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DATA EVALUATION REPORT

Study Type: Oncogenicity
Species: Mouse
Guideline: 83-2

TOX Project: 8-1103

I.D. No.: 53023-C

Accession No.: 407923-01

Caswell No.: 557C

Test Material: MCPA

Synonyms: 4-chloro-2-methylphenoxy acetic acid

Sponsor: Industry Task Force on MCPA

Testing Facility: Department of Toxicology
BASF Aktiengesellschaft
West Germany

Study Number: 80 S 0046/8358

Title of Report: Study on the Oncogenic Potential of MCPA in Mice.

Authors: B. Kuhborth, D.V.M.; K. Deckaidt, Ph.D.; D. Mirea, D.V.M.; K. Schilling, D.V.M.; D. Hildebrand, D.V.M.

Report Issued: July 14, 1988

Study Completed: July 26, 1986

Conclusions:

MCPA was administered to B6C3F1 mice for a period of 2 years at dietary levels of 0, 20, 100, and 500 ppm. This came to average daily doses of 3.2, 15.7, and 79.5 mg/kg in males and 3.9, 19.5, and 97.2 mg/kg in females over the entire 2-year period. There were 50 animals of each sex per group in the main study, 10 of each sex per group in a satellite study of 52 weeks in duration.

There was no indication of oncogenicity by the compound under the conditions of this study. There was an increased incidence of nontumorous renal lesions in both males and females at the 500 ppm dose level, which was considered to be compound related.

Classification: Core-Minimum

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Oncogenicity NOEL = 500 ppm (79.5 mg/kg/day in males, 97.2 mg/kg/day in females)

Chronic toxicity LEL = 500 ppm, based on renal lesions observed microscopically.

Chronic toxicity NOEL = 100 ppm (15.7 mg/kg/day in males, 19.5 mg/kg/day in females).

A. Materials:

1. Test Compound - Batch #T.B.H., test substance no. 83/46. Purity: 94.6%. Supplied by Diamond Shamrock Company in U.K., France and West Germany. A technical grade preparation was stored at 30, 40, and 50 °C for 2 years and found to be stable. The substance actually used in this study was tested at the beginning of the study, at 1 year and at the time of completion of the study. It is claimed narratively (in Vol. 1, page 27 of the report) that no decline in active ingredient was seen. Data to support the above claims were not submitted but are on file with the company.

2. Test Animals - Species: Mouse; Strain: F_1-CRL BR, which is a B6C3F1 form. Age: 42 days; Weight: 19 to 24 g males, 15.5 to 20 g females; Source: Charles River, Wilmington, MA, U.S.A., received on June 28, 1984.

B. Study Design:

The study was prolonged from an initially planned 78 weeks to 104 weeks, apparently because of an excellent survival rate in every group.

1. Animal Assignment - Animals were assigned to the following test groups:

Test Group	Dose in Diet (ppm)	Main Study 104 Weeks Male	Main Study 104 Weeks Female	Interim Sacrifice 52 Weeks Male	Interim Sacrifice 52 Weeks Female
1. Control	0	50	50	10	10
2. Low (LDT)	20	50	50	10	10
3. Mid (MDT)	100	50	50	10	10
4. High (HDT)	500	50	50	10	10

2. Basis for Dose Selection - A narrative summary of a 4-month preliminary range-finding study was presented without any data. Males and females received 0, 100, 300, 900, and 2700 ppm in the diet. Number of mice per group, age, and body weight were not indicated. "Neurological signs" were observed by the third day of the study in the 2700 ppm group. Body weight at the conclusion of the study "was below the initial weight" in mice of both sexes receiving the two highest doses. Increased serum GTP and ALP activities were seen at 2700 ppm. Decreased red cell count, hemoglobin and hematocrit were seen at 900 and 2700 ppm. At necropsy, mice in the 2700 ppm

group had "involutions of spleen, testes, uterus and ovaries." Histopathology changes in liver were seen with 2700 ppm consisting of "isolated cell necroses and cloudy swellings."

3. Diet Preparation - Diet was prepared at 4-week intervals and stored, apparently, at room temperature. Samples of treated food were analyzed for stability and concentration at all dose levels. Stability of all diet preparations over a 32-day period was tested prior to the start of the study, after the study began, then every 3 months for the duration of the study.

   Results - Data are shown in volume 6 of this report, in German, not translated.

   It is claimed narratively that analytical concentrations were correct within ± 10 percent, except in two instances with the 20 ppm diet at 5 and 14 months when the dosage was estimated at > 10 percent above the target dose. (Volume 1, pages 19 and 27 of submitted report).

4. Animals received food and water ad libitum.

5. Statistics - The following procedures were utilized in analyzing the numerical data: ANOVA, followed by Dunnett's test for feed consumption, body weight, and compound intake. For hematology, t-test with Nalimov's correction were used.

6. Compliance

   - A signed Statement of Confidentiality Claim was provided.
   - A signed Statement of Compliance with GLP was provided.
   - A signed Quality Assurance Statement was provided.

C. Methods and Results:

1. Observations - Animals were inspected daily for signs of toxicity and twice daily for mortality. In addition they underwent palpation and examination once weekly.

   Toxicity/Mortality (Survival) - Survival rate in the main study is shown at quarterly intervals for each group in the table which follows.

Test Day	91	182	273	364
Males				
0 ppm	50 = 100%	50 = 100%	49 = 98%	48 = 96%
20 ppm	50 = 100%	50 = 100%	50 = 100%	50 = 100%
100 ppm	50 = 100%	50 = 100%	50 = 100%	50 = 100%
500 ppm	50 = 100%	49 = 98%	49 = 98%	49 = 98%

Test Day	455	546	637	728
Males				
0 ppm	47 = 94%	47 = 94%	45 = 90%	45 = 90%
20 ppm	50 = 100%	50 = 100%	49 = 98%	47 = 94%
100 ppm	50 = 100%	50 = 100%	49 = 98%	47 = 94%
500 ppm	49 = 96%	46 = 92%	44 = 88%	42 = 84%

Test Day	91	182	273	364
Females				
0 ppm	49 = 98%	49 = 98%	49 = 98%	49 = 98%
20 ppm	49 = 98%	49 = 98%	50 = 96%	48 = 96%
100 ppm	50 = 100%	50 = 100%	50 = 100%	50 = 100%
500 ppm	50 = 100%	50 = 100%	49 = 100%	50 = 100%

Test Day	455	546	637	728
Females				
0 ppm	49 = 98%	49 = 98%	49 = 98%	43 = 86%
20 ppm	47 = 94%	47 = 94%	46 = 92%	41 = 82%
100 ppm	49 = 98%	47 = 94%	44 = 88%	40 = 80%
500 ppm	46 = 92%	46 = 92%	41 = 82%	40 = 80%

No effects of compound treatment on survival were seen either in the main study (see above) or in the satellite groups (not shown). Survival rate to 2 years was 80 percent or greater in all male and female groups.

No effect of compound treatment on clinical signs or palpation findings were seen during the course of the study.

2. Body Weight - Animals were weighed weekly for 12 to 13 weeks, then every 4 weeks. In the main study, body weight in males became slightly lower than controls in mid ($p < 0.05$) and high ($p < 0.01$) dose groups between days 21 to 84. Body weight was again reduced in high-dose males between days 252 and 644, in mid dose between days 392 and 504. Final body weights of males were 1.8 or 2.0 g less than controls in the two highest dose groups but no significant difference. In females, slight decreases were seen sporadically only in the high-dose

group, such as between days 7 and 21 ($p < 0.05$ to 0.01), weeks 77 and 84 ($p < 0.05$). No significant differences in body weight of females were seen at termination day 735. No decreases in body weight were seen in the satellite studies which had only 9 or 10 of each sex per group.

3. Food Consumption and Compound Intake - Consumption was determined and mean daily diet consumption was calculated. Efficiency and compound intake were calculated from the consumption and body weight gain data.

Food Consumption/Food Efficiency/Compound Intake - There were no effects on food consumption at any time period with any of the three dose levels during the entire course of this study.

Compound intake averaged over the entire course of this study for each dose group was as follows:

Dose (ppm)	Males		Females	
	Main Group	Satellite Group	Main Group	Satellite Group
20	3.2	3.6	3.9	4.4
100	15.7	17.2	19.5	22.2
500	79.5	86.6	97.2	108.5

Results are given in mg/kg/day.

4. Ophthalmological Examinations - Not performed.

5. Blood was collected at 52 and 104 weeks for hematology. All surviving animals in the satellite group were used at 52 weeks, 10 of each sex per group of the main study were used at 104 weeks. Blood was obtained from the retroorbital sinus before killing, without prior fasting.

a. Hematology

X		X	
X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*		
X	Leukocyte count (WBC)*	X	Mean corpuscular HGB (MCH)
X	Erythrocyte count (RBC)*	X	Mean corpuscular HGB concentration (MCHC)
X	Platelet count*	X	Mean corpuscular volume (MCV)
	Blood Clotting Measurements (Thromboplastin time) (Clotting time) (Prothrombin time)		Reticulocyte count

*Required for subchronic and chronic studies.

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In the satellite groups no effects on red or white blood cell parameters in either males or females were seen.

In the main groups, some changes were noted but they were considered sporadic and not compound related because of an absence of dose relationship, values obobtained were within normal limits, and such changes were not noted in both sexes. The changes recorded included increase in MCV in low-dose males ($p < 0.05$), increase in hemoglobin in mid-dose females ($p < 0.05$), increased erythrocytes in mid-dose females, increased hematocrit in females at low- ($p < 0.05$) and mid-dose ($p < 0.01$), and decrease in leukocyte count in low-dose males ($p < 0.01$). Sporadic effects were also seen in differential white cell count.

An increase in Howell-Jolly bodies of red cells were seen in 1, 2, 4, and 0 males, 2, 0, 0, and 5 females of control, low-, mid-, and high-dose groups, respectively, in the main 104-week study. This suggests a possible increased incidence in the high-dose females, especially because 3/10 animals in the high-dose female group also showed some red cell associated morphological changes. However, there were no consistent findings of anemia or an anemic process in these five high-dose females. The investigators believe this, too, is an incidental finding.

b. Clinical Chemistry - Not performed.

6. Urinalysis - Not performed.

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

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* 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 nonrodent studies.

Complete histopathology of all organs was performed only for control and high-dose groups. In addition, histopathology of trachea, liver, kidneys and thyroids were performed for low- and mid-dose groups as well. Mesenteric lymph nodes and other lymph nodes near tumor locations were examined in all animals with tumors.

a. Organ Weight - Statistical analyses were performed for both absolute and relative (to brain) organ weights. Significant differences found for absolute organ weights were similar to that found for relative organ weights, except where indicated below. Therefore, the tables which follow, extracted from the submitted report, show only absolute organ weights.

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ABSOLUTE ORGAN WEIGHTS AFTER 104 WEEKS OF TREATMENT

		Males			
		Group 0 0 ppm	Group 1 20 ppm	Group 2 100 ppm	Group 3 500 ppm
Heart (g)	Mean	.203	.198	.199	.191 #
	SD	.0198	.0167	.0235	.0196
	N	45	47	47	41
Liver (g)	Mean	1.341	1.286	1.222 ##	1.288
	SD	.1343	.1276	.1344	.1586
	N	35	43	40	38
Kidneys (g)	Mean	.676	.677	.660	.680
	SD	.0734	.0660	.0741	.0663
	N	45	47	47	41
Spleen (g)	Mean	.082	.075	.076	.079
	SD	.0426	.0248	.0355	.0331
	N	43	46	46	41
Testes (g)	Mean	.231	.226	.219	.218
	SD	.0501	.0139	.0202	.0226
	N	43	47	47	41
Brain (g)	Mean	.495	.496	.496	.499
	SD	.0153	.0136	.0171	.0160
	N	45	47	47	41
Adrenal (g)	Mean	.0061	.0060	.0068	.0060
	SD	.00158	.00167	.00139	.00158
	N	44	47	46	41

# $p < 0.05$
$p < 0.01$

		Females			
		Group 0 0 ppm	Group 1 20 ppm	Group 2 100 ppm	Group 3 500 ppm
Heart (g)	Mean	.162	.156	.149 ##	.150 #
	SD	.0198	.0185	.0194	.0203
	N	42	41	40	39
Liver (g)	Mean	1.275	1.204	1.197	1.264
	SD	.1780	.1477	.2052	.2291
	N	39	39	35	34
Kidneys (g)	Mean	.457	.451	.441	.498 ##
	SD	.0474	.0535	.0413	.0557
	N	40	40	39	37
Spleen (g)	Mean	.152	.134	.131	.149
	SD	.0679	.0506	.0442	.0531
	N	35	38	35	33
Brain (g)	Mean	.502	.501	.496	.498
	SD	.0183	.0182	.0205	.0157
	N	42	41	40	39
Adrenal (g)	Mean	.0083	.0083	.0076	.0079
	SD	.00178	.00204	.00180	.00200
	N	41	41	39	39

# $p < 0.05$
$p < 0.01$

Heart weights were significantly lower than controls in high-dose males and in mid- and high-dose females. Liver weights were significantly decreased in mid-dose males, not in high-dose males nor in any treated female groups. No effect on absolute testes weight was seen in the table above but relative testes weight was reduced ($p < 0.05$) in high-dose males. All of these organ weight effects were considered to be of no biological relevance because there was no dose dependency and no histopathology changes. However, the kidney weight increase seen for high-dose females ($p < 0.01$) in the above table, were considered as compound related because of accompanying renal histopathology changes.

b. Gross Pathology - No changes were noted in either sex.

c. Microscopic Pathology

1) Non-neoplastic - The only organ with treatment-related lesions appeared to be the kidneys, predominantly at high dose level. This included increased incidences of intratubular calcification and tubular hyaline-proteinaceous casts in both

males and females. There was also an increased incidence of renal tubular epithelial focal hyperplasia in high dose males, and in mid and high dose females.

The table which follows, extracted from the submitted report, is a summary of these renal lesions observed in all animals on test in the main study.

Incidence of Non-Neoplastic Lesions - Main Study Groups

Sex	Male				Female			
Dose Group	0	1	2	3	0	1	2	3
Animals	50	50	50	50	50	50	50	50
Kidneys	50	50	50	50	50	50	50	50
- Vacuolization	4	.	1	.	.	.	.	.
- Calcification	9	11	11	27	.	1	2	9
- Hyaline Granules, ep.	1	.	.	.	2	.	.	1
- Hyaline Cast, Tubular	26	32	25	36	15	14	26	33
- Cyst	1	6	11	5	.	2	.	.
- Hydronephrosis	.	.	.	.	.	1	.	.
- Infiltrates	23	20	18	11	18	24	19	15
- Hyperplasia	9	12	10	32	.	.	7	4
- Pyelitis	1	.	.	.	.	.	.	.
- Nephritis, Interst.	2	7	6	4	4	2	5	1
- Nepropathy	.	.	1	.	.	.	.	.

In the satellite groups killed at 52 weeks, there was no increased incidence of any organ lesion form noted, including the kidneys.

2) Neoplastic - A summary table of all neoplastic lesions in all organs of all animals, taken from the submitted report, follows.

Leydig cell tumors in the testes occurred in two high-dose males, none in the controls. This would not be expected to be statistically significant.

It was concluded by the investigators that there were no differences between control or treated groups on incidence of any tumor type, individual or total tumors, no difference in number of animals with tumors, including benign, malignant, or metastasizing. The number of animals with one primary tumor, with more than one primary tumor, or with vascular tumors, were no different in controls vs. treated animals. The investigators further concluded that MCPA administered via the feed at a concentration up to 500 ppm had no oncogenic potential in B6C3F1 mice.

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D. Discussion:

This study was originally designed as an 18-month study with B6C3F1 mice but was extended to a 2-year study, apparently because of the excellent survival rate. Even after 2 years, survival rate was 80 percent or better in every male or female group of the study. There was no significant effect of compound treatment at any dose level on survival.

Doses selected were 0, 20, 100, and 500 ppm in the diet, which came to an average daily dosage of 3.2, 15.7, and 79.5 mg/kg for males, 3.9, 19.5, and 97.2 mg/kg for females of the main study. These doses were selected on the basis of a preliminary 4-month study in which doses of 900 and 2700 ppm resulted in unacceptable toxicity for both sexes. In the main 2-year study, there were 50 of each sex per group. In a satellite study, 10 mice of each sex received identical treatments but were killed after only 52 weeks. Hematology was performed at 52 weeks with blood from all survivors in the satellite study, and at 104 weeks with blood from 10 of each sex per group in the main study.

Although there were no apparent decreases in food intake by the treated main study groups, there was evidently a decrease in body weight that was significant at numerous time intervals in mid- and high-dose-treated males and high-dose-treated females. No significant differences in body weight were seen in males or females during the last weeks of the study or at terminal kill on about day 728.

In hematology performed for the 2-year main study, sporadic changes, mainly increases in red cell parameters, were seen that were not dose related. There was no indication of such changes in the satellite 1-year study. In the preliminary 4-month study, decreases in red cell parameters at 900 and 2700 ppm were described and these appeared to be compounded related at such high doses. Decreases in red cell parameters were not seen at any of the dose levels in this 2-year mouse study with doses up to 500 ppm.

Decreases in organ weights, such as heart in males and females mainly at high dose, liver in females at mid-dose are considered sporadic because there was no dose relationship and they were not accompanied by histopathology changes. However, the significant increase in kidney weights in high dose-treated females was considered compound related even though it was not evident in males, because it was accompanied by histopathology changes.

No gross pathology changes were observed in any male or female treated group of the satellite or main study.

Histopathology changes were seen only in kidneys of high-dose male and female treated groups killed after 2 years. This included increased incidences of intratubular calcification and tubular hyaline-proteinaceous casts in both sexes. There was also an increased incidence of renal tubular epithelial focal hyperplasia in high dose males and in mid and high dose females. Renal lesions were not seen in the 1-year satellite study even at 500 ppm.

There was no indication of an increased incidence of tumors in any organs or in number of animals with tumors in any treated groups. The investigators concluded that up to 500 ppm in the diet, MCPA was nononcogenic in B6C3F1 mice after 2 years.