelium	1	0	0	1	-	-	-	-	-	-	-	-
narrowing, lumen	1	0	0	1	-	-	-	-	-	-	-	-
suppurative inflammation	1	0	0	1	-	-	-	-	-	-	-	-
DIGESTIVE SYSTEM												
glandular stomach	(0)				(5)				(4)			
erosion	-	-	-	-	1	0	0	1	0	0	0	0
exocrine pancreas	(0)				(5)				(4)			
decrease, zymogen granules, acinar cell	-	-	-	-	0	0	0	0	1	0	0	1
liver	(1)				(5)				(4)			
congestion	1	0	0	1	-	-	-	-	-	-	-	-
necrosis, hepatocyte, focal	1	0	0	1	0	0	0	0	1	0	0	1
vacuolation, hepatocyte	1	0	0	1	3	0	0	3	4	0	0	4
hemorrhage	-	-	-	-	1	0	0	1	0	0	0	0
microgranuloma	-	-	-	-	5	0	0	5	1	0	0	1*
URINARY SYSTEM												
kidney	(0)				(5)				(4)			
vacuolation, tubular epithelium	-	-	-	-	3	0	0	3	1	0	0	1
cellular infiltration, lymphocyte	-	-	-	-	0	0	0	0	2	0	0	2
REPRODUCTIVE SYSTEM												
uterus	(0)				(5)				(4)			
dilatation, lumen	-	-	-	-	0	0	0	0	1	0	1	2
vagina	(0)				(5)				(4)			
dermoid cyst	-	-	-	-	-	-	-	1\$	-	-	-	0
ENDOCRINE SYSTEM												
adrenal gland	(1)				(0)				(0)			
hypertrophy, cortex	0	0	1	1	-	-	-	-	-	-	-	-
pituitary gland	(0)				(5)				(4)			
Rathke's pouch	-	-	-	-	1	0	0	1	0	0	0	0
thyroid gland	(0)				(5)				(4)			
ultimobranchial remnant	-	-	-	-	1	0	0	1	2	0	0	2
NERVOUS SYSTEM												
sciatic nerve	(0)				(5)				(4)			
cellular infiltration, lymphocyte	-	-	-	-	1	0	0	1	0	0	0	0
INTEGUMENTARY SYSTEM												
subcutaneous tissue	(1)				(0)				(0)			
congestion	1	0	0	1	-	-	-	-	-	-	-	-

Grade of histopathological finding; 1:slight, 2:moderate, 3:marked T:Total - :Not examined \$:benign
 Numbers in parentheses indicate no. of animals examined microscopically at this site
 Significant difference from control group; Fisher: *p≤0.05.

Table 6 Summary of reproductive performance and estrous cycle in rats treated orally with O,O'-diethyl dithiophosphate in the combined repeated dose and reproductive/developmental toxicity screening test

Dose level	0 mg/kg	30 mg/kg	100 mg/kg	300 mg/kg
No. of pairs mated	12	12	12	10
No. of pairs copulated	12	12	12	10
No. of pregnant females	12	11	12	7
Copulation index (%) ^{a)}	100.0	100.0	100.0	100.0
Fertility index (%) ^{b)}	100.0	91.7	100.0	77.8 (9)
Estrous cycle				
No. of animals examined	12	12	12	12
Mean estrous cycle (Days, Mean \pm S.D.)	4.2 \pm 0.3 (12)	4.1 \pm 0.2 (12)	4.1 \pm 0.2 (12)	4.7 \pm 1.4 (10)
Irregular estrous cycle (%) ^{c)}	1 (8.3)	0 (0.0)	0 (0.0)	2 (20.0)

- a) (No. of animals with successful copulation/no. of animals mated) \times 100
b) (No. of pregnant animals/no. of animals with successful copulation) \times 100
c) No. of animals having irregular estrous cycle
d) (No. of animals having irregular estrous cycle/no. of animals examined) \times 100
Values in parentheses are expressed no. of animals observed

Table 7 Findings of delivery in dams treated orally with O,O'-diethyl dithiophosphate and observations on their pups in the combined repeated dose and reproductive/developmental toxicity screening test

Dose level	0 mg/kg	30 mg/kg	100 mg/kg	300 mg/kg
No. of pregnant females	12	11	12	6
No. of dams delivered live pups	12	11	12	6
Duration of gestation (Day, Mean \pm S.D.)	22.3 \pm 0.5	22.3 \pm 0.5	22.4 \pm 0.5	22.7 \pm 0.5
No. of corpora lutea (Mean \pm S.D.)	187(15.6 \pm 1.4)	195(17.7 \pm 2.5)	193(16.1 \pm 2.1)	103(17.2 \pm 2.9)
No. of implantation sites (Mean \pm S.D.)	170(14.2 \pm 1.9)	166(15.1 \pm 1.3)	173(14.4 \pm 1.2)	85(14.2 \pm 3.3)
No. of pups born (Mean \pm S.D.)	157(13.1 \pm 2.4)	153(13.9 \pm 1.5)	161(13.4 \pm 1.9)	79(13.2 \pm 3.2)
No. of live pups born (Mean \pm S.D.)				
Total	157(13.1 \pm 2.4)	149(13.5 \pm 1.5)	158(13.2 \pm 1.7)	70(11.7 \pm 3.7)
Male	75(6.3 \pm 1.9)	77(7.0 \pm 2.2)	82(6.8 \pm 2.9)	34(5.7 \pm 2.3)
Female	82(6.8 \pm 1.8)	72(6.5 \pm 2.5)	76(6.3 \pm 2.9)	36(6.0 \pm 1.8)
Sex ratio (Male/female, Mean \pm S.D.)	0.99 \pm 0.41	1.46 \pm 1.41	1.51 \pm 1.09	0.95 \pm 0.34
No. of live pups on day 4 (Mean \pm S.D.)				
Total	156(13.0 \pm 2.4)	146(13.3 \pm 1.4)	157(13.1 \pm 1.6)	55(11.0 \pm 2.2)
Male	74(6.2 \pm 1.9)	75(6.8 \pm 2.3)	82(6.8 \pm 2.9)	28(5.6 \pm 2.1)
Female	82(6.8 \pm 1.8)	71(6.5 \pm 2.5)	75(6.3 \pm 3.0)	27(5.4 \pm 0.5)
No. of dead pups (Mean \pm S.D.)	0(0.0 \pm 0.0)	4(0.4 \pm 0.7)	3(0.3 \pm 0.6)	9(1.5 \pm 3.2)
No. of cannibalism (Mean \pm S.D.)	0(0.0 \pm 0.0)	0(0.0 \pm 0.0)	0(0.0 \pm 0.0)	0(0.0 \pm 0.0)
Gestation index ^{a)} (%)	100.0	100.0	100.0	100.0
Implantation index ^{b)} (% Mean \pm S.D.)	91.1 \pm 10.6	86.4 \pm 11.8	90.5 \pm 9.6	83.0 \pm 17.1
Delivery index ^{c)} (% Mean \pm S.D.)	91.9 \pm 6.9	92.3 \pm 7.9	92.9 \pm 8.4	92.8 \pm 4.9
Live birth index ^{d)} (% Mean \pm S.D.)	100.0 \pm 0.0	97.5 \pm 4.7	98.4 \pm 4.1	90.0 \pm 21.4
Viability index on day 4 ^{e)} (% Mean \pm S.D.)				
Total	99.4 \pm 2.2	98.1 \pm 3.3	99.5 \pm 1.8	89.6 \pm 15.7
Male	98.6 \pm 4.8	97.2 \pm 6.3	100.0 \pm 0.0	91.0 \pm 12.4
Female	100.0 \pm 0.0	98.7 \pm 4.3	98.6 \pm 4.8	88.3 \pm 19.3*

- a) (No. of females with live pups/no. of pregnant females) \times 100
b) (No. of implantations/no. of corpora lutea) \times 100
c) (No. of pups born/no. of implantation sites) \times 100
d) (No. of live pups born/no. of pups born) \times 100
e) (No. of live pups on day 4 after birth/no. of live pups born) \times 100
Significant difference from control group; * $p\leq$ 0.05.