UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

TXR No.: 0051628

MEMORANDUM

DATE: March 13, 2003

SUBJECT: Mecoprop-p: Report of the Cancer Assessment Review Committee

FROM: Jessica Kidwell, Executive Secretary
Cancer Assessment Review Committee
Health Effects Division (HED) (7509C)

TO: Kit Farwell, Toxicologist
and
Tim Dole, Risk Assessor
Reregistration Branch 1
Health Effects Division (HED) (7509C)

Tyler Lane, Chemical Review Manager
Reregistration Branch 3
Special Review and Reregistration Division (7508C)

The Cancer Assessment Review Committee met on January 15, 2003 to evaluate the carcinogenic potential of Mecoprop-p. Attached please find the Final Cancer Assessment Document.

cc: R. Hill
J. Pletcher
Y. Woo

CANCER ASSESSMENT DOCUMENT

Evaluation of the Carcinogenic Potential of

MECOPROP-p

PC code 129046

FINAL
MARCH 13, 2003

CANCER ASSESSMENT REVIEW COMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS

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DATA PRESENTATION: Kit Farwell, DVM

Kit Farwell, D.V.M.

DOCUMENT PREPARATION: Jessica Kidwell

Jessica Kidwell, Executive Secretary

COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the assessment unless otherwise stated).

Karl Baetcke	Karl T. Baetcke
William Burnam	W Burnam
Marion Copley	Marion Copley
Abdallah Khasawinah	D. Khasawinah
Nancy McCarroll	Nancy McCarroll
Tim McMahon	
Esther Rinde	Esther Rinde
Jess Rowland	Jess Rowland
Linda Taylor	Linda Lee Taylor
Yintak Woo	See attached sheet

NON-COMMITTEE MEMBERS IN ATTENDANCE (Signature indicates concurrence with the pathology report and statistical analysis of data, respectively)

John Pletcher, Consulting Pathologist	See attached sheet
Lori Brunsman, Statistical Analysis	Lori L. Brunsman

OTHER ATTENDEES: Tim Dole (RRB1), Mark Howard (SRRD)

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EXECUTIVE SUMMARY

On January 15, 2003, the Cancer Assessment Review Committee (CARC) of the Health Effects Division of the Office of Pesticide Programs met to evaluate the carcinogenic potential of mecoprop-p.

Dr. Kit Farwell of Reregistration Branch 1 described the 18-month carcinogenicity study in B6C3F1/CrlBR mice and the 104-week chronic toxicity/carcinogenicity study in Wistar rats by detailing the experimental design; reporting on survival and body weight effects, treatment related non-neoplastic and neoplastic lesions, statistical analysis of the tumor data, the adequacy of the dose levels tested; and presenting the weight of the evidence of carcinogenicity of mecoprop-p, including the structure activity relationship data. Nancy McCarroll discussed the mutagenicity studies.

Mecoprop-p (d-isomer, 92.7%) was administered in the diet to 50 male and 50 female B6C3F1/CrlBR mice at concentrations of 0, 25, 250, or 2500 ppm (0, 4, 40, or 592 mg/kg/day in males; 0, 4, 46, or 732 mg/kg/day in females) for 18 months. The high-dose group was sacrificed at 12 months due to severe body weight loss. A second study was conducted to provide a high-dose group. B6C3F1/CrlBR mice (50/sex/dose) were fed diets containing mecoprop-p (d-isomer, 92.7%) for 18 months. Dietary concentrations were 0 or 700 ppm in males, and 0 or 800 ppm in females (0 or 112 mg/kg/day in males; 0 or 188 mg/kg/day in females).

Mecoprop (racemic mixture, 92.7% purity) was administered to groups of 75 male and 75 female Wistar rats at dietary concentrations of 0, 20, 100, or 400 ppm (0, 1.1, 5.5, and 22.2 mg/kg/day for males and 0, 1.4, 6.9, and 27.9 mg/kg/day for females) for 104 weeks.

The CARC concluded that mecoprop-p showed evidence of carcinogenicity based on the following:

- **Evidence of carcinogenicity (liver tumors) was seen in one sex (female) of one species (mouse) treated with mecoprop-p.** Female B6C3F1/CrlBR mice in the 1999 study had significant increasing trends and significant pair-wise comparisons of the 800 ppm dose group with the controls for hepatocellular adenomas ($p < 0.05$) and combined hepatocellular adenomas and/or carcinomas ($p < 0.01$). This study had only 2 dose groups, 0 and 800 ppm. When the 1996 and 1999 studies were combined, there were statistically significant trends in hepatocellular adenomas and combined hepatocellular adenomas and/or carcinomas, both at $p < 0.01$. There was a significant pair-wise comparison of the 250 ppm female dose group with the controls for combined hepatocellular adenomas and/or carcinomas at $p < 0.05$. There were also significant pair-wise comparisons of the 800 ppm female dose group with the controls for hepatocellular adenomas ($p < 0.05$) and combined adenomas and/or carcinomas ($p < 0.01$). The incidence for hepatocellular adenomas in females (10% at 800 ppm) was within the

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historical control range for this testing facility (0 - 10%). The incidence for hepatocellular carcinomas in females (10% at 250 ppm and 8% at 800 ppm) exceeded the historical control range (0 - 6%). The CARC considered the increase in liver tumors to be treatment-related in females.

- There was no treatment-related increase in any tumors in male B6C3F1/CrlBR mice treated with mecoprop-p.

- **The CARC concluded that the dose levels of 800 ppm and 700 ppm were adequate, but not excessive, in females and males, respectively, to assess the carcinogenicity of mecoprop-p in mice as follows:**

  Females: The 2500 ppm dose was clearly excessive due to severe body weight loss--females in this group weighed 64% of controls on day 315. However, dosing at 800 ppm and below was considered adequate, but not excessive, in females based upon kidney toxicity (increased absolute/relative kidney weights) and increased incidence of renal calcification and chronic nephropathy, graded mainly minimal, in the 250 ppm and 800 ppm groups, and decreased body weights in the 800 ppm group (weights were 90-92% of controls for the last 4 months of the study).

  Males: The 2500 ppm dose is considered excessive due to severe body weight loss--males in this group weighed 73% of controls on day 315. Males in the 700 ppm group could have tolerated a higher dose, but dosing is considered adequate, when toxicity in the carcinogenicity study is considered together with toxicity in the subchronic mouse study. In the carcinogenicity study, male body weights in the 700 ppm group were 91-95% of controls for the last 4 months of the study. The 700 ppm male group had increased relative kidney weight (105% of controls) and increased incidence of microscopic lesions of renal calcification and chronic nephropathy (generally classified minimal or slight). In the subchronic mouse study with mecoprop-p, males in the 1000 ppm group weighed 92% of controls after 90 days of treatment. Cumulative body weight gain for the 1000 ppm group was significantly decreased throughout most of the study and was 64% of controls at the end of the study. Other toxicity seen in the 1000 ppm group in the subchronic study included elevated alkaline phosphatase activity (130% of controls), elevated urea and creatinine (115% of controls), and decreased triglycerides (72% of controls). It is reasonable to assume that the toxicity (excessive decrease in body weight gain) seen in the subchronic mouse study at 1000 ppm would be even more adverse in a chronic study, and, therefore, the CARC concluded that the dose of 700 ppm chosen for the carcinogenicity study was reasonable.

- **There was no treatment-related increase in tumors in male or female Wistar rats treated with mecoprop (racemic mixture), however, dosing in the rat chronic toxicity/carcinogenicity study was considered to be inadequate.** There were no effects

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on body weight or mortality and minimal toxicity (increased absolute and relative kidney weights) occurred at the high dose (400 ppm). Three subchronic feeding studies in Wistar rats with mecoprop or mecoprop-p did not support the doses selected in the combined study as there was very minimal (increased kidney weights) or borderline (decreases in hematological parameters) toxicity seen at doses ranging from 400-500 ppm after 90 days. Doses of 2500 and 3000 ppm induced adverse effects (decreases in body weight/body weight gain, food consumption, food efficiency, increased water consumption, alterations in clinical chemistry and hematology parameters, increased absolute and relative liver weights; and liver and adrenal gland histopathology) after 90 days.

- None of the various forms of mecoprop induced gene mutations in bacteria or cultured mammalian cells. There was no compelling evidence of clastogenicity in the *in vitro* studies. Mecoprop-p, mecoprop-p-DMA and mecoprop-p 2-EHE were negative in the mouse micronucleus and/or bone marrow chromosomal aberration in Chinese hamsters assays. There was equivocal evidence for *in vivo* clastogenicity and sister chromatid exchange (SCE) induction with the racemic mixture.

- Mecoprop-p is structurally related to several compounds, including other phenoxy herbicides. Ciprofibrate, methyl clofenapate and clofibric have been shown to be rodent hepatocarcinogens. Another closely related pesticide, Cloprop, has also been shown to induce liver tumors in mice.

- There are no mode of action studies available at this time.

In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999), the Committee classified mecoprop-p into the category **"Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential"** by the oral route based on the occurrence of hepatocellular adenomas and carcinomas in female B6C3F1/CrlBR mice treated with mecoprop-p. Quantification of carcinogenicity is not required. **[Note: If, based on mecoprop-p's pattern of use, a second cancer study is needed, then the CARC has determined that the current chronic toxicity/carcinogenicity study in the rat is not adequate and should be repeated with mecoprop-p.]**

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I. Introduction

On January 15, 2003, the Cancer Assessment Review Committee (CARC) of the Health Effects Division of the Office of Pesticide Programs met to evaluate the carcinogenic potential of Mecoprop-p. This was the first time that this compound was assessed for carcinogenicity by the CARC.

II. Background Information

Regulatory Background: Mecoprop-p is a member of the chlorophenoxy class of herbicides. This class of herbicides function by mimicking the action of auxins, plant growth hormones. Mecoprop-p consists of the dextro or R isomer only, while mecoprop is a 50:50 racemic mixture of the two isomers.

Current and/or past registrations of mecoprop and mecoprop-p include the acid forms, dimethyl amine salts, ethylhexyl esters, and potassium salts. An industry task force has been formed to deal with regulatory issues of mecoprop-p, however, the task force does not represent all the registrants, some of whom may wish to keep mecoprop registrations.

Mecoprop-p is used in combination with other herbicides for broadleaf weed control in residential and commercial turf and golf courses. There are no crop uses and no residue tolerances. Since there are no food uses, carcinogenicity studies were not required by EPA guidelines. Mecoprop-p is registered for use as a selective herbicide on small grains in Europe, and carcinogenicity studies were conducted to fulfill European regulatory requirements.

Table 1. Chemical Codes

Chemical	Chemical Form	Chem Code	CAS #
Mecoprop-p	Acid form of d-isomer	129046	16484-77-8
Mecoprop-p-DMA	Dimethyl amine salt	031520	66423-09-4
Mecoprop-p 2-EHE	Ethylhexyl ester	031564	unknown
Mecoprop-p K^+ salt	Potassium salt	None	unknown
Mecoprop	Acid form of racemic mixture	031501	7085-19-0
Mecoprop-DMA	Dimethyl amine salt	031519	32351-70-5
Mecoprop 2-EHE	Ethylhexyl ester	031563	28473-03-2
Mecoprop K^+ salt	Potassium salt	None	1929-86-8

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Toxicity Summary: The older toxicity studies used mecoprop, while the newer toxicity studies generally used mecoprop-p. Both mecoprop and mecoprop-p were tested in rat subchronic and developmental studies. In general, toxicity was similar between mecoprop and mecoprop-p in subchronic and developmental studies, although NOAELs for the racemic and isomeric forms sometimes varied.

Toxicity in the subchronic and chronic studies in mice, rat, and dog studies with mecoprop and mecoprop-p was generally not severe and included decreased body weights and elevated liver and kidney weights. Liver enzymes were elevated in subchronic studies in mice and rats with mecoprop-p, both at 2500 ppm. Hepatocellular adenomas and carcinomas were increased in female mice in the carcinogenicity study. In the mouse carcinogenicity study there was an increased incidence of chronic nephropathy. Urea and creatinine were slightly elevated in subchronic rat and mouse studies. There were decreases in hematological parameters in subchronic rat and dog studies.

There were no toxicity studies in which relative toxicities of the dimethyl amine (DMA) salt or the ethylhexyl ester (EHE) forms could be directly compared to the acid forms of mecoprop. However, a special metabolism study examined the dissociation/ degradation of mecoprop-p-DMA to mecoprop-p *in vitro*. The reviewer concluded that at physiological pH, mecoprop-p-DMA would dissociate into the free acid (mecoprop-p) and that in the *in vivo* situation it would be the free acid, and not the salt, which is absorbed, distributed, and metabolized. In addition, pharmacokinetic parameters for mecoprop-p, mecoprop-p-DMA, and mecoprop-p-EHE were all very similar.

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III. Evaluation of Carcinogenicity Studies

1. Carcinogenicity Study in Mice

References: Mellert, W; Deckardt, K; Kuttler, K; Hildebrand, B. (1996). Mecoprop-p - carcinogenicity study in B6C3F1/CrlBR mice. Administration in the diet for 18 months. Department of Toxicology of BASF Aktiengesellschaft (FRG). Project Number: 76S0002: 91102. June 21, 1996. MRID 44953601. Unpublished.

and

Mellert, W; Deckardt, K; Kuttler, K; Hildebrand, B. (1999). Mecoprop-p - carcinogenicity study in B6C3F1/CrlBR mice. Administration in the diet for 18 months. (Supplementary study) Department of Toxicology of BASF Aktiengesellschaft (FRG). Project Number: 76S0002/91142. January 20, 1999. MRID 44895501. Unpublished.

A. Experimental Design

B6C3F1/CrlBR mice (50/sex/dose) were fed diets containing mecoprop-p (d-isomer, 92.7%) for 18 months. Dietary concentrations were 0, 25, 250, or 2500 ppm; approximately 0, 4, 40, or 592 mg/kg/day in males and 0, 4, 46, or 732 mg/kg/day in females. The high-dose group was sacrificed at 12 months due to severe body weight loss.

A second study was conducted to provide a high-dose group. B6C3F1/CrlBR mice (50/sex/dose) were fed diets containing mecoprop-p (d-isomer, 92.7%) for 18 months. Dietary concentrations were 0 or 700 ppm in males, and 0 or 800 ppm in females; approximately 0, or 112 mg/kg/day in males, and 0 or 188 mg/kg/day in females. This study was conducted 3 years later by the same lab and used the same procedures and same strain of mice as in the first study.

B. Discussion of Tumor Data

Survival Analysis

The statistical evaluation of mortality indicated no significant incremental changes with increasing doses of mecoprop-p in female mice in the 1996 study, the 1999 study, or the 1996 and 1999 studies combined (Memo, L. Brunsman, 12/18/02, TXR No. 0051421). The statistical evaluation of mortality was based upon the Thomas, Breslow and Gart computer program.

Tumor Analysis

As shown in Tables 2, 3, and 4, treatment-related increases in liver tumors were observed in female mice (Memo, L. Brunsman, 12/18/02, TXR No. 0051421). There were no treatment-related tumors observed in male mice.

1996 Study: There were no significant trends or significant pair-wise comparisons of the dosed groups with the controls in the 1996 study. The statistical evaluation included the 0, 25, and 250 ppm groups only. The 2500 ppm group was sacrificed early due to severe body weight loss and did not receive necropsies.

1999 Study: Female mice of the 1999 study had significant increasing trends, and significant pair-wise comparison of the 800 ppm dose group with the control group, for liver adenomas ($p < 0.05$) and adenomas and/or carcinomas combined ($p < 0.01$). Hepatocellular tumors were not increased in males. This study had only 2 dose groups, 0 and 800 ppm.

1996 and 1999 Studies Combined: When the 1996 and 1999 studies were combined, there were statistically significant trends in liver adenomas and adenomas and/or carcinomas combined, both at $p < 0.01$, in females. There was a significant pair-wise comparison of the 250 ppm female dose group with the controls for liver adenomas and/or carcinomas combined at $p < 0.05$. There were also significant pair-wise comparisons of the 800 ppm female dose group with the controls for liver adenomas ($p < 0.05$) and adenomas and/or carcinomas combined ($p < 0.01$).

The statistical analyses of the female mice were based upon the Exact trend test and the Fisher's Exact test for pair-wise comparisons.

Historical Control Data: The incidence for hepatocellular adenomas in females (10% at 800 ppm) was within the historical control range for this testing facility (0 - 10%). Control groups in the 1987 and 1997 studies had an incidence of 10% for hepatocellular adenomas. The mean incidence for hepatocellular adenomas was 3.5% from 1994-1997 and 4.0% from 1987-1997.

The incidence for hepatocellular carcinomas in females (10% at 250 ppm and 8% at 800 ppm) exceeded the historical control range (0 - 6%). There was an incidence of 6% for hepatocellular carcinomas in female controls in one 1994 study and an incidence of 2% in 1987; the incidence in all the other 4 time periods was 0%. The mean incidence for hepatocellular carcinomas from 1994-1997 was 1.5% and from 1987-1997 was 1.3%.

Historical control data are shown in Table 5.

TABLE 2. Mecoprop-p - 1996 B6C3F1/CrlBR Mouse Study

Female Liver Tumor Rates[+] and Fisher's Exact Test and Exact Trend Test Results (p values)

	Dose (ppm)		
	0	25	250
Adenomas	1/50	1[a]/49	3/50
(%)	(2)	(2)	(6)
p =	0.1678	0.7475	0.3087
Carcinomas	3[b]/50	2/49	5/50
(%)	(6)	(4)	(10)
p =	0.1846	0.5097	0.3575
Combined	4/50	3/49	8/50
(%)	(8)	(6)	(16)
p =	0.0676	0.5114	0.1783

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.

[a]First adenoma observed at week 79, dose 25 ppm.

[b]First carcinoma observed at week 79, dose 0 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

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TABLE 3. Mecoprop-p - 1999 B6C3F1/CrlBR Mouse Study

Female Liver Tumor Rates[+] and Fisher's Exact Test and Exact Trend Test Results (p values)

	Dose (ppm)	
	0	800
Adenomas (%)	0/49 (0)	5[a]/48 (10)
p =	0.0266*	0.0266*
Carcinomas (%)	0/49 (0)	4[b]/48 (8)
p =	0.0562	0.0562
Combined (%)	0/49 (0)	9/48 (19)
p =	0.0012**	0.0012**

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.

[a]First adenoma observed at week 79, dose 800 ppm.

[b]First carcinoma observed at week 67, dose 800 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

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TABLE 4. Mecoprop-p - Combined 1996 and 1999
B6C3F1/CrlBR Mouse Studies

Female Liver Tumor Rates[+] and Fisher's Exact Test
and Exact Trend Test Results (p values)

	Dose (ppm)			
	0	25	250	800
Adenomas	1/99	1[a]/49	3/50	5/48
(%)	(1)	(2)	(6)	(10)
p =	0.0061**	0.5541	0.1101	0.0144*
Carcinomas	3/99	2/49	5/50	4[a]/48
(%)	(3)	(4)	(10)	(8)
p =	0.0989	0.5369	0.0844	0.1576
Combined	4/99	3/49	8/50	9/48
(%)	(4)	(6)	(16)	(19)
p =	0.0032**	0.4240	0.0156*	0.0054**

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.

[a]First adenoma observed at week 79, dose 25 ppm.

[b]First carcinoma observed at week 67, dose 800 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

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Table 5. Historical Control Data for 18 Month Feeding Studies with B6C3F1 Mice.

Study #	Study Dates	Males		Females	
		Hepatocellular Adenomas	Hepatocellular Carcinomas	Hepatocellular Adenomas	Hepatocellular Carcinomas
8607	6/86 - 12/87	8%	4%	10%	2%
8593	8/86 - 2/88	2%	12%	0%	0%
91105	3/93 - 9/94	2%	20%	2%	0%
91102	12/92 - 7/94	6%	14%	2%	6%
91142	11/95 - 5/97	8%	4%	0%	0%
91143	12/95 - 6/97	NR	NR	10%	0%

From pages 135-137 in study report, MRID 44895501, 1999. NR = Not Reported
n = 50 for all studies

C. Non-Neoplastic Liver Lesions

Microscopic liver lesions were generally comparable between groups (Table 6). Although basophilic foci appeared increased in 700 ppm males and 800 ppm females when compared to concurrent controls, this may have been because control values were low in comparison to controls in the 1996 study. The registrant submitted historical control data for basophilic foci in B6C3F1 mice, which ranged from 6-20% in males and 0-14% in females.

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Table 6. Liver: Selected Microscopic Lesions (all animals)

Lesion	Males				Females			
	0 ppm	25 ppm	250 ppm	700 ppm	0 ppm	25 ppm	250 ppm	800 ppm
Cellular Alteration [a] - Basophilic Foci	8	7	4		6	4	1	
Focal Fatty Infiltration[a]	8	11	13		10	10	7	
Hypertrophy [a]	NR	NR	NR		NR	NR	NR	
Regen. Hyperplasia [a]	NR	NR	NR		NR	NR	NR	
Focal Necrosis [a]	7	2	5		7	8	5	
Cellular Alteration [b] - Basophilic Foci	4			11	0			4
Focal Fatty Infiltration[b]	8			6	5			6
Hypertrophy [b]	0			2	0			0
Regen. Hyperplasia [b]	0			1	0			0
Focal Necrosis [b]	9			5	7			5

a From pages 136 of study report (MRID 44953601, 1996)
b From page 123 of study report (MRID 44895501, 1999)
NR = Not reported. n = 50 for all groups
NOTE: Microscopic examination of tissues was not performed for the 2500 ppm group which was sacrificed early.

D. CLINICAL FINDINGS

In the 1996 study, the 2500 ppm group had increased incidences of abdominal masses palpated in males (41 vs 10 in controls) and females (47 vs 12). In other groups which received histological examinations, abdominal masses sometimes correlated with hepatocellular neoplasia, though the masses were often associated with non-neoplastic changes. Since mice in the 2500 ppm group did not receive necropsies, the nature of these masses could not be determined.

E. Adequacy of Dosing for Assessment of Carcinogenicity

Females: The 2500 ppm dose was clearly excessive due to severe body weight loss. Females in this group weighed 64% of controls on day 315. However, dosing at 800 ppm and below is considered adequate, but not excessive, in females based upon kidney toxicity (increased absolute/relative kidney weights) and increased incidences of renal calcification and chronic nephropathy, graded mainly minimal, in the 250 ppm and 800 ppm groups, and decreased body weights in the 800 ppm group. There were increases in absolute kidney weight (114%) and relative kidney weight (121%) in 250 ppm females and increases in both absolute (115%) and relative kidney weight (126%) in 800 ppm females when compared to controls. Increased kidney

weights were accompanied by increased incidences of microscopic lesions of renal calcification and chronic nephropathy (generally classified minimal or slight) in these 2 dose groups. Urine is the major excretory route for mecoprop-p. Body weight for 800 ppm females was 90-92% of controls for the last 4 months of the study.

Males: The 2500 ppm dose is considered excessive due to severe body weight loss. Males in this group weighed 73% of controls and females weighed 64% of controls on day 315. Males in the 700 ppm group could have tolerated a larger dose, but dosing is considered adequate when toxicity in the carcinogenicity study is considered together with toxicity in the subchronic mouse study. In the carcinogenicity study, male body weights in the 700 ppm group were 91-95% of controls for the last 4 months of the study. The 700 ppm male group had increased relative kidney weight (105% of controls) and increased incidence of microscopic lesions of renal calcification and chronic nephropathy(generally classified minimal or slight).

In the subchronic mouse study with mecoprop-p, males in the 1000 ppm group weighed 92% of controls after 90 days of treatment. Cumulative body weight gain for the 1000 ppm group was significantly decreased throughout most of the study and was 64% of controls at the end of the study. Other toxicity in the 1000 ppm group in the subchronic study included elevated alkaline phosphatase activity (130% of controls), elevated urea and creatinine (115% of controls), and decreased triglycerides (72% of controls). It is reasonable to assume that the toxicity (excessive decrease in body weight gain) seen in the subchronic mouse study at 1000 ppm would be even more adverse in a chronic study, and, therefore, the CARC concluded that the dose of 700 ppm chosen for the carcinogenicity study was reasonable.

2. Combined Chronic Toxicity/Carcinogenicity Study in Rats

Reference: Kuhborth, B., et al. 1988. Study on the chronic toxicity and oncogenic potential of MCPP in rats. BASF AG, Department of Toxicology, 6700 Ludwigshafen/Rhein, Germany. Laboratory report number 71S0047/8352, August 23, 1988. MRID 40937501. Unpublished.

A. Experimental Design: Mecoprop (racemic mixture, 92.7% purity), was administered to groups of 75 male and 75 female Wistar rats at dietary concentrations of 0, 20, 100, or 400 ppm (0, 1.1, 5.5, and 22.2 mg/kg/day for males and 0, 1.4, 6.9, and 27.9 mg/kg/day for females) for 104 weeks.

B. Discussion of Tumor Data: No treatment-related neoplastic lesions were observed in male or female rats in this study.

C. Adequacy of the Dosing for Assessment of Carcinogenicity: Dosing was considered inadequate. There were no effects on body weight or mortality and minimal toxicity occurred in this study. Absolute and relative kidney weights of high-dose males were increased by 11% (N.S.) and 18% ($p \leq 0.01$), respectively, at 52 weeks and by 13% (≤ 0.01) and 11% ($p \leq 0.01$), respectively, at 104 weeks compared with those of controls. In the mid-dose group, absolute and relative kidney weights were increased by 3% (N.S.) and 15% (≤ 0.01), respectively, at 52 weeks and by 7% ($p \leq 0.01$) and 4% (N.S.) at 104 weeks. The increases in kidney weights were not associated with any treatment-related gross or microscopic findings in the kidney, however, increased kidney weights have occurred in subchronic studies in rats with mecoprop.

There were 3 subchronic feeding studies in Wistar rats with mecoprop or mecoprop-p. These studies did not support the doses selected in the combined study as there was very minimal (increased kidney weights) or borderline (decreases in hematological parameters) toxicity seen at doses ranging from 400-500 ppm after 90 days. Doses of 2500 and 3000 ppm induced adverse effects (decreases in body weight/body weight gain, food consumption, food efficiency, increased water consumption, alterations in clinical chemistry and hematology parameters, increased absolute and relative liver weights; and liver and adrenal gland histopathology).

1. In the first study (MRID 00158359), Mecoprop (racemic mixture) was administered to Wistar rats in the diet for 90 days at concentrations of 0, 50, 150, or 450 ppm. Toxicity was limited to increased kidney weights. Absolute and relative kidney weights were significantly ($p \leq 0.05$ or 0.01) increased in the 150 ppm males (113%), 450 ppm males (115%), and 450 ppm females (107%) and relative kidney weights were increased for 150 ppm females (109%). Creatinine was elevated slightly in high-dose females (116% of controls).

2. In the second study, (MRID 41013910), either the racemic (92.7%) or D-isomer

(Mecoprop-p, 99.4%) was administered to groups of 10 male and 10 female Wistar rats in the diet at concentrations of 0, 50, or 400 ppm for 90 days. Absolute kidney weights of all treated males and high-dose D-form females were 5-8% greater than that of the controls. No other toxicity was noted in the study.

3. The third study was a subchronic neurotoxicity study: Wistar rats (15/sex/group) were fed diets containing 0, 75, 500, 2500 (males only) or 3000 (females only) ppm Mecoprop-p (d-isomer) for at least 90 days. At 500 ppm in males, there were borderline decreases in hematological parameters in males (hematocrit was 95% of controls) and decreases in triglyceride (66%) and cholesterol (81%) concentrations in comparison to controls. At the high dose of 2500 ppm in males and 3000 ppm in females there were decreases in body weights (18%), body weight gains (27-29%), food consumption (5-19%, males; 12-19% females), and increased water consumption (27-55 %, males; 59-84%, females). At this dose, there was also increased alkaline phosphatase in males and females and ALT activity, decreased calcium levels, decreased chloride levels, decreases in total protein and globulin levels, increases in urea and creatinine levels, and increased number of transitional epithelial cells in the urine. There were also increased liver weights, decreases in the absolute adrenal gland weights, and grossly discolored adrenal glands. Microscopic lesions of the liver included cytoplasmic eosinophilia and granular cytoplasm, bile duct proliferation, and central hypertrophy. Lipid accumulation was noted in the adrenal cortexes,

IV. Toxicology

1. Metabolism

Metabolism Study #1: In a metabolism study (MRID 44362701, 1997), [^{14}C]-Mecoprop-P (d-isomer) was administered orally at doses of 5 mg/kg (single dose) and 14-day repeated dose, or a single dose of 100 mg/kg. Absorption was rapid and peak plasma concentration was attained at 1.8 and 4.2 hours, respectively, for the single low-dose and single high-dose groups.

Excretion was also rapid and complete regardless of dose. Total excretion was >90% by 24 hours and near 100% by 168 hours regardless of dose. Urinary excretion accounted for 61% to 76% of the administered dose over a 168-hour period for the different dose groups. Fecal excretion accounted for 4% to 13% of the administered dose over a 168-hour period for the various dose groups. Greater than 90% of the urinary excretion occurred within 24 hours and >90% of the fecal excretion occurred within 48 hours for all dose groups.

The maximum plasma concentration (C_{max}) was similar for males and females, regardless of dose, possibly indicating saturation of absorption in the high dose group. AUC values were disproportionate for the low- and high-dose groups, thereby indicative of nonlinear kinetics. The

$t_{1/2}$ was approximately 5 hours for the low-dose group and 8 hours for the high-dose group.

A major metabolite identified as MCPP-OH was found in both the urine and feces. As a urinary metabolite, it accounted for up to 33% of the administered dose in male rats. Urinary excretion of MCPP-OH in females was 4-6 fold less than males and fecal excretion of MCPP-OH was about 3-6 fold less in females than in males. Although other urinary metabolites were detected, none represented more than 1.5% of the administered dose. MCPP-OH in the feces represented, at most, 3.60% of the administered dose of Mecoprop-P.

Metabolism Study #2: In a metabolism study (MRID 44362702), groups of five male Wistar rats given [^{14}C]-Mecoprop-P-EHE or [^{14}C]-Mecoprop-P-DMA (d-isomers) orally at doses of 5 mg/kg. Recovery of administered test material was acceptable and ranged from 87.38% (Mecoprop-P-EHE) to 102.03% (Mecoprop-P-DMA).

Both the ester (Mecoprop-P-EHE) and the dimethylamine derivative (Mecoprop-P-DMA) were efficiently absorbed following a single oral dose of 5 mg/kg. Maximum plasma concentration was attained at 3.6 and 2 hours, respectively for Mecoprop-P-EHE and Mecoprop-P-DMA. Within 24 hours, 68% (ester) and 83% (dimethylamine) of the dose was absorbed. Elimination half-time was 8.356 and 6.606 hours, respectively, for the ester and dimethylamine derivative. Urine was the primary route of excretion, accounting for 71% (Mecoprop-P-EHE) and 86% (Mecoprop-P-DMA) of the administered dose over a 168-hour time period. Most urinary excretion occurred in the first 24 hours. There was no detectable excretion via expired air and fecal excretion accounted for < 5% of the administered dose. Accumulation in the tissues was limited to <1 μg equivalent/g tissue and appeared to be primarily associated with the gastrointestinal tract and organs of excretion. The small amount of radioactivity detected in the skin was likely the result of contamination with urine and cage debris.

Most of the excreted radioactivity was associated with parent compound. A hydroxylated metabolite, MCPP-OH, accounted for 16.34% (ester) and 21.70% (dimethylamine) of the administered dose detected in the urine. MCPP-OH was also detected in the organic extractable portion of the feces but represented <2% of the administered dose for both Mecoprop-P derivatives. Unidentified urinary metabolites accounted for <3% of the dose and unidentified fecal metabolites accounted for 0.1% or less of the administered dose.

This metabolism study is classified Acceptable and satisfies the guideline requirements for a metabolism study (85-1) in rats.

Metabolism Study #3: This study (MRID 43717201) was intended to examine the dissociation/ degradation of mecoprop-p-dimethylammonium (MCPP-p-DMA) to mecoprop-p (MCPP-p) in the presence of a series of *in vitro* matrices representing the progression of the test material in the body following oral intake. (^{14}C)-MCPP-p-DMA was incubated *in vitro* with rat plasma, stomach content, gastro-intestinal tract (GIT) or post-mitochondrial liver fraction (S9) for 30 minutes. All

incubate extracts were subjected to HPLC analysis. Results indicated that all of the administered (^{14}C)-MCPP-p-DMA in plasma, stomach contents, gastro-intestinal tract and liver (S9) was converted into (^{14}C)-MCPP-p.

It should be noted that MCPP-p-DMA is a basic compound and therefore at physiological pH it will be dissociated into the free acid (mecoprop-p) and dimethylamine. Also, it should be noted that in the *in vivo* situation it would be the free acid, and not the salt, which is being absorbed, distributed, and metabolized. This metabolism/degradation study is acceptable (nonguideline).

Comparison of pharmacokinetic parameters: The pharmacokinetic parameters for mecoprop-p (MRID 44362701) were compared to pharmacokinetic parameters for mecoprop-p-DMA and mecoprop-p-EHE. Pharmacokinetic parameters for all 3 compounds were very similar. The following parameters were similar: C_{max}, plasma $_{t1/2}$, AUC, plasma concentrations at various time points, % excretion in urine, % excreted in urine as mecoprop-p, and % excreted in urine as hydroxy-mecoprop.

2. Mutagenicity

Mutagenicity testing results are shown in Tables 9, 10, 11, and 12. None of the various forms of mecoprop induced gene mutations in bacteria or cultured mammalian cells.

Mecoprop-p was positive in human lymphocytes only at single concentrations in one assay without S9 activation and in another assay with S9 activation. In both studies, the induction of chromosome aberrations occurred at cytotoxic concentrations and the types of aberrations (chromatid and chromosome breaks) are generally considered to be a secondary effect attributed to cytotoxicity rather than clastogenicity. Mecoprop-DMA, in the presence of S9 activation was also positive, inducing chromatid and chromosome breaks but only at a cytotoxic level. On the other hand, Mecoprop-p 2-EHE induced chromatid and chromosome breaks in the presence of S9 activation at a single noncytotoxic dose but the aberration rate was within the historical control range of the performing laboratory.

The four human lymphocyte studies of the different mecoprop forms indicate induction of chromosome aberrations in the presence of S9 activation at cytotoxic levels. Although there is one instance where positive data were obtained in the presence of S9 activation at a non-cytotoxic concentration, the aberration frequency was within the historical range of the performing laboratory. Based on these considerations, it was concluded that there is no compelling evidence of clastogenicity in the *in vitro* studies.

Mecoprop-p, mecoprop-p-DMA and mecoprop-p 2-EHE are negative in the mouse micronucleus and/or bone marrow chromosomal aberration in Chinese hamsters assays up to either overtly toxic doses or doses that are cytotoxic to the bone marrow (mecoprop-p-DMA).

These negative data are in contrast to the positive findings for the racemic mixture of mecoprop in the chromosomal aberration and SCE assays in Chinese hamster bone marrow. However, the positive result in the chromosome aberration assay was observed at a dose that was cytotoxic to the bone marrow, produced only chromatid and chromosome breaks and was seen only at the 6-hour harvest. These types of induced aberrations would likely result in cell killing, hence, the damage would be lost from the daughter cells. The lack of aberrations at the 24- and 48-hour harvests supports this assessment. Mecoprop was, nevertheless, weakly positive in the *in vivo* sister chromatid (SCE) assay in Chinese hamsters at two doses(presumed to be cytotoxic to the bone marrow) and a lower dose. Although the values for the SCE frequencies were low, they were statistically significant. It was concluded, therefore, that while the evidence for clastogenicity is equivocal, the possibility that the racemic mixture of mecoprop may have clastogenic potential can not be ruled out.

Table 9. Mutagenicity Testing with Mecoprop

Study Type	Results
Ames MRID 00158361	Tested in strains TA1535, TA1537, TA1538, TA100, TA98 ± S9 at concentrations up 5000 ug/plate. **Negative**, classified **acceptable.**
Chromosomal Aberrations in Bone Marrow MRID 00158362	Chinese Hamsters dosed up to 3800 mg/kg. One HDT animal died, MDT and HDT animals had clinical signs. MCPP was **weakly positive for clastogenic activity** in HDT animals sacrificed at 6 hours and accompanied by a 56% decrease in mitotic index (MI). Considered equivocal because the types of induced aberrations (chromatid and chromosome breaks) would likely induce cell killing and would be lost from the daughter cells. At 24 hours, aberrations were increased in HDT animals, but not with statistical significance. Classified **unacceptable**, pending submission of requested data.
Sister Chromatid Exchange in Bone Marrow MRID 00158363	Chinese Hamsters dosed up to 3800 mg/kg. Clinical signs in MDT and HDT animals persisted up to time of sacrifice at 24 hours. **Weakly positive** for increasing SCEs at 470 mg/kg (3.77 SCE/cell) and 3800 mg/kg (5.31 SCE/cell) vs 3.06 SCE/cell for vehicle control. Classified **acceptable.**

Table 10. Mutagenicity Testing with Mecoprop-p

Study Type	Results
Ames MRID 41013909	Tested in strains TA1535, TA1537, TA1538, TA100, TA98 ± S9 at concentrations up to 5000 ug/plate. **Negative**, classified **acceptable.**
Ames MRID 42980101	Tested in strains TA1535, TA1537, 1538, TA100, TA98 ± S9 at concentrations up to 1000 ug/plate. Classified **acceptable, negative** for mutagenicity.
Ames MRID 42860803	Tested in strains TA1535, AT1537, TA98, and TA100 at concentrations up to 5000 ug/plate ±S9. **Negative** for mutagenicity, classified **acceptable.**

Study Type	Results
CHO/HGPRT Gene Mutation MRID 42947807	Tested in Chinese Hamster lung fibroblast V79 cells at concentrations up to 4000 ug/mL -S9 and up to 4500 ug/mL +S9. The 2 higher concentrations were cytotoxic. **Negative** for mutagenicity and classified **acceptable.**
CHO/HGPRT Gene Mutation MRID 43113401	Tested in CHO cells up to cytotoxic concentrations (800 ug/mL +/-S9). **Negative** for mutagenicity. Classified **acceptable.**
In vitro Mammalian Cytogenetics MRID 42947806	Tested in human lymphocytes at concentrations up to 400 ug/mL, -S9, and up to 1600 ug/mL +S9. **Aberrations** increased at 1600 ug/mL +S9, but 76% decrease in mitotic index (MI) and value (4%) was within historical control range (0-5%). Upgraded to **acceptable.**
In vitro Mammalian Cytogenetics MRID 43189501	Tested in human lymphocytes at concentrations up to 600 ug/mL, -S9, and up to 2000 ug/mL +S9. Dose-related trend for **clastogenic activity** -S9 only. Reduction (>50%) in MI at 600 ug/mL (20 hrs and 44 hrs) and at 300 ug/mL (44 hrs), but at 300 ug/mL (20 hrs) increase in chromosomal aberrations (chromatid and chromosome breaks). Classified **acceptable.**
Chromosomal Aberration in Bone Marrow MRID 41013908	Chinese Hamsters dosed up to 2600 mg/kg. Two HDT animals died, clinical signs seen in all 3 dose groups. Classified **acceptable, negative** for clastogenicity.
Micronucleus Assay MRID 42947808	Tested in a mouse micronucleus assay at doses up to 500 mg/kg. Clinical signs seen at HDT. **Negative** assay, classified **acceptable.**
In vivo UDS MRID 44895502	Tested in Wistar rats up to a toxic dose (500 mg/kg). Clinical signs seen at this dose. **No evidence** for unscheduled DNA synthesis. Classified **acceptable.**

Table 11. Mutagenicity Testing with Mecoprop-p-DMA

Study Type / MRID	Results
Ames MRID 42860801	Tested in strains TA1535, AT1537, TA98, and TA100 at concentrations up to 5000 ug/plate ±S9. **Negative** for mutagenicity, classified **acceptable.**
HGPRT Gene Mutation MRID 42936802	Tested in CHO cells at concentrations up to 3000 ug/mL -S9 and up to 2500 ug/mL +S9. The highest concentration was cytotoxic. **Negative** for mutagenicity and classified **acceptable.**
In vitro Mammalian Cytogenetics MRID 42936803	Tested in human lymphocytes at concentrations up to 1000 ug/mL, -S9, and up to 5000 ug/mL +S9. **Clastogenic** with activation, but only at a cytotoxic concentration (2500 ug/mL) Negative with -S9. Only chromatid and chromosome breaks were seen. Classified **acceptable.**
Micronucleus Assay MRID 42860804	Tested in a mouse micronucleus assay at doses up to 576 mg/kg. Clinical signs seen at MDT and HDT 48 hours after treatment. **Negative** assay, classified **acceptable.**

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Table 12. Mutagenicity Testing with Mecoprop-p 2-EHE

Study Type / MRID	Results
Ames MRID 42860802	Tested in strains TA1535, AT1537, TA98, and TA100 at concentrations up to 5000 ug/plate ±S9. **Negative** for mutagenicity, classified **acceptable.**
CHO/HGPRT Gene Mutation MRID 42936804	Tested in CHO cells at concentrations up to 250 ug/mL -S9 and up to 500 ug/mL +S9. **Negative** up to cytotoxic and/or solubility limits. Classified **acceptable.**
In vitro Mammalian Cytogenetics MRID 42936805	Tested in human lymphocytes at concentrations up to 80 ug/mL, -S9 and up to 320 ug/mL +S9. MCPP-p-EHE **induced** structural aberrations (chromatid and chromosome breaks) at the highest +S9 concentration, which was insoluble but non-cytotoxic. Classified acceptable.
Micronucleus Assay MRID 42860805	Tested in a mouse micronucleus assay at doses up to 3128 mg/kg. Clinical signs and mortality at HDT. **Negative** assay, classified **acceptable.**

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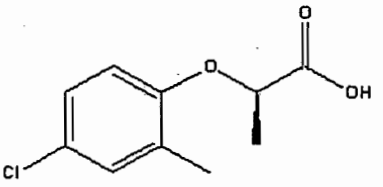
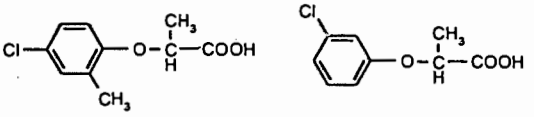
3. Structure-Activity Relationship

Mecoprop-p
MCPP-p
(R)-2-(4-chloro-o-tolyloxy)propionic acid
PC: 129046
CAS REG. NO. 16484-77-8



Mecoprop-p is structurally related to other registered phenoxy herbicides, 2,4-D, 2,4-DB, 2-methyl-4-chlorophenoxyacetic acid (MCPA), and 2-methyl-4-chlorophenoxybutyric acid (MCPB). An increase in peroxisome proliferative activity of chlorinated phenoxyacetic acids and related compounds has long been suspected to be associated with the hepatocarcinogenic activity of these compounds (Woo and Arcos, 1989). MCPA, 2,4-D and 2,4-DB have not been shown to be rodent carcinogens, whereas, ciprofibrate, methyl clofenapate and clofibric have been shown to be rodent hepatocarcinogens with potencies roughly parallel to their peroxisome proliferative activity. SAR analysis indicates that ring chlorination and branching at the carbon immediately adjacent to the terminal carboxylic acid are important structural features for positive peroxisome proliferative activity and potential carcinogenic activity. Mecoprop contains both of these features and there is evidence of increases of palmitoyl CoA in the subchronic mouse study at a dose of 2500 ppm (not measured in the lower dose groups). These observations suggest that induction of liver tumors in mice by mecoprop could be a result of peroxiosome proliferation; however, no mode of action studies were provided for mecoprop. Another closely related pesticide, cloprop, has also been shown to induce liver tumors in mice.

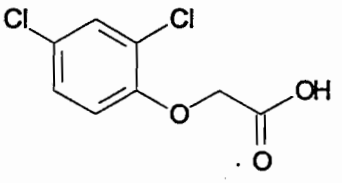


Mecoprop Cloprop

27

None of the compounds summarized below have been classified as human carcinogens, although cloprop was never evaluated. See summaries below.

2,4-D
2,4-dichlorophenoxyacetic acid
PC 030001
CAS 94-75-7



The HED Cancer Peer Review Committee classified 2,4-D as a "Group D"- Not classifiable as to a human carcinogenicity. That is, the evidence is inadequate and cannot be interpreted as showing either the presence or the absence of a carcinogenic effect.

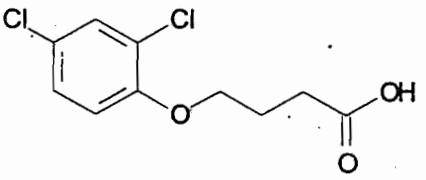
There was an increased trend for brain astrocytomas in male Fisher 344 rats and suggestive to weak and conflicting evidence of non-Hodgkin's lymphoma from several epidemiological studies. There was no evidence of tumor induction in female rats or male or female B6C3F1 mice, however, the CPRC concluded that the highest dose tested in neither study was sufficiently toxic to adequately test for carcinogenicity. Repeat studies were conducted in rats and mice at adequate doses, but neither study showed statistically significantly increased tumor incidence in either species or sex.

Mutagenicity studies showed consistently negative results without activation and positive and negative results with activation. The CPRC concluded that although cytogenic activity was seen there was no concern for mutagenicity.

Metabolism studies in the rat indicated that 85 to 94% of the parent was excreted unchanged in the urine with 0% -1.3% of 2 un-characterized compounds and 4 to 10% was excreted as the parent in feces. Total excretion (98 to 99.5%) occurred within 48 hours.

The National Toxicology Program has reported that 2,4-D is a "weak" peroxisome proliferator.

2,4-DB
2,4-Dichlorophenoxybutyric acid
PC 030801
CAS 94-82-6



There was no evidence of carcinogenicity in the rat chronic/onco study. In the CD-1 mouse study, doses were 0, 25, 250, or 750 ppm. The high-dose group was terminated at week 66 rather than week 78 because of high mortality beginning at week 58. The incidence of hepatic adenomas in males was 4/70, 2/70, 3/69, 1/70 and for hepatic carcinomas in males was 0/70, 1/70, 4/69, 3/70 in the respective dose groups. Historical control data from the testing facility from 1984 to 1990 showed incidences of hepatocellular adenoma to range from 2-11% and for hepatocellular carcinomas to range from 0-10%.

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An Ames test and a UDS assay were negative. An HGPRT test showed weak mutagenic activity with activation at doses immediately below those causing high levels of cytotoxicity.

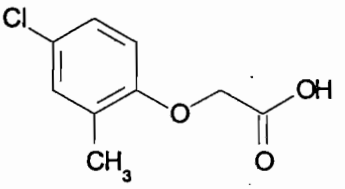
In a rat metabolism study, much of the radioactivity was excreted in the urine as glucuronide and sulfate conjugates of 2,4-dichlorphenol and 2,4-D.

2,4-DB-DMA
2,4-dichlorophenoxybutyric acid dimethylamine salt
PC 030819
CAS 2758-42-1

There are no guideline toxicity studies for the dimethyl amine salt of 2,4-DB. Three mutagenicity studies were classified unacceptable but could have been upgraded if more data had been submitted. A UDS test was positive and an Ames test and CHO chromosomal aberrations assay were negative.

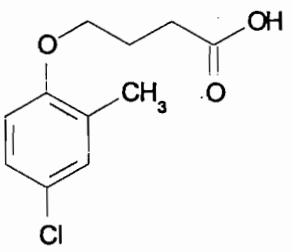
The propose pathway is identical to that of 2,4-DB: urinary excretion of 2,4-DB, 2,4-D, and 2,4-DCP conjugates.

MCPA
2-methyl-4-chlorophenoxyacetic acid
PC 030501
CAS 94-74-6



No dose related tumors were seen in rat or mice guideline studies. A chromosomal aberrations study in human lymphocyte cells was positive and an *in vivo* sister chromatid exchange study had a weakly mutagenic response. The remaining 6 *in vivo* and *in vitro* mutagenicity studies conducted were negative. MCPA is excreted in the urine (74-86%; 53%-69% as the parent and 7-13% as the hydroxymethyl metabolite and 2-5% in the feces). Total excretion occurred within 192 hours (98%).

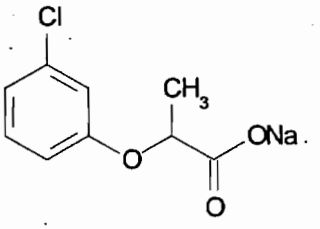
MCPB
2-methyl-4-chlorophenoxybutryic acid
PC 019201
CAS 94-81-5



29

No carcinogenicity studies are available for MCPB. A battery of mutagenicity studies were negative. One study for chromosomal abnormalities with S9 produced chromosomal abnormalities at high doses.

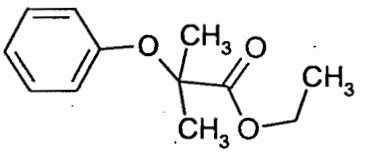
Cloprop
3-chlorophenoxy-2-propionic acid
PC 021201
CAS 101-10-0



Liver adenomas/carcinomas and liver carcinomas had significant pair-wise increases in male mice at the highest dose tested. Liver adenomas and carcinomas were increased in females at the two lowest doses, but not at the highest dose tested. The carcinogenicity of cloprop was never evaluated by HED because the registration was withdrawn.

Cloprop was negative in a battery of mutagenicity studies. There are no metabolism studies in rats, but in goats, cloprop is excreted as the parent.

Clofibrate
2-(4-Chlorophenoxy)-2-methylpropanoic acid, ethyl ester
PC: N/A
CAS 637-07-0



Clofibrate is a hypolipidaemic drug used in humans. In rats, this drug causes increased incidence of hepatocellular carcinomas and is a peroxisome proliferator. There is no evidence of carcinogenicity in humans.

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4. Subchronic Toxicity

a. Executive Summary for Subchronic Study with Mecoprop-p in Mice:

In a subchronic oral toxicity study (MRID 43059201), Mecoprop-p acid (96.5% a.i., Lot No. 91-1) was administered to groups of 10 male and 10 female B6C3F1 mice in the diet for 90 days at concentrations of 0, 100, 1000, or 2500 ppm. Time-weighted average doses were 0, 20, 220, and 740 mg/kg/day, respectively, for males and 0, 30, 330, and 930 mg/kg/day, respectively, for females.

No treatment-related mortalities or clinical signs of toxicity were observed in any animal during the study. Body weights of the high-dose males and females were significantly ($p \leq 0.05$ or 0.03) less than those of the controls beginning on day 63 and continuing until termination (90% and 94% of controls for males and females, respectively, on day 91). Body weights of the mid-dose groups were significantly ($p \leq 0.05$) less than the controls on day 91 (92% and 94% of controls for males and females, respectively). Lower terminal body weights ($p \leq 0.05$ or 0.01) occurred in high-dose males and all treated females. Body weight gains by the mid- and high-dose groups were consistently less, in a dose-related manner, than those of the control groups throughout the study. Food consumption was not affected by treatment.

ALP activity was increased in high-dose males and females (277% and 211% in males and females, respectively) and ALT activity was increased in high-dose females (211% of controls). ALP (males and females) and ALT (females) activities were also elevated in mid-dose animals approximately 125-138%, but not with statistical significance. Palmitoyl-CoA oxidation was significantly increased in liver homogenates from high-dose males (1150%) and females (1600%) compared with the controls but was not measured in low- and mid-dose groups. Urea and creatinine were elevated in mid- and high-dose males (115-121% of controls) and urea was elevated in mid- and high dose females (123-136%). No treatment-related changes in hematology parameters were seen in males or females.

At necropsy dark brown discoloration of the liver was observed in all high-dose animals. Absolute liver weights were increased in high-dose males and females (135-149%, respectively) as were relative liver weights (155% and 177%, respectively). There were decreased absolute kidney weights in males, and decreased absolute adrenal weights of females.

Eosinophilic pigments were observed in hepatocytes and renal tubular epithelial cells from all high-dose males and females and in hepatocytes from one mid-dose female. A decrease in lipid storage observed in mid- and high-dose animals was also noted.

The NOAEL and LOAEL will be determined when this chemical is evaluated by HIARC.

3\

b. Executive Summary for Subchronic Study with Mecoprop in Rats:

In a subchronic oral toxicity study (MRID 00158359), Mecoprop technical (92.7% a.i., Batch No. TPH 83/47) was administered to groups of 15 male and 15 female Wistar rats in the diet for 90 days at concentrations of 0, 50, 150, or 450 ppm (MRID 00158359). Dose ranges for the treated males and females were 3-6, 9-18, and 26-55 mg/kg/day, respectively.

All animals survived to scheduled sacrifice. No treatment-related clinical signs of toxicity were observed in any animal during the study. Body weights and food consumption were similar between treated and control groups for both sexes. Clinical chemistry, urinalyses, and hematology parameters were comparable between groups; creatinine was elevated slightly in high-dose females (116% of controls). No treatment-related lesions were found by ophthalmoscopic examination, gross necropsy, or microscopic examination of tissues.

Absolute and relative kidney weights were significantly ($p \leq 0.05$ or 0.01) increased in the mid-dose males (113%), high-dose males (115%), and high-dose females (107%) and relative kidney weights were increased for mid-dose females (109%).

The NOAEL and LOAEL will be determined when this chemical is evaluated by HIARC.

c. Executive Summary for Subchronic Study with Mecoprop and Mecoprop-p in Rats:

In a 7-week oral toxicity study (MRID 41013910), either the racemic (92.7% a.i., Batch #83/47) or D-isomer (Mecoprop-p, 99.4% a.i., Batch #83/20) of Mecoprop was administered to groups of 10 male and 10 female Wistar rats in the diet at concentrations of 0, 50, or 400 ppm. Dose ranges for the animals given the racemic form were 3.32-6.04 and 27.13-47.56 mg/kg/day, respectively, for males and 4.13-5.66 and 31.69-44.66 mg/kg/day, respectively, for females. Dose ranges for animals given the D-form were 3.33-6.12 and 26.34-48.1 mg/kg/day, respectively, for males and 4.02-5.74 and 31.82-45.88 mg/kg/day, respectively, for females.

All animals survived to scheduled sacrifice. No treatment-related clinical signs of toxicity were observed in any animal during the study. Body weights and food consumption were similar between treated and control groups for both sexes. No biologically significant changes in hematology or clinical chemistry parameters were found. No treatment-related lesions were found by gross necropsy or microscopic examination of tissues. Absolute kidney weights of all treated males and high-dose D-form females were 5-8% greater than that of the controls.

The NOAEL for both the racemic and D-form of Mecoprop is 400 ppm (27.12-47.56 and 26.34-48.1 mg/kg/day, respectively) and the systemic toxicity LOAELs are not identified.

This study is classified **acceptable/non-guideline**. This study does **not** satisfy the guideline requirements for a subchronic toxicity study in rats because doses were insufficient to elicit

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toxicity.

d. Executive Summary for Combined Subchronic / Neurotoxicity with Mecoprop-p:

In this combined subchronic feeding and neurotoxicity study, male and female Wistar rats (15/sex/group) were fed diets containing 0, 75, 500, 2500 (males only) or 3000 (females only) ppm Mecoprop-p for at least 90 days. Selected animals underwent neurobehavioral screening (FOB and motor activity), 10/sex/dose had gross and histopathological exams and 5/sex/dose were perfusion fixed *in situ* for examination of nervous system tissues.

Throughout the study, mean body weights of high-dose animals were significantly decreased (-18% at terminal sacrifice) from the concurrent control values. Overall body weight gains were 27 to 29% lower in high-dose animals. There were decreases in food consumption in high-dose animals (-5 to -19%, males; -12 to -19%, females) and food efficiency (-18 to - 45%, males; -65%, females). Water consumption was increased 27-55% in males and 59-84% in females at the high-dose level.

Hematological parameters were significantly, and markedly, decreased in high-dose animals, while borderline, but statistically significant, decreases were noted in mid-dose males. The hematocrit in mid-dose males was 95% of controls and in high-dose males and females was 81% and 85% of controls, respectively.

There was increased alkaline phosphatase activity in high-dose males (173% of controls) and females (198%) while ALT activity was elevated in high-dose females only (155%). High-dose animals had decreased calcium levels (males and females), decreased chloride levels (high-dose females), and decreases in total protein and globulin levels (males and females). There were decreases in triglyceride and cholesterol concentrations in mid- and high-dose males and high-dose females.

Urea concentration was increased in high-dose males (116% of controls) and females (127%) and creatinine levels were increased in high-dose males (112%). The number of transitional epithelial cells were increased in the urine of high-dose males.

High-dose males and females had significantly increased absolute liver weights (115% and 155% of controls, respectively) and increased relative liver weights (141% and 189%, respectively) and decreases in the absolute adrenal gland weights. Adrenal glands were grossly discolored in 10/10 females and 9/10 males in the high-dose group.

All high-dose males and females had cytoplasmic eosinophilia and granular cytoplasm in the livers. There was also bile duct proliferation (4/10 males, 3/10 females) and central hypertrophy (2/10 males). At the high-dose level, lipid accumulation was noted in the adrenal cortexes of 8/10 males and 10/10 females.

No treatment-related effects were noted for the neurobehavioral screening. There were no treatment-related effects on gross or microscopic exam of the nervous system.

The NOAEL is 75 ppm (5 mg/kg/day) and the LOAEL is 500 ppm (35 mg/kg/day) based upon alterations in clinical chemistry and hematology parameters in males. The NOAEL in females is 500 ppm (35 mg/kg/day) and the LOAEL in females is 3000 ppm (240 mg/kg/day) based upon decreases in body weight, food consumption, and food efficiency; increased water consumption; alterations in clinical chemistry and hematology parameters; increased absolute and relative liver weights; and liver and adrenal gland histopathology).

This study is classified **acceptable** and satisfies guideline requirements for both a subchronic feeding study (§82-1) and a subchronic neurotoxicity screening battery (§82-7) in the rat.

5. Chronic Toxicity

1. Executive Summary for Carcinogenicity Study with Mecoprop-p in Mice:

In a carcinogenicity study (MRID 44953601, 1996), mecoprop-p (92.7%, batch no. 91-1) was administered to B6C3F1/CrlBR mice in the diet for 18 months. There were 50 mice/sex/dose. Dietary concentrations were 0, 25, 250, or 2500 ppm; approximately 0, 4, 40, or 592 mg/kg/day in males and 0, 4, 46, or 732 mg/kg/day in females. The high-dose group was sacrificed at 12 months due to severe body weight loss.

A second study was conducted to provide a high-dose group. In the second carcinogenicity study (MRID 44895501, 1999), mecoprop-p (92.7%, batch no. 91-1) was administered to B6C3F1/CrlBR mice in the diet for 18 months. There were 50 mice/sex/dose. Dietary concentrations were 0 or 700 ppm in males, and 0 or 800 ppm in females; approximately 0, or 112 mg/kg/day in males, and 0 or 188 mg/kg/day in females. This study was conducted by the same lab and used the same procedures as in the first study.

Mortality was not affected by treatment. Body weights were decreased in 700 ppm males (approximately 91-96% of controls and in 800 ppm females approximately 90-95% of controls) during the last 6 months of the study. The 2500 ppm group experienced severe weight loss and was sacrifice early. Males in the 2500 ppm group weighed 73% of controls and females weighed 64% of controls on day 315. Food consumption and food efficiency were not affected by treatment, however, food spillage was noted in both studies.

There were increases in absolute kidney weight (114%) and relative kidney weight (121%) in 250 ppm females, increases in relative kidney weight (105%) in 700 ppm males, and increases in both absolute (115%) and relative kidney weight (126%) in 800 ppm females when compared to controls. Microscopic lesions of renal calcification and chronic nephropathy were increased in incidence (generally classified minimal) in 250 ppm females, 700 ppm males, and 800 ppm

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females.

Relative liver weights were increased in 700 ppm males (112%) and 800 ppm females (114%) compared to controls; absolute liver weights were not affected by treatment. Basophilic foci in livers was increased in 700 and 800 ppm animals.

The 2500 ppm group was sacrificed after approximately 1 year and animals were not necropsied, but increases in abdominal masses were palpated in males and females in this group.

The NOAEL is 25 ppm, equivalent to 4 mg/kg/day and the LOAEL is 250 ppm, equivalent to 46 mg/kg/day, based upon increased kidney weight and increased incidence of chronic nephropathy and renal calcification in females. When considered together, these 2 studies are classified **acceptable/guideline** and **satisfy guideline requirements** for a carcinogenicity study in mice.

2. Executive Summary for Chronic Toxicity/Carcinogenicity Study with Mecoprop in Rats:

In a combined chronic toxicity/carcinogenicity study (MRID 40937501), MCPP (92.7% a.i., batch/lot # 83/47) was administered to groups of 75 male and 75 female Wistar rats at dietary concentrations of 0, 20, 100, or 400 ppm (0, 1.1, 5.5, and 22.2 mg/kg/day for males and 0, 1.4, 6.9, and 27.9 mg/kg/day for females). Groups of 10 rats of each sex and dose were sacrificed at 52 weeks for interim evaluation (Satellite group I). Groups of 15 rats of each sex and dose (Satellite group II) were maintained to study termination at 104 weeks along with the main study animals.

No treatment-related or toxicologically significant effects occurred on survival, clinical signs, body weight, weight gain, food consumption, incidences of ophthalmoscopic abnormalities, hematologic parameters, clinical chemistry parameters, urinalysis parameters, serum thyroxine (T4) or triiodothyronine (T3) levels (measured after 52 weeks only), gross lesions, or microscopic lesions. The only notable postmortem change was the increased kidney weight in males. Absolute and relative kidney weights of high-dose males were increased by 11% (N.S.) and 18% ($p \leq 0.01$), respectively, at 52 weeks and by 13% (≤ 0.01) and 11% ($p \leq 0.01$), respectively, at 104 weeks compared with those of controls. In the mid-dose group, absolute and relative kidney weights were increased by 3% (N.S.) and 15% (≤ 0.01), respectively, at 52 weeks and by 7% ($p \leq 0.01$) and 4% (N.S.) at 104 weeks. The increases in kidney weights were not associated with any treatment-related gross or microscopic findings in the kidney, however, increased kidney weights have occurred in subchronic studies in rats with mecoprop.

The NOAEL and LOAEL will be determined when this chemical is evaluated by HIARC.

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V. Committee's Assessment of the Weight-of-Evidence

1. Carcinogenicity

The CARC concluded that mecoprop-p showed evidence of carcinogenicity based on the following:

- **Evidence of carcinogenicity (liver tumors) was seen in one sex (female) of one species (mouse) treated with mecoprop-p.** Female B6C3F1/CrlBR mice in the 1999 study had significant increasing trends and significant pair-wise comparisons of the 800 ppm dose group with the controls for hepatocellular adenomas ($p < 0.05$) and combined hepatocellular adenomas and/or carcinomas ($p < 0.01$). This study had only 2 dose groups, 0 and 800 ppm. When the 1996 and 1999 studies were combined, there were statistically significant trends in hepatocellular adenomas and combined hepatocellular adenomas and/or carcinomas, both at $p < 0.01$. There was a significant pair-wise comparison of the 250 ppm female dose group with the controls for combined hepatocellular adenomas and/or carcinomas at $p < 0.05$. There were also significant pair-wise comparisons of the 800 ppm female dose group with the controls for hepatocellular adenomas ($p < 0.05$) and combined adenomas and/or carcinomas ($p < 0.01$). For the combined 1996/1999 studies, the incidence of liver adenomas was 1/99, 1/49, 3/50, 5/48 for the 0, 25, 250, and 800 ppm dose groups, respectively. The incidence of combined liver adenomas and/or carcinomas was 4/99, 3/49, 8/50, and 9/48 for the 0, 25, 250, and 800 ppm dose groups, respectively. The incidence for hepatocellular adenomas in females (10% at 800 ppm) was within the historical control range for this testing facility (0 - 10%). The incidence for hepatocellular carcinomas in females (10% at 250 ppm and 8% at 800 ppm) exceeded the historical control range (0 - 6%). The CARC considered the increase in liver tumors to be treatment-related in females.

- There was no treatment-related increase in any tumors in male B6C3F1/CrlBR mice treated with mecoprop-p.

- **The CARC concluded that the dose levels of 700 and 800 ppm were adequate, but not excessive, in males and females, respectively, to assess the carcinogenicity of mecoprop-p in mice as follows:**

  Females: The 2500 ppm dose was clearly excessive due to severe body weight loss--females. However, dosing at 800 ppm and below is considered adequate, but not excessive, in females based upon kidney toxicity (increased absolute/relative kidney weights) and increased incidences of renal calcification and chronic nephropathy, graded mainly minimal, in the 250 ppm and 800 ppm groups, and decreased body weights in the 800 ppm group (weights were 90-92% of controls for the last 4 months of the study).

Males: The 2500 ppm dose is considered excessive due to severe body weight loss--males in this group weighed 73% of controls on day 315. Males in the 700 ppm group could have tolerated a larger dose, but dosing is considered adequate when toxicity in the carcinogenicity study is considered together with toxicity in the subchronic mouse study. In the carcinogenicity study, male body weights in the 700 ppm group were 91-95% of controls for the last 4 months of the study. The 700 ppm male group had increased relative kidney weight (105% of controls) and increased incidence of microscopic lesions of renal calcification and chronic nephropathy(generally classified minimal or slight). In the subchronic mouse study with mecoprop-p, males in the 1000 ppm group weighed 92% of controls after 90 days of treatment. Cumulative body weight gain for the 1000 ppm group was significantly decreased throughout most of the study and was 64% of controls at the end of the study. Other toxicity in the 1000 ppm group in the subchronic study included elevated alkaline phosphatase activity (130% of controls), elevated urea and creatinine (115% of controls), and decreased triglycerides (72% of controls). It is reasonable to assume that the toxicity (excessive decrease in body weight gain) seen in the subchronic mouse study at 1000 ppm would be even more adverse in a chronic study, and, therefore, the CARC concluded that the dose of 700 ppm chosen for the carcinogenicity study was reasonable.

- **Although there was no treatment-related increase in tumors in male or female Wistar rats treated with mecoprop (racemic mixture), the negative finding is inconclusive because dosing in the rat chronic toxicity/carcinogenicity study was considered to be inadequate.** There were no effects on body weight or mortality and minimal toxicity (increased absolute and relative kidney weights) occurred at the high dose (400 ppm). Three subchronic feeding studies in Wistar rats with mecoprop or mecoprop-p did not support the doses selected in the combined study as there was very minimal (increased kidney weights) or borderline (decreases in hematological parameters) toxicity seen at doses ranging from 400-500 ppm after 90 days. Doses of 2500 and 3000 ppm induced adverse effects (decreases in body weight/body weight gain, food consumption, food efficiency, increased water consumption, alterations in clinical chemistry and hematology parameters, increased absolute and relative liver weights; and liver and adrenal gland histopathology).

2. Mutagenicity

- None of the various forms of mecoprop induced gene mutations in bacteria or cultured mammalian cells. There was no compelling evidence of clastogenicity in the *in vitro* studies. Mecoprop-p, mecoprop-p-DMA and mecoprop-p 2-EHE were negative in the mouse micronucleus and/or bone marrow chromosomal aberration in Chinese hamsters assays. There was equivocal evidence for *in vivo* clastogenicity and SCE induction with the racemic mixture.

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3. Structure Activity Relationship

- Mecoprop-p is structurally related to several compounds, including other phenoxy herbicides. Ciprofibrate, methyl clofenapate and clofibric have been shown to be rodent hepatocarcinogens. Another closely related pesticide, cloprop, has also been shown to induce liver tumors in mice.

4. Mode of Action Studies

- There are no mode of action studies available at this time.

VI. Classification of Carcinogenic Potential

In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999), the Committee classified mecoprop-p into the category **"Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential"** by the oral route based on the following weight-of-the-evidence considerations:

(i) When the 1996 and 1999 carcinogenicity studies were combined, there was a statistically significant increase in the occurrence of hepatocellular adenomas and combined hepatocellular adenomas and/or carcinomas in female B6C3F1/CrlBR mice treated with mecoprop-p at 250 and 800 ppm. The incidence of hepatocellular carcinomas exceeded the upper range of historical controls. There was no treatment-related increase in tumors in male mice.

(ii) Mecoprop (racemic mixture) was not carcinogenic to male or female Wistar rats, however, dosing for the chronic toxicity/carcinogenicity rat study is considered inadequate. **[Note: If, based on mecoprop-p's pattern of use, a second cancer study is needed, then the CARC has determined that the current chronic toxicity/ carcinogenicity study in the rat is not adequate and should be repeated with mecoprop-p.]**

(iii) There is no mutagenicity concern for mecoprop-p.

(iv) There is a lack of data on the mode of action.

VII. Quantification of Carcinogenic Potential

Quantification of carcinogenicity is not required.

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