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DATA EVALUATION REPORT

STUDY TYPE: 90-Day Oral Toxicity Study (rat)

TOX. CHEM. NO.: 320 MRID NO.: 116494

TEST MATERIAL: 2,4-DP Acid; 95% pure; white crystalline solid

REPORT NUMBER(S): R-5419/a

REGISTRANT: Union Carbide, Agricultural Products Co., Inc.

TESTING FACILITY: TRAAL Institute Voor Voedingsonderzoek TNO (Centraal Institut for Nutrition and Food Research)

CITATION: Til, H.; Leegwater, D.; Kuper, F. (1977) Subchronic (90-day) Oral Toxicity Study with 2,4-DP in Rats: Report No. R-5419/a. Final Report. (Unpublished study received Mar 28, 1979 under 264-2221; prepared by Centraal Instituut Voor Voedingsonderzoek TNO, Neth., submitted by Union Carbide Agricultural Products Co., Inc., Research Triangle Park, NC; CDL: 237984)

CONCLUSIONS: Groups of Wistar derived SPF-albino rats (15/sex/dose) were administered 2,4-DP at dietary concentrations of 0, 100, 500, and 2500 ppm for 13 weeks. High dose males and females showed decreases in body weights, food consumption, and food efficiency; significant changes in the parameters of hematology, clinical chemistry, and urinalysis; and increases in relative weights of heart, kidney, and liver. Histopathology data showed increased incidence of both kidney and liver lesions in all treated males and females relative to the controls. Based upon the reported data, the LOEL is 100 ppm (LDT).

Although this study was well conducted, the NOEL of 2, 4-DP for this experiment could not be established. In addition, absolute organ weights were not presented, and insufficient amount of information was reported on the individual-animal histopathology data. This study is, thus, classified as supplementary.

A. MATERIALS: 2,4-DP acid; white crystalline solid; 93.3% purity. Details of composition are presented in Appendix 1

Test animals: 3 1/2 weeks old Wistar derived SPF-albino rats which weighed 40-60 gm were obtained from Central Institute for the Breeding of Laboratory Animal TNO, Ziest, The Netherlands.

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned randomly to the following test groups:

Test Group	Dose in diet (ppm)	Main Study 13 Weeks male	female
1 Cont.	0	15	15
2 Low (LDT)	100	15	15
3 Mid (MDT)	500	15	15
4 High(HDT)	2,500	15	15

2. Diet preparation

Diet was prepared monthly and stored under refrigeration. Samples of treated food were analyzed for stability and concentration. Results of the analyses are presented in Table 1. The compound in the diet was found to be reasonably stable, and the actual concentrations of 2,4-DP in the diet were found to be fairly close to the designated concentrations.

3. Animals received food and water ad libitum.

4. Statistics - The following procedures were utilized in analyzing the numerical data:

   a). Student-t-test
   b). Wilcoxon-test
   c). Chi-square-test

5. Quality assurance statement was signed and included in the report.

Table 1. Levels of 2,4-DP analyzed in the 3 batches of diets used in the 13-week toxicity study in rats

group no.	levels of 2,4-DP preparation in the diet (ppm)[3]	levels of 2,4-DP analyzed[1]			
		batch 1		batch 2	batch 3
		0 day	28 days (at 18°C)	21 days (at 10°C)	10 days (at 10°C)
9193	0	< 10	-[2]	< 1	< 1
9194	100 (87)	96	94	98	96
9195	500 (435)	460	500	460	460
9196	2500 (2175)	2440	2500	2400	2460

[1]) analyses corrected for a recovery of 77-78 %

[2]) not determined

[3]) figures in parenthesis are the levels of 2,4-DP in the diet based on a pure 2,4-DP content of the techn. Wirkstoff of 87 per cent (see annexe 1)

Data taken from submission; MRID No. 116494

C. METHODS AND RESULTS:

1. Observations

Animals were inspected daily for signs of toxicity and mortality.

Toxicity: In high dose animals, 2 females showed retardation in growth relative to the controls; several males and females also showed muscular weakness. Increased incidence of abnormalities were not observed in mid and low dose animals relative to the controls.

Survival rates of treated animals and controls were comparable.

2. Body weight

Animals were weighed twice a week for the first 4 weeks of the study and once a week thereafter. The body weights of the test animals are presented in Table 2.

Statistically significant decreases in body weights were observed in 2,500 ppm males and females relative to the controls. The body weights of mid and low dose animals were comparable to those of the controls.

3. Food consumption and food efficiency:

Food consumption was determined, and the mean weekly food intake and food efficiency values were summarized in Table 3.

Both 2,500 ppm male and female rats consumed less food than the controls, but the difference was not statistically significant. Food efficiency values for both 2,500 ppm males and females were decreased, and the decrease of that in females appeared to be more marked (Table 3).

4. There was no indication that ophthalmalogical examinations were performed.

Table 2. Mean body weights of rats fed 2,4-DP at dietary levels of 0-2500 ppm for 13 weeks

group no.	2,4-DP in the diet (ppm)	mean body weights (g) at day																	
		0	3	7	10	14	17	21	24	28	35	42	49	56	63	70	77	84	91
		15 males/group																	
9193	0	64 (1.3)	79 (1.2)	102 (1.4)	119 (1.9)	142 (2.3)	157 (2.3)	182 (2.9)	197 (3.1)	214 (3.4)	240 (2.7)	262 (5.1)	295 (3.5)	308 (4.9)	314 (5.6)	331 (5.9)	342 (7.1)	355 (7.8)	363 (8.1)
9194	100	64 (1.0)	82 (1.1)	104 (1.6)	121 (2.2)	143 (2.2)	161 (2.4)	184 (2.7)	200 (2.7)	218 (3.1)	250* (3.0)	276* (3.4)	294 (4.3)	306 (4.8)	314 (4.7)	326 (6.1)	341 (5.0)	354 (5.8)	356 (7.2)
9195	500	64 (1.3)	81 (1.6)	102 (1.8)	120 (2.3)	141 (2.8)	156 (3.2)	178 (3.6)	196 (4.0)	213 (4.1)	244 (4.4)	270 (5.4)	290 (6.5)	307 (6.6)	313 (7.7)	327 (8.3)	340 (8.6)	353 (8.7)	358 (9.0)
9196	2500	64 (1.0)	80 (0.9)	96** (1.5)	108*** (1.8)	127*** (2.2)	144*** (2.3)	161*** (2.8)	168*** (3.1)	183*** (4.4)	202*** (5.8)	229*** (6.8)	251*** (7.0)	267*** (6.8)	264*** (7.2)	277*** (8.2)	289*** (8.2)	298*** (8.7)	297*** (10.4)
		15 females/group																	
9193	0	64 (2.0)	75 (1.8)	94 (1.7)	106 (2.0)	121 (2.3)	131 (2.4)	142 (2.5)	148 (2.6)	156 (3.0)	168 (2.9)	182 (3.1)	193 (2.9)	200 (3.2)	203 (3.4)	210 (3.3)	214 (3.4)	217 (3.1)	220 (3.4)
9194	100	64 (1.0)	76 (1.1)	93 (1.2)	105 (1.4)	121 (2.0)	129 (1.9)	141 (2.1)	147 (2.4)	153 (2.4)	167 (3.0)	180 (3.1)	190 (3.3)	196 (3.6)	199 (4.0)	206 (3.9)	210 (3.7)	214 (4.1)	218 (4.2)
9195	500	64 (1.6)	75 (1.8)	92 (2.0)	104 (2.6)	117 (3.3)	125 (3.4)	135 (3.7)	142 (3.4)	149 (3.9)	160 (4.1)	172 (4.4)	183 (4.5)	189 (5.0)	192 (4.9)	200 (4.9)	204 (4.9)	209 (5.0)	213 (5.1)
9196	2500	64 (1.6)	75 (1.8)	88 (2.3)	98* (2.7)	109** (3.6)	117** (4.1)	126** (4.9)	130** (5.3)	132** (6.2)	140** (7.2)	154** (8.0)	164** (9.0)	168** (9.9)	168** (9.8)	173** (10.2)	176** (10.3)	180** (10.3)	175** (10.4)

* P < 0.05; ** P < 0.01; *** P < 0.001

The standard error of the mean is given in brackets

Data taken from submission, ~~Hat~~ MRID No. 116494

9

1
5
1

Table 3. Mean food intake and food efficiency figures of rats fed 2,4-DP at dietary levels of 0-2500 ppm for 13 weeks

2,4-DP in the diet (ppm)	food intake (g/rat/day) in week												food efficiency (gain/food) during week		
	1	2	3	4	5	6	7	8	9[1])	10	11	12	0-2	0-4	0-12
	15 males/group														
0	12.5	15.5	17.0	17.1	17.2	18.5	20.0	18.1	16.9	17.6	17.3	17.8	0.40	0.34	0.20
100	12.5	15.4	16.6	17.2	18.0	18.5	18.4	17.1	16.1	16.6	17.0	17.4	0.41	0.36	0.20
500	12.0	15.1	16.5	16.9	17.5	18.9	19.0	17.0	16.3	16.8	16.9	17.4	0.41	0.35	0.20
2500	10.8	12.3	14.1	14.3	14.4	16.8	16.7	16.8	14.5	15.5	15.7	15.5	0.39	0.33	0.19
	15 females/group														
0	10.9	12.4	12.3	12.3	12.3	13.3	13.1	12.7	11.9	12.5	12.3	12.5	0.35	0.28	0.15
100	10.7	12.1	12.2	12.0	12.5	12.1	12.7	12.4	11.6	12.0	11.8	12.2	0.36	0.27	0.15
500	10.5	11.9	11.9	12.1	12.3	12.5	12.8	12.7	11.7	12.4	11.9	12.6	0.34	0.26	0.14
2500	9.9	10.5	10.8	10.0	10.1	11.2	11.5	11.0	10.0	10.4	10.8	11.7	0.32	0.24	0.12

[1]) rats were overnight fasted for determinations of blood glucose and BUN and for urine examinations

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5. Blood was collected at 4, 8, and 12 weeks for hematology and clinical analysis from 5 animals. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
x	Hematocrit (HCT)*	x	Leukocyte differential=count*
x	Hemoglobin (HGB)*		Mean corpuscular HGB (MCH)
x	Leukocyte count (WBC)*		Mean corpuscular HGB conc.(MCHC)
x	Erythrocyte count (RBC)*		Mean corpuscular volume (MCV)
	Platelet count*		Reticulocyte count
	Blood Clotting Measurements		

* Required for subchronic and chronic studies

In 2,500 ppm males consistent decreases in packed cell volume, hemoglobin, and erythrocytes were observed in weeks 4, 8, and 12 (Table 4). At certain periods of the study decreases in hemoglobin and erythrocytes were also observed in 2,500 ppm females, and these decreases were statistically significant at week 12 (Table 4).

TABLE 4

Mean Hematological Findings in Control and 2,4-DP Treated Rats
(Data were extracted from the submission; MRID No. 116494)

Dose (ppm)	Hb (g/100 ml)	pack cell volume (%)	erythrocytes ($10^6/mm^3$)
MALE		week 4	
0	14.8 ± 0.18	47.6 ± 0.60	6.6 ± 0.23
2500	13.5 ± 0.26*	44.3 ± 0.80*	6.4 ± 0.18
		week 8	
0	16.5 ± 0.15	48.2 ± 0.64	7.3 ± 0.19
2500	15.5 ± 0.25*	44.5 ± 0.74*	6.8 ± 0.15
		week 12	
0	16.0 ± 0.23	47.6 ± 0.92	7.4 ± 0.10
2500	15.4 ± 0.24	46.0 ± 0.89	7.1 ± 0.14
FEMALE		week 12	
0	16.2 ± 0.28	46.9 ± 0.83	7.2 ± 0.14
2500	15.2 ± 0.29*	44.4 ± 0.97	6.7 ± 0.13*

* $p < 0.05$

b. Clinical Chemistry

X	Electrolytes:	X	Other:
x	Calcium*	x	Albumin*
	Chloride*		Blood creatinine*
	Magnesium*	x	Blood urea nitrogen*
	Phosphorous*		Cholesterol*
x	Potassium*		Globulins
x	Sodium*	x	Glucose*
	Enzymes	x	Total Bilirubin*
x	Alkaline phosphatase (AP)	x	Total Serum Protein*
	Cholinesterase#		Triglycerides
	Creatinine phosphokinase*°		Serum protein electrophoresis
	Lactic acid dehydrogenase		
x	Serum alanine aminotransferase (also SGPT)*		
x	Serum aspartate aminotransferase (also SGOT)*		
	gamma glutamyl transferase		
	glutamate dehydrogenase		

* Required for subchronic and chronic studies
\# Should be required for OP
° Not required for subchronic studies

Although the results indicate that not all parameters of clinical chemistry were examined, several parameters were affected in 2,500 ppm treated male and female rats. At week 13, marked changes were observed in blood urea nitrogen, SGOT, SGPT, AP, total plasma protein, and Na^+ levels of 2,500 ppm males and females (Table 5). Some of these changes were statistically significant as indicated in Table 5. In addition, plasma albumin was significantly decreased in 500 and 2,500 ppm males and 2,500 ppm females.

TABLE 5
Clinical Chemistry Parameters Affected by 2,4-DP Treatment At Week 13

(Data extracted from the Submission, MRID No. 116494)

ppm	BUN mg %	SGOT R-F units	SGPT R-F units	AP B-L units	Total protein gm %	Na^+ mg/L
Male						
0	15±0.4	55±2.0	39±1.6	13.7±0.8	6.6±0.1	3400±49
2500	18±0.6*	66±2.4*	50±3.6*	29.8±2.8†	5.8±0.1†	3230±123
Female						
0	18±0.8	58±1.8	40±1.5	11.3±0.6	6.2±0.16	3460±87
2500	22±1.3*	73±6.5†	44±2.8	18.7±2.1†	5.6±0.15*	3250±16*

* : $p < 0.01$; † : $p < 0.001$

6. Urinalysis°

Urine was collected from animals at week 13. The CHECKED (X) parameters were examined.

X		X	
x	Appearance*	x	Glucose*
x	Volume*	x	Ketones*
x	Specific gravity*		Bilirubin*
x	pH	x	Blood*
x	Sediment (microscopic)*		Nitrate
x	Protein*		Urobilinogen

* Required for chronic studies
° Not required for subchronic studies

No significant differences in the above parameters were observed between the 2,4-DP treated and control rats. However, the results of kidney function tests and electrolyte determination in urine indicated decreases in the levels of Na^+ and K^+ in the urine of both 2,500 ppm males and females. The decreases of Na^+ and K^+ levels in males and K^+ level in females were statistically significant (Table 6). Urine volume was increased in 2,500 ppm males with associated statistically significant decrease in specific gravity.

TABLE 6

The Na^+ and K^+ Levels In Urine of 2,4-DP Treated Rats
(Data extracted from the submission, MRID No. 116494)

ppm	Na^+ (mg/100 ml)	K^+ (mg/100 ml)
Male	week 13	
0	124 ± 17	1149 ± 76
2500	74 ± 11*	443 ± 56***
Female	week 13	
0	163 ± 20	1043 ± 57
2500	131 ± 20	641 ± 61***

* : $p < 0.05$ *** : $p < 0.001$

7. Sacrifice and Pathology -
All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs in addition were weighed.

X		X		X	
	Digestive system		Cardiovasc./Hemat.		Neurologic
	Tongue	x	.Aorta*	x	.Brain*†
x	.Salivary glands*	x	.Heart*	x	Periph. nerve*#
x	.Esophagus*	x	.Bone marrow*	x	Spinal cord (3 levels)*#
x	.Stomach*	x	.Lymph nodes*	x	.Pituitary*
x	.Duodenum*	x	.Spleen*	x	Eyes (optic n.)*#
	.Jejunum*	x	.Thymus*		Glandular
x	.Ileum*		Urogenital	x	.Adrenals*
x	.Cecum*	x	.Kidneys*†		Lacrimal gland#
x	.Colon*	x	.Urinary bladder*	x	Mammary gland*#
	.Rectum*	x	.Testes*†		.Parathyroids*††
x	.Liver*†	x	Epididymides	x	.Thyroids*††
x	Gall bladder*#	x	Prostate		Other
x	.Pancreas*	x	Seminal vesicle	x	Bone*#
	Respiratory	x	Ovaries*†	x	Skeletal muscle*#
x	.Trachea*	x	.Uterus*	x	Skin*#
x	.Lung*				All gross lesions and masses*
	Nose°				
	Pharynx°				
x	Larynx°				

* Required for subchronic and chronic studies
° Required for chronic inhalation
In subchronic studies, examined only if indicated by signs of toxicity or target organ involvement
† Organ weights required in subchronic and chronic studies
†† Organ weight required for non-rodent studies

a. Organ weight

The effects of 2,4-DP on organ weights of the treated animals are shown in Table 7. In 2,500 ppm males, there were significant increases in relative organ weights such as heart, kidney, liver, brain and testes. In 2,500 ppm females, statistically significant increases in relative kidney and liver weights were observed.

It should be noted that the absolute organ weights of the experimental animals were not reported, and these data should be presented for validating the relative organ weigts.

Table 7 .Body weights (in g),relative organ weights (in g/100 g body weight) and their standard deviations of groups of 15 male and 15 female rats after an experimental period of 13 weeks

group no.	ppm 2,4 DP in the diet	body weight	heart	kidney	liver	spleen	brain	testicles/ ovaries	thymus	thyroid	adrenal
					15 MALES /group						
9193	0	361.	.321	.60	3.32	.158	.52	.39	.101	.0069	.0112
		(8.)	(.005)	(.01)	(.07)	(.008)	(.01)	(.03)	(.006)	(.0003)	(.0004)
9194	100	355.	.323	.61	3.24	.155	.54	.92	.099	.0057*	.0134**
		(8.)	(.006)	(.02)	(.08)	(.007)	(.02)	(.03)	(.005)	(.0004)	(.0004)
9195	500	357.	.324	.72***	3.18	.141	.53	.98	.093	.0061	.0125*
		(9.)	(.009)	(.02)	(.04)	(.005)	(.01)	(.05)	(.004)	(.0004)	(.0003)
9196	2500	295.***	.351**	.68***	4.31***	.135	.62***	1.12***	.096	.0075	.0139**
		(10.)	(.009)	(.01)	(.13)	(.008)	(.02)	(.05)	(.005)	(.0005)	(.0007)
					15 FEMALES /group						
9193	0	221.	.373	.65	2.99	.173	.79	.0339	.150	.0085	.0303
		(4.)	(.015)	(.02)	(.07)	(.009)	(.01)	(.0021)	(.013)	(.0007)	(.0063)
9194	100	218.	.371	.72	3.02	.184	.81	.0370	.143	.0102	.0262
		(4.)	(.012)	(.07)	(.05)	(.005)	(.01)	(.0021)	(.006)	(.0006)	(.0010)
9195	500	213.	.356	.74*	3.10	.179	.83	.0343	.146	.0100	.0266
		(5.)	(.008)	(.03)	(.06)	(.008)	(.02)	(.0018)	(.006)	(.0005)	(.0007)
9196	2500	191.*	.369	.80**	4.54***	.167	1.00	.0315	.123	.0104	.0260
		(12.)	(.019)	(.05)	(.39)	(.008)	(.13)	(.0021)	(.008)	(.0010)	(.0013)

* 0.01 ≤P <0.05
** 0.001 <P <0.01
*** P <0.001

UNDER EACH MEAN ITS STANDARD-DEVIATION (IN BRACKETS) IS GIVEN.

(DATA TAKEN FROM the Submission; MRID 116494)

b. Gross pathology

Increased incidences of greenish discoloration of liver and kidney in males and of liver in females of 2,500 ppm groups relative to the controls were observed.

c. Microscopic pathology

Histopathology data indicate that increased incidences of liver and kidney lesions were observed in all treatd males relative to the controls. Table 8 shows the summary data of the incidence of both kidney and liver lesions which are compiled from the individual animal data by this reviewer.

TABLE 8

Summary Of The Incidence Of Liver And Kidney Lesions* In Controls And 2,4-DP Treated Rats

(Data derived from the individual animal recording of the submission, MRID No. 116494)

ppm	Liver	Kidney
Male		
0	4/15	1/15
100	6/15	6/15
250	5/15	6/15
2500	15/15	5/15
Female		
0	4/15	0/15
100	5/15	3/15
250	10/15	2/15
2500	14/15	4/15

* For details of these lesions, please see Appendix 2.

No tumor incidence was observed in any experimental animals.

It should be noted that insufficient amount of information was presented in the individual-animal histopathology data.

D. DISCUSSION:

This study was previously reviewed (Holder, Tox. Doc. No. 001995), however, this reviewer does not agree with certain conclusions stated in the previous DER. The study is re-evaluated.

Based upon the data reported, dietary administration of 2,4-DP at concentrations of 100, 500, and 2,500 ppm produced compound related effects in all treated animals. The toxicity seen in 2,500 ppm rats was particularly marked. The toxic effects include (a) decreases body weights, food consumption, and food efficiency; (b) decreases in hemoglobin, packed cell volume, and erythrocytes; (c) increases in the levels of SGPT, SGOT, BUN, & AP; (d) decreases in total protein, albumin, and Na^+ in blood; (e) decreases in urinary Na^+ and K^+ excretion; (f) increases in the relative weights of liver, kidney, and heart; and (g) increases in the incidence of greenish discoloration of liver with gross examination.

In addition, histopathology data indicate that 2,4-DP caused increased incidence of kidney lesions in both male and females at 100 ppm (LDT) as well as 500 and 2500 ppm. Increases in the incidence of liver lesions was also observed at 500 and 2500 ppm females and 2500 ppm males. Therefore, based upon the reported data, NOEL of 2,4-DP can not be establised The LOEL is 100 ppm (LDT).

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Pages _____ through _____ are not included in this copy.

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COMPOUND: 2,4-DP ; CONTROL

GROUP NO.: 3193 A+B ♂ ANIMAL NO.:

ABNORMALITIES	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	TOTAL
LIVER																
1. DISSOCIATION-LIKE APPEARANCE OF THE HEPATOCYTES a) slight																
b) moderate/marked																
2. HEPATOCYTES WITH TOO HOMOGENEOUS CYTOPLASM																
3. PRONOUNCED CENTROLOBULAR EOSINOPHILIA																
4. DIFFUSE SLIGHT SINGLE CELL DEGENERATION																
5. A few small foci of RES cell proliferation, occasionally accompanied by a single necrotic hepatocyte	X			X							X			X		4
6. Slight periportal aggregates of mainly mononuclear inflammatory cells																
7. Scattered vacuolisation of hepatocellular cytoplasm																
KIDNEY																
1. Tubular nephrosis a) slight														X		1 1/15
b) moderate																
2. Unilateral hydronephrosis																
3. A few small calcareous deposits in the corticomedullary layer																
4. Focal infiltrates of mainly mononuclear inflammatory cells																
5. A few colloid-filled cysts in the cortex																
6. A few hemorrhagic tubules																
7. Slight focal vacuolisation of cytoplasm of tubular epithelium																
SPLEEN																
1. Increased amount of iron in the red pulp																
THYMUS																
1. Involution																
2. A few colloid-filled cysts																

COMPOUND: 2,4-DP (100 ppm)

GROUP NO.: 9194 A+B ↑ C ANIMAL NO.:

ABNORMALITIES	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	TOTAL
LIVER																
1. DISSOCIATION-LIKE APPEARANCE OF THE HEPATOCYTES a) slight																
b) moderate/marked																
2. HEPATOCYTES WITH TOO HOMOGENEOUS CYTOPLASM																
3. PRONOUNCED CENTROLOBULAR EOSINOPHILIA																
4. DIFFUSE SLIGHT SINGLE CELL DEGENERATION																
5. A few small foci of RES cell proliferation, occasionally accompanied by a single necrotic hepatocyte				X	X		X	X				X	X			6
6. Slight periportal aggregates of mainly mononuclear inflammatory cells								X								1
7. Scattered vacuolisation of hepatocellular cytoplasm																
KIDNEY																
1. Tubular nephrosis a) slight	X						X			X				X		4 6/15
b) moderate/marked									X							1
2. Unilateral hydronephrosis									X							1
3. A few small calcareous deposits in the corticomedullary layer																
4. Focal infiltrates of mainly mononuclear inflammatory cells			X				X		X							3
5. A few colloid-filled cysts in the cortex									X							1
6. A few hemorrhagic tubules																
7. Slight focal vacuolisation of cytoplasm of tubular epithelium																
SPLEEN																
1. Increased amount of iron in the red pulp																
THYMUS																
1. Involution																
2. A few colloid-filled cysts																

16

(e)

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COMPOUND: 2,4-DP ; 500 ppm

GROUP NO.: 9195 A.B ♂ ANIMAL NO.:

ABNORMALITIES	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	TOTAL
LIVER																
1. DISSOCIATION-LIKE APPEARANCE OF THE HEPATOCYTES a) slight																
b) moderate/marked																
2. HEPATOCYTES WITH TOO HOMOGENEOUS CYTOPLASM																
3. PRONOUNCED CENTROLOBULAR EOSINOPHILIA												X				1
4. DIFFUSE SLIGHT SINGLE CELL DEGENERATION																
5. A few small foci of RES cell proliferation, occasionally accompanied by a single necrotic hepatocyte			X		X		X					X		X		5
6. Slight periportal aggregates of mainly mononuclear inflammatory cells			X				X					X				3
7. Scattered vacuolisation of hepatocellular cytoplasm												X				1
KIDNEY																
1. Tubular nephrosis a) slight	X	X	X	X								X			X	6 6/15
b) moderate																
2. Unilateral hydronephrosis																
3. A few small calcareous deposits in the corticomedullary layer																
4. Focal infiltrates of mainly mononuclear inflammatory cells																
5. A few colloid-filled cysts in the cortex																
6. A few hemorrhagic tubules		X														1
7. Slight focal vacuolisation of cytoplasm of tubular epithelium																
SPLEEN																
1. Increased amount of iron in the red pulp																
THYMUS																
1. Involution																
2. A few colloid-filled cysts																

COMPOUND: 2,4-DP (2,500 ppm)

GROUP NO.: 9196 A,B ♀ ANIMAL NO.:

ABNORMALITIES	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	TOTAL
LIVER																
1. DISSOCIATION-LIKE APPEARANCE OF THE HEPATOCYTES a) slight											X	X	X	X		4
b) moderate/marked	X	X	X	X	X	X	X	X	X	X					X	11
2. HEPATOCYTES WITH TOO HOMOGENEOUS CYTOPLASM	X	X	X	X	X	X	X	X	X	X					X	11
3. PRONOUNCED CENTROLOBULAR EOSINOPHILIA	X	X	X	X	X	X	X	X	X	X					X	11
4. DIFFUSE SLIGHT SINGLE CELL DEGENERATION	X	X	X	X	X	X	X	X	X	X					X	11
5. A few small foci of RES cell proliferation, occasionally accompanied by a single necrotic hepatocyte	X	X	X			X										4
6. Slight periportal aggregates of mainly mononuclear inflammatory cells						X		X	X			X				4
7. Scattered vacuolisation of hepatocellular cytoplasm																
KIDNEY																
1. Tubular nephrosis a) slight					X			X		X			X			4
b) moderate																
2. Unilateral hydronephrosis																
3. A few small calcareous deposits in the corticomedullary layer				X												1
4. Focal infiltrates of mainly mononuclear inflammatory cells																
5. A few colloid-filled cysts in the cortex																
6. A few hemorrhagic tubules																
7. Slight focal vacuolisation of cytoplasm of tubular epithelium																
SPLEEN																
1. Increased amount of iron in the red pulp																
THYMUS																
1. Involution																
2. A few colloid-filled cysts											X					1

5/15

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COMPOUND: 2,4 DP (0ppm; control)

GROUP NO.: 9193 A+B ♀ ANIMAL NO.:

ABNORMALITIES	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	TOTAL
LIVER																
1. DISSOCIATION-LIKE APPEARANCE OF THE HEPATOCYTES a) slight																
b) moderate/marked																
2. HEPATOCYTES WITH TOO HOMOGENEOUS CYTOPLASM																
3. PRONOUNCED CENTROLOBULAR EOSINOPHILIA																
4. DIFFUSE SLIGHT SINGLE CELL DEGENERATION																
5. A few small foci of RES cell proliferation, occasionally accompanied by a single necrotic hepatocyte		X									X	X	X			4
6. Slight periportal aggregates of mainly mononuclear inflammatory cells											X					1
7. Scattered vacuolisation of hepatocellular cytoplasm																
KIDNEY																
1. Tubular nephrosis a) slight																
b) moderate																
2. Unilateral hydronephrosis																
3. A few small calcareous deposits in the corticomedullary layer																
4. Focal infiltrates of mainly mononuclear inflammatory cells																
5. A few colloid-filled cysts in the cortex																
6. A few hemorrhagic tubules																
7. Slight focal vacuolisation of cytoplasm of tubular epithelium																
SPLEEN																
1. Increased amount of iron in the red pulp									X							1
THYMUS																
1. Involution																
2. A few colloid-filled cysts																

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COMPOUND: 2,4-DP (100 ppm)

GROUP NO.: 9194 A1B ♀ ANIMAL NO.:

ABNORMALITIES	71	72	79	80	81	82	83	84	85	86	87	88	89	90	TOTAL	
LIVER																
1. DISSOCIATION-LIKE APPEARANCE OF THE HEPATOCYTES a) slight																
b) moderate/marked																
2. HEPATOCYTES WITH TOO HOMOGENEOUS CYTOPLASM																
3. PRONOUNCED CENTROLOBULAR EOSINOPHILIA																
4. DIFFUSE SLIGHT SINGLE CELL DEGENERATION																
5. A few small foci of RES cell proliferation, occasionally accompanied by a single necrotic hepatocyte	X		X				X	X						X	5	5/15
6. Slight periportal aggregates of mainly mononuclear inflammatory cells	X														1	
7. Scattered vacuolisation of hepatocellular cytoplasm																
KIDNEY																
1. Tubular nephrosis a) slight	X		X					X							3	3/15
b) moderate																
2. Unilateral hydronephrosis																
3. A few small calcareous deposits in the corticomedullary layer																
4. Focal infiltrates of mainly mononuclear inflammatory cells	X							X							2	
5. A few colloid-filled cysts in the cortex								X							1	
6. A few hemorrhagic tubules																
7. Slight focal vacuolisation of cytoplasm of tubular epithelium																
SPLEEN																
1. Increased amount of iron in the red pulp																
THYMUS																
1. Involution																
2. A few colloid-filled cysts																

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COMPOUND: 2,4-DP (500 ppm)

GROUP NO.: 9195 A+B ♀ ANIMAL NO.:

ABNORMALITIES	91	92	93	94	95	96	97	98	99	100	101	102	103	104	105	TOTAL
LIVER																
1. DISSOCIATION-LIKE APPEARANCE OF THE HEPATOCYTES a) slight													X			1 10/15
b) moderate/marked																
2. HEPATOCYTES WITH TOO HOMOGENEOUS CYTOPLASM																
3. PRONOUNCED CENTROLOBULAR EOSINOPHILIA																
4. DIFFUSE SLIGHT SINGLE CELL DEGENERATION																
5. A few small foci of RES cell proliferation, occasionally accompanied by a single necrotic hepatocyte	X			X		X				X	X			X		6
6. Slight periportal aggregates of mainly mononuclear inflammatory cells		X				X	X	X			X		X			6
7. Scattered vacuolisation of hepatocellular cytoplasm																
KIDNEY																
1. Tubular nephrosis a) slight					X											1 2/15
b) moderate																
2. Unilateral hydronephrosis																
3. A few small calcareous deposits in the corticomedullary layer																
4. Focal infiltrates of mainly mononuclear inflammatory cells																
5. A few colloid-filled cysts in the cortex					X											1
6. A few hemorrhagic tubules																
7. Slight focal vacuolisation of cytoplasm of tubular epithelium															X	1
SPLEEN																
1. Increased amount of iron in the red pulp																
THYMUS																
1. Involution																
2. A few colloid-filled cysts																

COMPOUND: 2,4-DP (2500ppm)

GROUP NO.: 9196 A+B ♀ ANIMAL NO.:

ABNORMALITIES	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120	TOTAL	
LIVER																	
1. DISSOCIATION-LIKE APPEARANCE OF THE HEPATOCYTES a) slight																	
b) moderate/marked			X		X	X		X	X		X					6	14/15
2. HEPATOCYTES WITH TOO HOMOGENEOUS CYTOPLASM			X	X	X	X	X	X	X	X	X	X	X	X	X	13	
3. PRONOUNCED CENTROLOBULAR EOSINOPHILIA																	
4. DIFFUSE SLIGHT SINGLE CELL DEGENERATION					X						X					2	
5. A few small foci of RES cell proliferation, occasionally accompanied by a single necrotic hepatocyte	X				X											2	
6. Slight periportal aggregates of mainly mononuclear inflammatory cells								X						X		2	
7. Scattered vacuolisation of hepatocellular cytoplasm																	
KIDNEY																	
1. Tubular nephrosis a) slight									X	X						2	4/15
b) moderate																	
2. Unilateral hydronephrosis																	
3. A few small calcareous deposits in the corticomedullary layer				X												1	
4. Focal infiltrates of mainly mononuclear inflammatory cells																	
5. A few colloid-filled cysts in the cortex			X													1	
6. A few hemorrhagic tubules																	
7. Slight focal vacuolisation of cytoplasm of tubular epithelium																	
SPLEEN																	
1. Increased amount of iron in the red pulp																	
THYMUS																	
1. Involution							X									1	
2. A few colloid-filled cysts																	