7/18/88

BS-1540
TXR-687

Reviewed By: Irving Mauer, Ph.D., Geneticist
Section VI, Toxicology Branch/HED (TS-769C)
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DATA EVALUATION REPORT

006877

I. SUMMARY

Study Type: Mutagenicity

TB Project No.: (N/A-RS)
Caswell No.: 559
MRID No.: 00158361
Shaugh. No.: 031501

Accession No.: N/A

Chemical: MCPP [2-(4-chloro-2-methylphenoxy) propionic acid]

Synonyms: Mecoprop
CAS: 7085-19-0

Sponsor: BASF

Testing Facility: (BASF) Gewerbehygiene und Toxikologie

Title of Report: Report on the Study of 2-(4-chloro-2-methylphenoxy) propionic acid in the Ames Test

Authors: G. Engelhardt and H. Zeller

Study Number: (None given)

Date of Issue: German Original: March 18, 1981;
translation by M. Ruff, April 27, 1981

TB Evaluation/Conclusions:

Negative for reverse gene mutation in S. typhimurium (Ames Test) in the presence and absence of mammalian metabolic activation (S-9 mix) at concentrations ranging up to 5000 ug/plate (slight toxicity reported at this highest level).

Classification (Core-Grade):

Provisionally acceptable, pending clarification or resolution of the apparent deficiencies detailed in TB Conclusions.

II. DETAILED REVIEW

A. Test Material: MCPP (Mecoprop)

Description: (None given)
Batch (Lot): 80/538
Purity (%): 96%
Solvent/Carrier/Diluent: Dimethylsulfoxide (DMSO)

B. Test Organisms: Bacteria

Species: Salmonella typhimurium
Strains: TA1535, TA1537, TA1538, TA100, TA98 (all his^-)
Age: (N/A)
Weights--Males: (N/A)
Females: (N/A)
Source: BASF (G&T)

C. Study Design (Protocol):

No formal protocol was included in the report, but a list of authoritative references for this type of study was provided.

No quality assurance measures were mentioned.

D. Procedure/Methods of Analysis:

Cultures of the five histidine-requiring bacterial tester strains were exposed to DMSO (solvent control) or to 20, 100, 500, 2500, or 5000 ug/plate of the test substance, both in the absence or presence of mammalian metabolic activation consisting of the Aroclor 1254-stimulated microsomal enzyme fraction from male Sprague-Dawley rats (S-9), plus NADPH-generating cofactors (=S-9 mix). Positive control substances (mutagens) appropriate for each strain and activation condition were run concurrently. Four plates were used for each concentration of the test article as well as for each control.

After 48-hour incubation at 37 °C, revertant colonies (his^+) were counted. The authors offered the following evaluation criteria for a positive response:

1. Doubling the background (solvent) incidence of revertants;

2. A dose-response; and

3. Reproducible results.

Results:

Although it was stated that two experiments were performed (February 18-20 and March 6-8, 1981), the data as presented (pages 13 and 14 of the Report) in two tabulations (attached to this DER) do not confirm this, but rather appear to represent the results of only one complete assay. As depicted in Table 1, the nonactivation test with TA98 had to be repeated because of the failure of the positive control (4-nitro-o-phenylenediamine) to react. Other than this, there is no evidence of a repeat assay.

In none of the tester strains did the test article produce any increased reversions over control, with or without activation. In fact, at the highest concentration (5000 ug/plate), slight toxicity was recorded as evidenced by reduced background (his$^-$) growth in TA1537 plates (Table 2), and decreased revertants in TA98 plates (Table 1).

By contrast, as shown in the tabulations, the positive controls responded positively, with increases in revertants ranging from about 20 to 70 times background.

TB Conclusions:

The study appears to have been conducted in a manner to support the negative results reported. Acceptability, however, is reserved, pending clarification or resolution of the following deficiencies:

1. Description of the nature of the test material.

2. If the entire assay was repeated on the dates suggested, supply the missing data. Tables 1 and 2 do not reflect a repeat. If the entire assay was not repeated, a confirmation of the negative already recorded is necessary.

3. Quality Assurance measures (if performed).

Table 1

AMES TEST: 2-(4-chloro-2-methylphenoxy)propionic acid

Dose µg/plate	S-9 Mix	TA 98				TA 98				TA 100			
0*	+	44	30	34	42					108	94	108	103
20	+	33	42	43	40					110	125	101	124
100	+	34	44	32	42					119	104	107	116
500	+	27	33	44	39					117	114	125	113
2 500	+	-	34	26	34					107	106	113	126
5 000	+	19	23	22	26					100	95	107	142
10 2 aminoanthracene	+	1540	1500	1800	1650					2250	2150	2250	2050
0*	-	24	20	18	27	20	18	20	20	124	139	100	105
20	-	29	20	20	23	18	21	19	16	127	119	120	123
100	-	18	24	19	26	16	17	20	22	131	123	115	125
500	-	23	29	21	18	24	15	17	18	138	143	110	144
2 500	-	25	19	17	25	19	21	16	13	118	117	126	126
5 000	-	15	10	16	16	13	14	14	16	99	122	119	126
10 4-nitro-o-phenylenediamine	-	x	x	x	x	745	820	745	843	2200	2350	2200	2250

* solvent control - DMSO

x = positive control substance showed no reaction

Table 2

AMES TEST: 2-(4-chloro-2-methylphenoxy)propionic acid

Dose µg/plate	S-9 Mix	TA 1535				TA 1537				TA 1538			
0*	+	20	20	19	22	13	11	11	12	28	26	31	22
20	+	15	18	13	17	15	11	14	13	31	19	28	26
100	+	14	13	16	18	12	10	11	9	26	23	19	21
500	+	19	11	12	14	15	12	8	3	28	21	29	20
2 500	+	9	8	11	15	4	5	3	4	24	12	15	20
5 000	+	10	9	11	17	B	B	B	(B)1	-	16	11	4
10 2-aminoanthracene	+	321	428	415	339	127	97	103	92	1450	1400	1480	1300
0*	-	20	17	13	12	6	8	7	7	18	13	12	12
20	-	21	12	15	17	5	8	10	7	17	12	19	13
100	-	22	13	12	10	6	11	11	8	18	15	13	14
500	-	12	13	13	13	7	7	5	5	12	11	9	12
2 500	-	12	13	11	15	4	6	6	3	15	13	10	9
5 000	-	11	17	14	13	(B)4	(B)4	(B)2	(B)4	8	11	10	10
5 NBMC	-	2150	2350	2200	2350								
10 4-nitro-o-phenylene diamine										260	244	334	210
100 9-aminoacridine chloride monohydrate						447	530	462	572				

* solvent control - DMSO

B = reduced his⁻ background growth

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DATA EVALUATION REPORT

I. SUMMARY

Study Type: Mutagenicity - Multiple Tests in Fungi (Aspergillus nidulans)

TB Project No.: (N/A-RS)
Caswell No.: 559
MRID No.: 00128760
Shaugh. No.: 031501

Accession No.: N/A

Chemical: MCPP [2-(4-chloro2-methylphenoxy) propionic acid]

Synonyms: Mecoprop

Sponsor: N/A (Published article)

Testing Facility: Orto Botanico, L'Universita di Roma (Italy)

Title of Report: Mutagenic and Recombinogenic Action of Pesticides in Aspergillus nidulans

Authors: M. Bignami, F. Aulicino, A. Velcich, A. Carere and G. Morpurgo

Study Number: MUTATION RES. 46:395-402 (1977)

Date of Issue: 1977

TB Evaluation/Conclusions: (NO DETAILED REVIEW PREPARED.)

This document is a published survey article which reported the testing of 13 pesticides (including MCPP) in Aspergillus nidulans strains for mutation to 8-azaguanine resistance (assayed in haploid strain 35), and for mitotic recombination and nondysjunction leading to haploidization (assayed in diploid strain P).

Although MCPP was among eight compounds reported as negative for all genetic end-points, the article does not meet our test data requirements because of the following major deficiencies:

A. Incomplete procedures:

1. Test compounds were not characterized.
2. Dose ranges of compounds (including MCPP) reportedly negative were not given.

3. No positive controls were included (although 5 of the 13 compounds tested positive for at least one genetic end-point).

B. Inadequate expression of results, which were reported only qualitatively (+/-).

Classification: UNACCEPTABLE

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Secondary reviewer: Judith W. Hauswirth, Ph.D. Judith W. Hauswirth 5/2/85
Section VI, Tox. Branch (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: 81-3 Acute Inhalation Toxicity Study

TOX. CHEM NO: 559 MRID NO.: 400241-01

TEST MATERIAL: 2-(4-chloro-2-methylphenoxy) propionic acid.

SYNONYMS: Mecoprop

STUDY NUMBER: 13I0047/83

SPONSOR: The T.P.H. Technical Committee

TESTING FACILITY: BASF Aktiengesellschaft, Dept. of Toxicology, Ludwigshafen, West Germany.

TITLE OF REPORT: Acute Inhalation Toxicity LC_{50} 4 hours (rat) Dust Aerosol study of Mecoprop (MCPP).

AUTHOR(S): H. Klimisch

REPORT ISSUED: November 14, 1985

CONCLUSION: The study is considered invalid because the aerosol contained too few (<25%) respirable (<1 um) particles. Acute inhalation exposure of 10 rats/sex to Mecoprop for four hours at levels of 5.4, 9.5, or 12.5 mg/l lead to 3/20, 4/20, and 5/20 deaths, respectively with signs of irregular breathing, and bloody nasal discharge accompanied by lung congestion.

LC50 Indeterminate

Toxicity Category: Indeterminate

Classification: core - Invalid

A. MATERIALS:

1. Test compound: Mecoprop (MCPP). Batch = T.P.H. -Charge WH 8367, Purity 92.7%.

2. Test animals: Species: Rat, Strain: SPF Wistar /Chbb:THOM: Age: 8-9 weeks at start of dosing. Weight: Males, 284± 19.8g, Females, 189±14.2g Source: Dr. K. Thomae GmbH, D-7950, Biberach FRG

Rats were fasted overnight before dosing. Animals were observed daily and clinical findings recorded on each workday. Rats were weighed prior to dosing, and on days 7, and 14. Gross necropsy was performed on all animals that died on study and on all survivors which were sacrificed on day 14. Doses and lethality are presented in the table under results.

A head and nose only exposure system (INA 20) consisting of a 55 l glass and steel chamber in which the animals were restrained in tubes was used. The test material was milled and mixed with 1% Aerosil. A dust-air mixture was generated with vibration dust partitioning equipment and the concentration was adjusted by varying the aperture and the amplitude of oscillation of the metering beaker. Air flow was set at 1500 l/hour for both the injector and conditioned dilution air. An exhaust air system maintained a 10% flow of air to prevent dilution of the breathing zone with lab air.

Sampling of the chamber concentrations was hourly for group 3 and every half hour for groups 1 and 2. A millipore pump pulled air through 4 mm Millipore filters at a velocity of 1.25 m/sec for 1-2 liters immediately adjacent to the animals's noses.

Chamber concentrations were determined gravimetrically on a Mettler balance by weighing the filter before and after sampling, with corrections for the excipient.

Particle size analysis was by means of a Andersen Stack Sampler Mark III 30 minutes after the beginning of the session in a 3-9 l sample collected on glass-fiber collecting discs, a back-up filter, and on the walls of the impactor.

RESULTS:

Measured concentrations in mg/l (± s.d. measured, and the mass median aerosol diameters (± geom. s.d.) are given below. The complete particle size analyses are also attached.

CONCENTRATION MG/L	MASS MEDIAN DIAMETER UM
12.5±2.32,	4.1±2.3
9.5±1.27	6.2±2.3
5.4±1.36	5.6±2.3

There were several deaths at each exposure level, shown in the table below. Except for 3 deaths in the 12.5 mg/l group (1M,2F) on day 1, all deaths ocurred on the day of exposure.

Dose mg/L	Males deaths/dosed	Females deaths/dosed
5.4	2/10	1/10
9.5	2/10	2/10
12.5	3/10	2/10

Clinical signs of toxicity that were seen were irregular respiration, bloody nasal discharge, ataxia, apathy, and at the highest dose, agression in some males. All signs were reported as reversed by day 12.

While rats in all exposure groups gained weight by day 14 and mean body weights were not significantly different, exposed rats in all dose groups gained much less weight than historical air controls. (Controls, 69g M, 43g F; G1, 37g M, 14g F; G2, 43g M, 19g F; G3 36g M, 19g F)

The four hour LC50 from the study was > 12.5 mg/l.

Gross necropsy showed no findings among day 14 survivors. Those who died on study showed lung congestion, slight edema, some darkened areas, and in one high dose rat, beginning focal bronchopneumonia.

A signed quality assurance statement was present.

DISCUSSION

While this study seems to have been carefully conducted and reported, it is being rated as invalid, primarily due to the very small % of particles < 1um in size. We regard a MMD of 1um and 25% < 1um as a rough guide to the % of particles considered to be adequate to evaluate this route of toxicity. Given the potent eye irritation (Category I) seen for this material, and by analogy, the expected pulmonary irritation, this concern is underscored.

The particle size analyses of the test groups led to the following results:
(The amounts of the material determined in the particle size analysis were not corrected for the added excipient (see 1.5.2.)).

Test group: 1

Stage	EACD 50% (µm)	mg	Percentage distribution	Cumulative distribution in %
Pre-impactor	25.6	11.89		
Cascade impactor				
0	29.5	0.88	4.2	95.8
1	18.2	0.65	3.1	92.7
3	8.5	2.08	10.0	82.7
4	5.5	7.93	38.1	44.6
5	2.8	5.69	27.3	17.2
7	1.2	2.91	14.0	3.3
Backup filter	< 1.2	0.68	3.3	-
		Σ 20.82	100.0	

	mass (mg)
Pre-impactor	11.89
Cascade impactor	20.82
wall losses	28.58

The MMAD 50% = 5.5 µm
(geometrical standard deviation = 2.0)

was calculated from the results of the particle size analysis.

A respirable dust fraction that might reach the alveoli of

83%

was obtained from the results of the particle size analysis.

Test group: 2

Stage	EACD 50% (µm)	mg	Percentage distribution	Cumulative distribution in %
Pre-impactor	26.6	17.24		
Cascade impactor				
0	29.5	2.14	4.3	95.7
1	18.2	1.77	3.6	92.1
3	8.5	7.60	15.4	76.7
4	5.5	21.23	43.0	33.7
5	2.8	10.65	21.6	12.1
7	1.2	4.31	8.7	3.4
Backup filter	< 1.2	1.67	3.4	-
		Σ 49.37	100.0	-

	mass (mg)
Pre-impactor	17.24
Cascade impactor	49.37
wall losses	39.01

The MMAD 50% = 8.2 µm
(geometrical standard deviation = 2.3)

was calculated from the results of the particle size analysis.

A respirable dust fraction that might reach the alveoli of

77%

was obtained from the results of the particle size analysis.

Test group: 3

Stage	EACD 50% (µm)	mg	Percentage distribution	Cumulative distribution in %
Pre-impactor	26.6	4.01		
Cascade impactor				
0	29.5	0.35	1.8	98.2
1	18.2	0.48	2.5	95.7
3	8.5	0.89	4.6	91.0
4	5.5	4.36	22.8	68.2
5	2.8	8.89	46.4	21.8
7	1.2	2.79	14.6	7.2
Backup filter	< 1.2	1.38	7.2	-
		Σ 19.14	100.0	-

	mass (mg)
Pre-impactor	4.01
Cascade impactor	19.14
wall losses	17.12

The MMAD 50% = 4.1 µm
(geometrical standard deviation = 2.3)

was calculated from the results of the particle size analysis.

A respirable dust fraction that might reach the alveoli of

91%

was obtained from the results of the particle size analysis.

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7-18-88
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Judith W. Hauswirth
7/18/88

DATA EVALUATION REPORT

I. SUMMARY

Study Type: Mutagenicity

TB Project No.: (N/A-RS)
Caswell No.: 559
MRID No.: 00158362
Shaugh. No.: 031501

Accession No.: N/A

Chemical: MCPP [2-(4-chloro2-methylphenoxy) propionic acid]

Synonyms: Mecoprop
CAS: 7085-19-0

Sponsor: BASF

Testing Facility: (BASF) Department of Toxicology

Title of Report: Cytogenic Investigations in Chinese Hamsters After a Single Oral Administration of MCPP: ne Marrow Analysis

Authors: G. t and H. Gelbke

Study Number: 47/8306

Date of Issue: April 1, 1985

TB Evaluation/Conclusions:

Presumptively positive for clastogenic activity in Chinese hamster bone marrow cells 6 and 24 hours after a single oral dose of 3800 mg/kg, a level that also caused clinical signs and cytotoxicity (decreased mitotic index).

Classification (Core-Grade):

Inconclusive because of deficiencies described in TB evaluation on last page of this DER.

II. DETAILED REVIEW

A. Test Material: MCPP Technical

Description: Yellow-brown solid
Batch (Lot): 83/47
Purity (%): 92.7%
Solvent/Carrier/Diluent: Suspended in 0.5% CMC for oral administration

B. Test Organism: Rodent

Species: Chinese hamster
Strain: (Not stated)
Age: 7 to 13 weeks
Weights--Males: (Mean for both sexes = 23.82 g)
Females: (Mean for both sexes = 23.82 g)
Source: BASF

C. Study Design (Protocol):

No formal protocol was included. In its place a list of authoritative literature references were appended from which, the authors stated, the test procedure for this type of study was based.

A quality assurance statement was included attesting to two audits of the study and/or final report.

D. Procedure/Methods of Analysis:

Groups of five males and five females were gavaged once at three dose levels of test article: 60, 470, and 3800 mg/kg, and sacrificed 6, 24, and 48 hours after dosing. A negative (solvent) control group of 10 males and 10 females was given the CMC vehicle only and sacrificed 24 hours later, while a positive control of 5/sex received 60 mg/kg cyclophosphamide, CP (a known clastogen) and killed after 24 hours. At the scheduled sacrifice times, bone marrow was removed from both femora of each animal and microscopic slide preparations made according to standard (referenced) procedures for chromosome (metaphase) analysis; three to four slides were prepared from each animal. All animals were examined for gross pathological changes of major internal organs (not specified).

One hundred metaphases per animal were scored for type* and incidence of structural chromosome aberration, as well as for changes in chromosome number.** Mitotic indices were calculated from 1500 cells per animal from all test groups.

Data were analyzed statistically by both Fisher's Exact Test and the Mann-Whitney U-test, and levels of significance determined at both the 0.01 and 0.05 levels.

Results:

In preliminary toxicity testing (complete range of doses not stated) to select doses for the main chromosome assay [which also served for the SCE study conducted about the same time, see BASF Report No. 8307], "some" animals died (numbers unspecified), following single doses down to 4640 mg/kg.

All animals treated at 3830 mg/kg survived, but showed dyspnea, apathy, tremors/twitching, piloerection, and squatting posture 15 minutes postdose, followed by narcosis and staggering 2 hours later, the latter lasting about 3 hours. All animals apparently recovered 2 to 3 days later. Hence, 3800 mg/kg was chosen as the MTD for the cytogenetics assay. A mid-dose level of 470 mg/kg was selected, since 464 mg/kg in the toxicity test caused a less severe degree of the first group of signs as seen at 3830 mg/kg, but no staggering or narcosis.

MAIN ASSAY

Clinical Signs:

After administration of the test substance, the highest-dose group (3800 mg/kg) displayed apathy, piloerection, irregular respiration, accompanied in a few animals (not specified) by squatting, trembling, and twitching for 15 minutes postdose. One hour later, staggering (again, in an unspecified number of high-dose animals) was also recorded. It was reported that one high-dose animal died 1 day after administration of the test substance.

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*Gaps, breaks (including fragments and deletions), exchanges, pulverization. Metaphases with "multiple" (5 or more) aberrations were to be scored separately.

**Aneuploidy and polyploidy.

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Fifteen minutes after administration, an unspecified number of mid-dose animals manifested irregular respiration, piloerection, atony, and (for "some") twitching and squatting, persisting for 1 day postdose (again, number of affected animals unspecified).

Low-dose animals were apparently free of any signs of clinical toxicity (none reported).

Necropsy:

No changes in any internal organ (not specified), attributable to the test compound, were reported in any animal.

Chromosomal Analysis:

(Report Tables 1 through 8, summaries; Report Tables 6 through 19, individual animal data.)

Although low- and mid-dose animals scheduled for sacrifice at 6 and 48 hours were treated, and bone marrow prepared for microscopic examination at these sacrifice intervals, slides from these time groups were not scored for cytogenetic abnormalities.

Since there were no consistent differences between MCPP-treated males and females in any dose group for any time period (Tables 6-19), data and statistical analyses were summarized by the authors for both sexes combined (Tables 1-5).

Compared to the 24-hour control values involving simple breakage (27 aberrant metaphases including gaps, 7 without them, and no exchanges, multiple aberrant cells or pulverization), only high-dose groups (3800 mg/kg) were found to have increased incidences of metaphases with aberrations (see summary tabulation on page following).

At the 6-hour sacrifice, 34 aberrant metaphases including gaps (3.4%) were found, distributed among 9 of 10 animals (only 12 cells, 1.2%, were aberrant, however if gaps were excluded), statistically significant by both methods of analysis. Six of 10 hamsters sacrificed 24 hours after MCPP administration also had increased structural chromosome change (2.1% aberrant metaphases with, and 0.8% without, gaps), which, however, did not reach the 5 percent level of statistical signiticance by either method. In neither group were exchanges or disintegration of chromosome structure observed. The 48-hour sacrifice group displayed no increase in chromosome aberration.

Table: Cytogenetic Abnormalities Induced in Chinese Hamsters (Males and Females Combined) 6, 24, and 48 Hours After Oral MCPP Treatment (Reconstructed From Tables 1 Through 19 of Final Report)

Aberrations[1] (ABs)	MCPP (mg/kg): 0[2]	60	470	3800	CP (mg/kg) 60
6-Hour Sacrifice					
No. Animals				9	
Total ABs (percent)	(1.33)[3]			3.40**	
No. of Mult. ABs				3	
Aneuploidy (Percent)				0	
Polyploidy (Percent)				0.9	
24-Hour Sacrifice					
No. Animals	18	8	7	6	10
Total ABs (percent)	1.35	1.50	1.50	2.10	26.10**
No. of Mult. ABs	0	0	0	1	95
Aneuploidy (Percent)	0	0	0	0	0.10
Polyploidy (Percent)	1.10	1.10	1.50	1.60	2.70
48-Hour Sacrifice					
No. Animals				5	
Total ABs (percent)				0.78	
No. of Mult. ABs				0	
Aneuploidy (Percent)				0	
Polyploidy (Percent)				1.44	

[1]100 metaphases per animal were evaluated.
[2]10 males and 10 females in the control only; 5/sex in all other groups.
[3]Mean of 10 historical controls.
**Significantly different ($p < 0.01$) from 24-hour control value.

With respect to changes in chromosomal number, no aneuploid cells were found in any MCPP-treated animal, or in controls. Polyploid cells, however, were observed in all groups, in comparable numbers: 9, 16, and 13 among high-dose animals sacrificed at 6, 24, and 48 hours, respectively.

All 10 CP-treated animals showed some degree of structural chromosomal damage 24 hours after the single dose of 60 mg/kg. A total of 261 aberrant metaphases counting gaps was recorded; when gaps were excluded the authors claimed 222 cells were aberrant, including 125 with complex rearrangements ("exchanges") and 95 multiple aberrant, "and 24 cells with disintegration of chromosomal structure."

> [NB: Although these are the totals recorded in Report Tables 18 and 19, there must have been a miscount in the slides of one or more animals. The 24 cells with disintegration could not have been counted among "aberrant metaphases," which leaves 220 such cells: 95 multiples plus 125 exchanges.]

Twenty-eight cells from the CP group showed increases in chromosome number, 27 polyploids (2.7%) and one aneuploid, not significantly different from CMC-controls (1.1%), according to the authors.

Mitotic Index (Report Tables 20-23):

Slight [but apparently nonsignificant] decreases were calculated for the 6-hour high-dose test group and the positive controls, as summarized in the following tabulation from the test of the Report:

Test Groups	Mitotic Index (%) 6 hour	24 hour	48 hour
Solvent control (0.5% CMC)	-	5.80	-
3800 mg/kg	2.53	6.03	5.32
470 mg/kg	-	6.74	-
60 mg/kg	-	5.39	-
Positive control (Cyclophospha-mide)	-	2.89	-

Authors' Conclusions:

1. Only in bone marrow from high-dose animals sacrificed at 6 hours, where clear evidence of toxicity occurred, was there a marginal but significant increase in chromosomally-aberrant cells. Although aberrations also increased in 24-hour samples, the increase did not reach the level of significance.

2. Only a minority of animals treated at 3800 mg/kg contributed to these increases (2 males each with 6% and 1 female with 8% at 6 hours; 1 male with 7% and 1 female with 5%--compared to the control rate of 1-4%).

3. Therefore, the authors could not draw any firm conclusions as to the clastogenic activity of MCPP.

TB Evaluations/Conclusions:

Quality Assurance measures were included by a statement attesting to inspections at the start of the study and audit of the final report.

The study was conducted with procedures apparently adequate to generate valid results, and we agree with the authors' equivocal conclusion, to the extent the data permit. Perhaps the authors could have arrived at a firmer conclusion had all the slides been examined and scored, including those from both the low- and mid-dose groups at 6 hours and 48 hours. We strongly recommend these be analyzed and the data submitted with the appropriate statistical analyses.

Until then, TB concludes that MCPP was weakly positive for clastogenic activity in Chinese hamster bone marrow cells following acute oral administration of 3800 mg/kg, the highest of three doses (negative at 60 and 470 mg/kg), a level which was also clinically and cytologically toxic.

We further request identification of the "internal organs" stated to have been examined for any gross pathological changes.

Therefore, the study is considered incomplete, but can be upgraded to acceptable with submission of the missing data and information described above.